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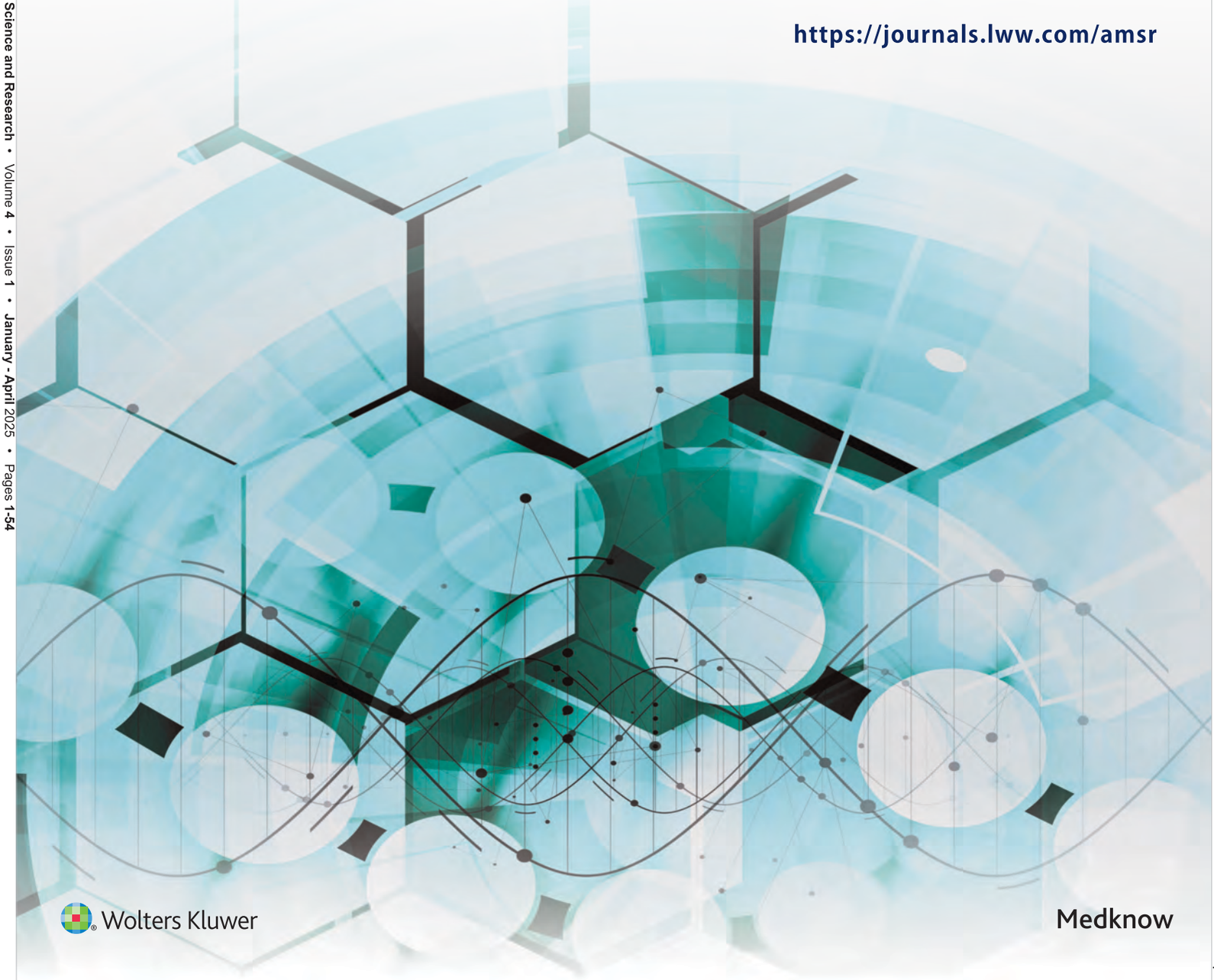

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Editorial

Success of anti-amyloid therapy answers few but raises many questions

The success of anti-amyloid mono-clonal antibodies (MAB) in Alzheimer's disease (AD) is a remarkable breakthrough in research in neurodegenerative disorders and offers hope for millions of sufferers. It establishes the role of protein aggregation as the prime-mover of neurodegeneration. The 'amyloid-cascade hypothesis'was criticized because amyloid plaques were omnipresent in post-mortem brain in cognitively healthy individuals, and no correlation was demonstrated with distribution and load of plaque with pattern and severity of cognitive impairment. Opponents also argue that there are several other patho-mechanisms including *tau* hyperphosphorylation, oxidative stress, inflammation, defective cerebral glucose metabolism, vascular pathology, mitochondrial dysfunctions, etc. which also play some role in disease pathogenesis. However, clinical improvement through Alzheimer's Disease Assessment Scale (ADAS-Cog_{13}) and ADCS-iADL (the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory) in tandem with plaque removal with use of donanemab,[1] suggests that amyloid lowering in the earlier stages of the disease is likely to produce clinical benefit and also establishes the role of amyloid in the orchestration of Alzheimer's pathogenesis. In the Traiblazer-Alz 2 study donanemab significantly slowed clinical progression at 76 weeks in early symptomatic AD and amyloid and *tau* pathology in those with low/medium *tau* and in the combined low/medium and high *tau* pathology population.[2] There were several setbacks before the first success with aducanumab in 2023. Pharmaceutical industries invested several million USD to get a breakthrough and amyloid was their best bet. The fascinating hypothesis, with amyloid as the primary culprit was chased by several companies before being successful in clinical trials. However, Alzheimer's drug discovery was marred with unprecedented controversies.[3] While many anti-amyloid MABs have failed, a few have succeeded in clinical trials and this has been linked to the rate and degree of amyloid removal from the brain.[4] The Clarity AD study for lecanemab[5] and Traiblazer-Alz 2 for donanemab[2] showed clear benefit for patients with early symptomatic AD and these two drugs received full approval from US FDA. They are currently being used in several countries including USA and Japan. These drugs are yet to be available in India and many other countries in low and medium income countries (LMICs) where majority of the AD patients live. Cost is one of the limiting factors for the use in these countries, apart from the availability of biomarkers which are essential to immunotherapy.

Beside these, there are several other problems for regular use of anti-amyloid MABs in clinical practice. The agents were used in subjects with clinical diagnosis of mild cognitive impairment (MCI) and early AD who were biomarker positive. Here lies the problem of using these agents, since image-based biomarkers are not widely available and lumbar puncture for testing cerebrospinal fluid (CSF) biomarkers is difficult for many elderly individuals. Efforts to replace these with more easily accessible plasma-based biomarkers are currently being explored. For this, plasma-based biomarkers need to undergo further studies in diverse ethnic populations for determining cut-off level to discriminate diseased from healthy individuals. Amyloid-related imaging abnormalities (ARIA), the adverse effect encountered in all anti-amyloid MABs are linked to several factors including ApoE4 carriers, cerebral amyloid angiopathy, and presence of microhemorrhages[6] and also in African descends in some earlier clinical trials. Another issue of MABs regular use in subjects of AD lies the unavailability of randomized controlled trials of these agents in diverse ethnic populations. Testing in all racial and ethnic populations is essential to prove the effectiveness as well as safety of these agents and to provide confidence to the clinician to use them across the globe.

In clinical practice, many individuals carry mixed pathologies in their brain, e.g. alpha-synuclein, TDP-43 and vascular pathologies often coexist with amyloid plaques. It would also be interesting to know how these anti-amyloid MABs do in such patients. These MABs have been tested in selected individuals with late-onset typical AD. However, around 20-30% of AD subjects can have atypical clinical phenotype, and it is argued that these individuals carry pure

AD pathologies in their brain.[7] Anti-amyloid antibodies also need to be tested in these atypical AD subjects.

The success of anti-amyloid MABs was based with the strong determination that removal of amyloid from brain would result in clinical improvement. This came from changes in our concept of AD pathogenesis. In 2007, the International Working Group (IWG) revised the 1984 diagnostic criteria for AD and was the first to propose that the diagnosis of AD in patients with cognitive deficits could be anchored around the presence of biomarkers to support more accurate and earlier disease diagnosis.[8] The biological construct of the disease came from prospective study of disease biology along with cognitive changes in dominantly inherited Alzheimer's network (DIAN) coupled with discoveries of image-based and fluid-based biomarkers.[9] It is said that AD pathology start growing in the brain decades before symptom onset, and amyloid (A) deposition is the primary and initial event, followed by deposition of *tau* (T) and subsequent neurodegeneration (N), the basis for ATN framework. To accommodate the contribution of other factors, an X is added to this framework that signifies all others including neuroimmune dysregulation, synaptic dysfunction and blood-brain barrier alterations, etc.[10] Since amyloid is not the only agent involved in disease pathogenesis, we expect more effective pharmaceutical agents targeting these diverse patho-mechanisms in the near future for treating the disease. As in many other diseases like infection, cancer, etc. multiple agents with different targets would be an effective treatment strategy in future. In the logical conclusion of this framework, it is now argued that AD is a continuum from presymtomatic stage to clinically overt dementia. The biological construct gave the strong foundation to test anti-amyloid MABs in early symptomatic individuals. This also justifies the logic of preserving cognition before much of neurodegeneration happens. However, while it is important to 'catch those young' the proposition is going far beyond that, making an AD diagnosis in asymptomatic individuals. This however raises several questions, which would be difficult to address. Logically, an elderly might carry amyloid and *tau* pathology in his brain without throwing an iota of symptoms. Can we ethically label them having Alzheimer's disease? This carries the risk of social discrimination for employment, promotion, and insurance with additional psychological stress, notwithstanding. There is more dilemma for the physicians, how to treat them. Removing amyloid and *tau* from brain are justified to prevent inevitable neurodegeneration. But, to prove that removal would be beneficial, prospective interventional studies are needed. Some of these questions hopefully, may be answered in the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) study and a companion to the ground-breaking Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study.[11] We will be eagerly waiting how things will unfold in next few years.

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Review Article

Unraveling the cardiorenal metabolic syndrome: A deep dive into the Indian population's health crisis

Niladri Dingal

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Abstract

Cardiorenal metabolic syndrome (CRMS) is emerging as a health crisis in the Indian population, marked by the interplay of cardiovascular disease, renal dysfunction, and metabolic disorders. This study delves into the multifaceted nature of CRMS, highlighting its rising prevalence driven by lifestyle changes, urbanization, and dietary habits. With a growing burden of obesity, hypertension, and diabetes, the Indian demographic faces unique challenges that exacerbate the risk of CRMS. The study explores the pathophysiological mechanisms underlying this syndrome, emphasizing the interdependence of heart, kidney, and metabolic health. Effective screening strategies tailored to the Indian context, including the use of anthropometric measurements and comprehensive metabolic panels, are vital for early detection and intervention. The discussion extends to pharmacological and nonpharmacological management approaches, underscoring the importance of lifestyle modifications alongside medication adherence. Community engagement and education are pivotal in fostering awareness and promoting preventive measures. By analyzing the implications of CRMS on public health, this study aims to illuminate the urgent need for integrated healthcare solutions and policy initiatives that address the unique challenges faced by the Indian population. Ultimately, it advocates for a comprehensive framework that combines appropriate research, prevention methods, and management strategies to combat the growing threat of CRMS, ensuring a healthier future for individuals and communities across India.

Keywords: Cardiometabolic risk, cardiorenal metabolic syndrome, cardiorenal risk, metabolic syndrome

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INTRODUCTION

Cardiorenal metabolic syndrome (CRMS) is a complex and multifaceted condition that intertwines cardiovascular, renal, and metabolic disorders, significantly impacting overall health and enhancing the risk of morbidity and mortality.[1] It is characterized by the interplay of neurohormonal, inflammatory, and hemodynamic factors, making it more intricate than simple hemodynamic disturbances. This syndrome is associated with a group of risk factors, including high glycemic burden, raised blood pressure, obesity, and dyslipidemia, which are increasingly prevalent in the global population.[2] These risk factors contribute to a vicious cycle where metabolic dysregulation exacerbates cardiovascular and renal impairment, ultimately leading to high morbidity and mortality.

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Additionally, CRMS has a slight male predominance in its occurrence.[3] The healthcare burden posed by CRMS is substantial, straining healthcare systems worldwide as it necessitates comprehensive management methods that address the multifactorial nature of the syndrome. The economic impact is further compounded by the high costs associated with managing comorbid disease states such as diabetes, chronic kidney disease (CKD), and cardiovascular disease which are prevalent among individuals with cardiorenal syndrome. Understanding the interplay between the factors contributing to CRMS and the subsequent healthcare challenges is crucial for developing integrated care models that promote better health outcomes and reduce the overall burden of this debilitating syndrome.[4]

EPIDEMIOLOGY OF CARDIORENAL METABOLIC SYNDROME IN THE INDIAN POPULATION

CRMS is increasingly acknowledged as a significant public health concern in India, reflecting the composite interplay between cardiovascular diseases, metabolic disorders, and CKD. The epidemiological landscape of CRMS in the Indian population reveals alarming trends, particularly among urban and elderly that is, 65 years or above demographics. Studies indicate that nearly 40% of elderly urban South Indians[5] have metabolic syndrome, which is strongly associated with coronary artery disease (CAD). This high prevalence underscores the urgent need for targeted interventions and public health strategies. The nationwide prevalence of metabolic syndrome in urban Indian populations has been reported to be around 31.6%, with notable gender differences: 22.9% in men and 39.9% in women.[6] This disparity highlights the need for gender-specific approaches in managing and preventing CRMS. Furthermore, the age-adjusted prevalence rates suggest that metabolic syndrome is a growing concern across various age groups, particularly among older adults who are more susceptible to its adverse effects.

Globally, CRMS is recognized as a growing concern, particularly in developed nations where lifestyle-related diseases are prevalent. The prevalence of metabolic syndrome varies significantly across different regions, with estimates ranging from 20% to 40% in various populations.[7] For example, in the United States, the prevalence of metabolic syndrome is approximately 34%, whereas in European countries, it ranges from 20% to 30% depending on the specific population studied.[8] In comparison, the prevalence of metabolic syndrome in India is notably higher, particularly among urban populations. This discrepancy can be accredited to different factors, including genetic predispositions, dietary habits, and the rapid pace of urbanization that has led to lifestyle changes. Additionally, the burden of cardiovascular diseases in India is projected to escalate.

GENETIC PREDISPOSITIONS IN THE INDIAN POPULATION

The Indian population exhibits several genetic predispositions that contribute to the high occurrence of CRMS and its components, particularly metabolic syndrome and CAD. Research studies indicate that Asian Indians have a significant genetic susceptibility to these conditions, which is compounded by lifestyle factors and environmental influences.[9] The Indian population exhibits several genetic predispositions that contribute to various health conditions, particularly those related to CRMS. Here are some notable examples:

1. Thrifty genotype hypothesis

The thrifty genotype hypothesis suggests that certain genetic traits that were advantageous for survival in ancestral environments may predispose individuals to metabolic disorders in modern contexts. In India, this is reflected in the higher prevalence of diabetes and obesity in individuals with specific genetic backgrounds, particularly in urban populations where lifestyle changes have led to increased caloric intake and reduced physical activity.[10]

2. Insulin resistance genes

Certain genetic variants associated with insulin resistance have been identified in the Indian population. For instance, polymorphisms in genes such as insulin receptor substrate 1 (*IRS1* and peroxisome proliferator-activated receptor gamma (*PPARG*) are associated with an intensified risk of type 2 diabetes mellitus and metabolic syndrome. These genetic factors play a pivotal role in the higher incidence of insulin resistance observed in South Asians compared with other ethnic groups.[11]

3. Lipid metabolism variants

Genetic predispositions affecting lipid metabolism are also prevalent in India. Variants in genes such as apolipoprotein E (*APOE*) and lipoprotein lipase (*LPL*) have been associated with dyslipidemia, which is a significant risk factor for cardiovascular diseases. The presence of specific alleles can lead to altered lipid profiles, increasing the risk of atherosclerosis and other cardiovascular complications.[12]

4. Hypertension-related genes

Hypertension is a major component of CRMS, and certain genetic predispositions have been linked to its prevalence in the Indian population. Variants in genes such

as angiotensinogen (*AGT*) and angiotensin-converting enzyme (*ACE*) are associated with increased blood pressure and cardiovascular risk.[13] These genetic factors, combined with environmental influences, contribute to the high rates of hypertension observed in India.

5. Genetic diversity and endogamy

India's diverse population structure, characterized by multiple endogamous groups and consanguineous marriages, leads to a unique genetic landscape. This genetic diversity can result in the concentration of specific genetic traits within certain communities, which may predispose them to particular health conditions. For example, certain tribal populations may exhibit higher rates of genetic disorders due to limited gene flow and increased prevalence of recessive traits.[6]

6. CKD susceptibility

Inherited factors also play a role in the susceptibility to CKD among the Indian population. Variants in genes related to kidney function and structure, such as apolipoprotein L1 (*APOL1*), have been linked to a higher risk of CKD,[14] particularly in certain ethnic groups within India. This genetic predisposition, combined with environmental factors like diabetes and hypertension, exacerbates the burden of kidney disease.

Moreover, studies have shown that South Asians, including Indians, tend to have a greater percentage of body fat and a higher tendency for central obesity compared with other ethnic groups, even at lower body mass indices. This unique fat distribution pattern is linked to a higher risk of insulin resistance and cardiovascular diseases, further highlighting the genetic factors at play. The interplay between genetic predispositions and environmental factors, such as diet and physical activity, creates a complex landscape for CRMS in the Indian population. Understanding these genetic underpinnings is pivotal for developing targeted prevention and treatment modalities that address the specific needs of this population. As research continues to evolve, it is essential to consider both genetic and lifestyle factors in managing and mitigating the impact of CRMS in India.

PATHOPHYSIOLOGICAL MECHANISMS BEHIND CARDIORENAL METABOLIC SYNDROME

CRMS is a complex interplay of dysfunction involving the heart, kidneys, and metabolic processes. This syndrome highlights the intricate relationships between these organs, where dysfunction in one can lead to or increase dysfunction in the other. Understanding the pathophysiology of CRMS requires a comprehensive look at how each organ is involved in this multifactorial disease process.

1. **Heart involvement**

The heart is often the initial organ affected in CRMS, with conditions such as hypertension, heart failure, and CAD playing pivotal roles. Hypertension can lead to left ventricular hypertrophy, which increases the heart's oxygen demand and can precipitate heart failure. The heart's ability to pump effectively diminishes, leading to reduced cardiac output and subsequent renal hypoperfusion. This hypoperfusion activates compensatory mechanisms, including the renin–angiotensin–aldosterone system (RAAS), which further exacerbates hypertension and fluid retention, creating a vicious cycle. Moreover, myocardial ischemia can occur due to reduced blood flow, often linked to atherosclerosis. The resulting ischemic heart disease can lead to heart failure, which is characterized by fluid overload and congestion. This congestion can cause renal impairment due to increased venous pressure, leading to a drop in glomerular filtration rate (GFR) and worsening kidney function.[15,16]

2. **Kidney involvement**

The kidneys play an important role in regulating fluid balance, electrolytes, and blood pressure. In CRMS, renal dysfunction can arise from several mechanisms. Renal hypoperfusion due to decreased cardiac output leads to a reduction in GFR. The kidneys respond by activating the RAAS, which promotes sodium and water retention, further increasing blood volume and exacerbating hypertension. CKD can also result from systemic conditions such as diabetes and hypertension, which are prevalent in CRMS. As kidney function declines, the accumulation of uremic wastes can lead to systemic inflammation and oxidative stress, further damaging both the kidneys and the heart. This creates a feedback loop where worsening kidney function leads to increased cardiovascular risk, including arrhythmias and heart failure.[17]

3. **Metabolic dysfunction**

Metabolic syndrome is characterized by a group of conditions, including obesity, insulin resistance, dyslipidemia, and hypertension. In CRMS, adiposity plays a notable role in the pathophysiology. Excess adipose tissue, particularly visceral fat, releases pro-inflammatory cytokines and adipokines, which contribute to systemic inflammation and insulin resistance. This metabolic derangement can lead to endothelial dysfunction, promoting atherosclerosis and increasing cardiovascular risk. Particularly, insulin resistance is detrimental as it affects both cardiac and renal function. It can lead to increased sodium retention

by the kidneys, exacerbating hypertension and fluid overload. Additionally, insulin resistance is associated with dyslipidemia, characterized by elevated triglycerides and low high-density lipoprotein (HDL) cholesterol, further increasing cardiovascular risk.[18]

4. **Neurohormonal activation**

The interplay between the heart, kidneys, and metabolic processes is mediated by neurohormonal activation. The RAAS is a central player, as its activation leads to vasoconstriction, increased blood pressure, and sodium retention. In CRMS, the overactivity of the RAAS can lead to maladaptive changes in both the heart and kidneys, promoting hypertrophy, fibrosis, and ultimately organ dysfunction. Sympathetic nervous system activation is another critical component. Increased sympathetic tone can lead to elevated heart rates, increased myocardial oxygen demand, and further renal vasoconstriction, compounding the effects of heart failure and renal impairment.[19,20]

5. **Inflammatory and oxidative stress**

Chronic inflammation and oxidative stress are significant contributors to the pathophysiology of CRMS. Inflammatory markers such as C-reactive protein are often raised in individuals with metabolic syndrome, indicating a state of systemic inflammation. This inflammation can damage endothelial cells, promoting atherosclerosis and increasing the risk of cardiovascular events. Oxidative stress, resulting from an imbalance between reactive oxygen species production and antioxidant defenses, further exacerbates tissue damage in both the heart and kidneys. It contributes to endothelial dysfunction, inflammation, and fibrosis, leading to a decline in organ function.[21]

SCREENING STRATEGIES FOR CARDIORENAL METABOLIC SYNDROME IN THE INDIAN POPULATION

CRMS is a multifarious condition that involves the interplay between cardiovascular health, renal function, and metabolic disorders. Given the high prevalence of CRMS in India, effective screening strategies are essential for early detection and management.[22,23] Here is a detailed overview of screening strategies tailored for the Indian population.

