CASE REPORT

WHAT'S BEHIND A PROLONGED FEBRILE SYNDROME?

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Abstract: Infection with Mycobacterium tuberculosis continues to have a high prevalence worldwide, particularly among immunocompromised individuals, and can pose numerous diagnostic challenges. We report the case of a 49-year-old male with uncertain tuberculosis history, admitted for pain in the right iliac fossa and confusion. Also, the patient presented over the last year loss of appetite, significant weight loss and evening-onset fever. Despite pulmonary imaging findings suggestive of tuberculosis, the acid-fast bacilli smear taken from tracheal secretions obtained via bronchoscopy was negative. The neurological course was unpredictable; consequently, the patient developed gait disturbance, meningitis and subsequently, a stroke, accompanied by acute respiratory failure requiring orotracheal intubation, with a positive nucleic acid amplification test (NAAT) result. Thus, the final diagnosis was established as multisystemic tuberculosis with pulmonary and neurological involvement.

Keywords: *tuberculosis, acute respiratory failure, bronchoscopy.*

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1. Introduction

It is estimated that approximately 22% of the world's population is infected with Mycobacterium tuberculosis [1]. The lung is the organ most commonly affected by this bacteria. Extrapulmonary involvement occurs through hematogenous spread or lymphatic dissemination originating from the pulmonary focus [2].

Relevant clinical manifestations consist in cough lasting at least 2–3 weeks, hemoptysis, lymphadenopathy, weight loss, fatigue, fever and night sweats [3]. Other patients may have few or no symptoms at all and are classified as having subclinical tuberculosis [4].

The results of imaging tests, such as chest X-rays, are useful for establishing a preliminary diagnosis. A definitive diagnosis of pulmonary tuberculosis is confirmed when Koch's bacillus is isolated from a secretion or body fluid (e.g., sputum culture, bronchoalveolar lavage, or pleural fluid) or from tissue (e.g., pleural biopsy or lung biopsy) [5]. The following laboratory tests are used for this purpose: sputum acid-fast bacilli (AFB) smear and nucleic acid amplification testing (NAAT). A positive NAAT result (with or without a positive AFB smear) in a person at risk for tuberculosis (with no history of treatment for pulmonary tuberculosis) is considered sufficient for the diagnosis of TB [5].

2. Case presentation

We present the case of a 49-year-old male patient with a known medical history of umbilical hernia, active smoking, chronic

alcoholism, and uncertain TB background (the sputum smear test for AFB came back negative 20 years ago, but there are no medical records to confirm). He was admitted to the Department of Internal Medicine of the Clinical Emergency Hospital of Bucharest, Romania, presenting with pain in the right iliac fossa and confusion installed approximately three weeks previously. One week before being admitted to the Internal Medicine Department, the patient was admitted to the general surgery ward with suspicion of acute appendicitis, which was later ruled out.

It is worth noting that, over the past year, the patient has experienced the following symptoms: loss of appetite, occasional episodes of nausea and vomiting, significant weight loss and evening fever (380C). So far, the patient has not been prescribed any long-term medical treatment.

On physical examination, the patient appeared lethargic, cachectic, with a body mass index (BMI) of 15 kg/m2, with high fever (390C). He had pale, dehydrated skin, as well as a hypotonic and hypokinetic musculoskeletal system. Upon examination of the pulmonary system, we detected crackles in the lower third of the right lung field and the peripheral oxygen saturation (SpO_2) was 98% on room air at rest. The patient had tachycardia (with a heart rate of 110 bpm) with rhythmic heart sounds, without detectable heart murmurs, and a normal blood pressure (110/70 mmHg). The patient presented with spontaneous abdominal pain and tenderness in the right iliac fossa, with no signs of peritoneal irritation. He had hepatomegaly that was painless on palpation and a normal spleen. The urinary tract examination was normal. Regarding neurological status, the patient was mildly temporospatially disoriented, but had no focal neurological signs and no signs of meningeal irritation.

