Aster Medical Journal

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Mental Disorders
Disorders that Run Hand in Hand

Technology
Using A.I. to Detect Breast Cancer

Colovesical Fistula
A Complication of Sigmoid Diverticulitis

AI&ML *in* Clinical Medicine

Artificial Intelligence (AI) and **Machine Learning** (ML) have emerged as game-changers, offering unprecedented opportunities to enhance patient care, streamline diagnostics, and revolutionize treatment approaches.

Shaping the future of healthcare

SIEMENS Healthineers

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May 2023

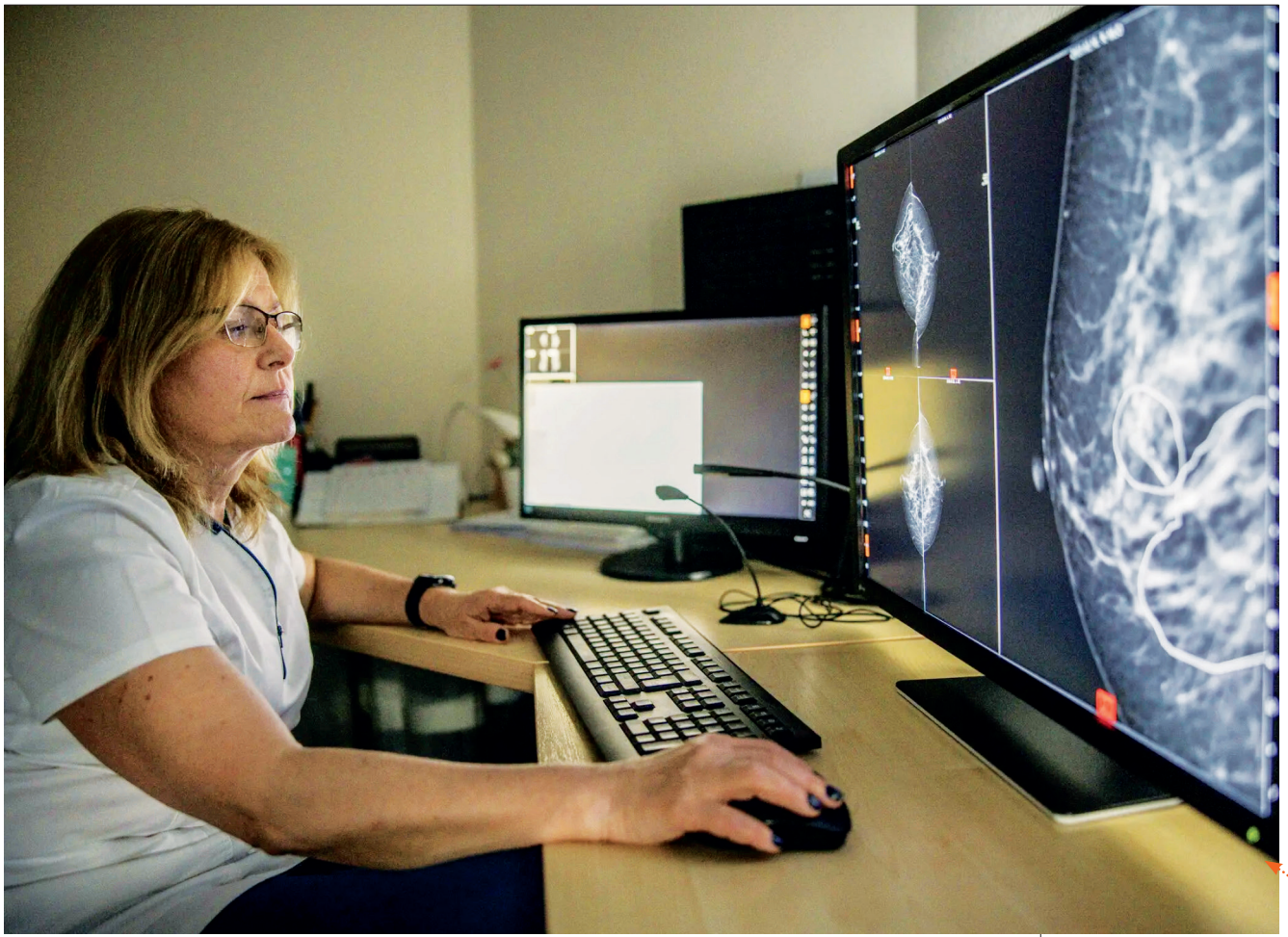

Photo credit: Akos Stiller

Dr. Éva Ambrózay, a radiologist at Bács-Kiskun County Hospital with more than two decades of experience, has been using A.I. software to help look for signs of cancer that doctors may have missed.

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Health professionals will figure out how to work with AI and machine learning as we grow along with the technology. AI and machine learning will not put health professionals out of business; rather, they will make it possible for health professionals to do their jobs better and leave time for the human–human interactions that make medicine the rewarding profession we all value.

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Original Study

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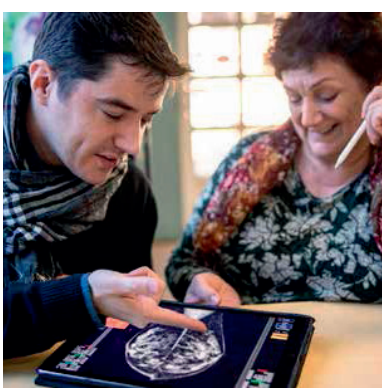
Feature

Inside a dark room at Bács-Kiskun County Hospital outside Budapest, Dr. Éva Ambrózay, a radiologist with more than two decades of experience, peered at a computer monitor showing a patient's mammogram. Two radiologists had previously said the X-ray did not show any signs that the patient had breast cancer. But Dr. Ambrózay was looking closely at several areas of the scan circled in red, which artificial intelligence software had flagged as potentially cancerous.



IN EVERY ISSUE

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ON THE COVER

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GO GREEN

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Prologue

Unleashing the Potential of AI in Medicine: Promises and Challenges

Artificial intelligence (AI) has emerged as a revolutionary technology with immense potential to transform various industries, and medicine is no exception. In recent years, AI has made significant strides in healthcare, offering unprecedented opportunities to enhance diagnostics, improve treatment outcomes, streamline administrative processes, and ultimately revolutionize patient care. However, alongside its promises, the integration of AI in medicine also presents a unique set of challenges that must be addressed for its successful implementation.

This issue of *AMJ* aims to explore the promises and challenges associated with the adoption of AI in medicine, along with clinical research and case studies.

AI algorithms can analyze vast amounts of medical data, including patient records, imaging scans, and genetic information, to assist clinicians in accurate and timely diagnoses. AI-powered diagnostic systems can identify patterns and anomalies that might be missed by human observers, leading to more precise and early detection of diseases and improving patient outcomes.

By leveraging AI, medical professionals can develop personalized treatment plans tailored to individual patients' specific characteristics. AI algorithms can analyze genetic information, medical history, lifestyle data, and real-time patient monitoring, enabling the delivery of targeted therapies and medications. This approach holds the potential to improve treatment effectiveness while minimizing adverse effects. The drug discovery and development process can be time-consuming and expensive. AI can accelerate this process by analyzing vast amounts of biomedical data and predicting potential drug candidates. Machine learning algorithms can identify patterns in large-scale genomics and proteomics datasets, aiding in the discovery of new therapeutic targets and the repurposing of existing drugs, ultimately reducing the time and cost of bringing new drugs to market.

Moreover, AI technologies, such as natural language processing and machine learning, can automate administrative tasks, including documentation, billing, and scheduling. This automation allows healthcare providers to allocate more time to direct patient care, reducing administrative burdens, and enhancing operational efficiency.

While the promise of AI in medicine is evident, it also raises potential challenges. The integration of AI in medicine raises ethical and legal considerations. Issues related to data privacy, patient consent, transparency, and algorithm bias must be carefully addressed. Ethical guidelines and regulatory frameworks need to be established to ensure the responsible use of AI in healthcare, safeguarding patient rights, and ensuring fairness and accountability.

In conclusion, the promises of AI in medicine are vast, offering potential benefits in diagnostics, personalized medicine, drug discovery, and administrative efficiency. With careful planning, collaboration, and adherence to ethical guidelines, AI has the power to revolutionize medicine and improve patient outcomes.

Dr Azad Moopen, MD, FRCP
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Aster DM Healthcare

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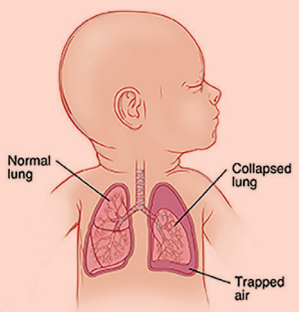
Case Reports



Editorial

AI has become an indispensable tool

This issue of *AMJ* focuses on AI in medicine, and we also have two original studies published along with clinical case reports , review articles and feature stories.

As a practicing clinician, I find myself at the intersection of two worlds: the ever-evolving field of clinical medicine and the rapidly advancing realm of artificial intelligence. AI has gradually woven itself into the fabric of healthcare, promising a future of enhanced diagnostics, improved treatment plans, and ultimately better patient outcomes. However, my perspective on AI in clinical medicine is not one of fear or apprehension, but rather a nuanced and optimistic viewpoint.

AI has become an indispensable tool in the daily practice of many clinicians around the world. It assists in analyzing vast amounts of patient data, providing valuable insights, and augmenting decision-making processes. With its ability to sift through mountains of medical literature in a matter of seconds, AI equips us with up-to-date knowledge and evidence-based guidelines, empowering us to deliver the best possible care to patients. It acts as a supportive partner, providing a second opinion grounded in data and experience.

Moreover, AI has revolutionized the field of medical imaging. Its proficiency in pattern recognition enables earlier and more accurate detection of diseases, such as cancer or cardiovascular disorders. By meticulously scrutinizing radiological images, AI algorithms act as reliable collaborators, flagging abnormalities that might otherwise escape the human eye. This not only expedites the diagnostic process but also reduces the chances of misinterpretation and subsequent delays in treatment.

While AI has undoubtedly brought about remarkable advancements, I firmly believe that its role should be complementary to, rather than a replacement for, human physicians. The art of medicine lies in the delicate balance between science and empathy, and this is a realm where AI cannot yet tread. The human touch, the ability to connect with patients on an emotional level, and the intuition developed through years of experience cannot be replicated by algorithms.

However, I am not oblivious to the challenges that lie ahead. Ensuring the ethical use of AI in clinical medicine is of utmost importance. Safeguarding patient privacy, maintaining transparency in algorithmic decision-making, and addressing biases are essential aspects that demand constant vigilance.

As I envision the future of AI in clinical medicine, I see a harmonious synergy between technology and human expertise. I see AI as a trusted ally, empowering physicians to practice at the pinnacle of their abilities. Together, we can embrace the potential of AI while upholding the fundamental tenets of medicine, ultimately paving the way for a brighter and healthier future for all.

Happy reading!.

Dr Geetha Philips, MD, FRCP

Don't Rely on Sugar Substitutes for Weight Loss, Advises WHO

The World Health Organization (WHO) has issued a new guideline on non-sugar sweeteners (NSS), advising against their use for controlling body weight or reducing the risk of noncommunicable diseases (NCDs).

The recommendation is based on a comprehensive review of available evidence, indicating that the long-term use of NSS does not provide any significant benefits in terms of reducing body fat in adults or children. Moreover, the review highlights potential adverse effects associated with prolonged NSS consumption, such as an increased risk of type 2 diabetes, cardiovascular diseases, and mortality in adults.

Francesco Branca, WHO Director for Nutrition and Food Safety, emphasizes, "Replacing free sugars with NSS does not contribute to long-term weight control. Instead, individuals should explore alternative methods of reducing their free sugar intake, such as consuming foods naturally rich in sugars, like fruits, or opting for unsweetened food and beverages. NSS are non-essential components of the diet and offer no nutritional value. Reducing overall dietary sweetness, starting from an early age, can significantly enhance health."

The recommendation applies to everyone, except individuals with pre-existing diabetes, and covers all synthetic and naturally occurring or modified non-nutritive sweeteners that are not categorized as sugars found in processed foods and beverages or sold separately for consumer use. Common NSS include acesulfame K, aspartame, advantame, cyclamates, neotame, saccharin, sucralose, stevia, and stevia derivatives.

Study Finds 1.63 Million Excess Deaths among Black Americans in the Past Two Decades

According to a study published in JAMA, the number of black individuals in the US who died between 1999 and 2020 exceeded what would have been expected if their mortality rates were on par with those of white people by 1.63 million.

This disparity in excess deaths resulted in a loss of more than 80 million years of life, primarily due to premature mortality from heart disease and comparatively higher infant mortality rates. A black infant born in the US is 2.3 times more likely to die within their first year than a white infant.

Birth of Three-Parent Baby Using IVF in the UK

In a significant scientific development, a baby has been conceived in the UK using an in vitro fertilization (IVF) procedure involving the DNA of three individuals. The objective of this technique, known as mitochondrial donation treatment (MDT), is to prevent the transmission of incurable diseases to children. During the MDT procedure, embryos are created by combining the biological parents' sperm and eggs with mitochondria from a donor's eggs. Over 99.8% of the child's DNA originates from their biological mother and father. This approach aims to safeguard offspring from genetic disorders associated with maternal mitochondrial mutations. Since mitochondria are inherited exclusively from the mother, any harmful mutations in these "cellular powerhouses" can affect all of her children.

Although commonly referred to as "three-parent babies," it is crucial to note that over 99.8% of the baby's DNA is derived from their biological parents.

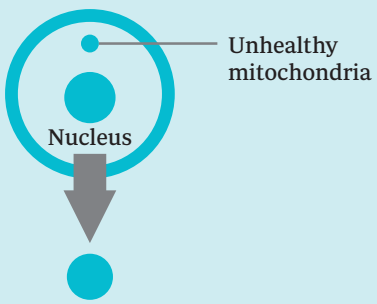
Researchers at the Newcastle Fertility Centre in the UK pioneered the study of MDT, also known as mitochondrial replacement therapy (MRT). The research sought to assist women with mitochondrial mutations in conceiving children without the risk of passing on genetic disorders.

The brief

John Zhang of the New Hope Fertility Clinic performed the procedure that used DNA from three people to create a baby boy.

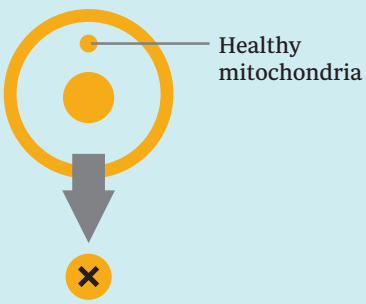
How mitochondrial donation treatment works

1 Mother's fertilised egg



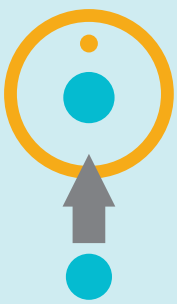
Parents' nuclear material removed and kept

2 Donor's fertilised egg



Donor nuclear material removed and destroyed

3 Donor egg



Parents' nuclear material placed inside donor egg

Pioneering Fetal Brain Surgery: A Historic Breakthrough in Saving Lives

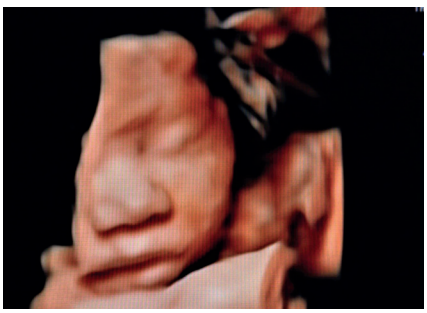
In a remarkable medical achievement, doctors have successfully performed brain surgery on a fetus, marking a significant milestone in the field of prenatal medicine.

The groundbreaking operation, carried out on a baby girl near Boston, is part of a clinical trial aiming to prevent life-threatening complications that could arise from certain brain conditions.

The seven-week-old unborn baby was diagnosed with a vein of Galen malformation, a condition characterized by an abnormal connection between a vein and an artery in the brain. This connection causes blood to accumulate in a pocket, leading to potential risks such as brain damage, heart problems, and respiratory difficulties after birth, which could be fatal.

To tackle the situation, the parents decided to enroll their unborn child in a pioneering clinical trial that involved in-utero surgical intervention. The procedure was successful in saving the baby's life and shows promise for treating similar brain conditions in the future. Fetal brain surgery could revolutionize the approach to these conditions.

The vein of Galen malformation was initially detected during a routine ultrasound at 30 weeks of pregnancy. This condition arises when an artery's high-pressure blood flow stretches the thin walls of a



connected vein, resulting in a ballooning effect. The baby's health is at risk as the excessive pressure diverts blood from other areas of the brain, potentially causing damage. Additionally, the increased strain on the heart can lead to heart failure, while other organs, especially the lungs and kidneys, may be adversely affected.

Previous studies suggest that the placenta offers some protection to fetuses with this condition. However, once the umbilical cord is clamped at birth, the burden on the newborn's heart increases significantly, leading to potential severe illness. Recognizing the urgency, several medical teams are exploring the possibility of treating the condition before birth.

One such team, comprising experts from Boston Children's Hospital and Brigham and Women's Hospital, initiated a clinical trial in 2020 to investigate the efficacy of fetal brain surgery. In this particular case, the girl's mother volunteered for the trial. At 34 weeks, the mother underwent a two-hour experimental operation, while being awake and listening to music through headphones.

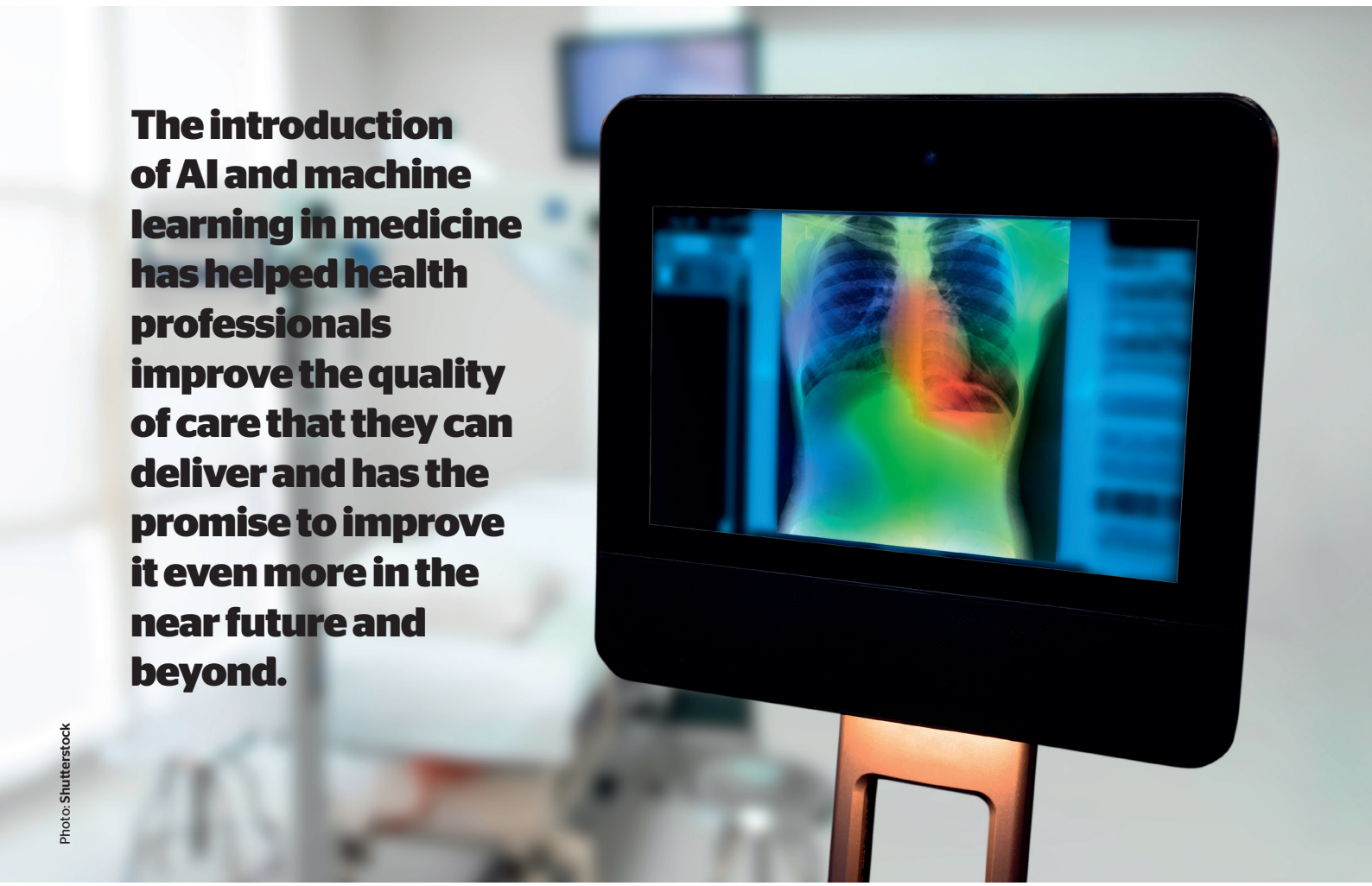
The procedure involved using ultrasound imaging to guide a needle through the mother's abdomen, uterus wall, and the fetus's skull, reaching the malformation in the brain. Tiny platinum coils were delivered through a catheter to block the connection between the artery and the vein, reducing blood flow. Throughout the surgery, the team closely monitored the fetus's brain blood flow until it returned to healthy levels. The baby girl was born healthy a few days later, with no further treatment required for the malformation.