1. Risk factor identification

The first step in screening for CRMS involves identifying individuals at risk based on established risk factors. Key risk factors include:

- **Obesity**: Central obesity, measured by waist circumference, is a significant indicator of metabolic syndrome. In India, waist circumference thresholds of >90 cm for men and >80 cm for women are commonly used.
- **Hypertension**: Regular blood pressure monitoring is crucial, as hypertension is both a risk factor and a consequence of CRMS.
- **Dyslipidaemia**: Screening lipid profiles, including total cholesterol, low-density lipoprotein (LDL), HDL, and triglycerides help to identify dyslipidemia, which is prevalent in metabolic syndrome.
- **Diabetes**: Fasting blood glucose and glycated hemoglobin levels should be assessed to identify insulin resistance and diabetes, which are critical components of CRMS.

2. Anthropometric measurements

Given the socioeconomic diversity in India, simple anthropometric measurements can serve as effective screening tools[24]:

- **Body mass index (BMI)**: While BMI is a common measure, it may not accurately reflect body fat distribution, especially in Asian populations. Therefore, it should be used alongside waist circumference.
- **Waist-to-height ratio**: This emerging screening tool is gaining attention as a predictor of metabolic syndrome. A waist-to-height ratio of >0.5 is considered indicative of increased risk.

3. Comprehensive metabolic panel:

A comprehensive metabolic panel should be conducted to assess various biochemical markers[18]:

- **Lipid profile**: Regular screening for lipid abnormalities is essential, particularly in individuals with positive family history of cardiovascular disease or metabolic disorders.
- **Renal function tests**: Serum creatinine and estimated GFR should be monitored to assess kidney function, especially in individuals with diabetes or hypertension.

4. Use of screening tools and questionnaires

Implementing standardized screening tools can enhance the identification of at-risk individuals:

- **Metabolic syndrome criteria**: The International Diabetes Federation and the National Cholesterol Education Program criteria can be used to diagnose metabolic syndrome based on the presence of specific components (e.g., truncal obesity, high blood pressure, dyslipidemia, and hyperglycemia).
- **Questionnaires**: Utilizing validated questionnaires that assess lifestyle factors, dietary habits, physical activity levels, and family history can help identify individuals at risk for CRMS.

5. Community-based screening programs

Given the high burden of CRMS in India, community-based screening initiatives can be effective[23]:

- **Health camps**: Organizing health camps in urban and rural areas can facilitate mass screening for hypertension, diabetes, and dyslipidemia. These camps can also provide education on lifestyle modifications.
- **Mobile health units**: Utilizing mobile health units to reach underserved populations can improve access to screening and early intervention.

6. Integration of technology

Leveraging technology can enhance screening efforts:

- **Telemedicine**: Telehealth platforms can facilitate remote consultations and follow-ups, allowing healthcare providers to monitor patients with risk factors for CRMS.[25]
- **Wearable devices**: Encouraging the use of smart wearable devices that track physical activity, heart rate, and other health metrics can promote awareness and self-monitoring among individuals at risk.

7. Regular follow-up and monitoring

Once individuals are identified as at risk, regular follow-up is crucial:

- **Periodic assessments**: Regular monitoring of blood pressure, lipid profiles, and renal function should be scheduled to track changes and initiate early interventions.
- **Lifestyle modification programs**: Implementing structured lifestyle modification programs focusing on diet, physical activity, and weight management can significantly reduce the risk of developing CRMS.

Strategies to counter CRMS—successful strategies to counter CRMS include both pharmacological and nonpharmacological approaches.

PHARMACOLOGICAL MANAGEMENT

1. Antihypertensive agents[15,26]
   - **ACE inhibitors and angiotensin receptor blockers (ARBs):** ACE inhibitors and ARBs are commonly prescribed to manage hypertension and provide renal protection. They bring down proteinuria and slow the progression of CKD while also improving cardiovascular outcomes.
   - **Calcium channel blockers**: These agents can effectively lower blood pressure and are particularly useful in patients with hypertension and heart failure.
2. Diuretics
   - **Loop diuretics**: These are essential for managing fluid overload in heart failure and CKD. They help reduce blood volume and alleviate symptoms of congestion.
   - **Thiazide diuretics**: Often used in conjunction with loop diuretics for better blood pressure control and to manage edema.[27]
3. Antidiabetic medications
   - **Metformin**: This cheap and effective drug for type 2 diabetes mellitus improves insulin sensitivity and has cardiovascular benefits.[28]
   - **Sodium-glucose co-transporter 2 inhibitors**: These agents not only help control blood glucose levels but also provide renal protection and reduce cardiovascular risk. They are particularly beneficial in patients with heart failure and CKD.[29]
   - **Glucagon-like peptide 1 receptor agonists**: These medications improve glycaemic control and have been shown to have cardiovascular benefits.[30]
   - **Trizepatide**: provides good glycemic control, and weight reduction in obese patients along with cardiac and renal protection.[31]
4. Lipid-lowering agents
   - **Statins**: Statins are crucial for managing dyslipidemia and reducing cardiovascular risk. They help lower LDL cholesterol and have anti-inflammatory properties that may benefit both heart and kidney health.
5. Heart failure medications
   - **Beta-blockers**: These are used to manage heart failure and reduce heart rate, improving cardiac output and reducing mortality in heart failure patients.
   - **Mineralocorticoid receptor antagonists (MRAs)**: These agents help manage heart failure and provide renal protection by reducing fibrosis and inflammation.
6. Novel therapies
   - **Potassium binders**: New potassium binders are emerging to manage hyperkalemia, especially in patients with CKD and heart failure, allowing for the safe use of RAAS inhibitors.[32,33]
   - **Finrenone**: This nonsteroidal MRA is indicated to reduce the risk of GFR decline, devolvement of end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in CKD in type 2 diabetes mellitus.[34]

NONPHARMACOLOGICAL MANAGEMENT

1. Lifestyle modifications
   - **Dietary changes**: A heart-friendly diet low in sodium, saturated fats, and refined sugars is essential. The Mediterranean diet or dietary approaches to stop hypertension diet can be beneficial.[35]
   - **Weight management**: Achieving and maintaining a healthy weight through caloric restriction and balanced nutrition is crucial for managing obesity, a key component of CRMS.[36]
2. Physical activity
   - **Regular exercise**: Engaging in systematic physical activity (at least 150 min of moderate-intensity exercise per week) can improve cardiovascular health, enhance insulin sensitivity, and aid in weight management.[37]
3. Smoking cessation
   - **Tobacco control**: Smoking is an important risk factor for both cardiovascular and renal diseases. Programs aimed at smoking cessation can significantly reduce the risk of complications associated with CRMS.[38]
4. Monitoring and Education
   - **Regular health checkups**: Routine monitoring of blood pressure, blood glucose, lipid levels, and renal function is mandatory for early detection and management of complications.
   - **Patient education**: Educating patients about the importance of adherence to treatment, lifestyle changes, and recognizing symptoms of worsening heart or kidney function can empower them to manage their condition effectively.
5. Psychosocial support
   - **Mental health management**: Addressing mental health issues such as depression and anxiety, which are common in patients with chronic diseases, can improve adherence to treatment and overall quality of life.[39]

CONCLUSION

CRMS represents a significant and escalating health crisis in the Indian population, driven by a composite interplay of genetic, lifestyle, and environmental factors. As we have explored, the burden of this syndrome is exacerbated by rising rates of obesity, hypertension, diabetes, and cardiovascular diseases, all of which are becoming increasingly prevalent across diverse demographics in India. Addressing this multifaceted issue requires a concerted effort from healthcare professionals, policymakers, and the community at large. Comprehensive screening strategies, early detection, and tailored management approaches are essential to mitigate the impacts of CRMS. Furthermore, promoting awareness and education about the importance of lifestyle modifications—such as a balanced diet and regular physical activity—can empower individuals to take charge of their health. As we navigate this health crisis, it is imperative to foster an integrative framework that combines pharmacological and nonpharmacological interventions, ensuring that both healthcare systems and individuals are equipped to combat the challenges posed by CRMS. By prioritizing research, enhancing healthcare accessibility, and implementing community-based programs, India can pave the way toward a healthier future, ultimately reducing the burden of CRMS and improving the quality of life for millions.

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Original Article

Indian Essential Medicine List for mental disorders: Time to revisit

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Abstract

Background: Management of mental health issues remains far from satisfactory. The majority of these mental health disorders can be effectively managed by ensuring the availability of quality drugs in appropriate dosage forms. The essential drug list is the most effective instrument in ensuring the availability of these drugs to the majority of the population without financial burden.

Aim and Objective: This study was performed to compare the drugs mentioned for mental disorders between the 21st World Health Organization (WHO) essential drug list, 5th Indian Essential Drug List, and 22nd WHO Essential Drug List to find out the need to update the Indian Essential Drug List.

Materials and Methods: This descriptive study was carried out in the Department of Pharmacology at Dr. B. R. Ambedkar State Institute of Medical Sciences, Mohali, Punjab, India. The 5th National Essential Medicine List (NEML; latest edition) was compared with the 21st WHO Essential Drug List released in 2021 and the 22nd WHO Essential Drug List (latest edition) to find out the categories and subcategories of drugs, number of drugs mentioned in each category, drugs which are present in WHO Essential Medicine List (EML) but absent in Indian EML and vice versa.

Results: A total of 17 drugs are mentioned in the 5th NEML for mental disorders compared with 25 in the 21st WHO Essential Drug List and 47 in the 22nd WHO Essential Drug List. Three subcategories: drugs for alcohol use disorders, drugs for nicotine use disorders, and drugs for opioid use disorders were mentioned in in 22nd WHO Essential Drug List but are absent in the 21st WHO Essential Drug List and 5th NEML. Important drugs, which are absent in Indian EML are risperidone therapeutic alternatives: aripiprazole, olanzapine, paliperidone, and quetiapine in psychotic disorders; fluoxetine therapeutic alternatives: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline in depressive disorders; and acamprosate calcium and naltrexone for alcohol use disorder.

Conclusion: There is a need to update Indian EML for the effective management of mental disorders.

Keywords: Essential drug list, India, mental disorder, public health, WHO

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INTRODUCTION

Essential drugs meet the healthcare needs of the majority of the population and are effective, safe, and cost-effective. The first list of essential drugs was introduced by Tanzania in 1970 and the World Health Organization (WHO) introduced its first list of essential drugs consisting of 208 drugs in 1977. In India first National Essential Medicine List (NEML) was launched in 1996.[1] A recent NEML was published in 2022.[2]

Medicine plays a pivotal role in public healthcare, especially in the developing countries. According to India's National Health Policy 2017, the "Right to health is a fundamental right" of every person and it aims to achieve the optimum level of health and well-being by integrating preventive and promotive healthcare activities into developmental policies and ensuring access to universal health-related services without financial burden.[3]

Mental health is an important pillar of the health of a person, mental health problems remain a leading cause of morbidity and mortality as mental health cases are increasing globally.[4] the problem of mental health disorders in India is approximately 2443 disability-adjusted life years per 10,000 population; the age-adjusted suicide rate per 100,000 population is 21.1 according to the WHO. Mental health just not only causes health problems but also causes financial loss to society.[5] The burden of mental illness on both health and financial loss may be much higher than estimated.[3] Keeping in line with universal health access, India adopted a universal mental health policy in 2014 to provide access to universal mental health treatment and this policy was revised in 2017.[6] Despite of high prevalence of mental health burden, there is a huge treatment gap for the management of mental health problems.[7] The World Health Report 2001 recommends improvement in access to psychotropic medicine can improve the healthcare needs of persons suffering from mental disorders.[8] Around 75% of the population suffering from mental disorders in low- and middle-income countries have limited access to essential medicines.[9] The first framework was developed by WHO and the Management Science of Health in 2000 focusing on key components such as rational selection, availability, affordability, and appropriate use of essential medicines, and ever since is revised every 2 years to update the essential medicine in mental disorders.[8] Currently, the 23rd essential drug list is being released by WHO in 2023.[10] and the latest recent NEML was published in 2022.[2] The aim of this study compare the WHO Essential Medicine List (EML) 2021, NEML 2022, and WHO EML 2023 as the WHO EML acts as a guide for other countries to adopt or adapt their essential drug list according to their health needs and standard treatment guidelines.

MATERIALS AND METHODS

This was an observational, descriptive study carried out from July 2023 to August 2023. This study compared the WHO EML 2021, NEML 2022, and WHO EML 2023 to find out the need to update Indian EML. Ethics committee permission was not taken as it was a comparison of three databases.

The 21st and 22nd WHO and 5th India List of Essential Medicines were accessed to identify essential medicines for mental health disorders. Drugs written in the following categories of the section on mental and behavioral disorders were included: drugs used in psychotic disorders, drugs used in mood disorders (including depressive and bipolar disorders), drugs for anxiety disorders, drugs used for obsessive-compulsive disorders, and drugs for disorders due to psychoactive substance use.

In this study, WHO EML was kept as standard, and lists were compared for the following parameters:

(1) Presence of categories or subcategories.
(2) Number of drugs in each category or subcategory.
(3) Drugs, which are present in WHO EML but missing in Indian NEML.
(4) Drugs, which are present in Indian EML but missing in WHO EML.

For each drug, the formulation (differentiating between oral, intramuscular, and long-acting formulations), strength, and dose recommended by WHO were also recorded.

RESULTS

A comparative study was done to determine the necessity of updating according to the WHO EML.

The 22nd WHO EML is in current use and contains 47 drugs for mental disorders under six subcategories. Under the category of Medicines for Mental and Behavioral Disorders, six subcategories are there in all three EMLs, whereas under the last subcategory of disorders due to psychoactive substance use, it is further subcategorized into three categories: drugs for alcohol use disorders, drugs for nicotine use disorders, and drugs for opioid use disorders in 22nd WHO EML. These three subcategories were missing in the earlier 21st WHO EML and 5th National List of Essential Medicine (NLEM) [Table 1].

Table 1: Comparison of categories, subcategories, and number of medicines between the 21st World Health Organization Essential Medicine List (WHO EML), 5th Indian EML, and 22nd WHO EML

Subcategories	WHO EML 2021	National list of essential medicine (NLEM) 2022	WHO EML 2023	Number of drugs in WHO EML 2021	Number of drugs in NLEM 2022	Number of drugs in WHO EML 2023
Psychotic disorders	+	+	+	8	4	14
Depressive disorders	+	+	+	7	3	7
Bipolar disorders	+	+	+	3	3	4
Generalized anxiety and sleep disorders	+	+	+	1	2	8
Obsessive compulsive disorders and panic attacks	+	+	+	1	2	7
Disorders due to psychoactive substance use	+	+	+	5	3	7
-Drugs for alcohol use disorders	–	–	+			2
Drugs for nicotine use disorders	–	–	+			3
Drugs for opioid use disorders	–	–	+			2

The 22nd WHO EML contains 47 drugs, whereas the 21st EML contains only 25 drugs including therapeutic alternatives to primary drugs that are similar in efficacy and safety to it. The number of drugs in the 5th NLEM is far less than WHO EML's, it contains only 17 drugs without any therapeutic alternatives [Table 1].

The drugs that are present in 21st WHO EML but absent in 5th NLEM are chlorpromazine and paliperidone in psychotic disorders, fluoxetine therapeutic alternatives: citalopram, fluvoxamine, paroxetine, and sertraline in depressive disorders, diazepam in generalized anxiety and sleep disorders, bupropion, varenicline, and methadone in disorders due to psychoactive substance use, whereas there are certain drugs, which are present in 5th NLEM but absent in 21st WHO EML such as clonazepam and zolpidem in generalized anxiety and sleep disorders and fluoxetine in obsessive-compulsive disorders and panic attacks [Table 2].

The drugs, which are present in 22nd WHO EML but absent in 5th NLEM are haloperidol decanoate, zuclopenthixol decanoate, chlorpromazine, paliperidone, and risperidone therapeutic alternatives: aripiprazole, olanzapine, paliperidone, and quetiapine in psychotic disorders; fluoxetine therapeutic alternatives: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline in depressive disorders; quetiapine in bipolar disorders; diazepam and fluoxetine and its therapeutic alternatives: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline in generalized anxiety and sleep disorders; fluoxetine and its therapeutic alternatives: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline in obsessive compulsive disorders and panic attacks; and acamprosate calcium, naltrexone, varenicline, and methadone in disorders due to psychoactive substance use, whereas there are certain drugs, which are present in 5th NLEM but absent in 22nd WHO EML such as clonazepam and zolpidem in generalized anxiety and sleep disorders [Table 2].

While there are certain drugs, that are added in 22nd WHO EML compared with 21st WHO EML such as haloperidol decanoate, zuclopenthixol decanoate, and risperidone therapeutic alternatives: aripiprazole, olanzapine, paliperidone, and quetiapine in psychotic disorders; fluoxetine therapeutic alternatives: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline in depressive disorders; quetiapine in bipolar disorders; and fluoxetine and its therapeutic alternatives: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline in generalized anxiety and sleep disorders. Fluoxetine and its therapeutic alternatives: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline in obsessive-compulsive disorders and panic attacks and acamprosate calcium and naltrexone in disorders due to psychoactive substance use. None of the drugs is deleted from the 21st WHO EML [Table 2].

In addition, information about the dosage form for each drug is mentioned in WHO EMLs but not in detail in NLEM as fluphenazine (injection 25 mg/mL in 1 mL ampoule) is mentioned in 22nd WHO EML, whereas in NLEM it is mentioned as fluphenazine (injection 25 mg/mL) [Table 2].

DISCUSSION

The present study aimed to compare the EML for mental disorders of 21st and 22nd WHO EMLs with the list

Table 2: Comparison of presence or absence of medicines in 21st WHO EML, 5th Indian EML, and 22nd WHO EML

Disorder category according to the WHO EML	WHO EML 2021	NLEM 2022	WHO EML 2023
Psychotic disorders	Chlorpromazine (injection 25 mg/mL in 2 mL ampoule, oral liquid 25 mg/5 mL, tablet 100 mg) Fluphenazine (injection 25 mg in 1 mL ampoule) Haloperidol (injection 5 mg/1 mL ampoule, tablet 2/5 mg) Paliperidone [prolonged release injection (25, 50, 75, 100, and 150 mg)] Risperidone (oral 0.25–6.0 mg) Complementary list Chlorpromazine (injection 25 mg/mL, oral liquid 25 mg/5 mL, tablet 10, 25, 50, and 100 mg) Clozapine (solid oral dosage form 25 to 200 mg) Haloperidol (5 mg/mL injection, oral liquid 2 mg/mL, solid oral dosage 0.5, 2, and 5 mg)	Clozapine (tablet 25/50/100 mg) Fluphenazine (injection 25 mg/mL) Haloperidol (tablet 2/5/10/20 mg, oral liquid 2 mg/5 mL, injection 5 mg/mL) Risperidone (tablet 1/2/4 mg, oral liquid 1 mg/mL, Long-acting injection 25/37.5 mg)	Fluphenazine (injection 25 mg/mL in 1 mL ampoule) Therapeutic alternatives: haloperidol decanoate, zuclopenthixol decanoate Haloperidol (tablet 2/5 mg) Therapeutic alternatives: chlorpromazine Haloperidol (injection 5 mg/1 mL ampoule) olanzapine (injection 10 mg) Paliperidone [prolonged release injection (25/50/75/100/150 mg)] Risperidone (oral 0.25–6.0 mg) Therapeutic alternatives: Aripiprazole, olanzapine, paliperidone, and quetiapine Complementary list Clozapine (solid oral dosage form 25 to 200 mg)
Depressive disorders	Amitriptyline (tablet 25 and 75 mg) Fluoxetine (solid oral dosage form 20 mg) (therapeutic alternatives: citalopram, escitalopram, fluvoxamine, paroxetine, sertraline)	Amitriptyline (tablet 10, 25, 50, and 75 mg) Escitalopram (tablet 5, 10, and 20 mg) Fluoxetine (capsule 10, 20, 40, and 60 mg)	Amitriptyline (tablet 25/75 mg) Fluoxetine (solid oral dosage form 20 mg; therapeutic alternatives: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline
Bipolar disorders	Lithium (solid oral dosage form 300 mg) Valproic acid (tablet enteric coated 200 and 500 mg) Carbamazepine (tablet 100 and 200 mg)	Lithium (tablet 300 mg) Sodium valproate (tablet 100, 200, and 400 mg, modified release tablet 300 and 500 mg) Carbamazepine (tablet 100, 200, and 400 mg, Modified release 200 and 400 mg, Oral liquid 100 mg/5 mL)	Carbamazepine (tablet 100, 200, and 400 mg) Lithium (solid oral dosage form 300 mg) Quetiapine (tablet 25, 100, 150, 200, and 300 mg), Modified release 50, 150, 200, 300, and 400 mg, Valproic acid (tablet enteric coated 200 and 500 mg)
Generalized anxiety and sleep disorders	Diazepam (tablet 2 and 5 mg)*	Clonazepam (tablet 0.25 and 0.5/1 mg) Zolpidem (tablet 5 and 10 mg)	Diazepam (tablet 2/5 mg)* (therapeutic alternatives; lorazepam) Fluoxetine (solid oral dosage form 20 mg; therapeutic alternatives: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline)
Obsessive-compulsive disorders and panic attacks	Clomipramine (Capsule 10 and 25 mg)**	Clomipramine (capsule 10, 25, and 75 mg) Fluoxetine (capsule 10, 20, 40, and 60 mg)	Clomipramine (capsule 10/25 mg) Fluoxetine (solid oral dosage form 20 mg; therapeutic alternatives: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline)
Disorders due to psychoactive substance use	Bupropion (tablet 150 mg sustained release) Nicotine replacement therapy (NRT) (chewing gum 2/4 mg, Transdermal patch 5–30 mg/16 h, 7–21 mg/24 h) Varenicline (Tablet 0.5/1 mg) Complementary list Methadone (concentrate for oral liquid 5 mg/mL, 10 mg/mL, oral liquid 5 mg/5 mL, and 10 mg/5 mL) Therapeutic alternative: buprenorphine	Buprenorphine (tablet SL 0.4 mg) Buprenorphine + naloxone (tablet SL 0.4 + 0.1 and 2 + 0.5 mg) Nicotine (NRT oral dosage 2/4 mg)	Acamprosate calcium (tablet 333 mg) Naltrexone (tablet 50 mg) Bupropion (tablet 150 mg sustained release) NRT (chewing gum 2/4 mg, transdermal patch 5–30 mg/16 h, 7–21 mg/24 h) Varenicline (tablet 0.5/1 mg) Complementary list Methadone (concentrate for oral liquid 5 mg/mL, 10 mg/mL, oral liquid 5 mg/5 mL, and 10 mg/5 mL) Therapeutic alternative: Buprenorphine

