CASE PRESENTATION

Rifampicin-resistant miliary/ meningeal tuberculosis case presentation and mini review

Nadia Abdulkareem Al Ani,[a] Hiba Adnan Hameed,[b] Mohammad Yahya Abdulrazaq.[c]

ABSTRACT

Miliary and meningeal Tuberculosis (TB) is a linked and life-threatening bacterial infection caused by *Mycobacterium tuberculosis* that triggers inflammation of the meninges. They are the most severe and lethal form of tuberculosis. Diagnosis is challenging due to nonspecific presenting symptoms and the low count of Mycobacterium bacilli in body fluids, which limits the yield of positive bacteriological diagnosis with conventional methods. Rifampicin resistance adds challenges to treatment. Here, we present a 21-year-old female from Baghdad diagnosed with a case of miliary TB radiologically and clinically proved to be rifampin-resistant TB meningitis by Genexpert Ultra. We highlight the importance of compliance with treatment in the prevention of drug resistance and the role of Genexpert Ultra, which is available in our institution in Iraq, in providing rapid and accurate diagnosis of this lethal disease, hence improving the outcome of the management.

Key words: Tuberculosis, meningitis, miliary, rifampicin resistance.

INTRODUCTION

Tuberculosis (TB) is one of the oldest infectious diseases known to affect humans.[1] It is estimated that approximately 2 billion people worldwide are infected with *Mycobacterium tuberculosis*, of whom 10–15% will develop active clinical disease during their lifetime.[2]

Tuberculous meningitis (TBM), which results from the dissemination of TB to the central nervous system, is the most severe and disabling form of extrapulmonary TB. It represents a medical emergency associated with high rates of morbidity and mortality.[3,4] Following primary infection, M. tuberculosis can spread haematogenous from the initial site of infection, cross protective barriers, and invade the central nervous system. Once established, the pathogen triggers a complex inflammatory response involving both peripheral and resident immune cells. This response initiates a cascade of pathological processes that may either contain the infection or lead to significant brain injury.[4]

Intra cerebral and spinal pathology in TBM is largely driven by a dysregulated inflammatory response, which can result in meningitis, tuberculoma formation, arteritis, obstruction of cerebrospinal fluid (CSF) flow, and vascular complications, including stroke.[3] Consequently, delayed diagnosis or treatment is associated with a high frequency of neurological sequelae and mortality.[5,6]

Several factors increase the risk of developing TBM, including poverty, malnutrition, overcrowding, residence in or migration from TB-endemic regions, primary TB infection in young children, and immunodeficiency related to ageing or conditions such as HIV infection and cancer.[7,8]

The clinical presentation of TBM is highly variable and ranges from rapidly progressive meningitis to slowly progressive cognitive decline or dementia. However, a characteristic

a: MBChB, DM. Pulmonologist, the National Tuberculosis Institute. Baghdad, Iraq *b:* MBChB, FIBMS; Family medicine specialist. National Tuberculosis Institute. Baghdad, Iraq. *c:* MBChB, CABM, FIBMS; Consultant pulmonologist & Internist, National Tuberculosis Institute. Baghdad, Iraq.

Corresponding Author: **Nadia Abdulkareem Al Ani**, E-mail: **nadiaalan553@yahoo.com**.

prodromal phase is often observed and may persist for several weeks, presenting with low-grade fever, malaise, headache, dizziness, vomiting, and personality changes. As the disease progresses, patients may develop severe headaches, altered mental status, and cranial neuropathies. Seizures are relatively uncommon in adults with TBM, and classic signs of bacterial meningitis, such as neck stiffness and high-grade fever, may be absent.[9]

The severity of tuberculous meningitis can be classified using a system developed by the British Medical Research Council. Stage I patients are fully conscious and rational, with no neurological signs. Stage II patients are confused or have neurological signs such as cranial nerve palsy or hemiparesis. Stage III patients are comatose or stuporous with more severe neurological signs.[10]

Diagnosis of TBM is often delayed by the insensitive and lengthy culture technique required for disease confirmation. GeneXpert represents the most significant advance in TBM diagnostics over the past decade.[11] Early diagnosis and prompt initiation of TB treatment offer the best chance of a good neurological outcome. Without appropriate treatment, the disease will invariably progress, resulting in neurological impairment, CNS damage, and often death.[11,12]