Medical professionals worldwide are lauding this historic achievement as a significant step forward in addressing challenging conditions. Experts believe that fetal brain surgery holds immense potential not only for treating vein of Galen malformations but also for addressing other blood vessel problems and brain tumors. However, thorough assessment of potential risks and determining suitable candidates for the procedure will be crucial.

The success of this case offers hope for future applications of fetal brain surgery. By intervening before birth, medical practitioners can provide a chance of survival and improved outcomes for infants facing life-threatening conditions. While further research and trials are necessary, the medical community is optimistic about the future possibilities offered by this groundbreaking procedure.

By **Charlotte J. Haug, M.D., Ph.D., and Jeffrey M. Drazen, M.D.**

Artificial Intelligence & Machine Learning in Clinical Medicine



The introduction of AI and machine learning in medicine has helped health professionals improve the quality of care that they can deliver and has the promise to improve it even more in the near future and beyond.

Photo: Shutterstock

As computers and the concept of artificial intelligence (AI) were almost simultaneously developed in the 1940s and 1950s, the field of medicine was quick to see their potential relevance and benefit.[1,2] In 1959, Keeve Brodman and colleagues claimed that "the making of correct diagnostic interpretations of symptoms can be a process in all aspects logical and so completely defined that it can be carried out by a machine."[3] Eleven years later, William B. Schwartz wrote in the Journal, "Computing science will probably exert its major effects by augmenting and, in some cases, largely replacing the intellectual functions of the physician."[4] He predicted that by the year 2000, computers would have an entirely new role in medicine, acting as a powerful extension of the physician's intellect.

However, by the late 1970s, there was disappointment that the two main approaches to computing in medicine — rule-based systems and matching, or pattern recognition, systems — had not been as successful in practice as one had hoped. The rule-based systems were built on the hypothesis that expert knowledge consists of many independent, situation-specific rules and that computers can simulate expert reasoning by stringing these rules together in chains of deduction. The matching strategies tried to match a patient's clinical characteristics with a bank of "stored profiles," which we now refer to as "illness scripts,"[5] of the findings in a given disease. More effort was put into understanding the clinical decision-making process itself.[6] It became clear that the key deficiencies in most previous programs stemmed from their lack of pathophysiological knowledge. When such knowledge was incorporated, the performance greatly improved.

Nevertheless, in the 1980s, computers were not up to the task. The rule-based systems had by 1987 proved useful in a variety of commercial tasks but had not worked in clinical medicine. Indeed, Schwartz and colleagues noted that "the process is so slow that it is impractical even with modern high-speed computers."[7] They continued: "After hearing for several decades that computers will soon be able to assist with difficult diagnoses, the practicing physician may well wonder why the revolution has not occurred."[7]

Progress in Data Science

In the 1950s, computers were large and slow. The first hard-disk drive was the IBM Model 350 Disk File, introduced in 1956. It had a total storage capacity of 5 million characters (just under 5 MB). The first hard drive to have more than 1 GB in capacity was the IBM 3380, introduced in 1980. It was the size of a refrigerator and weighed 550 lb (250 kg); the price was $100,000. But integrated-circuit technology was improving. In 1965, Gordon Moore, cofounder of Fairchild Semiconductor and Intel, predicted that the number of transistors in an integrated circuit, and, hence, its potential computing power, would double every 2 years. His prediction was right; this change in semiconductor density is known as Moore's law. However, Moore's law tells us more than the number of transistors per square centimeter, since other aspects of technological progress, such as processing speed and the price of electronic products, are strongly linked to Moore's law. With more dense circuits, computer memory and computing speeds increased, and today, pocket-

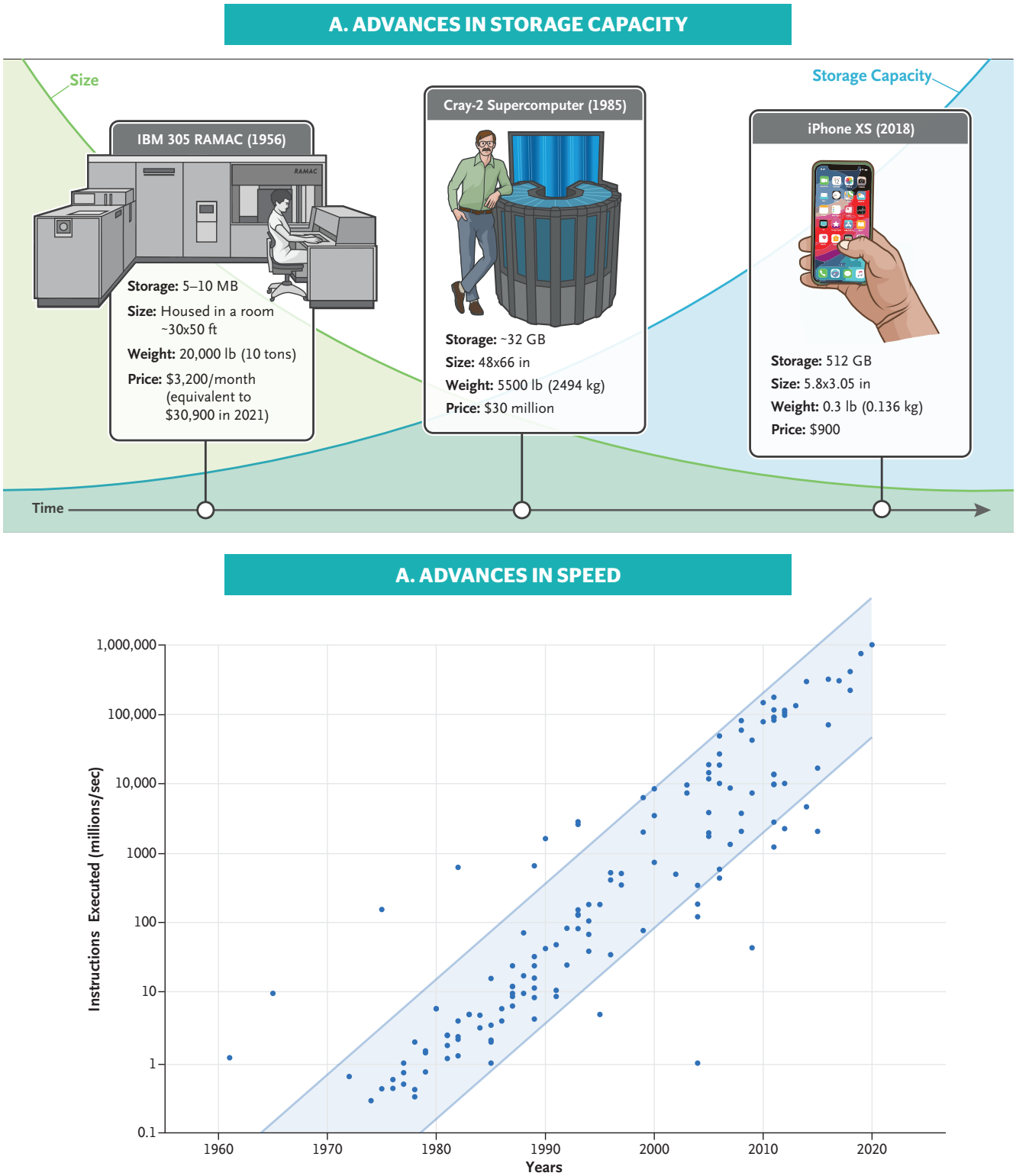


Figure 1. Improvements over 50 Years in the Ability of Computers to Store and Process Data.

Panel A shows advances in data storage, in terms of both physical size and cost per unit of storage. RAMAC denotes random access method of accounting and control. Panel B shows advances in the speed of computing. Each dot represents an individual machine type and the approximate year of its introduction. These improvements in storage and speed have allowed machine learning to progress from a dream to reality. Data in both panels are estimates from many types of system architecture and are derived from multiple public sources.

sized devices that are more powerful than the 1980s supercomputers, which took up entire rooms, are common and available at a fraction of the price (Fig. 1).

Progress in data science is not simply a matter of increased performance, speed, and storage. In addition to the type of information found in libraries, data generated in organizations, and established systems designed to gather and codify data, new forms of technology can use data that are both people-generated and machine-generated. These data are often chaotic and unstructured. Data now come from many additional sources, including social networks, blogs, chat rooms, product-review sites, communities, website pages, email, documents, images, videos, and music, along with wearable and environmental sensors. Many people open aspects of their medical records and personal genetic data for online access by anyone. Storage capacity is so great that vast portions of the corpus of recorded human knowledge and activity can be stored and readily accessed.

We are now able to use unstructured data to identify untold relationships among elements in the data, allowing the use of dynamic data and data with multiple contexts that, when approached and analyzed in nontraditional ways, provide actionable insights into human behavior.

Once we had the data, we needed more than data; we needed ways to identify and process the data. Google became the leader in online searching by harnessing the searches performed by others to identify what people wanted to know. This required a second revolution, mathematical algorithms that could rapidly, and with reasonable reliability, track this behavior and aid the end user in finding particular information. More dense information storage and faster computing allowed for practical, real-time solutions of mathematical expressions that could be used to find relationships in the data that were previously unknowable. As a result, data science could flourish and flex its muscles in a way that was previously impossible.

We are now able to use unstructured data to identify untold relationships among elements in the data, allowing the use of dynamic data and data with multiple contexts that, when approached and analyzed in nontraditional ways, provide actionable insights into human behavior. Neural networks became more sophisticated as the computing power allowed functional real-time output to data queries. Transformers (i.e., deep-learning models that differentially weigh the importance of each part of the input data) made natural-language processing possible. With this approach, the complexities of the underlying computer models, and the corpus of data from which those models could draw, grew and became more powerful. The goal of a computer that could emulate certain aspects of human interaction went from an impossible dream to a reality.

The connectedness allowed by data science is driving a new kind of discovery. People are using social networks to draw their own connections between friends, things, events, likes, dislikes, places, ideas, and emotions. Governments are analyzing social networks to stop terrorist acts. Businesses are mining social and transactional information for connections that will help them discover new opportunities. Scientists are building massive grids of connected data to tease out new findings, using AI and machine learning. As addressed in more detail below, these advances have allowed the emergence of computers that can help you perform tasks that previously had been tedious. The Star Wars character C-3PO was a crude version of the AI-based virtual assistants (e.g., Apple's Siri, Google's Assistant, and Amazon's Alexa) that have become part of our daily life and can help us perform defined tasks. Anyone who

has used one of these devices has experienced their convenience (e.g., instructing the virtual assistant to "set the oven timer for 20 minutes" so that food is properly cooked) but also the annoyance of having the assistant break into a conversation with some unrelated facts. AI and machine learning constitute the driving force behind these devices.

AI & Machine Learning in Medicine

In the 1990s and into the early 2000s, even with slow computers and limited memory, the problem of having machines successfully perform certain medical tasks that were repetitive, and therefore prone to human error, was being solved. Through a substantial investment of money and intellectual effort, computer reading of electrocardiograms (ECGs) and white-cell differential counts, analysis of retinal photographs and cutaneous lesions, and other image-processing tasks has become a reality. Many of these machine-learning– aided tasks have been largely accepted and incorporated into the everyday practice of medicine.

The performance of these machine tasks is not perfect and often requires a skilled person to oversee the process, but in many cases, it is good enough, given the need for relatively rapid interpretation of images and the lack of local expertise.

However, the use of AI and machine learning in medicine has expanded beyond the reading of medical images. AI and machine-learning programs have entered medicine in many ways, including, but not limited to, helping to identify outbreaks of infectious diseases that may have an impact on public health; combining clinical, genetic, and many other laboratory outputs to identify rare and common conditions that might otherwise have escaped detection; and aiding in hospital business operations (Fig. 2). In the months to come, the Journal will publish other review articles that take a selective look at AI and machine learning in medicine in 2023. But before the first article appears, in about a month's time, it is important to consider the overriding issues that need to be considered as we learn to work hand in hand with machines.

Unresolved Issues in AI and MachineLearning in Medicine

Establishing Norms

As noted above, the use of AI and machine learning has already become accepted medical practice in the interpretation of some types of medical images, such as ECGs, plain radiographs, computed tomographic (CT) and magnetic resonance imaging (MRI) scans, skin images, and retinal photographs. For these applications, AI and machine learning have been shown to help the health care provider by flagging aspects of images that deviate from the norm.

This suggests a key question: what is the norm? This simple question shows one of the weaknesses of the use of AI and machine learning in medicine as it is largely applied today. How does bias in the way AI and machine-learning algorithms were "taught" influence how they function when applied in the real world? How do we interject human values into AI and machine-learning algorithms so that the results obtained reflect the real problems faced by health professionals?

What issues must regulators address to ensure that AI and machine-learning applications perform as advertised in multiple-use settings? How should classic approaches in statistical inference be modified, if at all, for interventions that rely on AI and machine learning? These are but a few of the problems that confront us; the "AI in Medicine" series will address some of these matters.

Role of AI and Machine Learning in Clinical Practice

Pitfalls aside, there is much promise. If AI and machine-learning algorithms can be reduced to clinically useful "apps," will they be able to weed their way through mountains of clinical, genomic, metabolomic, and environmental data to aid in precision diagnosis? Can AI and machine-learning–driven apps become your personal scribe and free up your time spent on documentation so that you can spend more time with patients? Can the apps prompt you to ask a key question that could help in the differential diagnosis? Can they outwit the AI and machine-learning algorithms, used by insurance companies, that make it difficult for you to order a positron-emission tomographic–CT scan or collect reimbursement for the time you spent with a patient and the patient's family? In each area, progress has been made. Is it good enough?

Clinical Research on AI and Machine-Learning Applications

The evaluation of progress has its own set of problems. In traditional clinical research, when progress takes the form of a new drug for

A. PRESENT

Public Health

Identification of outbreaks by monitoring Internet traffic

Contact tracing within an outbreak

Tracking of cases, outcomes, and relationships to local factors

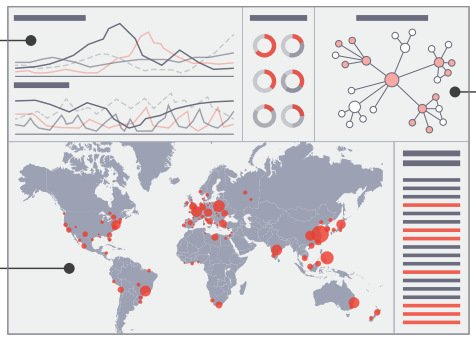
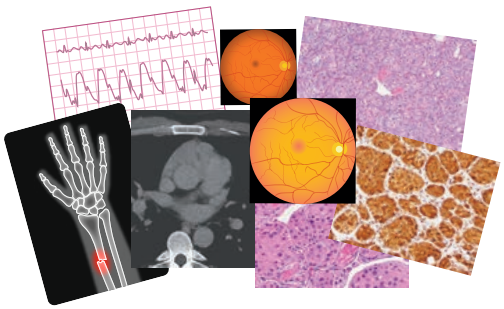


Image Analysis



Clinical-Trial Performance

Decision support in trial design

Patient identification, recruitment, and retainment

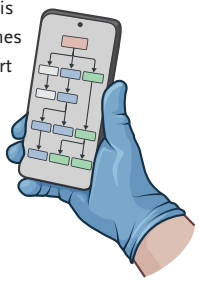
Outcome and side-effect monitoring

Retrieval of Medical Information

Use of multiple information sources about a patient to make a diagnosis

Internet search engines

EMR decision support

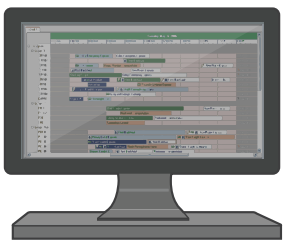


Operational Organization

Operating-room scheduling

Billing and collections

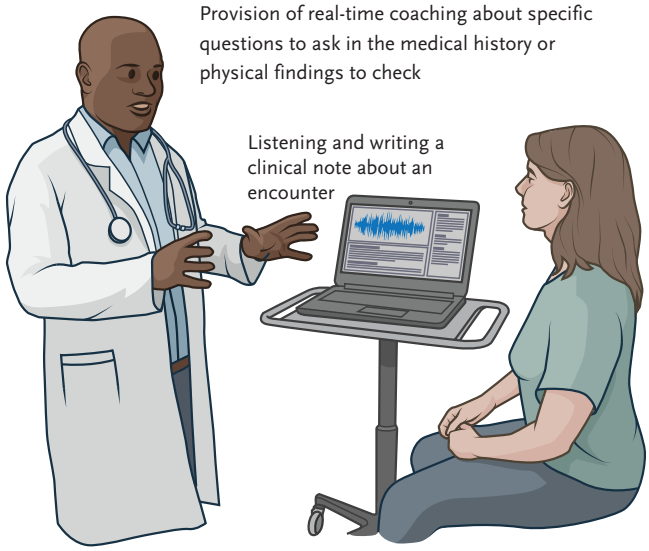
Patient follow-up



B. FUTURE

Provision of real-time coaching about specific questions to ask in the medical history or physical findings to check

Listening and writing a clinical note about an encounter



Serving as a teacher and an assessor in medical education

Creating realistic "flight simulators" for simple and complex patient encounters

Figure 2. Spectrum of Artificial Intelligence (AI) in Medicine.

Panel A shows selected areas of public health and medicine in which AI has an established but evolving role. These tools are already helping medical professionals do their jobs as partners in practice. EMR denotes electronic medical record. Panel B shows areas of medical practice in which AI has begun to have an influence but has not yet reached the stage of common use.

a definable condition, the standards for testing and accepting the drug as an advance are well established. When the intervention is an AI and machine- learning algorithm rather than a drug, the medical community expects the same level of surety, but the standards for describing and testing AI and machine-learning interventions are far from clear.

What are the standards to which AI and machine learning–based interventional research should be held, if an app is going to be accepted as the standard that will shape, reform, and improve clinical practice? That research has three components. First, the research must be structured to answer a clinically meaningful question in a way that can influence the behavior of the health professional and lead to an improvement in outcomes for a patient. Second, the intervention must be definable, scalable, and applicable to the problem at hand. It must not be influenced by factors outside the domain of the problem and must yield outcomes that can be applied to similar clinical problems across a wide range of populations and disease prevalences. Can AI and machine learning–driven care meet these standards — ones that we demand from a novel therapeutic intervention or laboratory-based diagnostic test — or do we need to have a unique set of standards for this type of intervention? Third, when the results of the research are applied in such a way as to influence practice, the outcome must be beneficial for all patients under consideration, not just those who are similar to the ones with characteristics and findings on which the algorithm was trained. This raises the question of whether such algorithms should include consideration of public health (i.e., the use of scarce resources) when diagnostic or treatment recommendations are being made and the extent to which such considerations are part of the decision-making process of the algorithm. Such ethical considerations have engaged health professionals and the public for centuries.[8]

Use of AI and Machine-Learning Applications in Conducting Clinical Research

AI and machine learning have the potential to improve and possibly simplify and speed up clinical trials through both more efficient recruitment and matching of study participants and more comprehensive analyses of the data. In addition, it may be possible to create synthetic control groups by matching historical data to target trial enrollment criteria. AI and machine learning may also be used to better predict and understand possible adverse events and patient subpopulations. It seems possible that AI could generate "synthetic patients" in order to simulate diagnostic or therapeutic

outcomes. But the use of AI and machine-learning applications and interventions introduces a set of uncertainties that must be dealt with both in protocols and in reporting of clinical trials.[9,10]

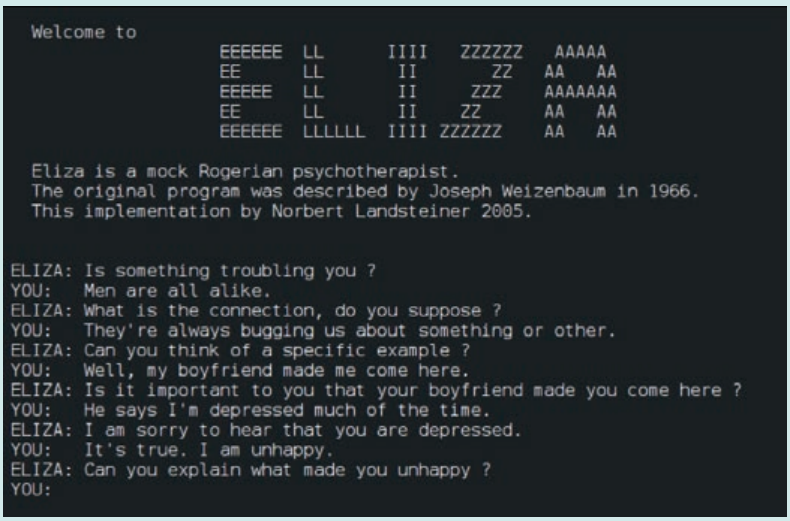
In this AI in Medicine series, we plan to cover progress, pitfalls, promise, and promulgation at the interface of AI and medicine. It is important to understand that this is a fast-moving field, so to some extent, what we publish may have the resolution of a snapshot of the landscape taken from a bullet train. Specifically, things happening in close temporal proximity to publication may be blurred because they are changing quickly, but the distant background will be in reasonably good focus. One area of substantial progress in AI and machine learning (i.e., in the foreground, in our snapshot analogy) is the appearance of sophisticated chatbots that are available for use by the general public. Although chatbots have only recently been introduced at a level of sophistication that could have an impact on daily medical practice, we believe that their potential to influence how medicine is practiced is substantial and that we would be remiss not to address that potential as well as possible problems related to their use.