NLEM: National List of Essential Medicines, WHO EML: World Health Organization Essential Medicine List
*Medicine for anxiety disorder according to the WHO EML
**Medicine for obsessive-compulsive disorders according to the WHO EML

composed by India's 5th NLEM. While the categories given in the three essential drug lists are the same a subcategory of disorders due to psychoactive substance use is further subcategorized into three categories: drugs for alcohol use disorders, drugs for nicotine use disorders, and drugs for opioid use disorders in the 22nd WHO EML selection of essential drug is the first step toward improvement in rational drug use and well-being of population at large. Substance abuse is a global public health concern and drugs used in NEML for the management of these disorders are not enough to tackle all these disorders. According to the 2019 report on the "National Survey on Extent and Pattern of Substance Use in India," (14.6%) between the age of 10 and 75 years are current users of alcohol, and out of them, 5.2% are alcohol dependents, 2.8% are cannabis users, 2.06% are opioid users, 1.7% of children and adolescents, and 0.58% adults are inhalant users and problem of substance abuse is higher in younger population than in older population.[11] Alcohol abuse is rampant just not in India but globally also.[12] Finally, WHO has incorporated the subcategory for drugs for alcohol use disorders and acamprosate calcium and naltrexone have been listed as an essential drug for alcohol abuse disorders in the 22nd EML but in the 5th NLEM, there is no provision for such drugs, keeping in line with current WHO EML, these medicines must be incorporated in next EML, but in India NLEM is not updated every 2 years. As current NLEM was updated after 7 years. Similarly, according to the Global Adult Tobacco Survey 2 survey report 2016, there are 267 million tobacco users in India, making it the country with the second largest number of tobacco users in the world.[13,14] Nicotine replacement therapy (NRT), bupropion, and varenicline are effective first-line drugs for tobacco use disorder, all these drugs are incorporated in EML by WHO in the 21st and 22nd lists but in the 5th NLEM only NRT is present, bupropion and varenicline should also be incorporated to deal with tobacco disorders more effectively. For the management of opioid abuse disorders, buprenorphine and buprenorphine + naloxone are incorporated into in 5th NLEM but methadone, which is present in both the 21st and 22nd WHO EML lists but is absent in the 5th NLEM. Both methadone and buprenorphine are effective and relatively safe for the management of opioid use disorder, though buprenorphine has a lower risk for overdose, methadone seems to retain patients for longer periods and both drugs are helpful for the reduction of human immunodeficiency virus risk behaviors in opioids abuser patients.[15]

The current study also observed that the total number of drugs written in all the categories is considerably lower in Indian NLEM than in the WHO EMLs. Both first-generation and second-generation antipsychotic drugs are effective for the management of positive symptoms of psychosis but second-generation antipsychotic drugs are more effective for the management of negative symptoms of psychosis as well these drugs have better tolerability profiles.[16] Many second-generation drugs such as risperidone therapeutic alternatives: aripiprazole, olanzapine, paliperidone, and quetiapine have been added to the 22nd WHO EML, which are not there in the 5th NLEM, addition of these drugs in essential drug list will help in the better management of psychosis and resistant psychosis patients.

Selective serotonin reuptake inhibitors (SSRIs) are considered to be first-line antidepressants because they have better tolerability profile,[17] fluoxetine therapeutic alternatives: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline are present in both 21st and 22nd WHO EMLs, whereas in 5th NLEM only escitalopram is present as fluoxetine therapeutic alternative, other fluoxetine therapeutic alternatives can be added for better management of depressive disorders in line with WHO EML. Over the recent years, second-generation antipsychotic drugs have been suggested as first-line drugs for the management of acute manias and useful for the management of bipolar mania,[18,19] which is not present in both 21st WHO EML and 5th NLEM but has been added to 22nd WHO EML, which will help in the better management of mania disorders.

SSRIs and serotonin–norepinephrine reuptake inhibitors are considered first-line drugs for the management of generalized anxiety disorders, though benzodiazepines were effective but also poorly tolerated[20] only diazepam was mentioned in the 21st WHO EML but in the 22nd WHO EML, SSRIs fluoxetine and therapeutic alternatives: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline have been added and in 5th NLEM only clonazepam (benzodiazepine) is listed as an essential drug for the management of generalized anxiety disorder has a prevalence of 5.8% in Indian population.[21] For the management of insomnia, benzodiazepines are effective but because of side effects and next-day sedation, are not the preferred drug.[22] In both the 21st WHO EML and 22nd WHO EML only diazepam (benzodiazepine) is mentioned, whereas in the 5th NLEM, clonazepam (benzodiazepine) and also zolpidem are mentioned, which has rapid onset and shorter duration of action than in diazepam, has similar side effect profile but carry less risk of tolerance and abuse, perception of zolpidem as a safer option to diazepam is not true[23,24] so better alternative drug for management of insomnia is required in all the three EML's.

Information about the dosage form of a drug is important as many organizations rely on essential medicines lists for procurement of medicine. The 5th NLEM has not provided the details about the dosage form for parenteral preparations of all the drugs just not especially about drugs for mental disorders, revision is required to incorporate the detailed information about the dosage form of each drug.

The 5th NLEM, which came in 2022 was prepared based on the 21st WHO EML, and now in 2023 WHO published 22nd WHO EML, which has incorporated many new drugs for the management of mental disorders giving scope of hope for improvement in the next NLEM.

CONCLUSION

Essential drugs need updating to meet the mental health requirements of the public and the 22nd WHO EML has incorporated many new drugs giving a ray of hope for the next NLEM to meet the public health demands.

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Conflicts of interest
There are no conflicts of interest.

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Original Article

An observational study of effect of probiotic–prebiotic therapy on uremic toxins in patients with chronic kidney disease

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Abstract

Objectives: To determine the effect of use of prebiotic and probiotic supplements in patients with chronic kidney disease (CKD) on uremic toxins, that is, indoxyl sulfate (IS) and para-cresol sulfate (PCS).

Materials and Methods: A prospective observational study was done on 25 pre-dialysis CKD patients, that is, CKD stage 3–5. Laboratory investigations were done at admission and after 8 weeks, which included blood urea nitrogen (BUN), creatinine, PCS, and IS. The patients were initiated on pre and probiotic therapy, two capsules containing 30 billion CFU thrice daily with meals (90 billion CFU/day) for 8 weeks. The patients were followed-up after an 8-week period.

Results: Compared to pre-therapy, in post-therapy, there were significantly lower BUN (31.32 ± 13.35 mg/dL vs. 40.44 ± 15.85 mg/dL), creatinine (3.09 ± 1.35 mg/dL vs. 3.73 ± 1.44 mg/dL), serum PCS (90.2 vs. 129.4), and IS (51.1 vs. 84.3) ($P < 01$). CKD stages 3, 4, and 5 were present in 7 (28%), 10 (40%), and 8 (32%) patients, respectively. CKD stage was not significantly associated with the decrease in uremic toxin levels.

Conclusion: In CKD patients, oral intake of the pre–probiotic bacterial drug was safe and easily accepted. Pre–probiotic administration resulted in significant reductions in uremic toxins levels – BUN, creatinine, PCS, and IS.

Keywords: Chronic kidney disease, hemodialysis, prebiotic, probiotic

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INTRODUCTION

Chronic kidney disease (CKD) is a noncommunicable disease that affects around 10% of the global population.[1,2] The overall prevalence of CKD has been reported in the range of 4.83%–4.98%, with an incidence of 0.49%/year.[3] In India, CKD prevalence has reached alarming levels, with estimates varying from 4% to 20%.[4-6]

Diagnosis and management of CKD remains important since toxic metabolite concentrations accumulating in blood and other metabolic compartments continuously result in progression from CKD to end-stage renal disease. This accumulation occurs due to increased production of toxins [i.e., uremic retention solutes (URSs)] by the dysbiotic microbiota along with decreased renal clearance. These include protein-bound URSs, such

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as indole-3-acetic acid, *p*-cresyl glucuronide, indoxyl sulfate (IS), and *p*-cresyl sulfate (PCS). Among them, IS and PCS are extensively researched protein-bound URSs.[7]

IS causes endothelial dysfunction, accelerates the CKD progression, and is involved in bone-mineral diseases linked to CKD. Serum level of free PCS, which is measured as p-cresol, independently predicts new cardiovascular disease (CVD) events, as well as independently associated with overall mortality. The only source of PCS and IS is bacterial fermentation of dietary amino acids, which takes place in the large intestine.[8]

Because colonic microbiota produces many uremic solutes during the fermentation process of proteins, intestinal microbiota are crucial for accumulation of uremic toxins.[9] Therefore, reducing generation of uremic toxins by adjusting the microbiota's bacterial composition as well as colonic transit time (CTT) suggests a potential treatment approach. Administration of prebiotics and probiotics improves the colonic environment by increasing the available carbohydrate-to-nitrogen ratio, increasing production of short-chain fatty acids, lowering colonic pH, lengthening CTT, and inhibiting activity of enzymes that catalyze reactions, resulting in IS as well as PCS; the use of prebiotics and probiotics has been proposed to improve the colonic environment.[10]

Probiotics are characterized as living microorganisms that confer health advantages to the host when taken in adequate amounts.[11] In contrast, prebiotics are nondigestible food components that selectively stimulate the activities and growth of specific colonic bacteria, thus enhancing the health of the host and yielding advantageous effects.[12] There are multiple possibilities for improvement in CKD patients' outcomes using probiotics and prebiotics.

Not many studies have been carried out on this topic, especially on the role of pre-probiotic therapy on IS and PCS. Thus, we conducted this study to assess the effect of consumption of prebiotic and probiotics on the serum levels of IS and PCS in CKD patients.

MATERIALS AND METHODS

This study was a prospective observational study in design and conducted at a tertiary care center from August 2015 to April 2016. Ethical clearance was obtained before beginning the study (CSP/MED/15/MAR/22/02). The study population included pre-dialysis CKD patients, that is, CKD stage 3–5, in the age group of 18–75 years, who presented to an outpatient clinic during the study period. The exclusion criteria included patients with Crohn's disease, CVD, uncontrolled hypertension, ulcerative colitis, HIV/AIDS/liver disease, previous renal transplant, irritable bowel syndrome, or on maintenance hemodialysis. Pregnant or nursing women were also excluded. The study also excluded patients who were receiving antibiotics during the screening or within 14 days prior to it. The patients who were hospitalized within past 3 months due to infections were also excluded.

CKD was defined by either proteinuria (persistent) or below 90 mL/min per 1.73 m² of eGFR, which is also known as the estimated glomerular filtration rate, in two separate occasions within a 3-month period. Based on the NKF/KDOQI classification system, patients were then categorized into stages I through V for descriptive purposes.[13]

Informed consent was sought by each patient, and then examination was done to document demographic parameters like age, sex, body mass index, and presence of any co-morbidities. The underlying cause of CKD was also recorded. The cause of CKD was also noted. The patients were started on pre and pro biotic therapy—two capsules consisting of 30 billion CFU three times a day with meals (totaling 90 billion CFU daily) for a duration of 8 weeks.

The contents of the medicine were as follows:

(1) *Bifidobacterium bifidum* 5 billion CFU.
(2) *Lactobacillus acidophilus* 5 billion CFU.
(3) *Streptococcus thermophilus* 5 billion CFU.
(4) Lactitol monohydrate 100 mg.

Standard laboratory methods were used for assessment of biochemical parameters including urea and creatinine. For measuring serum PCS and IS levels, HPLC, that is, high-performance liquid chromatography, was used. Sample collection was done twice, once before initiation of therapy and once after 8 weeks of treatment.

Follow-up of the patients was done after 8 weeks during which repeat blood sample was taken only for testing urea, creatinine, PCS, and IS. The primary endpoint for assessing efficacy was change in serum PCS and IS levels at 8 weeks compared to values at baseline. The secondary endpoint was alteration in levels of serum creatinine and blood urea.

Statistical analysis

The data presentation and statistical flow of analysis are shown in Figure 1. The association of a decrease in uremic toxins with CKD stage was analyzed using the Kruskal–

Wallis test. Paired *t* test was used for comparison of blood urea nitrogen (BUN; mg/dL) and creatinine (mg/dL) across follow-up as these parameters were normally distributed. For non-normally distributed data, that is, serum PCS and serum IS, the Wilcoxon signed rank test was used for comparison across follow-up.

RESULTS

The participants' mean age was 56.44 ± 11.1 years. The number of males and females was 13 (52%) and 12 (48%), respectively. Hypertension and diabetes mellitus were noted in 18 (72%) and 11 (44%) cases, respectively. The mean BMI was 23.77 ± 3.48 kg/m^2 [Table 1].

Diabetic nephropathy was present in 10 (40%) cases; CKD—undefined and tubulointerstitial disease in four (16%) cases each; glomerular diseases, specifically IgA nephropathy and systemic lupus erythematosus-related glomerular disease in two (8%) cases each; and one (4%) case each was associated with hypertensive nephrosclerosis, ADPKD, and FSGS. The mean eGFR was 22.7 ± 12.94 mL/min, as shown in Table 2.

CKD stages 3, 4, and 5 were present in 7 (28%), 10 (40%), and 8 (32%) patients, respectively [Figure 1].

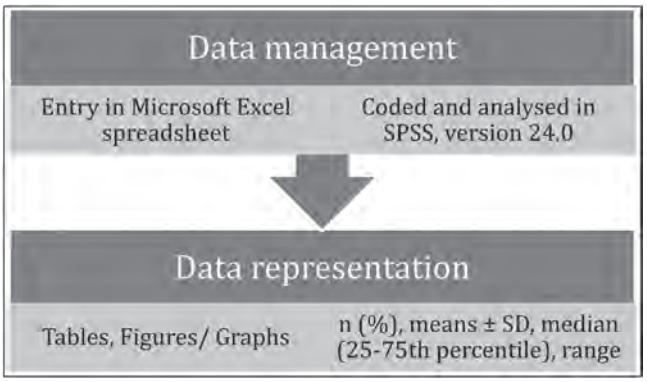

Figure 1: Statistical analysis. SPSS: Statistical Package for Social Sciences, IBM manufacturer, Chicago, IL, USA. Data normality was assessed by the Shapiro–Wilk test. Statistical significance: $P < 0.05$

Compared to pre-therapy, in post-therapy, there were significantly lower BUN (31.32 ± 13.35 vs. 40.44 ± 15.85 mg/dL, $P < 01$), creatinine (3.09 ± 1.35 vs. 3.73 ± 1.44 mg/dL, $P < 01$), serum PCS (90.2 vs. 129.4, $P < 01$), and serum IS (51.1 vs. 84.3, $P < 01$) [Table 3].

CKD stage was not significantly associated with the decreased uremic toxin levels, including BUN ($P = 0.301$), creatinine ($P = 0.135$), serum PCS ($P = 0.648$), as well as serum IS ($P = 0.254$) [Table 4].

DISCUSSION

The study results indicated that pre–probiotic therapy holds a significant role in decreasing the uremic toxin levels, not only in terms of conventional markers, that is, BUN and creatinine, but also in advanced markers, that is, IS and PCS. Likewise, Meijers *et al.*[14], found that oral intake of the prebiotic oligofructose-enriched inulin was well-tolerated, resulting in significantly decreased p-cresol production and PCS serum levels among hemodialysis patients, with a median decrease of 20% ($P = 0.01$). Lim *et al.*[15] also reported that serum IS levels were reduced after probiotic administration for a duration of 6 months. However, no significant change was seen in levels of BUN and PCS. Esgalhado *et al.*[16] reported that prebiotics: resistant starch decreased IS levels (22.1 mg/dL vs. 27 mg/L, $P = 08$), while urea (45.9 ± 12.2 mg/dL vs. 48.2 ± 12.7 mg/dL, $P = 0.50$), creatinine (8.5 ± 2.8 mg/dL vs. 8.4 ± 2.3 mg/dL, $P = 0.52$), and PCS (84.5 mg/dL vs. 79.1 mg/L, $P = 0.95$) remained unaffected. Borges *et al.*[17] also found that following probiotic supplementation, serum urea (149.6 ± 34.2 mg/dL vs. 172.6 ± 45.0 mg/dL) and IS (31.2 ± 15.9 mg/dL vs. 36.5 ± 15.0 mg/dL) significantly reduced ($P = 0.02$ for both). However, creatinine did not significantly change (9.6 ± 7.7 mg/dL vs. 14.3 ± 0.8 mg/dL) and PCS levels (46.3 ± 32.7 mg/dL vs. 50.4 ± 29.0 mg/L; $P > 0.05$). The subtle differences in the associations may be because of population heterogeneity.

This was in accordance to a systematic review including 23 studies, comprising 931 patients on hemodialysis,

Table 1: Demographic characteristic distribution

Demographic characteristics	*n* (%)	Mean ± SD	Median (25th–75th percentile)	Range
Age (years)	–	56.44 ± 11.1	54 (49–65)	40–75
Gender				
Female	13 (52.00%)	–	–	–
Male	12 (48.00%)			
Co-morbidities				
Diabetes mellitus	11 (44.00%)	–	–	–
Hypertension	18 (72.00%)	–	–	–
Body mass index (kg/m^2)	–	23.77 ± 3.48	24 (20.8–26.3)	18.4–30.2

Table 2: Renal status of patients

Parameters	*n* (%)	Mean ± SD	Median (25th–75th percentile)	Range
Basic kidney disease				
ADPKD	1 (4.00%)	–	–	–
CKD U	4 (16.00%)			
Diabetic nephropathy	10 (40.00%)			
Glomerular disease FSGS	1 (4.00%)			
Glomerular disease IgA nephropathy	2 (8.00%)			
Glomerular disease SLE	2 (8.00%)			
Hypertensive nephrosclerosis	1 (4.00%)			
Tubulointerstitial disease	4 (16.00%)			
eGFR (mL/min)	–	22.7 ± 12.94	18 (14–24)	8–54

Table 3: Comparison of uremic toxins between pre and post-therapy

Uremic toxins	Pre-therapy (*n* = 25)	Post-therapy (*n* = 25)	*P* value
BUN (mg/dL)	40.44 ± 15.85	31.32 ± 13.35	< .0001*
Creatinine (mg/dL)	3.73 ± 1.44	3.09 ± 1.35	< .0001*
Serum *p*-cresyl sulfate	129.4 (98.3–204.5)	90.2 (62.6–106.2)	< .0001†
Serum indoxyl sulfate	84.3 (67.9–116.7)	51.1 (42.6–93.5)	<. 0001†

*Paired *t* test, †Wilcoxon signed-rank test

Table 4: Association of decrease in uremic toxins with CKD stage

Decrease in uremic toxins	CKD III (*n* = 7)	CKD IV (*n* = 10)	CKD V ND (*n* = 8)	Total	*P* value
BUN (mg/dL)	10 (5–11.5)	6.5 (4.5–13)	12 (10–14.25)	10 (6–14)	0.301‡
Creatinine (mg/dL)	0.3 (0.3–0.45)	0.4 (0.3–0.575)	0.55 (0.5–1.025)	0.5 (0.3–0.6)	0.135‡
Serum *p*-cresyl sulfate	59.5 (41.2–91.9)	39.05 (35.475–101.125)	40.55 (32.025–57.475)	45.5 (34.7–96.1)	0.648‡
Serum indoxyl sulfate	23.2 (15.55–33.2)	33.85 (23.475–64.55)	21.7 (16.5–36.75)	23.7 (18–34.5)	0.254‡

‡Kruskal–Wallis test

as intervention (including probiotics, prebiotics, and synbiotics) significantly reduced the PCS levels ($P = 01$).[18] While comparing the efficacy of both prebiotics and probiotics, Yu *et al.*[19] found that prebiotics was better than probiotics in decreasing IS and BUN ($P < 0.05$). In contrast to their analysis, we used both pre andprobiotic therapy, and it showed significant results.

At one end, supplementing with probiotics is recommended as an adjuvant therapy to enhance gut microbiota balance, which supports patients' intestinal barrier integrity and metabolic regulation. Based on what is presently known, probiotic supplements have the potential to change the microbiota in the gut, boost saccharolytic activity, and encourage the production of more advantageous byproducts for the host. Increased saccharolytic activity has the potential to reduce intestinal inflammation and the synthesis of protein-bound uremic solutes by inhibiting the proteolytic activity. A healthy intestinal wall may arise from less inflammation, which will aid in preventing bacterial translocation and disruption of the intestinal transport mechanisms.[20]

Prebiotics were usually added as it assists the host by working symbiotically with probiotics. Prebiotics not only supply energy to saccharolytic bacteria but can also lengthen transit times (reduce constipation), increase stool weight (reduce diarrhea), cause few adverse effects, as well as enhance patients' quality of life. Additionally, prolonged transit time will foster growth of saccharolytic bacteria, which will decrease the generation of PCS and IS by proteolytic bacteria.[12]

As for the organisms, the most utilized strains are Bifidobacterium, Streptococcus, and Lactobacillus – which were used in the current study. Though the use of one particular probiotic strain in CKD is justified, the use of multiple strains also showed significant improvement in the uremic toxins without any significant side effects.[17]

The study holds strength in analyzing two advanced markers to uremic toxins of GI pathology. It can be decreased by pre–probiotic therapy. This is important for reducing complications associated with the CKD progression and for mitigating CVD events.[21] Moreover, the study holds strength in introducing pre-probiotic therapy in the clinical settings for the betterment of CKD patients under the purview of the rising incidence of CKD.

