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A case report: A multidrug-resistant tuberculous meningitis case, household contact with an multidrug-resistant pulmonary tuberculosis patient

Adriana Socaci[1],[2]*, Mihuta Camil[1], Hogea Elena[1],[3]

[1]Clinical Hospital for Infectious Diseases and Pneumology "Dr. Victor Babes", Timisoara, Romania.

[2]Vasile Goldis Western University of Arad, Romania.

[3]Victor Babeş University of Medicine and Pharmacy of Timisoara, Romania.

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***Corresponding Author:** Adriana Socaci ,Clinical Hospital for Infectious Diseases and Pneumology "Dr. Victor Babes", Timisoara, Romania.
Email: adriana_socaci@yahoo.com"

Abstract

Background: Drug-resistant tuberculous meningitis is not frequently reported in the literature and is difficult to diagnose and treat. Early recognition of this condition is essential to prevent serious complications. The optimal treatment is unknown and has very high morbidity and mortality. Guideline treatment includes at least four effective core second-line anti-TB drugs.

Case description: We describe a multidrug-resistant tuberculous meningitis in a 19-year-old female patient who had close contact with a confirmed case of active pulmonary tuberculosis multidrug-resistant (MDR). The diagnosis of Tuberculosis (TB) was confirmed by molecular and bacteriological investigation from cerebrospinal fluid. GeneXpert MTB/RIF performed showed rifampicin resistance and a first- and second-line drug resistance test using GX-XDR showed TB resistance to isoniazid, rifampicin, quinolones, kanamycin, capreomycin, and aminoglycosides.

Discussion: This case report aims to discuss diagnostic criteria, evolutionary particularities, and management of MDR tuberculous meningitis.

Conclusion: Tuberculous meningitis is the most common form of central nervous system tuberculosis, it requires vigilance in establishing the correct diagnosis and management. Correct combination and duration of the most effective drugs in MDR tuberculous meningitis are the keys to correct treatment.

Keywords: Meningitis; Tuberculosis; Multidrug resistance (MDR); GeneXpert MTB/RIF.

Introduction

Any organ or system in the body might become affected by tuberculosis. Patients with disseminated TB may experience extrapulmonary involvement alone or in conjunction with a pulmonary focus [1].

One of the most severe forms of extrapulmonary tuberculosis is tuberculous meningitis (TBM), which accounts for 70-80% of instances of neuro tuberculosis. TBM is caused by Mycobacterium tuberculosis [2]. Reports on drug-resistant TBM are limited due to the rarity of the disease and the difficulty of isolating mycobacteria from the cerebrospinal fluid. If TBM is not treated right away, it is associated with a high frequency of neurologic sequelae and mortality [3-5]. Subependymal or subpial tubercles commonly referred to as "Rich foci" seeded during bacilli of a primary infection or a disseminated illness, break into the subarachnoid space to cause the sickness. Young children with primary TB and individuals with immunodeficiency brought on by aging, malnutrition, drug users, or illnesses like HIV and cancer are among those who are more at risk for TBM [5-7].

Early diagnosis can be challenging due to the wide clinical spectrum and potential for non-specificity. Early detection and treatment of these disorders are necessary for a better outcome. Clinical signs included a fever lasting more than seven days, a headache, or stiffness in the neck. If the diagnosis is obtained early, before an irreversible neurological disability is established, the clinical response to antituberculous therapy in all forms of neuro tuberculosis is excellent [1]. The typical clinical presentation, abnormalities in neuroimaging, changes in CSF fluid, and response to anti-tuberculosis medications all contribute to the diagnosis.

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The development of medications that are effective against the resistant strains is crucial since the advent of drug-resistant tuberculosis poses a severe danger to the control of this virus. It is necessary to conduct more studies on the epidemiology, immunological processes, diagnosis, therapy, and prevention of TBM [2].

Description

We present a case of a 19 years old female, who attended the emergency room (ER) with a 4-day history of vomiting, photophobia, intense occipital headache, asthenia, and fatiguability. Otherwise, no cough, no fever, sweating, or loss of appetite was reported. The patient noted no difficulty of breathing or signs of trismus. She had no significant medical history, and no medical treatment, she is an active smoker and does not consume any drugs or alcohol, and also she reported no known allergies.

The patient worked in a fast food restaurant being in daily contact with many people. She lives with her fiance in a rental apartment, not large enough with a size of 4x10 m^2, the ventilation and natural lighting were lacking. Her brother-in-law was diagnosed with MDR pulmonary tuberculosis more than 8 months ago, and they met frequently.

