CASE REPORT

Beyond the Obvious: Unveiling the Diagnosis When Symptoms Mislead

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Abstract. *Persistent inflammatory syndrome is a frequently encountered and challenging condition in internal medicine. In cases when a definitive diagnosis is not established, this disease necessitates a thorough diagnostic approach to rule out infections, autoimmune disorders, and cancers.*
Case presentation: *We present the case of an asymptomatic patient hospitalized with a significant inflammatory syndrome, in whom initial infection screening failed to reveal any diagnosis that might account for the biological abnormalities. In the lack of a diagnosis and the persistence of the inflammatory condition despite broad-spectrum antibiotic therapy, computed tomography examination of the chest, abdomen, and pelvis with contrast substance was performed, which identified a lung lesion with malignant features. The diagnostic management continued by bronchoscopy, bronchoalveolar lavage, and cytological, bacteriological, and molecular examinations, which revealed the presence of Mycobacterium tuberculosis.*
Conclusions: *This case contributes to the understanding of tuberculosis as an "oncologic mimic" in cases of unexplained prolonged inflammatory syndrome, underscor the value of rigorous diagnostic approaches in atypical presentations and emphasizing the diagnostic vigilance required in patients with risk factors for this infectious disease.*

Keywords: *persistent inflammatory syndrome, tuberculosis, diagnosis, oncological mimic*

1.INTRODUCTION

Tuberculosis (TB) remains a significant global health challenge, with recent reports highlighting the resurgence of the disease as the leading infectious cause of mortality worldwide [1]. According to the 2024 global tuberculosis report by the World Health Organization (WHO), the number of new cases reached 8.2 million in 2023, a stark increase from previous years [1]. In 2023, 55% of individuals diagnosed with tuberculosis were male, 33% female, and 12% children and early adolescents [1]. This trend places this disease at the forefront of global health concerns, surpassing even COVID-19 in its impact on public health [1]. The same report also emphasizes the disproportionate burden experienced by low- and middle-income countries, which account for 98% of the global tuberculosis cases [1]. Socioeconomic factors, including poverty, inadequate healthcare infrastructure, malnutrition, and comorbidities such as

human immunodeficiency virus (HIV) infection and diabetes, substantially increase the prevalence of tuberculosis in these areas, leading to delayed diagnosis and treatment [1-2]. Therefore, numerous new tuberculosis cases can be ascribed to five risk factors: malnutrition, HIV infection, alcohol use disorders, smoking (particularly among men), and diabetes [1].

Approximately 10% of tuberculosis infections are associated with alcohol usage, which adversely affects the immune system at multiple phases of infection [4]. Initially, the host's cellular immunity is compromised by alcohol consumption, which elevates the likelihood of contracting Koch's bacillus [4]. Additionally, the reactivation of latent infections and the progression of active tuberculosis may be facilitated by alcohol consumption [4,5].

The complexity of tuberculosis diagnosis is further heightened by its atypical presentations, especially in instances of asymptomatic patients [6]. Such cases frequently exhibit persistent inflammatory markers but lack the conventional clinical symptoms or radiological evidence of infection, confounding the diagnosis process [6,7]. In economically advanced nations, infectious causes of chronic inflammation have diminished; however, in low-income regions, this pathogenic mechanism remains a substantial factor for these biological abnormalities [6].

Due to the increased incidence of tuberculosis in low-income regions, healthcare providers should regard it as a possible etiology when encountering unexplained inflammation [7]. The diagnosis of tuberculosis is frequently delayed in patients with good functional status. This delay could be caused by clinicians failing to suspect pulmonary tuberculosis due to uncommon symptoms, a lack of expertise, or relying on initial negative chest X-rays, which may not detect the infection in its early stages [6,7].

2.CASE PRESENTATION

A 58-year-old male patient with a history of chronic alcohol intake and 30 pack-years of smoking, but no notable medical history, presented to the emergency department following an accidental ground-level fall. The patient reported marked fatigue but denied experiencing fever, cough, or chills.