Limitations

The present study was limited by short-term follow-up. Also, it was a single-center study. Multicentric studies would provide more information on this regard. Third, cost-effective analysis was not done in terms of these markers as they may be costly. Fourth, risk association of decrease

in these markers in relation to the stage of CKD showed no significant association, which might be because the study was not powered statistically to assess the changes in uremic toxin levels in relation to different CKD stages.

CONCLUSION

Oral administration of a pre–probiotic bacterial regimen was safe in patients with CKD stages III, IV, and V (pre-HD). The administration of pre–probiotic resulted in significant reductions in uremic toxin levels—BUN, creatinine, PCS, and IS. Future comprehensive clinical studies, assessing dose escalation, are necessary to evaluate the potential benefits of gut-based probiotic administration.

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Data availability
Data are available on request in the Excel sheet.

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Conflicts of interest
There are no conflicts of interest.

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Brief Report

A retrospective study on nutrition risk assessment and nutritional management of head and neck cancer patients undergoing surgery in a tertiary care teaching hospital

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Abstract

Head and neck cancer (HNC) patients often face diverse nutritional challenges before, during, and after cancer treatment. Malnutrition, sarcopenia, and likely unintentional weight loss during treatment are associated with compromised quality of life, inferior treatment outcomes, and increased morbidity; even in patients whose body mass index (BMI) is not a good indicator of malnutrition. The objectives of this study were to detect nutritional risk in HNC patients undergoing surgical intervention and assess the dietary interventions done accordingly. Work planned to document the patient's clinical condition, assess the nutrition risk by Nutrition Risk Screening (NRS) tool 2002, the diet given orally or via nasogastric tube as per the severity of malnutrition, surgical complications, primary etiology, infections, and other secondary causes of malnutrition. A total of 70 subjects were selected by simple random sampling from the list of all HNC patients discharged or transferred from the Otorhinolaryngology intensive care unit (ICU) during the period from July 2023 to December 2023. Bedhead tickets and ancillary documents retrieved from the Medical Records Section served as source documents. The average BMI of 70 patients was 20.4 (standard deviation = 3.04) kg/m^2, and they were distributed as 34% underweight, 46% normal, 13% overweight, and 7% obese at admission. NRS 2002 indicated that 100% were at nutrition risk (score 5 or 6) following surgery as they were all in ICU and because of comorbidities. Dietary supplementation along with kitchen feed had been introduced to these patients, as soon as permissible after surgery, and gradually increased as per requirement. However, most required Ryle's tube feeding (85.71%), and 82.86% of patients were placed on a high-protein diet initially. The nutrition care process (NCP) was continued under the dietician's supervision throughout the hospital stay. Supervised NCP is essential for HNC cancer patients in the postsurgical period as all are at high nutrition risk, irrespective of BMI, and require ICU stay. Feeding challenges must be met in addition to recommending a diet appropriate to the current nutritional status.

Keywords: Enteral nutrition, head and neck cancer, NRS 2002, nutrition care process, nutrition risk assessment

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INTRODUCTION

Head and neck surgery is applied to treat conditions affecting the head, oral cavity, throat, larynx, nose, ear, local lymph glands, and sinuses, including both benign and malignant tumors in the head and neck region. A prominent surgical advance of recent times has been the development and popularization of transoral access techniques for oropharyngeal, supraglottic, and glottic cancers, via transoral laser microsurgery and transoral robotic surgery.[1] Head and neck cancer (HNC) encloses malignant neoplasms of the upper aerodigestive tract and as per recent findings; it is the seventh most common type of cancer worldwide. The 5-year survival for HNC ranges from 33% to 97%. Tobacco, alcohol, human papillomaviruses, and Epstein–Barr virus are associated with the pathogenesis of head and neck squamous cell carcinoma (HNSCC)—the most common subtype of HNC. Surgical resection is one of the principle treatments for HNSCC and is often lengthy and complex. Unfortunately, it frequently removes parts of organs that are important for speaking, swallowing, and breathing. Reconstruction of these critical structures is a key component of the surgical plan in most major HNC surgeries. Free flap surgery is the most common approach to restore resected tissue and allows functional recovery after major HNC surgery; however, the multiple donor sites in free flap surgeries increase the duration and complexity of the surgical process. Therefore, before surgery, identifying modifiable factors that predispose patients to complications is important. Preoperative anemia, intraoperative blood loss, and inappropriate blood count will further lower blood hemoglobin concentrations and suppress immunity and it requires appropriate management. Other vitals, such as blood glucose level are also taken to be considered.[2]

As a critical aspect of care for HNC patients undergoing surgery, a comprehensive nutritional regimen tailored to meet individual nutritional needs constitutes the cornerstone of supportive treatment. A holistic patient-centered approach combining nutritional risk assessment, tailoring diets, and leveraging supplements effectively, is the key to combat malnutrition, improve treatment outcomes, and enhance quality of life (QoL) in this patient population.[3] According to the enhanced recovery after surgery (ERAS) protocol, preoperative and postoperative nutritional management plays a vital role in patients' early mobility, restoration of normal metabolism, and return to an acceptable QoL. According to the international guidelines,[4] the nutrition care process (NCP) should be initiated within 24–48 h of admission and early enteral nutrition intervention escalates the recovery rate in critically ill patients. Particularly, in head and neck surgery the patient's nutritional requirement is likely to be very high due to diminished nutrient deposition, loss of nutrients during surgery, inability to chew or ingest properly, alteration of metabolic rate, and immobility during the critical phase. The high incidence of malnutrition may lead to extreme loss of muscle mass and disruption of various metabolic processes.[5]

HNC patients often face multiple nutritional challenges throughout the treatment due to the metastatic condition and perioperative complex that may hamper normal eating function along with nutrient deposition. Common treatment-related side effects, such as dysphagia, odynophagia, dysgeusia, xerostomia, thick saliva, mucositis, nausea, and vomiting, all further impair the patient's ability to accept and maintain adequate oral intake. Malnutrition, sarcopenia, and unintentional weight loss during and after treatment are associated with poor QoL, poor treatment outcomes, and increased morbidity; even in patients whose body mass index (BMI) is not a highly significant indicator of malnutrition. The main nutrition goal for HNC surgery patients is to maximize enteral nutrition intake through tube feeding to prevent or limit muscle mass and fat loss, preserve lean body mass, minimize treatment delays and unplanned hospitalizations, and improve treatment outcomes.[4,6-8] Malnutrition adds significantly to both morbidity and mortality in cancer patients and HNC patients are particularly at risk in this regard.[9] Some studies have shown that prophylactic enteral nutrition can improve QoL and nutrition status and reduce the risk of malnutrition. However, other studies suggested that prophylactic enteral nutrition therapy may negatively affect QoL due to social isolation and prolonged tube dependency although these findings are under supervision.[10]

We planned the present study aiming to detect nutritional risk in HNC patients undergoing surgical intervention in our tertiary care teaching hospital setting and assess the dietary interventions done subsequently. We assessed the type of intervention done along with their timing and documented the potential benefits of nutrition treatment under surveillance.

AIMS AND OBJECTIVES

The broader objective of the study is to detect the nutritional risk of the patients who need surgical intervention along with the supervision under critical care unit and to incorporate the diet as per patients' requirements.

Therefore, the primary objectives of this study would be:

- To judge the nutrition risk.
- To ensure the early nutrition intervention.

- To modify the principle of dietary recommendation.

The secondary objectives would be:

- To document the consequences of nutrition treatment under surveillance.
- To modify the nutritional treatment of surgical and critically ill patients.

MATERIALS AND METHODS

The study conformed to the Declaration of Helsinki principles and received due approval from the Institutional Ethics Committee (IEC). Considering the retrospective nature of data collection, a waiver of the informed consent requirement was granted by the IEC.

Adult subjects (age 18+ years) were selected, irrespective of gender, by simple random sampling from the list of all HNC patients discharged or transferred from the Otorhinolaryngology intensive care unit (ICU) during the period from July 2023 to December 2023. Patients with critical surgical or postsurgical complications likely to lead to mortality were excluded. No formal sample size calculation was done. However, it was estimated that 70 cases selected randomly over 6 months would be reasonable representation for the estimated 70 adult cases admitted during this period.

Bedhead tickets and ancillary documents retrieved from the Medical Records Section of the hospital served as source documents. Work planned to record information on the patient's clinical condition, such as diagnosis, mobility status, hemodynamic stability, biochemical parameters, gastrointestinal (GI) functioning, and muscle wasting, and then to assess the nutrition risk by the Nutrition Risk Screening (NRS) tool 2002.[11,12] This is a simple scoring system used for hospitalized patients and comprises four items for initial screening: BMI < 20.5 kg/m^2, weight loss within 3 months, reduced dietary intake in the last week, and whether the patient is in the ICU. If the response to all four items is "No," then the patient is at low nutrition risk, and weekly rescreening is recommended. If the response to any item is "Yes," then the final screening is done based on three parameters: Nutritional impairment based on recent weight loss and ranging in severity from 0 to 3, severity of disease graded from 0 to 3, and age, which is scored 1 if 70 years or above and 0 otherwise. A total score >3 indicates the patient is at nutrition risk and requires initiation of NCP (food, oral supplements, tube feeding, and/or parenteral nutrition as appropriate).

The subsequent nutrition intervention was captured from the diet plan for enteral nutrition, either orally or through nasogastric tube feeding, as per the severity of malnutrition and the patient's capability to accept oral intake. Surgical complications, probable primary etiology of malnutrition, infections, and other secondary causes of malnutrition were also recorded. In all cases, dietary supplementation along with kitchen feed had been introduced to patients, as soon as enteral nutrition therapy was permissible, and then gradually increased as per requirement.

Data have been summarized by routine descriptive statistics, namely mean and standard deviation (SD) for numerical variables that are normally distributed, the median and interquartile range for skewed numerical variables, and counts and percentages for categorical variables. Key variables have been expressed with a 95% confidence interval (CI) calculated with a normal approximation to the binomial. Data were transcribed to a Microsoft Excel spreadsheet and subsequently analyzed by MedCalc version 19.6 (MedCalc Software Ltd., Ostend, Belgium, 2020) software.

RESULTS

A total of 70 study participants undergoing HNC surgery showed a male-to-female ratio of 11:3 with a mean (SD) age of 18–70 (46.4) years. The average BMI was 20.4 (SD = 3.04) kg/m^2, and the BMI was distributed as 34% underweight, 46% normal, 13% overweight, and 7% obese at admission. Considering significant comorbidities, 10 patients had diabetes, 11 faced stress-induced hyperglycemia, 6 were hypertensive, and 6 had dyselectrolytemia. Less than five participants each had anemia, hypothyroidism, acute kidney injury, or liver issues. Comorbidities were not mutually exclusive.

The types of surgery encountered were mandibulectomy, thyroidectomy, septoplasty, tympanoplasty, laryngectomy, glossectomy, and mastoidectomy.

Baseline NRS 2002 scoring indicated that all 70 subjects (100%) were at nutrition risk (score 5 or 6) and merited placement on an appropriate nutrition care plan. The initial feeding strategy has been depicted as a bar chart in Figure 1 and the diet plan in Figure 2.

As seen from Figures 1 and 2, the majority (85.71%; 95% CI = 77.52%–93.91%) of the patients were placed on tube feeding post-surgery; only a few (11.43%) were allowed to be fed orally. One patient underwent total parenteral nutrition (TPN) and one was on feeding jejunostomy. High protein supplement was recommended for most (82.86%; 95% CI = 74.03–91.69%) of the patients; some (12.86%)

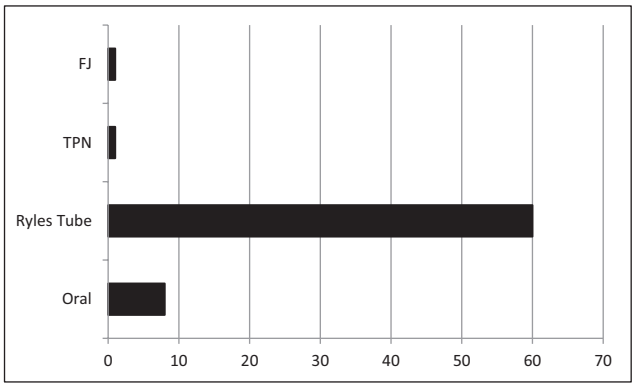

Figure 1: Initial postsurgical feeding strategy in 70 head and neck cancer patients. FJ: feeding jejunostomy, TPN: total parenteral nutrition

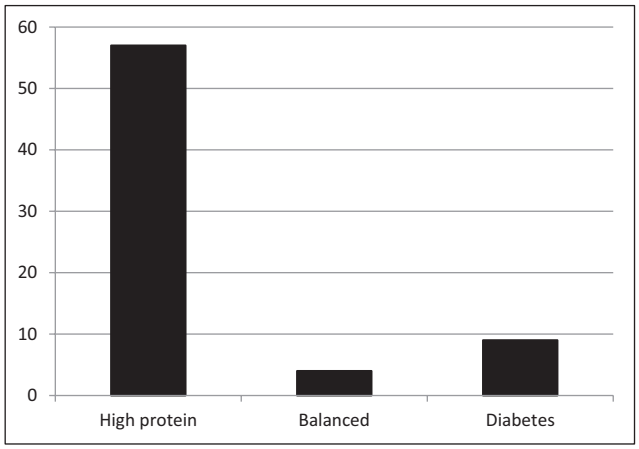

Figure 2: Postsurgical diet plan in 70 head and neck cancer patients

were given a diabetic diet, and few (4.29%) were placed on a balanced diet.

According to ERAS protocol, feed should be started within 6 h of surgery if feasible. In our setting this protocol was followed, that is, solid food 6 h before, liquid feed 2 h before surgery, and water introduced after 6 h of surgery (ERAS protocol). After plain water tolerance was established, supplements were introduced by tropic feeding. The calorie requirement was determined by the patient's clinical condition along with consideration of biochemical parameters and co-morbidities. High protein and balanced composition were applicable for most patients, diabetic supplements were offered to those who were already diabetic or who faced stress-induced hyperglycemia and hypoglycemia. Few cases had acute kidney injury; hyperkalemia and dyselectrolytemia were also seen due to renal insufficiency. Albumin is not a regular nutrition supplement, but many cases had hypoalbuminemia, in which case green coconut water and egg whites were recommended. For patients who were able to take foods orally, soup, milk, and fruit juice were recommended from the hospital kitchen along with supplementation. TPN was initiated in one critical case and a feeding jejunostomy tube was inserted for another case. In both cases, individualized diet prescription was generated with proper micronutrient distribution and maintained chemical balance (isotonic).

The NCP was continued under the dietician's supervision throughout the hospital stay. At the time of transfer out or discharge 70 (100%, SD = 0.48) were still at high nutrition risk. There are plans to extend this study for a further period of 6 months at least with another 70 participants to enable more complete coverage of the spectrum of clinical cases and surgeries encountered in our teaching hospital.

DISCUSSION

Patients with HNC require multidisciplinary management,[3-6] including dietician-supervised NCP before and especially after surgery that spans proper assessment of nutritional status, estimation of calorie and nutrient requirements, diet planning, attention to dietary feeding practices, counseling, and adherence maintenance. In the authors' busy hospital setting, administrators and head and neck surgeons both appreciate the necessity of nutritional management but remain cognizant of the difficulty in incorporating nutritional support in the multimodality treatment algorithms of head and neck malignant disease because of the difficulty in enlisting trained dietician support for all cases.

There remains a deficit within the literature of nutritional research specifically addressing patients with HNC. Furthermore, there are no guidelines regarding the nutritional management of HNC patients, preoperatively or postoperatively, although most authors recommend aggressive nutritional support and early enteral feeding in patients with a functioning GI tract with appropriate.[4,13-15] Unfortunately, we did not come across any Indian studies on this topic in the last 5 years.

Patients in our series had undergone various types of surgery, including mandibulectomy, thyroidectomy, septoplasty, tympanoplasty, laryngectomy, glossectomy, and mastoidectomy, many of them as radical procedures. The majority were underweight even before surgery and suffered further weight loss in the aftermath of the procedure. All required ICU admission and many had one or more significant comorbidities. Unsurprisingly, 100% of the cases in our series were at high nutritional risk and therefore merited a supervised NCP with individualized attention. The NRS 2002 tool is simple, and although we applied it retrospectively after extracting data from the patient's medical records, it can be easily applied in the clinic even by nondieticians to assess nutrition risk before surgery and periodically thereafter. The

availability of online calculators (e.g., https://www.mdcalc.com/calc/4012/nutrition-risk-screening-2002-nrs-2002) makes the application of this tool still simpler.

The risk assessment must be followed by proper nutritional intervention in all high-risk patients to improve treatment outcomes and QoL. However, the intricacies of an individualized nutrition care plan make the involvement of a dietician somewhat mandatory in this scenario.[16] Dietitians lead on the recommendation, provision, monitoring, and counseling of nutrition support, the route of administration could be via the oral, other enteral, or parenteral route. Oral nutrition support includes dietary counseling, kitchen feed recommendations, food fortification advice, and high energy/protein oral nutritional supplements. Tube feeding can be required on a short-term or long-term basis and dietitians decide on the type of tube and timing of placement along the modification of diet. The lack of availability of trained dietician support can become a major hindrance in the optimum care of HNC surgery patients.

Our study has limitations, the major one being the retrospective nature of data collection. However, it is unlikely that wrong data will have confounded results because most standard information likely to be well-recorded has been accessed. Another limitation is the unicentric nature of the study, but we believe that since surgical procedures and care paradigms will be similar in other HNC surgery facilities, results will not be substantially different. The limited time duration of the present study we hope to overcome by extending the study in time and sample size so that a more complete spectrum of surgical procedures can be covered.

In conclusion, we can say that HNC surgery patients are universally at high nutrition risk, irrespective of baseline BMI, and require individualized nutrition care plans as part of the multimodality management of such cancers. Nutrition risk screening, formulation of appropriate diet plan, institution of early enteral feeding, dietary supplementation, and diet counseling are components of the care plan, and because of the intricacies involved, require dietitian support for implementation. The result should be better treatment outcomes, fewer complications, and improved QoL for the patients.

Author contributions

Conception or design of the work, the definition of intellectual content, literature search, clinical studies, and experimental studies: KPC, DB, and AH. Data collection and acquisition: KPC. Data analysis and interpretation: AH and KPC. Drafting the article, manuscript preparation, and manuscript editing: KPC, DB, and AH. Critical revision of the article: AS, DB, and AH.

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Conflicts of interest

There are no conflicts of interest.

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Case Series

Rare presentations of a common infection

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Abstract Dengue infection can present as dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). The World Health Organization (WHO) has coined the term "expanded dengue syndrome" (EDS) for cases that do not fit into either DHF or DSS. These cases showcase unusual symptoms in various organs such as the cardiovascular system, nervous system, kidneys, gut, and hematological system, and are increasingly being reported as EDS. EDS is globally on the rise with unusual characteristics and greater severity. There are escalating reports of rare manifestations involving severe organ complications that are often overlooked. This case series compiles rare presentations of expanded dengue syndrome, providing crucial insights for early dengue diagnosis, especially during ongoing epidemics, which may be life saving.

Keywords: CVT, dengue, pancreatitis, pulmonary thromboembolism

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INTRODUCTION

Dengue is a rapidly spreading arboviral infection transmitted by Aedes mosquitoes and highly endemic in about 30 countries of South East Asia, of which India, Myanmar, Indonesia, Thailand, and Sri Lanka contribute to more than half of the global burden of dengue. The incidence of dengue has increased by thirtyfold over the past five decades, according to global estimates, with the maximum number of reported cases witnessed in 2019.[1] Dengue virus has four serotypes and various subtypes within these serotypes.

Infection with one serotype does not provide immunity to others, allowing all four serotypes to co-circulate in endemic areas. Dengue fever was classified into two groups by the World Health Organization (WHO): uncomplicated dengue and severe dengue in 2009. Clinically, severe dengue is characterized by severe bleeding manifestations, organ dysfunction, or plasma leakage, while others are categorized as uncomplicated dengue. In 2012, the WHO introduced, "expanded dengue syndrome" to describe cases of dengue hemorrhagic fever (DHF) and dengue fever with unusual presentations.[1] Four confirmed cases of dengue with atypical presentations have been discussed in detail under expanded dengue syndrome (EDS).

CASE DESCRIPTION

Case 1: Severe dengue with cerebral venous thrombosis (CVT)

A 26-year-old female was brought to the emergency department of JNMCH, Aligarh, with complaints of headache for 10 days, fever with chills for 4 days, and red pinpoint rashes all over the body for 4 days. Headache

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which was diffuse initially, turned retro orbital and dull aching was not relieved on medication completely for 3 days; vomiting for more than seven episodes, which was projectile and non-bilious for 1 day; blurring of vision, with gradual onset with progressive worsening for 6 h. She later developed diplopia during the hospital stay. There was no history of seizures, bleeding manifestations, altered sensorium, use of oral contraceptive pills, head injury, recent childbirth, abortions, ear discharge, head and neck infections, or history of similar complaints in the past. On examination, the patient was observed to be flushed, and red pinpoint rash was present on all of the extremities and trunk. She was diagnosed with Glasgow coma scale (GCS) of E4V4M6, bilateral pupils were dilated and sluggish to react, and left-sided Babinski's sign was positive. Blood pressure at presentation was 90/60 mm Hg, pulse rate was 104 bpm, respiratory rate of 28 cycles/min, and fever of 101°F. Fundus examination was suggestive of grade IV papilledema. No signs of meningeal irritation, no neurological deficit, and no bowel and bladder involvement were observed. On biochemical investigation, hemoglobin was 9.3 g/dL (11.5–17.0 g/dL), mean corpuscular volume of 65 μm^3 (80–100 μm^3), total leucocyte count of 4100 mm^3 (4000–10,000 mm^3), hematocrit was 35.4 L% (37–54 L%), platelet count was 100 × $10^3/mm^3$ (1 lakh) (150–500 × $10^3/mm^3$), dengue serology—nonstructural protein 1 (NS1Ag) reactive, IgM dengue ELISA was positive, malaria parasite quantitative buffy coat (MPQBC)—negative, IgM typhi dot was negative, prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer, and international standardized ratio were within normal limit, blood urea was 9 mg/dL (9–20 mg/dL), serum creatinine—0.5 mg/dL (0.3–1.3 mg/dL), random blood glucose was 90 g/dL (74–106 g/dL), urine analysis was normal, liver function was within normal limit, total serum protein, albumin were within normal limit, ultrasound whole abdomen was normal, blood culture was negative, urine culture was negative, stool culture sensitivity was negative, chest X-ray was normal, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), and human immunodeficiency virus-non reactive. Magnetic resonance imaging (MRI) of brain suggested long segment dural venous thrombosis, leading to hemorrhagic transformation in the venous infarct with involving the right parietal lobe with mass effect as shown in Figures 1 and 2. Anti-phospholipid antibody panel (APLA) was negative, anti-nuclear antibody by immunofluorescence was negative, and electrocardiogram (ECG) showed normal sinus rhythm.

