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Editorial

Digital Diabetology in Daily Practice

Healthcare Technology Comes Calling

With the easy availability of access to internet, especially on mobile devices, the last decade has seen rapid progress in digital health care. Diabetes care has been keeping pace with this march of technology[1]. Today, as technology empowers patients and healthcare professionals like never before, we focus on the clinical aspects of technology in diabetes, or "digital diabetology", as the title of this article says. Broadly, there are five aspects of digital health whereclinicians can help their patients.

Of Lifestyle Disease and "An App for That"

The increasing occurrence of type 2 diabetes in our midst has overwhelmed healthcare practitioners. This has been accompanied by digital tools which can assist the person with diabetes to follow dietary advice, be physically active and reduce stress. These tools have been shown to meaningfully improve glycemic markers such as HbA1c. Importantly, many of these tools are free, and can be accessible to all. Listing these apps is beyond the scope of this article. Doctors and caregivers must themselves study the application and its usefulness before advising digital tools that promise to change lifestyle. While we know of the well-known promise of technology to solve the world's problems (remember the adage "there's an app for that"), there are many concerns with these digital lifestyle apps.[2] For instance, while some tools write about the remission of type 2 diabetes, the sustainability (or, more importantly, the lack of it) of remission beyond the short term needs to be discussed with our patients. Security concerns also exist – and any digital tool must clearly spell out how the data is used. Third, reputability of the service provider, based on high quality research publications and endorsement by government regulatory bodies are important to consider. Taken together, a personalized and ongoing consultation, or for that matter teleconsultation with doctors, nutritionists, behaviour therapists and exercise experts is still the best choice when it comes to motivating and lifestyle change for health improvement. Admittedly, this is not easy to implement in a country like India, given its more than 76 million people with diabetes. Given this reality, we as healthcare practitioners could be cautiously optimistic of health care tools that promise to improve adherence to lifestyle change.

The "Class" Monitor

The sheer class of technology in empowering diabetes care is best brought out in the monitoring of glycemia. This is where digital diabetes care is literally blooming

in the management of hyperglycaemia. From the days of urine glucose testing and the years of the archaic and unreliable glucose meters, we have now entered the era of smart monitoring. Today, connected glucometers that sync data from the glucose meter to the mobile phone are a reality and several glucose meters offer this advantage. These glucose meters are often appreciated by patients too[3]. Such connected glucose meters facilitate remote monitoring and tele-diabetology practice[4]. For instance a health care provider sitting in the clinic can access blood glucose data of the patient, offering health care advice remotely.

Even more exciting is the Continuous Glucose Monitoring (CGM) system. While the glucose meters mentioned above can detect blood glucose levels at a point in time, CGM device scan sense glucose continuously by simple subcutaneous devices and transmit it to a screen. Data can be downloaded and analysed by doctors; the use of CGM has been supported by guidelines[5]. More importantly, this data can be directly seen by patients helping them make lifestyle changes in accordance with their blood glucose patterns, making this CGM into a "moving selfie" of blood glucose levels. Not surprisingly, companies are connecting such CGMs with lifestyle modifying apps and promising a remission of type 2 diabetes. But more excitingly both industries and individuals have been connecting the CGM devices to insulin treatment algorithms in type 1 diabetes. This is because people with type 1 diabetes require insulin injections long term, and the pain of testing and injection can, to some extent be attenuated by these Do-It-Yourself (DIY) devices which connect CGMs to insulin delivery systems[6]. The use of this DIY device does raise some ethical dilemmas though as these connected systems require more research[7]. While these CGM systems do reduce glycemic variability, the targets to be achieved for CGM parameters of variability with a view to preventing diabetic complications remains to be established[8]. Nevertheless it is true that these CGM devices do reduce variability and prevent hypoglycaemic episodes, facilitating overall better glycemic patterns.

A Tech Treat

One of the biggest advantages of technology in diabetes is it's potential to impact therapeutics. The promise of technology in lifestyle interventions has been mentioned above. Also well-known are the simple alarm-based pill reminders, which could potentially improve adherence[9]. While the potential of mobile text messaging for preventing the progression of prediabetes to diabetes is well known[10], more studies are needed.

However, it is known that technology can help adjust medications, for example, insulin doses. A recent study showed that people with type 2 diabetes who were started on basal insulin could be assisted by an app which helps implement a basal insulin-titration schedule to reach appropriate glycaemic targets[11].

However, the most classical implementation of technology is continuous subcutaneous insulin therapy also referred to as CSII or insulin pump treatment. Newer versions of this technology promise to transform type 1 diabetes care[12]. This treatment, in which a battery powered chip pushes a syringe pump's insulin through a tubing directly into the subcutaneous space is an accepted therapy of type 1 diabetes; recent versions of this machine can adjust insulin dosing according to the ambient glucose levels: this works in ways similar to, though nowhere close to a true artificial pancreas. This system is also referred to as a closed loop system, because it closes the loop between glucose sensing and insulin delivery. Such closed loop systems are shown to give a more precise insulin delivery, reducing or even stopping insulin from entering the body when correctly predicting hypoglycaemia. On the otherhand the close loop system can increase the insulin dose during hyperglycaemia. A variant of this closed loop system is the bionic pancreas – which, in addition to insulin dosing, also avoids hypoglycaemia by timely infusion of a blood glucose raising hormone, i.e. in this case, glucagon[13].

It is Complicated

Complications due to diabetes can be diagnosed early via technology. A classic example is the increasing use of artificial intelligence in ophthalmic hand-held fundus cameras, which could identify both early and advanced diabetes related retinopathy[14]; it is important to note that these tools have limitations. Similarly, early detection of neuropathy and postural instability via fall and gait detection have been studied[15]. An early sign of diabetic kidney disease is hypertension and this can be diagnosed early by wearables. Detection of hypertension, heart failure and arrhythmias using technology is being increasingly discussed, though there are challenges with analysis and smart handling more than data acquisition[16]. In future, it might be possible to predict and diagnose diabetes-related complications via point of care, and multi-analyte detecting sensors. It is hoped that the appropriate use of technology could help diagnose and treat diabetes related complications early.

The Idea is HIS

With the increasing availability of Electronic Medical Records (EMR) and Hospital Information Systems (HIS), telemedicine for diabetes care is becoming a reality. It is important, firstly, to decide whether the person with diabetes can be managed over telemedicine, or whether the disease, its complications and comorbidities require a hospital visit[17]. A first time telemedicine consultation can be challenging, while follow up consultations are possibly simpler. Tele-diabetology for podiatry care, also referred to as tele-podiatry, has been described, and a recent article suggests that tele-podiatry could serve as a triage for bringing the sicker diabetic foot patients to hospital; at the same time, ideally all diabetic foot patients should visit a hospital for their care[18]. It is possible, however, to have a diabetes related consultation to be delivered via telemedicine in certain scenarios, and there have been guidelines for this. While choosing an appropriate EMR, doctors should choose a product that is secure and ensures privacy; after all, the entire data of the patient belongs to the patient and the doctor/ hospital/ platform/ provider has merely been entrusted with looking after it.

Thoughts for Today and the Future

Technology is enabling research like never before-indeed CGM-based outcomes can be included in research studies of anti-diabetes medications, as was elucidated by a recent study from India[19]. Another, unrelated point is that with the advent of social media, the spectrum of digital diabetology has become a tool for information, as well as misinformation. As doctors, we have a responsibility to educate and make people aware of the right approaches to diabetes management. Given this, it is important that we prevent misinformation by proactively conducting awareness sessions for both people with diabetes as well as the larger general population. Misinformation can harm – an example is the case of statin discontinuation in people with baseline diabetes and cardiovascular disease in Denmark[20]. In this Danish study, it was shown that negative news stories about statins lead to statin discontinuation in people who have diabetes and cardiovascular disease. The study also concluded that such early stoppage of statins increases the risk of cardiovascular events such as myocardial infarction and cardiovascular death[20]. Given the all-pervasive nature of digital media today, we health care professionals should fight misinformation by conducting educational programs that help convey the correct information.

While the revolution of artificial intelligence and digital health sweeps over the healthcare domain, we as doctors could welcome it as another tool in our armoury. Embellishing clinical art and intuition with the science of data may indeed help patients. In future, artificial intelligence may build in the "art of medicine" and even artificial empathy and compassion. But for the moment, a good history taking, clinical examination, interpreting laboratory tests/ imaging and discussing treatment decisions are the best tools that we have. And if we indeed already have these skills, refining them further with technology-enabled data and tools can only help healthcare progress further as we help our patients to heal.

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Original Article

Gall Bladder Polyps : A Paradigm Shift – Need for Reappraisal of Guidelines

Inakshi Chrungoo[1], Surbhi Abrol[2], Aseem Mahajan[3], Rajni Bhardwaj[4], Harbinder Singh Bali[5], R K Chrungoo[6]

Background : Gall Bladder Polyps are mucosal lesions that project from the Gall Bladder wall into the Gall-bladder lumen. They form morphologically distinct lesion/s with internal characteristics different than that of neighboring structures as verified by microscopic examination. About 4-6% are picked up clinically, 2-12% in Cholecystectomy specimens and 4% on Ultrasound.

Materias and Methods : A three calendar year retrospective single surgical unit study compromised of 1442 cholecystectomies performed for benign Gall Bladder Disease. The patient were subjected to Ultrasound of abdomen for diagnosis and routine clinic work up. The Gall Bladders Harboring Polyps were examined grossly for site ,number, and microscopy for histological details.

Results : In a total number of 40 cases of Gall Bladder Polyp, females outnumbered males.

This series spreads over age groups of 3rd decade - 9th decade, most of the patients were seen in 6th decade of life. Youngest patients were 27 years old and oldest one was 85 years old. Incidentally, none of the old patients had evidence of malignancy on histopathology in their Gall Badder Polyp, only 2% were necessitated for a pre-operative diagnosis of Gall Bladder Polyps alone. Rest required it for presence of Gallstones with or without Polyp. None of >10mm size showed any malignant change on histopathological examination. On the Contrary, among the polypoid lesions <10mm size, one polypid lesion (7mm) showed a malignant change (Carcinoma in situ)

Conclusion : A predictive model for neoplastic potential of Gall Bladder Polyp may support clinical decision to achieve an ideal therapeutic outcome. Hence a need for reappraisal of management guidelines.

[*J Indian Med Assoc* 2022; **120(6):** 13-8]

***Key words* : Gall Bladder Polyp (GBP), Polypoid Lesions of Gallbladder (PLG), Laparoscopic Cholecytectomy (LC), Endoscopic Ultrasound (EUS), Photoacoustic imaging.**

Gall Bladder polyps are mucosal lesions that project from the Gall bladder wall into the Gall bladder lumen. By definition Gall Bladder Polyp is a protrusion of mucosa that is clearly recognizable either on the gross bench or by examination of the glass slide and that formed a morphologically distinct lesion with internal characteristics different than that of neighboring structures as verified by microscopic examination.

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Editor's Comment :

- Polypoid Lesions of Gall Bladder (PLG) are benign in nature yet some early carcinomas may resemble benign polyps.
- Since smaller polyps may rarely present as malignancy, it would be worthwhile to closely put polyps smaller than 10 mm (and more than 5- 6mm) under a suspicious surveillance.
- A predictive model for neoplastic potential of GBP may support clinical decision to achieve an ideal therapeutic outcome. Hence a need for reappraisal of management guidelines.

These polyps are one of the most common diseases Worldwide[1]. Majority are diagnosed as an incidental finding on routine investigation or in Gall Bladder operation, in the specimen. While most Polyps are benign in nature, some early Carcinomas may resemble Benign Polyps. About 4-6% are picked up in clinical practice and 2-12% are picked up in Cholecystectomy specimens and 4% are picked up on Ultrasound examination of Hepatobiliary system in adults[2]. Male sex[3] and Dyslipidaemia (a higher non-HDL-c/HDL-c ratio)[4] have also been reported to be associated with Gall Bladder Polyps.

The Polyps are mostly Benign. Malignant ones are rare (Piechart 1).

GB Polyps

- Neoplastic
  - i) Primary a) Adenocarcinoma
    b) Clear cell carcinoma
    c) Melanoma
  - ii) Metastatic
- Non-neoplastic
  - i) Adenomas a) Tubular
    b) Papillary
    c) Mixed
  - ii) Mesenchymal Tumors
    a) Fibroma
    b) Lipoma
    c) Haemangioma
  - iii) Pseudotumors
    a) Cholesterol Polyps
    b) Cholesterosis
    c) Inflamatory Polyps
    d) Hyperplasia and Adenomyometosis

Histologically (Task in *et al* 2020) polyps are classified into :

- Non-neoplastic polyps
  - i) Fibromyoglandular polyps
  - ii) Cholesterol polyps
  - iii) Polypoid pyloric gland metaplasia
  - iv) Inflamatory polyps
- Neo plastic polyps
  - i) Intracholecystic neoplasms
  - ii) "Incipient" intracholecystic neoplasms
  - iii) Polypoid invasive carcinoma
  - iv) Non-neoplastic polyps harboring dysplasia.

The following two facts have to be considered while managing the polypoid lesions of Gall Bladder that :

(a) while as early cancer in the Polypoid lesions can be treated by Cholecystectomy alone, and

(b) if neglected or delayed, a resultant Gall Bladder cancer carries a very dismal prognosis.

Therefore a correct diagnosis and a fair surveillance is warranted and mandatory for good outcome[5].

Not with standing early reports about smoking to be inversely related to presence /occurrence of Gall Bladder Polyps[6], yet later report[7] presenting results of a meta-analysis showed increased risks of Gall Bladder Disease in smokers.

However, definite risk factors include: General factors:

- Obesity
- Dyslipidaemia
- Congenital Polyposis Syndroms eg. Peutz-Jeghers, Gardener Syndrome[8]
- Indian ethnicity[9]

Pathological factors :

- Size of the Polyp/s 10 mm
- Single sessile broad based polyp
- Polyps broader than tall
- Polyps with adjacent wall thickening
- 2 mm or more increase in the size of Polyps during surveillance

Transabdominal Ultrasound is the most ideal diagnostic tool with a sensitivity & specificity of 93% and more than 95 % respectively. Generally polyps of >5 mm size are easily demonstrable. In case of many Polyps, largest one decides the plan of management while as Polyps dimensions (size) can be a predictor of tumorous lesion[10,11].

Predictions of malignancy in Polypoid lesions of Gall Bladder[12] are scored as given in Table 1.

The sensitivity, specificity and accuracy for the risk of malignancy with scores of 3 or more being 81.6%, 86.7% and 84.4%, respectively. However, Since Trans-abdominal Ultrasound has a high false positive rate (85.1%) for diagnosis of Gall Bladder Polyps, further study of alternative imaging modalities and re-evaluation guideline are warranted[13].

Endoscopic Ultrasound (EUS) is considered to be superior to the conventional transabdominal Ultrasound, because of its higher resolution of images and its scoring system is as follows :-

- Maximum diameter(in mm)

  +

- Internal Echo Pattern Score

(Heterogenous = 4, Homogenous = 0)

- Hyperechoic spot score (Presence = -5, Absence = 0)

Scores of 12 or more are a strong risk factor, the sensitivity; specificity and accuracy being 78%, 83% and 83% respectively[14].

Photoacoustic imaging is an ex-vivo study used in differentiating cholesterol versus Neoplastic Polyps and Benign *versus* Malignant Polyps of the Gall Bladder. A study showed a distinguishable photoacoustic spectral patterns and therefore, suggested this method could be used for differentiating Malignant from Benign Polyps[15].

Table 1 — *Ultrasound based scoring system for differential diagnosis of polypoid lesions of Gall Bladder*

Feature	0	1
Max. diameter	< 13.9mm	≥ 13.9mm
Base width	<3.4 mm	≥ 3.5mm
Height/width Ratio	>1.05	≤ 1.05
Hyperechoic Spots	Presence	Absence
Blood flow	Absence	Presence

Abdominal CT is incapable of detecting low density lesions and its sensitivity for diagnosis of Gall Bladder Polyps is only between 44% and 77%[16].

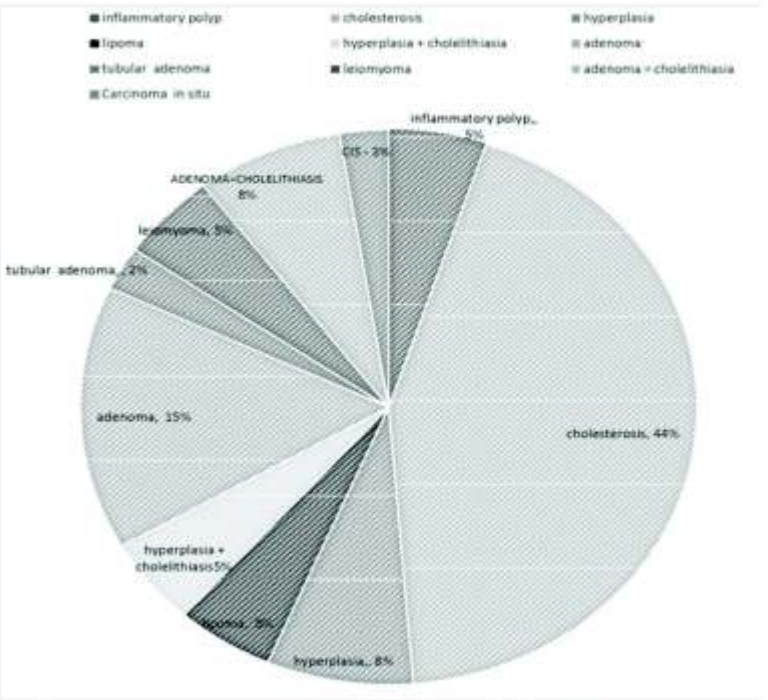
Summing up it is a diagnostic challenge to determine which polyps are likely to be malignant or undergo malignant transformation in order to determine which patients require Cholecystectomy on priority.

Aims and Objectives

To evaluate the pattern of the Gall Bladder Polyp disease in our setup and to authenticate need for change/modification of management guidelines.

Material and Methods

A three calendar year retrospective single Surgical Unit study compromised of 1442 Cholecystectomies performed for Benign Gall Bladder Disease. The patient were subjected to Ultrasound of abdomen for diagnosis and routine clinic work up. After obtaining an informed consent for operation and pre-operative fitness for surgery, Laparoscopic Cholecystectomy (LC) was performed. The specimens retrieved were individually subjected to histopathology examination. The Gall Bladders harboring polyps were examined grossly for site, number and microscopy for histological details.



Pie Chart 1 — Histopathological Depiction of various Gall Bladder Polyp Specimens

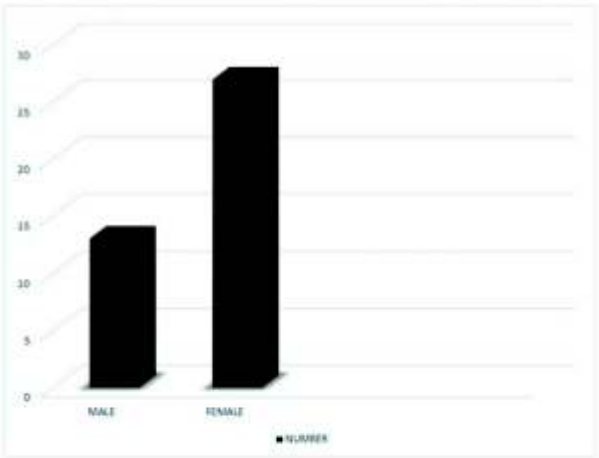


Fig 1 — Illustrating gender pre-disposition of Gall Bladder Polyps in our study

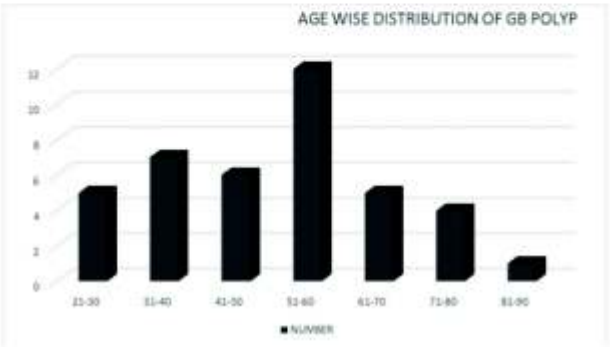


Fig 2 — Agewise Distribution of GB Polyp

Observations

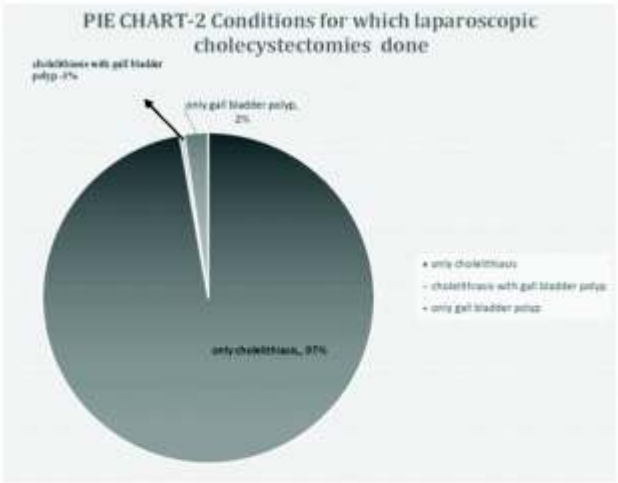
In a total number of 40 cases of Gall Bladder Polyp, females outnumbered males (27;13)(Fig 1).

This series spreads over age groups of 3rd decade - 9th decade, most of the patients were seen in 6th decade of life. Youngest patients were 27 years old and oldest one was 85 years old (Fig 2).

Incidentally, none of the old patients had evidence of malignancy on histopathology in their Gall Bladder Polyp (Piechart 1 and Fig 2).

Out of total number of Laparoscopic Cholecystectomies (n=1442), only 2% were necessitated for a pre-operative diagnosis of Gall Bladder Polyps alone. Rest required it for presence of Gallstones with or without Polyp (Piechart 2).

Out of the total number of 40 polypoid lesions, 23 were equal to or more than 10 mm in size and interestingly none of them showed any malignant change on Histopathological Examination (Piechart 3).



On the Contrary, among the polypoid lesions <10mm size, one polypid lesion (7mm) showed a malignant change (Carcinoma in situ)(Images 1&2).

Discussion

Gall Bladder Polyps (GBP) are found in more than 4% of adult abdominal ultrasounds but their growth pattern and association with gall bladder cancer are poorly defined. Although most are thought to have no malignant potential yet a minority (ie, 4% to 10%) are adenomas which do have a malignant potential[3]. However distinction between adenomas and non-adenomas is usually made after surgery, so if surgery is not performed the clinician must decide whether

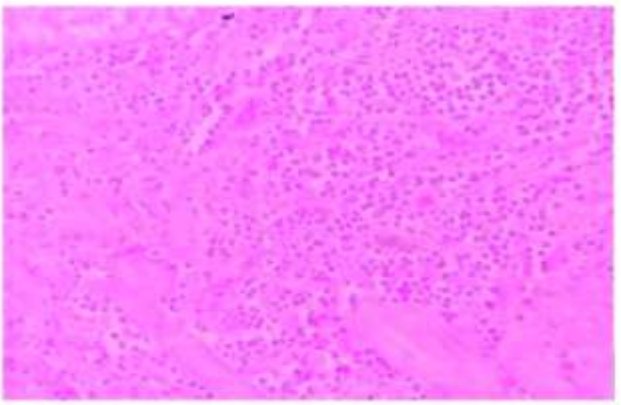


Image 1 — H&E Stained, High power microscopic picture showing carcinoma in situ

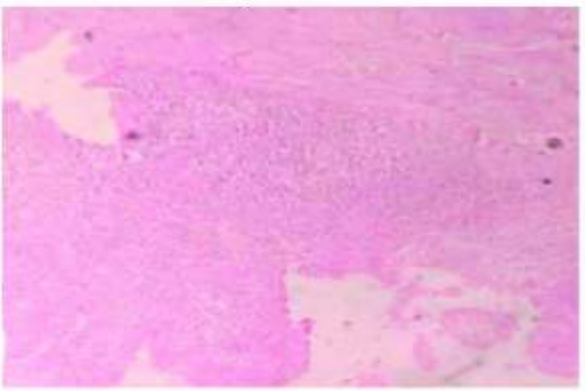
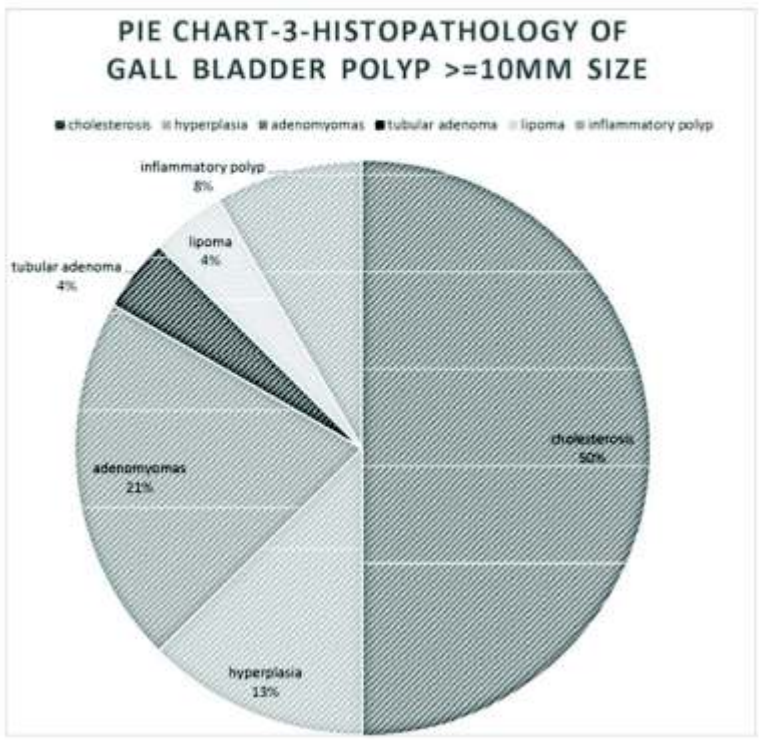


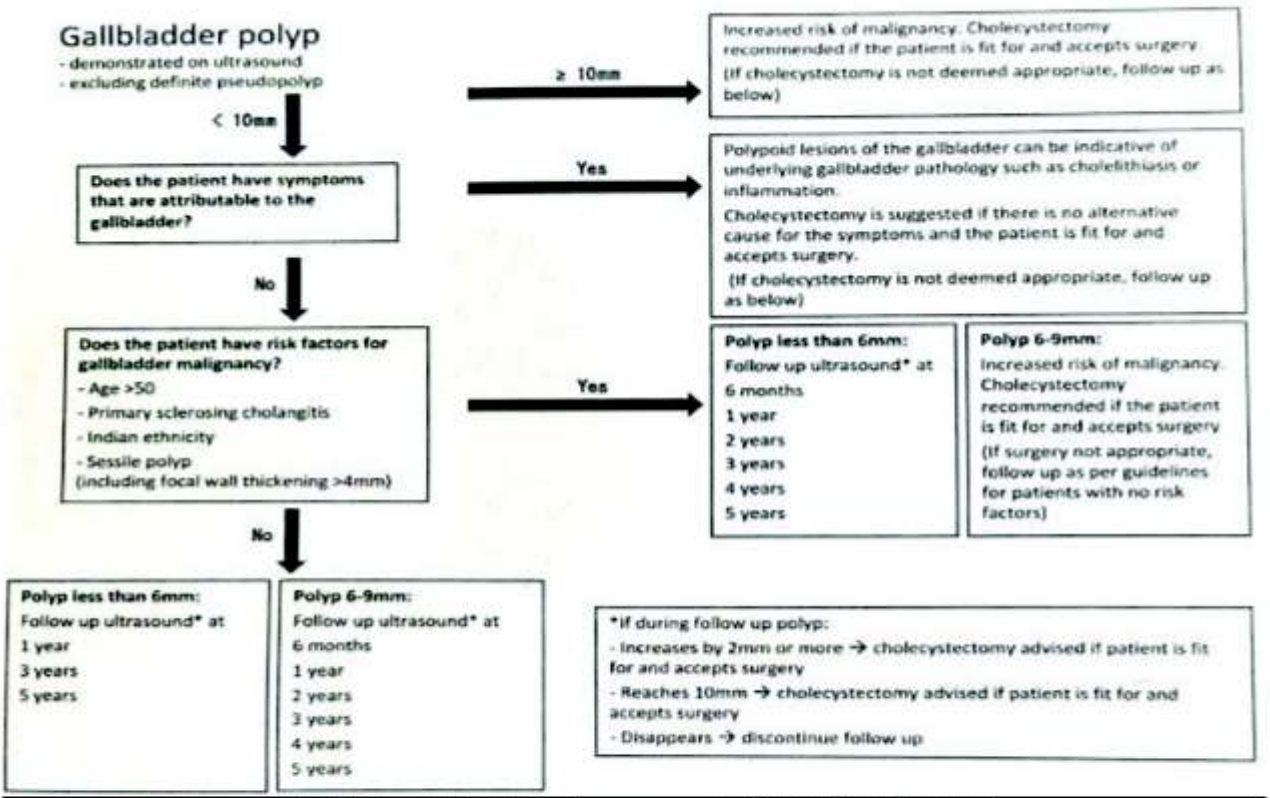
Image 2 — H&E Stained, Low power microscopic picture of gall bladder carcinoma in situ



and how best to perform surveillance, during the wait and watch period. The indications for laparoscopic Cholecystectomy for Gall Bladder cancer prevention are still a matter of discussion[17].