Current WHO guidelines for TBM suggest treatment with 2 months of rifampicin (RMP), isoniazid (INH), pyrazinamide (PZE) and ethambutol (ETB) followed by 10 months of RMP and INH, Although initiation of this regimen before the onset of coma is the strongest predictor of survival from TBM, this regimen does not take into account the differential ability of anti-tuberculosis drugs to penetrate the brain.[13]

Nowadays, TB control is challenged by the emergence of drug resistance to more anti-TB drugs, resulting in multi-drug resistance (MDR), pre-extensively drug-resistant (Pre-XDR), and extensively drug-resistant (XDR) TB.[14] Drug-resistant TB (DR-TB) is caused by the Mycobacterium tuberculosis strain, which is resistant to at least one anti-TB drug. Drug resistance has mainly occurred as a result of poor treatment outcomes, poor treatment adherence, poor quality of drugs, and poor infection control practices.[15]

The prevalence of drug-resistant strains of M. tuberculosis is increasing globally, and the World Health Organisation (WHO) estimates that 7.4% of tuberculosis cases globally are resistant to isoniazid (INH) and 3.3% are multidrug-resistant, defined as resistance to at least isoniazid and rifampin.[16] Second-line drugs include medications other than first-line drugs, such as fluoroquinolones, aminoglycosides, ethionamide, cycloserine, aminosalicyclic acid, linezolid, and clofazimine.[17]

Another important lethal form of TB is miliary TB, which is a life-threatening form of disseminated TB resulting from the haematogenous (bloodborne) spread of Mycobacterium tuberculosis. It is characterised by tiny, discrete lesions (1–2 mm) in multiple organs.[18] Miliary tuberculosis (TB) often presents as TB meningitis, and the two conditions are frequently linked. Miliary TB results from TB bacteria spreading through the bloodstream; because the brain and spinal cord have a high blood supply, they are primary targets for this spread.[19]

CASE PRESENTATION

We present a 21-year-old female patient from Baghdad who reported no significant past medical or surgical histories apart from a history of being in contact with a family member with pulmonary tuberculosis.

The patient consulted a physician at a hospital for a productive cough, fever, night sweats, loss of appetite, and clinically significant weight loss (about 15 kilograms over 2 months) of a few weeks' duration. A chest X-ray (**Figure 1**) showed bilateral diffuse small nodular opacities uniformly distributed throughout both lung fields, which were also documented by the chest CT scan (**Figure 2**). At that time, the patient's cough was non-productive, preventing the conduct of a sputum laboratory

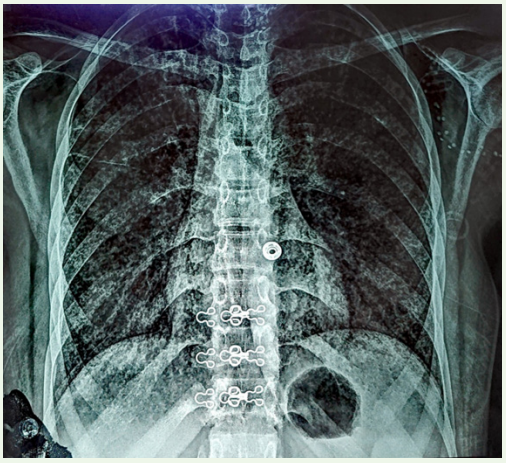

Figure 1 | Chest X-Ray PA view shows diffuse micronodular shadows involving both lung fields, no consolidation patch or cavitation seen. No pleural effusion noticed. No enlarged hilar lymph nodes seen.

examination. Based on the radiological appearance, the patient was diagnosed with miliary TB, and the patient was referred to the TB centre for treatment. There she was diagnosed as miliary TB and was started on the first-line anti-TB drugs; started on the initial phase with four tablets daily of a fixed-dose formula of rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, and ethambutol 275 mg. At home, the patient took the drugs for only 10 days and discontinued her medications deliberately due to the development of gastric upset and vomiting without consulting her treating physician. Two weeks after discontinuation of drugs, the patient started to complain of headache, photophobia, disturbed level of consciousness, and vomiting. She was admitted to Medical City Hospital in Baghdad for further management. On examination, the patient was febrile and irritable, with neck stiffness, and had a Glasgow Coma Scale (GCS) of 14 out of 15. Her brain CT scan was normal. Cerebrospinal fluid (CSF) was aspirated, and the cytology showed increased white blood cell (WBC) and protein levels and decreased sugar levels. CSF ultra-gene expert detected Mycobacterium tuberculosis with rifampicin resistance. The patient was diagnosed with TB meningitis with rifampicin resistance and enrolled on second-line anti-TB on 29 April 2025 individualised long oral regimen for 18-20 months as follows: bedaquiline 1000 mg daily /2 weeks then 200mg once daily/MWF for 22 weeks, Lovofloxacillin 1000mg daily, Linezolid 600mg daily, Clofazimine cap 100mg daily, and Cycloserine 250 mg /3 times daily with Pyridoxine 50 mg /3 times daily. The patient

