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Pneumologia

A Case Report of concurrent SARS-CoV-2 infection and multi-drug-resistant tuberculous meningitis

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Abstract

English:

Infrequently documented, drug-resistant tuberculous meningitis presents diagnostic and treatment challenges, particularly during SARS-CoV-2 coinfection. Timely identification is crucial to prevent severe complications, yet the optimal treatment course remains uncertain, marked by elevated morbidity and mortality rates. Standard guidelines recommend at least four potent second-line anti-TB drugs. Amid a pandemic, it's vital not to solely focus on COVID-19 but to explore various aspects. This case outlines a 20-year-old with multi-drug-resistant tuberculous meningitis and SARS-CoV-2, in contact with an MDR pulmonary tuberculosis case. Diagnosis involved molecular and bacteriological cerebrospinal fluid examinations. GeneXpert MTB/RIF revealed rifampicin resistance, and subsequent testing indicated TB resistance to multiple drugs. Tuberculous meningitis, a predominant manifestation, demands careful attention for accurate diagnosis and strategic management. The judicious selection and duration of efficacious drugs are pivotal in treating MDR tuberculous meningitis.

Keywords

Meningitis • SARS-CoV-2 • Tuberculosis MDR • GeneXpert test

Raport de caz de infecție concomitentă cu SARS-CoV-2 și meningită tuberculoasă multirezistentă la medicamente

Rezumat

Romanian:

Meningita tuberculoasă multi-drog rezistentă (MDR), rar documentată în literatura medicală, prezintă provocări atât diagnostice cât și în privința tratamentului, în special în timpul coinfecției cu virusul SARS-CoV-2. Identificarea timpurie este crucială pentru a preveni complicațiile severe. Totuși, cursul optim de tratament în timp rămâne neclar, marcat de rate crescute de morbiditate și mortalitate. Ghidurile recomandă standard cel puțin patru medicamente de linia a doua anti-TB. Deși am trăit timpuri pandemice, a fost vital pentru pacienți ca personalul medical să nu se concentreze doar pe boala COVID-19, ci să exploreze în totalitate și cu acuratețe problemele medicale conexe sau de fond. Acest articol tratează cazul unei tinere de 20 de ani cu meningită tuberculoasă multidrog-rezistentă și infectie SARS-CoV-2, care a avut contact cu un caz de tuberculoză pulmonară MDR. Diagnosticul a implicat examene moleculare și bacteriologice ale lichidului cefalorahidian. Testul GeneXpert MTB/RIF a evidențiat rezistență la rifampicină, iar testele ulterioare au indicat rezistența tuberculozei la mai multe medicamente. Meningita tuberculoasă necesită o atenție deosebită pentru diagnosticul precis și managementul strategic. Selecția judicioasă și durata medicamentelor eficiente sunt esențiale în tratarea meningitei tuberculoase MDR.

Cuvinte-cheie

Meningită • SARS-CoV-2 • Tuberculoză MDR • Test GeneXpert • Coinfecție

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1. Introduction

Tuberculosis (TB) can affect various organs, and disseminated TB may involve organs beyond the lungs. Tuberculous meningitis (TBM), a severe extrapulmonary form, constitutes a significant portion of neurotuberculosis cases [1]. The rarity of drug-resistant TBM cases is attributed to diagnostic challenges. Untreated TBM poses high risks of neurologic sequelae and mortality, underscoring the need for prompt intervention [2-4]. “Rich foci,” subpial tubercles formed during primary infection, contribute to TBM development. Those at risk include young children with primary TB and immunocompromised individuals.

Early detection of these disorders is challenging due to their varied clinical presentation. Timely identification and treatment are crucial for favorable outcomes. Clinical indicators include prolonged fever, headaches, and neck stiffness. Early diagnosis enables positive responses to antituberculous therapy [5-7].

COVID-19, primarily targeting the respiratory system, can also impact the nervous system. Neurological manifestations, such as encephalopathy, range from confusion to severe cognitive deficits. Given the rising threat of drug-resistant TB, there’s an urgent need for effective medications. Research should focus on the epidemiology, immunology, diagnosis, therapy, and prevention of TBM [8].