Joint Guidelines (Algorithm 1), regarding management and follow-up of Gall Bladder Polyps, between European Society of Gastrointestinal and Abdominal Radiology (ESGAR), European Association for Endoscopic Surgery and other Interventional Techniques (EAES), International Society of Digestive Surgery-European Federation (EFISDS) and European Society of Gastrointestinal Endoscopy (ESGE), were put forth in 2017[18].

Pre-operative determination of the nature of Gall Bladder lesions is however, fraught with challenges[1]. For Gall Bladder Polyps size measurement has been used as the simplest way to estimate the potential nature of the lesion with one centimeter remaining the most commonly



Algorithm 1 — Joint guidelines for management of Gall Bladder Polyp, 2017

used rule of thumb criteria for a polyp (GBP) removal. This cut-off size however, has been debated[19]. Generally the opinion prevails that Polypoid Lesions of Gall Bladder (PLG) greater than or equal to 10 mm require Cholecystectomy, if the patient is fit and accepts surgery. Polyps smaller in size than this need a surveillance; bigger the size more strict the surveillance – especially in presence of risk factors viz. old age (age>50 years) increasing polyp size (especially at base), wide based single sessile polyp, absence of echogenicity, concomitant presence of Gall Stones, increased vascularity in the Polyp etc. A polyp that increases by 2 mm during follow up requires Cholecystectomy.

In spite of rigid guidelines, surprises may spring up on histopathology of Polyps by manifesting malignant or pre-malignant pathology. The authors have known one such case, a 56 year old non co-morbid (with no risk factor) women presenting with a 7 mm polyp –advised surveillance. Having been lost to follow up, she presented with an advanced Gall Bladder cancer 9 months later. (not included in this study). Another patient (Fig 3) with only a 7 mm Polyp turned out to be a ca- in situ. David Kasle *et al*[20] have drawn the attention towards strong surveillance in Polyps of even lesser magnitude and suggested a change of practice. Wennmacker *et al*[21] have raised doubts about the threshold of the size of 10 mm in GB Polyps, as lacking evidence.

Even the findings of Szpakowski and Tucker[3] call into question the European Societies recommending follow up of Gall Bladder Polyps. Their study suggested that the natural history of these Polyps is to grow over time. This is clearly evident in our series wherein most of the lesion were more than 10 mm, although benign had grown over a period of time. They suggested a pro-active monitoring and changing the threshold to recommend early Cholecystectomy[22].

The authors of the guidelines of management, themselves, had hinted at a re-appraisal of these guidelines by September, 2021 or earlier as the need be[18].

Conclusions

Most Polypoid Lesions of Gall Bladder (PLG) are benign in nature yet some early Carcinomas may resemble benign polyps. It might be difficult to accurately predict or diagnose the pathologic status pre-operatively. Our study highlights 2 important aspects of the management of Gall Bladder Polyps. 60% were large solitary, sessile and some even

associated with presence of stones and of these none showed pre-malignant or malignant nature. On the other hand a small Polyp of 7 mm size showed a pre-malignant change (ca-in situ). Since smaller Polyps may rarely, present malignancy, it would be worthwhile to closely put polyps smaller than 10 mm (and more than 5- 6mm) under a suspicious surveillance, especially if accompanied with any one or more of the risk factors, particularly in view of increasing reports of malignancy in smaller polyps and of otherwise in Polyps of sizes 10mm or more. A predictive model for Neoplastic potential of GBP may support clinical decision to achieve an ideal therapeutic outcome. Hence a need for reappraisal of Management Guidelines.

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Original Article

Typhoid Outbreak during the Pandemic of COVID-19 : A Report

Vikram Khan[1], D B Zala[2], A A Sanghai[3], V K Das[4]

Background : In the 19th Week of 2020, Integrated Disease Surveillance Programme (IDSP) noted an unusual increase in the number of fever cases in Routine Syndromic Surveillance.

Objectives : The unusual increase of fever cases were investigated to identify the agent, the source of infection and to propose recommendations for control measures.

Methods : Active surveillance of fever cases done, blood samples, stool samples and water samples were collected from the affected area. The secondary data of indoor and outdoor patient were collected from the nearest health facilities.

Result : It was a single peak outbreak of typhoid, started from 1st May, 2020, had peaked during the 19th Week of May, 2020 and ended on 31st May, 2020. The epicentre of the outbreak was the residential colony of Industrial labour. The outbreak of Typhoid occurred due to conditions generated due to the pandemic of COVID -19. Two sources of active infection were found. First, contaminated supply of drinking water and second a food-handler, who was the carrier of Typhoid.

Interpretation and Conclusion : It is a lesson to learn that the local communicable diseases should be monitor during the pandemic. Otherwise, that can cause the situation of co-epidemic.

[*J Indian Med Assoc* 2022; **120(6):** 19-22]

***Key words* : Enteric fever, *Salmonella typhi*, Surveillance.**

Typhoid (enteric) fever is an acute febrile illness caused by *Salmonella enterica* serovar *typhi* (*S typhi*)[1-4]. The global annual burden was estimated at approximately 12 million cases[1,2,5]. The incidence of typhoid and paratyphoid varies geographically, with South-Central and South-East Asia having the highest incidence typically exceeding 100 cases per 100,000 person-years for Typhoid[6]. Most of the outbreaks were reported due to drug-resistant strain of *Salmonella typhi*[7-10]. However, the other common identified risk-factors include a lack of clean drinking water, poor sanitation, inadequate hygiene practices and low socio-economic status[11-13], In some instances, the originating infection may be a chronic carrier who persistently sheds the bacterium as a result of infection of the gall bladder[14]. In India, typhoid incidence rates declined in 19 century[4]. However, typhoid fever outbreaks continue to be reported in the various States and Cities of India as Chandigarh,[14] Maharashtra[15,16], Bangalore[7], West Bengal[8,9,13], Pondicherry[10], Rajasthan[17,18]. However, only limited outbreaks of typhoid were subjected to the proper epidemiological investigation[15,16]. Typhoid surveillance is an integral part of the Integrated Disease Surveillance Programme (IDSP) in India. In the 19th Week of 2020, IDSP noted an unusual increase in the fever cases from the Village Surangi. The outbreak was investigated to identify the causative agent and source of infection,

Editor's Comment :

- This study is a lesson to be learned that surveillance of the local outbreak-prone diseases should not be overlooked, even during the pandemic. Otherwise, it may lead to co-epidemic conditions.

Materials and Methods

Study Setting :

The district of Dadra Nagar Haveli (DNH) is situated at latitude, 20°54'41" N to 20°21'36" N and Longitude – 72°54'41" N to 73°13'13" N in the Western Ghat. The 487 sq km area is forest hill area, occupied by mainly tribes (population 4.5 lakh) in 72 villages and one town. Owing to the subsidiary in taxes, many large (20), medium (564) and small (2118) industries have been established in this District of India. Approximately 2.5 lakh skilled and unskilled workforce comes to the

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DNH from different states of India. The Surangi is a village of the District DNH, located at 20°09'19.1"N 73°00'43.7"E. The total geographical area of the village is 1012.97 hectares and the total population of 5,016 peoples.

Epidemiological Investigations —

During regular surveillance of fever under the IDSP unusual health events were reported from Surnagi Village of PHC Amboli in the week No 19 of the year 2020. The Rapid Response Team reached at the place on date 15/05/2020 and collected data from the patients of concerned locality like as age, gender, food habits, source of drinking water, profession and last date of visit at nearest Health Centers. Furthermore, the passive data of indoor and outdoor patients along with laboratory results were collected from concern health institutions. All the patients having symptoms of fever, headache, abdominal discomfort, loss of appetite, constipation, diarrhoea, dry cough, malaise and rash along with relative bradycardia were examined by the clinician. The blood samples were collected from the patients having symptoms of fever, headache, abdominal discomfort, loss of appetite, constipation, diarrhoea, dry cough, malaise and rash along with relative bradycardia.

Laboratory Investigations —

In routine, all health institutions are using Widal Tube Test (Tulip Diagnostics Private Limited) method as per IDSP protocols. The 15 ml blood was collected from the patient suffering from fever within the last 7-10 days, inoculated immediately into brain heart infusion broth (HiMedia Laboratories Pvt Ltd). The inoculated samples were kept in the incubator for 7 days. The causative organism was identified and Antimicrobial Sensitivity Test was done as per IDSP protocol.

Environmental investigations :

After the open interviews among suspected/ confirmed patients, health workers and local leaders, a hypothesis generated that the food handlers of the cafeteria may be the carrier or supply of water may be contaminated. The hygienic practices of food handlers were reviewed and stool samples were collected. The premises were examined to assess the sanitary situation and supply of water. The water samples were also collected from various sources like taps and tube well. The bacteriological analysis of water samples were done by the H_2S method.

Results

Epidemiological Investigations :

A total of 174 clinical suspected and laboratory-confirmed cases of typhoid were reported during the outbreak. The median age of patients was 22 years (Range 2 months – 50 years), 8.62 % of patients were required hospitalization and there no death was encountered. The attack rate among the age group of 15 to 24 years was 5.87 per 10,000 populations, followed by 2.05 in 25 to 34 years, 0.49 in 35 to 44 years, and 0.47 in 0 to 4 years. The lowest attack rate (0.08) was noticed in the age group of above 45 years followed by 0.22 in the 5 to 14 years. On the basis of gender-wise analysis, it was observed a male-biased trend. The outbreak started on 1st May 2020, peaked during the 19th Week of May, 2020, and ended on 31st May, 2020 (Fig 1). All clinically suspected/confirmed cases were residing in the same colony and all were working in the same industry.

The colony was a hostel-like structure with the common facility of kitchen, dining hall, toilet, bathroom and drinking water facility. A total 368 residents of the affected area were clinically examined. Out of 368, a total of 54 patients were found symptomatic as per case definition at the time of RRT visit. The blood samples were collected from symptomatic patients on the spot with verbal consent. Out of 54 blood samples, nine (16.67 %) blood culture samples were found positive for *Salmonella typhi*. Total 40 (74.07%) blood samples were found positive for Widal test at a cut off of 1/160 for H and O antigen. Total of five samples of stools were obtained from food handlers. Out of that one person was found as a career of *Salmonella typhi*. Total ten water samples were collected, out of that four samples were found bacteriological positive. The isolated organism (*Salmonella typhi*) from the affected area was susceptible to the following antibiotics, ampicillin, Amoxicillin / Clavulanic acid, Piperacillin / Tazobactam, Cetriaxone, Cefoperazone / Sulbactum, Cefepime, Ertapenem, Imipenem, Meropenem, Ciprofloxacin, Tigecycline, Colistin and Trimethoprime/ Sulfamethaxone. However, the isolated strain showed intermediate resistance to Nitrofurantoin and resistance to Cefuroxime, Cefuroxime Axetil,

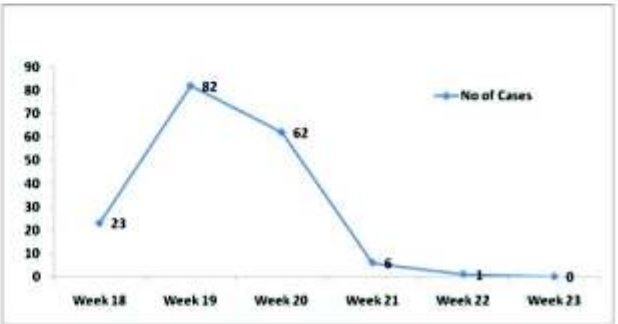

Fig 1 — Showing weekly trend of positive cases

Table 1 — *Showing antibiotic sensitivity pattern of isolates (N=9)*

Antibiotic	MIC	Interpretation
Ampicillin	≤2	S
Amoxicillin / Clavulanic acid	≤2	S
Piperacillin / Tazobactam	≤4	S
Cefuroxime	4	R
Cefuroxime Axetil	4	R
Cetriaxone	≤1	S
Cefoperazone / Sulbactum	≤8	S
Cefepime	≤1	S
Ertapenem	≤0.5	S
Imipenem	≤0.25	S
Meropenem	≤0.25	S
Amikacin	≤2	R
Gentamicin	≤1	R
Nalidixic Acid	≥32	R
Ciprofloxacin	1	S
Tigecycline	≤0.5	S
Nitrofurantoin	64	I
Colistin	≤0.5	S
Trimethoprime / Sulfamethaxone	≤20	S

Amikacin, Gentamicin, Nalidixic Acid and Nitrofurantoin (Table 1). All the patients also received ceftriaxone either alone or in combination with other drugs and all were recovered.

Discussion

The present report is a classical example of the co-epidemic. The outbreak of typhoid occurred due to conditions generated due to the pandemic of COVID-19. The complete lockdown was implemented on the 15th week of 2020 in India. All kinds of movement were restricted during the lockdown; the peoples were surviving with minimum available resources. Therefore, the outbreak was happened due to overcrowding, poor hygiene & sanitation and unavailability of safe drinking water, in the residential area. The unsafe drinking water, poor sanitation, inadequate hygiene practices, drug-resistant and asymptomatic carriers are the common cause of the typhoid outbreak in India[1,11]. In the present investigation, two sources of active infection were found. First, was contaminated supply of water and second food-handler, who was the carrier of typhoid. However, dense population, unplanned construction, poor sewerage systems, poor sanitation and inadequate hygiene practices were contributing to making the residents of the hotspot more vulnerable. The single peak and one-month duration of the outbreak indicate that the source of infection was common in the outbreak which is in accordance with earlier outbreak reports of typhoid[11]. In the previous investigation, the high attack rate of typhoid was reported in 0-4 year age group and we found low attack rate in said age group because the maximum proportion of cases belongs to the 20-24 year age group.[4] In the present investigation, the high attack rate was observed in the age group 15 to 24 years, followed by 25 to 34 years and 35 to 44 years. This highest attack rate in the working-age group of people might be due to the same age group of migrant workers of the residential campus of industry. In the blood culture, 16.67 % of samples were found positive for only *Salmonella typhi*. This indicates that the active transmission was ongoing at the time of the investigation. In India, the multidrug-resistant is an important cause of typhoid outbreak[2, 3, 7-10, 13] but the organism isolated from the blood culture of all patients in the present investigation was found sensitive to the common antibiotic. The findings of the study verified the existence of a single outbreak of typhoid cases with a single strain of the organism.

Conclusion :

On the basis of observations, we formulated a number of recommendations. The vaccination policy of typhoid may be implemented to vulnerable populations like industrial labour. The health status, availability of safe drinking water, adequate sanitation and hygiene practices may be monitored in the time frame. From the present study, it was concluded that prompt surveillance, early detection and management of the patient is helpful to contain the outbreak. Furthermore, it is a lesson to learn that the local communicable diseases should be monitored during the pandemic. Otherwise, that can cause the situation of co-epidemic.

Limitations :

The outbreak was restricted up to industrial colony where most of the residents were migrated, males of working age group those were residing without family. Therefore, the findings of the present study were not representing the actual scenario of the local population. The samples of water were tested by H_2S Method, which is indirect evidence of *Salmonella typhi* in water. Moreover, the sero-typing of the isolate was not performed.

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Original Article

Outcome of Concurrent Chemoradiation in Inoperable Muscle Invasive Urothelial Carcinoma of Urinary Bladder in terms of Locoregional Response and Toxicities — A Longitudinal Study in a Tertiary Care Hospital

Sarmila Das[1], Amitabha Chakrabarti[2], Sourav Kumar Ghosh[3]

Background : The presenting study was performed to assess the efficacy in terms of tumour response and toxicity profile of a curative intent organ preservation approach in Inoperable Non-metastatic Muscle-Invasive Urinary Bladder Carcinoma.

Materials and Methods : Prospective Interventional Single-Arm, Single Center study with a duration of one and half year in which 47 patients with Muscle-invaded Bladder Cancer were treated with Radiotherapy with 64 Gy in 32# along with Concurrent Chemotherapy with three weekly injection Cisplatin in dose of 70 mg/m^2. Response evaluation was done using both Clinical and Radiological means and categorized using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. For adverse events measurement: NCI CTCAE (Common Terminology Criteria for Adverse Events, v4.1) and RTOG/EORTC Acute and Late Morbidity criteria was used.

Results : Of the 47 patients who completed chemoradiation, complete treatment response was seen in 25 patients (53.2%), 17 patients (36.2%) had partial response on initial assessment and one patient had disease progression both in form of locoregional and distant (lung) metastasis. Stable disease found in 4(8.5%). Patients with residual disease were advised to undergo salvage treatment. Grade 3 Nephrotoxicity reported in one patient, Grade 2 Cystitis in 32 patients (68.1%), while Grade 2 Diarrhoea occurred in four patients (8.5%). Hematological toxicity attributable to Chemoradiotherapy included Grade 2, Grade 3 Neutropenia seen in 6.4% and 2.1% respectively and Grade 2 Anaemia in 4.3% patients.

Conclusion : Concurrent Chemoradiotherapy is well-tolerated, effective and convenient curative treatment option for patients with Inoperable Non-metastatic Muscle Invasive Carcinoma of Urinary Bladder.

[*J Indian Med Assoc* 2022; **120(6):** 23-8]

***Key words* : Urinary Bladder Urothelial Carcinoma, Chemoradiation, Toxicities, Local control.**

Urinary Bladder Malignancy is the 10th most commonly presenting malignancy Worldwide[1]. It is the second most common malignancy of genitourinary system. The incidence of Bladder Cancer has been steadily rising over the past three decades. Urothelial carcinoma is the most common histologic type of Bladder Cancer (approximately 90%). Approximately 75% of diagnosed Tumors are superficial and about 25% of new diagnoses are Muscle-Invasive Bladder Cancer (MIBC)[2], which carry a worse prognosis compared to Non-Muscle Invasive disease with higher rates of metastasis and cancer mortality in 6 months if remain untreated. About one third of Non-MIBC (NMIBC) eventually progress to muscle-invasive disease[2,3]. Neoadjuvant Chemotherapy (NAC) followed by Radical Cystectomy (RC) with bilateral Pelvic Lymphadenectomy is considered as the gold-standard for MIBC. It has been shown to offer good pelvic control rates (85-90%) and acceptable cancer-specific survival [5-year Overall Survival (OS): 40-60%][4]. Radical Cystectomy comprises of resection of bladder, regional Pelvic Lymph Nodes (extended Lymph Node dissection) and adjacent organs like Uterus or Prostate gland with various modes of urinary diversion[5]. This procedure is associated with postoperative morbidity rates of up to 30% and, moreover, Urinary diversion has a great impact on long term Urinary, Metabolic, Gastrointestinal and Sexual function, significantly affecting the patient's Quality of Life (QOL)[6].

Editor's Comment :

- Incidence of Urinary Bladder Cancer is steadily increasing in last few years.
- Different treatment options available to combat this cancer should be evaluated and awareness about these options is important.

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Due to the morbidity associated with surgical approach, many patients are not candidates to undergo surgery due to poor performance status or older age or they simply choose to undergo alternative less invasive modality. Over the past decades, there is gradually increasing trends and evidences to support bladder preserving conservative options. Two groups of patients can benefit from this approach: patients with organ-confined disease who have a strong preference to avoid aggressive surgery and comorbid patients who are not candidates for surgical intervention. Single modality Bladder-preservation consisting of only Transurethral Resection of Bladder Tumour (TURBT), Chemotherapy alone or Radiotherapy yield poorer outcome in terms of locoregional tumour control and long-term survival[7]. Multimodal Bladder preservation protocol consists of Maximal Transurethral Resection of the Bladder Tumor (TURBT) followed by Chemoradiotherapy (CRT), known as Trimodal Therapy (TMT). Survival outcomes after TMT for carefully selected patients are comparable to RC but without the risks of perioperative mortality and morbidity[8].

Till date, no randomised study directly compared Radical Cystectomy with the bladder-sparing approach. Several studies presented TMT oncologic outcomes comparable to RC, with 5-year and 10-year overall survival at 57% and 39%, respectively[8]. Long-term data as given by the Radiation Therapy Oncology Group (RTOG), has established selective bladder-preserving treatments as a safe and effective alternative to Cystectomy. As a result, Multimodal Bladder preservation therapy is now approved as an option by the Major Scientific Societies Guidelines (National Comprehensive Cancer Network, European Association of Urology EAU) for selective patients[9].

However, the existing studies do not unanimously support the use of bladder preservation modalities. A study in 2018, claimed that TMT resulted significantly decreased OS and Cancer-Specific Survival (CSS) and more burden of expenditure in 2011[10]. As a result of still conflicting evidence, more research is needed to better understand the efficacy of TMT as an alternative treatment option for MIBC.

The patients who are surgically or medically not fit for Cystectomy, comprise a poor cohort for any curative mode of treatment and in more need of this conservative management.

Our purpose, at a Tertiary Care Hospital, was to assess the achievability, toxicity profile and locoregional response of tumor following treatment with the Concurrent Chemoradiotherapy in Inoperable locally advanced Muscle Invasive Urinary Bladder Urothelial Carcinoma.

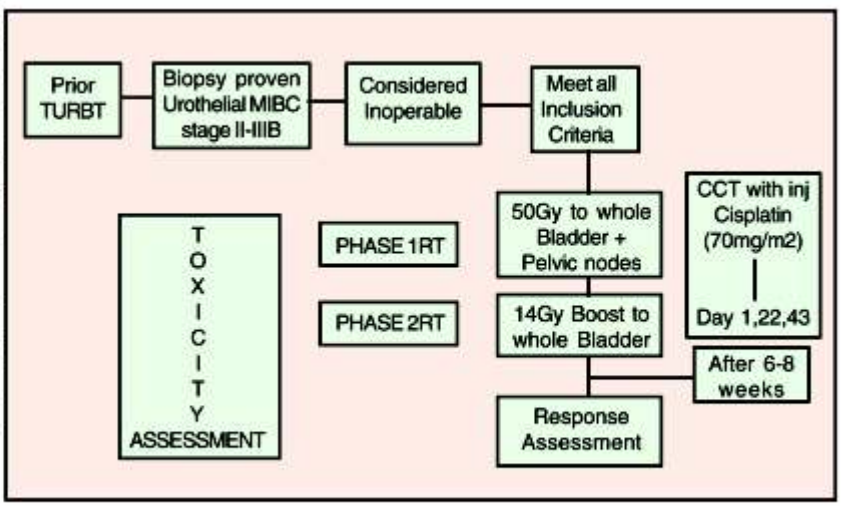
Materials and Methods

Selection of Patients :

This Prospective, Interventional Single-arm study was conducted at the Radiotherapy Department of R G Kar Medical College & Hospital, Kolkata, over a period of 18 months. Fiftytwo patients with a primary non-metastatic Muscle Invasive Urothelial Carcinoma of Urinary Bladder presenting with the Eastern Cooperative Oncology Group (ECOG) performance status ≤2, staged T2-T4aN0-2M0, age 18-75 years, were recruited from January, 2020 to January, 2021 with written informed consent. Cancer staging was done according to the American Joint Committee on Cancer 8th edition TNM Staging and patients were considered inoperable either surgically or medically. Exclusion criteria were any other malignancy, evidence of distant metastasis, uncontrolled morbidity, psychiatric illness, informed consent not granted and patients with any contraindication to chemoradiotherapy. Accrual was started only after getting ethical clearance certificate from Institutional Ethics Committee.

After the Baseline assessment, Radiological pre-treatment Metastatic Work-up was done as inclusion pre-requisites. After the attempt of Maximal TURBT, biopsy proved Muscle Invasive Urothelial Bladder Cancer (T2-T4a) patients were treated by External Beam Radiotherapy + Concomitant Chemotherapy.