With regard to the laboratory tests performed upon admission, there were noted mild normochromic normocytic anemia with a hemoglobin of 11.48 g/dL, leukocytosis (11,170/mm3) with neutrophilia (9440/mm3) and low inflammatory syndrome with high C-reactive protein (14.11 mg/L) and high fibrinogen (426 mg/dL). Moderate hyponatremia was also observed, with a serum sodium level of 127 mmol/L. Two sets of blood cultures were collected, both of which came back negative. The urine culture also came back negative. The following viral markers were negative: hepatitis C virus (HCV) antibodies, HIV antibodies and hepatitis B surface antigen. The electrocardiogram showed only sinus tachycardia.

With regard to imaging studies, transthoracic echocardiography showed normal data, with the exception of a few valvular abnormalities without hemodynamic impact: mild tricuspid regurgitation, mild mitral regurgitation and a thin layer of pericardial fluid of 11mm. The anteroposterior abdominal X-ray showed normal results. The chest X-ray (Fig. 1) revealed a pseudomacronodular opacity of costal intensity, with a heterogeneous structure and irregular margins, located in the middle third of the right lung, with associated alveolar foci, reticular opacities and band-like opacities.

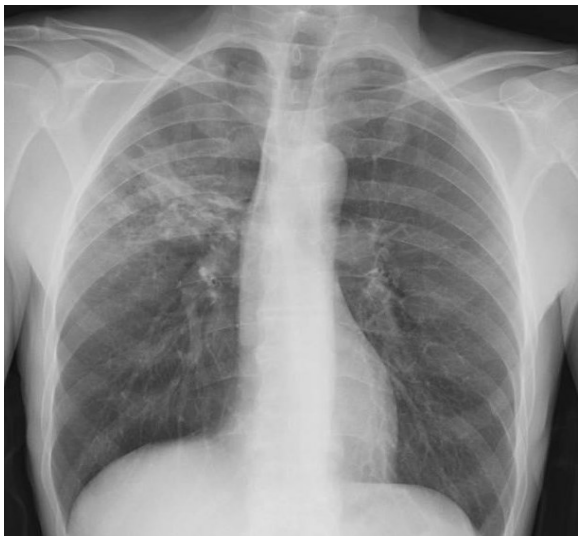

Fig. 1. Chest X-ray: pseudomacronodular opacity of the right lung

At this point, we have formulated the following interim diagnoses: right middle lobe consolidation under observation, mild normochromic normocytic anemia, pericardial effusion and moderate hyponatremia.

Furthermore, to obtain a comprehensive imaging evaluation, a contrast-enhanced CT scan of the thoracoabdominal and pelvic

regions was performed. There were observed areas of pulmonary consolidation with air bronchogram and central microcalcifications of the right lung. In the periphery, multiple interstitial micronodules were observed that tend to coalesce, giving a "tree-in-bud" appearance (Fig. 2).

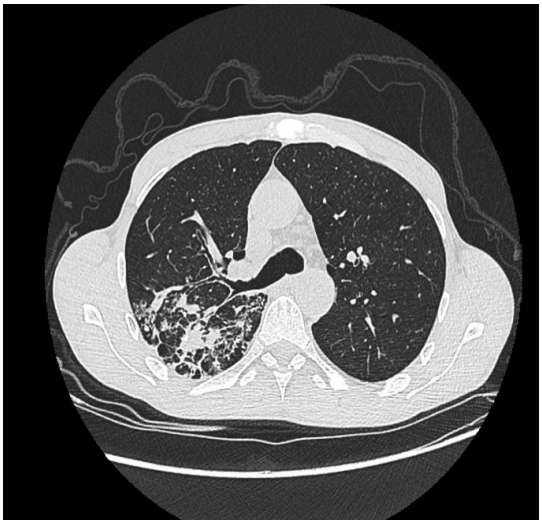

Fig. 2. Chest CT scan: tree-in-bud pattern

In addition, the CT scan revealed that the terminal ileum and the ileocecal valve had thickened walls along their entire circumference and an edematous appearance of the submucosa (Fig. 3). In addition, contrast uptake was observed posterior to the thoracic spinal cord during the venous phase.