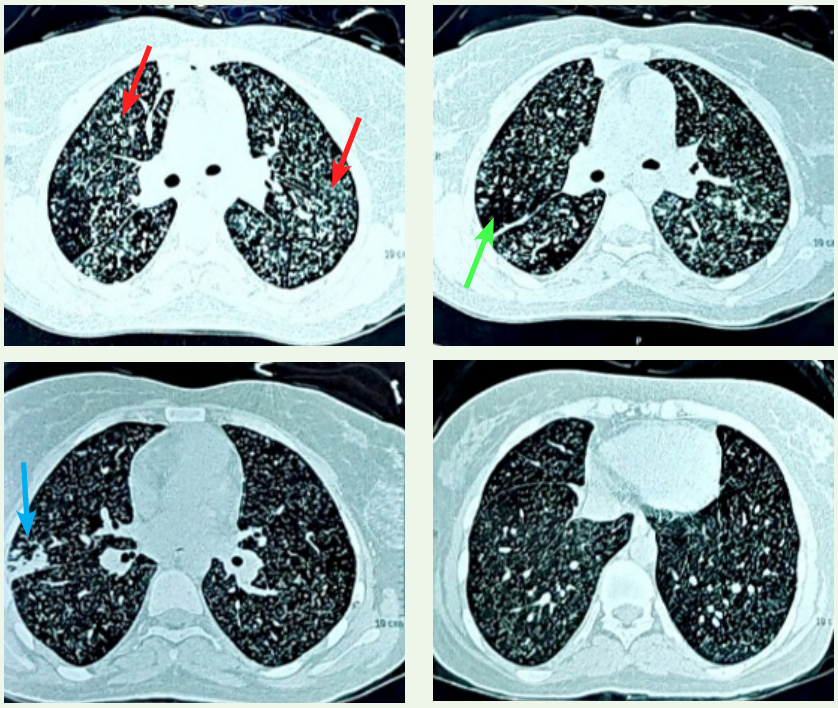

Figure 2 | CT Scan Chest Lung window. Sections from many levels shows innumerable micro nodules spreading through both lungs (red arrows) with small consolidation patches seen at right mid-zone, with a cavity inside (blue Arrow). Scattered ground glass opacities (green arrow. No enlarged hilar lymphnodes seen. No pleural effusion noticed.

received prednisolone 40 mg daily in the first month and tapered off in the second month. Patient improved clinically and was discharged home with a plan for monthly follow-up examination.

DISCUSSION

In 1700, John Jacob Manget [1] described a form of disseminated tuberculosis (TB) and likened the tiny tubercles evident on gross pathological examination to those of innumerable millet seeds in size and appearance. He coined the term miliary TB (derived from the Latin word miliarius, meaning related to millet seed) to denote this fatal form of disseminated TB.[20] Miliary TB is a rare manifestation of TB. Fewer than 2% of TB cases present with miliary disease. It is described as lymphohaematogenous dissemination of M. tuberculosis, usually from central foci, with subsequent infiltration into various organs, including the liver, bone marrow, spleen, lungs, and meninges, forming small, caseating granulomas measuring 1-3 mm.[21]

Our patient is a 21-year-old female from Baghdad with no past medical or surgical history but a family history of pulmonary tuberculosis. She presented with a productive cough, fever, night sweats, loss of appetite, and weight loss of about 15 kilograms over 2 months. At the hospital, the patient was diagnosed with miliary TB based on her contact with a TB patient, clinical features and miliary shadows seen on chest x-ray and CT scan. Bacteriological confirmation was not conducted because the patient could not provide sputum at the time of hospital admission. The patient was referred to the TB centre to start treatment as a case of miliary TB.

