DOI: 10.7860/JCDR/2025/75571.21428

Case Series

Microbiology Section

The *Cryptococcus neoformans* Challenge in Immunocompromised Patients: A Two Year Case Series from Western Rajasthan with Review of Literature

SNIGDHA PUROHIT[1], ASHINA SINGLA[2], RACHNA PRIYADARSHINI[3], SHAVETA KATARIA[4], EKADASHI RAJNI[5]

ABSTRACT

Cryptococcosis is a severe opportunistic fungal infection caused by *Cryptococcus neoformans* or *Cryptococcus gattii* (critical fungal pathogens), primarily affecting immunocompromised individuals such as those with Human Immunodeficiency Virus (HIV), postorgan transplant patients, or those on prolonged immunosuppressive therapy. Tuberculosis (TB) and cryptococcal meningitis are leading causes of morbidity and mortality in advanced HIV disease. This case series highlights five patients with varied clinical presentations, including postrenal transplant complications, co-infection with TB and disseminated disease in HIV-positive individuals. Diagnosis relied on cerebrospinal fluid analysis, cryptococcal antigen testing and advanced imaging techniques. Treatment included liposomal amphotericin-B, fluconazole and supportive therapies. Despite aggressive management, outcomes varied, with some patients surviving while others succumbed to the infection. The series underscores the challenges in diagnosing and managing cryptococcosis, particularly in resource-limited settings, as well as the increased mortality associated with co-infection, which is a public health concern. Therefore, authors emphasise the need for improved diagnostic tools and integrated management strategies for better patient outcomes. With the rise in case studies of cryptococcosis, there is an increase in awareness; however, to control this menace, a high level of alertness and surveillance must be maintained at both clinical and laboratory levels. Only then can this "awakening giant" be contained.

Keywords: *Cryptococcus neoformans*, Human immunodeficiency virus, Transplant, Tuberculosis

INTRODUCTION

Cryptococcosis is a serious opportunistic fungal infection caused by *Cryptococcus neoformans* (*C. neoformans*) or *Cryptococcus gattii* (*C. gattii*). It causes self-limiting diarrhoea in immunocompetent hosts, while in immunocompromised patients, it can result in severe diarrhoea with weight loss and malabsorption. *C. neoformans* is found globally, primarily in bird droppings and can spread to the central nervous system, while *C. gattii* is typically found in tropical areas and is even linked to eucalyptus trees [1]. The first indigenous case of cryptococcosis was reported in a patient from Calcutta in 1941, though the case was confirmed in the USA. In 1946, Krainer diagnosed the first Indian case in Poona [2,3]. Its prevalence has been reported as 2.3% and 6.8% among Acquired Immunodeficiency Syndrome (AIDS) patients globally and in India, respectively, with approximately 625,000 deaths annually among patients with HIV worldwide [4].

Laboratory diagnosis of cryptococcosis is done through cultures (blood and cerebrospinal fluid), India ink preparations, cryptococcal antigen tests and radioimaging. Recently, the World Health Organisation (WHO) classified *C. neoformans* as a critical fungal pathogen [5]. Timely diagnosis and appropriate antifungal treatment are crucial for improving patient outcomes, as the disease can lead to severe complications and high mortality if untreated. Therefore, this fungus is considered an emerging giant that is increasingly being reported by many investigators from various parts of our country, likely due to increased awareness of human fungal infections and improved diagnostic techniques [6-10]. Here, a case series of cryptococcosis involving patients with post-renal transplants, HIV, TB and disseminated infection is reported. This series highlights the varied presentations and challenges in diagnosing and managing cryptococcosis in different clinical contexts.