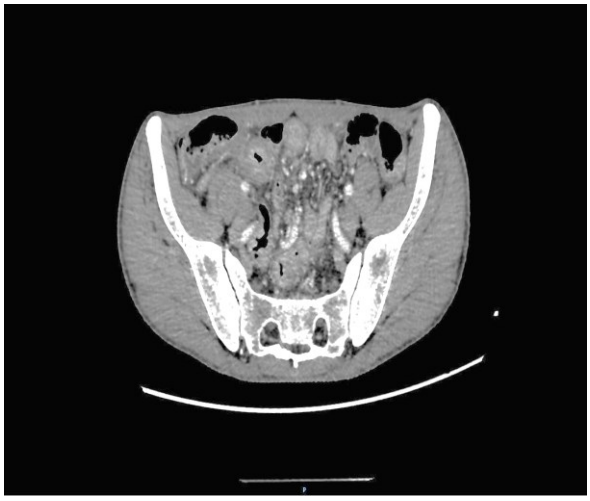

Fig. 3. CT scan: edematous appearance of the submucosa of the ileocecal valve

To investigate the confusion syndrome, a native brain CT scan was performed, which showed no findings suggestive of acute ischemia, hemorrhagic lesions or tumor masses.

Based on a review of the current clinical, laboratory, and imaging data, the suspicion of Mycobacterium tuberculosis infection affecting the digestive tract and lungs has arisen. In addition, the bronchoscopy revealed a normal macroscopic appearance of the upper and lower airways, so no biopsy samples were necessary. The Ziehl-Neelsen stain performed on the secretion obtained by bronchial lavage was negative for AFB. On the other hand, the bacterium Stenotrophomonas maltophilia was detected at a concentration of 80,000 colony-forming units (CFU)/mL, susceptible to levofloxacin.

Functional examinations of the digestive tract were performed; on one hand, the gastrointestinal endoscopy revealed erythematous gastroduodenitis. On the other hand, the colonoscopy revealed localized hyperemia and edema of the ileocecal valve mucosa, which prevented the conventional colonoscope from advancing further, so biopsies could not be taken.

Clinically, the confusional syndrome progressively worsened, a finding that could not be explained by the presence of hyponatremia, which responded partially to treatment, with variations in serum sodium of up to 8 mmol/L over a 24-hour period.

Eight days after admission, the patient developed gait disturbance, so a neurological consultation was requested. The following findings were observed: ataxic paraparesis of the lower extremities and absent osteotendinous reflexes in those extremities, paresthesia and hypoesthesia at the T7-T8 sensory level, but without any sign of meningeal irritation. Subsequently, the patient underwent contrast-enhanced magnetic resonance imaging of the cervicothoracic region, which revealed an arteriovenous fistula with perimedullary venous dilations; however, the feeding artery could not be identified. Therefore, the lumbar puncture was contraindicated. In addition, an intramedullary signal was observed in the anterior and posterior horns at the T4-T5

level, indicating possible intramedullary ischemia.

Up to this point, the patient had received empirical antibiotic therapy with piperacillin-tazobactam, 4,5 g every 8 hours, but the febrile syndrome persisted. Consequently, metronidazole, 500 mg every 12 hours and linezolid, 600 mg every 12 hours were added, resulting in remission of the febrile syndrome. Subsequently, the patient developed neck stiffness, raising suspicion of tuberculous meningitis; based on the infectious disease consultation, emergency antituberculosis therapy was initiated: isoniazid 100 mg/day, rifampin 500 mg/day, ethambutol 750 mg/day, pyrazinamide 1250 mg/day.