Addressing drug-resistant TB is crucial for controlling the virus, emphasizing the need for research into effective medications. The complexity of TBM and the expanding spectrum of COVID-19-associated neurological manifestations underscore the importance of advancing our understanding and developing comprehensive strategies for diagnosis, treatment, and prevention [1,8].

2. Case report

We present the case of a 20-year-old female who arrived at the emergency room (ER) with a 10-day history of vomiting, photophobia, an intense occipital headache, asthenia, cough, sore throat, and fatigue. There was no reported fever, sweating, or loss of appetite. The patient also mentioned slight difficulty breathing but no signs of trismus. She has no significant medical history, prior medical treatment, or known allergies. She is an active smoker and does not consume drugs or alcohol.

The patinent was employed at a fast-food establishment, engaging in daily interactions with numerous people. She shares a relatively small rental apartment, measuring 4x10 m², with her fiancé. The living space is deficient in proper ventilation and natural light. Additionally, her brother-in-law received a diagnosis of multidrug-resistant pulmonary tuberculosis over six months ago, and they had frequent interactions.

Upon admission to the ER, the physical examination revealed a body temperature of 36.5 °C, blood pressure of 106/70 mmHg, a heart rate of 97 beats/min, and SpO2=97%. Palpation of both sides of the neck and torso revealed tenderness, and no lymph nodes were noted. Lung auscultation revealed clear sounds.

Multiple laboratory blood test parameters were analyzed. In Table 1, we have indicated only the pathological parameters. Furthermore, the procalcitonin level yielded a negative result, and all other blood test outcomes fell within the normal range, including SARS CoV-2 rapid test.

Cerebral imaging revealed no pathological processes: there were no density alterations in the supra or supratentorial brain substance, normal extracerebral liquid spaces, symmetric ventricles at the midline, and sinuses and mastoid cells exhibited normalcy with no alterations in bone structure.

In the initial neurological assessment, there were no observed signs of neurological deficits, and the patient remained conscious and cooperative. Despite this, suspicion of bacterial meningitis persisted. Consequently, a lumbar puncture was conducted, and the biochemical and cytological analyses of the cerebrospinal fluid are detailed in Table 2. SARS-CoV-2 PCR was not performed on the cerebrospinal fluid sample.

Table 1. Pathological blood test chemistry and CBC[1].

Biochemical Parameters	Normal Range	Value
WBC[2]	4.000-10.000 µ/L	10.64 µ/L
Neutrophils	40-60 %	81.73 %
Lymphocytopenia	20-40 %	8 %
C-Reactive Protein	<3 mg/l	26.5 mg/l
Serum Creatinine	0.7-1.3 mg/dl	0.6 mg/dl
ESR[3]	<10 mm/1h	35 mm/1h

[1]Complete Blood Count [2] White Blood Cell [3]Erythrocyte Sedimentation Rate.

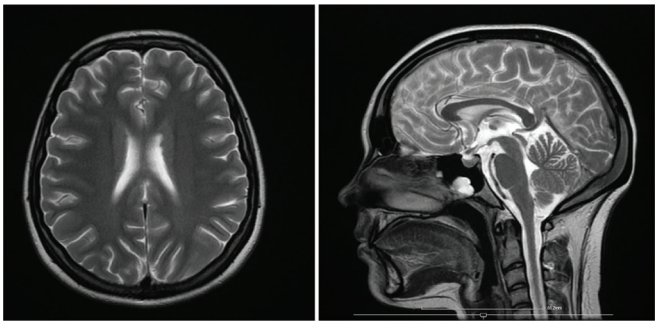

Figure 1. MRI axial and midsaggital section of brain. No pathological findings.

Table 2. Cerebrospinal fluid analyzed.