Chatbots in Medicine

In this issue of the Journal, an article by Lee et al.11 introduces the GPT-4 chatbot and its medical applications. The article was written by a team of researchers who work for the entities that created GPT-4, a chatbot with a broad education that includes medical knowledge. Before we see the future, a quick look at the past will be helpful. A chatbot is a computer program that uses AI and natural-language processing to understand questions and automate responses to them, simulating human conversation. A very early medical chatbot, ELIZA, was developed between 1964 and 1966 by Joseph Weizenbaum at the Artificial Intelligence Laboratory of the Massachusetts Institute of Technology (Fig. 3).

Chatbot technology is now almost everywhere, from customer service to personal virtual assistants, as noted above. With the powerful comput-

A



B

Question:
A 12-year-old girl is brought to the emergency department by her mother because of a 1-week history of worsening leg swelling. The patient also noticed blood in her urine yesterday. The bleeding has not recurred. She had an upper respiratory tract infection and sore throat 1 week ago that caused her to miss several days of school. Medical history is otherwise unremarkable, and she takes no routine medications. Menarche has not yet occurred. BMI is 20 kg/m^2. Vital signs are temperature 37.0°C (98.6°F), pulse 78 beats/min, respiratory rate 12 breaths/min, and blood pressure 136/84 mm Hg. Pulse oximetry while the patient is breathing ambient air shows an oxygen saturation of 100%. Physical examination shows erythema of the posterior pharynx, mild cervical lymphadenopathy, and 3+ pitting edema in both knees. Results of urinalysis are shown:

Protein	150 mg/dl
Blood	Positive
Leukocyte esterase	Positive
Nitrite	Negative
White cells	5–10/high-power field
Red cells	10–25/high-power field
Casts	1–2/low-power field

Results of which of the following laboratory studies are most likely to be abnormal in this patient?
(A) Bleeding time
(B) Erythrocyte count
(C) Serum concentration of C3
(D) Serum IgA concentration
(E) Serum rheumatoid factor assay

The correct answer is (C) Serum concentration of C3. This patient has signs and symptoms of acute poststreptococcal glomerulonephritis (APSGN), a type of glomerular disease that typically occurs 1 to 3 weeks after a streptococcal infection of the skin or pharynx. APSGN is mediated by immune complexes that deposit in the glomerular basement membrane and activate the complement pathway, leading to inflammation, hematuria, proteinuria, and reduced glomerular filtration rate. The resulting fluid retention causes hypertension and edema. The serum C3 level is usually low in APSGN, reflecting complement consumption. The other laboratory studies listed are normal or not relevant in APSGN. Bleeding time is a measure of platelet function, which is not affected by APSGN. Erythrocyte count may be slightly elevated due to hemoconcentration, but not significantly. Serum IgA concentration is elevated in IgA nephropathy, another type of glomerular disease that can cause hematuria and proteinuria, but it is not associated with streptococcal infection or low C3 level. Serum rheumatoid factor assay is used to diagnose rheumatoid arthritis, an autoimmune disorder that does not cause APSGN.

Figure 3. Chatbots in Medicine.

Panel A shows a screen shot of output from a very early medical chatbot called ELIZA, which was developed by Joseph Weizenbaum at the Artificial Intelligence Laboratory of the Massachusetts Institute of Technology between 1964 and 1966. Panel B (courtesy of Lee et al.11) shows input and output from the GPT-4, a chatbot that is expected to be introduced in 2023. BMI denotes body-mass index.

ers available today, language models have hundreds of billions of parameters, which can be used to generate new text. This ability, combined with an almost infinite amount of available (Internet) data with which to train the network, means that language models can do more and more, as shown by the Chat Generative Pre-trained Transformer, or ChatGPT.

ChatGPT is a language model trained by OpenAI. It was introduced publicly in November 2022 (https://openai .com/blog/chatgpt) and has demonstrated a new way in which AI-driven machines can interact with people. The new-generation chatbots hold the promise of being a scribe and coach, but with some key caveats. Many of these caveats were described by the developers of ChatGPT at its launch but warrant special consideration when used in medicine, as detailed by Lee et al.11 In their current iteration, the new generation of chatbots can help with the medical documentation problem and answer key questions that could help in the differential diagnosis, as noted above. But it is difficult to know whether the answers provided are grounded in appropriate fact. The onus would be on clinicians to proofread the work of the chatbot, just as clinicians need to proofread clinical notes that they dictate. The difficulty is that such proofreading may be beyond the expertise of the user. Proofreading a note on a patient visit is likely to be well within the range of the provider's expertise, but if the chatbot is asked a question as a "curbside consult," the veracity of the answer may be much harder to determine.

The application of greatest potential and concern is the use of chatbots to make diagnoses or recommend treatment. A user without clinical experience could have trouble differentiating fact from fiction. Both these issues are addressed in the article by Lee and colleagues,11 who point out the strengths and weaknesses of using chatbots in medicine. Since the authors have created one such entity, bias is likely.

Nevertheless, we think that chatbots will become important tools in the practice of medicine. Like any good tool, they can help us do our job better, but if not used properly, they have the potential to do damage. Since the tools are new and hard to test with the use of the traditional methods noted above, the medical community will be learning how to use them, but learn we must. There is no question that the chatbots will also learn from their users. Thus, we anticipate a period of adaptation by both the user and the tool.

Conclusions

We firmly believe that the introduction of AI and machine learning in medicine has helped health professionals improve the quality of care that they can deliver and has the promise to improve it even more in the near future and beyond. Just as computer acquisition of radiographic images did away with the x-ray file room and lost images, AI and machine learning can transform medicine.

Health professionals will figure out how to work with AI and machine learning as we grow along with the technology. AI and machine learning will not put health professionals out of business; rather, they will make it possible for health professionals to do their jobs better and leave time for the human–human interactions that make medicine the rewarding profession we all value.

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Clinical Utility of Cartridge-based Nucleic Acid Amplification Test and Tuberculosis Culture in Diagnosing Mycobacterium Tuberculosis in Various Clinical Syndromes

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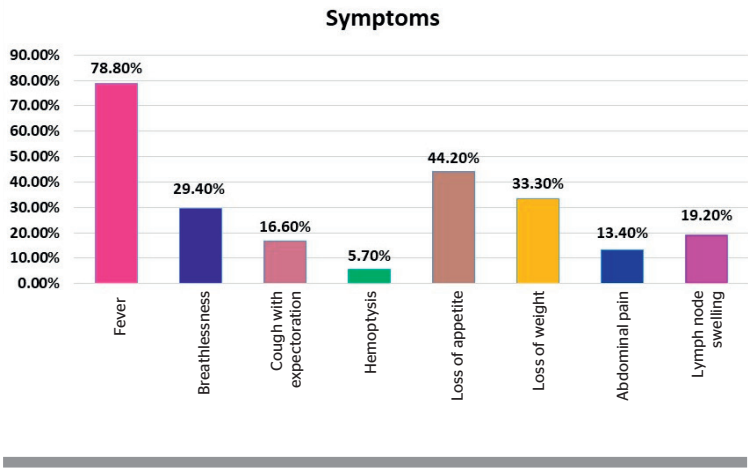
Abstract

Tuberculosis (TB) is still considered a major health disease leading to mortality specifically in India and worldwide. Rapid and early diagnosis can play a very important role in prevention of transmission and mortality. Various guidelines have proposed usage of different diagnostic tests to arrive and confirm the diagnosis of TB. Current study was a prospective, observational study in MTB patients with a positive result on at least one of the three modalities (CB NAAT, TB Culture, AFB Microscopy). The objective was to evaluate the clinical and diagnostic utility of CB NAAT and TB culture in patients with various clinical syndromes of MTB. A total of 156 subjects, of which majority were in the age group of > 50 years (53.2%), followed by 21 to 30 years (17.94%) and 41to 50 years (14.7%) were included. 35 patients were found to be only culture positive, with the other 2 tests being negative. The incremental yield of adding culture was found to be 22.43%. 20 patients out of the total 156 cases (12.8 %) were either smear or CB NAAT positive, but culture negative. 1 patient (0.64%) had Rifampicin resistant Multi-Drug Resistant (MDR) TB. The present study showed a sensitivity and specificity of CB NAAT like PPV and NPV but there may be a positive association between CB NAAT and TB culture.

Figure 1. Bar diagram showing symptoms on presentation among subjects



INTRODUCTION

Tuberculosis (TB) is a major public health disease that ranks as the second most leading cause of death worldwide. From a public health perspective, early and rapid diagnosis of TB is important because of its potential for transmission. [1] In 2018, incidence of TB in India was 2.69 million with mortality rate of 32 per lakh population. India constitutes 24% of total TB burden. A great majority of the cases are fully preventable and treatable. [2] The Revised National Tuberculosis Control Program (RNTCP) recommends the use of sputum smear microscopy for acid fast bacilli (AFB), nucleic acid amplification test (Gene Xpert) and Mycobacterium Culture, for the diagnosis of pulmonary tuberculosis (PTB). [3] Sputum microscopy is relatively inexpensive and quick but has poor sensitivity as compared to other two modalities [4] After the introduction of broth-based media drug susceptibility testing (DST), the results time reduced to weeks. However, the contamination rate limits its utility in a resource limited setting. To overcome these limitations, in 2008, the World Health Organization (WHO) certified and endorsed the line probe assay as a molecular method for the rapid diagnosis of TB and simultaneous detection of rifampicin (RMP) and isoniazid (INH) resistance. [5]

CB NAAT is an example of RT-PCR. It can detect Mycobacterium tuberculosis (MTB) and their DST patterns for the first line drug RMP in smear positive (including scanty), smear negative and culture positive samples. Gene Xpert provides accurate and rapid diagnosis, while culture is the most sensitive, but takes between 2 to 8 weeks to yield results and is not useful in rapid diagnostics. [3]

The published CB NAAT detection threshold is approximately 100- 130 colony forming units (cfu)/ml of sample. In comparison, the detection threshold is <10 cfu/ml for mycobacterial liquid culture and is >5000 cfu/ml for Ziehl Neilson staining for acid fast bacilli (AFB) via standard microscopy in sputum. [6]. The results of CB NAAT can help to speed up the decision-making process involved in the diagnosis of tuberculosis, so that early anti-tuberculosis treatment can be initiated, and it also reduces infectious periods. These can lead to cost savings. The current study was carried out to evaluate the clinical and diagnostic utility of CB NAAT and TB culture in patients with various clinical syndromes of MTB.

METHOD:

This was a prospective, observational study conducted at Aster Medcity from 3rd June 2018 to 30th November 2019. Patients with a positive result on at least one of the three modalities (CB NAAT, TB Culture, AFB Microscopy) were included. Samples from patients which had been tested by less than or equal to 2 of the following tests were excluded from the study: 1. CB NAAT, 2. TB Culture, 3. AFB Microscopy. Primary objective of the study was to identify the diagnostic gain in simultaneous testing with AFB smear, CB NAAT and MTB culture in diagnosis of tuberculosis. Evaluation of the correlation between positivity of CB NAAT and TB culture and assessment of the sensitivity of CB NAAT in diagnosis of MTB from various specimens were the secondary objectives. Data from electronic medical records as well as lab records are used to fill the proforma for the respective patients. Diagnostic gain is calculated as the net difference in number or percentage of patients diagnosed by simultaneous testing with each specific tests. For calculating sensitivity of CB- NAAT, TB culture is taken as gold standard.

The statistical analysis is performed by IBM SPSS Statistics 20 version. All categorical

Table 1. Clinical signs on presentation among subjects

CLINICAL SIGNS	Count	%
Pallor	14	8.5
Clubbing	12	7.6
Lymphadenopathy	39	25
Dull note on percussion	14	8.9
Reduced breath sounds	20	12.8
Bronchial breath sounds	15	9.61
Abdominal tenderness	27	17.3
Shifting dullness	5	3.2
>10	160/551 (29%)	142/475 (30%)

Table 2. Clinical diagnosis on presentation among subjects

CLINICAL SIGNS	Count	%
Pneumonia	25	16
Tuberculosis	81	52
Lung malignancy	10	6.4
Pyrexia of unknown origin	14	9
Lymphoma	11	7
Intestinal malignancy	6	3.8
Chronic liver disease	5	3.3
Inflammatory bowel disease	4	2.5
Total	156	100

Table 3. Sensitivity, Specificity, PPV and NPV of AFB smear with TB Culture as gold standard.

Smear	TB	No TB	Total
Smear Positive	59	15	74
Smear Negative	77	1161	1238
Total	136	1176	1312

Table 4. Sensitivity, Specificity, PPV and NPV of CB NAAT with TB Culture as gold standard.

CB NAAT	TB	NO TB	TOTAL
CB NAAT Positive	101	20	121
CB NAAT Negative	35	1156	1191
Total	136	1176	1312

variables are described as frequency and percentage. All Continues variable are described as mean ± SD. Normality is checked by Kolmogrov-smirnove test. Independent samples t-test is used to compare the mean values between two groups, Mann Whitney u test is used to test the significance among the non-parametric data. Pearson Chi-square test is used to find the association between categorical variables. P value of <0.05 was considered statistically significant. Sensitivity and Specificity are used to check diagnostic accuracy of the test.

RESULTS

The study included a total of 156 subjects, of which majority were in the age group of > 50 years (53.2%), followed by 21 to 30 years (17.94%) and 41to 50 years (14.7%). Hence majority of subjects were in the older age group. Majority of subjects were males 51% and 49% were females

Most common symptoms among the subjects were fever in 78.8%, loss of appetite in 44.2%, loss of weight in 34.3%, 29.4% with breathlessness, 16.6% hard cough with expectoration, 19.2%with lymph node swelling, 13.4% with abdominal pain and 5.7% with haemoptysis.

Most common clinical finding was lymphadenopathy in 25% of patients followed by abdominal tenderness (17.3%) and reduced breath sounds. 9.61% patients have bronchial breath sounds, 8.9% had dull note on percussion and pallor, 7.6% had clubbing and 3.2 % of patients had shifting dullness.

Most common clinical diagnosis on presentation among subjects was Tuberculosis in 52% of patients (including pulmonary, extra pulmonary and disseminated TB). 16% of patients were diagnosed as pneumonia, 9% as pyrexia of unknown origin, 7% as lymphoma, 6.4% as lung malignancy, 3.8% as intestinal malignancy, 3.3% as chronic liver disease and 2.5% as inflammatory bowel disease

60% of patients were diagnosed to have Pulmonary TB, 38% Extra pulmonary TB and 2% with Disseminated TB.

Figure 2. Bar diagram showing clinical signs on presentation among subjects

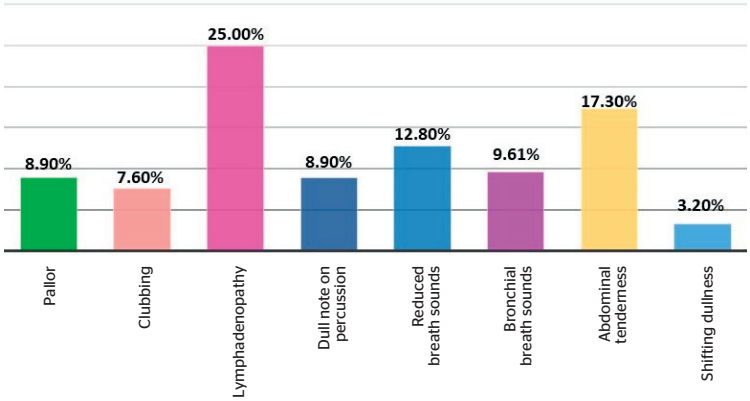
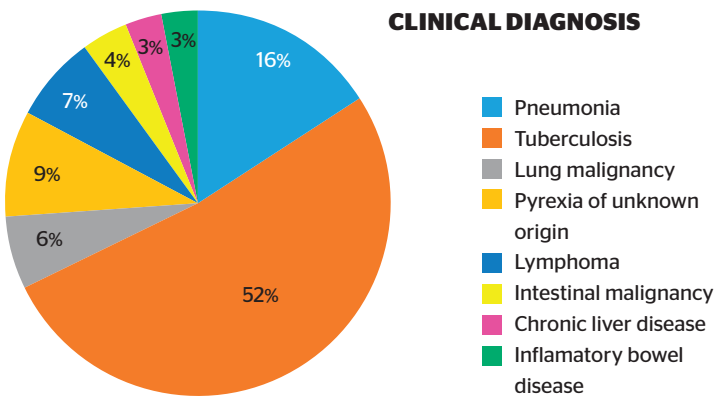


Figure 3. Clinical diagnosis on presentation among subjects



1312 patients fitting into the clinical criteria for Tuberculosis underwent the bundled TB diagnostic testing in our centre in the last 17 months. 156 patients were bundle positive, i.e., had at least one test positive.

64 patients were smear positive. 121 patients were CB NAAT positive. 136 patients were Culture positive. The combined approach of smear plus CB NAAT yielded 121 patients, out of which 101 were also culture positive.

For AFB microscopy, the sensitivity was found to be 43.38%, Specificity of 98.7%, PPV of 79.72% and NPV of 93.7%, calculated against the gold standard of Mycobacterium culture. The accuracy of AFB microscopy is calculated as 93%. [Table 3]

For CB NAAT, the sensitivity was found to be 74.34%, Specificity of 98.29%, PPV of 83.47% and NPV of 97.06%, calculated against the gold standard of Mycobacterium culture. The accuracy of CB NAAT was calculated as 96%. Table 4]

35 patients were found to be only culture positive, with the other 2 tests being negative. The incremental yield of adding culture was found to be 22.43%.

20 patients out of the total 156 cases (12.8 %) were either smear or CB NAAT positive, but culture negative. 1 patient (0.64%) had Rifampicin resistant Multi-Drug Resistant (MDR) TB.

25 out of 36 samples interpreted as 'very low' in CBNAAT were positive for TB culture. i.e; 69.4% of patients. 89.5% of patients with CB NAAT interpretation 'low', 96.6% of patient with 'medium' and 100% of patients with 'high' were culture positive for Mycobacterium Tuberculosis.

Sensitivity of CB NAAT in diagnosing Mycobacterium tuberculosis from various clinical specimens were calculated with TB Culture as gold standard. Highest sensitivity was for pus (100%), followed by lymph node (85%), BAL (81.8%), sputum (78.26%), Tissue (60.50%) and least sensitivity for body fluids (30%).

DISCUSSION

One of the most convenient ways of detecting pulmonary TB is by sputum examination with 2 samples as per RNTCP. The sensitivity of this test depends on several factors such as sample quality, the load of bacilli and the immune status of the patient and hence it is variable. Based on different studies, the sensitivity of sputum examination is around 40-80% because of which significant number of patients can be missed on routine sputum examination This contributes to open cases in community, facilitating spread of bacilli to susceptible hosts [7]. Thus, there is a need for a test with higher sensitivity to pick up the false negatives in high clinical suspicion of TB. Following the availability of CB NAAT for the detection of TB which has higher

Figure 4. Percentage of pulmonary, extra pulmonary and disseminated TB among subjects.

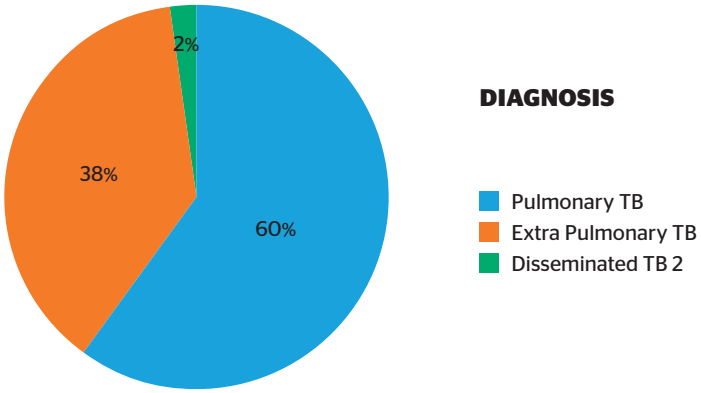


Figure 5. Percentage of pulmonary, extra pulmonary & disseminated TB among subjects.

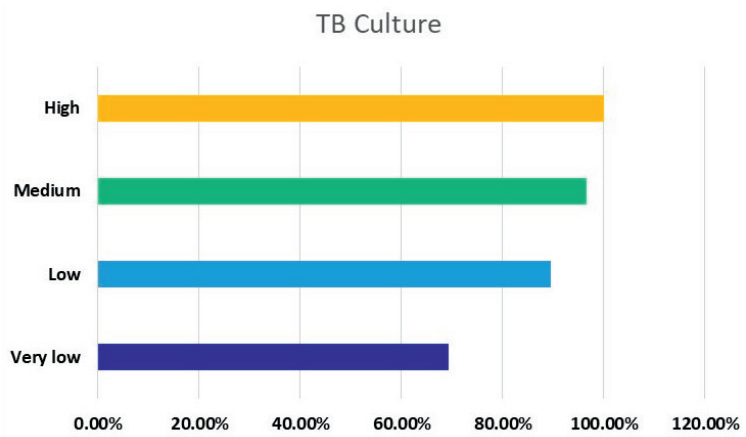
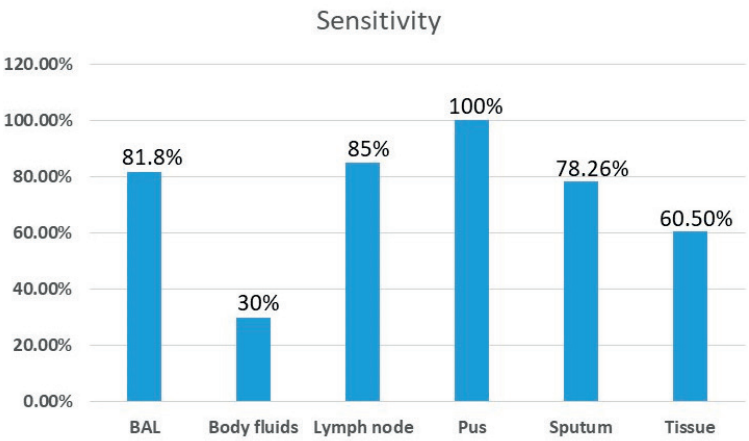


Figure 6. Bar diagram showing sensitivity of CB NAAT in diagnosing Mycobacterium tuberculosis from various clinical specimens.



sensitivity, it has been efficiently utilized to detect sputum negative case of TB. This contributes to increase in the TB detection in patients.