Miliary tuberculosis (TB) is a potentially lethal disease if not diagnosed and treated early. Diagnosing miliary TB can be a challenge, perplexing even the most experienced clinicians. Clinical manifestations are nonspecific, [22] and the criteria for the diagnosis of miliary TB are a miliary pattern on chest X-ray, or a biopsy or autopsy evidence of miliary organ involvement. [23] Miliary nodules and ground-glass opacities (GGOs) are the predominant HRCT findings in patients with miliary tuberculosis, and HRCT scans are helpful for early diagnosis and proper management.[24]

Our patient enrolled on first-line anti-TB drugs; however, the patient discontinued her medications after 10 days due to presumed gastric upset and vomiting. Two weeks later, she started to complain of headache, photophobia, disturbed level of consciousness, and vomiting. On admission to the hospital, she was febrile and irritable with neck stiffness and a Glasgow Coma Scale of 14.

Clinical presentation of TB meningitis is highly variable, ranging from a rapidly progressive meningitis syndrome to a slowly progressive dementia. However, some commonalities have been identified. According to a review, a prodromal phase characterised by low-grade fever, malaise, headache, dizziness, vomiting, and personality changes can be observed. It may persist for a few weeks, after which patients can then develop severe headaches, altered mental status, and cranial neuropathies. Seizures are uncommon manifestations of tuberculous meningitis in adults. Classic features of bacterial meningitis, such as stiff neck and high-grade fever, may be absent.[25] Headache, vomiting, meningeal signs, focal deficits, vision loss, cranial nerve palsies, and raised intracranial pressure can result from basilar meningeal fibrosis and vascular inflammation.[26,27]

A brain CT scan of our patient was within normal. CT of the brain shows pathological changes in the great majority of patients with TBM. In addition, it helps assess the complications associated with the disease. [28] Infarcts were much more common in children than in adults and were sometimes asymptomatic. Radiological abnormalities sometimes developed during treatment and often did not resolve completely. Many patients had severe residual neurological problems.[29]

The diagnosis of TBM in our patient was based on cerebrospinal fluid (CSF) examination, which showed elevated white blood cell and protein levels and a low sugar level. CSF Ultra

GeneXpert testing, available at the National TB Institute laboratory in Baghdad, revealed Mycobacterium tuberculosis with rifampicin resistance.

GeneXpert Ultra (Xpert MTB/RIF Ultra) is the upgraded, next-generation version of the original GeneXpert (Xpert MTB/RIF) assay. Both run on the same GeneXpert instrument, but ultra utilises modified chemistry and additional genetic targets to provide faster, significantly more sensitive tuberculosis (TB) detection. GeneXpert Ultra (Xpert MTB/RIF Ultra) requires 15 colony-forming units (CFU) per ml of sputum, nearly a 10-fold improvement over the original GeneXpert (Xpert MTB/RIF), which requires 115 CFU per ml to be positive.[30] Characteristic cerebrospinal fluid (CSF) findings of TBM include a lymphocytic-predominant pleocytosis, elevated protein, and low glucose. CSF acid-fast smear and culture have relatively low sensitivity, but yield increases with multiple large-volume samples. Nucleic acid amplification of CSF by polymerase chain reaction (PCR) is highly specific, but suboptimal sensitivity precludes ruling out TBM with a negative test.[31]

The patient was diagnosed with TB meningitis with rifampicin resistance, which is the most severe form of infection caused by Mycobacterium tuberculosis, causing death or disability in more than half of those affected.[32]

The World Health Organisation (WHO) End TB strategy aims to reduce mortality due to tuberculosis (TB) to less than 5% by 2035. However, mortality due to multidrug-resistant tuberculosis (MDR-TB) remains particularly high. Globally, almost 20% of patients started on MDR-TB treatment die during the course of treatment every year, [31] our patient enrolled on second-line anti-TB in April 2025, an individualised long oral regimen for 18-20 months with good response. Treatment for drug-resistant TB meningitis (TBM) typically lasts 18-24 months, significantly longer than the standard 12-month course for drug-susceptible TBM. MDR-TBM required tailored, second-line regimens based on drug susceptibility testing (DST) to ensure the drug penetration of the blood-brain barrier.[33]

This case illustrates the complexities of treating MDR-TB with CNS involvement, emphasising the importance of selecting drugs based on both CNS penetration and the feasibility of enteral administration. Also, a significant relation is present between the military and meningeal TB; 10 to 30% of adults with miliary TB also have TB meningitis, and 20 to 40% of children with miliary TB develop meningitis, making it a critical paediatric complication. Conversely, about one-third of all patients who arrive at a hospital with TB meningitis are found to have underlying miliary TB.[34]

CONCLUSION

Rifampicin resistance in Tuberculosis meningitis is a critical medical situation because rifampicin is the most powerful antibiotic in the standard TB regimen, with a high mortality rate, which can approach 100% if not treated with a specialised second-line regimen. Genexpert Ultra should be considered in the diagnostic work-up because bacterial counts in spinal fluid are often low.