CASE SERIES

Case 1

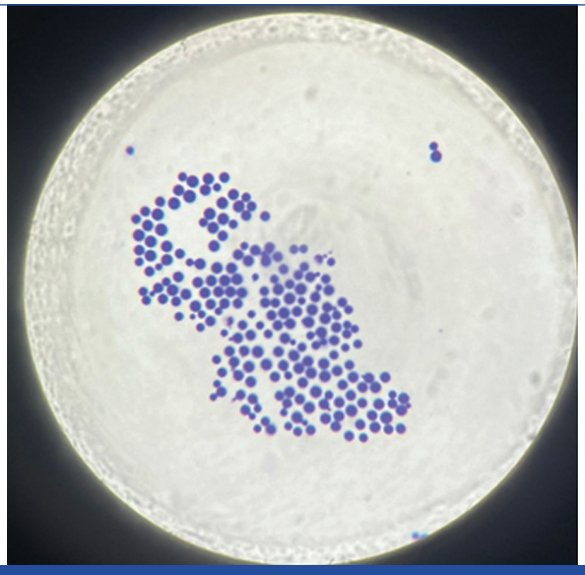
A 50-year-old male patient presented to the Outpatient Department (OPD) with complaints of generalised weakness, loss of appetite, vomiting and headache persisting for 13 days. On physical examination, the patient was afebrile, conscious and haemodynamically stable (pulse: 74/min, BP: 120/80 mmHg). The physical examination revealed photophobia, neck stiffness and rigidity. His medical history included a successfully treated COVID-19 infection two years prior and a renal transplant. There was no past history of similar complaints. Routine laboratory investigations were performed, revealing deranged renal function (urea: 55.3 mg/dL, serum creatinine: 1.6 mg/dL). An ophthalmological examination detected papilledema, following which a lumbar puncture was performed. A provisional diagnosis of meningitis as a post-renal transplant complication, along with acute kidney injury and acute gastritis, was established. CSF analysis and radiological investigations were conducted, as demonstrated in [Table/Fig-1] and [Table/Fig-2-4]. The final diagnosis for this patient was cryptococcal meningitis. The patient was managed with oral moxifloxacin (400 mg), fluconazole (150 mg), immunosuppressants and other symptomatic treatments. The patient showed symptomatic improvement and was discharged on immunosuppressants and maintenance medications, with specific instructions for administering liposomal amphotericin-B. The patient was monitored for relapses or other medical issues related to the case, but no such events have been documented to date.

Cases 2-5 [Table/Fig-1-8]

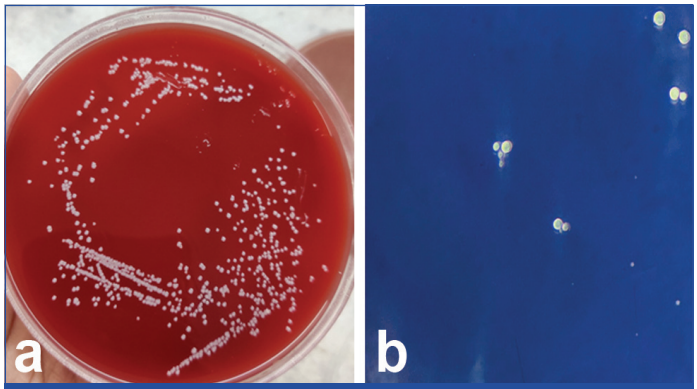
For the remaining cases (Cases 2-5), the patients were aged between 30 and 57 years and three were female while one was male. They predominantly presented with fever, headache and