In the National TB plan, three tests are recommended for diagnosis of TB. These are AFB microscopy, CB NAAT, and chest X ray [2]. In our study, we have evaluated the contribution of CB NAAT in case detection of tuberculosis to reinforce the significance of CB NAAT and to identify the diagnostic gain in simultaneous testing with AFB smear, CB NAAT and MTB culture in diagnosis of tuberculosis. The present study showed a sensitivity of 74.34% and specificity of 98.29% for CB NAAT. PPV and NPV were 83.47% and 97.06%, respectively. AFB smear had a sensitivity of 43.38%, specificity of 98%, PPV of 9.72% and NPV of 93.%. The accuracy of AFB Microscopy and CB NAAT was 93% and 96% respectively.

We recommend a combined approach of smear microscopy with concurrent GeneXpert and culture for diagnosis of tuberculosis. The threshold for detection is high for smear (>5,000 cfu/ml) and GeneXpert (100-130 cfu/ml) while that for culture is low (<10 cfu/ml). A combined approach confers the advantage of smear and GeneXpert giving a quick diagnosis of TB along with detection of possible Rifampicin resistance, as well as

Table 6. Sensitivity of CB NAAT in diagnosing Mycobacterium tuberculosis from various clinical specimens.

Specimen	Sensitivity
BAL	81.80%
Body fluids	30%
Lymph node	85%
Pus	100%
Sputum	78.26%
Tissue	60.50%

Table 5. Correlation between positivity of CB NAAT and TB Culture.

			TB		Total
			Grown	No Growth	
CBNAAT	Very Low	Count	25	11	36
		% within CBNAAT	69.40%	30.60%	100.00%
	Low	Count	34	4	38
		% within CBNAAT	89.50%	10.50%	100%
	Medium	Count	28	1	29
		% within CBNAAT	96.60%	3.40%	100.00%
	High	Count	14	0	14
		% within CBNAAT	100.00%	0 0.0%	

culture for identifying cases with low bacterial load, thus increasing the yield.

Several other studies also have shown similar findings. A study was conducted by D. Pragati Raoand K. Lakshmi Sowjanya for 2 months from February to March 2016. Out of 231 HIV positive patients, 59 cases (25.54%) had tuberculosis. Sputum smear for AFB negative and GeneXpert positive were 45 (76.27%). 8 (13.55%) cases were Rifampicin resistance and 51 (86.44%) were sensitive out of all tuberculosis patients [8]. A study conducted by Bansal D et al. for a period of 1 year where a total of 3033 pulmonary specimens were included in the study undergoing Gene Xpert; out of which 604 specimens were from HIV positive patients. In 85 (14.07%) HIV positive patients (out of 604) MTB was detected and RIF was sensitive (14.07%). In 06 (0.99%) HIV positive patients MTB, was detected and RIF resistance was found [9].

In a study by Kumari et al. GeneXpert MTB/RIF test showed a sensitivity of 60% and specificity of 97.9% for diagnosing TB Meningitis, the NPV was 95.9% and PPV was 75%. Singh et al. [10] showed that LJ culture had sensitivity, specificity, PPV and NPV of 8%, 100%, 100%, and 33.01%, respectively, and overall, nested Solomons et al., culture, Genotype and Xpert combined performed best with 56% sensitivity and 98% specificity.

The results of CB NAAT are reported as high, medium, low or very low depending upon the Ct value (number of cycles required for the fluorescent signal to cross the threshold) of the MTB target present in the sample. According to our study, CB NAAT has a lower sensitivity in body fluids (30%) and higher sensitivity in pus (100%). Sensitivity of lymph node sample was 85%, BAL (81.8%), sputum (78.26%) and tissue (60.5%). The prevalence of extrapulmonary TB (EPTB) is showing a rising trend. The heterogenous clinical presentations, paucibacillary nature and difficulty in obtaining specimens (often requiring invasive procedures) make the diagnosis of EPTB, a challenging task and hence the requirement for a rapid, simplified, and cost-effective diagnostic tool arises. This is where CBNAAT plays an important role leading to early initiation of appropriate therapy, improved treatment outcomes, minimizing morbidity and mortality [7].

Previous studies of the MTB/RIF assay have reported a sensitivity of 100% for smear-positive respiratory and non-respiratory samples. Sensitivity for smear-negative samples was 57% and 37%, respectively. Another study conducted by Zeka et al. showed an improved sensitivity of 100% for smear-positive extrapulmonary tuberculosis and 63% for smear-negative EPTB [11]. A study conducted by S B Rufai assessed the sensitivity of the MTB/RIF assay for the diagnosis of tuberculosis by using ascitic fluid samples, keeping MGIT-960 as the gold standard. Out of 67 patients, the MTB/RIF assay was positive in only 12 (17.9%) cases while 82.1% was negative. The study showed that the diagnostic yield of the MTN/RIF assay was low even in culture-positive specimens (70.5%), indicating that in highly proteinaceous body fluids, such as ascitic fluid, Xpert MTB/RIF negative cases must be investigated further using other phenotypic methods. Xpert MTB/RIF has, however, a high positive predictive value (PPV), meaning that if GeneXpert is positive, the ATT can be started without waiting for other investigations [12].

A study conducted by Grant Theron on the determinants of PCR performance concluded a low

mycobacillary load in extrapulmonary samples as compared to pulmonary specimens is primarily responsible for the low sensitivity of the MTB/RIF assay in the diagnosis of extrapulmonary tuberculosis [13]. According to a meta-analysis finding of Denkinger et al [14], sensitivity among pleural fluid was 46% and sensitivity among lymph node specimens was 83%. Another meta-analysis finding of Penz et al [15], suggested sensitivity among pleural fluid was 37% and lymph node specimen was 87%. A recently published study by Sharma et al [16], regarding the utility of GeneXpert in diagnosing EPTB has shown an overall sensitivity of 71% and PPV ranging from 98 to 100%.

Major limitations of our study are smaller sample size and single centre study. Moreover, the incidence and prevalence of disease in different geographical areas might affect the conclusion. Since the CB NAAT is a constant, the statistical association between positivity of CB NAAT and TB culture was not done, only descriptive study was possible.

CONCLUSION

The present study showed a sensitivity and specificity of CB NAAT like PPV and NPV. AFB smear had a lower sensitivity and specificity like other tests. There may be a positive association between CB NAAT and TB culture. As the Ct value decreases, the probability for detection of Mycobacterium tuberculosis by TB culture increases. i.e., the samples with low CT value (interpreted as 'high') had higher percentage of positive cases compared to those with high Ct value (interpreted as 'very low'). According to our study, CB NAAT has a lower sensitivity in body fluids and higher sensitivity in pus.

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Original Study

Fever with Thrombocytopenia in an Intensive Care Unit of a Tertiary Care Centre: A Prospective Study

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Keywords:
Fever, Thrombocytopenia, Intensive Care Unit and Tertiary Care Centre

Abstract

Introduction: Fever is a pervasive and ubiquitous concept in human myth and science. Fever as an illness has inflicted human civilization since ages, which was later recognized as a common manifestation of varied diseases. Many times prolong fever is accompanied by thrombocytopenia. The differential diagnosis of the clinical entity includes viral infections and haematological diseases. Fever with thrombocytopenia is most frequently caused by infections (50–70%) eg. viral infections, bacteremia, or fungaemia and frequently associated with patients suffering with septic shock.

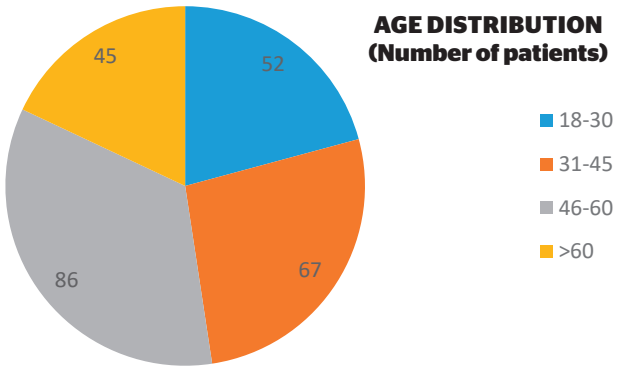
Objectives: The present study aim is to understand the etiology of febrile thrombocytopenia in a medical intensive care unit (MICU) of a tertiary care center, various bleeding manifestations at different platelet levels and outcome in these patients.

Methods: The study was carried out at Aster Medcity, Kuttisahib Road, Cheranelloor, Kochi – 682027, Kerala, India in a MICU from 6th June 2018 to 29th February 2020. This was a prospective, non-randomized study to identify cases of fever with thrombocytopenia in MICU. This study was conducted after the institutional ethics committee's approval. The participants (>18 years age) having history of fever with thrombocytopenia (platelet<1.5 lac/micro Liter or µL) who were hospitalized in 'ICU of Department of Medicine' were recruited after written informed consent.

Results: Out of the 250 cases, 231 patients (92.4%) had good recovery and 19 patients (7.6%) expired during their stay at the intensive care unit.

Conclusion: This was the first of its kind study of this region. In our analysis, infectious etiologies were found associated with majority of patients with febrile thrombocytopenia and the most prevalent among them was Dengue. In 30% of patients, bleeding manifestations took place. Purpura and petechiae were the most frequent symptoms. Only a small number of individuals needed platelet transfusions because of severe thrombocytopenia (10,000/ µL) or life-threatening hemorrhagic symptoms. Of the 250 patients, 231 patients (92.4%) survived ICU stay and were ultimately discharged, while 19 patients (7.6%) expired.

Figure 1. Pie Chart Showing Age Distribution of Patients with Febrile Thrombocytopenia



INTRODUCTION

In human myth and science, fever is a universal issue. Ancient cultures believed fever as a disease, but later medical research revealed it 'a common symptom' of many diseases.[1] Fever epidemics had always dragged attention of the mankind since ages, , which can be traced in the historical records of every race and nation.

The average body temperature is 37.0°C (98.9°F). Fever is affected variably by the measurement site, tidal variation, vigorous activity, hormonal and menstrual status, individual variations, and environmental influences.[2] It is a common practice to estimate a patient's body temperature by oral readings. However, mouth breathing, breathing rate, and recently consumed hot or cold liquids can affect the results[3] and certain modern thermometers can accurately measure temperatures in the ear canal, which is unaffected by these effects.[4] The core body temperature reflected by rectal temperature, is typically 0.3 to 0.60 °C higher than oral temperature. Normal body temperature follows a diurnal rhythm, rising in the afternoon and falling in the early morning. Normal ranges fall between 96.5 and 98.9 °F and 35.8 to 37.2 °C.[5]

Fever is defined as an increase in body temperature above the typical circadian range as a result of a disturbance in the anterior hypothalamic thermoregulatory region. Fever is also defined by morning temperature of more than 37.2°C (98.9°F) or by night time temperature of more than 37.7°C (99.9°F).[6,7] The first thermometer was made by a Dutch 'Gabriel Daniel Fahrenheit' in the early eighteenth century.[4]

Since the time of Hippocrates and the Roman Empire, medical fraternity had given detailed description of fever and its various patterns of presentations. Fever is generated by endogenous pyrogens, secreted from host inflammatory cells, such as lymphocyte activating factor, mononuclear cell factor, and interleukin-1. Dr. Paul Beeson in 1948 discovered Interleukin 1(IL-1), which is now known to play a significant role in fever and thermoregulation.

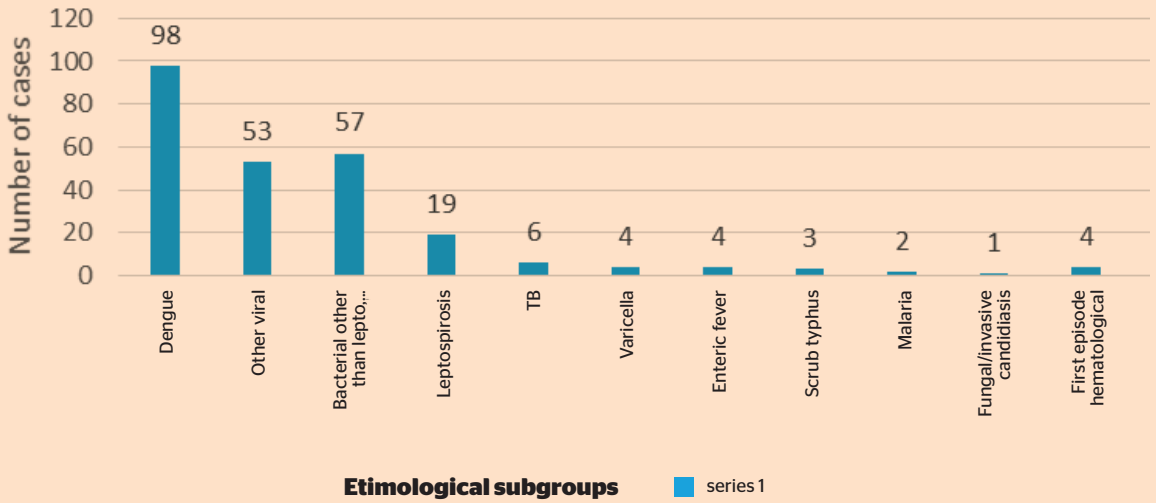
Platelet count less than 1.5 lac/ µL is called as thrombocytopenia.[5] This is caused by a decrease production in bone marrow, increase destruction, or an increase in sequestration in an enlarged spleen.[8,9] Petechiae on the skin and hemorrhages from the mucosa of the gastrointestinal and genitourinary tracts are the two cardinal signs of thrombocytopenia. In thrombocytopenic patients, intracranial bleeding is a rare event but may cause serious complications.[10]

History, physical examination, complete blood count (CBC) results, and peripheral blood smear examination are important factors in the initial evaluation of thrombocytopenic patients and ruling out false thrombocytopenia.[11] When there is prolong fever, it is often accompanied by thrombocytopenia. The differential diagnosis of the clinical entity includes viral infections and haematological diseases. Fever and thrombocytopenia is most frequently caused by infections (50–70%) eg. viral infections, bacteremia, or fungaemia, and frequently associated with patients suffering with septic shock.[12]

Most common infections causing febrile thrombocytopenia are:

1. **Viral infections:** Arbovirus- Dengue, Yellow fever; Rodent borne virus- Hanta, Lassa virus; others- HIV, CMV, Parvo virus B19, HSV.
2. **Bacterial infections:** Gram positive and Gram negative septicemia, Typhoid, Leptospirosis, Miliary Tuberculosis, Borreliosis, Rickettsial infections.[13]
3. **Protozoal infections:** Malaria, Visceral Leishmaniasis
4. **Others:** Hematological causes-leukemia, lymphoma, Auto immune diseases, post chemotherapy, CLD patients with portal hypertension, drug induced thrombocytopenia.[14]

Figure 2. Bar Diagram Showing Various Etiological Subgroups of Febrile Thrombocytopenia



Most cases of fever and thrombocytopenia are treated outside the realm of an ICU. When patients with fever and thrombocytopenia are admitted to MICU with additional issues such as hemodynamic instability or multiple organ system involvement, there is a significant risk of morbidity and mortality.[15]

The main objectives of the study is to a) identify cases of fever with thrombocytopenia in MICU as per laid out criteria b) evaluate etiologies of febrile thrombocytopenia, c) evaluate bleeding manifestations and platelet count at the time of the bleeding manifestations and d) follow up the outcome of patients admitted with fever and thrombocytopenia.

METHODS

The study was carried out at Aster Medcity, Kuttisahib Road, Cheranelloor, Kochi – 682027, Kerala, India in MICU from 6th June 2018 to 29th February 2020. This was a prospective, non-randomized study to identify cases of fever with thrombocytopenia. This study was conducted after the institutional ethics committee's approval. The participants (>18 years age) having history of fever with thrombocytopenia (platelet<1.5 lac/micro Liter or µL) who were hospitalized in 'ICU of Department of Medicine' were recruited after written informed consent.

The duration of the study was twenty months. The patients (>18 years age) having history of fever with thrombocytopenia were recruited in the study based on the following selection criteria:

Inclusion criteria:

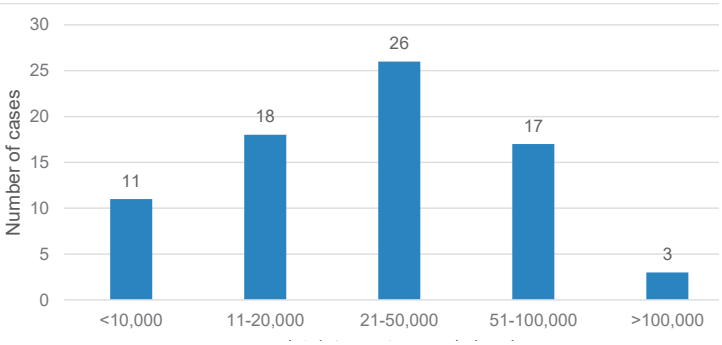
1) Patients admitted in MICU
2) Age > 18 years
3) History of fever as per definition
4) Platelet count less than 1.5 lac/ µL (confirmed by peripheral blood smear)

Exclusion criteria:

Known case of immune thrombocytopenic purpura, malignancy, post chemotherapy, chronic liver disease with portal hypertension, and known case of auto immune diseases.

A total 250 patients were enrolled in the study. The study protocol was approved by institutional scientific and ethical committee of Aster Medcity, Cochin. During the study period, all patients admitted in MICU with fever and thrombocytopenia were screened according to the inclusion and exclusion criteria. The investigation reports were followed up regularly to identify the etiology, and the patients were closely monitored for bleeding manifestations. Once a definitive diagnosis was made, targeted therapy was offered along with symptomatic and supportive measures. Platelet counts were monitored on a daily basis throughout the period of stay in the ICU. Platelet transfusions were administered in case of severe bleeding manifestations or a platelet count less than 10,000/ µL. All the patients included in the study were followed up till the patient was discharged from the MICU.

Figure 3. Bar Diagram Showing Platelet Distribution among Patients with Bleeding Manifestations



Statistical Analysis

Data was analyzed using the Microsoft excel spreadsheet.

RESULTS

Of the total 250 patients enrolled in the study, 51 (20.4%) were between 18- 30 years age group, 67 (26.8%) were between 31-45 years age group, 89 (35.6%) were between 46-60 years age group and 43 (17.2%) were above 60 years as shown in Fig. 1. Among 250 subjects 173 (69.2%) were males and 77 (30.8%) were females.

Etiological Distribution

Of the total 250 cases of fever with thrombocytopenia, infection was found to be the major cause, attributed to 246 cases out of 250 (98.4%). Among the type of infection, predominant was viral amounting to 156 cases (63.41%), followed by bacterial with 82 patients (33.33%). Among the etiological subgroups, dengue fever was the most common cause amounting to 98 cases (39.2%). Other viral causes were attributed in 50 patients (20%), leptospirosis in 19 patients (7.6%),tuberculosis in 6 patients (2.4%), varicella and enteric fever in 4 patients (1.6%), scrub typhus in 3 patients (1.2%), malaria in 2 patients (0.8%), fungal infection (invasive candidiasis) in 1 patient (0.4%) as shown in Fig. 2. Platelet count distribution among patients with febrile thrombocytopenia shown in Table 1.

Distribution of Bleeding Manifestations

Petechiae /purpura were the most common bleeding manifestations encountered in 36 cases (48%). Gastro Intestinal (GI) bleeding was found in 27 cases (36%), ecchymosis in 19 cases (25.33%), Genito urinary (GU) bleeding in 13 cases (17.33%), nose bleeding in 4 cases (5.3%) and ICH (intracranial haemorrhage) in 1 patient (1.33%) as shown in Fig. 3.

Distribution According to Etiology and Bleeding Manifestations

Out of 98 cases of dengue, 49 cases (50%) had bleeding manifestations. Out of 82 cases of bacterial infections, 16 cases (19.5%) had bleeding manifestations. In 19 cases of leptospirosis, 7 patients (36.84%) had bleeding manifestations. 1 patient each, with malaria (50%), Scrub typhus (33%) and varicella encephalitis (25%) had bleeding manifestations as shown in Fig. 4.

Mortality versus Etiology

In the study, 19 cases (7.6%) suffered mortality, out of which 11 cases (57.89%) died due to bacterial infections (non-leptospirosis), 3 cases (15.78%) died due to viral infections and dengue was the cause of death in one patient (5.2%). 16.7% patients with severe thrombocytopenia i.e, Platelet count< 10,000/ µL suffered mortality. However there was no statistical significant association between severity of thrombocytopenia and mortality (Fishers exact test -P value = 0.275) as shown in Table 2.