On admission to ER physical examination revealed a body temperature of 36.7 °C, blood pressure of 100/65 mmHg, a heart rate of 100 beats/min, and SpO2=96%. Palpation of both sides of the neck and torso revealed tenderness and no lymph nodes were noted. The lungs were clear on auscultation. Laboratory blood tests showed: white blood cell count at 10.64 U/L, neutrophils 81,73% and lymphocytopenia at 11%, C-reactive protein at 6.5 mg/l, serum creatinine 0.6 mg/dl, ESR at 35 mm/1h, negative procalcitonin and the rest of the blood tests within normal limits. Cerebral does not detect pathological processes: No density changes at the level of the supra or supratentorial brain substance. Normal extracerebral liquid spaces. Symmetrical ventricles at the midline. Sinuses, mastoid cells of normal appearance. No changes in bone structures. During the initial neurological examination, there were no signs of neurologic deficits, the patient is conscious and cooperative but the suspicion of bacterial meningitis persists. Therefore, a lumbar puncture is performed and the biochemical and cytological analyses of the cerebrospinal fluid showed: low glucose of 29 mg/dl, elevated protein levels of 2.00 g/l, lymphocytic 576 U/L, red blood cell 300 U/L.

Thus it is decided to hospitalize the patient in the infectious diseases department to continue the investigations and to start the treatment.

On day 1 of admission, the patient's general condition is stationary. Other medical tests are performed: several blood cultures - negative, pharyngeal and nasal exudates - absent bacterial growth, multiplex PCR - based respiratory viral panels test for influenza, respiratory syncytial virus, adenovirus, parainfluenza virus, adenovirus, coronavirus, rhinovirus, enterovirus, and human metapneumovirus - negative. Another set of blood tests with biochemistry, inflammatory markers, and blood count was performed. In addition, serologies for human immunodeficiency virus (HIV), hepatitis B, and hepatitis C were negative.

A Thoracic CT scan showed: Minimal left pleural fluid (maximum size 13 mm) with an enclosed appearance. Fine pulmonary condensation with subpleural air bronchogram in the lower singular and anterior of the left lower lobe. Paramediastinal pulmonary microcode left upper lobe. Pericardial fluid accumulation with a thickness of 7 mm.

Cardiovascular consultation was performed along with echocardiography and electrocardiography that revealed: minimal pericardial fluid reaction.

Empiric treatment is initiated intravenously with: Vancomycin 1g every 12h, Meropenenum 2g every 12h, Manitolum 4x125mg every 12h, Dexamethasone sodium phosphate, 8 mg/2ml every 12h, Furosemidum 20mg/2ml every 24h, Glucosum 10% 500ml every 12h, NaCl 0.9% 500ml every 6h, Vitamin C 750mg, Vitamin B1 (Thiamine), Vitamin B-6 (Pyridoxine).

On day 2 of admission the general condition of the patient worsens slightly, being psycho-motor agitated and the headache intensifies. A lumbar puncture is performed again and the cerebrospinal fluid specimen was sent for bacteriological analysis for Mycobacterium tuberculosis complex and banal germs.

Direct examination after special Ziehl-Nielsen staining was positive for 6+ BAAR and cultures on liquid medium Mycobacteria Growth Indicator Tube (MGIT) were positive after 15 days thus confirming the molecular diagnosis.

A molecular test using GeneXpert MTB/RIF resulted in the detection of Mycobacterium Tuberculosis with the detection of Rifampicin resistance. In response to this Rifampicin resistance, we performed other molecular tests, including GenoType MTBDRplus to confirm rifampicin resistance and also to investigate resistance to other anti-TB drugs with the detection of Hydrazide, Ethionamide, Quinolone, Amikacin, Kanamycin, and Capreomycin.

The sputum examination for tuberculosis was negative on the Ziehl-Nielsen smear as well as for the GeneXpert MTB/RIF test and culture on a liquid medium (MGIT).

Following the bacteriological, and molecular results, and the radiological investigations, the diagnosis was settled: Secondary pulmonary tuberculosis infiltrative nodular upper left lobe, MDR tuberculous meningoencephalitis, and polyserositis. Treatment was initiated based on molecular and bacteriological data by the WHO recommendations and depending on the disponibility of the hospital pharmacy at that moment, until new acquisitions of medicines according to the patient's needs. The patient was put on a short-term protocol with Ethambutol, Pyrazinamide, Moxifloxacin, and Cycloserine. After 3 days, subsequently, the patient was put on a long-term protocol consisting of 6 months of Bedaquiline, Moxifloxacin, Linezolid, Delamanid, and Cycloserine.

After 2 months of treatment, the general condition improves significantly. The anti-bacillary drugs appear to be well tolerated, and the patient is still being monitored. Bacteriological control examinations for tuberculosis after 2 months show: direct examination after special Ziehl-Nielsen staining negative and GeneXpert MTB/RIF resulted in no detection of Mycobacterium Tuberculosis.