Patient details	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	50	57	45	49	30
Sex	Male	Male	Female	Female	Female
Presenting complaints	Generalised weakness, loss of appetite, vomiting, headache for 15 days.	Fever and productive cough for one month, rashes over trunk and chest pain for 15 days, decreased urine output for one week.	Headache, dizziness, vertigo, frequent fall for five days.	Low-grade fever, joint pain, significant weight loss for 5-6 months, abdominal pain, vomiting, burning micturition, headaches and red, scaly, itchy rashes on her neck and arms for 7-10 days.	Fever, generalised weakness, vomiting and headache for 15 days.
Underlying disease	Post-RAR, AKI, Acute gastritis	HIV positive, EP-TB, Cardiomyopathy	HIV positive	HIV positive, cryptococcal dissemination pancytopenia, severe anaemia and tinea corporis	HIV positive
Sample collected	CSF	CSF	CSF	Blood	Blood
Cell cytology	15 cell/mm^3, 92% lymphocytes, 8% neutrophils	NT	45 cell/mm^3, 95% lymphocytes, 5% neutrophils.	NT	NT
Gram's stain	Gram positive BYC seen [Table/Fig-2].	Gram positive BYC seen [Table/Fig-2].	Gram positive BYC seen [Table/Fig-2].	Gram positive BYC seen [Table/Fig-2].	Gram positive BYC seen. [Table/Fig-2].
Blood agar, India Ink stain	Colonies were white, mucoid, smooth and non haemolytic Encapsulated yeast cells [Table/Fig-3a,b].	Colonies were white, mucoid, smooth and non haemolytic Encapsulated yeast cells [Table/Fig-3a,b].	Colonies were white, mucoid, smooth and non haemolytic Encapsulated yeast cells [Table/Fig-3a,b].	Colonies were white, mucoid, smooth and non haemolytic Encapsulated yeast cells (Table/Fig-3a,b].	Colonies were white, mucoid, smooth and non haemolytic Encapsulated yeast cells. [Table/Fig-3a,b].
Cryptococcal Antigen test	Positive [Table/Fig-4].	Positive [Table/Fig-4].	Positive [Table/Fig-4].	Positive [Table/Fig-4].	Positive [Table/Fig-4].
Blood Culture	NT	NT	NT	Positive [Table/Fig-3].	Positive [Table/Fig-3].
CSF Culture	Positive	Positive	Positive	NT	NT
Culture on SDA	Positive [Table/Fig-5].	Positive [Table/Fig-5].	Positive [Table/Fig-5].	Positive [Table/Fig-5].	Positive [Table/Fig-5].
Radiological findings	NT	NCCT Brain- age related atrophy and bilateral periventricular ischaemic degeneration [Table/Fig-7]. Chest X-ray- Bilateral pleural effusion.	MRI Brain- infarcts in fronto-parietal cortex. Chest X-ray- bilateral pleural effusion [Table/Fig-6,8].	NT	MRI Brain- multiple infarcts in fronto-parietal cortex. [Table/Fig-6].
Treatment	Oral fluconazole, moxifloxacin and Immunosuppresants.	Injection liposomal amphotericin B, flucytosine, vancomycin and ATT.	Injection amphotericin B, oral fluconazole and trimethoprim/ sulphamethoxazole	Oral itraconazole, ceftriaxone, levocetirizine and topical antifungal treatments (luliconazole cream and clotrimazole powder). Escalated to include piperacillin-tazobactam, vancomycin, levofloxacin and trimethoprim-sulfamethoxazole. ART was advised.	Inj piperacillin -tazobactam, liposomal amphotericin B. ART was adviced.
Outcome	Survived	Died	Survived	LAMA	LAMA

[Table/Fig-1]: Clinical and microbiological characteristics of Cryptococcal meningitis.
AKI: Acute kidney injury; ART: Anti retroviral treatment; ATT: Anti tubercular therapy; BYC: Budding yeast cells; CSF: Cerebrospinal fluid; EPTB: Extra pulmonary TB; HIV: Human immunodeficiency virus; MRI: Magnetic resonance imaging; NCCT: Non contrast computed tomography; NT: Not tested; LAMA: Left against medical advice; RAR: Renal allograft rupture



[Table/Fig-2]: Gram stained showing round budding yeast cells of *Cryptococcus neoformans* (1000X) (Cases 1-5).

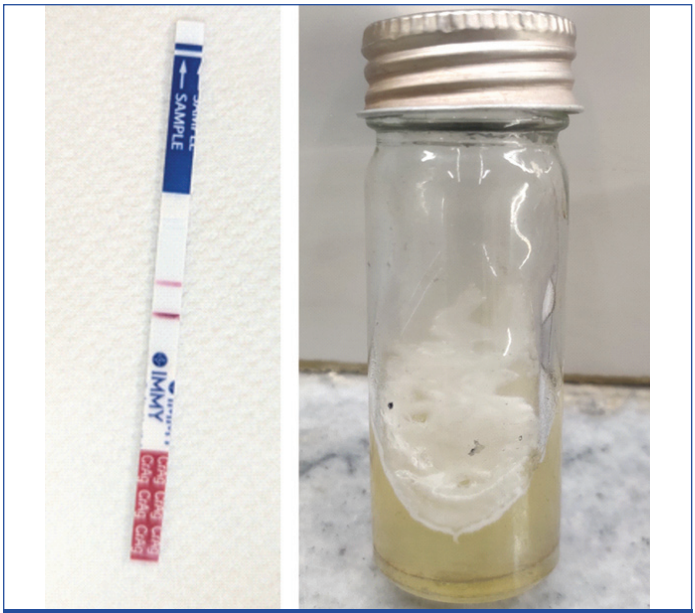


[Table/Fig-3]: a) Sheep Blood agar showing white, mucoid, smooth and non haemolytic colonies of *Cryptococcus neoformans* (Cases 1-5); b) India Ink showing capsulated yeast cells of *Cryptococcus neoformans* (400X) (Cases 1-5).