Based on examination and investigations, the patient was diagnosed as a case of severe dengue with CVT (superior sagittal, right transverse sinus, sigmoid sinus, and proximal right internal jugular vein) with hemorrhagic transformation in the right parietal lobe with grade IV papilledema with uncrossed diplopia of the right eye with moderate microcytic hypochromic anemia.

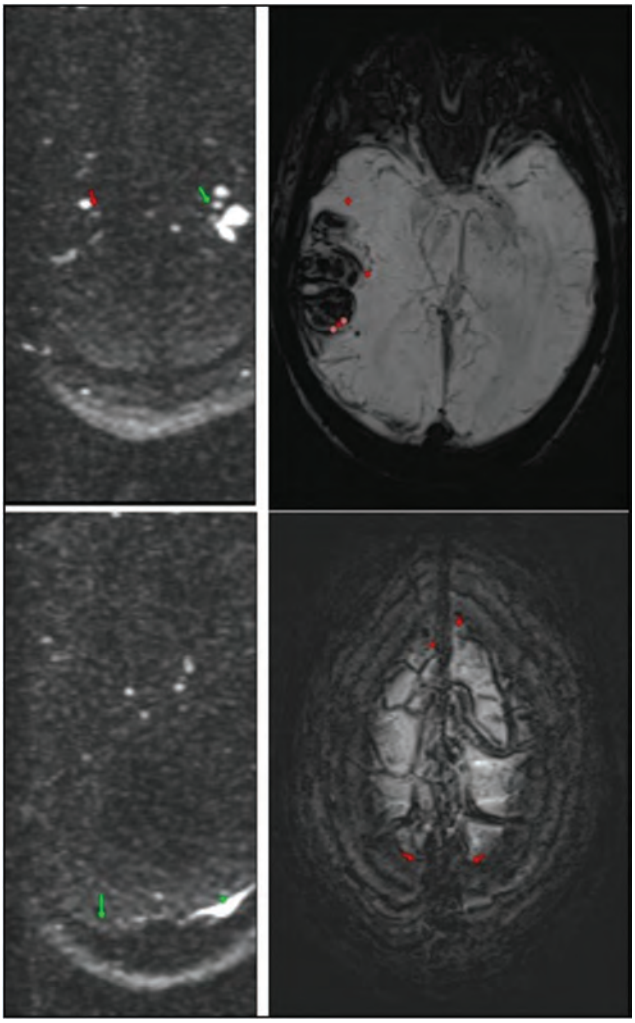

Figure 1: A case of cortical vein thrombosis complicated by venous hemorrhage Image 1 and 3 (on right side) MR venogram showing there is a filling defect in right sigmoid and right transverse sinus. Image 2 (on left upper side) – axial SWI sequence shows multiple blooming areas in the right temporal lobe s/o bleed

The patient was admitted in the intensive care unit, and severe dengue and shock were actively managed with inferior vena cava (IVC)-guided fluid and strict input and output monitoring. The patient was initiated on subcutaneous enoxaparin at a dosage of 1 mg/kg/day, administered in two divided doses, with daily monitoring of platelet counts and APTT values. Following 3 days of subcutaneous heparin administration, she was initiated on oral warfarin, while maintaining the International Normalized Ratio (INR) between 2 and 3. Intracranial tension (ICT)-lowering drugs such as mannitol and acetazolamide have been initiated once shock was corrected. The patient was

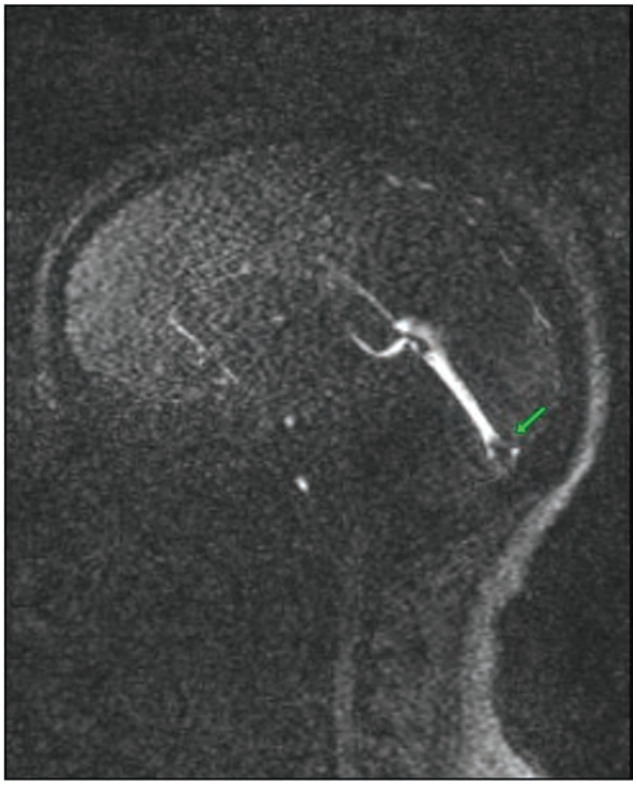

Figure 2: MR venography sagittal section showing the filling defect in sagittal sinus

discharged later after which she was switched to apixaban 2.5 mg 12-hourly interval.

Case 2: Dengue with pancreatitis

A 17-year-old male with no prior history was brought to the emergency department with complaints of generalized weakness and fatigue for 10 days; high-grade fever for 5 days associated with retro orbital pain, malaise, and red pinpoint rash for 3 days; intractable vomiting, (20 episodes) for past 1 day; and acute onset pain in the abdomen for 4 h, severe in intensity, localized around the umbilicus, radiating to the back. On examination, the patient was febrile (with a pulse rate of 104 bpm, respiratory rate of 32 cycles/min, blood pressure of 100/72 mm Hg, and saturation of 88% at room air), conscious, oriented, and visibly distressed due to pain. There was no abdominal distention, with tenderness over the epigastric region, without any guarding and rigidity. Bowel sounds were 5/min, without hepatosplenomegaly. Biochemical tests showed thrombocytopenia with a platelet count of 2000/mm^3 (150–500 × 10^3/mm^3); hematocrit of 56 L% (37–54 L%); hemoglobin 19 g/dL (11.5–17.0 g/dL); total leukocyte count of 24,000/mm^3 (4000–10,000 mm^3), with neutrophilic predominance; creatinine of 1.4 mg/dL (0.3–1.3 mg/dL); a positive dengue Ig M enzyme linked immunosorbent assay (ELISA) test; serum amylase of 1587 U/L (30–110 U/L); serum lipase of 2432 U/L (23–300 U/L); blood urea nitrogen of 30 mg/dL (9–20 mg/dL); liver function tests were suggestive of nonsignificant elevations; ALT was 89 U/L (0–50 U/L); ALP was 165 U/L (28–126 U/L); AST was 116 U/L (15–59 U/L); and total bilirubin was 1.6 mg/dL (0.2–1.3 mg/dL), of which direct bilirubin was 1 mg/dL (0.0–0.2 mg/dL) and indirect bilirubin of 0.6 mg/dL (0.0–1.1 mg/dL). The lipid profile was normal, PT of 23 s (9.5–13.5 s), international standardized ratio INR of 1.5 (1.18), negative MPQBC, and Ig M typhi dot. Radiological findings by chest X-ray was suggestive of right-sided pleural effusion, ultrasound of the whole abdomen showed bulky pancreas, and pleural tap was transudative and had normal parameters. Contrast-enhanced computerized tomography of the abdomen after 72 h suggested bulky pancreas with peripancreatic inflammatory changes with right-sided pleural effusion with a CT severity score of 6/10, and the bedside index of severity in acute pancreatitis score (BISAP) of 3 as shown in Figures 3 and 4.

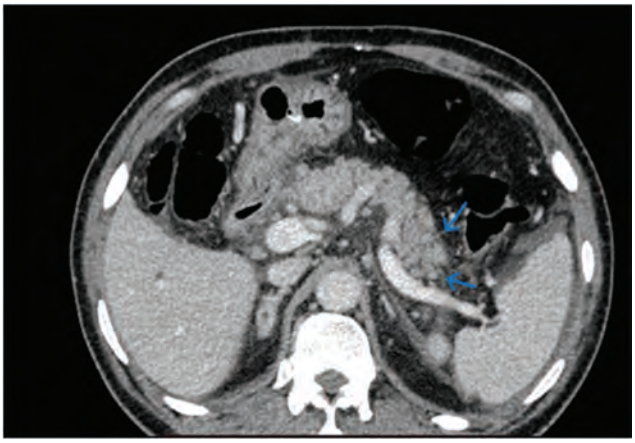

Figure 3: Axial post contrast computerized tomography image shows there is mildly bulky body of pancreas with mild adjacent inflammatory changes in the form of peripancreatic fat

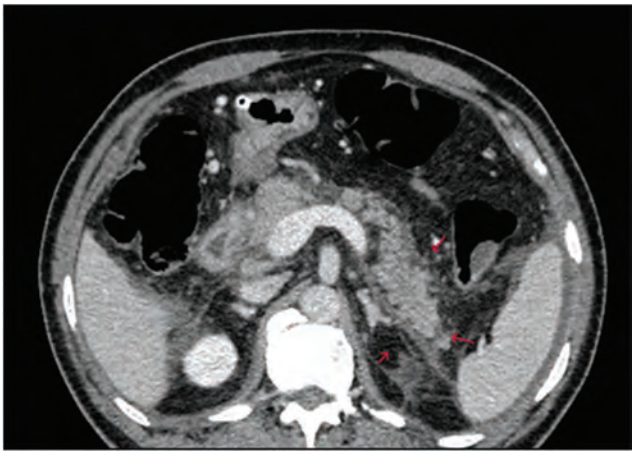

Figure 4: Axial post-contrast computerized tomography shows in a case of pancreatitis. There is fat stranding and heterogeneity noted in the peripancreatic region and in peri renal fat with thickening of the renal fascia (red arrows)

Based on all parameters, he was diagnosed as a case of severe dengue with acute interstitial pancreatitis. He was admitted in intensive care unit, five units of random donor platelets and one unit of single-donor platelet were transfused to increase platelet count to 58,000/mm^3 (150–500 × 10^3/mm^3), intermittent continuous airway positive pressure (CPAP) for respiratory distress was given, and fluid administration and supportive care for pancreatitis were also given. The patient responded well and was discharged after 14 days of hospital stay in hemodynamically stable and asymptomatic conditions.

Case 3: Dengue with bilateral optic neuritis

A 40-year-old male without any known comorbidities or addictions presented with retro orbital headache, myalgia, arthralgia for 10 days, and fever for 6 days. He started experiencing nausea for 4 days and multiple episodes of vomiting for 2 days, which improved on medication. He had a single episode of blood in stool for 1 day, and sudden onset of painful blurring of vision in both eyes for 5 h, which became more pronounced on eye movements and relieved at rest. On examination, the patient was conscious, coherent, cooperative, with GCS of 15; and the pupil was mid-dilated in both eyes and sluggishly reacting. His vitals were stable, had good capillary refill time, tourniquet test yielded positive results, blood pressure was recorded to be 92/68 mm Hg, pulse rate of 100/min, no visible pallor, multiple petechiae over the trunk, and grade-I external hemorrhoids. Cardiovascular, respiratory, and gastrointestinal tract examination results were within normal limits. Non-contact tonometry was 16 and 14 mm Hg in right and left eyes, respectively (normal 10–20 mm Hg). Ocular moments were full in all gazes in both eyes, projection of eyes was accurate in all quadrants in both eyes, and color vision and contrast of both eyes was reduced to 11.22% by Pelli Robson Contrast Sensitivity test (normal 100%). The anterior segment of the eye was unremarkable on slit lamp examination. Fundus examination on indirect ophthalmoscopy revealed B/L pale optic disc, suggesting secondary optic atrophy as shown in Figure 5.

On laboratory testing, he had a hemoglobin of 10.4 g/dL (11.5–17.0 g/dL), hematocrit of 49 L% (37–54 L%), platelet count of 12000 mm^3 (150–500 × 10^3/mm^3), nonstructural protein 1 (NS1Ag) and IgM dengue are positive, PT, INR, and active thromboplastin time (aPTT) were within normal limits, MPQBC was negative, scrub typhus was negative, and liver and renal function tests were within normal limits. X-ray of the chest was normal, and ultrasound of the whole abdomen was normal. Electrocardiogram was suggestive of a normal sinus rhythm. MRI of the spine was normal, and MRI of the brain with optic nerve cuts was suggestive of bilateral optic neuritis as shown in Figure 6. Based on clinical, laboratory, and radiological profiling, he was diagnosed as a case of severe dengue with optic neuritis. He was managed by blood product transfusion; he was started on the optic neuritis treatment trail (ONTT) protocol. On the first day of admission, methylprednisolone was administered via injection at a dosage of 250 mg every 6 h for 3 days, followed by oral methylprednisolone at a dosage of 1 mg/kg/day for 11 days, which was subsequently tapered over the next 3 days. He improved symptomatically; platelet count increased to 1 lakh mm^3 by 11th day, that is, day of discharge.

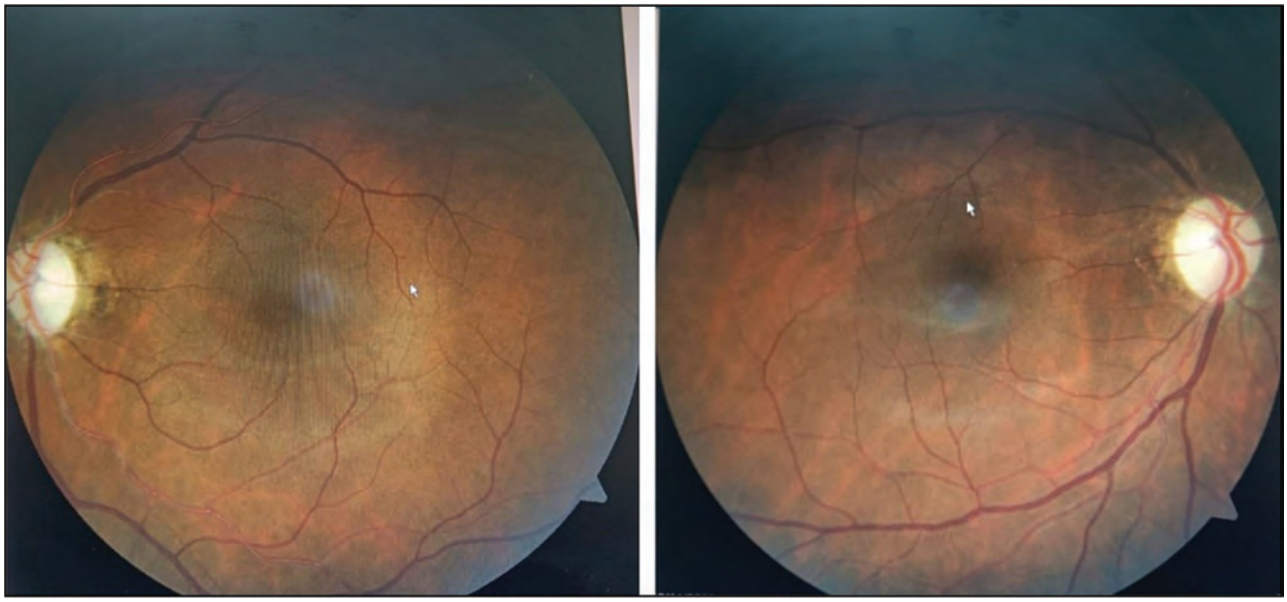

Figure 5: Left: left eye, pale fundus. Right: right eye, pale fundus

Case 4: Dengue with pulmonary venous thromboembolism

A 50-year-old male presented with high-grade fever for 6 days worsening over past 2 days associated with lightheadedness and shortness of breath for 1 day and chest pain diffuse, non-radiating, not associated with nausea, vomiting, or diaphoresis for 2 h. He also complained of decreased urine output for past 1 day. On examination, the patient appeared distressed and apprehensive, although he was conscious, cooperative, and oriented. The pulse rate was 112 bpm, respiratory rate of 32 cycles/min, saturation (SpO_2) of 95% at room air, and blood pressure of 92/70 mm Hg. Bilateral fine crepitations were heard in inspiration on auscultation of the chest. Other system examinations were otherwise normal. Serial ECG showed sinus tachycardia, and X-ray of the chest showed increased broncho-vascular markings. The patient was put on supplemental oxygen therapy, and Foley catheter was inserted to monitor shock, and blood and urine samples were sent for further examination. Cardiac troponin I was elevated via serial measurements, brain natriuretic peptide was > 25,000 pg/mL (900 pg/mL 50–75-year cutoff), and echocardiography showed enlarged right atrium, right ventricle, mild tricuspid regurgitation, left ventricular ejection fraction of 50–55%, and IVC diameter of 2.6 cm. On laboratory investigations, hemoglobin was 9.6 g/dL (11.5–17.0 g/dL), platelet count was 23,000/mm^3 (150–500 × 10^3/mm^3), total leukocyte counts of 11,000 mm^3 (4000–10,000 mm^3), hepatic and renal function tests were within normal limits, urine routine culture was positive for 3+ blood, 1+ protein, MPQBC was negative, and nonstructural protein 1 (NS1Ag) dengue, dengue IgM, and dengue IgG were positive. D-dimer level was 2365. 69 ng/mL (< 500 ng/mL). His symptoms further worsened, and oxygen saturation (SpO_2) decreased to 85% at room air, and there was a fall in blood pressure to 80/60 mm Hg. He was transferred to the intensive therapy unit for inotrope and oxygen support. Arterial blood gas analysis revealed respiratory acidosis and partial pressure of oxygen/oxygen saturation (PaO2/SpO2) ratio of 380; thus, urgent computer tomography pulmonary angiogram was done, which confirmed bilateral pulmonary thromboembolism in main pulmonary arteries as shown in Figure 7. He was diagnosed with severe dengue with pulmonary thromboembolism with acute respiratory distress syndrome. His condition further deteriorated, requiring mechanical ventilation. Blood products have been transfused, and low-molecular-weight heparin has been initiated. Despite timely intervention and best of supportive care, the patient succumbed on the third day of admission.

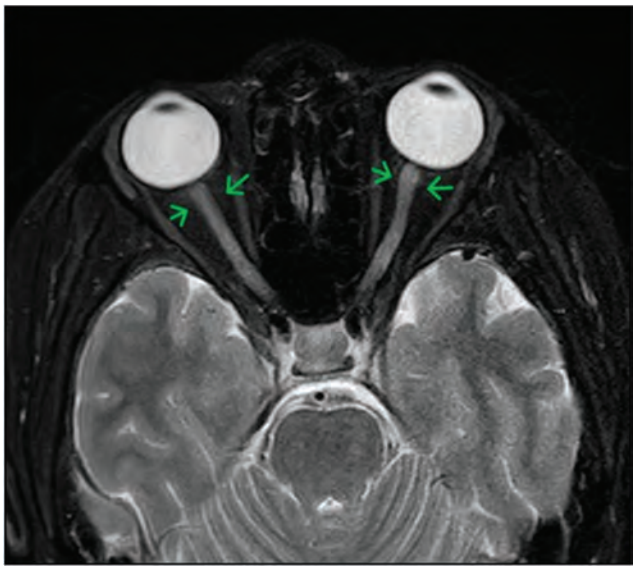

Figure 6: Axial T2 FS shows there is altered signal in intra orbital segment of B/L optic nerve with mild haziness in B/L intra orbital fat

DISCUSSION

We have discussed summaries of four confirmed cases of dengue with atypical and life-threatening manifestations. These cases were observed in JNMCH, Aligarh, a tertiary

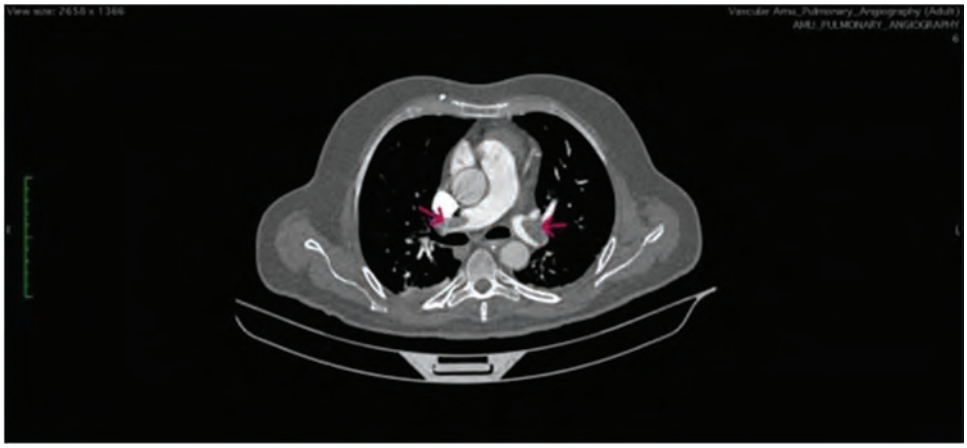

Figure 7: Axial post contrast computerized tomography image shows a large filling defect (thrombus) in the B/L pulmonary artery. Red arrows

Table 1: Severe dengue with cerebral venous thrombosis previous studies

Publication	Age (years)/ gender	Clinical features	MRI findings	Treatment	Outcome
Sharma *et al.*[3]	30/F	Fever, headache, altered sensorium, and right hemiparesis	Venous thrombus in transverse sinus, left straight sinus, left internal jugular vein, and acute left temporal hematoma with mass effect	Decompressive craniotomy, eltrombopag, steroids, and anticoagulation	Improved
Hameed *et al.*[17]	25/M	Visual blurring, headache, fever with rash, papilledema, and right upper limb weakness	Thrombus in superior sagittal sinus, right transverse sinus, and right straight sinus	Anticoagulation	Improved
Vasanthi *et al.*[18]	16/M	Diplopia, headache, and fever	Bilateral transverse sinus thrombosis	Anticoagulation	Improved
Tilara *et al.* [19]	30/M	Seizures, fever, and headache	Thrombus in superior sagittal sinus, transverse sinus, and right straight sinus	Anticoagulation	Improved
Manchanda *et al.* [20]	22/M	Fever and headache	Thrombus in left transverse and left sigmoid sinus	Anticoagulation	Improved

center in Uttar Pradesh, northern India, during a dengue outbreak between the months July and October 2023. All the cases presented with severe thrombocytopenia without hemorrhagic manifestations. Cases 2 and 4 presented with plasma leakage, and case 4 presented with shock. Cases 1, 2, 3, and 4 tested positive for Ns1Ag, while case 3 also showed IgM dengue reactivity. Case 4 tested positive for Ns1Ag, IgM, and IgG dengue. All cases had atypical manifestations, and case 4 had a fatal outcome.