Discussion

Across the world, TB is still a serious public health issue that primarily affects underdeveloped nations [8]. Moreover, due in part to co-infection with HIV, its prevalence has increased in wealthy countries. According to the 2019 WHO report, there were 10 million new cases and 1.5 million fatalities [9]. TB typically affects the lungs or other organs on occasion (extrapulmonary). Tuberculous meningitis localization is rare. A significant obstacle to national, regional, and international TB control strategies is drug-resistant TB. Fluoroquinolones and aminoglycosides are two second-line antibacterials against which some MDR pathogens have established additional resistance mechanisms. Around 200,000 fatalities and 500,000 new cases of MDR-TB or rifampicin-resistant TB (RR-TB) are reported each year globally [10].

Tuberculous meningitis is a subacute meningeal condition, which presents itself in different stages: The first stage is characterized by nonspecific symptoms: subfebrileness, headache, irritability, drowsiness, malaise, vomiting, photophobia, apathy and low weight/weight loss. In infants, it can be present symptoms: stagnation/loss of landmarks in development, fever, cough, altered consciousness, and convulsions. Neck stiffness is characteristically absent. It lasts about 1-2 weeks. The presence of signs and symptoms nonspecific makes it difficult to suspect and diagnose TBM in the first stage. A history of contact with a patient with an active form of tuberculosis (~ 50% cases) can be also important.

The second stage is usually characterized by an onset suddenly, with the following signs: lethargy, stiffness of the neck, positive meningeal signs, hypertonia, convulsions, vomiting, and focal neurological deficit. Along the way, the development of hydrocephalus occurs, the increase in intracranial pressure, encephalitis with orientation/movement/ movement disorders speech, involvement of the cranial nerves (30% -50% cases), the most common - the VI-th nerve, and loss of vision. Next comes the third stage, in which the association takes place posture of decortication/decerebration, hemiplegia, coma, and possibly death [11].

Seizures are a rare symptom of TBM in adults, and their presence should encourage the doctor to rule out other conditions including cerebral tuberculoma or bacterial or viral meningitis. In contrast, seizures are a common symptom of TBM in children, occurring in up to 50% of pediatric cases. When allowed to progress without treatment, coma, and death almost always ensue. In survivors of TBM, neurologic sequelae may occur that include mental retardation in children, sensorineural hearing loss, hydrocephalus, cranial nerve palsies, stroke-associated lateralizing neurological deficits, seizures, and coma [12].

TBM diagnosis can be challenging, and it can not even be supported by conclusive microbiologic confirmation but simply by clinical and early cerebrospinal fluid (CSF) findings. The likelihood of TBM is increased by several clinical traits, including greater symptom duration (>six days), significant CSF pleocytosis, and the presence of localized impairments. The following are typical CSF findings of TBM: lymphocytic-predominant pleocytosis. Total white cell counts are usually between 100 and 500 cells/µL. Very early in the disease, lower counts and neutrophil predominance may be present, elevated protein levels, typically between 100 and 500 mg/dL, low glucose, usually less than 45 mg/dL, or CSF: plasma ratio <0.5 [5].

With the crucial caveat that a single sample has limited sensitivity, in the range of 20%-40%, a CSF sample should be sent for an acid-fast smear. For a microbiologic diagnosis, several daily large volumes (10-15 mL) of lumbar punctures are frequently required; four spinal taps raise sensitivity to >85% [13-14]. Even though culture has a low sensitivity (40-80%) and can take many weeks, it should be used to assess medication susceptibility. Important prognostic and therapeutic ramifications of drug-resistance strains include TBM caused by isoniazid- (INH-) resistant M. tuberculosis strains.

It is important to stress that a negative CSF test for M. tuberculosis DNA or acid-fast bacilli does not rule out the diagnosis of TBM or eliminate the need for empiric therapy if the clinical suspicion is high. Mycobacterial DNA may be detectable in the CSF for up to a month after treatment begins, although the sensitivity of CSF smear and culture rapidly declines following treatment [5].

Through numerous research, molecular biology has proven to be successful even on paucibacillary samples by enabling the identification and detection of anti-TB medication resistance. The World Health Organization (WHO) recommends the quick, automated GeneXpert MTB/RIF nucleic acid amplification test for the simultaneous identification of MTC and rifampicin resistance in pulmonary and extrapulmonary specimens. In cerebral spine fluid, it is more than 80% sensitive [15] In our case, GeneXpert MTB/RIF allowed the identification of MTC and detection of rifampicin resistance.