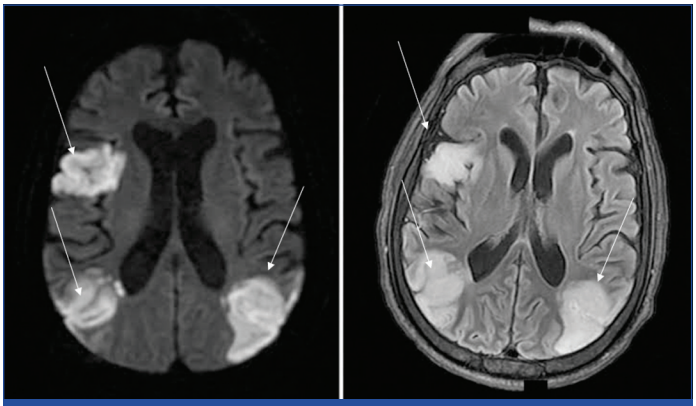
generalised weakness and had underlying illnesses such as HIV, extrapulmonary TB and kidney failure. There was no past history of similar complaints. Routine laboratory investigations were initiated, leading to a provisional diagnosis of meningitis. Their CSF and blood samples were further processed for gram staining, culture, India ink, cryptococcal antigen testing and radiological findings, which were suggestive of cryptococcal meningitis (final diagnosis) as shown in [Table/Fig-1-8]. They were treated with amphotericin B. Among these patients, one survived, two left against medical advice and one died. The patients were monitored for relapses, but no such events have been documented to date.

DISCUSSION

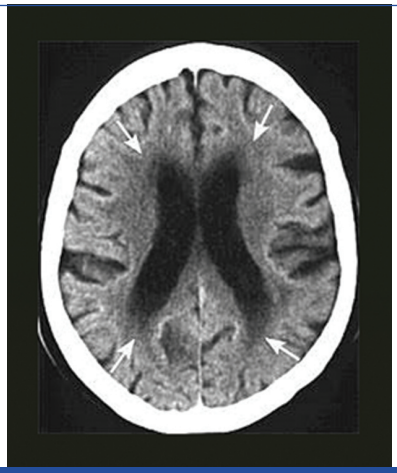
Cryptococcosis is the third most common invasive fungal infection in solid organ transplant recipients, causing a 50% mortality rate



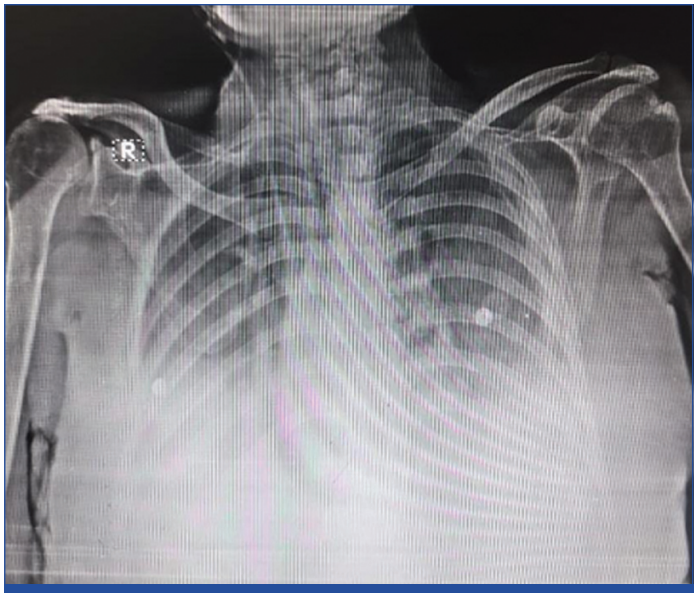
[Table/Fig-4]: Positive Cryptococcal antigen test (Lateral flow assay) (Cases 1-5).
[Table/Fig-5]: Sabouraud Dextrose Agar showing mucoid white colonies of *Crytpococcus neoformans* (Cases 1-5). (Images from left to right)



[Table/Fig-6]: MRI brain showing fronto-parietal infarcts (Case 3 and 5).