Study Schema :



Treatment :

After initial work up, Treatment Planning Computed Tomography (CT) simulation was performed and Three-Dimensional Conformal RT planning was done. Two phase Radiotherapy (RT) was given using a Linear Accelerator with 6-20 MV photons with shrinking field technique. The 1st Phase included RT of 50 Gy/ 25 fractions to the whole pelvic field encompassing the whole Urinary Bladder with local extension and draining pelvic lymph nodes, planned in empty Bladder. In the 2nd Phase, planned in full Bladder, field was reduced to cover the whole Bladder volume with 1-2.5 cm anisotropic margin and the boost dose given was 14 Gy in 7 fractions to a total dose of 64 Gy. There was no mid-treatment break for Intermediate Cystoscopic evaluation. During radiation, Complete Blood Counts and Serum Creatinine Levels were evaluated every week.

Concurrent Chemotherapy was given every 3 weeks with intravenous Cisplatin dose of 70 mg/m^2. In total, three cycles of chemotherapy were planned during RT.

Every patient was evaluated 6-8 weeks after completion of therapy with MRI Pelvis, Cystoscopy, Contrast-Enhanced CT scan of Abdomen and Thorax. Assessment of tumor response to the treatment was done according to revised RECIST guidelines version 1.1. Treatment-related Acute Hematological Toxicities (Anaemia, Neutropenia, and Thrombocytopenia) and non-hematological toxicities (Vomiting, Diarrhoea, and cystitis) were scored and reported using Common Terminology Criteria for Adverse Events version 4.0.

Management of Data and Statistical Analysis :

Software SPSS version 25.0 for Mac was used for interpretation and analysis of data recorded. Categorical variables were expressed as numbers and percentages, whereas comparisons were done using paired samples t-test. Cross tabulation was done to check associations as significance level, p-value <0.05.

Results

A total of 52 patients were recruited in the study. Among them, for 1 patient, treatment was stopped midway due to sudden aggravation of cardiological problem. 3 more patients were lost to treatment during EBRT. 1 patient completed full course of treatment but did not turn up for response assessment and follow up. Those total 5 patients were excluded from analysis. So, total 47 patients were analysed in this study (Tables 1 & 2).

Within the full period of this study, every patient was evaluated during RT in each week with blood for Hb, TC, DC, Platelet, Urea, Creatinine. Two patients

Table1 — *Distribution of study population according to clinico-pathological profile (n=52)*

Attributes	Category	Number	Percentage
Age	<60 years	18	34.6
	≥ 60 years	34	65.4
Gender	Male	45	86.5
	Female	7	13.5
Family History	Present	2	3.8
	Absent	50	96.2
Smoking Habit	Present	34	65.4
	Absent	18	34.6
Occupational exposure	Present	11	21.2
	Absent	41	78.8
Comorbidity	Present	28	53.8
	Absent	24	46.2
ECOG PS at presentation	0	7	13.5
	1	18	34.6
	2	27	51.9

Table 2 — *Tumor Related Factors (n=52)*

Variables		Number	Percent
T stage	T2	36	69.2
	T3	13	25
	T4	3	5.8
N stage	N0	39	75
	N1	5	9.6
	N2	8	15.4
Clinical TNM stage	Stage II	33	63.5
	Stage IIIA	11	21.1
	Stage IIIB	8	15.4
Multiplicity	Solitary	34	65.4
	Multiple/Diffuse	18	34.6
Completeness of TURBT :			
No visible tumor after TURBT		33	63.5
visible tumor after TURBT		19	36.5

(4.3%) had Grade 2 Anaemia, one patient had Grade 3 Neutropenia during Chemoradiotherapy course and managed conservatively (Table 3).

With Concurrent use of injection Cisplatin,13 recent (27.7%) patients had G1 nausea and vomiting during radiation period. Acute GI toxicity in form of Diarrhoea was seen in 20 patients (42.6), 4 patients (8.5%) had G2 Diarrhoea. Proctitis G1 was present in 8 patients (17.0%), while 1 patient (2.1%) had G2 proctitis in form of rectal discomfort, tenesmus and minor intervention required.

Cystitis is the m/c acute toxicity observed in the study population in form of increased urinary frequency, urgency, dysuria, incontinence, nocturia and haematuria. 14(29.8%) patients had G1 and 32(68.1%) had G2 Cystitis. 6 patients (12.8%) had only haematuria G2 and managed conservatively. G1 Nephrotoxicity was found in 20(42.6%), G2 in 2(4.3%) patients. One (2.1%) patient had G3 toxicity and this patient and other one developed bilateral

Table 3 — *Acute and late toxicities of definite chemoradiation in the study population (Grading by CTCAE version 4.0) (n=47)*

Toxicities	Grading	Number	Percentage
Anaemia	None	16	34.0
	G1	29	61.7
	G2	2	4.3
Neutropenia	None	27	57.5
	G1	16	34
	G2	03	6.4
	G3	01	2.1
Thrombocytopenia	None	25	53.2
	G1	22	46.8
Fatigue	None	28	59.6
	G1	18	38.3
	G2	1	2.1
Nausea / Vomiting	None	34	72.3
	G1	13	27.7
Diarrhoea	None	23	48.9
	G1	20	42.6
	G2	4	8.5
Proctitis	None	38	80.9
	G1	8	17
	G2	1	2.1
Haematuria	None	41	87.2
	G2	6	12.8
Cystitis	None	1	2.1
	G1	14	29.8
	G2	32	68.1
Nephrotoxicity	None	24	51.1
	G1	20	42.6
	G2	2	4.3
	G3	1	2.1
Hydronephrosis	No	45	95.7
	Yes	2	4.3

hydroneprosis, 2(4.3%) which is a late toxicity. One patient with hydronephrosis died in spite of having CR (Complete Response) (Tables 4 & 5).

Table 4 — *Assessment of the Locoregional Response of Definitive Chemoradiation in study population by using RECIST v 1.1. (n=47)*

Response	Status	Number	Percentage
RECIST v1.1	CR (Complete Response)	25	53.2
	PR (Partial Response)	17	36.2
	SD (Stable Disease)	4	8.5
	PD (Progressive Disease)	1	2.1
	Total	47	100

Table 5 — *Patterns of Failure in the study population till the last reported follow-up (n=45)*

Patterns of Failure	Status	Number	Percentage
Loco-regional Recurrence	Yes	5	11.1
	No	40	88.9
	Total	45	100
Distal Metastasis	Yes	4	8.9
	No	41	91.1
	Total	45	100

Discussion

Radical Cystectomy is still being considered as the gold standard for treatment of Muscle Invasive Urinary Bladder Cancer. However, it is an inherently morbid intervention with subsequent compromise of QOL with urinary diversion. This dilemma is more evident in elderly patients, where perioperative mortality is significantly higher as compared to younger patients. Many patients with MIBC have age-related comorbidities, such as renal function impairment, and cardiovascular or respiratory diseases which disqualify them from surgery. Given the increased life expectancy, the demand for alternative curative treatment for MIBC patients who are unfit for RC is increasing. With these considerations, Bladder Sparing conservative approach to Radical Cystectomy are attractive for both patients and clinicians.

Existing literature have opined Bladder Preservation Therapy as a convenient, safe, and effective approach with tolerable toxicities when compared with Radical Cystectomy along with a comparable Disease-Free and Overall Survival. Majority of patients treated under this protocol maintained good QOL, retained functional Bladder and preserved sexual function without compromising survival outcome.

Our study purposed to evaluate the tumor outcome and toxicities of Concurrent Chemoradiotherapy in Muscle Invasive Urinary Bladder Carcinoma, who are medically or surgically not fit for Cystectomy. A total of 52 patients were recruited in the study and were treated with curative intent by Concurrent Chemoradiation.

The baseline attributes in this study were congruent with the recent evidences. 65.4% (34) patients are above the age of 60 years with median age of the patients are 61.75 years. 86.5% patients are male with Male:Female ratio 6.4:1. Hafeez *et al*[11], reported in a pivotal study, the median age of the patients was 65 years with male preponderance (87.23%). Similar Male:Female ratio of 7.3:1 was seen in a study of Mitin *et al*[12].

Majority of the patients presented with T2 (69.2%) and T3 (25%) disease in our study, 63.5% patients had Clinical TNM stage II, 21.1% had stage IIIA and 15.4% had stage IIIB at presentation. Sang Jun *et al*[13]. in a Korean retrospective study (KROG14-16) reported 47.4%, 32.2% and 20.4% of stage II, stage III and stage IV respectively. This study also reported 63.8% patients presented with solitary tumour and 30.3% had multiple tumors, comparable to our study where solitary tumour and multiple tumor at presentation were 65.4% and 34.6% respectively. In all our 52 patients,

TURBT was attempted but Maximal TURBT, ie, no visible tumour after TURBT was seen in 63.5% and incomplete TURBT in 36.5% of patients. In GETUG 97-015 study with 53 patients Maximal TURBT was attempted for all patients but esteemed complete for only 33 (66%) patients[14].

As in our study, majority of patients are inoperable, continuous course of radiation was planned in protocol as done in the ERLANGEN protocol[15]. The conventional and mostly used radiotherapy fractional schedule with a dose of 64 Gy in 32 fractions over 6·5 weeks was delivered to the patients as done in the largest phase III UK BC2001 trial[16].

In our study, we use intravenous inj Cisplatin for its proven potent radiosensitizer properties in a dose of 70mg/meter^2 on days 1,21,43. This dose of cisplatin was validated in RTOG 88-02 trial[17]. Considering the compromised renal function in Bladder cancer patients a lower dose of Cisplatin instead of conventional 3 weekly dose (100mg/meter^2) was considered. Most of the patient tolerated this reduced dose cisplatin well.

Of the 47 patients who underwent full course of Chemoradiation, Complete Response (CR) was achieved in 25 patients (53.2%), Partial Response (PR) seen in 17 patients (36.2%) on initial assessment and one patient developed Progression of Disease (PD), both in form of locoregional and distant (lung) metastasis. Stable Disease (SD) found in 4(8.5%). All the patients with the residual disease were advised to undergo salvage treatment. Two patients were planned for salvage Cystectomy and thirteen patients for Palliative Chemotherapy, owing to inoperability. Two patients refused any further treatment. This is very similar to SWOG 9312 trial where out of the 53 total patients, 26 (49%) reported a Complete Response[18]. Recently RTOG 0524 included 66 patients with T2-T4 NXM0 disease who were considered medically inoperable and reported Complete Response rates at 1year 67.6% to 72.2%[19].

Hematological toxicity attributable to Chemo-radiotherapy included Grade 1, Grade 2, Grade 3 Neutropenia seen in 34%, 6.4% and 2.1% respectively. Grade 2 Anaemia occurred in 4.3% patients and Grade 1 Thrombocytopenia in 46.8%, Grade 2 Thrombo-cytopenia in none of patients. Hussain *et al* reported alike hematological profile in their study[20].

The most common toxicity recorded in present study was Cystitis followed by Diarrhoea. Grade 2 Cystitis was seen in 32 patients (68.1%), while Grade2 Diarrhoea occurred in 8.5% cases. Sabaa *et al*[21] reported Grade 1 or 2 Cystitis in 51.9% of patients and Grade 1 or 2 Diarrhoea in 35.6% of patients. Late toxicity in form of hydronephrosis developed in 2(4.3%), one of them died in spite of having initial CR.

In contrast to RC, treatment failure is a common concern for MIBC in the preserved Bladder. In our study, 3 patients (6.7%) with CR later developed in-bladder recurrence. In 2 patients with PR later developed locoregional recurrence (in-bladder and nodes) and distant(bone) progression, local (in-bladder) and distant(lung) progression. 1 patient with Stable Disease later developed bone only metastasis. Overall local recurrence till the last follow-up in the study was seen in 5 patients (11.1%). Previous studies reported in-bladder recurrence rates ranging from 19% to 58%, and muscle invasive recurrence was approximately half of non-muscle invasive recurrence. As reported by Rodel *et al*[15]. 5-year cumulative Bladder malignancy recurrence and MIBC recurrence rates was 41% and 28%, respectively. Regarding in-bladder recurrence sites, Tunio *et al*[22]. reported that 21% of patients having initial CR in tri-modality therapy showed MIBC recurrence, of which 69% were within the original MIBC site. Considering very short follow-up period of our study compared to these studies, these results are considerable.

Our results identified several prognostic factors related to response outcome, including patient age, T Stage, N Stage, multiplicity of tumor, Treatment time, Complete TURBT. Only Complete TURBT was associated with Complete Response and it was statistically significant. All other variables were found to be statistically insignificant, may be due to small sample size.

Presenting these findings, we opine that Concurrent Chemoradiotherapy with prior TURBT is well-tolerated with an acceptable rate of toxicities with good locoregional response and should be recommended in patients who are not candidates for surgery.

Limitation :

In the present study, there are several limitations. It was Single Institutional with a smaller sample size. It had a short median follow up to evaluate oncological outcome. We tried to identify associated variables as significant predictors of complete tumor response. However, there were few statistically significant predictors, likely due the lesser enrolment. With a Multi-Institutional study with larger sample size, significant predictors of tumor response could be identified.

Conclusion :

In patients with Muscle-Invasive Non-Metastatic Urinary Bladder Cancer who are unfit for surgery,

Concurrent Chemoradiotherapy could be considered as a effective and convenient therapeutic option with a high probability of local response, and tolerable toxicity profile.

More and more prospective multicentric researches with larger sample size and long term follow up are needed to confirm the results of our Single Institution study.

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Conflicts of Interest : None declared.

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Original Article

A study on Breakthrough Infections of COVID-19 from an Urban Healthcare Centre in Kerala

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Background and Aim : While India's vaccination drive against COVID-19 continues to progress, the number of Breakthrough Infections are also revealing an uptick due to Community spread of COVID-19. There is a dearth of data quantifying the extent of breakthrough infections, defined as infections following two doses of vaccine. We aimed to understand the occurrence of Breakthrough Infections among the public in the City of Thrissur, Kerala, India, during the recent surge of COVID-19 in Kerala.

Methods : Patients visiting the Internal Medicine Outpatient Department (OPD) in a private hospital in the City of Thrissur in Kerala, India were selected for the study. Subjects above the age of 18 years presenting to the OPD between August 01, 2021 and September 30, 2021 were surveyed through a short interview on the COVID-19 infection history, symptoms, severity and vaccination status.

Results : Of the 56 participants who tested positive for COVID-19, 38 had received both doses of vaccine and all had received their first dose of vaccine. 4 patients had no symptoms, 37 patients reported mild symptoms and nine patients reported moderate to severe symptoms.

Conclusion : Our study demonstrates the occurrence and describes the epidemiology of COVID-19 breakthrough infections in a City from the Indian State of Kerala in a real-world setting. We conclude the occurrence of Symptomatic Breakthrough Infections of COVID-19 in patients who had received two doses of the vaccine were mild in the majority of the patients (87%). Further research is required to understand the mechanisms behind these Breakthrough infections.

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***Key words* : COVID-19, Breakthrough infections, Coronavirus.**

Coronavirus disease 2019 (COVID-19) has taken a toll globally since its emergence in 2019. With millions of people being infected with a rising death toll world wide, the race for a vaccine could not have been any faster. Many pharmaceutical companies developed vaccines aiming to reduce hospitalization and mortality rates associated with COVID-19. A country highly affected by this virus is India, with over 450,000 deaths. In India, two vaccines were developed targeting this virus: ChAdOx1 nCoV-19 and Covaxin/ BBV152. Both vaccines require two doses. Covishield uses a weak version of the adenovirus, while Covaxin uses an inactivated SARS-CoV-2 virus[1-3].

Editor's Comment :

- Our study from an urban community setting, reveals that breakthrough infections do occur in vaccinated individuals. However, the severity of disease is less intense. With proper physical distancing measures and use of personal protective equipment, we can reduce the community burden of COVID-19.

Vaccine Breakthrough Infections are defined as the detection of SARS-CoV-2 RNA or antigen in a respiratory specimen collected from a person ≥14 days after they have completed all recommended doses of an approved COVID 19 vaccine[4,5]. These Breakthrough Infections need to be understood better; however, accurate data from real world settings are very few[6]. Vaccines are effective in decreasing the risk of being infected with COVID-19 by 70-90% and also prevent severe infections[7-9]. These infections could occur due to the COVID-19 variants which may bypass vaccine-induced immunity[7]. A rising number of cases of vaccine Breakthrough Infections are being found in regions with a higher occurrence of COVID-19 cases.

During the months of August and September of

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2021, the State of Kerala in India witnessed a high daily count of COVID-19 cases with over 120,000 cases possibly due to a second wave[2]. We decided to study the real world occurance of vaccine breakthrough infections in patients presenting to an Outpatient Department (OPD) of a private hospital based in Thrissur, Kerala. In addition, there have been non-scholarly reports regarding Breakthrough Infections questioning the efficacy of the vaccine as the daily number of cases rise.

We investigated COVID-19 Breakthrough Infections in partially and fully vaccinated participants.

Materials and Methods

Study Setting and Participants

Patients visiting the Internal Medicine OPD at a private hospital in the city of Thrissur in Kerala, India were selected for the study. The OPD has a footfall of approximately 30 patients daily. Patients visiting the OPD came for routine examinations as well as some urgent care issues. Telemedicine patients and in-person visit patients were also included in the study.

Exclusion criteria : We excluded participants who were less than 18 years of age and those who tested negative for COVID-19 despite showing symptoms. Inclusion criteria: Participants above the age of 18 years presenting to the OPD between August 01, 2021 and September 30, 2021, were enquired through a short interview. A verbal informed consent was obtained from all the patients enrolled into the study, after providing them a written consent form in the local language which participants could read and understand (refer to Appendix A for a copy of the informed consent). For telemedicine patients, informed consent was obtained via text messages.

A medical professional enquired participants regarding their vaccination status and if they tested positive for COVID-19 any time after they received the first or second dose of the COVID-19 vaccine. If they tested positive (using PCR or Rapid Antigen Test), the date of the positive test was recorded along with the month when they received the COVID-19 vaccination. The type of COVID-19 vaccine administered was also recorded. They were further enquired on their symptoms during and after they tested positive for COVID-19 and whether they needed hospitalization. In addition, participants were asked for any residual symptoms. Symptoms were classified as mild (if they were self limiting or only required outpatient treatment), moderate if they required hospitalization but not needing intensive care and severe if ICU(Intensive Care Unit) care was needed. We tabulated the number of patients who were positive for COVID-19 and calculated the risk of mild, moderate and severe infections. Comorbidities of participants were assessed as well.

Statistical Analysis :

IBM SPSS version 27.0.1.0 was used for data calculation and analysis. Variables measured were age, gender, comorbidities, receipt of first dose of COVID-19 vaccine, receipt of second dose of COVID-19 vaccine, status of COVID-19 infection, hospitalization status due to COVID-19, symptoms of COVID-19 infection and residual symptoms. Missing values were coded as "999" on SPSS. Only COVID-19 positive patients were included in the analysis.We conducted descriptive analysis for demographic and comorbidities and cross-tabulation.

Results

Demographics

There were a total of 56 participants tested positive for COVID-19 (16 males and 40 females). The mean age was 48 years (SD ± 14 years). All patients (n=56) had received their first dose of the COVID-19 vaccine and 38 patients received the second dose of the vaccine. Most of the patients received COVISHIELD except one patient who had received COVAXIN.

Comorbidities and Symptoms

There were 28 patients with comorbidities.

Comorbidities included Diabetes Mellitus (n=14), Systemic Hypertension (n=11), Thyroid Disease (n=2), Dyslipidemia (n=1), Cardiovascular Disease (n=5), Lung Disease Including Asthma (n=6), Chronic Kidney Disease (n=1), Anemia (n = 1) and Cancer (n= 1).

Symptoms included fever, cough, sore throat, chills, throat pain, vomiting, body pain, dyspnea, delirium, and joint pains. They were categorized as asymptomatic, mild and moderate to severe hence, the exact percentage of participants reporting the type of symptom was not obtained. Moderate to severe symptoms included the requirement for inpatient care through hospitalization or requirement of supplemental oxygen, anticoagulants, steroids, severe cough and breathlessness needing Intensive Care Unit admission.

There were four patients that reported no symptoms, 37 patients reported mild symptoms and nine patients reported moderate to severe symptoms. Three patients were hospitalized. There was no mortality (Fig 1).

Recovery

All participants had recovered well. Recovery ranged from two days to 15 days. Four patients had residual shortness of breath and cough. The remaining patients did not have any residual symptoms. Overall, all patients recovered well.

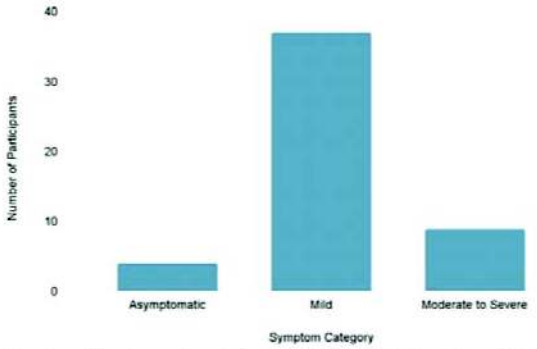

Fig 1 — Number of participants with a COVID-19 positive test and their respective presenting symptoms categories

Discussion

To the best of our knowledge, peer reviewed publications on breakthrough infections from Kerala, the Southern state of India, especially in a community setting, is limited[10-12]. In the beginning of April 2021, Indian Healthcare System and population were overwhelmed by COVID-19 cases and mortality due to a new variant B.1.617.2 (Delta) causing the second wave of COVID pandemic[13]. This study is unique in identifying the demographic characters and risk factors of breakthrough infections during the second wave of the COVID-pandemic in the Indian sub-continent.

Data from the Southern State of Kerala is interesting from an epidemiological standpoint since the state has reportedly less COVID-19 associated mortality compared to the rest of India. Also, Kerala reported high vaccine uptake very early during the roll out of India's vaccination campaign. However widespread community spread in an aging population living in highly dense communities might have caused breakthrough infections in susceptible populations. Most reported data on vaccine breakthrough infections are from North America and Europe and hence it is important to understand our study results highlighting the epidemiology of breakthrough infections in South India. Although genomic surveillance was not done in our cohort, it is quite possible that variants of concern B.1.617.2 and B.1.1.7 might have been major causative factors for the spread of Breakthrough Infections amongst vaccinated individuals similar to that documented in the AIIMS study published from New Delhi, the Capital City of India[14].

We have reported the risk factors and disease profile of Breakthrough Infections in a real-world setting. In an analysis reported by Antonell *et al* in a large cohort of 1.2 million COVID Symptom Study app users, less than 1 percent of the study population reported Breakthrough Infections[15]. The main risk factors characterized were frailty, age ≥60 years, residing in highly deprived areas and higher BMI.Vaccination was associated with reduced odds of hospitalization or having more symptoms in the first week of illness following the first or second dose, and long-duration (≥28 days) of symptoms following the second dose. Similarly, among those patients with Breakthrough infections due to delta variant requiring hospitalization (n=126) as reported by Bosch *et al* based on data from the state of Florida, risk factors identified were age, immunocompromised status and presence of comorbidities such as Diabetes, Chronic Kidney Disease, Coronary Artery Disease and Hypertension[16]. Data reported from Chile by Duarte et al reflect similar findings[17]. In this study of 38 breakthrough cases, only two patients developed moderate-severe disease. Both cases were adults over 60 years old and had comorbidities. A study on breakthrough infections among Healthcare Workers in Kerala was reported by Niyas *et al*[18]. All cases were mild because the affected individuals were younger (mean age 32 years), mostly women (67%) and did not have that many risk factors for severe disease. Among the 108 reported cases, there was no hospitalization or mortality. Comorbidities such as Diabetes, Hypertension, Malignancy and Chronic Lung Disease were present only in seven patients. Breakthrough infections occurred after two months of vaccination (mean = 69 days).

Dash *et al* has reported data from the State of Orissa, India but noted a 10 percent risk of hospitalization in those with Breakthrough Infections[19]. Age was identified as the main risk factor in this study. In the Desai *et al* study reporting the epidemiology of breakthrough infections among employees of the All India Institute of Medical Sciences (AIIMS), a Tertiary Care Hospital in New Delhi, India in the context of a huge surge in cases, the vaccine effectiveness of BBV152 was found to be only 50% (95% CI 33–62) against symptomatic laboratory-confirmed COVID-19[20]. It is interesting that our cohort did not demonstrate a higher rate of symptomatic infections despite having a higher age demographic. This must have been partly due to the strict adherence to public health measures, higher literacy rates and better socio-economic status among the people of Kerala.In another cohort reported from Delhi, India among healthcare workers (HCWs) by Sharma *et al*, 325 HCWs with a mean age of 29 years, predominantly men, had a 13% incidence of breakthrough infections[21]. Most Breakthrough Infections were mild without hypoxia or requirement of hospitalization. This is

possibly due to the younger age group of the study participants. Genomic surveillance of Breakthrough Infections from Kerala was reported by Philomina *et al* in a cohort of six patients[22]. Four patients were diagnosed with the B.1.1.7 variant of SARS-CoV-2 in the above study. A study from West Bengal, where a higher incidence of deaths among Health Care Workers (HCW) were reported even after months of rolling out vaccines revealed that about 37% HCW were hesitant to take the vaccines[23]. Our study clearly depicts that despite the rise in breakthrough infections, number of deaths or serious illness due to COVID-19 is negligible among the fully vaccinated individuals.Thus our study aids to address the vaccine hesitancy among the HCW and population at large and stresses the importance of complying with the required doses of COVID vaccines.

Limitations

Limitations of our study include the small sample size, sample selection only from an outpatient setting, lack of comparison data from the rest of the state, lack of data on exposure setting, socio-economic status, substance use, SARS CoV-2 gene sequencing and antibody titres (5, 24-26). Genetic sequencing is important as reported by Christensen *et al* based on breakthrough infections analyzed in Houston[25]. This group was able to confirm that the Delta variant caused a significantly higher rate of vaccine breakthrough cases (23.7% *versus* 6.6%) compared to all other variants combined. This study also documented that fully vaccinated individuals can transmit SARS-CoV-2 to others. We also cannot confirm the risk factor profile in individuals who may have received the two doses of the vaccine in a different dose interval schedule or in those who received mRNA based vaccines or mixed immunization. The main highlight of our study is that this data will be an important addition to the literature on COVID Vaccine Breakthrough Infections from various parts of India under diverse clinical and community settings. Our results are strengthened by the true documentation of asymptomatic and symptomatic infections through PCR testing.