Neuroimaging can be useful in the diagnosis of TBM. Basal meningeal enlargement and hydrocephalus are typical TBM neuroradiologic characteristics [5]. There may also be nodular-enhancing lesions, cerebral edema, and hypodensities brought on by cerebral infarcts. The imaging test of choice for identifying TBM-related anomalies is magnetic resonance imaging (MRI), which is superior to computed tomography (CT) for assessing the brainstem and spine. Nonetheless, CT is sufficient for a quick assessment of hydrocephalus associated with TBM for potential surgical intervention.

The MTB-DR plus and MTB-DRsl genotyping assays, in addition to the GeneXpert MTB/RIF, enable the diagnosis of MTC from lung clinical specimens or cultured samples. Rifampicin and isoniazid resistance are detected using the MTBDRplus test [7]. The MTB-DRsl test is made to look for ethambutol resistance on the embB gene, fluoroquinolone resistance on the rrs gene, and aminoglycoside resistance on the gyrA gene. For the identification of resistance to rifampicin, isoniazid, fluoroquinolones, and aminoglycosides, the MTBDRplus test

and the MTBDRsl test have a sensitivity higher than 80% [16]. In our case, the CSF was positive by GeneXpert MTB/RIF with the detection of rifampicin resistance. The MTBDRplus test confirmed resistance to rifampicin and isoniazid and the MTBDRsl test showed additional resistance to Hydrazide, Ethionamide, Quinolone, Amikacin, Kanamycin, and Capreomycin.

Primary drug resistance is defined as resistance in a patient who has never received TB treatment. Antibacillary medication resistance can also be secondary. Mycobacterium tuberculosis treatment places selection pressure on the population, which causes a decline in susceptible bacilli, a rise in drug-resistant mutations, and the formation of drug resistance (acquired resistance). It seems safe to assume that our patient has acquired primary drug resistance by being in contact with her brother-in-law.

The WHO recommends a brief regimen of 9-11 months for treating MDR-TB in all of its variants, which comprises a 4-6 month loading phase with high doses of amikacin, moxifloxacin, ethionamide, clofazimine, pyrazinamide, ethambutol, and isoniazid. Patients are given moxifloxacin, clofazimine, pyrazinamide, and ethambutol during the maintenance phase. 2020 saw an update to the WHO's recommendations that short regimens without injectables be replaced with shorter regimens that incorporate bedaquiline. If the three drugs have never been combined before, 2019 WHO trial that the FDA approved suggests bedaquiline, linezolid, and pretomanide for 9 months to treat multiresistant tuberculosis or XDR-TB [16].

Pyrazinamide has excellent penetration into the CSF and is a key drug in reducing the total treatment time for drug-susceptible TB. Given that the newer generation fluoroquinolones, such as levofloxacin, and moxifloxacin, have excellent CSF penetration and safety profiles as well as strong effectiveness against the majority of M. tuberculosis strains, FQN would seem to have considerable potential as part of the first-line therapy for TBM. The addition of an FQN to the usual regimen improved anti-TB performance as determined by several clinical parameters in a randomized controlled study for the treatment of TBM. Although there was no significant difference in mortality, the study's power was probably insufficient to show such a relationship. Among new anti-TB agents, bedaquiline (TMC207, a diarylquinoline) and demand (OPC-67683, a nitro-dihydroimidazo-oxazole) appear to be the most promising drugs [17].

It is advised to assess therapy tolerance as well as conduct clinical, bacteriological, and radiological surveillance. The use of new anti-TB medications like linezolid and bedaquiline has helped the prognosis of MDR pulmonary and extrapulmonary TB. The availability of still-active molecules affects the treatment's effectiveness. Those with XDR-TB and HIV infection have had high mortality, nevertheless. The rise of MDR and XDR strains as well as their synergistic connection with TB may help to explain this [15].

Prognosis is influenced by the neurologic state at the time of presentation and the length of time until treatment begins heavily influences the prognosis for TBM. When the diagnosis of TBM is suspected, empiric treatment should start right once because any delay in treatment can exacerbate the prognosis, even though the course of TBM is typically not as fast or fulminant as meningitis caused by pyogenic bacteria. According to several case studies, the death rate ranges from 7% to 65% in industrialized nations and from up to 69% in impoverished regions [18-19]. Comorbidities, substantial neurologic involvement at admission, rapid disease progression, and advanced or very young age all increase the chance of death. Up to 50% of survivors experience neurologic aftereffects [20].

Conclusion

Tuberculous meningitis is a rare presentation of tuberculosis. Tardive symptoms often lead to delayed diagnosis and treatment. Through this case, we highlight the importance of gene amplification tests in effectively and rapidly managing this disease. Early diagnosis and treatment can significantly reduce the high death rate linked to this condition. Generally speaking, the course of treatment should last at least 18 months and include at least four medications known or suspected to be effective against the M. tuberculosis strain.

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