The initial clinical examination revealed an altered general condition and cachexia. He was somnolent, temporospatially disoriented, and displayed bradypsychia and bradylalia. The physical examination further revealed signs of dehydration, including dry skin and mucous membranes, as well as dystrophic changes in the nails and hair. The respiratory examination showed normally conformed chest with bilateral vesicular breath sounds and no additional pulmonary sounds. His peripheral oxygen saturation was 95% in ambient air, indicating sufficient baseline oxygenation. The cardiovascular examination revealed regular heart sounds, a holosystolic murmur in the mitral area, radiating to left axilla, and a systolic murmur, graded II/III, in the aortic region, spreading to the carotid arteries. The patient lacked signs of peripheral congestion; the peripheral pulses were detectable. The abdominal examination indicated a non-tender abdomen with normal breathing movement. Bowel sounds were audible, and the stool's appearance was normal. The bilateral Giordano's maneuver was negative, with physiological urination.

At admission, the laboratory tests revealed leukocytosis with neutrophilia (leukocytes 17170/mm^3), moderate to severe normochromic normocytic anemia (hemoglobin 7.78 g/dL), inflammatory syndrome (C-reactive protein (CRP) 45.20 mg/dL), hypoglycemia (glycemia 70 mg/dL), mild hepatic cytolysis syndrome (aspartate aminotranspherase (AST) 93.4 IU/L), hypoproteinemia with hypoalbuminemia (total serum proteins 5.8 g/dL, serum albumin 2.47 g/dL), and mild hypokalemia

(potassium 3.14 mmol/L). Arterial blood gas (ABG) and urinalysis revealed no substantial pathological modifications, and the urine culture was negative.

The electrocardiogram (ECG) revealed sinus rhythm with heart rate of 50 beats per minute, QRS axis of -75 degrees, and signs of left ventricular hypertrophy (Sokolow-Lyon index 44 mm), with no significant changes in the ST segments and T waves.

Chest X-ray was conducted, and no pathological changes were identified. We also conducted serological tests to evaluate the presence of an HIV and hepatitis B and C virus infections in light of the precarious socioeconomic status of the patient. The results of these investigations were negative.

Immediately upon admission, broad-spectrum antibiotic therapy with ceftriaxone was initiated. The infectious diseases physician chose to enhance the treatment regimen by combining sumetrolim/sulfamethoxazole and piperacillin/tazobactam, because of increasing inflammatory markers. Surprisingly, the inflammatory syndrome persisted despite the administration of this antibiotic regimen,

At this moment, we considered the possibility of endocarditis and initially conducted transthoracic echocardiography, which was unable to exclude the presence of vegetations. Consequently, we proceeded with diagnostic management using transesophageal echocardiography, which ruled out endocarditis but revealed a bicuspid aortic valve, accompanied by mild aortic regurgitation. We also noted mild mitral regurgitation and mild-to-moderate tricuspid regurgitation. This investigation also reported an intact interventricular septum and patent foramen ovale with left-to-right shunt; mild diffuse hypokinesis of the left ventricle with normal contractility of the right ventricle; ectasia of the ascending aorta; and absence of pericardial effusion. In the lack of a diagnosis thus far, a contrast-enhanced computed tomography (CT) examination of the chest, abdomen, and pelvis was conducted, which revealed a 6/13 mm pulmonary nodule located in the apical segment of the right lower lobe, with spiculated margins, retractile effect on the oblique fissure and adjacent pleura, and non-homogeneous iodophilicity (Figure 1). This lesion strongly indicates a malignant tumor, although allows for a differential diagnosis of a tuberculous granuloma.