Outcome

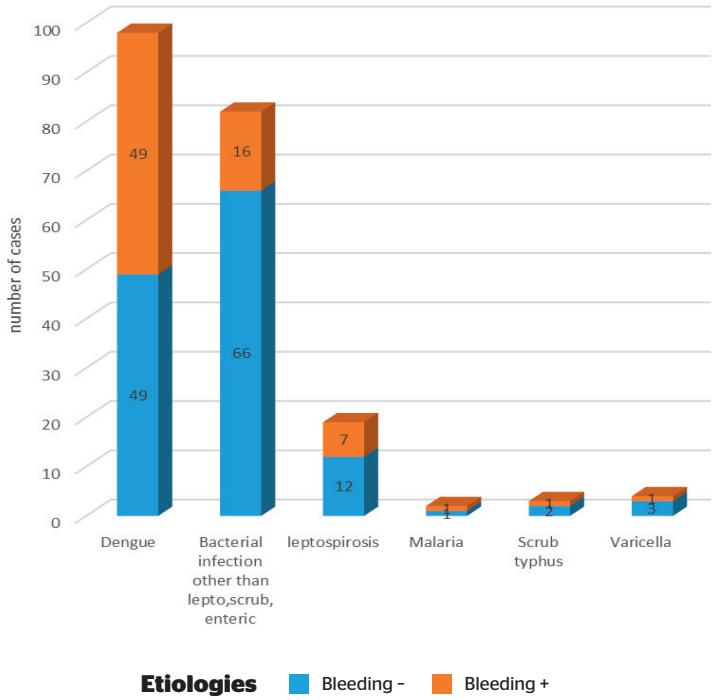
Out of the 250 cases, 231 patients (92.4%) recovered and 19 patients (7.6%) died in the ICU.

DISCUSSION

Febrile thrombocytopenia syndrome is frequently caused by infections, especially septicemia and dengue fever. In Kerala, dengue is commonly prevalent in rainy season from June to September. Febrile thrombocytopenia syndrome initially presents as flu without any bleeding tendency. Early detection and treatment of underlying cause leads to rapid clinical recovery and thrombocytopenia correction. The mortality seen in febrile thrombocytopenia is strongly associated with co-morbid conditions and is not associated with the degree of thrombocytopenia.

Nair et al.[16] carried out a similar study over a span of 1.5 years at St. Stephens Hospital, New Delhi. Total 109 patients were enrolled for the study, out of which 76 (69.7%) were male

Figure 4. Bar Diagram Showing Bleeding Manifestation in Different Etiologies



and 33 (30.3%) were female. These were recruited using selection criteria identical to our study. In Gondhali et al.17 study, 26% patients were found to be in the age group 21-40 years. The maximum number of fever with thrombocytopenia cases (35.6%) were found in the age group 46-60 years. As this study was conducted in an ICU, majority of the patients were middle-aged or older and had several co-morbidities. The adult population with robust immunity and no co-morbidities, suffering with febrile thrombocytopenia did not require ICU care and showed rapid recovery with minimum supportive treatment.

In Nair et al.[16] study, 29 cases were of septicemia were reported, which was the leading cause of fever with thrombocytopenia. Second most common cause was enteric fever (16 cases), followed by dengue (15 cases), megaloblastic anemia (13 cases), malaria (10 cases) and hematologic malignancies (4 cases) respectively.

In another similar study by Srinivas et al.[18] 41 cases of malaria were reported, which was the leading cause of fever with thrombocytopenia. Second common cause was enteric fever followed by septicemia, dengue, and leptospirosis.

Etiologies of fever with thrombocytopenia in the above studies differed due to regional and seasonal variations as shown in Table 3. In our study, 98 cases were of dengue, which was the leading cause of fever with thrombocytopenia. There were 82 cases of bacterial infections after excluding leptospirosis, enteric fever and scrub typhus. There were 19 cases of Leptospirosis, 6 cases of tuberculosis, 4 cases of enteric fever, 3 cases of scrub typhus, and 2 cases of malaria. On account of floods in Kerala during the study period, number of leptospirosis cases were high.

In our study, infections contributed 98.4% of the 250 cases, with 1.6 % cases of non- infectious etiology whereas in the Nair et al.[16] study infections amounted to 68% of the cases, and hematological conditions contributed to 15% of the cases.

In our study, 134 patients (53.6%) had platelet counts greater than 50,000/micro L, compared to 62 patients (56.8%) in Nair et al.[16] study. In our study, 81 (32.4%) patients had a platelet count between 21,000 and 50,000/micro L, compared to 28(25.7%) in Nair et al.[16] study. In our study, 13 (5.2%) patients had platelet count 10,000/micro L, compared to 19 patients (17.5%) in Nair et al.[16] study.

In Nair et al.[16] study, spontaneous bleeding accounted for 31 cases (68%) of bleeding manifestations, followed by 10 cases (22.22%) of petechiae/purpura,and other cases (4.88%) as shown in Table 4.

Petechiae/purpura was the most frequent presentation in a research by Gondhali et al.[17], with 14 (14%) cases, followed by GI bleed (melena and hematemesis) in 5 (5%), GU bleed in 2 (2%), and sub conjunctival haemorrhage with epistaxis in 1 (1%).

The most frequent bleeding manifestation in our analysis was petechiae/purpura, which had 36 cases (48%) followed by GI bleeding (27 cases, 36%), ecchymosis (19 cases, 25.33%), GU bleeding (13 cases, 17.33%), nasal bleeding (4 cases, 5.3%), and ICH in one patient (1.33%) as shown in Table 5.

In our study of 250 cases, 231 patients recovered and 19 patients died. 57.89% of mortality

Table 1. Platelet Count Distribution among Patients with Febrile Thrombocytopenia

Platelet range	Frequency	Percent
<10000	13	5.2%
11-20000	22	8.8%
21-50000	81	32.4%
51-100000	113	45.2%
>100,000	21	8.4%
Total	250	100.0

Table 2. Platelet Count and Mortality – Table To Find Out Association as Per Fishers Exact Test

Platelet ranges	Number of cases with in each range	Recovery	Total
<10000	6	5 (83.3%)	1 (16.7%)
11-20,000	40	35 (87.5%)	5 (12.5%)
21-50,000	114	109 (95.6%)	5 (4.4%)
51-100000	90	83 (92.2%)	7 (7.8%)

(11 cases) had bacterial infections other than leptospirosis, enteric fever, scrub typhus. 15.78% (3 cases) had other viral infection, 10.52% (2 cases) each of leptospirosis and varicella encephalitis and 5.2% (1 case) had dengue associated with cause of death.

In 19 cases of mortality, 3 cases had a platelet count below 10,000 /µL, 2 cases had platelet count in between 11-20,000/ µL and 5 cases had platelet count between 20,000 & 50,000/ µL. In 9 cases platelet counts were above 100,000 /µL.

CONCLUSION

Our study throws light on different causes of febrile thrombocytopenia and its accompanied bleeding manifestations, and patient outcomes. The etiology of febrile thrombocytopenia was assessed, and it was the first study of its type, conducted in this region. In our analysis, infectious etiologies accounted for majority of cases of febrile thrombocytopenia. The most prevalent infectious etiology was dengue. In 30% of patients, bleeding manifestations were reported. Purpura and petechiae were the most frequent bleeding tendencies. Only few patients needed platelet transfusions owing to severe thrombocytopenia (10,000/ µL) or life-threatening haemorrhagic symptoms. Of the 250 patients, 231 patients (92.4%) survived and discharged from ICU, while 19 patients (7.6%) died. Early diagnosis and prompt supportive care contributed to patient's survival. The patients in which mortality occurred, confounding factors like co-morbid conditions, coagulation abnormalities, etc. need to be evaluated in addition to the severity of thrombocytopenia.

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Table 3. Comparison of Etiologies with Other Study

Disease category	Nair et al.[16]		Present study	
	No. of cases	Percentage	No. of cases	Percentage
Dengue	15	13.8	98	39.2
Bacterial causes	29	26.6	82	32.8
Leptospirosis	0	0	19	7.6
Tuberculosis	0	0	6	2.4
Enteric fever	16	14.7	4	1.6
Scrub typhus	0	0	3	1.2
Malaria	10	9.2	2	0.8
Hematological	17	15.6	4	1.6
Varicella	0	0	4	1.6
Viral fever	20	18.3	48	18

Table 4. Comparison of Bleeding manifestations In Nair et al.[16] Study With Our Study

Bleeding manifestations	Nair et al.[16] study		Present study	
	No. of cases	Percentage	No. of cases	Percentage
Present	45	41.3	75	30
Absent	65	58.7	175	70

Table 5. Comparison of Distribution of Bleeding Manifestations in Gondhali et al.17 Study With Our Study

Bleeding manifestations	Nair et al.[16] study		Present study	
	No. of cases	Percentage	No. of cases	Percentage
Petechiae/purpura	14	14	36	48
GI Bleed	5	5	27	36
Ecchymosis	0	0	19	25.33
GU Bleed	2	2	13	17.33
Nose Bleed	1	1	4	5.3
ICH	0	0	1	1.33

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By Dr. Behere Nilam S

Disorders that run hand in hand

Understanding comorbidity of mental disorders with physical disorders

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On the context of increasing burden of mental disorders, it is important to note that mental disorders are heavily comorbid with many physical disorders. Not only do they exercise influence on pathogenesis of each other but also treatment plans and overall patient outcomes. Treatment of mental disorders can positively affect outcome of physical disorders. A thorough understanding of comorbidity models between these two categories of disorders can guide to better disease prevention and management plans.

COVID-19 pandemic has not only brought on the table, the challenges of an infectious disease management and prevention but has also raised a few critical questions about approaches to medicine. While managing COVID-19 pneumonias with an intention to treat a 'disease', the pandemic had us revisiting the dictum of "treat the patient and not the disease". These instances reminded that multiple illnesses do co-exist and exercise complex dynamic interplay in management and prognosis of each other. Further, it is not only a patient as a unit, but a patient, in-situ of his environment, socio-cultural setting, financial and occupational background has to be a target of intervention.

Mental illnesses have been a staggering example of how a patient's biological/medical, psychological and social functioning exercise influence on an illness. This is also an example of how comorbidity of multiple illnesses can remarkably impact the overall patient outcomes.

Burden of Mental Disorders

While WHO affirmatively states that there is "no health without mental health", mental health still remains largely unattended, worldwide. Common mental disorders, which include depression and anxiety disorders, has been found to be highly prevalent across the globe. Depression, most prevalent all mental disorders, is the 3rd leading cause of disease burden globally (>300 million; 4.4% of world population). Anxiety follows depression closely in global disease burden (around 250 m; 3.6% of world population)[1,2].

In India, approximately 1 in 40 people have had suffered depression in their lifetimes and 1 in 20 people are currently depressed. What's remarkable to note is that, the two most vulnerable age groups i.e. adolescent and geriatric populations, account for more than half of the total burden of mental illness[3]. With suicide being the leading cause of death for Indians from age group 15—39 years, the mental health scenario in India is all the more concerning.

With mental disorders being a significant inclusion of Non-communicable group of diseases, the UN declaration of sustainable developmental goals has laid emphasis on mental health specific targets[4]. While it is important to scale up interventions for mental wellbeing, dearth of mental health professionals in India and worldwide has been a major impediment. There are only 0.3 psychiatrists per 100,000 populations in India, against the WHO recommendation of 1 psychiatrist per 100,000 populations[3]. Inclusion of mental health in Comprehensive Primary Healthcare Package in Ayushman Bharat Yojana is a welcome step by Ministry of Health and Family Welfare and reinforces the necessity of treating mental illnesses on priority basis[5].

Treatment of common mental disorders is now a primary healthcare imperative. A strategy to address the huge mental health burden is by complementing treatment of other physical illnesses with screening and management of mental illness. This seems to be an effective and tangible strategy, as mental disorders are heavily comorbid with most other communicable and non-communicable diseases.

With the specific objectives of treating comorbidity of physical and mental disorders, it is important to understand how comorbidities exercise effects on each other.

Comorbidity Models

Dr Norman Sartorius, formerly the Director of the Division of Mental Health of WHO, urged the need to accept the fact that comorbidity of mental and physical disorders is the rule rather than an

Figure 1: **Models of comorbidity**

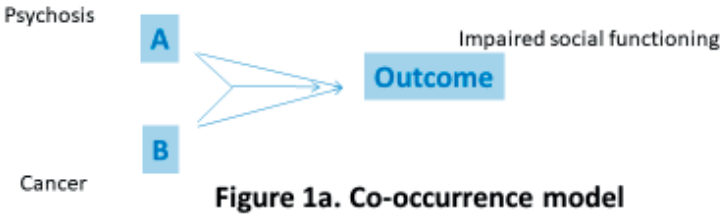


Figure 1a. Co-occurrence model

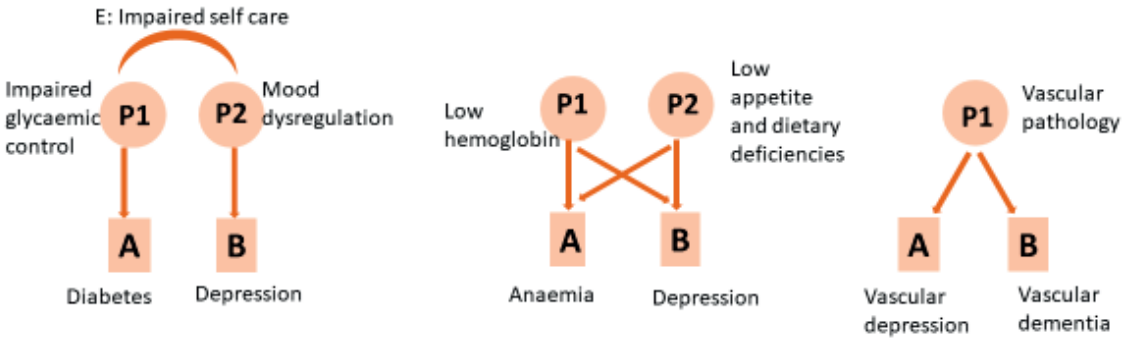


Figure 1b. Co-variance model

Abbreviations: E - Etiology, P - Pathogenesis, A and B - Disorders

exception[6]. Comorbidity, in the most simplified terms means presence of two distinct disorders. Comorbidity further could be a co-occurrence or co-variance. Figure 1a. shows co-occurrence where distinct additional clinical entity has existed or occurs during the clinical course of the index disease. The etiological factors are usually different for each of them although the outcomes can follow a common pathway. Psychosis and cancer could be an example of this, where the final outcome could still be same i.e. impaired social functioning.

Covariance, as shown in Figure 1b, could however have common underlying pathologies, or can influence course of each other. Depression, diabetes, hypertension, cardiovascular disorders usually follow covariance models.

1. Mental disorders as a cause of Physical disorders

Times, as old as that of Galen and Hippocrates, have raised speculations about psychological factors leading to physical illness. More recently, seminal work by Friedman and Rosenman[7] in 1974 and Matthews et al[8] in 1977 and a few others with accurate epidemiological methods, suggested that type A personality, with achievement- striving, irritable, angry characteristics had more probability of developing cardiovascular disorders. Unfavourable balance of LDL and HDL, elevated blood glucose levels, smoking and obesity, which are seen commonly in depression have been found to be causative of cardiovascular risk[9]. Excessive consumption of alcohol, similarly, can be causative of hepatic failure[10].

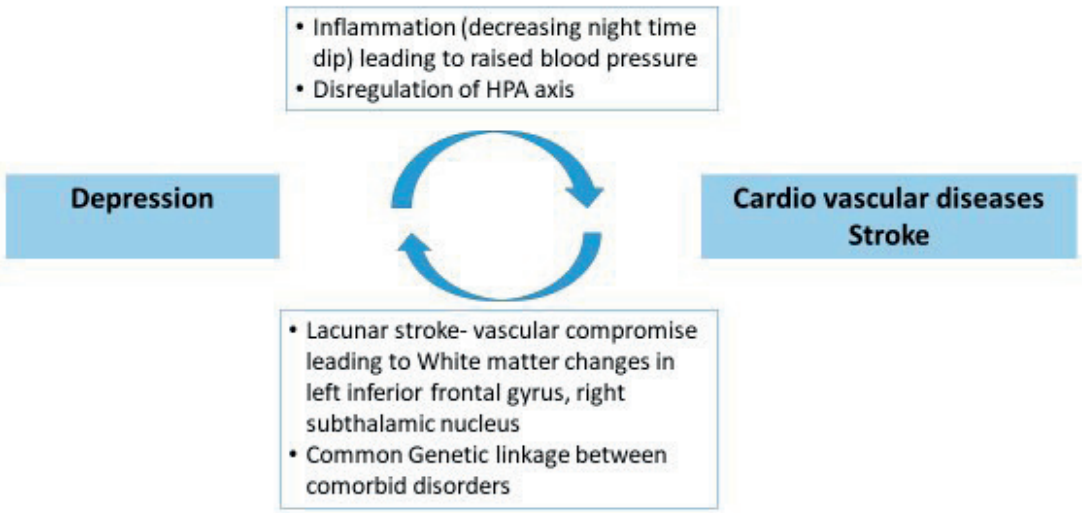
2. Mental disorders as consequence of physical disorders

Depression in hypothyroidism could be an example of how physical illness can consequently result into mental illness[11]. Higher prevalence of Depression and Anxiety disorders is seen in communicable diseases like HIV, Tuberculosis, Leprosy and most other diseases with chronic course.

3. Mental disorders and physical disorders with common etiological pathways

Vascular depression is a remarkable example of how common pathways can lead to differently presenting set of conditions. Krishnan et al[12] were the first to propose vascular changes that present as depression. The same vascular changes were found in pathogenesis of vascular dementias. In a few systematized epigenetic studies, polymorphisms of 5-Hydroxytryptamine by substitution of specific amino-acids have been found to be a common pathway of causation of depression as well as platelet aggregation abnormalities leading

Figure 2: **bidirectional factors of comorbidity**



to vascular pathologies[13]. Figure 2 shows bidirectional factors causing depression and cerbrovascular disorders like stroke.

With modern modalities of brain imaging, it is a growing consensus that most of the comorbid physical illness share common pathways of causation with mental illnesses. Furthermore, as the knowledge about neurobiology of mental illness is deepening, the compartments of cause and consequences of comorbidities are progressively blurring.

4. Mental illness as a medication adverse effect

A list of medications used to treat physical illness can be causative for mental illnesses. The converse also holds true for many psychotropic medications like anti-psychotics, anti-depressants, mood stabilizers and others. A few anti-tubercular drugs like Isoniazid, Rifampicin are known to cause psychosis. Corticosteroids are also causative of drug-induced psychosis. Certain anti-epileptic drugs like Levitiracetam are known to cause behavioural disturbances in children which include extroverted behaviours like irritability, agitation and aggressiveness.

Many first generation antipsychotics like Haloperidol and Trifluperazine result in extra-pyramidal side-effects and drug induced parkinsonism. Most of the second generation anti-psychotics like Olanzapine, Resperidone, Aripiprazole and Clozapine, on prolonged use, are known to cause metabolic syndrome, diabetes mellitus, weight gain, hypercholesterolemia and other cardio-vascular diseases. Mood stabilizers like Sodium Valproate can cause hepatic toxicity and thereby hepatic failure. While the list is long, it is important that all the drugs are used rationally and judiciously.

COMORBIDITY OF MENTAL DISORDERS WITH NON-COMMUNICABLE AND COMMUNICABLE DISEASES

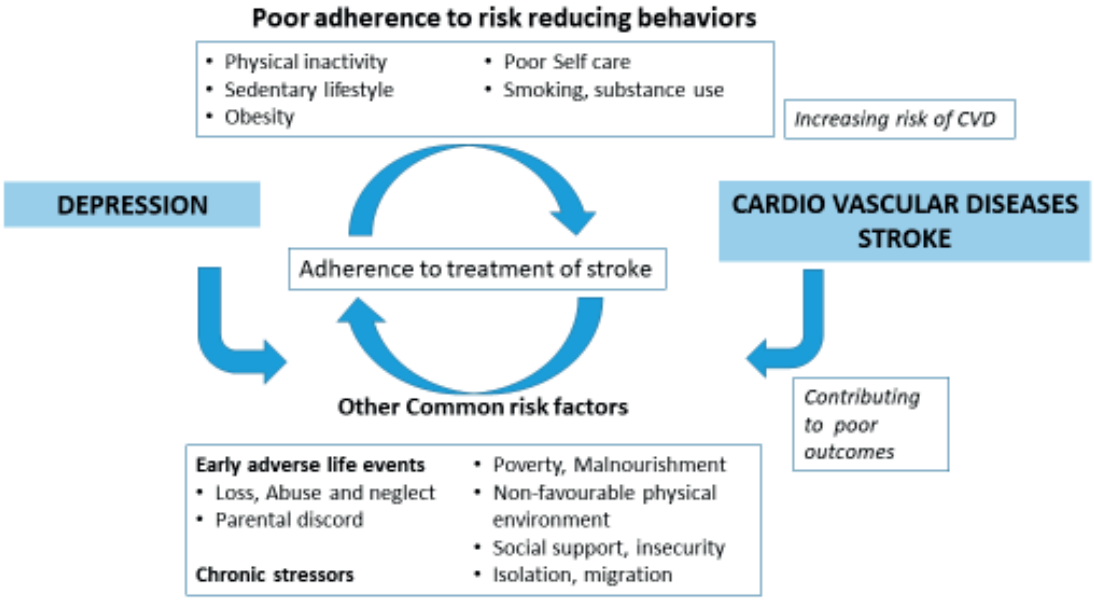
A. Mental disorders and Cardio-vascular Diseases

Several common well-recognized risk factors for cardiovascular disorders have been found in people with mental disorders. Patients are more likely to be overweight, more likely to smoke, more likely to have diabetes and dyslipidaemia.[14,15] Several meta-analyses of longitudinal studies have found depression to be a consistent predictor of subsequent first onset coronary artery disease[16], Stroke[17] and Myocardial infarction[18]. Figure 3 shows complex dynamics of risks and causation of cardiovascular disorders and depression.