Prospective Research

More research is needed about the Epidemiology of Breakthrough Infections in the setting of emerging variants. A recent study by Shenoy *et al* demonstrated that those with hybrid immunity may have the best protection against re-infections. This needs to be studied further in the light of waning immunity and spread of newer variants[27]. Also we need to understand the potential incidence or absence of long-COVID syndromes in those with Breakthrough Infections and reinfections. A further follow up of these patients for a longer period of time can shed light on the continued protection against emerging variants owing to their hybrid immunity against the COVID-19 virus.

Conclusion :

In conclusion, Breakthrough Infections are a major concern in India. Results from this study support the need for further investigation on the reasons behind breakthrough infections including protective mechanisms. Our research adds to the emerging literature of Breakthrough Infections and sheds light for future research. Our study demonstrates the occurrence and describes the epidemiology of COVID-19 breakthrough infections from an urban centre in the state of Kerala in a real-world setting. We reported mild symptomatic Breakthroughs of Cases of patients who have been affected with COVID-19 after taking the vaccination either first dose or both. Further research is required to understand the mechanisms behind these Breakthrough Infections. Also we need to follow such patients to understand if they get continued protection against emerging variants owing to their hybrid immunity against the COVID-19 virus.To minimize SARS-CoV-2 infection, at-risk populations must be targeted in efforts to boost vaccine effectiveness and infection control measures. Our findings might support caution around relaxing physical distancing and other personal protective measures in the postvaccination era, particularly around frail older adults and individuals living in more deprived conditions.

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Original Article

The Transition towards Virtual Teaching Learning Environment during COVID Pandemic : Medical Educator's Perspective

Jarina Begum[1], Syed Irfan Ali[2], D Lakshmi Lalitha[3], Manasee Panda[4], Padmini Thalanjeri[5]

Introduction : We are moving towards a technically advanced Medical Education. However, effectiveness of online Teaching, Learning (T/L) remained unknown until COVID-19 pandemic.

Aim : This study was planned to assess the perception of e-educators towards online T/L, the challenges and possible solutions during pandemic.

Methodology : A mixed method cross-sectional study was conducted among 126 medical educators through online google survey from July to September, 2020 in a Tertiary Heath Care Institute & 2 neighbouring medical college.

Result : Non-response rate was 32%, 72.2% were males, 63.9% were between 31 to 50 years of age, 58% were having 10 or more years teaching experience. 36.2% were from basic sciences, 69.5% were holding higher academic post. 61% preferred combination of face to face and e-learning Although online classes were helpful in terms of 63.8% convenience, (54%) flexibility, 77.5% felt difficulties teaching and assessing skills domain. The major challenges encountered were technical glitches, no active participation and suggested solutions were technical assistance, formative assessments and use of new T/L, assessment tools.

Conclusion : Although the change was negatively perceived, it's inevitable. Training of faculties, sensitization of students and conducive environment is needed to combat the challenges, to improve the e-education system in health profession.

[*J Indian Med Assoc* 2022; **120(6):** 34-9]

***Key words* : COVID Pandemic, Medical Educators, Online classes, Digital Literacy, e learning, Face to face learning**

We are moving towards a system where use of technology in education is very common. Although lockdowns and sudden closure of educational institutes occurred, educational programs were retained by adapting the solutions as per local condition and available resources[1].

The education sectors of India as well as World are badly impacted by this pandemic. Around 32 crore learners in India were restricted home bound unable to access the educational institute. However, it has worked as a catalyst for academic growth opportunity for various platforms and techniques, which have not been used before. The education sector has been fighting with digitising the challenges to wash away the threat of the pandemic[2]. The COVID-19 Pandemic has created uncertainty and disruption of education systems in human history, affecting teachers and learners adversely in all aspects of their lives in countries all over the Globe[3]. Online learning is an exciting way to learn about almost anything. It has bought a positive impact on the lives of students as well as teachers, using technology in the field of education. However, there is always much room for improvement and challenges in implementation as far as online teaching and learning concerned[4].

Editor's Comment :

- The medical education system has been affected adversely by the pandemic. However, planning appropriate strategies and timely action could help medical educators to handle challenges better and save the future of the young doctors.

The present study was planned to assess the perception of e-educators towards the online T/L, the challenges and possible solutions during pandemic to pave the path for future transformations in Medical Education.

Materials and Methods

A cross sectional study was carried out among 126 medical educators engaged in online teaching at a tertiary health care institute & 2 neighbouring medical colleges from July to September, 2020 after taking Ethical Committee approval (92IEC/GEMS & H/2020), using a pre-validated semi-structured

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questionnaire through online google survey form. Validation was done through sending the questionnaire to 6 medical education experts and piloting it among 12 faculty members of the institution, who were excluded from actual study. The value of Cronbach alpha was 0.76 which was at acceptable range. The questionnaire was then refined further as per the suggestions & expert comments.

Perception of medical educators involved in Online Classes was collected with the help of pre-validated semi-structured questionnaire through online google survey form. The medical educators were approached by complete enumeration of all faculties of 3 Medical Colleges which was around 185 faculties. Those who responded to the questionnaire completely were included in the study and those did not respond after multiple reminders were excluded. only 126 people responded to the questionnaire, thus accounting to non-response rate of 32%. The questionnaire was sent through personal WhatsApp messages. The questionnaire had total 20 questions with 6 MCQs on demographic details, 8 MCQs on use of different online platforms, experience of teaching & assessment of knowledge, skill competencies, 2 questions of advantages, limitations on 5-point Likert scale and 4 open ended question based on what is good or bad about these online classes, various challenges & possible solutions suggested.

Results

Non-response rate was 32%.72.2% were males, 63.9% were between 31 to 50 years of age. 36.2% were from basic sciences, most of them were holding higher academic post. (69.5%). Around 77.8% have no previous experience of online teaching (Table 1).

Although majority had no experience of online teaching & learning, all of them were aware of e learning and teaching through institutional orientation programme. Some of the synchronous way of e learning that the participants have used were cisco WebEx (80.9%), zoom (47.6%),WhatsApp (38.8%), google meet (35.7%), Microsoft team (16.7%), You tube (19%), Skype (7.9%) and others (6.3%) like go to Webinar, Moodle, Hangout etc. and asynchronous ways were WhatsApp(72.2%), google classroom (7.9%), google groups (2.4%), websites (35.7%), institutional LMS (9.5%) and others (2.4%).

Currently majority 47.2% were engaged in both UG and PG teaching activities, followed by only Ug or PGteaching.52.8% were contributing around 2-5 hours per week followed by 5-10 hrs/week (19.4%).

Majority (87%) of them were not comfortable with online teaching learning although it is more convenient.

Table 1 — *Socio demographic profile of E- Educators (N=126)*

	Variables	Percentages	Frequency
Gender :	Male	72.2%	91
	Female	27.8%	35
Age :	<30	23.5%	29
	31 to 50	63.9%	81
	>50 years	12.6%	16
Department :	Basic science	36.2%	46
	Para Clinical	34.5%	43
	Clinical	29.3%	37
Academic Position :	Professor	27.2%	34
	Assoc. Prof	42.3%	53
	Asstt. Prof	20.3%	26
	Tutors	8.7%%	11
	Others	1.5%	2
Teaching Experience :			
	<5 years	16.7%	21
	6 -10 years	25%	32
	>10 years	58.3%	73
Online teaching experience :			
	yes	22.2%	28
	No	77.8%	98
Target learners :	UG and PG	47.2%	59
	Only UGs	36.2%	46
	Only PGs	16.6%	21
Online T/L time duration :			
	<2 hours/week	27.8%	35
	3-5 hours/Week	52.8%	67
	5-10 hours/week	19.4%	24

The common advantages perceived were continuation of teaching & learning (78%), learning new skills (72%) and digital literacy(68%) (Fig 1).

About practice of e-learning after pandemic, most of the faculties (61%) preferred combination of F2F classroom & e-learning compared to only online or F2F teaching learning.

The limitations perceived by participants were cheating (83%), difficulty in teaching and assessing Skill Component (77.5%), Less Interaction (69.5%), online fatigue (62%) and difficulty in engaging students (59%) etc (Fig 2).

All of them used PPT (100%), few used SGD (55.6%), Webinars (44.2%), Journal (23.9%) club and others like Virtual Black board or White Board

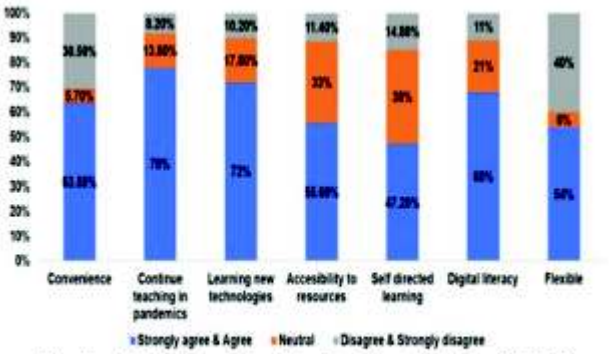

Fig 1 — Advantages of online Teaching-learning (N=126)

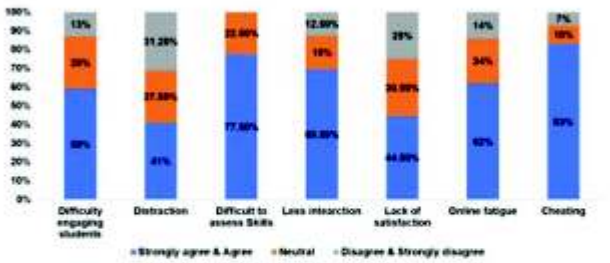

Fig 2 — Limitations of Online Teaching- Learning:(N=126)

presentations, video-based discussion as online techniques.

Majority (62.8%) confined teaching to cognitive domain, similarly 72.2% tried formative assessment focusing on cognitive aspect (89.3%) only. The common assessment tools used were MCQ, Extended matching questions, Viva, Kahoot quiz, Google Forms, written test with essay and short answered questions etc.

32.9% tried teaching skill related competency related to their subject through video demonstration, clinical examination on family member, drawings, online roleplay, images, case scenarios and visual illustrations, very few 8.6% tried assessing the same skills.

Challenges and Possible Solutions :

The main challenge encountered was technical glitches which could be managed only by uninterrupted internet connectivity, continuous power supply and adequate training on digital literacy for both teacher and students. Similarly, there was a huge problem of non-engagement during online classes, attributed to lack of active participation and interaction among students which could be easily tackled by using new innovative and challenging teaching learning techniques and an appropriate Learning Management system, teacher training and effective feedback system (Fig 3).

The overall opinion towards the changed system of Medical education due to COVID Pandemic brought up few important verbatims (Table 2).

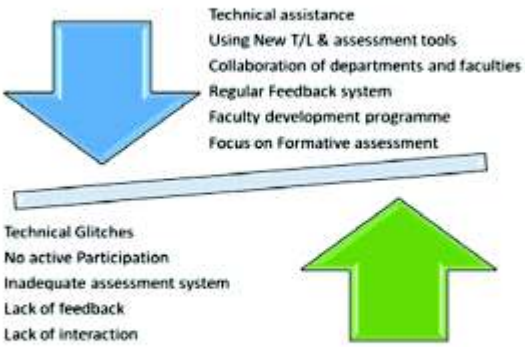

Fig 3 — Challenges and possible solutions perceived by E-educators (N=126)

Discussion

In India, the COVID-19 outbreak has been declared an epidemic and lockdown was imposed on March 25, 2020, which has changed the traditional education system to the educational technologies (EdTechs) model, where teaching and assessments are conducted online[5].

In present study, majority started teaching and learning online using synchronous and asynchronous online platforms. Open education has widened the scope of learning, opened up the creative minds and scope of online learning enabling them to receive the necessary educational inputs, training and skills even during the current pandemic situation[6].

The current study observed majority were not satisfied. However, they found it as an opportunity to continue teaching during pandemics, learning new skills and becoming a digital literate. The COVID-19

Table 2 — *Verbatim by the Participants (Medical educators)*

Positive Verbatim	Negative Verbatim
Online T/L is the best alternative during pandemic for keeping pace with syllabus and continue education.	Not satisfactory, non-sustainable yet only option we had, thus could be practiced as a temporary measure till pandemic ends
Change is difficult, but we had to do it anyways, so every educator must get adapted to online T/L as it provides opportunities to reach a larger section of students.	I am worried as online platforms are not much useful for medical education. Most students encounter technical problems and teachers not successful in engaging students, thus making it boring for both.
Taking the situation as curse takes us nowhere... so taking it as a challenge and keeping students engaged somehow during pandemic by online activities has helped unleashing the creativity and killing the boredom literally.	Theory is ok, but clinics, practical skills is difficult through online session, implementation of CBME components like ECE, AETCOM, FC, Integrated teaching etc were way more difficult than regular teachings.
If traditional classroom is a dish, Online/Virtual classroom teaching & learning is the salt & spice mixture. Without it the dish is bland... so we need it in future, but I must agree salt & spice only can't make up for the dish.	Online teaching is fine but can't replace physical face to face teaching and learning or assessment. We need to upgrade our entire education system to the highest level where both would be blended and become a routine part of curriculum. Or else no one can save our medical students from upcoming academic crisis.

pandemic forced us onto online platforms yet in the process medical educators evolved gradually, yet students felt that they learn better in physical classrooms (65.9%). The students also felt that the professors have improved their online teaching skills (68.1%) and online education is useful right now (77.9%), but it is stressful and affecting their health and social life.Similarly,few other studies found advantages of online learning were the ability to stay at home (69%), continuous access to online materials (69%), learning at your own pace (64%), and comfortable surroundings.The use of technologies has converted the entire teaching pedagogy to a learner centred, following which the digital literacy and expertise in technology are to be considered as the most essential qualifications[6-8].

As perceived by the study participants it was observed that cheating, difficulty in teaching and assessing skill, online fatigue were the limitations of online classes. Similarly in another study student experienced various disadvantages of online classes. There was no statistical difference between face-to-face and online learning in terms of increase knowledge, however, E-learning was considered less effective than face-to-face learning in terms of increasing skills and social competences . Students assessed that they were less active during online classes compared to traditional classes[8].

Likewise, a study showed that 54.1% of the respondents agreed that interactive discussion is achievable by means of e-learning. However, only 21.1% agreed that e-learning could be used for clinical aspects. It suggested a system for support and enthusiasm for providing valid solutions to reduce this disruption, such as online training and virtual clinical experience[9].

Despite limitations most of the faculties (61%) preferred combination of F2F classroom & e-learning compared to others after the pandemic. Likewise, among dental students, majorities agreed blended learning that combined classroom and distance learning can be implemented as Distant Learning resulted in more difficult communication and gave less learning satisfaction[10].

The current study has suggested possible solutions to challenges like training of faculties on online-teaching learning, effective feedback system and well-functioning Learning Management System (LMS). Few other studies recommended training faculty on using online modalities and developing lesson plan with reduced cognitive load and increased interactivities for maintaining academic integrity[11].

Studies has shown the pressure to deliver the content in a different platform as an e-educator made the faculties anxious and stressed. Barriers such as lack of skill and infrastructure, poor time management, and communication encountered which were planned to be tackled by encouraging effective time management, collaboration, engagement, positive online culture and maintaining interesting learning environment among student, teacher and online contents[12].

In the current study it was shown that, technical glitches and non-engagement during online classes were the major challenges faced by teachers. Similarly, four categories of barriers were noticed in another study related to home environment, institutional support barriers, technical difficulties and personal problems identified to damper their engagement in online teaching and assessments[5].

Faculties perceived it in both ways, positively and negatively mentioned in the verbatim which describes online teaching learning and assessment as best possible solution but a temporary measure to prevent academic crisis. Similarly, there was policy paralysis in handling the sudden shifting scenario of educational planning, management and organization during pandemic with their fractured technical infrastructure, academic incompetency and lack of resources. They recommended steps should be accounted in the wake of this pandemic; to develop such a curriculum that reflects the perceptible change in the content knowledge and learning experience of students as well as enable them to think critically[13].

As mentioned earlier in faculty verbatim which was collected by the open ended questions in the questionnaire, theory part was ok as far as imparting knowledge and finishing the syllabus was concerned, but the actual concern was teaching and assessing practical aspects with clinical skills and implementation of CBME components will be more difficult. Looking forward to a high quality, pedagogically sound, engaging, and collaborative online learning in the context of recently implemented CBME model and thus the COVID-19 pandemic can be realized if the medical education regulatory body (NMC), institutions and medical educators accept its need and make available-accessible and dependable digital infrastructure and technical support at institution level; training opportunities for medical educators, facilities and time for medical educators to structure and develop pedagogically sound online teaching and learning activities by aligning learning objectives, content, activities and assessment while ensuring optimal virtual

contact with learners[14].

Many faculties were concerned about the outcome of current type of medical education (where a medical student was not able to interact with a real patient).They felt online education was not much useful for medical students and for teacher Online teaching is Boring.While every student features a story of how COVID-19 has impacted their education, there is no doubt that the impacts of COVID-19 are going to be felt on a large scale. The panic within the community is visible with many confused minds. This is no different for medical students and faculty and the questions that arise regarding medical education and their future careers[15].

In another study the researcher identified vulnerabilities for students at several phases and addressed the hidden curriculum of COVID-19, its potential erosion of empathy among current medical students, and possible long-term consequences for future physicians and patients[16].

This study observed use of innovative online teaching learning strategies for covering the skill domain apart from knowledge among students. This is not only a time for advancement of medical education within the setting of active curricular innovation and transformation, but also a seminal moment for many disciplines in medicine.Several medical educators during the pandemic have used a 'develop, test and apply' model for educational innovations, reinforcing the concept of 'evidence-based medical education'[17,18].

Despite the challenges posed by the SARS epidemic, several resourceful initiatives were implemented, like the online problem-based learning technique sresulting in progress of medical education. These impressive feats illuminate how even in times of distress, solace can always be found[19].

As highlighted taking the situation as a curse takes us nowhere but taking it as a challenge will unleash the creativity. The same thoughts were shared by the author in a study where the students were satisfied with the overall shift into this collaborative e-learning environment and digital learning tools facilitated the performance and their peer sharing of knowledge. The role of informatics computer technologies was evident in promoting the students, research skills, and technical competencies[20].

Similarly, studies have found effectiveness of online teaching learning for undergraduate medical students and suggested its use in future teaching, learning and assessment programme. Other studies have mentioned that online teaching cannot replace classroom teaching, but it can complement the learner by making learning self-directed & an appropriate blending of both modes can be a step towards attaining the competency of lifelong learning[21,22].

Conclusion

Although the change was negatively perceived, it's inevitable. Training of faculties to become digitally literate, sensitization of students towards online education and conducive e learning environment is needed to combat the challenges during the pandemic. We must get prepared for future by addressing the issues of concern now as perceived by e-educators which will help embracing the change while transformation of medical education system.

Recommendations :

Inclusion, integration of online teaching learning at all levels of under-graduate medical education curriculum.

Development of Online teaching learning modules for future reference.

Implementation plan for online deliverable components of competency based medical education curriculum.

Awareness & Training of educators on digital literacy and use of technology and simulation-based teaching & assessment.

Innovative strategies for engaging students, remote learning, automated assessments (Formative), secured online examination (Summative) and analysis of learning outcomes.

Limitations : Online google forms, non-response, small sample, only medical educators'inclusion

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Original Article

Comparison of Effect of Combined Intravenous Amiodarone and Surgical Closure of OS ASD in Adults with Surgical Closure alone on Sinus Conversion of Concomitant Atrial Fibrillation — A Retrospective Case Series Analysis

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Closure of Atrial Septal Defect has been proposed to increase conversion of concomitant Atrial Fibrillation (AF) to Normal Sinus Rhythm (NSR). Amiodarone is known to convert AF to NSR. Our findings support the use of single intraoperative dose of intravenous Amiodarone for increased conversion of pre-operative AF to NSR in OS ASD patients undergoing closure on CPB, although the effect was short lasting. [*J Indian Med Assoc* 2022; **120(6):** 40-3]

Key words **: ASD Surgery, Amiodarone, Sinus Conversion.**

Amongst the Congenital Cardiac Disorders presenting in adulthood, ASD is the commonest, a prevalence of 0.2 to 0.7 per thousand[1]. with late presentation due to functional limitation, either because of development of arrhythmia or progression of pulmonary hypertension[1]. Atrial Fibrillation (AF) is the most common arrhythmia in adult ASD patients[2] and incidence increases with age being as high as 52% in patients aged > 60 years[3]. Hence, a significant number of adult patients have AF when they come for ASD correction. The ensuing tachycardia, impaired ventricular filling, decreased cardiac output with development of Atrial Fibrillation, renders the patient symptomatic[2], together with increased risk of developing thromboembolic complications in 17-18% of patients[4,5]. Several previous investigators who have studied the effect of ASD closure on concomitant AF in adult patients, have found mixed results[2,6-10]. Conversion to sinus rhythm is better seen with ASD closure in younger patients <25 years[11], in those with paroxysmal AF[2] or in older patients undergoing concomitant Maze[12] or radiofrequency ablation[13].

Among all anti arrythmic drugs evaluated for AF, amiodarone has shown the most promising results with successful conversion and maintenance of Normal Sinus Rhythm (NSR) in 50-70% patients[14-16]. Pre treatment with oral amiodarone and cardioversion resulted in NSR restoration in approx 80.6% non-surgical patients with persistent AF[17]. In the 2009 prospective, randomized case controlled study by Selvaraj *et al,* in rheumatic AF patients undergoing Elective Valve Replacement Surgery under CPB, a single intraoperative dose of IV amiodarone increased the conversion rate of AF to NSR in 73.5% patients after release of Aortic Cross Clamp (ACC), compared to 58.5% in control group[18].

Editor's Comment :

- In adult patients >40 years age with ostium secundum atrial septal defect (ASD) and concomitant atrial fibrillation, undergoing surgical closure of ASD under cardiopulmonary bypass, a single intraoperative Intravenous bolus dose of amiodarone probably increases rate of sinus conversion after aortic cross clamp removal.
- However, the effect is short lasting. For sinus conversion and long term maintenance, probably concomitant Maze or radiofrequency ablation may prove to be effective.

In our clinical practice, we found that using single intraoperative IV bolus dose of Amiodarone before CPB, in adult OS ASD patients with AF for rate control, not very infrequently, resulted in conversion to NSR, immediately after release of ACC.

Therefore, in this retrospective case series analysis, comprising adult OS ASD patients >40 years age with concomitant AF, undergoing ASD closure under CPB, we attempted to analyze the rate of sinus conversion and course of pre-operative AF after single intraoperative bolus dose of IV amiodarone, compared to those who did not receive such dose.

Material and Method

Twenty three adult patients, aged >40 years, with Ostium Secundum Atrial Septal Defect (OS ASD) with left to right shunt, who underwent surgical closure on Cardiopulmonary Bypass (CPB), between January, 2019 and 31st March, 2022 in Cardiothoracic OT of

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IPGME&R Kolkata, were reviewed for presence of concomitant Atrial Fibrillation prior to surgery. Eleven such patients with no features of Heart Failure pre-operatively, and uneventful postoperative recovery, were shortlisted and recruited in our retrospective case series analysis. Amongst them, 6 patients who had received intraoperative, pre-pump intravenous single bolus dose of Amiodarone at 3mg/kg were grouped into Group A (n=6) and 5 patients who had not received such a dose of IV Amiodarone were enlisted in Group B (n=5) or control group. Institutional Ethics Committee approval was taken.

All these patients had a pre-operative controlled ventricular rate <100 beats per minute (bpm) with the use of some oral rate control medication, digoxin, beta blocker (metoprolol) or a combination of both. Oral anticoagulation was managed prior to surgery as per institutional protocol.

On the day of surgery, in the Operation Theatre (OT), General Anaesthesia was induced in all patients with intravenous midazolam 0.05mg/kg, fentanyl 3µg/kg, propofol 2-3 mg/kg and intubation using rocuronium 1mg/kg, under continuous monitoring of ECG, Pulse Oximetry, Invasive Blood Pressure, BIS. Following institutional protocol, invasive arterial line was done under Local Anaesthesia prior to induction and central venous line post induction. Temperature probe, urinary catheter and Transesophageal Echocardiography (TEE) probe were inserted post induction. Pre-induction ventricular rate (baseline) was noted in all patients. Post induction TEE parameters were noted. There was no left atrial thrombi in any of the patients. Anaesthesia was maintained with 0.5 MAC isoflurane in O_2 and N_2O with intermittent vecuronium 0.01 mg/kg and fentanyl 0.5µg/kg , as and when needed, to maintain a BIS between 40-60. Heart rate prior to going on CPB was noted in all patients. Surgical repair was performed with the support of CPB. Aortic Cross Clamp (ACC) time and CPB time were noted. Most of the patients required minimal dose inotropes, dobutamine and/or adrenaline while weaning from CPB. The emerging rhythm together with heart rate after ACC removal, was noted in all patients. DC shock (20-30J), using internal cardiac paddles, was instituted on table, if ventricular rate was found to be >100bpm causing unstable haemodynamics. Rhythm at end of surgery was noted. Following institutional protocol, all patients were shifted to postoperative cardiac surgical ICU on ventilator, monitored and managed in the ICU for the next 24 hours. Following uneventful recovery, all patients were extubated within 24 hours following institutional protocol. Oral rate control medication the patient was on pre-operatively, was started in patients with Atrial Fibrillation and ventricular rate >100 bpm, orally or through ryles tube, as applicable. Since all the patients with AF were haemodynamically stable postoperatively in ICU, none received DC shock in the first 24 hours. The following recorded parameters were compared between the two groups:

Pre-operative patient related variables: age, sex distribution, body weight, presence of comorbidities (Hypertension, Diabetes, Previous Stroke), TEE parameters like Qp/Qs (pulmonary *versus* systemic blood flow ratio), ASD size, Left Atrial (LA) size, Left Ventricular Ejection Fraction (LVEF), Left Ventricular End Diastolic Diameter (LVEDD), Left Ventricular End Systolic Diameter (LVESD), Right Ventricular Systolic Pressure (RVSP).

Intraoperative Variables : pre-induction (baseline) ventricular rate, ventricular rate prior to going on CPB, ACC time, CPB time, inotrope requirement, need for blood transfusion and number of units transfused.

Primary Outcome Variables : rhythm after release of ACC (sinus, AF or other rhythm), number of patients requiring DC shock post CPB in OT, number of patients with AF at end of surgery, number of patients with AF at end of 24 hours in ICU.