REFERENCES

1. Özateş M, Kemaloglu S, Gürkan F, Özkan Ü, Hoşoglu S, Şimşek MM. CT of the brain in tuberculous meningitis: a review of 289 patients. *Acta Radiologica*. 2000 Jan;41(1):13-7.
2. Thwaites G, Chau TT, Mai NT, Drobniewski F, McAdam KP, Farrar J. Tuberculous meningitis. *Journal of Neurology, Neurosurgery & Psychiatry*. 2000 Mar 1;68(3):289-99.
3. Wilkinson RJ, Rohlwink U, Misra UK, Van Crevel R, Mai NT, Dooley KE, Caws M, Figaji A, Savic R, Solomons R, Thwaites GE. Tuberculous meningitis. *Nature reviews neurology*. 2017 Oct;13(10):581-98.
4. Angharad Grace Davis, Ursula Karin Rohlwink, Alizé Proust, Anthony A Figaji, Robert J Wilkinson, The pathogenesis of tuberculous meningitis, *Journal of Leukocyte Biology*, Feb 2019;105(2):267–280.
5. Girgis NI, Sultan Y, Farid Z, Mansour MM, Erian MW, Hanna LS, Mateczun AJ. Tuberculosis meningitis, Abbassia Fever Hospital-Naval Medical Research Unit No. 3-Cairo, Egypt, from 1976 to 1996. *The American journal of tropical medicine and hygiene*. 1998 Jan 1;58(1):28-34.
6. Bidstrup C, Andersen PH, Skinhøj P, Andersen ÅB. Tuberculous meningitis in a country with a low incidence of tuberculosis: still a serious disease and a diagnostic challenge. *Scandinavian journal of infectious diseases*. 2002 Jan 1;34(11):811-4.
7. Farer LS, Lowell AM, Meador MP. Extrapulmonary tuberculosis in the United States. *American journal of epidemiology*. 1979 Feb 1;109(2):205-17.