Elementes	Normal Range	Value
Glucose	40-70 mg/dl	29 mg/dl
Protein	0.15 to 0.45 g/L	2.00 g/l
Lymphocytic	0-3 µ/L	576 µ/L
Red Blood cell	Negative	300 µ/L

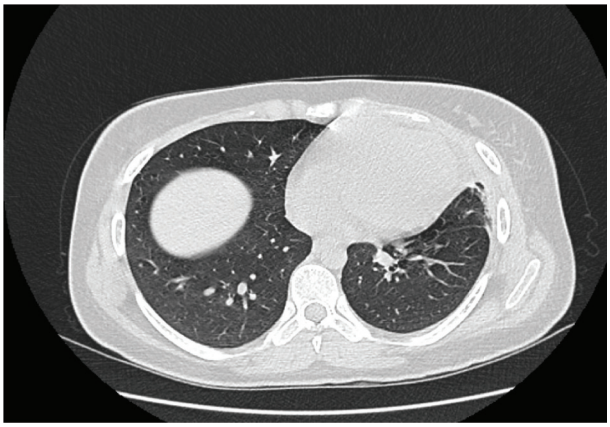

Figure 2. Thoracic CT-Scan axial: subpleural condensation lower left lobe.

As a result, it was decided to hospitalize the patient in the infectious diseases department to continue the investigations and initiate treatment.

On the first day of admission, the patient's general condition remained stable. Additional medical tests were performed, including several blood cultures (negative), pharyngeal and nasal exudates (absent bacterial growth), multiplex PCR-based respiratory viral panels for various viruses came positive for SARS-CoV-2. Serologies for HIV, hepatitis B, and hepatitis C (all negative).

A thoracic CT scan revealed a small amount of left pleural fluid (maximum size 13 mm) exhibiting an encapsulated appearance. Additionally, fine pulmonary condensation with a subpleural air bronchogram was observed in the lower singular and anterior regions of the left lower lobe (Figure 2). The left upper lobe displayed paramediastinal pulmonary microcode, and there was an accumulation of pericardial fluid with a thickness measuring 7 mm (Figure 3).

A cardiovascular consultation, along with echocardiography and electrocardiography, revealed minimal pericardial fluid reaction.

Empiric treatment was initiated intravenously with Vancomycin 1g every 12h, Meropenem 2g every 12h, Mannitol 4x125mg every 12h, Dexamethasone sodium phosphate 8 mg/2ml every 12h, Furosemide 20mg/2ml every 24h, 10% Glucose 500ml every 12h, NaCl 0.9% 500ml every 6h, Vitamin C 750mg, Vitamin B1 (Thiamine), and Vitamin B-6 (Pyridoxine).

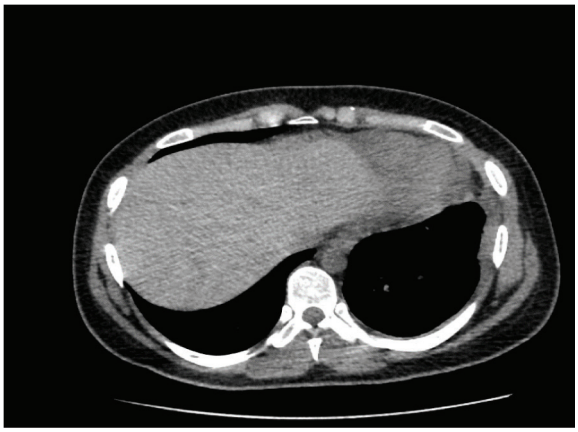

Figure 3. Thoracic CT-Scan axial: mediastinal window – enclosed left pleural fluid.

On the second day of hospitalization, the patient's overall condition showed a slight deterioration, marked by increased psychomotor agitation and intensified headache. Another lumbar puncture was carried out, and the cerebrospinal fluid sample was sent for bacteriological analysis to detect the presence of the Mycobacterium tuberculosis complex and common bacteria. The direct examination, following special Ziehl-Nielsen staining, revealed a positive result for 6+ Acid-Fast Bacilli (AFB), and cultures on liquid medium (MGIT) confirmed the molecular diagnosis after 15 days.