Statistical analysis :

The above data were summarized by routine descriptive statistics, namely mean and standard deviation for numerical variables and counts and percentages for categorical variables. Numerical variables were compared between groups by Student's 't' test. Categorical variables were compared between groups by Fischer's exact test. A P value ≤ 0.05 was considered to be statistically significant.

Observations

Amongst the 23 adult patients aged >40 years with OS ASD, who underwent surgical closure on CPB, between January, 2019 to 31st March, 2022, reviewed for our study, we found 11 patients (47.82%) with concomitant Atrial Fibrillation as baseline rhythm. These 11 patients who met our inclusion and exclusion criteria, were recruited and randomized into two groups. Group A (n=6) and control group Group B (n=5). Table 1 summarizes pre-operative patient related variables. Mean age was found to be 51.6 years in Group A and 50.4 years in Group B (P>0.05). Sex distribution was equal in Group A while in Group B 60% were male (P>0.05). Remaining variables including body weight, associated comorbidities, Qp/Qs, other echo parameters and intake of rate control drugs, were found to be comparable between the two groups (P>0.05). Compared to no patient of Group B, one patient in Group A had a prior h/o stroke (P<0.05).

Table 2 summarizes the comparison of intra-operative variables between the two groups. Mean CPB time,

Basal Heart Rate, use of inotropes while weaning from CPB, blood transfusion and number of units transfused, were found to be comparable between the groups (P>0.05). However, the mean ventricular rate just before going on CPB was found to be significantly lower in Group A compared to Group B (P=0.05).

A comparison of primary outcome variables between the two groups are summarized in Table 3. With regards to rhythm after release of Aortic Cross Clamp, 5 out of 6 (83.33%) patients in Group A presented in sinus rhythm versus no patient in Group B (P<0.05). Atrial fibrillation was the emerging rhythm in all 5 patients (100%) of Group B versus in only one patient of Group A (16.67%) (P>0.05). DC shock was required in 2 out of 5 (40%) patients of Group B with atrial fibrillation due to a higher ventricular rate and unstable haemodynamics, resulting in sinus conversion in one of them and a lower ventricular rate with improved haemodynamics in the other. In comparison, none of the patients in Group A required DC shock (P>0.05). Amongst the five in Group A who had initial sinus rhythm after Aortic Cross Clamp release, two of them reverted to Atrial Fibrillation by the end of Surgery, resulting in 3 out of 6 (50%) patients in Group A with AF at the end of surgery. In comparison, in Group B, except for one patient who converted to sinus rhythm after receiving DC shock, all other ie, 4 out of 5 (80%) patients had rhythm AF by the end of surgery (P>0.05). At the end of 24 hours after shift to ICU, 5 out of 6 (83.33%) patients in Group A regained AF, with maintenance of sinus rhythm in 1 out of 6 (16.67%) patient. In comparison in Group B, all the 5 (100%) patients had AF by the end of 24 hours in ICU (P>0.05).

Discussion

About 13-52% patients older than 40 years with ASD have a concomitant Atrial Fibrillation[1]. In our retrospective case series analysis, we found an incidence of 47.82% of concomitant pre-operative AF in OS ASD patients >40 years age who underwent surgical closure under CPB.

The two groups of patients in our analysis, were found to be comparable (P>0.05) with respect to preoperative patient characteristics, echo parameters, intraoperative variables except for aortic Cross Clamp time, which was significantly longer in control group B (P<0.05). After [a]miodarone IV bolus dose infusion, ventricular rate before going on CPB, was lower in Group A compared to control Group B patients with the difference being just at the level of significance (P=0.05). Conversion to NSR immediately after release of ACC was found in 83.33% patients in Group A, who received IV Amiodarone vs in no patient in control group B (P> 0.05). Atrial fibrillation was the emerging rhythm in 100% patients of control Group B vs in only one patient (16.67%) in group A. DC shock

Table 1 — *Pre-operative patient related variables*

	Group A (n=6)	Group B (n=5)	P value
Age in years (Mean±SD)	51.6±5.32	50.4±3.049	0.667
Sex (M/F)	2/4	3/2	0.7
Body weight (Mean±SD)	66.8±7.85	67±10.67	0.978
Comorbidities (no of pts)	6 out of 6 (100%)	3 out of 5 (60%)	0.182
Hypertension	2 out 6 (33.33%)	2 out of 5 (60%)	0.709
Diabetes	3 out of 6 (50%)	1 out of 5 (20%)	0.361
Previous stroke	1 out of 6 (16.67%)	0 out of 5 (0%)	0.014
Echo parameters			
Qp/Qs (Mean±SD)	2.92±0.277	2.98±0.443	0.775
ASD size in mm (Mean±SD)	21.82±1.267	21.38±1.118	0.228
LA size in mm (Mean±SD)	43.94±0.99	44.46±0.76	0.43
LVEF% (Mean±SD)	61.6±3.05	60.4±4.21	0.72
LVEDD in mm (Mean±SD)	42.64±1.02	41.86±1.05	0.077
LVESD in mm (Mean±SD)	26.34±0.517	26.44±0.591	0.806
RVSP mm Hg (Mean±SD)	44.76±0.702	44.86±0.709	0.777
Rate control drugs (no of patients) :			
Digoxin	2 out of 6 (33.33%)	2 out of 5 (40%)	0.136
B blocker	2 out of 6 (33.33%)	2 out of 5 (40%)	0.136
Both	2 out of 6 (33.33%)	1 out of 5 (20%)	0.576

Qp/Qs : Ratio of Pulmonary Blood Flow to Systemic Blood Flow; ASD : Atrial Septal Defect; LA : Left Atrium; LVEF : Left Ventricular Ejection Fraction; LVEDD: Left Ventricular End Diastolic Diameter; LVESD : Left Ventricular End Systolic Diameter; RVSP : Right Ventricular Systolic Pressure.

Table 2 — *Intraoperative variables*

	Group A (n=6)	Group B (n=5)	P value
CPB time in mins (Mean±SD)	75.5±0.791	76.26±2.040	0.488
ACC time (Mean±SD)	60±2.598	62.7±1.204	0.044
Basal HR in bpm (Mean±SD)	89.8±6.87	88.4±7.76	0.754
HR prior to CPB in bpm (Mean±SD)	79.4±6.107	89±3	0.05
Inotrope use (no of patients)	6 out of 6 (100%)	4 out of 5 (80%)	1.0
Blood transfusion (no of pts)	3 out of 6 (50%)	3 out of 5(60%)	0.7
No of transfused blood units (Mean±SD)	0.667±0.816	0.5±0.547	0.741

CPB : cardiopulmonary bypass; ACC : aortic cross clamp; Basal HR : preinduction ventricular rate.

Table 3 — *Primary outcome variables*

	Group A (n=6)	Group B (n=5)	P value
Rhythm at release of ACC (no of patients) :			
Sinus rhythm	5 out of 6 (83.33%)	0 out of 5 (0%)	0.0152
Atrial fibrillation	1 out of 6 (16.67%)	5 out of 5 (100%)	0.304
No of patients requiring cardioversion	0 out of 6 (0%)	2 out of 5 (40%)	0.461
No of patients with AF at end of surgery	3 out of 6 (50%)	4 out of 5 (80%)	0.545
No of patients with AF within 24 hours	4 out of 6 (66.67%)	5 out of 5 (100%)	0.454

ACC : Aortic Cross Clamp; AF : Atrial Fibrillation

for rate control had to be instituted in 40% patients of control Group B and in no patient of Group A. About 50% patients in Group A had reverted to AF by end of surgery compared to 80% patients in control Group B (P>0.05). At the end of 24 hours in ICU, 66.67% patients regained AF in Group A in comparison to 100% patients in control Group B (P>0.05).

In the 2013 retrospective study by Wi J *et al*[2], the investigators examined the clinical course of pre-operative AF after correction of ASD and/or after concurrent Maze operation in 40 patients who underwent ASD repair by surgical or transcatheter device closure. In patients with Parosxysmal AF (PAF), isolated ASD closure resulted in conversion to maintenance of sinus rhythm in 88% patients and continuation of AF in 12% patients. While in patients with Persistent AF (PeAF), isolated ASD closure resulted in sinus conversion and maintenance in 18% patients and continuation of AF in 82% patients. In PAF patients who underwent surgical closure with concomitant Maze procedure, 100% patients reverted to and maintained sinus rhythm, while in PeAF patients, surgery with Maze resulted in sinus conversion and maintenance in 75% patients and persistence of AF in 25% patients. All patients were on pre-operative oral anti-arrythmics. The investigators concluded that, most of the ASD patients with pre-operative Paroxysmal AF, maintained SR after correction of ASD, rationalizing this finding by the potential anti arrythmic effect of ASD correction resulting from haemodynamic correction and subsequent structural and electrophysiological reverse remodelling[19,20]. Haemodynamic correction was not found to be totally effective in reversing AF in patients with pre-operative Persistent AF. However, a concurrent Maze procedure was found to be very effective in maintaining SR in these patients. Therefore, a concurrent Maze procedure or transcatheter ablation before ASD closure, needs to be considered in patients with pre-operative persistent AF.

From our analysis, we can conclude that although single intraoperative bolus IV dose of Amiodarone may result in increased conversion to sinus rhythm, but the effect is short lasting. Therefore, probably concurrent Maze or transcatheter ablation before/after ASD closure needs to be considered for maintenance of NSR.

Limitations :

Firstly, a retrospective analysis of a small sample size makes the results of our analyzed data not accurate enough to be extrapolated on actual population, necessitating the need for larger prospective trials. Secondly, we did not have complete information on the type of concomitant AF ie, whether paroxysmal or persistent, because the data was collected retrospectively. Thirdly, a longer study period beyond first 24 hours is probably required for better analysis of the course of AF.

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Original Article

A Study of Changes in Refractive Status Pre and Post Pterygium Surgery among Patients of Tertiary Care Hospital of Ahmedabad City

Smita Thakkar[1], Hemaxi Desai[2], Krupali Raol[3], Ruchi Kabra[1], Khyati Sharma[4], Ronak Bhanat[4]

Background : Pterygium is a fibrovascular subconjunctival tissue also called Tenon's Capsular growth occurring mostly in the palpebral fissure area from the nasal aspect towards the limbus over the Cornea and in this process the Corneal Pathology is changed especially the epithelium and bowman's layer of the cornea are destroyed[1]. A major problem seen in most of postpterygium surgery is the complication of recurrence and it is usually seen in young patients with fleshy large pterygium[1]. This issue is addressed by Pterygium Surgery with either Conjunctival Autograft (CAG) or Amniotic Membrane Graft (AMG)[1]. Stem cells are present in limbal conjunctiva and in amniotic membrane, which provide a barrier between cornea and conjunctiva, preventing regrowth and also provide a smooth regular surface to the eyeball[2]. another reason and technique to prevent recurrence is by excising the pathological part of conjunctiva and resecting tenon's capsule up to far periphery[2].

Aims and Objectives : The aim of the study is to investigate pre-operative and postoperative difference between the amount of astigmatism prior to the surgery and after the Pterygium Excision Surgery with either CAG or AMG.

Materials and Method : A prospective cross-sectional study was undertaken of 26 cases, who underwent Pterygium Surgery under local anaesthesia with Conjunctival Autograft or Amniotic Membrane Graft for a period of one year in a Tertiary Healthcare Hospital. Pre-operative Best Corrected Visual Acuity, Anterior Segment Examination, Slit Lamp Examination, Dilated Retinoscopy and Fundus examination, Keratometry and Post mydriatic refraction was done. Then the patient underwent Pterygium Excision Surgery with Conjunctival Autograft or Amniotic Membrane Graft under local anaesthesia. All patients were re-examined 1 month after the surgery for final Refraction and Keratometry.

Result : Among total of 26 patients, the comparison between pre- and postoperative values of Refraction and of Corneal Astigmatism was performed using z test. The pre-operative Mean for Astigmatism was 1.70 and SD was 0.43. The postoperative mean for Astigmatism was 0.57 and SD was 0.26. The pre-operative Keratometry mean was 2.73 and SD was 0.14. The Post operative Keratometry Mean was 1.50 and SD was 0.55. (p value, 0.0001)

Conclusion: Pterygium is a lesion which also affects the ocular surface, thus leading to one of the causes for ocular surface abnormality. Pterygium surgeries results in elimination of the Pulling Factor and Corneal Curvature thus reducing or eliminating Astigmatism and thereby providing better visual restoration and cosmetic outcome.

[*J Indian Med Assoc* 2022; **120(6):** 44-6]

***Key words* : Pterygium, Refractive Status, Astigmatism, Keratometry.**

"Pterygium (plural pterygia) is a triangular fibrovascular sub-epithelial in growth of degenerative bulbar conjunctival tissue over the limbus onto the Cornea"[3]. Pterygium-induced Astigmatism is the major cause of Visual Impairment. Invasion of Pterygium on the Cornea gives rise to corneal astigmatism which is directly proportional to the area of the cornea encroached[4]. Pterygium encroaching on the Cornea primarily induces" with the rule Astigmatism"[4]. In "With the Rule" astigmatism there is flattening of the horizontal curvature and steepening of the vertical meridian of the Cornea[4]. The mainstay of treatment is Pterygium excision, with CAG or AMG.The indications are as follows : (a) Signs of visual disturbances, which may be due to induced astigmatism or involvement of pupillary area, (b) Inflamed Pterygium, (c) Ocular surface irregularity, leading to dryness of Cornea, (d) Patient insisting due to cosmetic reasons[5]. There are several reasons to understand the induction of Astigmatism in these cases - mainly due to mechanical friction induced by

Editor's Comment :

- Pterygium leads to considerable amount of astigmatism.
- Ocular surface irregularity is decreased significantly after Conjunctival Autograft (CAG) and Amniotic Membrane Graft (AMG) surgeries for pterygium.
- Pterygium surgery plays a significant role in reducing astigmatism.
- Pterygium with CAG and/or AMG reduces recurrence in considerable number of patients.
- In our study, females opted for undergoing pterygium surgery more than males due to cosmetic reasons.

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Pterygium and secondarily due to the surface irregularities[6]. The main problem in Pterygium Surgery is the tendency for recurrence, which is prevented by Limbal Stem Cell (LSC) as they form barrier between Cornea and Conjunctiva, Pterygium excision is followed by autologous Conjunctival Limbal Stem Cell (CLSC) graft or Amniotic Membrane Graft (AMG) for the same reason[6]. Our study, primarily aims to assess the changes in Corneal Astigmatism and Visual Acuity after Pterygium removal.

Materials and Method

This prospective cross-sectional study was performed in Department of Ophthalmology of GCS Medical College for a period of 1 year[4]. All patients diagnosed with pterygium in our OPD and agreeing to undergo Pterygium excision were included after obtaining informed consent. We excluded patients with Recurrent Pterygium, Pseudo Pterygium, Symblepharon, Double Pterygium and patients with any known Corneal Pathology. Thus total 26 cases of pterygium were selected. All the selected patients were evaluated in detail. In pre-operative assessment all patients were assessed for demographic factors, occupational details and History of Previous Ophthalmic, Medical and Surgical Conditions. All collected information was recorded in structured format. Following that detailed ocular examination carried out after taking consent. Which include Pre-operative unaided and best corrected visual acuity done by Snellen's chart, Anterior segment examination done by Slit Lamp Bio Microscopy, Dilated Retinoscopy, Keratometry by Bausch and Lomb Keratometer, Posterior segment examination by indirect Ophthalmoscope using 20D. Then the patient underwent Pterygium Excision Surgery, under local anesthesia. Observer's bias was minimized by appointing one investigator for the entire pre-operative assessment and designating one Surgeon for all the surgeries. All patients were re-examined 1 month after the surgery for the same parameters as described above by the same investigator.

Results

Most common age group affected was between 40-50 years (Fig 1).

In this study female (65%) are more compared to males (35%) (Fig 2).

Fig 3 shows that in this study 73% patients undergoing Pterygium excision with Conjunctival Autograft and 27% undergoing pterygium excision with Amniotic Membrane Graft (Table 1).

There is significant difference present in required

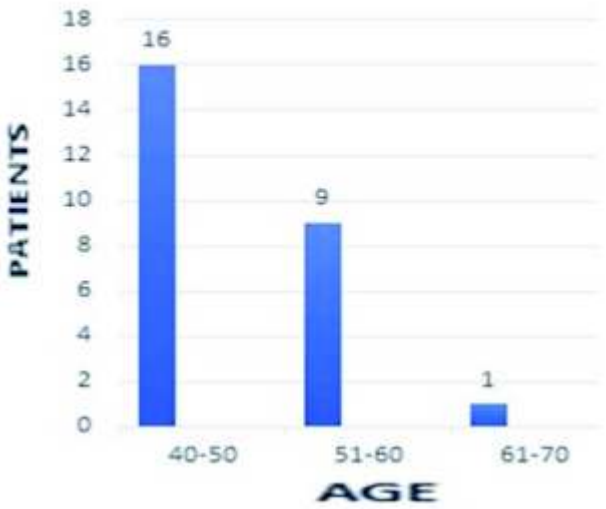

Fig 1 — Age Wise Distribution of Pterygium Patients

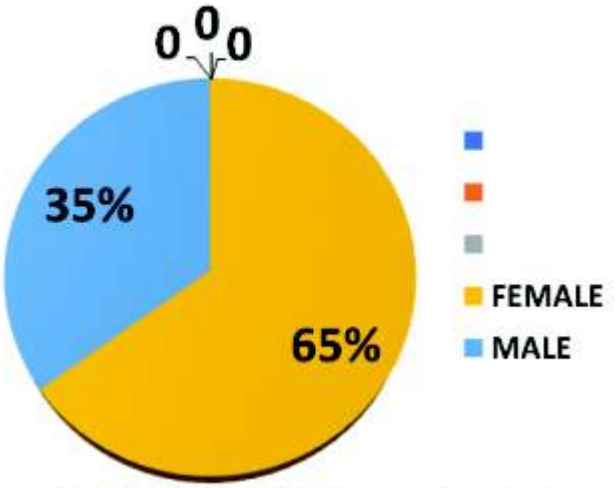

Fig 2 — Gender Wise Distribution of Pterygium Patients

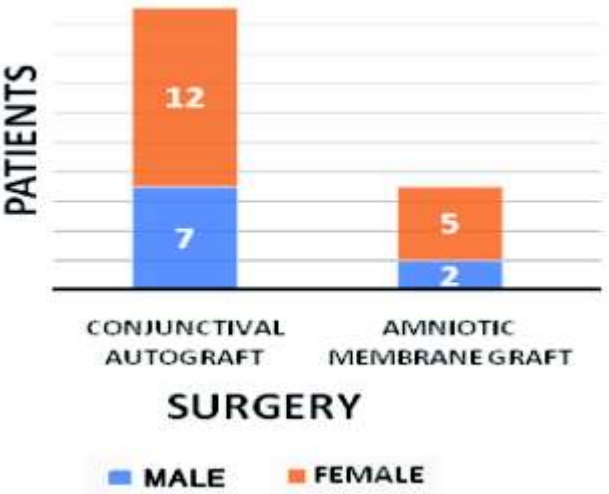

Fig 3 — Distribution of Pterygium According to Surgery

diopteric power of Cylinder and Keratometry mean (p =0.0001) pre- and postoperatively however there was no significant difference present between pre-operative and postoperatively best corrected visual acuity (p=0.35)

There is significant difference present in pre and postoperative KV mean (p=0.041) however, there was no significant difference present in KH mean (p=0.10).

Discussion

Pterygium is a widely occuring ocular condition. Despite its wide distribution, Pterygium is the most commonly found in areas of geographic latitude 40 degree around the equator such as India. Its prevalence varies in different environmental conditions; in India it ranges from minimal 10.42% to highest 72%.

In the current study, out of 26 patients, 17 were female (66%) and 9 were male (34%) Another study by R M Youngson *et al*[7], showed similar findings as our study in which 26 participants were male (38%)and 42 (62%)were female. Whereas Hilgergers JH *et al*[8] in their study showed male predominance.

It was noticed that in our study, majority of people belonged to age group of 40-50 years. Similar observation was noted by R.M Youngson *et al*[7] in their study (30-50 years)(Tables 2 & 3).

Sample size was small so we can't generalize findings to other population. Study population drawn from specific environment (Eye OPD of an Urban, Tertiary Healthcare Center).

Conclusion

Pterygium is known to affect refractive Astigmatism which can have a significant impact on quality of vision[4]. Pterygium surgery reduces the induced refractive Astigmatism significantly and restores the good visual outcome.

Table 1 — *Pre-operative and Postoperative Comparison of Visual Acuity and Astigmatism*

	Pre-operative	Postoperative (1 month)	P Value
BCVA (Logmar)	0.27±0.50	0.24±0.15	0.35
Cylinder (Diopter)	1.70±0.43	0.57±0.20	0.0001
KH-KV(D)	2.73±0.14	1.50±0.55	0.0001

Table 2 — *Comparison of pre-operative and postoperative (Astigmatism on auto-refractometer) in our study with other studies*

Study	Pre-operative Cylinder(d)	Postoperative Cylinder(d)	P Value
Present Study	1.70±0.43	0.57±0.20	0.0001
Maheshwari S Study(8)	4.40±3.64	1.55±1.63	<0.001
Yagmur *et al*[9]	4.64±3.02	2.33±2.26	0.003
Popat KB *et al*[1]	6.20±3.58	1.20±1.27	<0.05

Table 3 — *Comparison of pre-operative and postoperative (KH-KV) (Keratometric Astigmatism) in our study with other studies*

Study	Pre-operative (KH-KV) D	Postoperative (KH-KV) D	P Value
Present study	2.73±0.14	1.50±0.55	0.0001
Mohite *et al*[10]	3.046±1.20	1.486±0.63	<0.001
Aishwarya Thakre[11]	2.55±1.14	0.60±0.41	0.000

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Review Article

CNS Tuberculosis

K Muralidharan[1], Mugundhan Krishnan[2], Jyotirmoy Pal[3]

Tuberculosis can involve almost any organ of the body. In the Central Nervous System (CNS) it can cause meningitis, tuberculoma, abscess,spondylitis, arachnoiditis, myeloradiculitis or other manifestations. Around 10% of all patients with tuberculosis have CNS involvement. Tuberculosis is rampant in the developing world and has reemerged as a major public health menace with the HIV pandemic. Compared with HIV-negative individuals, HIV-positive individuals with TB are 5 times more likely to have CNS involvement. Laboratory confirmation of CNS TB is difficult and hence empirical treatment has to be initiated as early as possible based on clinical and radiological features. In this article,we review the CNS manifestations of tuberculosis and their diagnosis and treatment.

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Key words **: Tuberculoma, Meningitis, Abscess, Spondylitis, Pott's spine, myeloradiculitis, Optochiasmal arachnoiditis, Caseation, Ependymitis, Hydrocephalus, Optic neuritis, Adenosine deaminase.**

Tuberculosis (TB) is caused by the acid-fast bacillus Mycobacterium tuberculosis. TB accounts for 10 million new symptomatic infections and 1.4 million death globally, with a prevalence estimated at 25% of the world's population. Although pulmonary TB is the most common site of active disease, extrapulmonary TB is not uncommon, accounting for 10% to 40% of cases globally[1]. Risk factors for developing Central Nervous System (CNS) TB include malnutrition, alcoholism, concomitant malignancy, use of immunosuppressive medications, HIV infection, recent measles, and measles in childhood[1]. Although nervous system involvement is less common than involvement of other extrapulmonary sites, It is one of the most severe forms of TB and is associated with high mortality, especially among people with HIV[1].

Editor's Comment :

- Around 10 percent of patients with TB have CNS involvement.
- CNS TB includes TB meningitis, TB arachnoiditis, Tuberculoma and TB abscess.
- Cranial nerves 6,7 and 2 are frequently involved in TB meningitis.
- Stroke, seizures and hydrocephalus are frequent complications of TB meningitis.
- TB can also cause optic neuropathy, optochiasmatic arachnoiditis, subarachnoid hemorrhage, limbic encephalitis and NMO.
- Spinal TB causes spondylitis, radiculomyelitis, spinal arachnoiditis, intramedullary tuberculoma.
- Duration of treatment in CNS TB is 9-12 months.
- Laboratory confirmation of CNS TB is difficult and hence empirical treatment should be initiated as early as possible based on clinical and radiological features.

Classification of Neurological Tuberculosis :

(1) Tuberculosis meningitis
(2) Tuberculosis arachnoiditis
- Basal
- Opticochiasmatic
- Spinal

(3) Tuberculoma
- Intracranial
- Spinal

(4) Tuberculosis abscess

Tuberculous Meningitis :

The most common form of CNS TB is tuberculous meningitis, which can present as either insidious chronic meningitis or acute fulminant meningitis

Pathogenesis :

It was initially hypothesized that tuberculous meningitis resulted from an extension of infection into the subarachnoid space from a caseating focus in the adjacent cortex (the Rich focus). A later hypothesis agreed with this theory but also suggested that initial hematogenous dissemination could result in a meningeal or cortical focus that produced immediate or delayed tuberculous meningitis.

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Pathology of TB Meningitis :

- Meningitis
  - Inflammatory leptomeningeal exudate
  - Caseous necrosis
  - Proliferative opticochiasmatic arachnoiditis
- Vasculitis
  - Arteritis
  - Phlebitis
- Ependymitis and choroid plexitis
- Encephalitis
  - Cortical
  - Subependymal
  - Vasculitis and infarction
- Hydrocephalus
  - Communicating
  - Obstructive

Clinical Presentation :

Tuberculous meningitis can develop insidiously or in an abrupt manner similar to bacterial or viral meningitis. The most common symptoms of tuberculous meningitis include fever, headache, vomiting and apathy. Given the frequent involvement of the basilar meninges and ambient cistern in tuberculous meningitis, cranial nerve dysfunction is frequent, with cranial nerves VI (abducens), VII (facial), and II (optic) most often affected[1].

Stroke is one of the most common complications of tuberculous meningitis, occurring in approximately 30% to 60% of cases. These strokes are usually found in the basal ganglia because of involvement of small penetrating arteries that are surrounded by exudates in the basal cisterns, but abnormalities of the large anterior circulation arteries are also common due to tuberculous vasculopathy. Hypothesized stroke mechanisms include endothelial reactions to inflammatory exudates, proliferative and necrotizing arteritis, and hypercoagulable states.

Seizures are also common in tuberculous meningitis, occurring in 34% of individuals. The majority were focal onset, and nearly one-quarter presented with status epilepticus. Early seizures were associated with meningeal irritation, whereas late seizures were more common in those with tuberculomas, infarcts, and hyponatremia.