According to the WHO, dengue is one of the 17 neglected tropical diseases.[2] A diverse array of clinical presentations of dengue includes mild febrile illness to severe hemorrhagic complications. Clinical manifestations of dengue are broadly categorized as symptomatic and asymptomatic. Symptomatic dengue is further classified into undifferentiated fever, dengue fever (with or without hemorrhage), DHF (non-shock and with dengue shock syndrome), and EDS or isolated organopathy. EDS encompasses the uncommon expressions of dengue due to severe organ involvement, involving renal, neurological, hepatic, pulmonary, and other isolated organs. The severity may confirm the underlying comorbidities, co-infections, shock, or ongoing MODS. High-risk categories for EDS include expectant women, infants, the elderly, patients with comorbidities, those with hemoglobinopathies, and immunocompromised individuals. Although the exact pathogenesis of severe dengue manifestations remains unclear, they may be the result of a multifaceted interaction between the host's dysregulated immune system. Antibody-dependent enhancement, cytokine storm, vasculopathy, and coagulopathy are some of the hypothesized pathophysiological causes of severe dengue. Hypovolemia, resulting from increased vascular permeability and plasma leakage, is the critical determinant of disease severity in dengue. Due to the paucity of extensive studies, the pathogenesis of EDS is not clear. According to autopsy studies, reticuloendothelial organs including liver, spleen, and lymph nodes are targeted by the dengue virus [Table 1].

Table 2: Dengue with pancreatitis previous studies

Author	Type of study	Patients of dengue with acute abdomen	Patients with pancreatitis
Anju Dinkar *et al.*[6]	Retrospective cross-sectional	220	2
Khanna *et al.*[5]	Retrospective	20	8
Lee *et al.*[21]	Retrospective	71	3
Gupta *et al.*[22]	Prospective	165	2
Chandey *et al.*[23]	Prospective	309	9
Shashirekha *et al.*[24]	Retrospective	183	24

Case 1 describes a young female with CVT in the background of dengue infection. Coagulopathy, though rare in dengue, is multifactorial. Dengue virus is found to activate endothelial cells and increase thrombomodulin expression. Increase in aPTT values and a decrease in fibrinogen levels are notable findings [Table 2]. Of all the neurological complications of dengue, CVT and acute ischemic stroke have rarely been reported. Five cases of dengue with CVT have been reported in the literature. In a case reported by Sharma *et al.*[3], a 30-year-old female with massive intracranial hemorrhage secondary to CVT showed better outcomes with surgical decompression. Other reported cases also showed improvement with anticoagulation, emphasizing the role of adequate hydration in preventing CVT. Due to the absence of other attributable causes, strong laboratory and radiological evidence, and positive dengue serology, the diagnosis of severe dengue with CVT was made [Table 3].

In Case 2, we discussed the case of a 17-year-old male with dengue and acute pancreatitis during the critical phase of the illness. The proposed pathogenesis involves the direct invasion of the pancreas by the virus or autoimmune damage of pancreatic cells associated with inflammation

Table 3: Dengue with optic neuritis previous studies

Author	Age (years)/sex	Chief complaints	Treatment
Wen *et al.*[14]	Not reported	Not reported	High dose steroid
Subramanyam *et al.*[25]	17/M	Sudden onset loss of vision	Trimethoprim and sulfamethoxazole
Preechawat *et al.*[26]	20/M	Gradual visual loss of the right eye followed by the left eye	IV methylprednisolone
Sanjay *et al.*[27]	19/M 31/M 40/M	Gradual loss of vision	IV steroids
Haritoglou *et al.*[28]	25/F	Loss of vision	No treatment

Table 4: Dengue with pulmonary venous thromboembolism

Author	Age (years)/ gender	Treatment	Outcome
Agarwal *et al.*[12]	55/M	Anticoagulation	Improved
Poletto *et al.*[13]	38/W	Anticoagulation	Improved
Kamath *et al.*[15]	39/M	Anticoagulation	Improved
Hsu *et al.*[29]	71/F	Anticoagulation	Improved

and damage of the ampulla of vater. Acute pancreatitis is an uncommon manifestation of dengue infection. Pancreatic involvement was established by sonography in a study of 148 children with DHF who reported pain in the abdomen. Setiawan *et al.*[4] reported that 29% of patients showed pancreatic enlargement and elevated blood amylase and lipase levels. Both direct viral invasion and DHF-induced hypotension can result in pancreatitis in dengue. Nevertheless, no case series or publications have investigated the pancreatic histological findings in dengue to establish direct viral invasion [Table 4]. In 45 cases of dengue with acute peritonitis, Khanna *et al.*[5] reported eight cases of acute pancreatitis in 45 cases of dengue with acute pain in the abdomen. In a retrospective cross-sectional study done in Uttar Pradesh in India on 220 patients by Anju Dinkar *et al.*[6], two patients presented with acute pancreatitis. Multiple isolated reports of pancreatitis in dengue have been reported by Flor *et al.*[7], and Jain *et al.*[8] Pancreatitis in dengue is managed conservatively, although one needs to be watchful of the late presentation of pancreatitis and its associated complications.

Ocular manifestations of dengue are commonly seen in clinical practice, with a prevalence estimated as high as 40%.[9] These manifestations can affect one or both eyes and are primarily caused by immune-mediated damage to the endothelial cells. The spectrum of ocular manifestations of dengue includes anterior uveitis, exudative retinal detachment, optic neuritis, retinal vasculitis, branch retinal artery occlusion, ischemic optic neuropathy, retinal edema, and retinal pigment epithelial disturbance. While optic neuritis is relatively rare compared to other manifestations, it has been reported in some cases of dengue. One such case involved a patient with dengue and optic neuritis, which was confirmed through MRI and fundus examination findings, as well as the patient's positive dengue serology. This diagnosis was further supported by the patient's response to the ONTT protocol. In accordance with prior reported cases of dengue-associated optic neuritis, visual improvement was noted following the recovery from the critical illness.

Thromboembolic events are rarely reported in cases of dengue. In addition to the factors discussed above, a few studies suggest that the pathology may be related to the downregulation of the formatting of the thrombomodulin–thrombin protein C complex, along with lower levels of protein C, which are augmented by the degree of shock and capillary leakage.[10] A systematic review by Ivan Dandy *et al.* on thromboembolic events in dengue by observed that venous thromboembolism occurs more frequently in dengue shock syndrome than in dengue fever. Extended shock in DSS may trigger and accelerate microthrombus formation, leading to disseminated intravascular coagulation (DIC).[11] The incidence of pulmonary thromboembolism has been reported by a few authors worldwide. Age, triple positivity, and ongoing shock may have contributed to the insult in case 4, resulting in the mortality of the patient. Agarwal *et al.*[12], Poletto *et al.*[13], Wen *et al.*[14], and Kamath *et al.*[15] have all documented favorable outcomes in their reported cases of dengue with pulmonary embolism.

Fever in dengue typically lasts for 5–7 days in the febrile stage and is biphasic, with prolonged fever, that is, fever lasting for more than 7 days, while fever lasting up to 12 days is also observed and reported in few studies. In few cases of dengue, Saddleback fever is also observed, which is a biphasic fever that begins with a peak, then subsides and reappears, and is characterized by a temperature recorded over 37.5°C, accompanied by a minimum of 1 day of defervescence, succeeded by a subsequent peak lasting no less than 1 day. In a study by Ng *et al.*,[16] 572 patients (20.1%) had a prolonged fever, with 40 (7%) experiencing fever for more than 10 days and 6 (1%) for more than 14 days, and in 165 (5.8%) patients Saddleback fever was observed.

CONCLUSION

Close monitoring of atypical presentations of dengue complications is absolutely crucial for reducing the

mortality. The emergence of EDS demands vigilance and proactive management of severe cases, especially in endemic areas. This also presents an opportunity for extensive research and a deeper understanding of the disease beyond its typical manifestations.

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Author contributions
Dr. Ramindla Sruthi: Concept and design, critical review of manuscript, supervision, manuscript drafting, data collection, and interpretation of case 1. Dr. Saif Quaiser: Concept and design, critical review of manuscript, supervision, manuscript drafting, data collection, and interpretation of case 2. Prof. Anjum Parvez: Supervision, manuscript drafting, data collection, and interpretation of case 3. Dr Shan Ullah Khan: Manuscript drafting, data collection, and interpretation of case 4. Each author has reviewed and endorsed the final version of the manuscript and acknowledges that they are accountable for the work's accuracy and integrity.

Ethical approval
Necessary permission was obtained from the Ethical Clearance Committee of JNMCH, AMU, Aligarh.

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Conflicts of interest
There are no conflicts of interest.

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Case Report

Isolated renal hydatid cyst: Series of four cases

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Abstract Hydatid cysts are a zoonotic disease caused by the larval stage of *Echinococcus granulosus*. We present a series of four cases of primary renal hydatid cysts. Of these four patients, two underwent nephrectomy due to complete involvement of kidney, and two were treated by cystectomy. During the first 6 months of follow-up, no complications were reported, and all patients were doing well.

Keywords: *Echinococcus granulosus*, hydatid cyst, kidney, nephrectomy

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INTRODUCTION

Hydatid disease (HD) infection is transferred through the feco-oral route through consumption of vegetables and foods contaminated with stools of carnivorous animals containing eggs of the parasite. The liver is the most common site of involvement, followed by the lungs. Renal involvement with hydatid disease is seen in 2%–4% of patients, although isolated involvement of the kidney is even rarer. We, hereby, describe four cases of isolated renal hydatidosis with different presentations, who were treated surgically. Data for this observational study were collected retrospectively from the medical records section.

CASE REPORTS

Case 1

A 23-year-old male resident from Birbhum district, West Bengal, India, presented in Urology OPD with pain over the right flank region for 4 months. On abdominal examination, no ballotable lump was palpable and no tenderness was elicited. Upon evaluation, the patient was found not to have eosinophilia. Sonography of the right kidney showed that the mid and lower pole was replaced by a 12.4 × 11.2 × 9 cm multicystic space occupying lesion (SOL) with multiple small cysts placed peripherally in the SOL. The ultrasonogram (USG) was negative for cystic lesions in the liver and spleen. Chest X-ray showed no lesion in the lungs. Computed tomography (CT) scan showed an 11.8 × 8.3 cm, well-defined, non-enhancing, thick-walled cystic lesion with multiple daughter cysts in the interpolar region of the right kidney. CT showed that the entire kidney was occupied by cysts [Figure 1]. The patient was put on albendazole preoperatively. The patient then underwent a right open simple nephrectomy. The intra-operatively cystic lesion was isolated with gauze pieces soaked in povidone–iodine as a precautionary measure. During the 3-month follow-up, the patient was doing well.

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Case report 2

A 40-year-old female from Raghunathganj, West Bengal, India, was admitted with pain in the right flank region for 10 months. She has no palpable lump. USG showed a hypoechoic cystic lesion in the right lumbar region arising from the right kidney measuring 94 × 94 mm with internal echoes. CECT KUB showed a large exophytic cystic lesion with few curvilinear septation and calcific foci arising from the mid and lower pole measuring 9.1 × 8.8 × 8.2 cm [Figure 2]. Chest X-ray and USG abdomen were negative for any other site hydatid cyst lesion. The patient was put on albendazole pre-operatively. The patient underwent a right-sided laparoscopic simple nephrectomy because the cyst involved her pelvicalyceal system. Postoperatively, the patient was doing well during the 3-month follow-up.

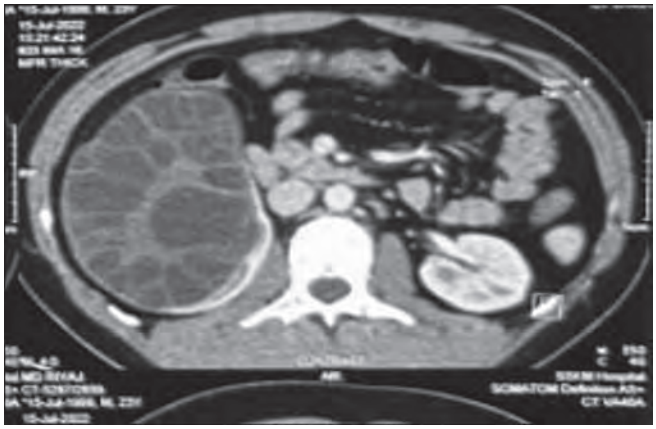

Figure 1: Right kidney shows a well-defined, non-enhancing, thick-walled cystic lesion with multiple daughter cysts

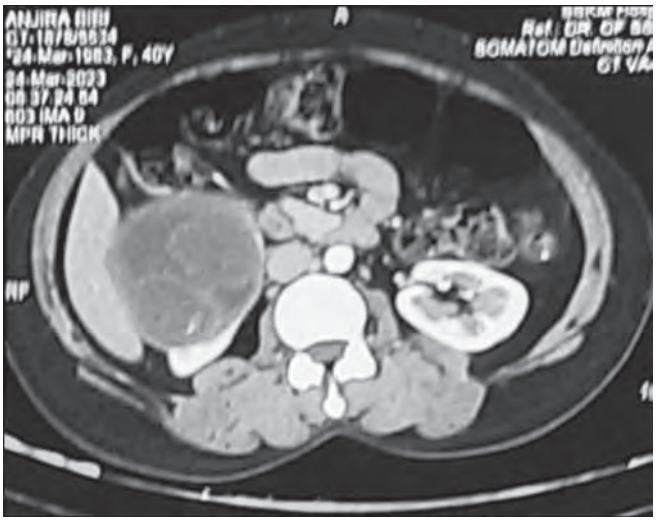

Figure 2: Multiple thick, internal septations and thin partial wall calcifications

Case report 3

A 42-year-old female from Kolkata, West Bengal, India, was admitted with off-and-on pain in the left flank region for the last 1 year. On clinical evaluation, she did not have a palpable lump. Her blood parameters were within normal limits without eosinophilia. On radiological evaluation, she was found to have a harbor hydatid cyst in the lower pole of the left kidney. CECT KUB was done, which suggested an oval cystic lesion of approximately 4 × 3 cm with laminated inner membranes and wall calcifications at the lower pole. She was given a 1-month course of Albendazole tablet at a dosage of 400 mg. The patient then underwent laparoscopic partial nephrectomy. The excised specimen was sent for histopathological examination, which showed ectocysts and endocysts of HD [Figure 3]

Case report 4

A 12-year-old female resident from Jangipur, West Bengal, India, was admitted with right flank pain for the last 4 months. Upon evaluation with USG and CECT, she was diagnosed with as a case of right renal hydatid cyst. Her echinococcal serology for IgG and IgM was negative. Her chest X-ray and USG abdomen were also negative for any other sites of hydatid cyst disease. Her CECT KUB suggested a hypodense cystic SOL of size 66.5 × 57 mm with internal septation noted in the midpole region with wall and septation taking enhancement [Figure 4]. After preoperative course of albendazole, the patient was planned for open right pericystectomy. Intraoperatively, her right kidney was isolated from the abdominal cavity by putting surgical pads soaked with Savlon (3% chlorhexidine + 6% cetrimide) around it. Thereafter, the cystic fluid was aspirated and a solicidal agent, that is, Savlon was injected into the cavity cyst, and the cyst was excised entirely, preserving the normal right kidney.

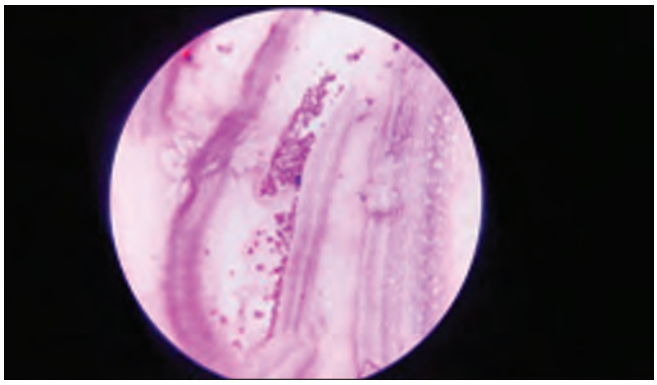

Figure 3: Microscopic section showing the laminated acellular outer layer with a single-cell germinal layer inside

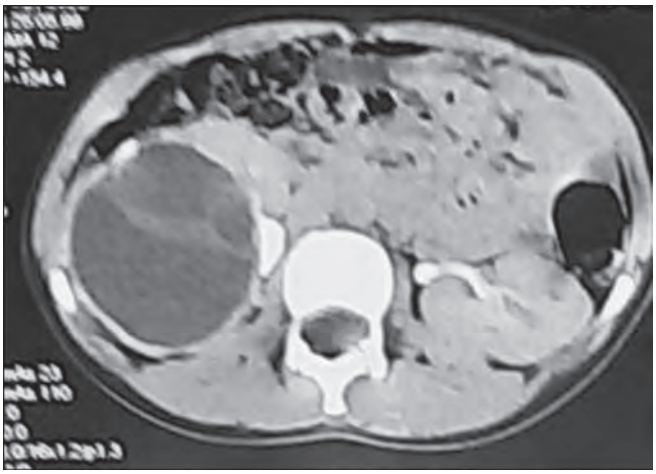

Figure 4: Cystic lesion with internal septation taking enhancement

DISCUSSION

HD is endemic in many parts of the world, especially in the Mediterranean, South America, the Middle East, Africa, Asia, and Australia. *Echinococcus granulosus* is the most common of the three species of *Echinococcus*. *Echinococcus multilocularis* is rare but the most virulent and *Echinococcus vogeli* is the rarest. The life cycle of *Echinococcus* involves two hosts, one definitive and the other intermediate. Humans act as an accidental intermediate host. In its life cycle, the adult *E. granulosus* resides in the small bowel of its designated hosts, which are mostly dogs or other carnivorous animals, and then gravid proglottids release eggs that are passed in the feces. These eggs are ingested by intermediate hosts, which are commonly sheep or other grazing animals. Humans can be infected accidentally if they ingest substances such as water or vegetables that are contaminated with *Echinococcus* eggs.[1] After ingestion, the eggs hatch in the intestinal mucosa, liberated larvae penetrate venules and are carried by the bloodstream to the liver. Approximately 3% of larvae that escape entrapment in the liver and lungs enter the systemic circulation and infect the kidneys. Usually, renal involvement, which constitutes about 2%–4% of all cases, is due to a secondary manifestation of the disease. Isolated renal hydatidosis is an uncommon presentation of *Echinococcal* disease and only occurs in about 2% of all cases.[2] Structurally, the hydatid cyst is made up of three layers. The outermost layer is the pericyst. It is formed by compressed host tissue and fibrous reaction. The middle layer is called as ectocyst, which is an acellular structure, and the innermost germinative layer, known as the endocyst, produces daughter vesicles containing protoscolices.[1] Clinical picture of renal hydatid cysts was vague and not characteristic to suggest the diagnosis. Most patients are asymptomatic or present with a flank mass and dull pain. A cystic rupture in the collecting system causing hydatiduria is pathognomonic of renal hydatidoses, although it is usually microscopic and is seen in only 10%–20% of renal hydatidoses.[3] No laboratory test is specific to HD. Eosinophilia is reported in approximately 25% of HD cases and may occur in other parasitic diseases. Negative serological tests do not exclude HD, and positive results neither confirm the diagnosis nor correlate with the pathological stage of renal HD. Serology may be beneficial after surgery to exclude recurrence.[4] Radiology plays a significant role in both reaching the diagnosis and evaluating the extent of the disease progression as well as in the preoperative planning phase if surgical intervention is to be utilized. CT scan remains a more accurate examination with respect to USG as it can accurately confirm the size and location of the lesion and whether any relation or involvement of neighboring tissue is present or not. The presence of daughter cysts within the mother cyst differentiates the lesion from simple renal cysts and from renal abscesses, infected cysts, and necrotic neoplasms.[5] The mainstay of treatment remains surgical intervention, as both medical management and interventional radiological procedures are limited in their effectiveness. In the last decades, albendazole has been used for the treatment of hydatid cysts. This drug can be used alone or jointly with surgical procedures. For the medical management, tab. albendazole 400 mg is given once daily for 3 weeks and then after 1 week of interval again one cycle of tab albendazole is given for 3 weeks. A total of 3 such cycles are given. Both laparotomy and laparoscopic approaches are utilized. The choice of surgical technique depends on multiple factors, including the size of the cyst, the local spread of the disease and involvement of surrounding structures, the presence of multiple or extra-renal cysts, and the results of renal function testing.[6] Kidney-sparing surgery is performed whenever possible, but if a cystectomy is not feasible, partial or total nephrectomy may be required. Percutaneous drainages is also described as a safe alternative to surgery, especially if the urinary collecting system is spared or preservation of renal tissue is required. It is important to note that there is evidence that dissemination of the disease remains a potential side effect in such cases.[7]

Although isolated renal HD is a rare entity compared to liver and lung involvement in our region, it should be considered in the differential diagnosis of renal SOLs. Clinical and serological findings can suggest but not confirm the diagnosis. Radiology plays a key role both in reaching diagnostic conclusions and providing support in the pre-surgical planning phase. The definitive diagnosis is only possible by histopathology. Open or laparoscopic surgical intervention remains the gold standard in management,

with conservative management and interventional radiological procedures offered in selected cases.