From a neurological standpoint, the patient's condition continued to worsen, manifesting as mixed aphasia with mutism, paraplegia of the lower limbs, and acute respiratory failure, with an SpO_2 of 70% in room air at rest. A contrast-enhanced CT scan of the brain revealed a subacute infarction in the left internal capsule. Given the severe respiratory failure, the intervention by colleagues from the intensive care unit was necessary. Non-invasive mechanical ventilation using the BiPAP mode was initially attempted, but without success. Subsequently, orotracheal intubation was performed, and vasopressor support with norepinephrine was initiated. Tracheal secretions were collected with difficulty, as they were present in very small quantities; the PCR test for Mycobacterium tuberculosis was positive.

The patient's condition progressively deteriorated, with exitus.

The final positive diagnosis was: Cardiac arrest unresponsive to resuscitation maneuvers, Acute hypoxemic-hypercapnic respiratory failure requiring orotracheal intubation, Pulmonary, neurological, and gastrointestinal septic shock, Systemic tuberculosis with multiple sites of involvement: pulmonary, neurological, and gastrointestinal, Left-sided internal capsule ischemic stroke, Cachexia, Chronic smoking and Chronic alcoholism.

3. Discussion

Miliary tuberculosis refers to a clinical condition resulting from the lymphohematogenous spread of Mycobacterium tuberculosis from the lungs, which manifests as the classic nodular appearance observed on X-ray or histopathological examination, resembling millet seeds; it can affect multiple organs and includes both pulmonary and extrapulmonary lesions [6].

The following risk factors are associated with the development of miliary tuberculosis: extreme ages and certain medical conditions, such as alcohol use disorder, malignancy, HIV infection, immunosuppression (corticosteroids, TNF-alpha–blocking agents, and other immunosuppressive agents), connective tissue disease (with or without iatrogenic immunosuppression), kidney failure, diabetes, pregnancy and solid organ or tissue transplantation [6].

Most patients with miliary tuberculosis have lung involvement, with the following symptoms: cough, shortness of breath and rales or rhonchi on physical examination [7].

Among the most common extrapulmonary sites are the lymphatic system, bones and joints, the liver, the central nervous system (CNS), and the adrenal glands [8]. When the liver is affected, the following symptoms may occur: diffuse abdominal pain or pain localized in the right upper quadrant, nausea, vomiting, and diarrhea [9]. If the peritoneum is involved, the patient presents with ascites, fever, abdominal pain and fatigue.

Tuberculosis of the CNS can present in the following forms: meningitis, tuberculoma, spinal arachnoiditis, and transverse myelitis [10]. Patients with tuberculous meningitis typically experience headaches, fever, vomiting, and altered consciousness [11]. There are three stages of illness based on mental status and neurologic signs [12]: Stage I – Alert and oriented with no focal neurologic signs, Stage II – Conscious but with confusion, lethargy, with or without mild focal signs such as cranial nerve palsies or hemiparesis, Stage III – Advanced illness with delirium, stupor, coma, seizures,

multiple cranial nerve palsies, and/or dense hemiplegia. Some patients may present with atypical features that mimic other neurologic conditions [13].
The complications of tuberculous meningitis include stroke with hemiplegia [14], seizures (generally focal), hydrocephalus, hyponatremia, vision loss and transverse myelitis.

CONCLUSIONS

This case highlights the difficulty of diagnosing tuberculosis in a young patient with a limited personal medical history who sought medical care late. The final diagnosis of multisystem tuberculosis with pulmonary and cerebral involvement was established late, as the patient presented with minimal respiratory symptoms and a small amount of sputum; furthermore, the presence of an arteriovenous fistula in the cervicothoracic region constituted a contraindication for performing a lumbar puncture. The prognosis was extremely poor given the neurological complications accompanied by severe respiratory failure, which ultimately led to exitus.

Author contributions:

M.P. and C.C.D. conceived the original draft preparation. M.P. and C.L.T. were responsible for the data acquisition, collection and assembly of the articles. M.P., C.L.T. and C.C.D. were responsible for the conception and design. C.C.D. and C.L.T. were responsible with the supervision of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law."

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