Hydrocephalus is a common complication of tuberculous meningitis.When CSF protein is greater than 500 mg/dL, obstruction of CSF flow can occur and produce subarachnoid block, leading to hydrocephalus.

Complications of TB Meningitis :

- Raised intracranial pressure, cerebral oedema, stupor
- Basal meningitis with cranial nerve palsies
- Focal neurological deficits
- Hydrocephalus
- Tuberculoma
- Tuberculosis abscess
- Opticochiasmatic pachymeningitis resulting in visual loss
- Tuberculosis arteritis and stroke
- Endocrie disturbances
- Hypothalamic disorder leading to loss of control of blood pressure and body temperature
- Diabetes insipidus
- Syndrome of inappropriate antidiuretic hormone secretion Internuclear ophthalmoplegia
- Hemichorea
- Spinal block
- Spinal arachnoiditis

Investigations[3] :

(1) Radiological Studies

Chest radiograph —

The chest radiographs reveal findings consistent with pulmonary TB in 25 to 50 per cent of adult patients and 50 to 90 per cent of children with TBM.

Neuroimaging —

The CT or MRI of the brain may reveal thickening and enhancement of basal meninges, hydrocephalus, infarction, oedema [often periventricular], and mass lesions due to associated tuberculoma or TB abscess. Common sites of exudates are basal cisterna ambiens, suprasellar cistern and Sylvian fissures. Hydrocephalus, Enhancements of basal meninges, cerebral infarction most frequently in the MCA territory, are seen (Fig 1).

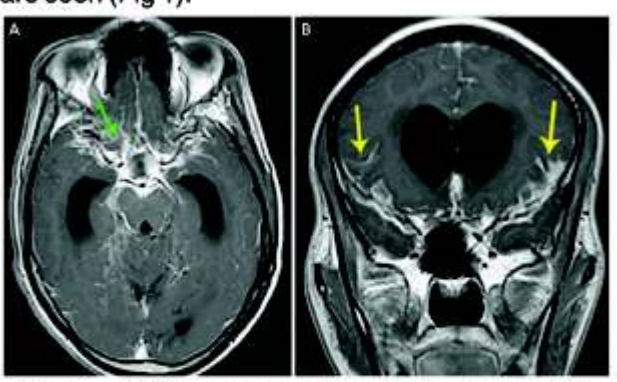

Fig 1 — Axial (A) and coronal (B) postcontrast T1-weighted MRIs reveal a thick basal exudate (A, green arrow) in the basal cisterns and leptomeningealenhancement (B, yellow arrows) in the frontotemporal regions bilaterally as well as acommunicating hydrocephalus.

(2)Tuberculin Skin Test

Tuberculin skin test is positive in 40 to 65 per cent of adults and in 85 to 90 per cent of children with TBM in western studies . However, TST lacks specificity in developing countries because of the possibility of previous sensitization to environmental mycobacteria and BCG vaccination.

(3) CSF

Because of the paucity of TB organisms in the CSF, diagnosis of CNS TB can be difficult.The most common pattern of CSF abnormalities in tuberculous meningitis is a mononuclear (ie, lymphocytic or monocytic) pleocytosis, low glucose, and markedly elevated protein.

Cytology and biochemistry : In TBM, the leucocyte count is usually between 100 to 500 cells/ il, but rarely can exceed 1000 cells/il. Predominantly, lymphocytes are increased in the CSF, although in the acute stage a polymorphonuclear response is not unusual. It is transient and replaced by lymphocytic reaction in the course of days to weeks. Occasionally, the cell count may be normal.

The CSF protein is generally between 100 to 200 mg/dl. In the presence of co-existing spinal meningitis and spinal block, the values can exceed 1 g/dl and the fluid may be xanthochromic. If allowed to stand, a pellicle or cobweb may form, indicating the presence of fibrinogen. The pellicle is highly suggestive but not pathognomonic of TBM.

The CSF glucose level is abnormal in majority of cases, being less than 40 per cent of the corresponding blood glucose level. Median glucose levels are reported to be between 18 to 45 mg/dl[3].

Adenosine Deaminase

Elevated ADA in the CSF accompanies most forms of meningitis and is closely correlated with levels of CSF protein. Although elevated ADA levels are not specific for tuberculous meningitis, elevated levels have been associated with poor prognosis of tuberculous meningitis in children. In one meta-analysis, ADA values greater than 8 U/L improved the diagnosis of tuberculous meningitis (sensitivity <59% and specificity >96%).

Acid-fast Bacilli Stain and Culture

CNS TB is difficult to diagnose using traditional Ziehl-Neelsen stain and mycobacterial culture.When only one CSF examination is performed, the sensitivity of smear and culture are 37% and 52%, respectively while if three CSF samples are examined, the yield increases to 87% and 83%.59 Unfortunately, CSF culture typically takes 2 to 4 weeks to become positive, so when CNS TB is suspected, empiric treatment for presumptive CNS TB should be initiated before confirmation[3].

Tuberculosis Polymerase Chain Reaction

Most PCR assays for M. tuberculosis detection amplify the MPB64 gene or IS6110. The sensitivity and specificity of PCR assays for M Tuberculosis are highly dependent upon the diagnostic criteria used, the amount of CSF sampled, and whether antituberculous therapy was administered before the collection of CSF.The PCR assays can be more sensitive than CSF culture, but diagnosis of tuberculous meningitis cannot be excluded on the basis of a negative PCR result

Cartridge-Based Nucleic Acid Amplification Test

This same-day detection of rifampin-resistant bacteria can influence the decision to switch to second-line agents . In tuberculous meningitis cases from India, CSF MTB/RIF Xpert, Xpert MTB/RIF Ultra, and multiplex PCR all demonstrated 100% specificity, but 71%, 28%, and 88% sensitivity, respectively[2].

(4) Biopsy

Biopsy can be a useful ancillary test for patients with solitary enhancing lesions or chronic meningitis with persistently negative cultures. Although the sensitivity of biopsy is unknown, examination of infected tissue with Ziehl-Neelsen staining, culture, and PCR assays should increase the diagnostic yield.

In practice, a combination of clinical and laboratory parameters is used to make clinical decisions in high-TB-burden settings, which often lack extensive CSF diagnostic testing. In these settings, a high degree of suspicion for TB is maintained even in the absence of confirmatory microbiological evidence from the CSF[2].

Tuberculoma:

Tuberculomas are space-occupying lesions consisting of granulomatous reactions to M Tuberculosis infection that are believed to arise from the hematogenous spread of mycobacteria to the brain parenchyma. Microscopic granulomatous foci, called Rich foci, develop over time, organizing into encapsulated granulomatous mass lesions. Tuberculomas are similar to tuberculous abscesses, but abscesses are often larger and have a pus-filled cavitary center[2].

Ten percent of patients with tuberculous meningitis also have tuberculomas; with one-third of such patients having multiple tuberculomas. The clinical presentation of CNS tuberculoma typically includes headache, seizures, focal neurologic deficits, and papilledema. Tuberculomas can develop in the brain; spinal cord; or subarachnoid, subdural, or epidural space and are often accompanied by surrounding edema and ring enhancement[4].

On neuroimaging, tuberculomas are typically space-occupying lesions.As the center of the tuberculoma caseates and becomes liquefied, neuroimaging characteristics on T2-weighted and

FLAIR MRI sequences change from hypointense to isointense to hyperintense[4]. While in adults, tuberculomas are typically supratentorial, in children, lesions are often infratentorial. The CSF of patients with tuberculomas is typically unremarkable, while the tuberculin skin test is positive in up to 85% and chest radiography is abnormal in 30% to 80% (Fig 2).

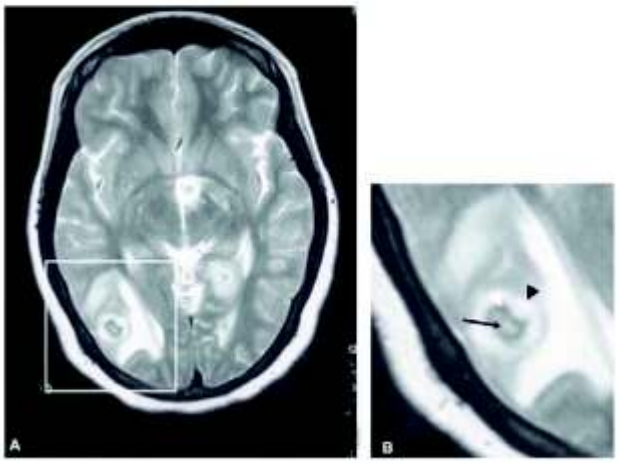

Fig 2 — MRI of the brain [T2-weighted image, axial view] showing characteristic appearance of a tuberculoma [A]. Close-up view of the lesion showing central hyperintense area [solid arrow] suggestive of caseation necrosis; surrounding hypointense rim [white arrow head] of fibrousis capsule; and a significant perilesional white matter oedema [black arrow head]

Tuberculous Abscess :

Tuberculous abscess occurs in less than 10% of patients with CNS TB and represents a later stage of tuberculoma. An abscess contains many more bacilli than a granuloma. The clinical symptoms produced by a tuberculous abscess typically include fever, headache, and focal neurologic deficits.

Differentiation between tuberculoma and tuberculous abscess can be difficult by neuroimaging, but an abscess wall tends to be thicker, can be multiloculated, and typically has contrast enhancement. On DWI sequences, MRI may demonstrate restricted diffusion in tuberculomas or abscesses with liquefied caseation but this is absent in lesions that have only solid caseation.

Other CNS Tuberculosis Manifestations :

TB has a myriad of uncommon CNS manifestations including optic neuropathy, optochiasmatic arachnoiditis, tuberculous encephalopathy, subarachnoid hemorrhage, limbic encephalitis, and a possible unproven association with neuromyelitis optica[1].

Optic neuritis/optic neuropathy

Most optic neuropathies are secondary to chronic increased intracranial pressure, mass effect from tuberculomas, or drug-associated toxicities. However, primary optic neuropathies have also been reported and can be the presenting sign of Central Nervous System (CNS) tuberculosis (TB). In these cases, optic neuritis occurs because of tubercular perineuritis, endarteritis of the optic nerve, or arachnoiditis of the optic nerve and/or chiasm.

Optochiasmatic arachnoiditis

Occurs in conjunction with tuberculous meningitis when accumulation of exudates in the basal cisterns leads to arachnoiditis of the optic nerves and chiasm, which manifests as slowly progressive vision loss and most commonly occurs in younger individuals. It also occurs as part of a paradoxical reaction after initiation of antituberculous treatment.

Tuberculous encephalopathy

It occurs most commonly in the pediatric population. Its clinical presentation ranges from focal neurologic deficits or confusion to seizures or coma. MRI shows extensive white matter changes, usually with contrast enhancement and sometimes diffuse cerebral edema, but CSF is usually normal or only mildly abnormal. It is thought not to be caused by direct infection of the CNS by TB but to be an immune-mediated reaction. Two mechanisms have been postulated : (1) an acute disseminated encephalomyelitis (ADEM)-like mechanism; and (2) an allergic (type IV hypersensitivity) reaction within the nervous systemto systemic TB protein. Early diagnosis and initiation of antituberculous treatment and steroids is imperative to reduce associated morbidity and mortality[1].

Subarachnoid hemorrhage

Occurs as a result of rupture of tuberculous cerebral aneurysms that develop in the setting of tuberculous meningitis[1].

Treatment :

The WHO recommends treatment of tuberculous meningitis in two stages: (1) the intensive phase: rifampicin, isoniazid, pyrazinamide, and ethambutol for 2 months followed by (2) the continuation phase: rifampicin and isoniazid for an additional 7 to 10 months (9 to 12 months of total treatment)[2,5]. Of the available antituberculous medications, isoniazid and pyrazinamide have the best penetration into the subarachnoid space.

Multidrug-resistant and extremely drug-resistant TB infections usually require prolonged treatment with additional antituberculous agents such as levofloxacin, bedaquiline, linezolid, clofazimine, cycloserine, and amikacin. In addition to antituberculous agents, concomitant steroids tapered over 6 to 8 weeks have also been shown to reduce mortality, severe disability, and disease relapse[2,5].

Corticosteroids

The WHO recommends initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6 to 8 weeks for all patients

with tuberculous meningitis.

Corticosteroids reduce intracranial pressure and decrease inflammation in the subarachnoid space, cerebrum, spinal cord, and small blood vessels. The theoretical harm of corticosteroids results from reducing meningeal inflammation, thus potentially decreasing penetration of antituberculous medications; from suppressing the immune system, which could lead to bacterial superinfection.

If corticosteroids are administered, dexamethasone is most often used at a dosage of 12 mg/d to 16 mg/d for 3 weeks, then tapered off over 3 weeks. For patients who experience worsening during or after tapering, corticosteroids can be extended for a longer period[6].

Spinal Tuberculosis :

TB can involve every compartment of the spine including bony structures, intradural and extradural spaces, the spinal cord, and nerve roots. The thoracic and lumbar regions are most commonly involved, but cervical involvement occurs in more than one quarter of affected individuals and is associated with more frequent neurologic sequelae than other locations[2].

Majority of cases of spinal TB occur in the absence of pulmonary disease. The most common manifestations of spinal TB are spondylitis and intradural tuberculous spinal infections including radiculomyelitis, spinal arachnoiditis, intramedullary tuberculomas, and myelitis

Spondylitis

Spondylitis, also known as Pott disease, is the most common form of spinal TB and accounts for 50% of cases of skeletal TB.It presents with insidiously evolving nonspecific back pain followed by kyphosis (clinically as a gibbus formation on the back), sensory symptoms, bowel and bladder symptoms, and, finally, paraparesis. Progression through these stages occurs over the course of months to more than 1 year.

Acute presentations of neurologic deficits are not uncommon because of vertebral fracture or abscess formation with subsequent spinal cord compression. Imaging classically shows edema and bony destruction of the vertebral body with paravertebral granulomatous exudates or abscess. The thoracic cord is the most common location, and spondylitis often involves three or more consecutive vertebral bodies while sparing the intervertebral discs[7] (Fig 3).

Intradural Tuberculous Spinal Infections

Intradural tuberculous spinal infections, including radiculomyelitis, spinal arachnoiditis, intramedullary tuberculomas, and myelitis, are seen most commonly in the setting of tuberculous meningitis because of the spread of inflammatory exudates from the cranial to the spinal compartment. These inflammatory exudates often settle in the lumbosacral subarachnoid space and present with a conusmedullaris or cauda equina syndrome. The subarachnoid space may also become irregularly obstructed because of these exudates, resulting in the formation of CSF loculations. Syrinx is a frequent late complication of tuberculous meningitis and spinal TB.

Tubercular radiculomyelitis is the most common intradural spinal manifestation of TB, occurring in nearly 40% of individuals with tuberculous meningitis. Tuberculous radiculomyelitis typically produces a subacute, gradually progressive, lower limb weakness with bladder dysfunction,paresthesia, radicular pain, and muscle wasting. Neuroimaging of tuberculous radiculomyelitis often reveals obliteration of the spinal subarachnoid space, loss of spinal cord landmarks, clumping of nerve roots, and nodular intradural enhancement.

Intradural extramedullary tuberculomas, intramedullary tuberculomas, and tuberculous abscesses occur in 20%, 9%, and 7% of patients, respectively.(2,8) Complications of these infections include spinal cord vasculitis and infarcts (Fig 4).

Diagnosis

For Pott disease, initial investigations usually include spinal imaging, which, in many high-TB-burden

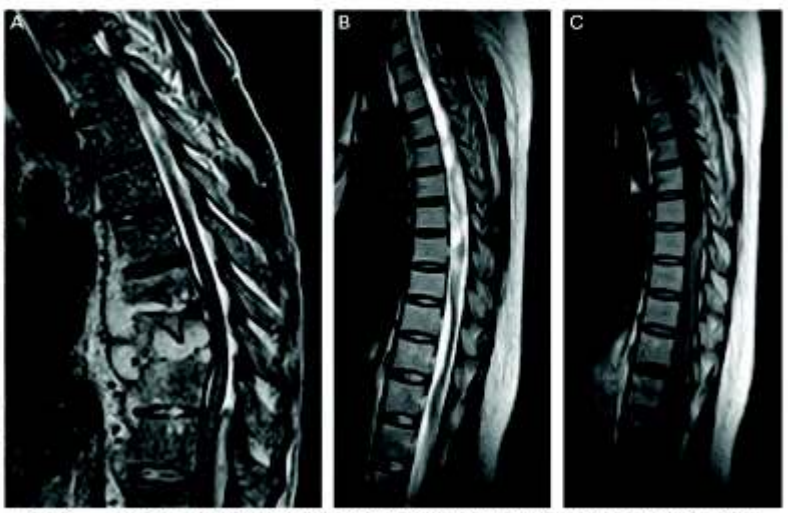

Fig 3 — Sagittal T2-weighted (A) image from thoracic spine MRI demonstrating vertebral body destruction, loss of disc height, erosion, and paravertebral masses consistent with tuberculous spondylitis. Sagittal T2-weighted (B) and T1-weighted (C) images from another

settings, may be limited to plain x-rays. If oblique views are obtained as part of the spine series, plain radiographs can demonstrate sensitivity as high as 70% for the diagnosis of spondylitis, although they may be normal early in the disease[2,9].

Radiolucencies and loss of definition of plate margins are the earliest findings in spondylitis followed by vertebral body destruction (most commonly involving the anterior portion of the vertebral body), endplate erosion, loss of normal disc height, sclerosis, and paravertebral masses. Where MRI is available, the combination of subligamentous spread, vertebral collapse, and large abscess collection with a thin wall was comparable to biopsy-obtained tissue studies in discriminating TB from non-TB etiologies.In cases of spinal arachnoiditis, CSF loculations are often visualized on MRI.

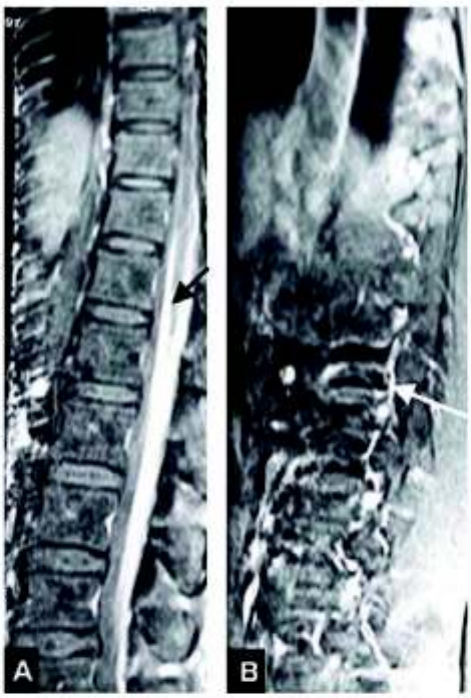

Fig 4 — Contrast enhanced MRI in a patient with spinal pachy arachnoiditis showing post-gadolinium enhancement of meninges [arrow] [A]; and nerve roots [arrow] [B] in a patient with spinal pachy arachnoiditis

With intradural spinal tuberculosis, CSF is often abnormal and shows a profile similar to tuberculous meningitis. In Pott disease, however, CSF is often normal, and bone biopsy, which is the gold standard to exclude alternative infectious and neoplastic etiologies, is often difficult in resource-limited settings.

Treatment of Spinal TB

Similar to tuberculomas, a presumptive diagnosis based on clinical presentation and x-ray findings (or other neuroimaging findings if available) is often required for all forms of TB of the spine and is followed by initiation of empiric TB treatment. TB treatment for 9 to 12 months (ie, intensive phase therapy for 2months followed by 7 to 10 months of continuation phase therapy) with adjuvant corticosteroids is recommended. Among individuals with spondylitis, surgical options, including decompression, stabilization, and correction of kyphoscoliotic deformities, are considered on a case-by-case basis[1,10].

Conclusion :

CNS TB is a common complication of pulmonary TB, which is difficult to diagnose. Diagnosis is most efficiently made through combining CSF examination with traditional methods of diagnosis, eg, Ziehl-Neelsen stain and mycobacterial culture, and with newer technologies. As the diagnosis of TB is frequently delayed by weeks, empiric treatment should be started when CNS TB is suspected. When possible, TB infection should be confirmed through culture of CSF or other tissue and drug susceptibility determined, as antituberculous treatment should be adjusted if multidrug-resistant TB or extensively drug-resistant TB is detected.

Concomitant treatment with steroids should be administered to all patients with tuberculous meningitis and strongly considered for other forms of CNS TB that are accompanied by edema. Although HIV coinfection does not typically alter the radiographic or neurologic presentation of CNS TB, ART can influence the natural history of CNS TB (eg, IRIS), so HIV status should be determined in all patients presenting with TB infection.

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Case Report

Management of Giant Mandibular Ameloblastoma — A Case Report

Supreet Ratnakar Prabhu[1], Maitree Prakashchandra Bavishi[2], Bhavin Kumar Dineshchandra Masariya[3], Enosh Nirmalkumar Steward[4]

Ameloblastomas are rare, locally invasive and slowly growing and tumours with high recurrence rate. If they are not treated on time, they can reach an emormous size. Benign mandibular swellings are broadly divided into odontogenic and non-odontogenic tumours. Ameloblastoma is one of the most common benign tumours of odontogenic origin which developed from epithelial cells and its elements and dental tissues in their various phases of development. Patients with Giant Ameloblastomas are very rare but they are widely found and diagnosed in developing countries because of painless growth and patient's fear of Surgery leading to delayed treatment. This paper presents a case of large Ameloblastoma of left side of mandible in a 25-year-old female patient which was successfully resected in toto. Patient refused for free fibula flap re-construction of the defect because of her apprehension for donor site morbidity.

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Key words **: Giant Ameloblastoma, Benign Lesions, Resection of mandible, Aggressive lesions.**

Ameloblastomas or Adamantinomas are rare tumours of jaw it constitutes 1-3% of all jaw tumours[1]. It is more common in mandible, it presents as slow growing, painless swelling causing expansion and local destruction of cortical bone and they can grow to enormous size over the years without any malignant change. Hughes *et al* proposed that the term 'Giant Ameloblastoma' be reserved for lesions that are truly large, causes gross asymmetry and regional dysfunction. Treatment of such a lesion poses a challenge due to its extreme size, its dimensions and weight, extent and bones involved, vital structures involvement and the extent that it compromises the oral function[2]. The Giant Ameloblastomas are usually treated by Radical Surgery and it leaves a huge defect which demands re-construction[3]. A case of 25 years old female patient presented here with Giant Ameloblastoma was resected in toto.

Editor's Comment :

- Early detection and removal of such aggressive lesions of jaws can prevent major defects of the jaws which reduces functional as well as aesthetic quality of life.
- Aggressive Ameloblastomas need to be resected completely along with positive margins to prevent recurrence rate and second Surgeries.
- Radiographic and histopathological correlation is very important in such lesions. Long standing aggressive Ameloblastomas needs radiological and histopathological rule-out for further spread.
- Reconstruction of such lesion defects are important and necessary but patients decisions and affordability status needs to be respected too.

Case Report

A 25-year-old female patient presented with a history of a painless left mandibular swelling since a year which was progressively increasing in size. The swelling was associated with parasthesia of her left side of face mainly over the jaw and she also had difficulty in chewing due to the mass over the left mandible. There was a large firm swelling over the left mandibular region which was non tender extending from left ramus region extending the midline till lateral incisor of right lower quadrant. The Temporomandibular Joint (TMJ) movement was normal on both sides. The mouth opening was normal. The occlusion on left quadrant was completely deranged due to lesion expansion. Overlying skin was stretched and intact. The colour of overlying skin was normal.

The CT-SCAN of the lesion revealed a huge lytic lesion involving the mandible, the largest of its bulk was present around the left mandibular body and ramus. It crossed right mandible side and reached till the parasymphysis region. The lesion measured 116 x 109 x 134 mm (AP x TR x CC). Expanded mandibular cortex was partly thickened and partly invisible. This lesion had internal multilocular cystic and solid enhancing components. Multiple internal calcifications were seen within the lesion. A few of the involved teeth had resorption of their roots. Muscles at the floor of mouth were displaced with loss of fat planes where infiltration cannot be entirely ruled out.

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Posteriorly, it compressed left parotid, sub-mandibular glands & SCM muscle with resultant compression of left IJV. No evident infiltration. Mandibular condyle was not involved by the lesion.

Routine blood investigations were done and Fine Needle Aspiration Cytology (FNAC) incisional biopsy of the lesion was taken. FNAC from the swelling yielded a hemorrhagic, cystic fluid consisting of inflammatory cells, occasional epithelial cells, scattered RBCs and cholesterol crystals in a fibrinous background. The patient was provisionally diagnosed with multicystic Ameloblastoma. The surgery was planned under general anesthesia. Extended transcervical incision was made over the lesion and the tumour mass was exposed. The tumour was removed in toto keeping the safe margins of 1.5cm from the healthy bone. Hemimandibulectomy was done from lower right canine region distally and subcondyle region on the left side proximally. The condyle was preserved. Primary closure was done of the defect after achieving proper hemostasis. The patient was examined postoperative after 10-15 days. The healing is satisfactory without and relevant complications. Suture removal was done. The histopathology report of the lesion confirmed the lesion to be multicystic Ameloblastoma. The histological subtypes of such aggressive Ameloblastoma consisted of combination of follicular type and plexiform type of Ameloblastoma. The cells consisted of columnar or palisaded ameloblasts-like cells and triangular shaped cells seen in the inner zone similar to stellate reticulum. Also, the cells showed epithelium proliferating in a 'cord like fashion'; hence the histological type of ameloblastoma consisted of both follicular as well as plexiform type (Figs 1-7).