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Conflicts of interest
There are no conflicts of interest.

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Case Report

Isolated muscular cysticercosis in the child: A case report with a review of the literature

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Abstract

Isolated muscular cysticercosis is a rare entity and deserves a note. A 4-year-old male child presented with swelling on the left shoulder region and was clinically diagnosed to have cystic swelling approximately 3 cm × 4cm in size with mild tenderness. On ultrasonography, it appeared to be a cystic swelling in the muscle most probably resembling muscular cysticercosis. The patient was investigated thoroughly for any additional cysts elsewhere in the body and was given medical treatment with oral albendazole and steroids for 6 months but the swelling kept on gradually increasing in size and became painful, hence it needed surgical excision. Intraoperatively, meticulous dissection of the cyst was done to prevent any anaphylactic reaction. Therefore, initial medical management followed by surgical excision was the modality of treatment, done in this rare case. Here, we aim to enhance the existing scanty literature and the rarity of this case and emphasize the timely medical and surgical management of the same.

Keywords: Cysticercosis, isolated, muscular, suprascapular

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INTRODUCTION

Cysticercosis is a parasitic infection caused by the ingestion of Taenia solium larvae. Humans are the definitive host, and pigs are the intermediate host. It is endemic to Africa, Asia, and South America, but due to immigration, the infection has become a worldwide issue.[1,2] The most common sites to be affected are the central nervous system, ocular, subcutaneous tissue, and muscles.[2-5] Isolated pediatric muscular cysticercosis is rare and even rare in children; thus, very few cases are reported in the literature. Here, we describe a case of a 4-year-old male child who presented with swelling in the left suprascapular region and was diagnosed as an isolated intramuscular cysticercosis. The case highlights the possible differentials that should be considered when a child from an endemic area presents with cystic swelling in the subcutaneous or muscular plane, thoroughly investigated for the same, and managed with a timely medical and surgical approach.

CASE REPORT

A 4-year-old male child presented with swelling in the left suprascapular region for 1 year. The swelling was nontender and had gradually increased in size. He also had a history of low-grade fever for 7–8 months, which was intermittent

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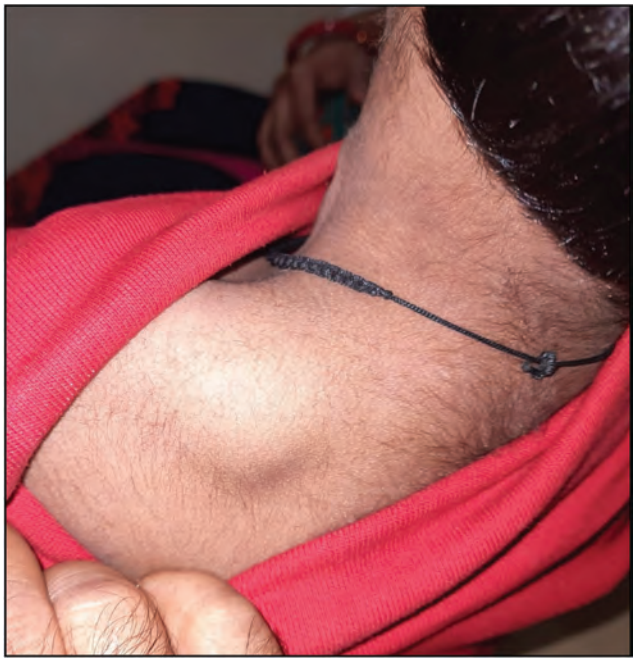

Figure 1: Cystic swelling in the left suprascapular region

and relieved with medications. There was no restriction on arm movements. The child or the family did not have any symptoms of cough or tuberculosis in the past. The patient was a nonvegetarian.

On presentation, the child was conscious, oriented, and active. On general examination, there was no lymphadenopathy, no other swellings over the body, and no systemic abnormality. He was hemodynamically stable. His weight was 12.85 kg, and his height was 98 cm; both the parameters were in the 3rd–50th percentile. On local examination, the swelling was well-defined, solitary, globular, nonfluctuant, soft, smooth, and with no erythema, but localized tenderness measuring approximately 3cm × 4cm in size [Figure 1].

With the help of a high-frequency linear transducer ultrasonography (USG) machine, few (4 in number), well-defined, oval, hypoechoic lesions with central calcific focus suggestive of intramuscular cysticercosis seen in levator scapulae [Figure 2].

Magnetic resonance imaging (MRI) brain and B-scan USG for optical imaging was within normal limits along with USG abdomen and pelvis. Blood investigations were normal.

MANAGEMENT

He was given medical treatment, in the outside hospital with oral albendazole (15 mg/kg/day) and steroids—oral

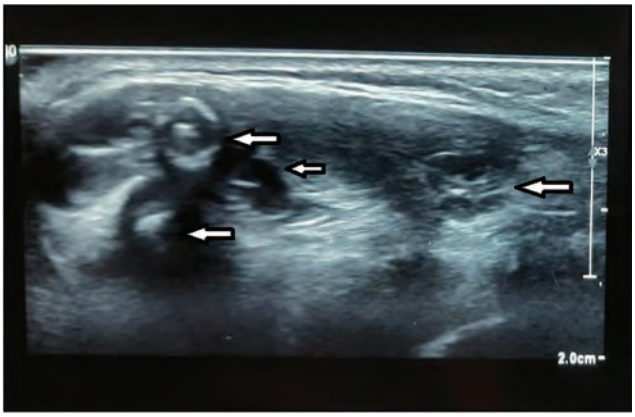

Figure 2: Ultrasonography showing hypoechoic lesion with central calcific focus

prednisolone (5 mg) for 6 months but the swelling kept on gradually increasing in size. Due to the gradual increase in size and localized tenderness, the decision was taken for wide local excision of the cyst under steroid cover to prevent an anaphylactic reaction [Figure 3]. Postsurgery, a normal diet was started, and was kept on albendazole (15 mg/kg/day).

Histopathology showed a hyalinized and calcified cystic lesion, which may represent a dead and calcified parasite. On follow-up, after 8 days postsurgery, the sutures were removed. On follow-up, after 15 days the postoperative area was well healed, and the child was stable and fine on later follow-up.

DISCUSSION

Humans are a definitive host and acquire the infection by ingestion of undercooked pork, unwashed vegetables, or fomites.[1,2] The mode of spread of infection is via blood[4] in the entire body mainly to the central nervous system, subcutaneous tissues, eyes, and muscles where there is a high blood supply.[2-5] After approximately 2 months, the gravid proglottids are released in the infected person's feces. Children are more prone to get infected via fomite spread.[5]

Isolated muscular cysticercosis is a rare disorder and hence the patient should be thoroughly investigated for spread to other organs.[4] Clinical manifestations for isolated muscular cysticercosis appear to be similar to other lesions like abscesses, epidermoid cysts, lipoma, neurofibromas, cold abscesses, and pyomyositis.[4-6] Isolated muscular involvement classically has no lethal outcomes.[7]

Clinical manifestations of muscular cysticercosis can be mass, pseudotumor, and pseudohypertrophy.[3,5] They can vary from no symptoms to symptoms such as pain, tender

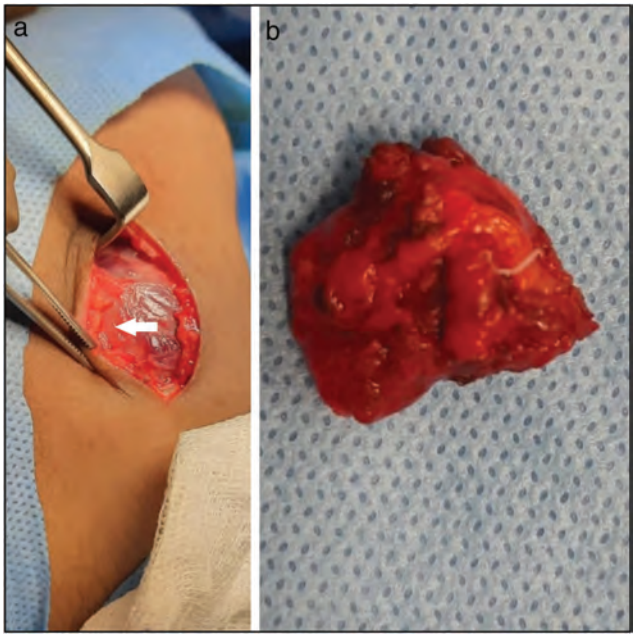

Figure 3: (a) Intraoperative photo of the cyst. (b) Specimen

swelling, myalgia, and nerve compression symptoms like paresthesia, and tingling numbness to the extremities.[3-5] Routine labs might show eosinophilia and raised erythrocyte sedimentation rate but are not diagnostic tests.[6,8]

High-resolution USG, the cyst has four appearances: (1) cyst with surrounding inflammatory mass due to death of parasite; (2) due to leakage from the breaking of the cyst wall, giving it an irregular appearance; (3) large irregular intramuscular cyst with eccentrically placed scolex; and (4) calcified cyst with multiple calcifications in soft tissues.[8]

TABLE OF REVIEW OF LITERATURE

Our case study showcased the fourth type in USG.[3,8] MRI shows hyperintensity on T2-weighted images and hypointensity on T1-weighted images where scolex can be identified to be hypointense.[4,6]

Noninvasive imaging modalities (local USG and MRI) are currently the standard diagnostic tests of choice for myo-cysticercosis. MRI is the most accurate for diagnosis.[7]

Some studies have tried fine needle aspiration cytology as a diagnostic method in which epithelioid cells, eosinophils, histiocytes, and structures resembling cysticercosis fragments were seen.[5] In histopathological studies, a starry sky appearance is seen.[6]

Medical treatment is to start the patient on steroids and albendazole or praziquantel. Albendazole at a dose of 15 mg/kg/day and praziquantel 50 mg/kg/day.[4,2] Steroids should be given before starting anti-helminthic drugs to prevent any anaphylactic reaction.[4,8] Newer medical trials are coming up with the use of etanercept (0.8 mg/kg/dose) to control the complications of neurocysticercosis.[9,10] As in our case, surgical management is given in patients who have symptoms due to nerve compression, vascular compression, or failure of medical management.

S. no	Study	Origin	Age and gender	Site	Management
1	Kanhere S BMPVGR. Isolated intramuscular cysticercosis: A case report.[4]	India	5.5 years boy	Calf and scapular region	Medical
2	Krishna Kumar HC, Satya Narayana P, Jagadish Kumar K. Isolated intramuscular cysticercosis in children: A case report.[5]	India	1.12-year-old, boy 2. 10-year-old boy	1. Right anterior axillary fold 2. Right forearm	Medical
3	Gaur S PPSND. Two case reports of isolated intramuscular cysticercosis: An uncommon pediatric pseudotumor.[7]	India	1.18-month-old boy 2.17-year-old girl	1.Left posterior aspect of the knee 2.Ventral aspect of arm	Medical
4	Present case	India	4-year-old boy	Left supra scapular region	Medical foreign body surgical

CONCLUSION

Thus, through this case report, we would like to conclude that intramuscular cysticercosis is rare in children. It should be kept as a differential when a child from the endemic area comes with cystic swelling. Early diagnosis and treatment can prevent the child from suffering from a multi-system involvement. We aim to enhance the already existing scanty literature and the rarity of this case and emphasize the timely medical and surgical management of the same.

Acknowledgements

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The

patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflict of interest
There are no conflicts of interest.

Financial support and sponsorship
Nil.

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Case Report

Renal unmasking postadrenalectomy: From hypokalemia to hyperkalemia in primary hyperaldosteronism

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Abstract This case highlights a patient who was evaluated for hypertension, hypokalemia, and metabolic alkalosis. Subsequently, she was diagnosed with an adrenal adenoma and underwent laparoscopic adrenalectomy. Her renal function was normal before the procedure. However, on follow-up, she was found to have gradually increasing creatinine levels, along with a shift from hypokalemia to hyperkalemia. Imaging studies also showed the presence of medullary nephrocalcinosis. The shift from hypokalemia to hyperkalemia is due to chronic suppression of the renin–aldosterone axis of the contralateral adrenal gland. Patients with primary hyperaldosteronism experience a state of hyperfiltration, which masks underlying renal dysfunction. The unmasking of renal dysfunction occurs postprocedure and was responsible for the renal issues observed. Chronic hypokalemia leading to tubular interstitial injury or kaliopenic nephropathy was the underlying cause of medullary nephrocalcinosis in this case. This case report highlights the importance of understanding renal dynamics in patients with primary hyperaldosteronism who have undergone adrenalectomy.

Keywords: Adrenal adenoma, adrenalectomy, hyperkalemia, nephrocalcinosis, primary hyperaldosteronism

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CASE SUMMARY

A 59-year-old lady, with a medical history including hypothyroidism, dyslipidemia, and systemic hypertension controlled by a single antihypertensive for 12 years, presented at a peripheral hospital due to recurrent headaches lasting for 3 months and three episodes of epistaxis each lasting a day. The evaluation revealed elevated blood pressure (200/100 mmHg), leading to optimization and modification of her antihypertensive regimen to include a beta-blocker and an alpha-blocker. No further blood tests were conducted at this stage. Despite adjustments to her medication, adequate blood pressure control remained elusive, necessitating escalating doses of antihypertensive medications.

Furthermore, evaluation was initiated due to the mentioned complaints, and additional blood tests were conducted, revealing hypokalemia. There was no history of consuming any other potentially offending medications, no reports of loose stools, no previous admissions for paralysis, and no significant family history of weakness. Additionally, there were no complaints of dry eyes, dry mouth, or dental caries. Subsequently, she was admitted to the peripheral hospital, where intravenous correction was administered to address the hypokalemia.

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She presented to our institute seeking evaluation for these complaints. Upon examination, her pulse rate was recorded at 64 bpm, with a blood pressure of 170/90 mmHg, and all other findings were unremarkable. Routine laboratory investigations were conducted, revealing a complete blood count showing a white blood cell count of 4850, a hemoglobin level of 10 g/dL, and a platelet count of 1.48 lakhs. Her serum creatinine was measured at 0.94 mg/dL, and urine analysis showed normal results. Additionally, her serum sodium level was 144 mmol/L, potassium level was 2.8 mmol/L, and bicarbonate level was 26.4 mmol/L.

The findings indicated hypokalemia with metabolic alkalosis, prompting further evaluation to ascertain the underlying cause.

A workup of hypokalemia was done, which is mentioned in Table 1.

Following the suspicion of an adrenal tumor based on the reported findings, the patient underwent a contrast-enhanced computed tomography of the abdomen, revealing a left adrenal lesion measuring 17 mm × 11 mm × 14 mm located in the lower part of the gland. Given the clinical presentation and the presence of the adrenal lesion, she subsequently underwent laparoscopic left adrenalectomy. The procedure proceeded without intraoperative or perioperative complications, and she was discharged in a stable condition on postoperative day 7. Her blood pressure was approximately 140/80 mmHg at the time of discharge, and she was prescribed a single antihypertensive agent (calcium channel blocker). Her creatinine level at discharge was recorded as 0.9 mg/dL.

Two weeks later, she returned for a follow-up visit, during which routine laboratory tests revealed the presence of hyperkalemia, necessitating medical intervention for correction. Her blood pressure remained stable around 140/80 mmHg, but her creatinine level had increased to 1.6 mg/dL. Medications were adjusted accordingly, and she was advised to continue regular follow-up appointments. Since the time of surgery, her creatinine values had consistently remained at 1.6 mg/dL, with potassium levels hovering around 5.10 mmol/L, and blood pressure being maintained on a single antihypertensive agent.

Furthermore, evaluation was pursued to determine the cause of the renal dysfunction. Urine analysis showed normal results. A subsequent ultrasound of the abdomen revealed the presence of multiple echogenic foci throughout the renal parenchyma, indicative of nephrocalcinosis, which had not been observed in previous scans.

Furthermore, evaluation for the cause of nephrocalcinosis commenced with the following investigations as shown in Table 2.

Despite thorough evaluation and workup, no specific cause of nephrocalcinosis was identified in this case.

DISCUSSION

Post-aldosterone-producing adenoma (APA) resection hyperkalemia is a well-documented condition, although its incidence and prevalence are not definitively known due to the predominant reliance on case reports and case series for its documentation.[1] As the number of primary aldosteronism (PA) diagnoses increases with the growing visibility of PA literature, post-APA resection hyperkalemia may become more common. Therefore, nephrologists and endocrinologists will need to be familiar with management options, as severe hyperkalemia can be life-threatening.

Results from the German Conn's Registry indicated that out of 110 patients, 18 (16%) developed postoperative hyperkalemia. Among these, 12 patients experienced transient hyperkalemia, whereas in 6 patients, hyperkalemia persisted for more than 11 months. Three of these six patients required emergency room treatment due to serum potassium levels exceeding 6.8 mmol/L.[2]

Older age appears to correlate with an increased likelihood of developing postoperative hyperkalemia in patients with primary hyperaldosteronism. According to a Korean study, individuals older than 53 years had significantly higher odds (odds ratio = 15.6) of developing postoperative hyperkalemia compared with those younger than 53 years.[3]

Table 1: Workup of hypokalemia

Sodium	144 meq/dL	Plasma aldosterone	29 ng/dL
Potassium	2.8 meq/dL	Aldosterone/plasma renin activity ratio	101
Chloride	105.5 meq/dL	Urine potassium	77 meq/dL
Bicarbonate	26.4 meq/dL		

Table 2: Evaluation for the cause of nephrocalcinosis commenced with the following investigation

Calcium	9.8 mg/dL
Phosphorous	4.4 mg/dL
Uric acid	5.8 mg/dL
Fasting parathyroid hormone	131 ng/mL

Duration of preoperative hypertension is another potentially important risk factor for developing postadrenalectomy hyperkalemia. In the study by Chiang *et al.*[3] postoperative hyperkalemics had longer duration of hypertension (12.8 ± 9.3 years vs. 6.7 ± 5.0 years; $P = 0.013$).

Impaired renal function is a significant risk factor for predicting postoperative hyperkalemia. The Chiang *et al.*'s[3] paper demonstrated that chronic kidney disease stages III to V were 30% more prevalent in patients who ultimately developed hyperkalemia.

Although overt preexisting renal impairment may be a significant factor in predicting postoperative hyperkalemia, there is now evidence suggesting that PA itself may induce hyperfiltration injury, potentially masking renal impairment until aldosterone-mediated hyperfiltration is reversed operatively.[4] Postadrenalectomy hyperkalemia in PA is believed to be secondary to hypoaldosteronism induced by suppression of the juxtaglomerular apparatus and the contralateral adrenal gland due to the volume-expanded state before unilateral adrenalectomy.[5]

PA is not a recognized cause of nephrocalcinosis and/or nephrolithiasis. There are few case reports linking hyperaldosteronism with nephrocalcinosis and/or nephrolithiasis.[6]

Various pathogenic mechanisms relating hyperaldosteronism with medullary nephrocalcinosis have been proposed. The earliest proposed mechanism is that chronic hypokalemia secondary to hyperaldosteronism can cause a tubular interstitial injury.[6] This is associated with elevated ammonia genesis and subsequent renal damage through the ammonia-activated alternate complement pathway. The renal cyst formation, interstitial inflammation, and medullary nephrocalcinosis may be related to ammonia-mediated nephropathy.[6] This has been aptly described as chronic kaliopenic nephropathy.

Hypercalciuria occurring in hyperaldosteronism is a well-recognized mechanism by which PA can cause nephrocalcinosis. Urinary calcium correlates with sodium excretion; each 100 mEq/dL increment in sodium excretion promotes an increase of 40 mg/dL in calcium excretion.[7] Increased urinary calcium excretion in PA could be due to the reduced reabsorption of sodium in aldosterone-insensitive tubular sites. Other proposed mechanisms include metabolic alkalosis associated with hypokalemic states, causing decreased calcium phosphate or oxalate solubility in the alkaline urine, thus predisposing to nephrocalcinosis.[8] Another mechanism involves PA-induced hypocitraturia. It is possible that through multiple ways, PA creates a milieu favorable for nephrocalcinosis.

Several unusual aspects of the case merit attention, including the transition from hypokalemia to hyperkalemia following the procedure, the onset of renal dysfunction, and the underlying etiology of medullary nephrocalcinosis.

Limitations of the study

This report describes the clinical course of a single patient, limiting the possibility of validating the findings to a larger population. Larger studies with more participants would be necessary, to validate the association between hyperkalemia and adrenal adenoma resection.

Furthermore, as the follow-up period, in this case, was relatively short, long-term monitoring of potassium levels and renal function would provide a better understanding of the trend of hyperkalemia or other potential complications after adrenal adenoma resection surgery.

CONCLUSION

Post-APA resection severe hyperkalemia may be a common entity and screening should be actively considered in high-risk patients. Older age, longer duration of hypertension, impaired preoperative and postoperative glomerular filtration rate, and higher levels of preoperative aldosterone are all risk factors that predict the likelihood of developing postoperative hyperkalemia. Fludrocortisone, sodium bicarbonate, loop diuretics, and potassium binders can be used for treatment.