A molecular analysis using GeneXpert MTB/RIF identified Mycobacterium Tuberculosis with Rifampicin resistance. In response to this resistance, additional molecular tests, including GeneXpert MTB/RIFb and GeneXpert -XDR plus, were conducted to validate rifampicin resistance and explore resistance to other anti-TB drugs such as Hydrazide, Ethionamide, Quinolone, Amikacin, Kanamycin, and Capreomycin.

Sputum examination for tuberculosis yielded negative results on both the Ziehl-Nielsen smear and the GeneXpert MTB/RIF test, as well as in culture on a liquid medium (MGIT).

Considering the findings from bacteriological, molecular, and radiological assessments, the diagnosis was confirmed as secondary pulmonary tuberculosis involving infiltrative nodular lesions in the upper left lobe, MDR tuberculous meningoencephalitis, and polyserositis.

Treatment was initiated based on molecular and bacteriological findings in accordance with WHO recommendations and the availability of medications in the hospital pharmacy at that time. The patient was placed on a prolonged regimen spanning 6 months, comprising Bedaquiline, Moxifloxacin, Linezolid, Delamanid, and Cycloserine.

After 2 months of treatment, there was a significant improvement in the patient's overall condition. The anti-bacillary drugs were well tolerated, and ongoing monitoring is

Table 3. Antibiogram result for Mycobacterium tuberculosis.

anti-TB substance	Result
RIF[1]	R
HYN[2]	R
STR[3]	R
EMB[4]	R
AMK[5]	R
LFX[6]	R
MXF[7]	R
ETH[8]	R

[1]Rifampicin [2]Isoniazid [3]Streptomicin [4]Ethambutolum [5]Amikaciunm [6]Levofloxacinum [7]Moxifloxacinum [8]Ethionamidum.

in place. Bacteriological control examinations for tuberculosis conducted at the 2-month mark revealed a negative direct examination following special Ziehl-Nielsen staining, and no Mycobacterium Tuberculosis was detected using GeneXpert MTB/RIF.

Beyond 4 months since the initial sample collection, the bacteriological examination of cerebrospinal fluid has yielded results, including the antibiogram for Mycobacterium tuberculosis (line one and two), as detailed in Table 3.

The patient is monitored monthly with bacteriological sputum tests for tuberculosis, having reached the 5th month of treatment, with both the direct bacteriological test and cultures returning negative results, and the patient is in an overall very good general condition.

3. Discussions

Globally, tuberculosis (TB) remains a significant public health concern, predominantly impacting underdeveloped nations [9]. Additionally, its prevalence has risen in affluent countries, partly due to co-infection with HIV. According to the 2019 World Health Organization (WHO) report, there were 10 million new TB cases and 1.5 million fatalities [10]. TB commonly affects the lungs but can also manifest in other organs (extrapulmonary). Tuberculous meningitis localization is uncommon. Despite testing positive for COVID-19, it would have been tempting to overlook her illness. However, thorough examinations during the initial assessment led to the correct diagnosis of meningitis.

A swift examination of COVID-19 cases suggests a limited occurrence of bacterial or fungal coinfections, with only 8% of patients identified as having such coinfections. However, the perception of low coinfection levels might be misleading due to widespread antibiotic use without confirmed culture evidence, potentially inhibiting pathogen growth.

Initially dismissing COVID-19 as the sole cause of the patient's symptoms, the team considered SARS-CoV-2's potential neurological manifestations, including meningitis, encephalitis, and Guillain-Barré syndrome. Reports also link tuberculosis meningitis to COVID-19, suggesting pre-existing conditions [11].

Drug-resistant tuberculosis (TB) poses a significant challenge to national, regional, and global TB control efforts. Fluoroquinolones and aminoglycosides, second-line antibacterials, face additional resistance mechanisms from some multidrug-resistant (MDR) TB pathogens. Annually, there are approximately 200,000 fatalities and 500,000 new cases of MDR-TB or rifampicin-resistant TB (RR-TB) reported worldwide [12].