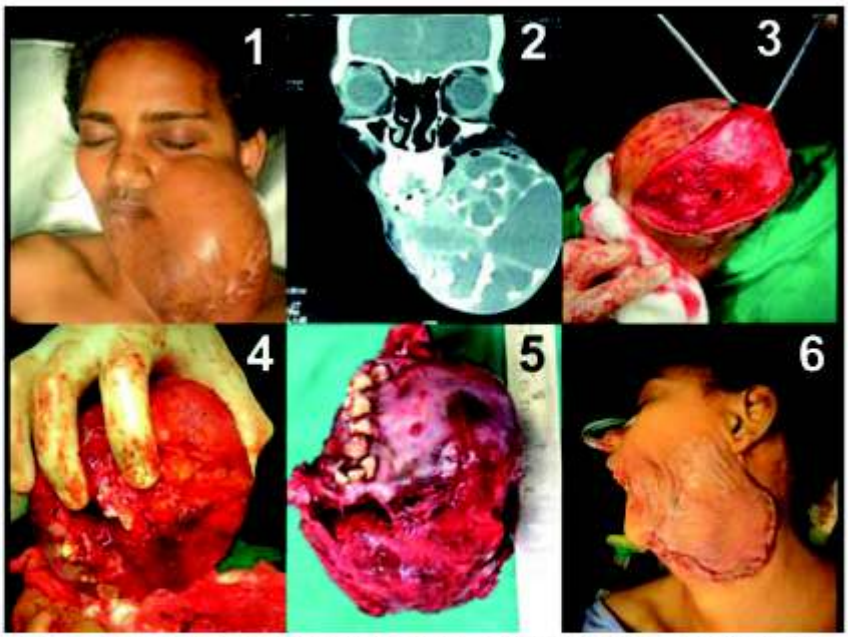

Fig 1 — Pre-operative view of the lesion; Fig 2 — Radiographic view of the lesion (CT-SCAN); Fig 3 — Cervical incision given for lesion exposure; Fig 4 — Lesion exposure and removal in toto; Fig 5 — Lesion removed completely; Fig 6 — Sutures taken after removal done

Discussion

Ameloblastoma are aggressive benign tumours originated from epithelium that may arise from the enamel organ, remnants of Odontogenic Keratocyst (OKC), dental lamina, dentigerous cyst or from the basal epithelial cells of the oral mucosa. It increases to great size and cause facial asymmetry, malocclusion, teeth displacement, loosening of teeth and pathologic fractures. Tumor size may range from 1 to 16 cm at presentation which result from bone expansion and soft tissue invasion. The clinical behaviour of the lesion is somewhere between benign and malignant lesion. The classification of the Ameloblastoma in the past was poorly deûned; the current concept is to classify the Ameloblastoma as solid/multicystic, classical

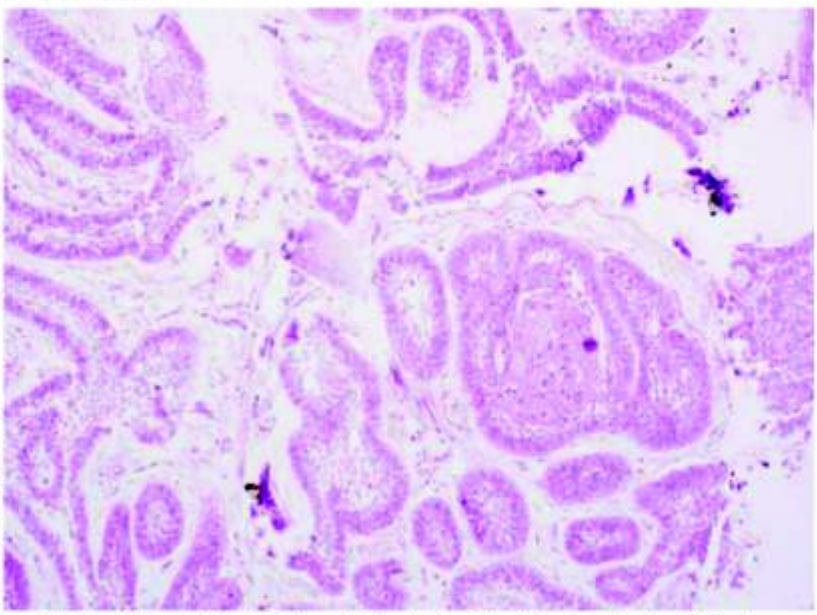

Fig 7 — Histopathological Report of the Lesion Confirming It to be Ameloblastoma (H&E, 10x)

intraosseous, peripheral or unicystic subtypes. This classification has direct bearing on the pathological behaviour of these variants. Solid or multicystic variants are aggressive locally and recur if they are not excised in toto. Unicystic Ameloblastoma was identified as distinct entity with less aggressive behaviour[4]. Treatment of ameloblastoma is primarily surgical. The conservative modalities include enucleation, cryosurgery and curettage and the radical modalities are marginal, segmental, and Hemiman-dibulectomy. The conservative modalities may be less aggressive but the recurrence rate up to 55–90% have been reported in the literature post it. Reconstruction of large mandibular defects as due to Giant Ameloblastomas poses a challenge. For mandibular and oral reconstruction, donor sites mainly include radial forearm, fibula, iliac crest and scapula. These sites are the primary sources of new vascularized bone and soft tissue. Among all these, fibula has many advantages including transfer of bone, soft tissue and skin[5].

Conclusion

Hence, the present case report gives a broad overview about a Giant Ameloblastoma of left side mandible which was resected completely. We recommend the radical approach for resection of these benign but such giant and locally aggressive tumours, resection with safe margin of at least 1.5-2 cm of healthy bone. Removal of lesion was done in toto with adequate safety margin and primary closure was done with fairly satisfactory cosmetic and functional results. Functional and esthetic results are better with free flaps, best among them being free fibula flap.

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Case Report

Perimortem Caesarean Section : A Guideline-based Management of Maternal Cardiac Arrest

Beenu Kushwah[1], Saurabh Patel[2], Mahendra Singh[3]

Maternal Cardiac Arrest is a rare event and Perimortem Caesarean Section (PMCS) has an established role in concurrence with maternal resuscitation to save the life of a dying mother as per various International Guidelines. Despite being a lifesaving procedure, this procedure has not yet gained acceptance amongst Obstetrician. Present case is first reported case of PMCS of this country where an out of Operation Theatre Perimortem Caesarean Section was performed with a positive maternal and foetal outcome.

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Key words **: Perimortem Caesarean Section, Maternal Cardiac Arrest.**

Cardiac arrest in pregnancy is a rare event with an incidence of around 1 in 36,000 pregnancies[1]. Perimortem Caesarean Section (PMCS) or Resuscitation Hysterotomy has been endorsed by various International Groups and should be performed as early as possible as it has maternal survival rate up to 40% and fetal survival rate up to 60-70%, if performed within 5 minutes of Cardiac arrest[2]. Rationale for this time limit is that a pregnant lady develops hypoxic injury more quickly because of certain physiological changes in pregnancy. Traditionally it has been said that maternal survival is best if Perimortem Caesarean Section is initiated as early as 4-minutes past Cardiac arrest called as "4 minutes rule", however, both maternal and neonatal survival have been reported even if it is performed at 10-15 minutes past arrest.[3]

Editor's Comment :

- All current guidelines for management of cardiac arrest in pregnancy agree on role of delivering the baby at earliest if there is no response to correctly performed CPR and proper manual displacement of uterus.
- Every Obstetrician should know the importance of Perimortem Caesarean Section to assist maternal resuscitation for pregnancies above 24 weeks.

Case Report

We report a case of 32-year-old second Gravida with 37 weeks period of Gestation. She was a known case of Hypertension at first visit during late first trimester and was started on tablet Labetalol 100mg twice a day for the same since 6 months before the pregnancy by a Physician as she was planning pregnancy, on which her Blood Pressure was well controlled. Her first trimester Echocardiography was normal with an ejection fraction of more than 60%. Her BP records remained normal on tablet Labetalol 100mg twice a day, throughout the course of antenatal visits. Because of COVID she could not come for Antenatal visit during second trimester and was advised to get a repeat Echocardiography at 34 weeks which she did not get done. She reported at 37 weeks of pregnancy for routine antenatal checkup but was admitted for a detailed workup in view of her chronic hypertensive status, her BP on admission was 130/80 mm Hg and urine albumin was 1+ by Urostix Test. Her Liver Function Test (LFT) and Renal Function Test (RFT) reports were normal. Her NST was also normal. Next day she started having mild uterine contractions and sudden onset of breathlessness with a surge in BP to 160/104 mmHg. On Examination her both side of chest was full of crepts and a bed side ECG showed features of Cardiac failure. She was immediately given a loading dose of intravenous Lasix and was attended by an Anaesthetist, who Intubated her as she was not maintaining O_2 saturation even on high flow of Oxygen by mask. She was then shifted to ICU where her BP started to fall abruptly and she went into Cardiac arrest. CPR was started with a simultaneous manual displacement of uterus. As CPR did not prove out to be beneficial to her, a decision was taken to perform a Perimortem Caesarean Section on ICU bed itself with a sterile scalpel, baby could be taken out within 5 minutes of initiation of Cardiopulmonary Resuscitation (CPR) and was handed over to paediatrician with a palpable heartbeat. There was a sudden improvement in maternal condition after the baby was taken out. She responded well to resuscitative measures and started maintaining her BP on Ionotropic drugs. After 48 hours she could be extubated and was shifted to General Care Ward after 72

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hours of PMCS. Her post Caesarean Echocardiography was done on next day which showed features of dilated Cardiomyopathy with ejection fraction of <15% for which she was managed by Cardiologist. On day 11 she was discharged from hospital in a good condition. On the other side baby remained intubated for 5 days followed by a further NICU stay of around 15 days. Both mother and baby were doing well past one month of PMCS.

Discussion

Role of Perimortem Caesarean Section after a failed CPR, has been established since 1980's.[4] An enlarged gravid Uterus beyond 24 weeks of pregnancy results in considerably reduced venous return due to aorta canal compression further compromising a failing Heart, in addition to it enlarged gravid Uterus interferes in performing efficient Chest compressions. PMCS helps in relieving both of these factors, considering it,all current guidelines recommend performing PMCS at the earliest to empty the Uterus[2].

PMCS should be performed at the site of event without spending time to shift the patient to Operation Theatre.[5] The only essential instrument which is required to performed this procedure is a scalpel. The choice of incision depends on Surgeon's preference. As the role of PMCS has been found to be very beneficial for maternal survival it is prudent only to carry out more and more drills and training courses to orient clinicians regarding this life saving procedure. To our best knowledge this is probably the first case in India where an out of Operation Theatre PMCS was performed with a positive maternal-fetal outcome. To conclude it is the quick decision making and immediate support from multidisciplinary team which can be a game changer while managing a case of an unexpected Maternal Cardiac Arrest.

Acknowledgement : Our special thanks to Dr Alok Singh (Senior Anaesthetist) and Dr K D Singh (Senior Cardiologist) for their constant support during the management of this case.

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Voice of Expert

Pandemics — The Current and the Future

Santanu Kumar Tripathi[1]

Dr Shambo Samrat Samajdar, MD, DM, conducted an online interview on behalf of the JIMA regarding the current and future Pandemics Scenario

Q 1 : After the nightmarish experience of two years of the COVID-19 pandemic, we in India are desperately trying to regain normalcy in public and professional life. But the Government of India has not yet officially called an end to the pandemic. On an average, more than 3 lakhs of RT-PCR tests for diagnosis of Covid-19 per day being done with a positivity rate of less than 0.1 per cent. When will this pandemic be really 'over'?

Ans : Let me start with quoting Michael Osterholm, the noted environment health expert and an infectious disease epidemiologist at the University of Minnesota, *"We are in totally uncharted territory from the perspective of understanding what a pandemic is, how it starts, how it unfolds, and how it ends."*

The onset or the end of a pandemic is not limited to geographic confinement of any given country. It is global. Truly, it is not easy to say when would the COVID-19 pandemic end. The pandemic was declared a public health emergency of international concern (PHEIC) by the World Health Organization (WHO) on 30th January 2020, and ever since the WHO has been continuously assessing the status of the pandemic. The WHO Expert Committee is actively considering when it's end can be officially declared. The 196 WHO member countries including India are bound by international health regulations to follow WHO recommendations in this regard. While the UK, Denmark, the Netherlands have functionally declared an end to the pandemic in their countries, other nations like New Zealand and Hong Kong are struggling with record-breaking surges. The real end of the pandemic would perhaps come only with the arrival of a 'final variant' of the SARS-Cov-2 virus that is too weak in terms of virulence and transmissibility. *"If I was a betting man, I would say probably in about 2, 3 years we will get to that point."* says Salim Abdool Karim, an epidemiologist and the chief COVID-19 scientist of South African government.

Q 2 : Do you think the COVID-19 pandemic could have been better controlled? Was the disastrous outcome entirely due to the virulent virus or could it considerably also be attributed to the social, political and public health system under-preparedness?

Professor Santanu K Tripathi

Ans : The risk of a pandemic has much to do with factors beyond just a biological model of an optimally virulent and transmissible pathogenic microbe. Despite being warned by a series of zoonotic disease outbreaks with SARS, Nipah, MERS, H7N7, Ebola, H1N1 viruses, having occurred in different parts of the world over *the past two decades*, we failed to prepare ourselves adequately for and appropriately respond to the COVID-19 pandemic. And it seemed as if the pandemic almost caught us totally unaware. On a positive note it may be said that the COVID-19 vaccines could be developed at an unprecedented speed. And the fast-track development was possible because of the readiness with different viral vaccine platforms. But when we consider the distribution of and access to the vaccines, it was far from equitable. It's all about awareness and preparedness. Preparedness for controlling the consequences of a pandemic is certainly important. But even more important is the need to tackle the cause of a pandemic. The under-preparedness in terms of social, political and public health system was grossly evident across borders of different countries.

Q 3 : SARS, Ebola, Zika, and now COVID-19 – why are disease epidemics and even pandemics becoming increasingly common day by day?

Ans : *"The number of new infectious diseases with epidemic potential has increased nearly four-fold over the past six decades. Since 1980, the number of new outbreaks per year has more than tripled."* says Alimuddin Zumla of University College London, London, UK. There are a number of factors responsible for this. The most striking of them are : (1) widespread deforestation and urbanization disturbing the biogeographical ecology and dynamics of infections, (2) increasing wild life trade and animal-human contact with compounded probability of spillover of pathogens from animals to humans, (3) climate change and frequent climate shock events leading to human

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displacement, migration and vulnerability to infections, (4) transnational spread of infections through more and more frequent air travels, and (5) disproportionately low emphasis on public health measures in preventing and controlling infectious disease outbreaks.

Q 4 : What strategies can be adopted to minimize spillover risks?

Ans : The strategies for minimizing spillover risks are multi-pronged. These include: (1) Remove all subsidies favoring deforestation and levy taxes to all projects that involve deforestation. (2) Strengthen wildlife management and regulate wildlife trade, and ban the trade of high-risk species like primates, bats, pangolins, civets, and rodents. (3) Increase public awareness on animal handling and risk of disease transmission. (4) Ensure cross-sectoral collaborations for zoonotic disease prevention and control. (5) Ensure early detection and control measures, including creating a library of virus genetics to pinpoint the source of a newly emerging pathogen early enough to slow or stop its spread. (6) Spend to reduce viral spillovers, or inter-species transmissions, in livestock.

Q 5 : What is the rationale for the One Health (OH) Approach in strategizing prevention and control of future pandemics?

Ans : We need to appreciate that we are in an era of pandemics and the Covid-19 pandemic is certainly not the last of it's kind. The next one may be more devastating. We need to understand the zoonotic link in infectious disease outbreaks of epidemic/pandemic proportions. With deforestation, wildlife trade, global travel etc. and consequent increasing probability of animal-human conflicts and contacts, there are escalating zoonotic risks through spillover and human transmission. We cannot afford to consider human health *in silo* any longer. It's time we unite human health, animal health and environmental health. And this OH Approach is the key to prevention and control of pandemics. We must primarily engage in identifying animal pathogens with potential for human pathogenicity, in understanding factors promoting their spillover to humans, and in continuous surveillance, risk forecasting and management. We need to also meaningfully operationalise the OH strategies through effective inter-sectoral convergence and coordination. The social, political and cultural considerations are to be integrated adequately in a balanced manner in our drive towards prediction and prevention of future pandemics. Trans-national collaboration is also extremely important.

Q 6 : Would you briefly explain WHO's Disease X concept for prevention and control of future pandemics?

Ans : Disease X is a placeholder name adopted by the WHO in 2018 to represent *a hypothetical, unknown pathogen* that could cause a future epidemic. This is to ensure that their planning is flexible enough to adapt to any future unknown pathogen with epidemic/pandemic potential and to engage in pre-emptive and broad measures like fast-track development of vaccines and other suitable medical countermeasures. This is also to encourage WHO projects to focus their research efforts on entire classes of viruses (e.g., flaviviruses), instead of just individual strains (e.g., zika virus), thus improving WHO capability to respond to unforeseen strains.

Q 6 : What you suggested would likely incur huge financial investment. How would that be possible for most low and middle income countries (LMICs) like India?

Ans : *"An ounce of prevention is worth a pound of cure."* Said Benjamin Franklin. The costs of preventing future zoonotic outbreaks like COVID-19, by preventing deforestation and regulating the wildlife trade, are as little as 2% of the economic and mortality costs of responding to the COVID-19 pandemic, which according to some estimates could reach even $20 trillion. Stimulus funding should be used to reduce the risk of disease spillover from animals to humans. In March 2020 as the Covid-19 pandemic was just starting to unfold, a proposal for a Fund for Global Health Security and Pandemic Preparedness was built on a call from global health policy experts. Such a Fund is meant for catalyzing sustainable financing to bridge the country-identified gaps in health security capacity. The idea was soon championed by other international agencies. The G20 leaders reached a consensus in early 2022 to establish a new Financial Intermediary Fund (FIF) at the World Bank for this purpose. Now the WHO and its member nations are to design the financing priorities, investment modalities, monitoring and evaluation, governance, and accountability structures for the FIF. It's time that the LMICs including India appropriately plan the program for OH operationalisation through context-specific understanding of the dynamics of cross-sectoral collaboration. Awareness and sensitization of all stakeholders are essential for optimum implementation of the OH approach.

To predict and prevent pandemics, go beyond 'in silo' – it's one earth and one health – break the borders – converge, coordinate and collaborate.

Prof. Santanu K. Tripathi,
Thank you for the valuable insight into 'Pandemics
— The Current and the Future'.

Drug Corner

Clinical Efficacy of Pancreatin Minimicrospheres Supplementation in Patients with Exocrine Pancreatic Insufficiency (EPI) : Real-world Evidence

Anish Desai[1], Sunaina Anand[2]

Background : Exocrine pancreatic insufficiency (EPI), characterized by reduced secretion or activity of pancreatic enzymes, causes improper absorption of food, excessive fat excretion in the stool, and malnourishment.

Methods : In this observational, real-world evidence study, patients with one or more of the following condition were enrolled: abdominal pain, acidity, diarrhea, nausea, or dyspepsia (as per ROME III criteria). Patients had either been diagnosed with gallstones, hypertriglyceridemia, alcohol consumption or undergone abdominal surgery. Patients were prescribed capsule Enzigest™10000 (pancreatin minimicrospheres) for one month.The severity and frequency of various gastric symptoms was measured at day 0 and day 30.

Results : 540 patients were enrolled with a mean age of 51.6 years. Enzigest significantly reduced the severity of functional dyspepsia by 88.67% ($p<0.001$) as per Rome III Criteria. There is significant improvement in frequency of symptoms (83.80%), abdominal pain severity (81.58%), epigastric pain (83.09%), nausea (84.35%) and vomiting by 89.62% (all $P<0.001$). The overall improvement in symptoms was significant ($p<0.001$). Enzigest was well tolerated.

Conclusion : Enzigest improved abdominal pain, dyspepsia, and acidity in patients with exocrine pancreatic insufficiency due to alcohol consumption, gallstones, hypertriglyceridemia, diuretic (Furosemide or Thiazide) or abdominal surgery. Enzigest containing pancreatin minimicrospheres can be an easy therapeutic option to counteract EPI.

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***Key words* : Abdominal Pain, Dietary Supplement, Dyspepsia, Exocrine Pancreatic Insufficiency (EPI), Pancreatin Minimicrospheres.**

Exocrine Pancreatic Insufficiency (EPI), characterized by reduced secretion or activity of pancreatic enzymes, occurs due to parenchymal dysfunction or ductal obstruction. Pre-existing pancreatic diseases lead to the maldigestion of food and subsequently malabsorption of nutrients[1]. EPI causes improper absorption of food, excessive fat excretion in the stool, and malnourishment[2]. When there is pancreatic enzyme insufficiency, fat is not digested, and it remains in the bloodstream, causing hypertriglyceridemia leading to major cardiovascular disorders[3].

Hypertriglyceridemia is one of the major causes of acute pancreatitis (AP), accounting for 10% of all cases. The precise mechanism by which hypertriglyceridemia causes AP [termed hypertriglyceridemic pancreatitis (HTGP)] is not fully understood. Hypertriglyceridemia [by causing an excess of free fatty acids (FFAs)] and elevated chylomicrons increase plasma viscosity, which may induce ischemia in pancreatic tissue and trigger organ inflammation.

Editor's Comment :

- Exocrine Pancreatic Insufficiency (EPI) is characterized by reduced synthesis or secretion of pancreatic enzymes and bicarbonate.
- Maldigestion of food and subsequent malabsorption of nutrients causes symptoms in patients with EPI.
- Enzigest™ improves abdominal pain, dyspepsia, and acidity in patients with exocrine pancreatic insufficiency due to alcohol consumption, gallstones, hypertriglyceridemia, diuretic (Furosemide or Thiazide) or abdominal surgery.
- Enzigest ™ supplementation can be an easy therapeutic option to counteract EPI.

Chronic Pancreatitis (CP) is the most common pancreatic disease associated with EPI. Clinically significant EPI in CP requires a reduction of almost 90% of pancreatic enzymes and is reported in 60%–90% of CP patients within 10-12 years from diagnosis[4]. The rate of EPI in those with early or idiopathic CP, who are most evaluated at a primary care level, has been reported to be 18.7%[5].

Certain drugs (thiazide diuretics, non-selective beta-blockers, estrogens, tamoxifen, bile-acids resins,

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corticosteroids, protease inhibitors, cyclosporine, retinoids, anti-epileptics and antipsychotics) cause secondary hypertriglyceridemia and acute pancreatitis[6,7].

There are multiple reported cases of Furosemide related pancratitis. Diuretics like Furosemide might impair pancreatic perfusion by diuresis and intravascular volume depletion. The exact mechanism is still unclear, and there are multiple hypotheses including pancreatic exocrine stimulation by furosemide, or hypersensitivity from an immunologic response against a drug-protein[8].

In India, Alcoholic Chronic Pancreatitis (ACP) is the second most common etiology of Chronic Pancreatitis (CP) after Idiopathic Chronic Pancreatitis (ICP)[9,10]. The prevalence of CP is very high in SouthIndia (114-200/1,00,000 population)[11]. The relationship between chronic alcohol consumption and the development of CP is well known. Among patients with alcoholic pancreatitis, the mean duration of alcohol intake is 18±11 years for men and 11±8 years for women[12].

Gastrointestinal (GI) surgery causes structural changes in the GI tract resulting in asynchrony between the release of enzymes and passage of nutrients. Changes in pancreatic enzyme secretion result in the malabsorption of nutrients, fats, and fat-soluble vitamins, leading to primary symptoms[13,14]. About 25% of patients after the Whipple procedure have long-term malabsorption and need supplemental enzymes for life. Other patients may need enzymes for a few months or years after surgery[15]. Some conditions that may cause pancreatic insufficiency include gall stones, blockage or narrowing of the pancreatic or biliary duct (the tubes that carry pancreatic juice or bile), pancreatic or duodenal tumors, cystic fibrosis, or pancreatitis. In India, the prevalence of Gallstone Disease (GSD) is 6.12%, corresponding to a significant burden on the healthcare system and one of the most common reasons for patients with abdominal pain[16]. Patients with biliary pancreatitis have pancreatic enzyme insufficiency[17].

Evidence suggests that Pancreatic Enzyme Replacement Therapy (PERT) improves fat absorption and clinical symptoms, especially pain. The ease of administration and lack of any significant side effects makes PERT the first choice in the medical treatment of pain. Literature suggests that these preparations should contain large amounts of proteases, amylase, and lipases, given four times a day[12].

Materials and Methods

(1) Setting and participants :

This was an observational, real-world evidence study in which treated patients were followed up for a month.Patients were recruited from 40 separate outpatient clinics. Eligible patients were aged more than 18 years, with one or more of the following conditions: abdominal pain, acidity, diarrhea, nausea, or dyspepsia (as per ROME III criteria). Patients had either been diagnosed with gallstones, hypertriglyceridemia, alcohol consumption, diuretic (Furosemide or Thiazide) or undergone abdominal surgery. Exclusion criteria included patients with a history of substance abuse, pregnancy or lactation, any severe disease, or seen unfit for the study. All participants gave written informed consent before the screening.

(2) Study product :

Patients were prescribed Enzigest™10000 (manufactured by Wallace Pharmaceuticals Pvt Ltd), to be taken before every meal for one month. Patients were advised not to take other Ayurvedic/herbal/ homeopathic dietary supplements or any alternative therapies during the treatment period. A record of these medications was maintained.

(3) Outcomes and follow-up :

The primary outcome measures included evaluation of symptoms at baseline and after 30 days of treatment. Health-related quality of life (HRQOL) was a secondary outcome measure assessed at the beginning and end of the treatment.

(4) Statistical analysis :

(a) Sample size consideration —

This was the first clinical evidence generation program to evaluate the effectiveness and tolerability of Enzigest™inexocrine Pancreatic Insufficiency (EPI) with no previous data available. A sample size of about 500 participants from 40 centers was considered adequate to address the evaluation objectives.

(b) Effectiveness and tolerability analysis —

Wilcoxon signed Rank Test was used to test the efficacy of parameters. Demographic data were analyzed using descriptive statistics. All tests were carried out at 5% significance.

Results

540 patients were consecutively included in the study. Patient characteristics are summarized in Table 1. The mean age of the patients was 51.6 years.

Enzigest significantly reduced the severity of

functional dyspepsia by 88.67% (p<0.001) as per Rome III Criteria (Fig 1).

There is significant improvement in frequency of symptoms (83.80%), abdominal pain severity (81.58%), epigastric pain (83.09%), nausea (84.35%), and vomiting by 89.62% (all P<0.001) as shown in Fig 2. The effectiveness data of Enzigest is shown in Table 2. Improvement in sickness (86.41%), loss of appetite (80.57), and retrosternal discomfort (85.38%) were observed after treatment with Enzigest. The reduction in diarrhea, bowel movement per day, and pain/cramping in the abdomen with bowel movement after treatment were 94.28%, 31.57%, and 78.33%, respectively (all p<0.001) as shown in Fig 3. The overall improvement in symptoms was significant (p<0.001) (Fig 4). No major adverse events were observed in the follow-up period in the study population.