[Table/Fig-7]: NCCT brain- age related atrophy and bilateral periventricular ischaemic degeneration.



[Table/Fig-8]: Chest X-ray showing bilateral pleural effusion (Case 3).

in kidney transplant patients [11]. The detection of cryptococcal antigen (CrAg) by lateral flow assay in CS F or plasma is highly recommended, as it is more sensitive and specific than India ink and culture. Treatment of cryptococcosis is particularly challenging in kidney transplant patients. Induction therapy is achieved by optimising immunosuppression with liposomal amphotericin B, while consolidation and maintenance are carried out with fluconazole. The comparative analysis of this case report and previously published reports is elaborated in [Table/Fig-9] [6-10].

The first case involves a post-renal transplant patient with cryptococcosis as an opportunistic infection. In such cases, patients usually present in the late post-transplant period, often after the discontinuation of antifungal prophylaxis, primarily due to the reactivation of latent infections. The likely reason behind this emergence is the widespread use of immunosuppressants, which leads to a decrease in the immune status of these patients [11].

Case 2 involved a rare co-infection of cryptococcosis and TB in an HIV-positive patient. Despite aggressive treatment, the patient unfortunately passed away, likely due to a misdiagnosis of cryptococcal meningitis as tuberculous meningitis, which delayed the correct diagnosis and appropriate treatment. This case highlights the global occurrence of cryptococcal and TB co-infections and emphasises the need for effective treatment of both alongside antiretroviral therapy. The lack of integration of fungal infection management in TB control programs and inadequate implementation of CrAg testing guidance in low-resource settings contributes to high mortality rates [5].

Case 3 highlights cryptococcal fungal disease in HIV-infected individuals, often defining AIDS in 60-70% of patients. The fungus's ability to synthesise melanin from catecholamines in Central Nervous System (CNS) tissue may contribute to its predilection for CNS invasion [12]. The fungal capsule's exopolysaccharides may further aid virulence by suppressing immune responses and enhancing

S. No.	Study region	Author (year of publication)	Immune status	Lab diagnosis	Treatment	Outcome
1.	East Java, Indonesia	Bramantono B et al., [6] (2020)	Immuno-compromised	Blood culture	HAART regimen along with fluconazole.	1 Survived
2.	Vellore, India	Suresh CS et al., [7] (2021)	Immuno-compromised	CSF, Brain tissue, Bone marrow culture and Cryptococcal Antigen test.	HAART regimen along with fluconazole and cotrimoxazole prophylaxis. Anti-tuberculous treatment.	1 Survived, 2 Died, 2 LAMA.
3.	Kerala, India	Mathew S et al., [8] (2022)	Immuno-compromised	India Ink, Culture	liposomal amphotericin B	3 Survived
4.	Indiana, USA	Barros K et al., [9] (2024)	Immuno-compromised	Blood cultures, CSF culture and Film Array® Meningitis/Encephalitis PCR (ME panel).	liposomal amphotericin B (LAmpB) and flucytosine (5- FC)	1 Survived

5.	Jaipur, India.	Choudhary S et al., [10] (2023)	Immuno-competent	CT-guided abscess biopsy.	IV Amphotericin B and 5-flucytosine followed by oral fluconazole.	Survived
6.	Jaipur, India.	Present study, 2025	Immuno-compromised	CSF and Blood culture and Cryptococcal Antigen test positive.	Injection liposomal amphotericin B, flucytosine and fluconazole.	2 Survived, 1 Died and 2 LAMA.

[Table/Fig-9]: A brief summary of case reports on Cryptococcal infection in immunocompromised patients [6-10].
CSF: Cerebro-spinal fluid; CT: Computed tomography; HAART: Highly active antiretroviral therapy; i.v.: Intravenous; LAMA: Left against medical advice

HIV replication. WHO guidelines recommend a combination of antifungals (amphotericin B, flucy tosine and fluconazole) for the initial treatment of cryptococcal meningitis; however, due to limited availability, high-dose fluconazole monotherapy was used in our setting [6]. The patient showed clinical improvement and was eventually discharged.

Cases 4 and 5 highlight the diagnosis of disseminated cryptococcosis through positive blood cultures via the VITEK-2 Compact system, showcasing the critical role of automated systems in diagnosing this infection. Additionally, the BioFire Film Array system, a type of multiplex nested PCR, can also be utilised for detecting such infections.