Tuberculous meningitis (TBM) manifests in distinct stages. The initial stage presents nonspecific symptoms like subfebrility, headache, irritability, and vomiting, making early detection challenging. Infants may display developmental stagnation, fever, cough, altered consciousness, and convulsions. Neck stiffness is notably absent in this stage, which typically lasts 1-2 weeks. A significant clue for suspicion is a history of contact with an active TB patient (present in about 50% of cases).

The second stage features a sudden onset with lethargy, neck stiffness, positive meningeal signs, convulsions, vomiting, and neurological deficits. Progression may lead to hydrocephalus, increasing intracranial pressure, and encephalitis with movement disorders, speech difficulties, and cranial nerve involvement (30%-50% of cases), often affecting the VI-th nerve, resulting in vision loss. The third stage may exhibit posturing, hemiplegia, coma, and potential fatality [13].

Seizures are an uncommon manifestation of tuberculous meningitis (TBM) in adults, necessitating the exclusion of other conditions like cerebral tuberculoma or bacterial/viral meningitis. Conversely, seizures are prevalent in pediatric TBM cases, occurring in up to 50% of instances, and if left untreated, can lead to coma and death. Survivors may face neurological complications, including mental retardation, sensorineural hearing loss, hydrocephalus, cranial nerve palsies, stroke-related deficits, seizures, and coma [14].

TBM diagnosis is challenging, relying on clinical and early cerebrospinal fluid (CSF) findings rather than conclusive microbiologic confirmation. Clinical indicators such as prolonged symptom duration (>six days), significant CSF pleocytosis, and localized impairments enhance the likelihood of TBM. Typical CSF findings include lymphocytic-predominant pleocytosis, total white cell counts ranging from 100 to 500 cells/μL, elevated protein levels (100-500 mg/dL), low glucose levels (<45 mg/dL), and a CSF: plasma ratio <0.5 [5].

While a single CSF sample has limited sensitivity (20-40%), an acid-fast smear should be sent for microbiologic diagnosis. Multiple lumbar punctures (10–15 mL) over several days can enhance sensitivity to over 85%. Culture, despite its time requirements (40–80% sensitivity), is crucial for

assessing medication susceptibility, especially in the case of drug-resistant strains. Notably, a negative CSF test for M. tuberculosis DNA or acid-fast bacilli does not exclude TBM diagnosis or the need for empiric therapy if clinical suspicion is high. Mycobacterial DNA may remain detectable in the CSF for up to a month after treatment initiation, although the sensitivity of CSF smear and culture decreases post-treatment.

Through extensive research, molecular biology has achieved success, even with paucibacillary samples, allowing for the identification and detection of anti-TB medication resistance. The World Health Organization (WHO) recommends the rapid GeneXpert MTB/RIF nucleic acid amplification test for simultaneous detection of MTC and rifampicin resistance in pulmonary and extrapulmonary specimens, with a sensitivity of over 80% in cerebral spinal fluid [15, 16]. In our case, GeneXpert MTB/RIF facilitated the identification of MTC and detection of rifampicin resistance.

Neuroimaging plays a crucial role in TBM diagnosis, with typical features including basal meningeal enlargement, hydrocephalus, nodular-enhancing lesions, cerebral edema, and hypodensities from cerebral infarcts. Magnetic resonance imaging (MRI) is preferred over computed tomography (CT) for assessing the brainstem and spine, while CT is suitable for a quick assessment of hydrocephalus, potentially necessitating surgical intervention.

Genotyping assays like MTB-DR plus and MTB-DRsl, along with GeneXpert MTB/RIF, aid in diagnosing MTC from clinical specimens. The MTBDRplus test identifies rifampicin and isoniazid resistance, while the MTB-DRsl test detects resistance to ethambutol, fluoroquinolones, and aminoglycosides. Both tests exhibit over 80% sensitivity for rifampicin, isoniazid, fluoroquinolones, and aminoglycosides resistance [17]. In our case, GeneXpert MTB/RIF confirmed rifampicin resistance, and the subsequent tests (MTBDRplus and MTBDRsl) revealed additional resistance to various medications.