B. Mental disorders and Diabetes

The relation between diabetes and depression is bidirectional: people with diabetes are more likely to develop depression, and depression is a risk factor for diabetes.[19,20] Diabetes is more common among people with psychosis and schizophrenia, because of the effects of atypical antipsychotic medications, links between diabetes and schizophrenia and cultural and lifestyle factors.

Figure 3: **Comorbidity of depression and stroke**



C. Mental disorders and cancer

About 25% of people with cancer have anxiety and/or depression.[21] Anxiety and/or depression in people with cancer is associated with a poorer quality of life, poorer compliance with treatment, longer hospitalization and a higher risk for suicide.[22] The lifestyle often associated with severe mental disorder increases the risk for cancer. For example, the rate of smoking among people with schizophrenia is as high as 80%, which increases their risk for lung cancer or pneumonia.

D. Smoking and mental health

One in three of all cigarettes smoked is smoked by a person with a mental disorder. People with long-term mental health problems face difficulty in quitting smoking than general population[23]. Nicotine increases the rate at which some antipsychotic drugs are metabolized, so that smokers require higher doses of the medication to achieve the same response

E. Mental disorders and communicable diseases

Communicable diseases with chronic course have been found to have heavy comorbidity with common mental illnesses like depression. 39% of HIV patients are reported to suffer from depression[24]. Prevalence of depressive symptoms in tuberculosis, in a study in India[25], was found to be as high as 84%. Similarly, higher prevalence of depression and anxiety disorders is also found in leprosy and many other diseases with chronic course. Adherence to medication regime was also found be inadequate in patients with chronic course of illness.

IMPORTANCE OF MANAGEMENT OF MENTAL HEALTH COMORBIDITIES

Treatment of mental disorders can prevent physical disorders

Techniques like behavioural activation, meditation and yoga, regular eating and sleeping habits are commonly recommended for treatment of depression and anxiety disorders. These healthy lifestyle methods have been found to prevent occurrence of NCDs.

Treatment of mental disorders improves adherence to treatment of physical disorders

Patients with mental wellbeing possess favourable attitudes towards long course management of communicable and non-communicable diseases.

Physical Impact of Mental Wellbeing

Studies have shown that high positive mood states (measured in terms of happiness, joy, contentment, and enthusiasm) lower morbidity, increased longevity, and reduced health symptoms.[26] Not only this but better endocrine function (lower levels of cortisol, epinephrine, norepinephrine) and better immune response (higher antibody production, greater resistance to illness) was found to be related to positive emotional

style[27]. Positive mood states lower inflammatory response and lower blood pressure. Higher levels of purpose in life, personal growth, and positive relationships lower cardiovascular risk (lower glycosylated haemoglobin, lower weight, lower waist-hip ratios, higher HDL cholesterol) and better neuroendocrine regulation (lower salivary cortisol throughout the day).[28]

Conclusions

1. It is very important to screen all patients with non-communicable diseases and long standing communicable diseases for common mental disorders like depression and anxiety disorder. Annexure 1 and 2 contain PHQ-9 and GAD scales for respective disorders.
2. It is also very important to obtain history of substance use in every patient presenting to a physician. Alcohol, tobacco and cannabis dependence is more common in population than presumed.
3. Simultaneous attention is warranted to both mental and physical illness.
4. Management of mild severity of depression and anxiety can be done by simple psychological interventions.
5. Management of moderate to severe variety of mental illness may require complex interventions and referral to a mental health professional.
6. Rational use of drugs is important to prevent complications and comorbidity.
7. Inversely, in patients with primary mental illness, physical symptoms are often neglected. Regular physical check-ups are recommended for patients with mental illness.

When a patient is the unit of treatment, effective management of all comorbidities may lead to greater patient satisfaction and better patient outcomes. After all, regaining of physical, occupational and social functionality should be the final goal of any health intervention.

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By **Dr Vivek Mundada**

Diagnosing Rare Diseases in a Resource-limited Setting: Using Telemedicine Approach

Medcare Women and Children Hospital recently collaborated with a genetic laboratory in India. Where needed, Clinical guidance or advice from the clinical geneticist and genetic counsellors was also provided in some cases. Such consultations were done online, and a Laboratory Coordinator was essential in facilitating communications between all the clinicians and patients.

Dr Vivek Mundada, Department of Paediatric Neuroscience, Medcare Hospital, Dubai, United Arab Emirates, Email: vivek.mundada@medcarehospital.com

A six-month-old female infant was referred by her paediatrician to me with a history of paroxysmal and stereotypical 'staring' episodes for a few weeks. On assessment, she had poor visual fixation, which looked like she was staring into something. On examination, she had dystonia in the limbs with some exaggerated deep tendon reflexes. She was still unable to sit with support and was just attempting to roll over from prone to supine.

With the probable visual impairment, she was referred to a paediatric ophthalmologist for further evaluation. He noticed "cherry red spots" on her retina. This child needed further metabolic and genetic workup for a confirmed diagnosis. Next-generation sequencing of the HEXA gene confirmed the diagnosis of GM2 gangliosidosis, which was confirmed by Sanger. The child had c.862G>A p.Gly288Arg variant in the HEXA gene. This diagnosis helped to explain the prognosis and to screen for other potential comorbidities in this child. Genetic counselling was also offered to the parents.

Although today this case can be confined to two paragraphs but organising such tests was like finding the needle in the haystack.

Why is this important?

Early detection of diseases may help in early intervention and treatment, which may either cure the disease or improve the outcome and quality of life of the patient. Spinal Muscular Atrophy is the best example of this. Gene replacement therapy is available for this condition. If given to any presymptomatic infant, they have the best outcome compared to someone who would receive it later in life. Moreover, it provides a full stop' to the parent's questions like 'what is wrong with my child' or 'what can be done 'what does the future lie for my children?

Moreover, additional further tests and frequent doctor's visits can be avoided. A study by Khneisser et al. estimated a reduction of the direct cost of care by 50% per detected case of inborn errors of metabolism [1]. The estimated difference in the price of care for a late detected case and a case detected by newborn screening was USD 82,000.

According to the Ministry of Health Statistics, congenital disorders are now known as the leading cause of infant mortality in the United Arab Emirates. The Middle East has high consanguinity rates, so genetic disorders are relatively common [2]. Paediatric neurological disorders encompass a large group of clinically heterogeneous diseases, of which many are known to have a genetic cause. Advances in nosological classifications and strategies for molecular testing have substantially improved the diagnosis, genetic counselling, and clinical management of many patients and have facilitated the possibility of prenatal diagnoses for future pregnancies [3]. A targeted and tailored therapeutic approach can be formulated based on the diagnosis. Precision medicine is on the rise in paediatric neurology, and one of the reasons is the accessibility and availability of appropriate investigations like genetic investigations.

Healthcare system in Dubai

Over 85% of Dubai's population Comprises residents of different nationalities, and healthcare is mainly driven by private institutes. The Public Healthcare system though open to all, is primarily used by Emirati Citizens. There are more than 130 private healthcare facilities in Dubai. Hence, many hospitals are not well equipped, and some services are usually unavailable or outsourced [4].

Insurance System for Advancing Healthcare in Dubai (ISAHD) is a comprehensive initiative of the Dubai Health Authority (DHA) intended to provide sustainable, high-quality healthcare in Dubai for nationals, residents and visitors, and this law has been effective since 2016 [5].

It is known that individuals with both genetic and other chronic medical conditions have difficulty obtaining health insurance. Also, these specialised tests come with high costs to the patients. The high cost of the test can be a significant barrier to even arranging such a test [6].

Method

Our hospital is a specialised hospital in Dubai catering to the healthcare needs of women and children. Specialised services like paediatric neurology have been shaping up in the hospital

for the last three years. Building up a multidisciplinary team and diagnostic services has been challenging, and gradually these services are shaping up. Since genetic tests cannot be performed in a hospital-based laboratory, we need to send these tests outside. In recent years, many laboratories have started processing the samples locally in Dubai. But previously, these samples were required to be shipped outside the country, like in Germany. Whole exome sequencing could cost 900-1200 Euros, while microarray could cost around 400-600 Euros. Some parents could not afford these tests, and the clinical care of the affected children got affected. Expats from India preferred to get these tests done in India since the tests are usually much cheaper there.

We requested sample test reports and quotations from different laboratories which operated in Dubai. Some of the Indian-based laboratories have operations in Dubai, and we invited them as well. Based on the consensus by the chief pathologist and the paediatric neurologist, one laboratory based in India was chosen, and an official collaboration was established between the hospital and the laboratory. The costs of the tests were almost the same as in India.

In recent years, many laboratories have started processing the samples locally in Dubai. But previously, these samples were required to be shipped outside the country, like in Germany. Whole exome sequencing could cost 900–1200 Euros, while microarray could cost around 400–600 Euros.

Results

Between January 2022 and November 2022, 35 referrals were made for genetic consultations and tests. A positive diagnosis was established in 10 children (28%) (table 1). Whole exome sequencing- solo was ordered in 77% of the cases, whereas tests like MLPA and gene panel NGS were ordered in the rest of the children. All these children received post-diagnosis genetic counselling through virtual platforms like Zoom from a registered genetic counsellor. Wherever an input of a clinical geneticist was needed, it was arranged by the same laboratory with their clinical geneticist in a similar way. All the queries by the referring physicians, as well as by the parents, were addressed by the clinical geneticist. If the clinical geneticist needed any additional clinical information, it was shared with him with the respective parent's consent by email.

In some cases, Sanger confirmation was needed, which was performed at no extra cost. This three-way communication was helpful in confirming the diagnosis. If any parent had any further queries, it was ensured that those were answered either by the paediatric neurologist or the clinical geneticist. A dedicated coordinator from the laboratory based in Dubai assisted and helped in arranging such consultations. Wherever there was confusion on the choice of the test, the clinical geneticist always provided the right and valuable guidance on the same after discussing the patient's clinical information.

In 5 cases (23%), parents of the index cases were also tested for Sanger confirmation. Such advice was offered by the clinical geneticist.

Discussion

Such collaboration with the Indian-based genetic laboratory has proven very useful for clinicians as well as patients since confirmed diagnoses were established in most of the children who needed such tests.

Costly tests like white cell enzymes, metabolic markers or neurotransmitters could be avoided due to these tests in all these 21 children.

Almost 400 million individuals suffer from some kind of rare disease in the world, and over two third of them are present in childhood. Despite advances in genetic and metabolic investigations, many of them remain undiagnosed.

Such diseases usually take a long time to get diagnosed. Moreover, many hospitals do not have laboratory facilities as well as experts to facilitate the diagnostic workup as they are limited to tertiary and quaternary centres only [7].

Although most of these conditions have a genetic cause, the average time from disease onset to accurate diagnosis for a rare disease is over four years [8]. An accurate diagnosis is needed to understand the prognosis and plan treatment for the child. Enzyme replacement therapy, gene replacement therapy, metabolites, etc., are now available for many rare diseases. It is essential to cut down this time as it is vital to have a diagnosis in hand to plan the appropriate management. This, in turn, can enhance the quality of life of the affected individual. Advances in genetic investigations and a reduction in the cost of such investigations have made these investigations more affordable to patients and their clinicians. Choosing the correct genetic test is very important. The geneticists also require accurate phenotypical information and family history to interpret the results. Although whole exome sequencing or whole genome sequencing-like tests are now available in most countries, they may not be the test of choice or universal in all rare diseases. Moreover, their result interpretation can sometimes be challenging due to a high incidence of rare benign variants and incomplete knowledge of them [9]. Hence, input by a clinical geneticist is essential in planning such genetic investigations and interpreting them in the clinical context.

We have tried to address these issues with the help of the genetic laboratory and the clinical geneticist based in India. With no clinical geneticist in the hospital team and a lack of such specialised genetic tests in the hospital laboratory, outsourcing these facilities was the only feasible option. This has reduced the cost to the patient significantly for such services. The patients could

Table 1. Genetic tests ordered and their results (WES- Whole exome sequencing; VUS- Variant of unknown significance; SMA- Spinal Muscular Atrophy; NF1- Neurofibromatosis type 1; MLPA- Multiplex Ligation Dependent Probe Amplification)

Patient	Test performed	Genetic test outcome	Interpretation
1	WES - SOLO	VUS in ZNF292 gene	
2	WES-SOLO	VUS in TBCD gene	
3	Microarray	arr[GRCh37]14q11.2 (21,019,129_22,102,374) x1 (Pathogenic)	5 (4.4%)
	Advised Sanger of twin sister	83 (92.2%)	7 (7.8%)
4	WES- SOLO	Pathogenic mutation in LMNA gene	Congenital muscular dystrophy
5	WES- SOLO	Pathogenic mutation in HEXA gene	GM2 Gangliosidosis
6	WES- SOLO	Pathogenic mutation in ERCC8 gene	Cockayne syndrome
7	SANGER CONFIRMATION	Heterozygous mutation in ERCC8 gene	
8	SANGER CONFIRMATION	No pathogenic mutation	
9	WES- SOLO	Pathogenic mutation in GNPTAB gene	Mucolipidosis II alpha/beta
10	WES- SOLO	Negative to clinical Indication	
11	WES- SOLO	Pathogenic mutation in MLC1 gene	Megalencephalic leukoencephalopathy
12	WES-SOLO	Negative to clinical Indication	
13	WES-SOLO	Pathogenic mutation in IDS gene	Hunter syndrome
14	WES-SOLO	VUS in OFD1 gene	
15	WES-SOLO	Likely pathogenic mutation in CSNK2B gene	Poirier-Bienvenu neurodevelopmental syndrome
16	SANGER CONFIRMATION	Heterozygous for COL6A2 gene	
17	SANGER CONFIRMATION	No pathogenic mutation	
18	MLPA+WES	Pathogenic mutation in SCN8A gene	Cognitive impairment with cerebellar ataxia
19	WES-SOLO	Pathogenic mutation in DYNC2H1gene	Short rib thoracic dysplasia with polydactyly

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Patient	Test performed	Genetic test outcome	Interpretation
20	SANGER CONFIRMATION	Heterozygous for MLC1 gene	
21	SANGER CONFIRMATION	Heterozygous for MLC1gene	
22	SANGER CONFIRMATION	No pathogenic mutation	
23	WES - SOLO	VUS in KCNT1 gene	
24	MLPA NF1	Negative	
25	WES - SOLO	VUS in WASHC5 gene	
26	WES-SOLO	No pathogenic mutation found	
27	WES-SOLO	VUS in RANBP2 gene	
28	WES-SOLO with epileptic encephalopathy Panel	No pathogenic mutation identified	
29	WES-SOLO with epileptic encephalopathy Panel	No pathogenic mutation identified	
30	WES-SOLO	Results awaited	
31	SMA MLPA	Negative	SUGGESTED FOR WES
32	SMA MLPA	Negative	SUGGESTED FOR WES
33	SMA MLPA	Negative	SUGGESTED FOR WES
34	WES SOLO	Results awaited	
35	WES SOLO	Results awaited	

be managed in a single centre as many parents usually prefer to travel to India or other countries to avail such facilities and expertise. Online genetic counselling has been proven beneficial in many studies [10, 11] and we adopted the same approach. This has also enabled continuity in clinical care and management as the same care providers and clinicians were involved in the disease presentation to the diagnosis process.

Conclusion

In a limited-resourced healthcare facility, a collaboration between experts and teams can be beneficial to fulfil the lacunae. Such a jigsaw approach can be helpful for patients as it reduces the cost and time needed to diagnose and manage many rare conditions. In today's times, many services like genetic counselling can be availed online. Hence experts from across borders and different countries can be included in the care of an affected individual.

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By Dr H V Shivaram & Dr Namitha Devaraj

Small Incision Rives Stoppa (SIRS) Technique for Simultaneous Ventral Hernia Mesh Repair During Bariatric Surgery

The simultaneous repair of ventral hernia along with bariatric surgery is the most suitable option to treat both morbid obesity and ventral hernia during the same hospitalization and anesthesia.

Introduction

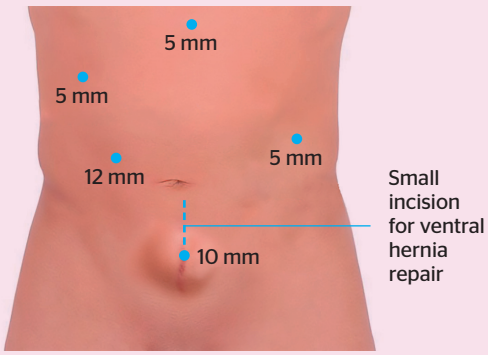
Bariatric surgery is the most effective method to treat morbid obesity and related comorbidities. With increasing prevalence of obesity, ventral hernia is a common problem faced. The prevalence of ventral hernia among morbidly obese patients undergoing gastric bypass is 8% [1] and this can be attributed to increased intra-abdominal pressure, abdominal wall weakness and obstructive airway disease [2]. The best method of managing ventral hernias in patients undergoing bariatric surgery is still debatable.

In bariatric surgeries enterotomies are created and hence classified as clean contaminated procedures. The laparoscopic ventral hernia mesh repair (IPOM – Intraperitoneal Onlay Mesh) when performed concomitantly with a bariatric surgery, places the mesh in contact with a sleeved or bypassed bowel, risking the mesh for infection [3]. In case of sleeve or gastric bypass leak, which is a known complication after any bariatric surgery, it will have disastrous consequences – peritonitis, mesh infection leading to mesh explantation and surgery to treat the leak. In case of recurrence of hernia, it would warrant another surgery. Hence, there is a need for a robust mesh repair technique which can be performed along with bariatric surgery safely without mesh bowel contact.

Surgical Technique

Morbidly obese patients who were willing for bariatric surgery and had midline ventral hernia were included. All were operated under general anaesthesia in supine position after giving prophylactic antibiotic. A 10mm supra umbilical port inserted by open technique. If the hernia is in the vicinity of the incision, contents are reduced before port placement. Other ports were inserted as required for the bariatric surgery (Fig. 1). Laparoscopy was performed to inspect the peritoneal cavity and the hernia defect (Fig. 2,3). If the hernia contents were irreducible earlier and was obstructing the view it was reduced laparoscopically. Then the bariatric surgery - Laparoscopic Sleeve Gastrectomy (LSG) or One Anastomosis

Figure 1: **Port marking and incision for ventral hernia repair**



Gastric Bypass (OAGB) was performed by the standard technique. Gastric calibration tube was used to guide stapling of the stomach and then removed at the end of the procedure after a leak test. In LSG, the stomach specimen is removed using an endobag. Pneumoperitoneum decompressed and ports retrieved.

Abdomen is painted again. The surgical team change their gloves. A vertical small incision of 4 to 5cm is made directly over the hernia and whenever possible the supraumbilical trocar incision was incorporated into it. Contents were reduced if not possible earlier (Fig. 4). Sac is dissected and excised. The retrorectus space is entered by separating the anterior and posterior rectus sheath lateral to the defect on either side using diathermy. The space between the rectus muscle and posterior rectus sheath is enlarged using a medium or small Deaver's retractor (Fig.5). The retractor is passed, lifting up the rectus abdominis superiorly towards epigastrium, inferiorly towards retropubic space and laterally upto the linea semilunaris, thus creating the retrorectus space. The midline dissection at linea alba is done under vision using cautery upto 6cm superior and inferior to the defect. Care is taken to safeguard the inferior epigastric artery. Thus, by using Deaver's retractor it is possible to create a large space for mesh placement in spite of a small skin incision.

Peritoneum along with posterior rectus sheath is closed using polydioxanone (PDS) suture. Because of the large retromuscular space, it is possible to place a 30X15cm medium weight polypropylene mesh (Fig. 6,7). Throughout the dissection and mesh placement, gentamicin irrigation (80mg gentamicin in 200ml saline) is done periodically. A suction drain can be placed as per surgeon's discretion. Anterior rectus sheath is closed using PDS. Skin is approximated using poliglecaprone or skin stapler (Fig. 8) https://youtu.be/MIYlD7QdXNs, https://youtu.be/zkzP-f5Aagfg. At the end of the surgery ultrasound guided Transversus Abdominis Block was given for analgesia. Post operatively, oral liquids was started after 6hours, mobilised and discharged after 48-72 hours as in case of any bariatric surgery.

Results

A total of 167 Bariatric surgeries were performed between June 2016 and November 2020 in our institution. Among them 21 patients had ventral hernia- 19 had uncomplicated midline ventral hernia of less than 5cm in the umbilical or epigastric region and were included for this study, remaining 2 underwent ventral hernia repair at a later date. All are under follow up.

Amongst the 19 patients who underwent SIRS with bariatric surgery, 12 had OAGB and 7 had LSG. The mean BMI was 48.04kg/m2 (36.7-62.1kg/m2). The mean operative time was 130 min (105-150min). Mean VAS on POD 1 was 2 (1-5) and was assessed by a single observer throughout. The mean hospital stay was 3days (2-5 days).

One patient had a sleeve leak requiring re-laparoscopy, leak site closure and nasojejunal tube insertion. However the mesh did not get infected. Patients were followed up every 6 months with a mean follow up of 47months (24-72months). None of our patients had any mesh related complications or recurrence on long term follow-up.