CONCLUSION(S)

Cryptococcosis is a serious infection in immunocompromised individuals, especially solid organ transplant recipients and HIV-positive patients. In renal transplants, the reactivation of latent *Cryptococcus* post-antifungal prophylaxis reduction requires careful long-term monitoring. Co-infection with TB in HIV patients complicates treatment, where misdiagnosis can be fatal. Advanced diagnostic tools, such as lateral flow assays and multiplex PCR, are essential for improving detection and management, ultimately reducing the global burden of this infection. With the rise in case studies of cryptococcosis, awareness has increased; however, to control this menace, a high level of alertness and surveillance must be maintained at both clinical and laboratory levels.

REFERENCES

[1] Kwon-Chung KJ, Bennett JE. Epidemiologic differences between the two varieties of *Cryptococcus neoformans*. Am J Epidemiol. 1984;120:123-30.
[2] Reeves DL, Butt EM, Hammack RW. Torula infection of the lungs and central nervous system: Reports of six cases with three autopsies. Arch Intern Med. 1941;68:57-79.
[3] Krainer L, Small JM, Hewlitt AB, Deness T. A case of systemic Torula infection with tumor formation in the meninges. J Neurol Neurosurg Psych. 1946;9:158-62.
[4] Islam N, Bharali R, Talukdar S, Hussain SA, Akand AH, Sarma HK. Occurrence and distribution of *Cryptococcus* species in environmental sources from lower Assam Belt of India. J Pure Appl Microbiol. 2020;14(4):2781-800.
[5] World Health Organization. Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV. WHO Press. 2022. ISBN: 978-92-4-005217-8. Licence:CC BY-NC-SA 3.0 IGO.
[6] Bramantono B, Danial A, Hadi U. A case of an AIDS patient with *Cryptococcus neoformans* infection. Pan African Med J. 2020;36(88):01-05.
[7] Suresh CS, Ninan MM, Zachariah A, Michael JS. Cryptococcosis with tuberculosis: Overlooked coinfections. J Glob Infect Dis. 2021;13:139-41.
[8] Mathew S, Kalanad A, Khan MM, Hameed AMA, Sathyapal A, Mohankumar P. Cryptococcal meningoencephalitis in post COVID period: Case series and review of literature. J Med Sci Health. 2022;8(2):166-72.
[9] Barros K, Tepper JW, Ramchandani J, Kelley MK, Kussin ML, Israel EN. Unusual presentation of disseminated cryptococcal infection complicated by myocarditis in a heart transplant recipient. Pediatric Transplantation. 2024;28:e14585.
[10] Choudhary S, Mishra RK, Pathan N, Vyas A, Sharma S, Gupta K. An unusual recurrent case of Cryptococcal sacroiliitis in an immunocompetent elderly female in Rajasthan, India. Med Mycol Case Rep. 2023;40:36-39.
[11] Meena P, Bhargava V, Singh K, Sethi J, Prabhakar A, Panda S. Cryptococcosis in kidney transplant recipients: Current understanding and practices. World J Nephrol. 2023;12(5):120-31.
[12] Baker RP, Chrissian C, Stark RE, Casadevall A. *Cryptococcus neoformans* melanization incorporates multiple catecholamines to produce polytypic melanin. J Biol Chem. 2022;298(1):101519.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Microbiology, MGUMST, Jaipur, Rajasthan, India.
2. Professor, Department of Microbiology, MGUMST, Jaipur, Rajasthan, India.
3. Postgraduate Resident, Department of Microbiology, MGUMST, Jaipur, Rajasthan, India.
4. Associate Professor, Department of Microbiology, MGUMST, Jaipur, Rajasthan, India.
5. Professor, Department of Microbiology, MGUMST, Jaipur, Rajasthan, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Shaveta Kataria,
305, UDB Emarald, Nandpuri, Janakpura, Malviya Nagar, Jaipur, Rajasthan, India.
E-mail: dimcikataria.25@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 19, 2024
- Manual Googling: Apr 19, 2025
- iThenticate Software: Apr 22, 2025 (11%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Sep 12, 2024**
Date of Peer Review: **Jan 06, 2025**
Date of Acceptance: **Apr 24, 2025**
Date of Publishing: **Sep 01, 2025**