Primary drug resistance occurs in patients who have never undergone TB treatment, while antibacillary medication resistance can also be secondary. Treating Mycobacterium tuberculosis exerts selective pressure, diminishing susceptible bacilli, increasing drug-resistant mutations, and fostering drug resistance (acquired resistance). It is plausible that our patient acquired primary drug resistance through contact with her brother-in-law.

The World Health Organization (WHO) recommends a 9–11 month regimen for treating multidrug-resistant TB (MDR-TB), encompassing a loading phase with amikacin, moxifloxacin, ethionamide, clofazimine, pyrazinamide, ethambutol, and isoniazid. The maintenance phase involves moxifloxacin, clofazimine, pyrazinamide, and ethambutol. Recent WHO updates suggest replacing short regimens without injectables with those incorporating bedaquiline. For new combinations, the FDA-approved 2019 WHO trial proposes bedaquiline, linezolid, and pretomanide for 9 months to treat multiresistant or extensively drug-resistant TB [16,17].

Pyrazinamide, with excellent CSF penetration, plays a crucial role in reducing treatment time for drug-susceptible TB. Newer fluoroquinolones like levofloxacin and moxifloxacin, with strong CSF penetration and effectiveness against most M. tuberculosis strains, show potential as first-line therapy for tuberculous meningitis (TBM). Adding a fluoroquinolone to the standard regimen enhances anti-TB performance, as evidenced by a randomized controlled study. While no significant difference in mortality was observed, the study's statistical power might have been insufficient to demonstrate such a relationship. Among new anti-TB agents, bedaquiline and delamanid appear promising [18].

It is advisable to evaluate therapy tolerance and conduct clinical, bacteriological, and radiological surveillance. The introduction of new anti-TB medications, such as linezolid and bedaquiline, has enhanced the prognosis for multidrug-resistant (MDR) pulmonary and extrapulmonary TB. The presence of still-active molecules significantly influences treatment effectiveness. Individuals with extensively drug-resistant TB (XDR-TB) and HIV infection face elevated mortality rates. The surge in MDR and XDR strains, coupled with their synergistic connection with TB, may contribute to this phenomenon [16].

Prognosis in tuberculous meningitis (TBM) is influenced by the neurological state at presentation, with the time until treatment initiation crucial for outcomes. Prompt initiation of empiric treatment is essential when TBM is suspected, as any delay can worsen the prognosis, although TBM typically progresses less rapidly than meningitis caused by pyogenic bacteria. Case studies indicate death rates ranging from 7% to 65% in industrialized nations and up to 69% in impoverished regions [19-20]. Risk factors for death include comorbidities, significant neurological involvement at admission, rapid disease progression, and advanced age or very young age. Up to 50% of survivors may experience neurological aftereffects [4].

4. Conclusions

Tuberculous meningitis, a rare manifestation of tuberculosis, often faces delayed diagnosis and treatment. Emphasizing the crucial role of gene amplification tests, such as GeneXpert MTB/RIF, is paramount for effective and rapid disease management. These tests play a pivotal role in early detection, identifying tuberculosis bacteria presence and their resistance to specific medications. Early diagnosis is vital for prompt

treatment initiation, essential in reducing the high mortality rate associated with tuberculous meningitis.

The standard 18-month treatment involves a combination of at least four medications effective against Mycobacterium tuberculosis. Supportive care may be necessary to alleviate symptoms like headaches, seizures, and increased intracranial pressure. Close monitoring by healthcare professionals throughout the treatment course is crucial to assess therapy tolerance, address side effects, and track progress.

In summary, tuberculous meningitis is a serious, albeit rare, form of tuberculosis requiring early detection and prolonged treatment. Gene amplification tests are invaluable for timely diagnosis, and a comprehensive treatment regimen is essential to improve patient outcomes, reducing complications and mortality risk.

Authors contributions

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Institutional Review Board Statement

The case report was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Clinical Hospital for Infectious Diseases and Pneumophthisiology “Dr. Victor Babeș“ Timișoara.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

Conflicts of Interest

The authors declare no conflict of interest.

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