Figure 5. Deaver's retractor for blunt dissection

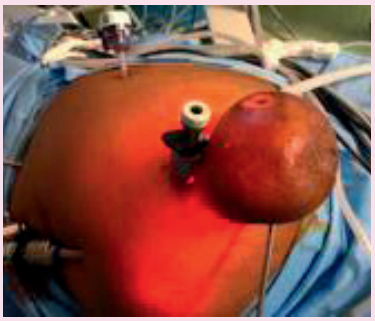


Figure 2. Ventral hernia as seen after insufflation.

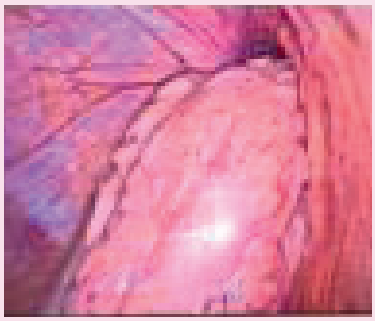


Figure 3. Laparoscopic view of ventral hernia content

Figure 4. Irreducible ventral hernia with omentum as its content

Figure 6. Placing of a 30X15cm polypropylene mesh

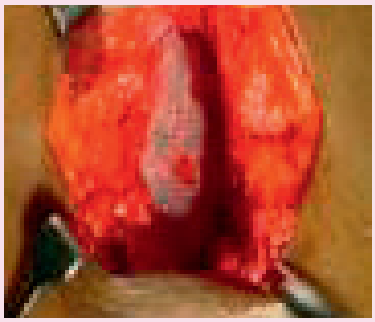


Figure 7. Mesh as seen in the retrorectus space.

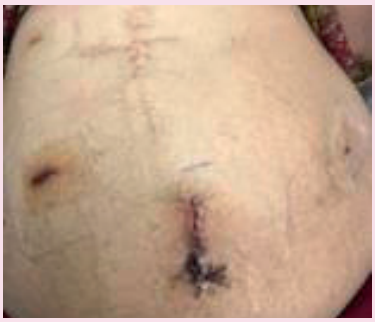


Figure 8. Post-operative wound

Discussion

Whenever simultaneous repair is done along with bariatric surgery IPOM is preferred. Intraperitoneal mesh usage is increasingly being avoided, in view of complications like bowel adhesions, obstruction and fistulisation [4]. Also, with the use of dual mesh procedure cost goes up. While IPOM repair is well-established, the current trend in most centres favours extra peritoneal mesh placement as in extended view totally extraperitoneal repair [5].

SIRS along with bariatric surgery is a novel technique conceived and designed in order to demonstrate its feasibility in obese patients with a ventral hernia. In our experience, SIRS technique for ventral hernia repair along with a bariatric procedure like OAGB, LSG can be considered routinely for appropriately selected midline ventral hernias as it has the advantage of placing a larger mesh using a small incision and without adding any morbidity or mortality. Also, the overall cost is reduced by using polypropylene mesh and no special instruments. This is the first such technique being described according to our knowledge. Additionally, in cases of leak, the mesh may not get infected and can be salvaged as it does not come in contact with the viscera. However, further studies with case control/randomisation and with larger numbers is recommended to support our study.

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Feature

By **Adam Satariano and Cade Metz**

Using A.I. to Detect Breast Cancer That Doctors Miss

Hungary has become a major testing ground for A.I. software to spot cancer, as doctors debate whether the technology will replace them in medical jobs.

Inside a dark room at Bács-Kiskun County Hospital outside Budapest, Dr. Éva Ambrózay, a radiologist with more than two decades of experience, peered at a computer monitor showing a patient's mammogram.

Two radiologists had previously said the X-ray did not show any signs that the patient had breast cancer. But Dr. Ambrózay was looking closely at several areas of the scan circled in red, which artificial intelligence software had flagged as potentially cancerous.

"This is something," she said. She soon ordered the woman to be called back for a biopsy, which is taking place within the next week.

Advancements in A.I. are beginning to deliver breakthroughs in breast cancer screening by detecting the signs that doctors miss. So far, the technology is showing an impressive ability to spot cancer at least as well as human radiologists, according to early results and radiologists, in what is one of the most tangible signs to date of how A.I. can improve public health.

Hungary, which has a robust breast cancer screening program, is one of the largest testing grounds for the technology on real patients. At five hospitals and clinics that perform more than 35,000 screenings a year, A.I. systems were rolled out starting in 2021 and now help to check for signs of cancer that a radiologist may have overlooked. Clinics and hospitals in the United States, Britain and the European Union are also beginning to test or provide data to help develop the systems.

A.I. usage is growing as the technology has become the center of a Silicon Valley boom, with the release of chatbots like ChatGPTshowing how A.I. has a remarkable ability to communicate in humanlike prose — sometimes with worrying results. Built off a similar form used by chatbots that is modeled on the human brain, the breast cancer screening technology shows other ways that A.I. is seeping into everyday life.

Widespread use of the cancer detection technology still faces many hurdles, doctors and A.I. developers said. Additional clinical trials are needed before the systems can be more widely adopted as an automated second or third reader of breast cancer screens, beyond the limited number of places now using the technology. The tool must also show it can produce accurate results on women of all ages, ethnicities and body types. And the technology must prove it can recognize more complex forms of breast cancer and cut down on false-positives that are not cancerous, radiologists said.

The A.I. tools have also prompted a debate about whether they will replace human radiologists, with makers of the technology facing regulatory scrutiny and resistance from some doctors and health institutions. For now, those fears appear overblown, with many experts saying the technology will be effective and trusted by patients only if it is used in partnership with trained doctors.

And ultimately, A.I. could be lifesaving, said Dr. László Tabár, a leading mammography educator in Europe who said he was won over by the technology after reviewing its performance in breast cancer screening from several vendors.

"I'm dreaming about the day when women are going to a breast cancer center and they are asking, 'Do you have A.I. or not?'" he said.

Hundreds of images a day

In 2016, Geoff Hinton, one of the world's leading A.I. researchers, argued the technology would eclipse the skills of a radiologist within five years.

"I think that if you work as a radiologist, you are like Wile E. Coyote in the cartoon," he told The New Yorker in 2017. "You're already over the edge of the cliff, but you haven't yet looked down. There's no ground underneath."

Mr. Hinton and two of his students at the University of Toronto built an image recognition system that could accurately identify common objects like flowers, dogs and cars. The

technology at the heart of their system — called a neural network — is modeled on how the human brain processes information from different sources. It is what is used to identify people and animals in images posted to apps like Google Photos, and allows Siri and Alexa to recognize the words people speak. Neural networks also drove the new wave of chatbots like ChatGPT.

Many A.I. evangelists believed such technology could easily be applied to detect illness and disease, like breast cancer in a mammogram. In 2020, there were 2.3 million breast cancer diagnoses and 685,000 deaths from the disease, according to the World Health Organization.

But not everyone felt replacing radiologists would be as easy as Mr. Hinton predicted. Peter Kecskemethy, a computer scientist who co-founded Kheiron Medical Technologies, a software company that develops A.I. tools to assist radiologists detect early signs of cancer, knew the reality would be more complicated.

Mr. Kecskemethy grew up in Hungary spending time at one of Budapest's largest hospitals. His mother was a radiologist, which gave him a firsthand look at the difficulties of finding a small malignancy within an image. Radiologists often spend hours every day in a dark room looking at hundreds of images and making life-altering decisions for patients.

"It's so easy to miss tiny lesions," said Dr. Edith Karpati, Mr. Kecskemethy's mother, who is now a medical product director at Kheiron. "It's not possible to stay focused."

Mr. Kecskemethy, along with Kheiron's co-founder, Tobias Rijken, an expert in machine learning, said A.I. should assist doctors. To train their A.I. systems, they collected more than five million historical mammograms of patients whose diagnoses were already known, provided by clinics in Hungary and Argentina, as well as academic institutions, such as Emory University. The company, which is in London, also pays 12 radiologists to label images using special software that teaches the A.I. to spot a cancerous growth by its shape, density, location and other factors.

From the millions of cases the system is fed, the technology creates a mathematical representation of normal mammograms and those with cancers. With the ability to look at each image in a more granular way than the human eye, it then compares that baseline to find abnormalities in each mammogram.

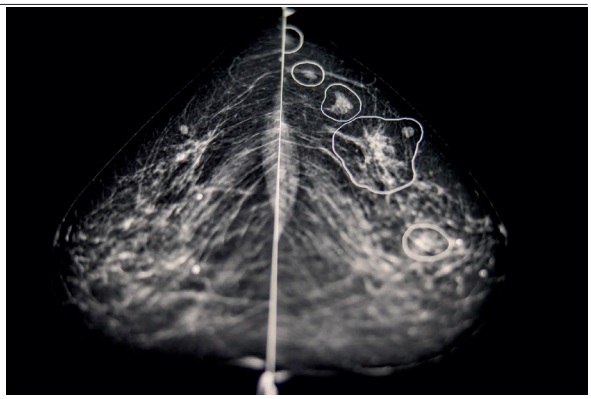
Last year, after a test on more than 275,000 breast cancer cases, Kheiron reported that its A.I. software matched the performance of human radiologists when acting as the second reader of mammography scans. It also cut down on radiologists' workloads by at least 30 percent because it reduced the number of X-rays they needed to read. In other results from a Hungarian clinic last year, the technology increased the cancer detection rate by 13 percent because more malignancies were identified.

Dr. Tabár, whose techniques for reading a mammogram are commonly used by radiologists, tried the software in 2021 by retrieving several of the most challenging cases of his career in which radiologists missed the signs of a developing cancer. In every instance, the A.I. spotted it

"I was shockingly surprised at how good it was," Dr. Tabár said. He said that he did not have any financial connections to Kheiron when he first tested the technology and has since received an advisory fee for feedback to improve

Last year, after a test on more than 275,000 breast cancer cases, Kheiron reported that its A.I. software matched the performance of human radiologists when acting as the second reader of mammography scans.

Peter Kecskemethy, a founder of Kheiron Medical Technologies, and his mother, Dr. Edith Karpati, who was a radiologist, with an X-ray data that was fed into A.I. models.



Possible anomalies in a breast cancer screen are highlighted by the A.I. software.

Photographs by Akos Stiller

the systems. Systems he tested from other A.I. companies, including Lunit Insight from South Korea and Vara from Germany, have also delivered encouraging detection results, he said.

Proof in Hungary

Kheiron's technology was first used on patients in 2021 in a small clinic in Budapest called MaMMa Klinika. After a mammogram is completed, two radiologists review it for signs of cancer. Then the A.I. either agrees with the doctors or flags areas to check again.

Across five MaMMa Klinika sites in Hungary, 22 cases have been documented since 2021 in which the A.I. identified a cancer missed by radiologists, with about 40 more under review.

"It's a huge breakthrough," said Dr. András Vadászy, the director of MaMMa Klinika, who was introduced to Kheiron through Dr. Karpati, Mr. Kecskemethy's mother. "If this process will save one or two lives, it will be worth it."

Kheiron said the technology worked best alongside doctors, not in lieu of them. Scotland's National Health Service will use it as an additional reader of mammography scans at six sites, and it will be in about 30 breast cancer screening sites operated by England's National Health Service by the end of the year. Oulu University Hospital in Finland plans to use the technology as well, and a bus will travel around Oman this year to perform breast cancer screenings using A.I.

"An A.I.-plus-doctor should replace doctor alone, but an A.I. should not replace the doctor," Mr. Kecskemethy said.

The National Cancer Institute has estimated that about 20 percent of breast cancers are missed during screening mammograms.

Dr. Constance Lehman, a professor of radiology at Harvard Medical School and a breast imaging specialist at Massachusetts General Hospital, urged doctors to keep an open mind.

"We are not irrelevant," she said, "but there are tasks that are better done with computers."

At Bács-Kiskun County Hospital outside Budapest, Dr. Ambrózay said she had initially been skeptical of the technology — but was quickly won over. She pulled up the X-ray of a 58-year-old woman with a tiny tumor spotted by the A.I. that Dr. Ambrózay had a hard time seeing.

The A.I. saw something, she said, "that seemed to appear out of nowhere."

Colovesical Fistula: A Complication of Sigmoid Diverticulitis – A Case Series

We present here the cases of two patients who presented with recurrent urinary tract infections (UTIs) and pneumaturia, as well as a third case who presented with recurrent attacks of lower abdominal pain. Diagnosis was confirmed through computed tomography (CT) imaging, magnetic resonance imaging (MRI) and/or cystoscopy.

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Keywords:

Colovesical Fistula, Sigmoid Diverticulitis, Adhesiolysis, Hartmann's procedure

Abbreviations:

EVF - Enterovesical fistulae
UTI - urinary tract infections
NPO – Nil per os
POD – Post operative day
CT – Computed Tomography
IV – intravenous
MRI – Magnetic Resonance Imaging

ABSTRACT

Colovesical fistula is a the most common type of enterovesical fistulae, and is most often caused by an inflammatory process, with diverticulitis being the most common cause. We present here the cases of two patients who presented with recurrent urinary tract infections (UTIs) and pneumaturia, as well as a third case who presented with recurrent attacks of lower abdominal pain. Diagnosis was confirmed through computed tomography (CT) imaging, magnetic resonance imaging (MRI) and/or cystoscopy. Surgical management is detailed and discussed, including single-staged & two-staged repairs.

INTRODUCTION

An enterovesical fistula (EVF) is a connection between the epithelialized surfaces of the urinary bladder and the gastrointestinal tract. The most common cause of colovesical fistula – which is an epithelialized tract between the colon and the urinary bladder – is diverticular disease, accounting for almost 80% of cases. [1, 2] Colonic adenocarcinoma which invades the urinary bladder and Crohn's disease are the second and third most common causes of colovesical fistula. Enterovesical fistulae are rarely iatrogenic, with radical prostatectomy accounting for a noteworthy proportion of rectourethral fistulae. [3,4]

The disease process of colovesical fistulae begins with the formation of false diverticula in the sigmoid colon, characterized by the protrusion of the mucosa and submucosa through the muscularis propria where the vasa recta enter the colonic wall to supply blood to the mucosa/submucosa (the point of entry of vasa recta is a place of relative weakness of the mesenteric side of the colonic wall). High intraluminal pressure, muscularis hypertrophy, abnormal peristalsis, and narrowing of the lumen, are all factors that contribute to the outpouchings known as diverticula.

The increased intraluminal pressure and altered colonic motility direct force radially into the diverticula, resulting in micro and macro perforations (diverticulitis), which can cause a diverticular abscess or phlegmon that ruptures into an adjacent organ, creating an inflammatory fibrous tissue tract between the two lumens, or a "fistula." [4, 5]

Fistulae are a rare complication of diverticular disease with an incidence rate of 5% [6] whereas up to 35% of Crohn's patients develop fistulas. [4]

CASE PRESENTATION

Case 1

A 59-year-old male was referred to the General Surgery Clinic from the Urology Department, with complaints of lower abdominal pain, pneumaturia, and recurrent urinary tract infections (UTIs). On clinical examination, the patient had suprapubic tenderness. His past medical history included hypertension which was controlled with one medication. Surgical history included multiple cystoscopies, one open surgery for management of urolithiasis, as well as a diagnostic laparoscopy for the biopsy of a retroperitoneal mass, which was found to be benign.

A Computed Tomographic (CT) scan revealed a small connection between the sigmoid colon and the left lateral wall of the urinary bladder, as well as an air locule in the urinary bladder. The benign retroperitoneal mass was also visualized and compared to previous CT scans, with no changes found. Cystoscopy showed an opening in the left lateral wall of the urinary bladder, thought to be the opening of the colovesical fistula. A colonoscopy done a few months prior to presentation revealed diverticulosis.

Surgical intervention involved cystoscopy with prophylactic ureteric stenting and a laparoscopic resection of the colovesical fistula as well as a sigmoidectomy and a Hartmann's procedure. Post-operatively, Foley's catheter was kept for 3 days, colostomy was functioning normally. The patient was started on a clear liquid diet on postoperative day (POD) 2 and gradually returned to a full diet over 3 weeks. A second surgery was performed 6 weeks later for reversal of colostomy and colorectal anastomosis. Post-operatively, the patient had a normal bowel movement on POD 4 and gradually returned to normal diet over 4 weeks. He developed a surgical wound infection, which was managed with daily drainage, washing, and dressing as well as intravenous (IV) antibiotics.

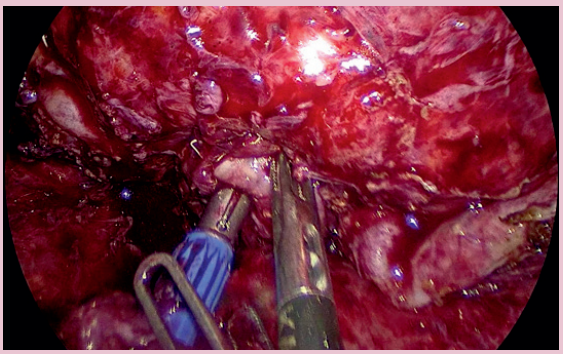

Figure 1: Using a circular stapler for colorectal anastomosis.

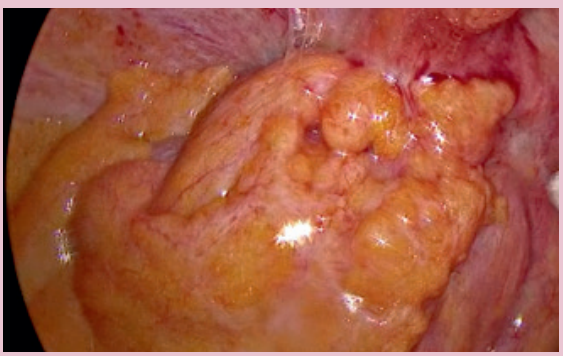

Figure 2: Laparoscopic image showing site of diverticular disease and abscess.

Case 2

A 52-year-old male was referred to the General Surgery Clinic by the Department of Gastroenterology after a colonoscopy revealed diverticulosis. The patient complained of lower abdominal pain and pneumaturia. He had no past medical or surgical history.

On examination, the patient had lower abdominal tenderness.

CT scan revealed air in the urinary bladder as well as a connection between the sigmoid colon and the urinary bladder.

A surgical plan was discussed with the patient with the risks explained, and consent was taken. Foley's catheter was inserted under general anesthesia. Surgery was started with a laparoscopic approach, revealing severe adhesions between the sigmoid colon, small intestines, appendix, and urinary bladder, forming a mass that was completely blocking the pelvic inlet. Adhesiolysis to free the small intestines was done first, after which a small perforation was found on the small intestinal wall. Extensive adhesiolysis was done to separate the sigmoid colon from the posterior wall of

the urinary bladder, and then around the sigmoid colon to enter the pelvis. Adhesiolysis was continued down to the level of the rectum, during which a pelvic abscess was found and drained. An intra-operative cystoscopy was performed revealing the opening of the fistula in the right lower segment of the bladder. An intra-operative digital rectal examination was also performed. The fistula tract was never seen, and no repair was performed on the bladder.

Primary colorectal anastomosis was ruled out due to the high risk of anastomotic failure anticipated because of the severe inflammatory state of the rectum, the pelvic abscess found intra-operatively, and leakage of stool from the resected portion of the colon. Hence, the descending colon was freed from adhesions to the lateral abdominal wall, and Hartmann's procedure was done, along with an appendectomy as well as resection and anastomosis of the perforated section of small intestines. Urine was clear throughout the surgery and cystoscopy ensured no bladder injury. Post-operatively, the patient was kept NPO until POD 2, then started on clear liquids when colostomy showed gas output. A Gastrografin enema was done to inspect the rectal stump for leakage on POD 5; no leak was detected. Foley's catheter was removed on POD 6.

The patient gradually returned to a normal diet with a plan for colorectal anastomosis in 6-8 weeks. The colorectal anastomosis was performed 7 weeks after the initial surgery, with a protective loop ileostomy, which was reversed 6 weeks later.

Case 3

A 68-year-old female was referred by the Gastroenterology Department, after MRI findings of sigmoid diverticulitis with a para-colic abscess, as well as mural thickening of the sigmoid colon & urinary bladder. Patient had presented with left lower abdominal pain radiating to the supra-pubic area, as well as burning on micturition. On examination, patient had supra-pubic tenderness. Her past medical history included hypertension, controlled with one medication. Conservative management including IV antibiotics & keeping the patient NPO, as well as CT-guided drainage of the abscess, failed to resolve the patient's symptoms.

Laparoscopic left hemicolectomy with recto-colic anastomosis was performed. During the surgery, the abscess was drained, a colovesical fistula was identified transected & closed, dissection carried to free the descending colon, resect the affected portion then perform the colorectal anastomosis; the specimen was removed via a midline, small infra-umbilical incision.

Post-operatively, Foley's catheter was kept for 2 days; patient was started on clear liquid diet on post-operative day 3 and gradually returned to normal diet over the course of 3 weeks.

DISCUSSION AND CONCLUSION

The most common presenting symptoms of enterovesical fistulae are terminal pneumaturia, fecaluria, abdominal pain, and recurrent UTIs. [7] Less frequent symptoms include hematuria, urine per rectum (on account of the urinary bladder being a very compliant organ and having a lower intraluminal pressure as compared to the colon), and an inflammatory mass [3] (similar to the operative findings in our second case). Other causes of pneumaturia, such as infections with gas-forming bacteria [8], must be excluded.

Charcoal or poppy seed tests, which involve the oral ingestion of either of the two and then evaluating urine for their presence, have shown high sensitivity for confirming the presence of enterovesical fistulae. [9, 10] These tests are simple and cheap to perform but provide no input on the etiology or anatomy of the fistula tract.