8. Centres for Disease Control and Prevention. Reported tuberculosis in the United States, 2013. Atlanta, GA: US Department of Health and Human Services, CDC. 2014 Oct.
9. Blumberg HM, Burman WJ, Chaisson RE, Daley CL. American Thoracic Society/ Centres for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. *American journal of respiratory and critical care medicine*. 2003 Feb 15;167(4):603.
10. Byrd T, Zinser P. Tuberculosis meningitis. *Current treatment options in neurology*. 2001 Sep;3(5):427-32.
11. Méchaï F, Bouchaud O. Tuberculous meningitis: challenges in diagnosis and management. *Revue neurologique*. 2019 Sep 1;175(7-8):451-7
12. Wilkinson RJ, Rohlwink U, Misra UK, van Crevel R, Mai NTH, Dooley KE, et al. Tuberculous meningitis. *Lancet Neurol*. 2017;16(7):581–598. doi:10.1016/S1474-4422(17)30095-8.
13. Davis A, Meintjes G, Wilkinson RJ. Treatment of tuberculous meningitis and its complications in adults. *Current treatment options in neurology*. 2018 Mar;20(3):5.
14. World Health Organization. Global Tuberculosis Report. Geneva: WHO press; 2017.
15. World Health Organization. Global Tuberculosis Report. Geneva: WHO press; 2019.
16. World Health Organization. Towards universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis by 2015: WHO progress report 2011. World Health Organization; 2011.
17. Hong SH, Im JG, Lee JS, Song JW, Lee HJ, Yeon KM. High resolution CT findings of miliary tuberculosis. *Journal of computer assisted tomography*. 1998 Mar 1;22(2):220-4
18. Kwas H. Miliary or disseminated tuberculosis: Epidemiology, diagnosis and management. *Revue Medicale de Liege*. 2024 Nov 1;79(11):724-30.
19. Loo E, Fish LE. Clinical Review of Current Best Practices for Tuberculosis Screening, Testing, and Treatment in the Urgent Care Setting. *J Urgent Care Med*. 2025;19(5):17-25.
20. Sharma SK, Mohan A, Sharma A. Challenges in the diagnosis & treatment of miliary tuberculosis. *Indian Journal of Medical Research*. 2012 May 1;135(5):703-30.
21. Kim JH, Langston AA, Gallis HA. Miliary tuberculosis: epidemiology, clinical manifestations, diagnosis, and outcome. *Reviews of infectious diseases*. 1990 Jul 1;12(4):583-90.
22. Sharma SK, Mohan A. Miliary tuberculosis. *Tuberculosis and nontuberculous mycobacterial infections*. 2021 Jan 13:415-35.
23. Mert A, Bilir M, Tabak F, Ozaras R, Ozturk R, Senturk H, Aki H, Seyhan N, Karayel T, Aktuglu Y. Miliary tuberculosis: clinical manifestations, diagnosis and outcome in 38 adults. *Respirology*. 2001 Sep 8;6(3):217-24.
24. Lee JY. Diagnosis and treatment of extrapulmonary tuberculosis. *Tuberculosis and Respiratory Diseases*. 2015;78(2):47–55. doi:10.4046/trd.2015.78.2.47.
25. Blumberg HM, Burman WJ, Chaisson RE, Daley CL. American thoracic society/centers for disease control and prevention/ infectious diseases society of America: treatment of tuberculosis. *American journal of respiratory and critical care medicine*. 2003 Feb 15;167(4):603.
26. Garg RK, Uniyal R, Pandey S, Tejan N, Rizvi I, Sharma PK, Kumar N, Malhotra HS. The spectrum of central nervous system manifestations in leprosy: a systematic review of published case reports and case series. *Transactions of The Royal Society of Tropical Medicine and Hygiene*. 2024 Mar;118(3):148-59.
27. Marx GE, Chan ED. Tuberculous meningitis: diagnosis and treatment overview. *Tuberculosis research and treatment*. 2011;2011(1):798764.
28. Gelb AF, Leffler C, Brewin A, Mascatello V, Lyons HA. Miliary tuberculosis. *American Review of Respiratory Disease*. 1973 Dec;108(6):1327-33.
29. Bhargava S, Gupta AK, Tandon PN. Tuberculous meningitis—a CT study. *The British Journal of Radiology*. 1982 Mar 1;55(651):189-96.
30. Vasconcelos G, Santos L, Couto C, Cruz M, Castro A. Miliary brain tuberculomas and meningitis: tuberculosis beyond the lungs. *European Journal of Case Reports in Internal Medicine*. 2020 Sep 14;7(12):001931.
31. Davis AG, Rohlwink UK, Proust A, Figaji AA, Wilkinson RJ. The pathogenesis of tuberculous meningitis. *Journal of leukocyte biology*. 2019 Feb;105(2):267-80.
32. Török ME. Tuberculous meningitis: advances in diagnosis and treatment. *British medical bulletin*. 2015 Mar 1;113(1):117-31.
33. Kizito E, Musaazi J, Mutesasira K, Twinomugisha F, Namwanje H, Kiyemba T, Freitas Lopez DB, Nicholas NS, Nkolo A, Birabwa E, Dejene S. Risk factors for mortality among patients diagnosed with multi-drug resistant tuberculosis in Uganda-a case-control study. *BMC infectious diseases*. 2021 Mar 22;21(1):292.
34. Vasconcelos G, Santos L, Couto C, Cruz M, Castro A. Miliary brain tuberculomas and meningitis: tuberculosis beyond the lungs. *European Journal of Case Reports in Internal Medicine*. 2020 Sep 14;7(12):001931.

Abbreviations list: Central Nervous system (CNS), Cerebrospinal fluid (CSF), Computed Tomography (CT), Ethambutol (ETB), Extensively drug-resistant (XDR) TB, Glasgow Coma Scale (GCS), High Resolution Computed tomography (HRCT), Human immune deficiency (HIV), Isoniazid (INH), Multi-drug resistance (MDR), Pre-extensively drug-resistant (Pre-XDR), Pyrazinamide (PZE), Rifampicin (RMP), Tuberculosis (TB), Tuberculous meningitis (TBM), White blood cell (WBC), World Health Organisation (WHO).

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