Declaration of patient consent

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Well-differentiated papillary mesothelial tumor of pleura: A case report

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Abstract

Mesotheliomas are rare neoplasms that primarily affect the mesothelial cells lining the lungs, abdomen, heart, or testicles. It is primarily caused by exposure to asbestos fibers, with a latency period of several decades before manifestation of symptoms. Due to overlapping cytomorphological features with lung carcinoma, a definitive cytological diagnosis still remains a challenge for pathologists. This case report presents a case of papillary mesothelioma; its clinical and radiological presentations, with special emphasis on cytological diagnosis; and the role of histopathology and Immunohistochemistry as a confirmatory tool. A 43-year-old factory worker reported to the Chest Outpatient Department (OPD), with chest pain and difficulty in breathing for the past 2 months. Radiological findings suggested a right-sided pleural mass with pleural effusion. FOB findings were unremarkable. Subsequently, CT-guided FNAC was done and slides submitted to cytopathology evaluation. The cytomorphological features indicated papillary mesothelioma, which was further confirmed by histopathology and immunohistochemistry. Though histopathology remains a gold standard for diagnosis of papillary mesothelioma, proper clinical and radiological correlation and thorough examination of the cytomorphological features on cytology smears can help in early diagnosis and better prognosis of the patients.

Keywords: Benign, mesothelioma, papillae, pleura

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INTRODUCTION

Mesothelioma is a malignant tumor that arises from the serosal membranes and commonly invades adjacent tissues.[1] It most commonly involves the pleura but may also occur in the pericardium, peritoneum, and tunica vaginalis to a much lesser extent.[1,2] It has been established that 80% of mesotheliomas can be directly attributed to asbestos exposure.[1] In 2021, based on the World Health Organization classification of pleural mesotheliomas, three important changes have been made: The adjective "malignant" has been removed for diffuse or localized mesotheliomas, recognizing that all mesotheliomas are malignant.[3] The nomenclature for the previously known entity "Well Differentiated Papillary Mesothelioma" has been changed to "Well Differentiated Papillary Mesothelial Tumor of the Pleura," and it is considered a benign/borderline lesion with propensity to recur and rarely invade.[3] Mesothelioma *in situ* is now a

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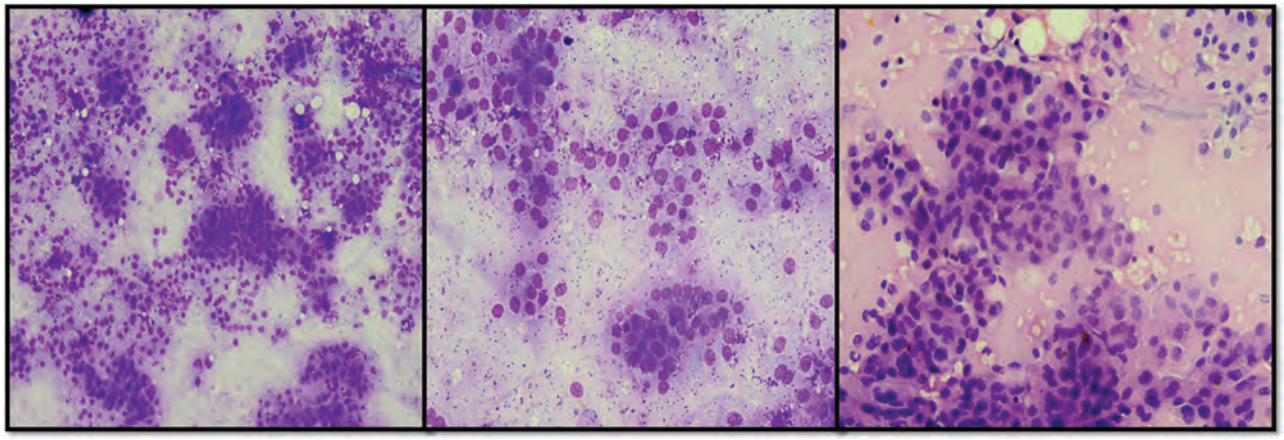

Figure 1: Smears revealed moderate cellularity with numerous papillary processes and clusters of mesothelial cells. The mesothelial cells show minimal pleomorphism, abundant dense cytoplasm, and occasional bi-nucleation and multi-nucleation. Occasional cells show cell inclusion and hump formation

recognized diagnostic category as a pre-invasive neoplastic mesothelioma.[2,3]

Because of this tumor's rarity and overlapping cytological features with other malignancy types, the histopathological findings and diagnostic immunohistochemical workup are essential in establishing the final diagnosis of mesotheliomas.

Aims and objectives

In this case report, we aim to study the cytological diagnostic criteria of papillary mesotheliomas arising in the pleura.

We also aim to study the utility of histopathology and immunohistochemical markers to reach a confirmatory diagnosis.

MATERIALS AND METHODS

After taking informed consent, a complete clinical and radiological case study was done. Consent of the patient was taken before undertaking any form of invasive procedures such as CT-guided fine needle aspiration and CT-guided biopsy.

There is no conflict of interest in this case study.

RESULT

A 43-year-old factory worker reported to the Chest OPD, with chest pain and difficulty in breathing for the past 2 months. Radiological findings suggested a right-sided pleural thickening with a solid cystic mass and pleural effusion. FOB findings were unremarkable. CT-guided fine needle aspiration was carried out, and smears revealed moderate cellularity with numerous papillary processes and clusters of mesothelial cells. The mesothelial cells show minimal pleomorphism, abundant dense cytoplasm, and occasional bi-nucleation and multi-nucleation. Occasional cells show cell inclusion and hump formation [Figure 1]. A provisional diagnosis of mesothelioma was made on cytology. A CT-guided tru-cut biopsy of the pleural mass was carried out and the sample sent for histopathological evaluation. Sections studied revealed a tumor lesion having a papillary architecture with a single layer of bland mesothelial cells and myxoid and fibrocollagenous cores in the papillae. No mitosis or necrosis was noted [Figure 2]. Immunohistochemistry was carried out, and it was found to be positive for markers CK5/6, calretinin, and EMA. WT1, TTF1, and CEA were found to be negative in this tumor [Figure 3].

In view of the overall features, a diagnosis of well-differentiated papillary mesothelial tumor was made.

DISCUSSION

Papillary mesothelial tumor (10.2%) is the second frequent cause of malignant pleural effusion. The most frequent cause is lung cancer (67.8%).[4] Pleural mesothelioma develops when asbestos fibers are inhaled and stick in the protective lining of the lungs (pleura). Over time, asbestos fibers cause inflammation and scarring within the lining, leading to progression of the disease.[5]

Malignant mesothelial tumor is a rare malignancy with a bad prognosis.[5] Malignant pleural mesothelioma (MPM) may be composed of sarcomatous, epitheliomatous, or mixed cell types.[6] It is not easy to discriminate malignant from benign pleural lesions, so the diagnostic sensitivity on pleural effusions could be increased using some ancillary

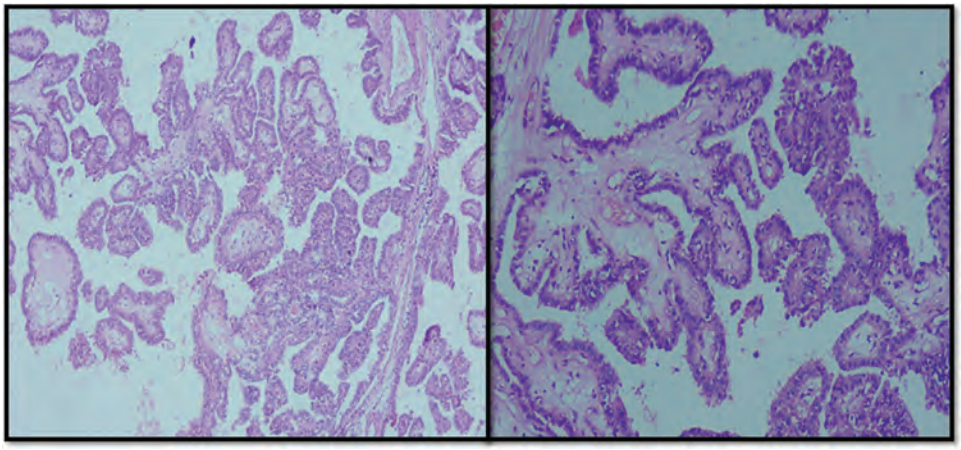

Figure 2: Sections studied revealed a tumor lesion having a papillary architecture with a single layer of bland mesothelial cells and myxoid and fibrocollagenous cores in the papillae. No mitosis or necrosis was noted

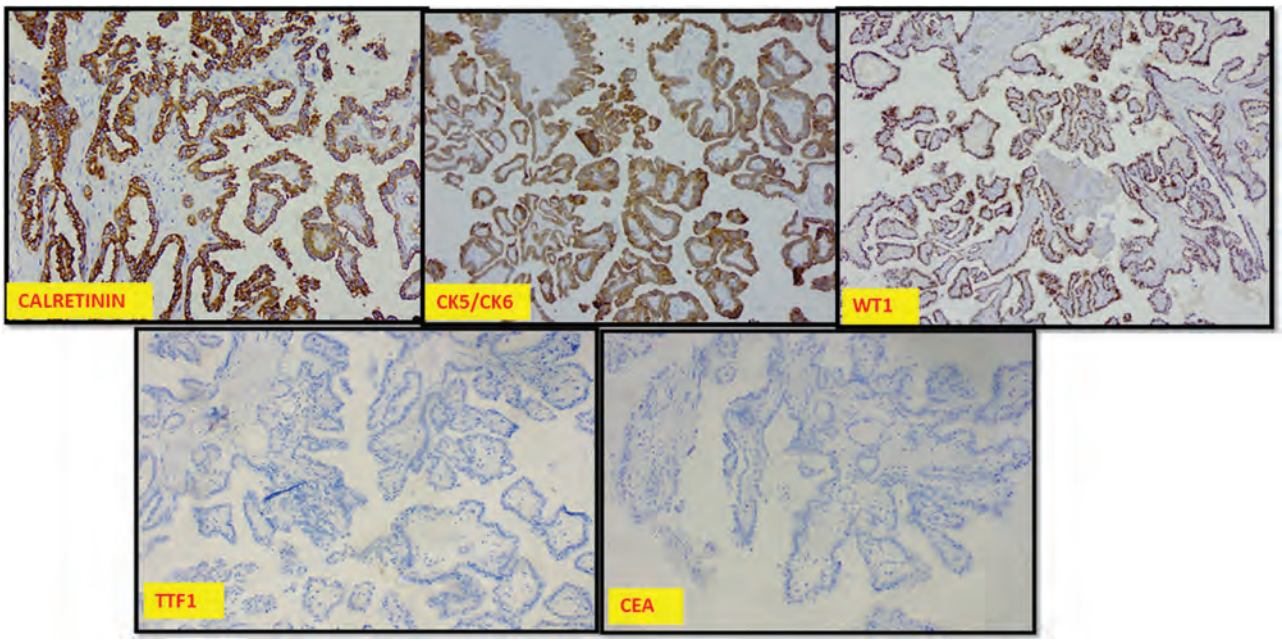

Figure 3: Immunohistochemistry was carried out, and it was found to be positive for markers CK5/6, calretinin, and EMA. WT1, TTF1, and CEA were found to be negative in this tumor

techniques, and immunohistochemical (IHC) tests are particularly valuable in differentiating MPM from reactive mesothelial hyperplasia.[7]

Several immunohistochemical (IHC) markers are now widely and reliably used to separate mesothelioma from carcinoma or other discohesive malignancies.[6] Typical mesothelial lineage markers include calretinin, CK5/6, and WT-1. WT-1 is a marker for mesothelial lineage, with 100% specificity for epithelioid mesothelioma and 64%–78% sensitivity for sarcomatoid mesothelioma.[8]

Malignant mesothelioma is seen in stages. Stage 1: early tumor growth occurs along the mesothelial lining of one lung. Stage 2: mesothelioma cancer cells have spread to nearby lymph nodes. Stage 3: Tumors have invaded deeper tissues in nearby organs and distant lymph nodes. Stage 4: Metastasis is present, and tumors have formed in distant parts of the body.[9]

ADI-PEG20 or pegargiminase is being hailed as the first drug of its kind to be incorporated successfully with chemotherapy in 20 years. Researchers say this new drug could bring hope to thousands of mesothelioma survivors and their families.[10]

CONCLUSION

Effusion cytology is an inexpensive, minimally invasive procedure which should be included in the diagnostic

workup of cases of suspected MPM. The positive pleural fluid cytological results may be considered an indicator for advanced MPM and therefore an indicator for poor outcomes. Thoracocentesis with pleural fluid cytology should be performed as the first step in the diagnosis of patients with suspected MPM.

The incidence of MPM is increasing worldwide and is likely to peak between the year 2015 and 2030. It is also worth considering that with the increasing incidence of MPM in developing countries, it is important to carry out cytological evaluation of effusion samples, as an easily performed and inexpensive diagnostic test.

Author contributions

Dr. Anuradha Bardia: formatting and completion of case study. Dr. Ayesha Afreen Islam: diagnosis and implementation of case study. Prof. Keya Basu: expert opinion on case study. Prof. Uttara Chatterjee: expert opinion on case study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Thimble bladder due to tuberculosis in a pediatric patient: A rare scenario

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Abstract Tuberculosis secondary affects the genitourinary system, has vague symptoms, and is uncommon in children younger than 3–10 years. Renal thimble bladder (TB) damage, including renal failure and decreased bladder capacity, results from a delayed diagnosis. Here, we will discuss a patient with a 9-year-old TB instance.

Keywords: Augmentation cystoplasty, GUTB, nephrectomy, thimble bladder

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INTRODUCTION

The principal cause of tuberculosis (TB) is *Mycobacterium tuberculosis*, which results in a granulomatous immunological response and a kind of tissue necrosis known as "caseous necrosis." One of the leading causes of death worldwide and one of the most noticeable and important community health issues is tuberculosis.[1] The respiratory system is the most common and contagious organ to be affected by TB, accounting for up to 45% of cases.[2] TB can affect any portion or organ of the body. The genito-urinary tract is a common extrapulmonary site of involvement by TB after lymph nodes.[2-4]

Different disorders, such as active infection and genitourinary tuberculosis (GUTB), can cause a reduction in bladder volume of up to 150–200 mL. In GUTB, a real bladder contracture occurred; the bladder has permanently lost its capacity because it no longer serves as a significant reservoir. Because of the decreased elasticity and compliance, the urinary bladder is reduced to a very low capacity (thimble bladder [TB]) once it has become infected with tuberculosis. This condition is typically irreversible and calls for surgical intervention in the form of either augmentation or diversion to hold back further damage to the upper tract.[5]

CASE REPORT

A 9-year-old female arrived to us with complaints of fever over the previous 21 months, as well as left flank discomfort and edema, and was examined for the same. Her usual blood tests, including hemoglobin (11.5 g), total leucocytes (6400 cells/cumm), kidney function tests (urea 21 and creatinine 0.8 mg/dL), liver function tests, and chest X-ray were normal. An ultrasound of the kidney, ureters, and bladder (USG KUB) revealed a left peri-nephric abscess, and a micturating cysto-urethrogram revealed right-sided grade 3 vesicoureteral reflux and a distorted pelvicalyceal system on the left side [Figure 1].

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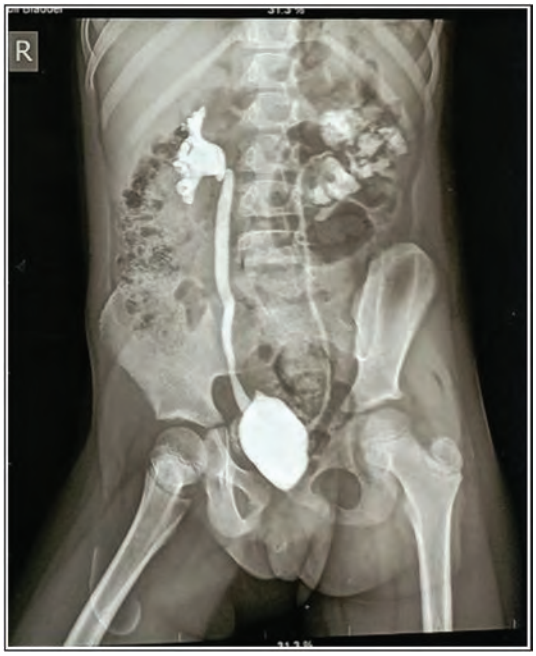

Figure 1: MCU - Showing right-sided grade 3 VUR and deformed PCS on the left side

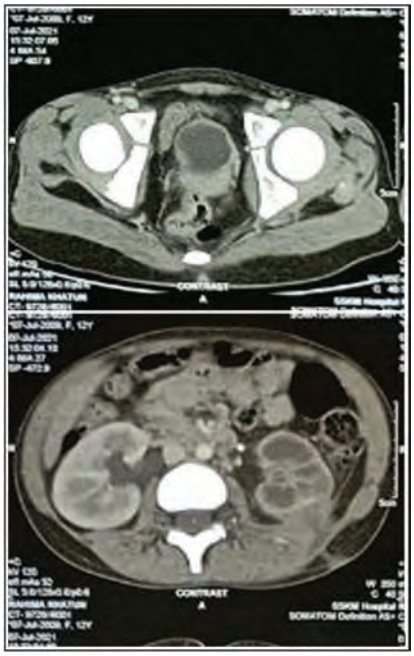

Figure 2: CECT KUB - No contrast excretion in delayed film from the left kidney, with a small capacity bladder

For collection, a left-sided pigtail drainage was done, and the pus was sent for CBNAAT testing, which came out positive; the pigtail was removed after 6 days. She returned with left-sided discomfort, burning micturition, and frequency. A contrast-enhanced computerized tomography (CECT) scan of the KUB reveals no contrast excretion in delayed film from the left kidney and a small bladder capacity [Figure 2]. According to diethylenetriamine pentaacetate, the glomerular filtration rate (GFR) of the left kidney was 0 mL/min and the deferential function was 0%. The decision was taken to do a left-open simple nephrectomy after taking consent from her family members, and same was performed. The specimen's histopathological examination (HPE) result indicated GUTB.

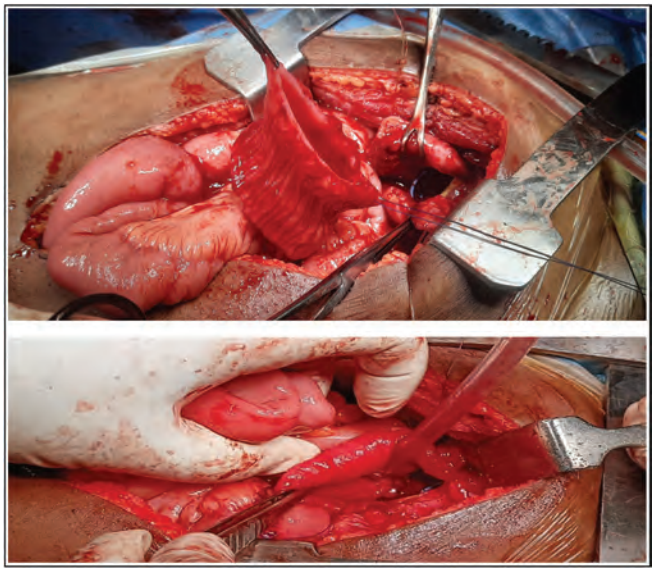

Figure 3: Ileal loop augmentation cystoplasty

She was put on anti-tuberculosis treatment (ATT) for 6 months after being diagnosed with GUTB on pus culture, and she was still being followed up on. During follow-up, she was discovered to have a very low urine bladder capacity; as a result, the decision to have an augmentation cystoplasty was made after 9 months of ATT completion, and ileal loop augmentation cystoplasty was performed [Figure 3].

DISCUSSION

GUTB is rarely seen among pediatric groups and contributes less than 5% of all tuberculosis cases.[2-4] The diagnosis of GUTB may be difficult because it can affect any part of the genitourinary system, may clinically present like lower urinary tract symptom to renal failure or chronic kidney diseases (CKD), and in more than 50% of patients, requires surgical intervention. The following test can be used to diagnose GUTB: (1) the confirmation of bacilli in body fluids like urine. (2) Radiological examinations namely Intravenous Pyelogram (IVP), Ultrasound of the Kidneys, Ureters and Bladder (USG KUB), and CECT KUB + urography in CKD pt Magnetic Resonance Imaging (MRI) can be used. (3) Newly available tests, such as whole-genome sequencing, can provide the complete genome of *Mycobacterium* species and give information regarding drug resistance and transmission patterns.

Microbiological and/or histopathological confirmation is required for the ultimate diagnosis of GUTB. As it is simple, quick, and economical, HPE is routinely used to detect GUTB.[6] In our case, the result of the renal specimen HPE was used for the final diagnosis.

The TB is the terminal sequel of GUTB, along with impaired renal function.[7] About one-third of cases of renal tuberculosis were found to be associated with secondary involvement of the urinary bladder.[8] In the initial stage of urinary bladder tuberculosis, the bladder shows non-specific changes and commonly presents as irritative voiding symptoms, but the later stage, due to chronic inflammatory changes, leads to a reduction in both capacity and compliance and presents as storage symptoms like frequency and urgency. Patients with TBs (because of mural fibrosis) can even present with incontinence.[9]

CONCLUSION

Early detection and complete treatment are the best methods to control TB. For that, high clinical suspicion and proper evaluation are needed in all suspected cases. Surgery remains one of the vital modalities of treatment for most patients with GUTB, in addition to ATT. After completion of ATT, follow-up is indicated as some may progress to compromised bladder conditions.

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Author contribution
Authors declared that they follow IJTB authorship criteria and approved final version of manuscript. A signed authorship declaration form has been submitted to the editorial office.

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