Imaging studies are used to visualize and delineate the fistulous tract. The American College of Radiology recommends CT scanning as the first-line imaging modality for the diagnosis of enterovesical fistulae. CT scan with oral contrast should be performed before IV contrast administration, to allow the visualization of Gastrografin (oral contrast) within the bladder, a finding suggestive of enterovesical fistula. Other indicative findings include colonic diverticula, wall thickening of the bladder and adjacent bowel, and the pathognomonic feature of air within the bladder. [11] CT scanning may not be able to accurately delineate the fistulous tract as compared to MRI, but it is useful in detecting the location of the fistula, as well as identifying extraluminal pathology and malignancy. [3,4]

A study recommended cystoscopy and urine cytology for fecal material as first-line investigations when suspecting an enterovesical fistula. [12] Cystoscopy visualization of an area of localized erythema, edema, and congestion in the bladder mucosa is suggestive of a fistula. [3]

Colonoscopy is used to find the bowel pathology causing the enterovesical fistula rather than visualizing the fistula tract, [3] and is recommended as a first-line investigation if malignancy is suspected on a CT scan. [13]

Once the presence of an enterovesical fistula is confirmed, surgical intervention is generally warranted,

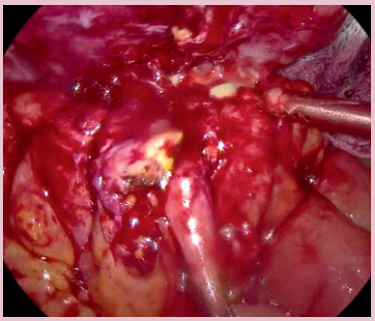

Figure 3: Drainage of abscess.

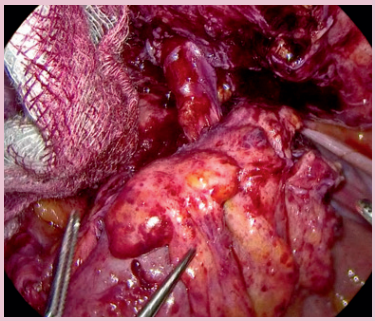

Figure 4: Colo-vesical fistula.

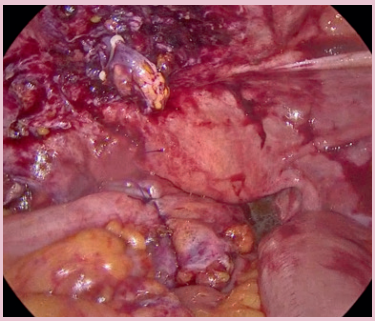

Figure 5: Colorectal anastomosis.

with conservative management reserved for those unfit for surgery, those with minimal symptoms with a nonmalignant origin of the enterovesical fistula, those with a nonresectable neoplastic process, and those who refuse surgical treatment. [3,4,11] Operative management can be single-staged (as with our third case) or multi-staged (as with our first 2 patients), depending on the location and cause of fistula, clinical condition of the patient, operative findings, and whether the patient was operated on electively or emergently. [3,5] The purpose of surgical intervention is to relieve the patient's symptoms and treat the underlying pathology, which meant definitive pelvic dissection as well as resection of the fistula and involved sections of the bowel, plus either a primary anastomosis with or without the creation of a diverting stoma or a Hartmann's procedure.

A single-staged repair should be the first option in most cases; it involves the resection of the fistula and involved segment of the bowel with primary anastomosis. Single-stage procedures in those with an inflammatory cause of fistula, are associated with decreased morbidity and shorter hospital stays. [14] Among the reasons to consider a multi-staged repair are severe inflammation, large pelvic abscesses, gross fecal contamination, advanced malignancy, inadequate bowel preparation in emergency cases, and intra-operative complications like ureteric injury. [3,14] A two-staged procedure involves the resection of the fistula and involved segment of the bowel, as well as primary anastomosis with a diverting/protective ileostomy, or a Hartmann's procedure. This should be the chosen pathway for those who would not survive an anastomotic leakage due to co-morbidities. A diverting ileostomy is usually reverted through the ileostomy site, whereas a Hartmann's procedure may need a laparotomy approach to restore intestinal continuity. Three-staged repair, involving a defunctioning colostomy, followed by resection and eventual anastomosis, is not usually recommended. It is usually reserved for patients with extensive comorbidities, associated fecal incontinence, or emergency cases presenting with sepsis.

Bladder repair depends on the intraoperative visualization of the fistulous tract, the presence of an abscess, and the underlying causative pathology. Partial cystectomy or ileal conduit may be necessary in cases of bladder malignancy. Methylene blue can be used to distend and visualize the fistulous tract, then excision of the tract with primary closure can be performed. Other methods of managing the bladder include suprapubic cystostomy, omental interposition, and bladder drainage with a urinary catheter. A study of 74 cases of enterovesical fistula caused by diverticulitis or Crohn's disease, concluded that bladder repair is only necessary when an obvious defect is seen. The majority of their patients were managed with post-operative urinary catheterization, which was sufficient for bladder healing. [15]

A retrospective study of 32 patients with enterovesical fistula due to diverticulitis reported no complications in patients who had their Foley's catheter removed on the 7th postoperative day, as compared to those who had late catheter removal. [16] There is no consensus on the need for prophylactic ureteric stenting. It is not associated with a high risk of complications and does not ensure the prevention of ureteral injury or detection of said injuries. [17, 18, 19]

In summary, we presented a case series of 3 patients with EVF managed surgically, with two cases of two-stage repairs involving Hartmann's procedure, and one of sigmoidectomy with primary colorectal anastomosis. Bladder repair was performed in the first case, fistulous tract was identified then cut & closed in the third case;

whereas, in the second case, the fistulous tract/defect in the bladder could not be visualized, deeming surgical repair unnecessary and urinary decompression with Foley's catheterization as the best option.

Through this case series, we concluded that surgical intervention of colovesical fistulae is preferred over conservative management, due to the repeated number of UTIs experienced by our patients during the period of conservative treatment, and the risk of urosepsis it carries. Decision regarding steps of repair should be individualized and based on surgical preparation and findings, mainly the ability to mobilize the colon for a safe, tension-free anastomosis.

STATEMENTS

Ethical Approval: This case series was presented to & reviewed by the Ethical Committee at Medcare Hospital, ethical clearance was provided to carry out the study at Medcare Hospital. Ethical approval decision reference number: MCH|Ethics|001, granted on 01/10/2022.

Informed Consent & Written Informed Consent: consent & written informed consent for publication of the cases details with any accompanying images was taken from all three patients involved in this case series. Written consent will be made available to the Editor upon request.

Conflict of Interest Statement: The authors have no conflict of interest to declare.

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Author Contributions: Dr. Hussam Al Trabulsi contributed to the acquisition, analysis and interpretation of the work; Dr. Issam Hreirati and Dr. Tala Muassess contributed to drafting the case series and revising it critically for important intellectual content. All three authors agreed to be accountable for all aspects of the work. Dr. Hussam Al Trabulsi provided the final approval of the version to be published.

Data Availability Statement: Data is available in Medical Records Department at Medcare Hospital, and would be provided upon reasonable request while protecting patients' anonymity.

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Case Report

Timely Diagnosis and Management of Spontaneous Pneumothorax in an One Day Old Baby

Here we report a case of newborn who in the absence of any other predisposing factors presented with pneumothorax of the right lung. The baby recovered after timely procedure of needle drainage followed by intercostal drain insertion due to early recognition of the pneumothorax.

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Keywords:

Intercostal drain, needle aspiration, spontaneous pneumothorax .

Abbreviations:

LSCS- Lower segment caesarian section, ICD – Inter costal Drain, NICU – Neonatal Intensive Care Unit, CT – Computed Tomography, CCAM – Congenital Cystic Adenomatoid malformation, CPAM- Congenital Pulmonary Airway malformation PIP Peak Inspiratory Pressure, PEEP – Positive End Expiratory Pressure, SIMV- Synchronous Intermittent Mandatory Ventilation

ABSTRACT

Spontaneous pneumothorax in newborn without risk factors is a rare entity. Timely diagnosis is needed to prevent mortality in such an event. Here we report a case of newborn who in the absence of any other predisposing factors presented with pneumothorax of the right lung. The baby recovered after timely procedure of needle drainage followed by intercostal drain insertion due to early recognition of the pneumothorax. Only a few case reports of spontaneous pneumothorax have been reported in the literature so far.

INTRODUCTION

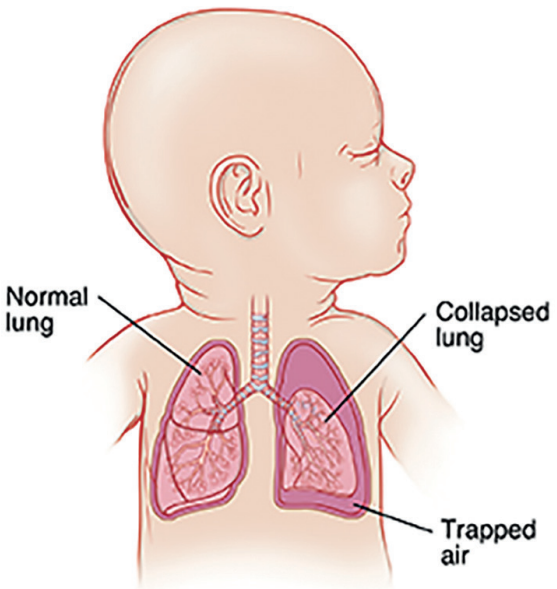
Spontaneous pneumothorax can be present after birth in 1–2% of all infants and may be symptomatic in approximately half of these. The rate can increase to up to 30% in patients who have concurrent underlying lung disease or who require mechanical ventilation. It is twice as high in males as compared to female infants. [1,2] If pneumothorax occurs during antenatal period fetal distress is the commonest presentation. This free accumulation of air between parietal and visceral pleura requires urgent intervention in order to re-expand the lungs. If pneumothorax occurs at birth, The high pulmonary pressure caused by the new onset of breathing or aggressive resuscitative measure could be the probable cause.[3] The early diagnosis and treatment of neonatal pneumothorax is critical and any delay in the intervention can turn lethal for the baby. Some specific risk factors in term newborn well known for pneumothorax are Respiratory distress syndrome, Meconium aspiration syndrome, Congenital malformations, Transient tachypnea of newborn and Mechanical ventilation.[4,5,6,7] Though many case reports of neonatal pneumothorax are published in the post surfactant era

in preterm babies, term baby developing spontaneous pneumothorax is a rare entity. The outcome is variable in such cases and is worst if not managed on time. [8]

We report a case of spontaneous pneumothorax of right lung without any risk factors who was diagnosed early due to high index of suspicion and managed successfully with a good outcome

CASE REPORT

A second gravida mother with no antenatal risk factors and normal scans and regular antenatal follow ups delivered a male baby at term gestation via caesarean section due to previous LSCS delivery and non-progress of labor. Baby weighed 3 kilograms at birth, did not need any resuscitation measures, cried immediately with an Apgar score of 8/10 at 1 minute and 9/10 at 5 minutes. Baby was shifted to mother's side after birth and initiated on breastfeeds. At six hours of age, baby was found to be pale, with saturations of 84 and tachypnea. Immediate transillumination test was done followed by chest x ray which confirmed a right sided pneumothorax. Immediate needle aspiration of the air was done with some improvement in the clinical condition but the air re-accumulated within an hour as evidenced by sudden deterioration with increased respiratory distress and desaturations despite the first aspiration again in NICU. Hence second needle aspiration was done while preparing for ICD insertion which was done shortly thereafter. The baby was ventilated and evaluated for other causes of respiratory distress such as cardiac conditions, infection, congenital pneumonia and congenital malformations of lung with blood tests, chest Xray and CT scan. Chest X ray showed right sided pneumothorax. Arterial blood gas done showed a pH of 7.286, pCo2-43.7, pO2-34.4, bicarbonate of 18.9, lactate of 5.91. Complete blood count showed a total count of 17,900 per microliter with neutrophils 58.7%, Absolute neutrophil count of 10.5, Hb of 13.6 grams per deciliter, platelet count of 2,32,000. C reactive protein was negative. Electrolytes done showed a Serum sodium of 145mmol/l, Serum Potassium of 4.12mmol/l. Renal parameters done showed creatinine of 0.53mg/dl, urea 32.40mg/dl. Neurosonogram and Ultrasound abdomen done were normal. 2D Echocardiography showed normal intracardiac anatomy with left sided aortic arch with no septal or valvular defects. CT scan was done to rule out congenital anomalies such as CCAM, CPAM or other solitary cysts which can rupture and cause pneumothorax in which case it can be recurrent were absent. Lung parenchyma was



reported normal except for the residual pneumothorax.

During subsequent course in the hospital, baby showed steady improvement with resolution of pneumothorax by day 5 when the ICD was removed, He was ventilated for five days on SIMV VC mode with minimal settings and Fio2-60%PIP-15, PEEP-5, IT-0.40 initially followed by steady reduction in Fio2 followed by PIP. As the pneumothorax had sealed and chest drain was removed by day 5 and he was extubated to Humidified High Flow nasal cannula oxygen on the sixth day which was also weaned off by day 7. Baby was shifted to mother's side by day 8 and discharged from the hospital with no complications by day 10 of admission. This baby is still under follow up, is doing well with no further complications due to the neonatal pneumothorax.

DISCUSSION

Spontaneous Pneumothorax is a condition where there is free air between the parietal and visceral pleural leaves within the thoracic cavity. It is reported to be 1-2% in newborns, 5-7% in those with birth weight below 1500g, but 30% in patients with an underlying lung problem and in need of mechanical ventilation.[9,10,11] One study found the frequency of pneumothorax was 3 per 1000 live births.[12] Single-lung ventilation, high peak inspiratory pressure, high positive end-expiratory pressure application, poor patient

Informed consent is taken from parents of baby for this case report.

synchronization with ventilator, high mean airway pressure, number of suction procedures are among the factors that can induce NP during mechanical ventilation. [13,14,15,16] In rare cases, it may resemble lobar emphysema or cystic adenomatoid malformation.[1] At birth, the alveoli opening happens in rapid sequence. If there is bronchial obstruction from aspiration of blood, meconium or mucus there may develop high transpulmonary pressure which can further lead to a rupture of the lung.[18] The spontaneous Pneumothorax is a life-threatening condition with high mortality rates (20-60%) are still reported. The prognosis is better in patients without pulmonary parenchymal disease. [19,20,21,22]

Improvement in oxygen saturation after drainage has a beneficial effect on the prognosis for pneumothorax.[23] Emergency pleural drainage may lead to which may occur in 14% to 25% which can range from drain misplacement to fatal iatrogenic lesions, in female patients long term it can lead to breast scarring as well.[24 ,25]

In our case there was no risk factor and all causes of spontaneous pneumothorax was ruled out. This baby's pneumothorax resolved without complication. Spontaneous pneumothorax should always be kept in mind when an acute respiratory distress arises in an otherwise normal newborn else the mortality rate will increase significantly.

Considering the literature data of mortality, it is evident spontaneous pneumothorax is fatal if not managed on time. Moreover, the management should be done by an expert to avoid the complication associated with pneumothorax. A neonatal resuscitation program trained personnel should be available for all deliveries to avoid the risk of pneumothorax as a complication of overzealous resuscitation.

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Fibroepithelial Polyp of the Prostatic Urethra – An Unusual Masquerader

Fibroepithelial polyp of the prostatic urethra is a rare congenital lesion. We report a case of a 34-year-old male who presented with a history of obstructive lower urinary tract symptoms. He had recurrent episodes of acute urinary retention, and had performed clean intermittent self-catheterization for the past 5 years.

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Keywords:

Infective endocarditis, Native valve endocarditis, Aortic stenosis, Streptococcus viridans

INTRODUCTION

Fibroepithelial polyp of the prostatic urethra is a rare congenital lesion. This is mostly diagnosed in the paediatric age group due to bizarre presentation, although some rare patients may present later in life. We report a case of a 34-year-old male who presented with a history of obstructive lower urinary tract symptoms. He had recurrent episodes of acute urinary retention, and had performed clean intermittent self-catheterization for the past 5 years. He was evaluated by a urologist and underwent transurethral resection of the prostate (TURP) two years ago, which revealed findings suggestive of benign prostatic enlargement. Despite undergoing the surgery, his urinary complaints persisted, and he was put on self-catheterization after undergoing TURP.

MATERIALS & METHODS

On evaluation, the patient had a Grade III prostatic enlargement, filling more than two thirds of the rectal lumen. The gland was normal in consistency, interspersed with soft boggy areas. No hard nodules were palpable.

An MRI scan of the pelvis revealed a heterogeneous, large, multi-cystic mass in the left retro-vesical space in the region of the seminal vesical bed, lying posterolateral to the prostatic urethra. The radiological impression was suggestive of a cystic tumour of the left seminal vesicle.

RESULTS & OBSERVATIONS

Cystoscopy detected a grade III enlargement of the left prostatic lobe. The huge median lobe was filling more than a third of the bladder, clearly obstructing the bladder outlet. The patient under-

went Laparoscopic/ Robotic Simple Prostatectomy with excision of the left seminal vesicle. Intra-operative findings suggested massive prostatic enlargement, protruding almost 8 cm into the bladder lumen. Areas of necrosis and pus-filled pockets were noted in the prostate. The specimen was submitted for histopathological examination. The patient was discharged with a catheter in situ. The catheter was removed after 10 days. The patient passed urine spontaneously, had good flow and minimal post void residual urine. He remains symptom-free on follow up.

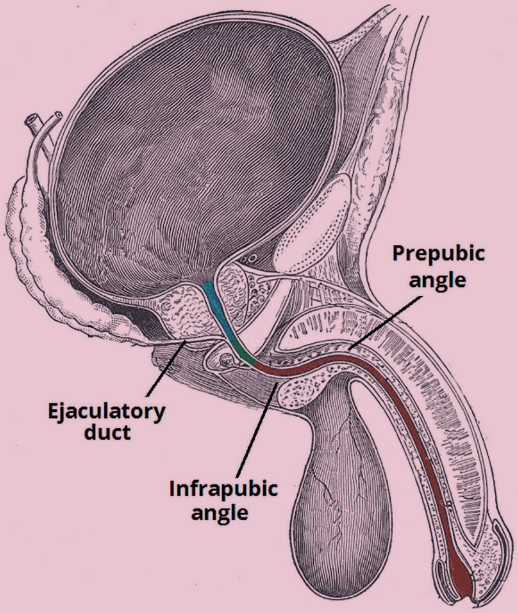
DISCUSSION

The specimen was received in the pathology laboratory in multiple pieces, the largest measuring 8 x 7.5 x 4 cm, with a smooth whitish surface on one aspect and a haemorrhagic raw area on the other aspect. Histological assessment of the tissue section revealed a polypoidal tissue, lined with a stratified squamous epithelium with a variably thick hyperkeratotic layer. The stroma was fibrous, and many cystic spaces lined with stratified squamous epithelium were noted. Neither cytological atypia nor mitosis were seen. There was evidence of associated patchy inflammatory foci.

A diagnosis of fibroepithelial polyp of the prostatic urethra was made. The differentials considered were prostatic-type urethral polyp and polypoidal urethritis. Prostatic-type urethral polyp, which is an uncommon polypoidal lesion of the urinary tract, is histologically characterized by delicate papillae, with a true fibrovascular core lined with prostatic epithelium and focal benign urothelial cells. Prostatic acini are often present in the polyp. On the other hand, polypoid urethritis, also known as papillary pseudo tumour of the prostatic urethra, is the urethral counterpart of polypoid cystitis. It is histologically characterized by polypoid and broad-based papillary structures, with marked stromal edema but no true fibrovascular cores.

CONCLUSION

Fibroepithelial polyp of the prostatic urethra is a rare congenital lesion, which can present as an uncommon cause of obstructive lower urinary tract symptoms in the paediatric age group and young males. This diagnosis needs to be considered in patients of this demographic presenting with bothersome voiding symptoms.



The infrapubic and prepubic angles of the male urethra.

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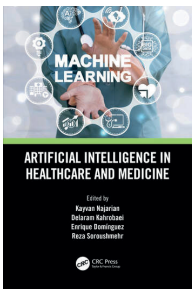
Artificial Intelligence in Healthcare and Medicine

The book targets clinical researchers and computational scientists seeking to understand the recent advances of artificial intelligence (AI) in health and medicine.



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This book provides a comprehensive overview of the recent developments in clinical decision support systems, precision health, and data science in medicine. The book targets clinical researchers and computational scientists seeking to understand the recent advances of artificial intelligence (AI) in health and medicine. Since AI and its applications are believed to have the potential to revolutionize healthcare and medicine, there is a clear need to explore and investigate the state-of-the-art advancements in the field. This book provides a detailed description of the advancements, challenges, and opportunities of using AI in medical and health applications.

Over 10 case studies are included in the book that cover topics related to biomedical image processing, machine learning for healthcare, clinical decision support systems, visualization of high dimensional data, data security and privacy, bioinformatics, and biometrics. The book is intended for clinical researchers and computational scientists seeking to understand the recent advances of AI in health and medicine. Many universities may use the book as a secondary training text. Companies in the healthcare sector can greatly benefit from the case studies covered in the book. Moreover, this book also:

- Provides an overview of the recent developments in clinical decision support systems, precision health, and data science in medicine.
- Examines the advancements, challenges, and opportunities of using AI in medical and health applications.
- Includes 10 cases for practical application and reference.

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