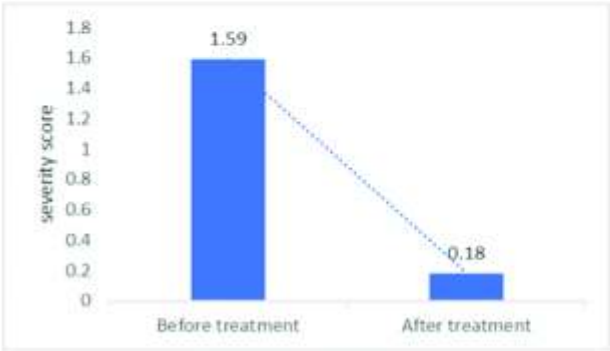

Fig 1 — Severity of functional dyspepsia

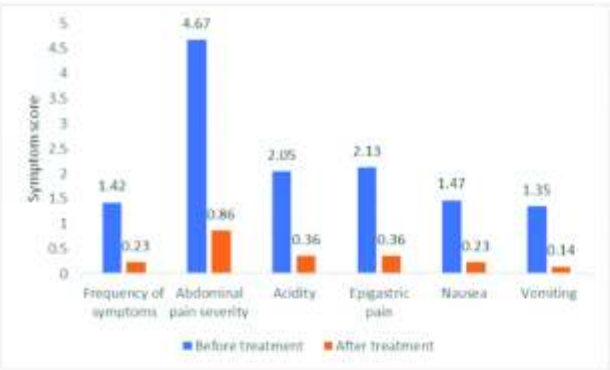

Fig 2 — Symptomatic improvement

Table 1 — *Baseline demographic details*

Parameter	n (%)
Sex :	
Male	369 (68.33%)
Female	170 (31.48%)
Gall stones	210 (38.89%)
Alcohol consumption	212 (39.26%)
Abdominal pain	474 (87.78%)
Acidity	451 (83.52%)
Diarrhea	119 (22.04%)
Nausea	358 (66.30%)
Dyspepsia-as per Rome III Criteria	271 (50.19%)

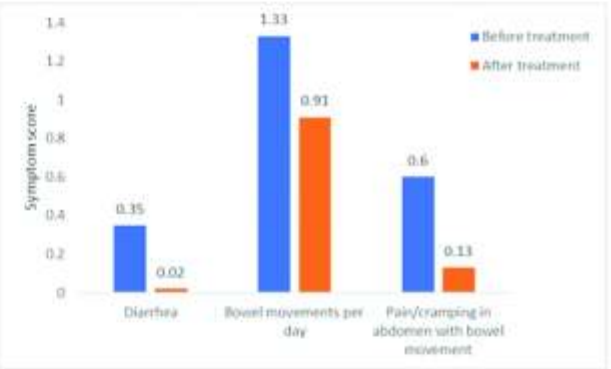

Fig 3 — Reduction in diarrhea

Table 2 — *Change in outcome measures*

Parameter	Before treatment (mean ± SD)	After treatment (mean ± SD)	% change	p value
Severity of functional dyspepsia	1.59±0.72	0.18±0.40	88.67%	<0.001
Frequency of symptoms	1.42±0.87	0.23±0.79	83.80%	<0.001
Abdominal pain severity	4.67±2.36	0.86±1.06	81.58%	<0.001
Overall assessment	0.79±0.71	1.86±1.01	135.44%	<0.001
Epigastric pain	2.13±1.05	0.36±0.57	83.09%	<0.001
Early satiety	1.53±1.09	0.31±0.48	79.73 %	<0.001
Nausea	1.47±0.97	0.23±0.46	84.35%	<0.001
Vomiting	1.35±1.01	0.14±0.37	89.62%	<0.001
Acidity	2.05±1.16	0.36±0.56	82.43%	<0.001
Sickness	1.62±1.08	0.22±0.50	86.41%	<0.001
Loss of appetite	1.75±1.22	0.34±0.61	80.57%	<0.001
Retrosternal discomfort	1.71±1.22	0.25±0.48	85.38%	<0.001
Diarrhea	0.35±0.55	0.02±0.14	94.28%	<0.001
Bowel movements per day	1.33±1.19	0.91±0.60	31.57%	<0.001
Pain/cramping in the abdomen with bowel movement	0.60±0.53	0.13±0.44	78.33%	<0.001

Discussion

To the best of our knowledge, no other study has evaluated the effect of pancreatic enzyme supplementation in a real-world setting. The current study showed that Enzigest, a pancreatic enzyme supplement, is effective in abdominal pain, dyspepsia, and acidity in patients with EPI due to various clinical conditions. Furthermore, it has excellent tolerability, as suggested by the lack of adverse events in the study population.

The management of CP involves managing pain and steatorrhea[8]. Clinical studies support the efficacy and safety of different pancreatic enzyme formulations, including enteric-coated minimicrospheres

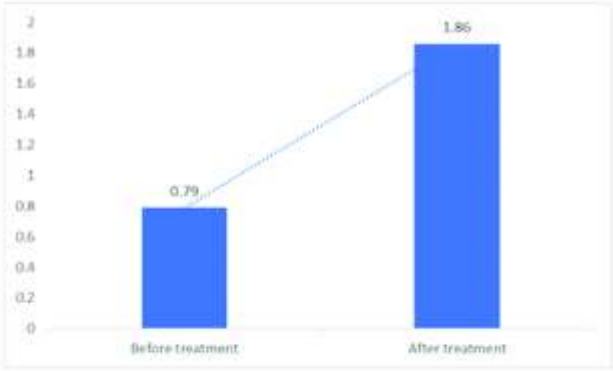

Fig 4 — Overall assessment

(MMS) containing protease, amylase & lipase[18-20]. Literature suggests that most CP patients can be managed with pancreatic enzyme supplementation[21]. According to a survey conducted in the Asia-Pacific region, most experts used pancreatic enzyme supplementation in clinical practice along with analgesics for pain relief[11]. Pancreatic enzymes enteric-coated MMS for one year significantly improved fat absorption, nitrogen absorption, and nutritional parameters, improvements in clinical symptoms, and favorable safety and tolerability profile in patients with PEI due to CP[22].

In our study Enzigest significantly reduced the severity of functional dyspepsia (88.51%), frequency of symptoms (84.01%), abdominal pain severity (81.6%), epigastric pain (83.3%), nausea (84.66%), and vomiting (89.47%). In few randomized, double-blind, placebo-controlled studies, PERT supplementation significantly increased fat absorption up to 88.6% and protein absorption up to 87.2% ($P<0.001$)[23].

PERT is the standard of care for PEI, whatever its etiology, and effectively improves maldigestion and the clinical symptoms associated with PEI. Pancreatic enzyme preparations are a life-saving substitution for a pivotal physiological function of the entire organism with exocrine pancreatic insufficiency. Pancreatic enzyme preparations, generically called pancreatin, are not alike. Instead, they present a wide variety of pancreatin compositions[24].

Lipase supplementation improves fat digestion and absorption, resulting in lesser steatorrhea and clinical improvement[25]. The proteases in the pancreatic enzyme supplement are hypothesized to inhibit overstimulation of duodenal Cholecystokinin (CCK) receptors, thereby reducing pain.

In this study, the effectiveness data of Enzigest demonstrated improvement in sickness, loss of appetite, and retrosternal discomfort. A meta-analysis concluded that PERT significantly increased the Coefficient of Fat Absorption (CFA) ($p<0.001$). Furthermore, the subgroup analysis indicated that standard forms of PERT displayed higher effectiveness. PERT is effective and tolerable in patients with EPI, especially using standard administration of PERT[2]. Although lower in incidence, chronic pancreatitis significantly reduces patients' quality of life. Alcohol consumption has increased in India due to rapid urbanization and increased affluence. This increase would increase the burden of alcohol-related pancreatitis and associated enzyme insufficiency in India[26].

CP ultimately leads to exocrine pancreatic insufficiency and progressive endocrine failure resulting in diabetes. The spectrum of chronic pancreatitis in India is changing, with increased occurrence in older patients, the incidence of milder diseases, including milder diabetes, increasing longevity, and increasing association with alcoholism and smoking[27].

The improvement in abdominal pain observed in this study most likely reflects an improvement in pain associated with PEI-related maldigestion rather than the characteristic severe abdominal pain often experienced by patients with CP. Pancreatic enzymes allow patients with pancreatic insufficiency to eat a regular diet and prevent the deleterious effects of continued nutrient malabsorption and malnutrition. Moreover, PERT could prevent the long-term complications of malabsorption such as cerebellar ataxia, increased prothrombin time and osteoporosis, and increased morbidity and mortality related to malnutrition[2].

After curing acute pancreatitis, management of exocrine insufficiency is a significant clinical challenge. Evidence suggests that oral pancreatic enzyme supplementation has a positive effect on managing AP and the global health status (less weight loss, less flatulence, improved quality of life). A double-blind, placebo-controlled, randomized study showed that oral pancreatic enzyme supplementation could be added to the treatment regimen of patients in a refeeding status after severe acute pancreatitis. Among 56 patients, 20 showed low faecal elastase values indicating pancreatic exocrine insufficiency after acute pancreatitis. The median time to recovery from exocrine pancreatic insufficiency was 14 days in the enzyme supplementation group and 23 days in the placebo group. Overall, the patients receiving enzyme supplementation had a better quality of life[28]. Enzyme supplementation positively affects the course of acute

pancreatitis if administered during the early refeeding phase after acute pancreatitis.

Many patients with pancreatic disease undergo cholecystectomy as part of the management of gallstone disease, which is associated with a risk of Bile Acid Malabsorption (BAM). Pancreatic enzyme supplementation could also help manage BAM, commonly called bile acid diarrhea[29]. Some patients develop transient pancreatic insufficiency following an episode of severe AP, and some authors recommend using PERT during the recovery phase[30]. In one retrospective study, 45% of patients with hypertriglyceridemia and pancreatitis had received oral pancreatic enzyme replacement therapy[31].

In our study, 38.89% of patients were diagnosed with cholelithiasis. Similarly, in Yan *et al*, 25% of patients with cholelithiasis had impaired pancreatic exocrine function[32]. Another study on gallstone patients found a high prevalence of pathological changes in exocrine pancreatic function based on faecal elastase-1 concentrations. Literature suggests that gallstones might cause chronic pancreatitis, as they cause acute pancreatitis[33]. Pancreatic enzyme supplementation should be prescribed for patients with symptoms of pancreatic exocrine insufficiency[34].

The treatment of EPI focuses on the management of symptoms. Patients are advised to follow a healthy low-fat diet, Pancreatic Enzyme Replacement Therapy (PERT), and vitamin and mineral supplementation[35]. The enzymes from the enteric-coated preparations are generally released more distally in the jejunum and ileum. Thus, enteric-coated enzyme preparations don't require co-prescription of a proton pump inhibitor or H2 receptor blocker, unlike non-enteric preparations[36].

This study has some limitations. Firstly, since this was an open-label, real-world evidence generation program, lacking a control group. It may be helpful to design a study that will take biochemical parameters and objective assessments into consideration. Further studies are encouraged to gather data from a larger sample size.

Conclusion

The novelty of this study is the demonstration that pancreatic enzyme supplementation improves abdominal pain, dyspepsia, and acidity in patients with exocrine pancreatic insufficiency due to alcohol consumption, gallstones, hypertriglyceridemia, diuretic (Furosemide or Thiazide) or abdominal surgery. The results obtained from this study show that supplementation with Enzigest can be an easy therapeutic option to counteract EPI.

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Image in Medicine

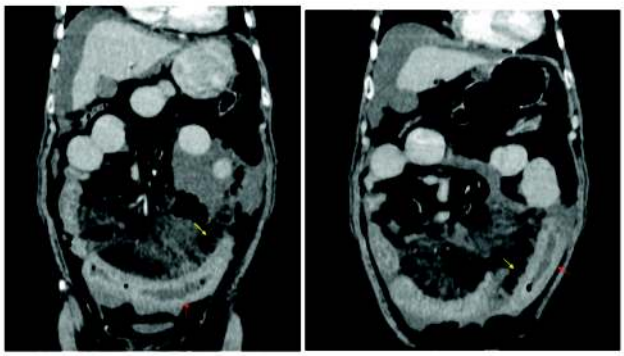
Bhoomi Angirish[1], Bhavin Jankharia[2]

Quiz 1

A 22-year-old male presented with severe abdominal pain and discomfort.

Questions :

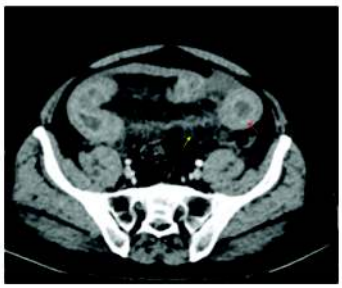
(1) What is the diagnosis ?
(2) What are the imaging findings?
(3) What are the extra-intestinal manifestations?



Answers :

(1) Long segment of symmetrical transmural ileal loop thickening (red arrow) is seen with prominence of mesenteric vasculature (yellow arrow). These imaging findings are suggestive of Crohn's disease. Crohn's disease is an idiopathic inflammatory bowel disease characterized by discontinuous gastrointestinal tract inflammation. The terminal ileum and proximal colon are most often affected.

(2) Bowel wall thickening with mural hyperenhancement and submucosal fat deposition is seen. There is engorement of the vasa recta (comb sign). Complications include stricture , fistulae and mesenteric / intra-abdominal abscess.



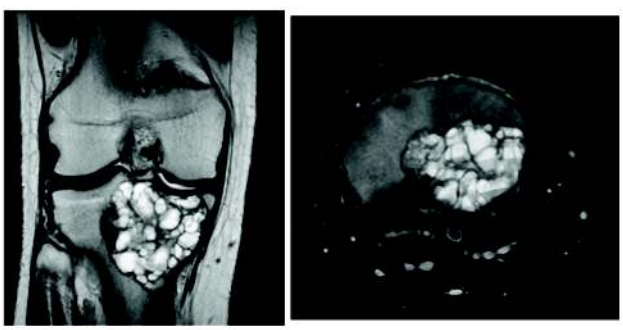
(3) There are many extra-intestinal manifestations. The commonly seen include- seronegative Spondyloarthritis, Sarcoiliitis, Primary Sclerosing Cholangitis, Autoimmune Hepatitis, Cirrhosis, Iritis, Uveitis.

Quiz 2

A 34-year-old male presented with pain in knee and swelling. There was no history of trauma.

Questions :

(1) What is the diagnosis?
(2) What is the imaging features of aneurysmal bone cyst?
(3) What are the differential diagnosis?



Answers :

(1) Well defined eccentric altered signal intensity showing fluid – fluid levels is seen in metaphysis of tibia reaching to articular surface. These imaging findings are suggestive of giant cell tumour (GCT) with secondary aneurysmal bone cyst (ABC), which was confirmed on biopsy.

(2) Primary ABC account for 1.4% of all primary bone tumours. 30-50% of ABCs occur secondary to primary tumours, such as GCT, chondroblastoma, chondromyxoid fibroma, fibrous dysplasia and osteosarcoma, GCT is the most common out of them. The ABC component of the lesion reveals fluid-fluid levels which show markedly increased signal intensity on T2W images. Focal areas of high T1 and T2 signal are also seen within the cysts presumably representing areas of blood of variable age.

(3) Similar imaging appearance are seen in telangiectatic osteosarcoma which also shows fluid-fluid levels. While telangiectatic osteosarcoma is associated with soft tissue component and wide zone of transition, ABC shows a narrower transitional zone. Cortical destruction, osteoid matrix mineralization and peripheral & nodular septal enhancement are other features of telangiectatic osteosarcoma.

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Student's Corner

Become a Sherlock Holmes in ECG

M Chenniappan[1]

Series 6 :

"When QRS is Wide, Your Eyes Also Should Be Wide"

This is the ECG of 40 years patient who presents withchest pain and dyspnea. This is the first ECG taken for him and it is a routine ECG.

Questions :

(1) How will you approach this ECG?
(2) What are the practical implications?
(3) Why is this clue is given?

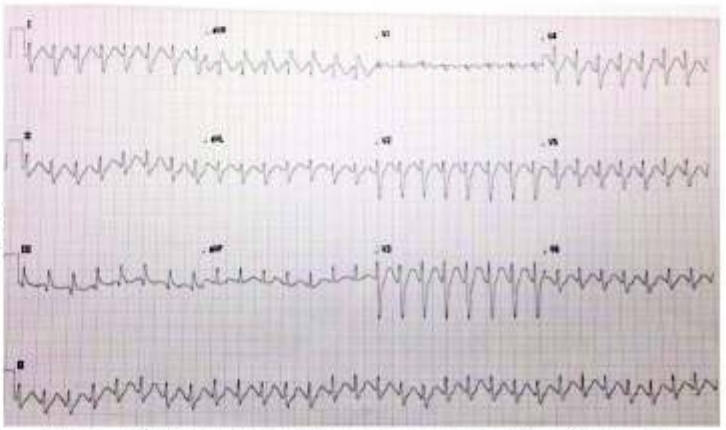

Fig 1 — This is the ECG of 40 years old female with confused state

Answers :

(1) This ECG shows wide QRS regular tachycardia. Once again common differentials are ventricular tachycardia, SVT with aberrancy and don't forget sinus tachycardia with basic intraventricular conduction disturbances such as Bundle Branch Block. Before diagnosing VT or SVT with aberrancy, in any wide QRS tachycardia always rule out sinus tachycardia with aberrancy as it may result in unnecessary anti arrhythmicdrugs, and shock which may lead on further complications not because of arrhythmia but because of treatment. Expand the Lead II or V1 (Fig 2) to see small slurs which appear on the downslope of T constantly with same PR interval which will confirm it is sinus tachycardia. Then let us look at what aberrancy it is. There are slurred S waves in V5, V6, LI and it looks like RBBB. But when you look at V1, there is no typical terminal delayed positivity to diagnose RBBB. So here we are dealing with wide QRS which is not probably due to classical Bundle Branch Block.

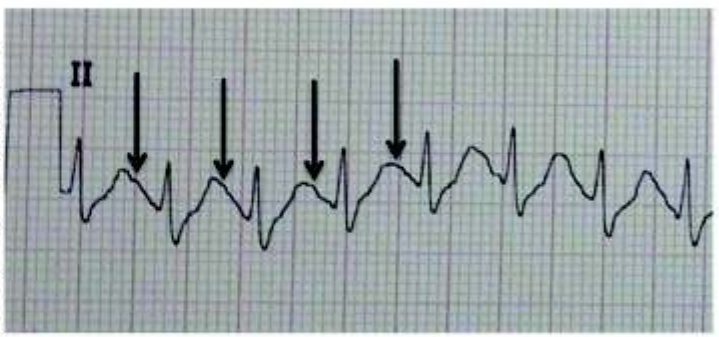

Fig 2 — Arrows Showing constant "blips" in the downslope of T indicating constant sinus P waves

The three important causes of wide QRS other than Bundle Branch Blocks are pre-excitation which is due to abnormal pathways like WPW syndrome, hyperkalemia and tricyclic antidepressant toxicity. Looking at our ECG WPW Syndrome and hyperkalemia are unlikely. So, we are dealing with ECG of tricyclic antidepressant toxicity. The 3 important ECG signs of TCA Toxicity are : (1) Sinus tachycardia, (2) Wide QRS more than 100msec. (3) Terminal R in avR more than 3mm. All the three signs are present in this ECG. Sinus tachycardia is due to inhibition of nor epinephrine reuptake, wide QRS is because of inhibition fast entry of Na during upstroke of action potential and terminal R wave is due to vulnerability of right bundle to get affected due to inhibition of Nafast entry.

(2) QRS duration of >160msec and R in avR>3mm predicts oncoming ventricular arrhythmia as well as seizures. The immediate treatment apart from basic resuscitation measures is intravenous soda bicarbonate whenever QRS is more than 100msec. All the other antiarrhythmic agents such as class IC drugs like flecainide, class II drugs like beta blockers, class III drugs like amiodarone and Class IV drugs like Calcium blockers are all contraindicated. The only drugs we can use in case of ventricular arrhythmias is IV Lignocaine and IV magnesium.

(3) The clue is given because whenever there is wide QRS rhythm either it is bradycardia or tachycardia, one should always look at the presence of p waves and their relationship to QRS. If there is constant relationship to QRS, and the P wave is not anormal, it is likely to be sinus tachycardia with BBB. If there is AV dissociation, if there is bradycardia it is complete heart block and if it is tachycardia, it is ventricular tachycardia. **So,we have to keep our eyes wide open in wide QRS rhythm to identify the P waves which are small blips and their relationship to QRS complexes.**

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Letter to the Editor

[The Editor is not responsible for the views expressed by the correspondents]

New Symptoms of COVID in the 3rd wave : Some Observations from Eastern India

Sir, — The 3rd wave of the Covid epidemic has hit West Bengal hard from the last week of December, 2021 and in January, 2022, the city of Kolkata was experiencing an exponential rise in cases. As clinicians of the city were grappling with the tsunami of new cases, some distinct clinical features of the illness became prominent. While some features were similar to the already known symptoms, there were few notable alterations which deserve attention. This communication is to describe the peculiarities of symptoms and signs of Covid, as experienced in this 3rd wave in Kolkata.

Most of the patients presented with sudden onset of fever. The suddenness was quite striking and the author can mention one case where a 29 year old man went to the office in the morning all hale and hearty and came back in the evening with high fever post-lunch. Most patients were able to recall the exact time when the fever started. This is in contrast to the earlier cases of COVID, when the fever would start gradually. The fever was also associated with rigor and moderate to severe body ache in many cases. The body ache was quite debilitating, involving mainly the muscles of back and neck. There was also associated joint pain and headache in a number of cases. Initially, this constellation of symptoms confused the clinicians and many thought of Dengue and Malaria as the first possibilities. This degree of body ache in COVID was not reported earlier.

There was also associated sore throat. However, cough was mild, there was no dyspnoea and oxygen saturation was completely normal in the majority. Many patients also complained of rhinitis. Other features like diarrhoea or rash, which were reported in the first wave, were extremely rare to non-existent. Also, anosmia had rarely been reported till now. In the author's experience, the presenting symptoms hold true for patients with or without co-morbidities. Also, differences in age did not have much effect on the course of illness.

Most patients responded well to symptomatic treatment and the usual period of illness was 4-5 days. Very few required a second visit to the clinic, let alone hospitalization.

Although a new strain (Omicron) of coronavirus is spreading across the globe, this current 3rd wave of Covid in Kolkata was mainly due to pre-existing strains. As per published reports, only a few cases were due to Omicron till now. Hence, the same strain as previous was changing its presenting features. This is just a preliminary observation. As more data is amassed, a fuller picture of the illness will emerge in the near future. However, preliminary reports from other parts of the world have depicted symptoms similar to the ones described here[1].

We post this communication for the clinicians. This Covid pandemic has been an eye-opener in multiple ways for all of us. As the virus mutates, the symptomology is also changing rapidly. Clinicians should be aware of the latest presentations of the illness so as to manage the cases effectively.

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Dengue — What is Essential to Know

Sir, — Dengue fever is the most important emerging viral disease of human in this world affecting humanity in the terms of morbidity and mortality. Dengue fever is an acute viral disease having the potential of causing large scale outbreaks. The risk of dengue has shown an increase in recent year due to rapid urbanization. There is no specific treatment for dengue fever, besides the dengue vaccine has along way to go, as any of the form dengue viruses can cause the disease, hence the vaccine must be tetravalent ie it needs to protect against all four viruses. It's a self limiting acute mosquito disease characterised by high grade fever, severe headache, muscle and joint pain, rash, nausea and vomiting. Dengue fever is caused by arboviruses and spread by Aedes mosquito. Some infection result in dengue hemorrhagic fever and its severe form Dengue Hemorrhagic Shock Syndrome (DSS) can threaten the patients life primarily through increased vascular permeability and shock. Platelet deficiency is not the cause of death in people suffering from Dengue.

According to International guidelines, unless a patient's platelet count is below 10,000, and there is spontaneous, active bleeding, no platelet transfusion is required. The outbreak of dengue in the City and Hospital beds are full and families are seen running around in search of platelets for transfusion. However what most people do not realize is that the first line of treatment for dengue is not platelet transfusion. It, in fact, does more harm than good if used in a patient whose counts are over 10,000.

The primary cause of death in patients suffering from dengue is capillary leakage which causes blood deficiency in the intravascular compartment, leading to multi-organ failure. At the first instance of plasma leakage from the intravascular compartment to the extravascular compartment, fluid replacement amounting to 20 ml per kg body weight per hour must be administered. This must

be continued till the difference between the upper and lower blood pressure is over 40 mmHg, or the patient passes adequate urine. This is all that is required to treat the patient. Giving unnecessary platelet transfusion can make the patient more unwell.

"While treating dengue patients, physicians should remember the 'Formula of 20' ie, rise in pulse by more than 20; fall of BP by more than 20; difference between lower and upper BP of less than 20 and presence of more than 20 hemorrhagic spots on the arm after a tourniquet test suggest a high-risk situation and the person needs immediate medical attention."

Dengue fever is a painful mosquito-borne disease. It is caused by any one of four types of dengue virus, which is transmitted by the bite of an infected female Aedes aegypti mosquito. Common symptoms of dengue include high fever, runny nose, a mild skin rash, cough, and pain behind the eyes and in the joints. However, some people may develop a red and white patchy skin rash followed by loss of appetite, nausea, vomiting, etc. Patients suffering from dengue should seek medical advice, rest and drink plenty of fluids. Paracetamol can be taken to bring down fever and reduce joint pains. However, aspirin or ibuprofen should not be taken since they can increase the risk of bleeding.

The risk of complications is less than 1% of dengue cases and, if warning signals are known to the public, all deaths from dengue can be avoided.

DENGUE NS1-Best test is NS1

Cannot be false +ve

Is + from day 1 to 7 ideally.

If on day 1 is -ve, repeat it next day.

Always ask for ELISA based NS1 tests as card tests are misleading.

Value of IgG & IgM dengue-In a pt with reduced platelets and looking "sick" on day 3 or 4 of illness, a very high titre of IgG with borderline rise in IgM signifies secondary dengue. These pts are more prone to complications.

In primary dengue IgG becomes + at end of 7 days, while IgM is + after day 4.

Immature Platelet fraction/IPF: A very useful test in Dengue for pts with thrombocytopenia.

If IPF in such a pt is > 10%, despite a platelet count of 20,000, he is out of danger & platelets will rise in 24 hrs.

If it is 6%, repeat the same next day. Now if IPF has increased to 8% his platelets will certainly increase within 48 hrs.

If it is less then 5%, then his bone marrow will not respond for 3-4 days & may be a likely candidate for pl transfusion.

Better to do an IPF even with borderline low platelet count.

A low Mean Platelet volume or MPV means platelets are functionally inefficient and such patients need more attention.

The essential above awareness regarding dengue patient management guidelines goes a long way in curing the patients.

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