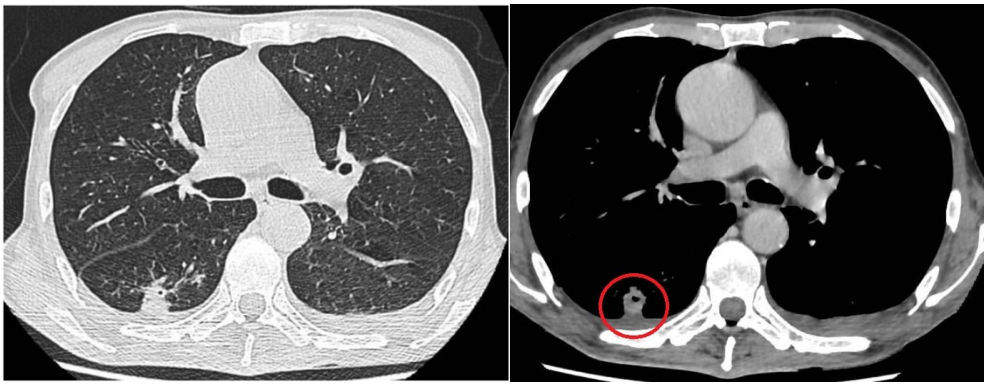

Figure 1. Pulmonary nodule in the lower lobe of the right lung (LID), measuring 16/13 mm, with spiculated margins, retraction effect on the oblique fissure and adjacent pleura, and non-heterogeneous iodophilicity.

The CT examination of the thorax also revealed minor centrilobular emphysema bilaterally, predominantly in the upper lobes; no definitive pathological lymphadenopathy in the axillary or mediastinal regions or in the pulmonary hila; an ectatic ascending aorta with a maximum diameter of 45 mm; the pulmonary trunk, right and left pulmonary arteries, and their branches exhibit normal caliber, homogeneous opacification, and

absence of intraluminal thrombi; calcifications present in the thoracic aorta wall; bilateral pleural effusion in minimal quantities, measuring 19 mm on the right and 6 mm on the left.

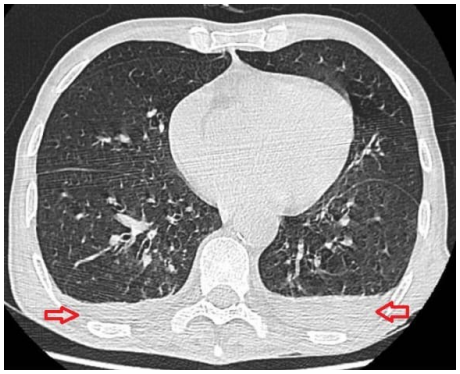

Figure 2. Bilateral pleural effusion in minimal quantities, measuring 19 mm on the right and 6 mm on the left.

The CT examination of the abdomen highlighted the liver with a maximum diameter of 19 cm, regular surface, and no primary or secondary focal lesions. Additionally, the gallbladder exhibited thin walls and no hyperdense stones, and the intrahepatic and extrahepatic bile ducts were not dilated. The spleno-portal-mesenteric venous axis was permeable and had a normal caliber. The spleen had an diameter of 12 cm and a regular surface. There were no focal lesions. The left adrenal gland had a maximal diameter of 15 mm and no tumors. The pancreas, right adrenal gland, and kidneys appeared normal on CT. The urinary bladder was semi-distended. The prostate had no CT-specific abnormalities. The colon and rectal ampulla showed no visible tumors. There was a small amount of peritoneal fluid in the rectovesical and pelvic recesses, with a maximum thickness of 15 mm. There was a lateral aortic lymphadenopathy of 10/7 mm. The abdominal aorta displayed mixed plaques, both calcified and soft. The celiac trunk showed homogeneous opacification. The superior mesenteric artery had a soft plaque at 18 mm from the origin, extending 20 mm in length and obstructing approximately 70% of the cross-sectional area. A partially occlusive mixed plaque was located immediately distal to the emergence of the right renal artery. We noted mixed plaques along the common iliac arteries bilaterally, the left external iliac artery, and the internal iliac arteries bilaterally. An occlusive thrombus extended distally along the common femoral artery and superficially on the right side of the right external iliac artery, without any visible reperfusion in the scanned sections. Collateral circulation originating from the right internal iliac system reperfused the right deep femoral artery.

Subsequently, we attempted to get sputum samples for Ziehl-Neelsen smear and cultures; however, the patient's noncompliance precluded their collection. In these conditions, we decided to perform bronchoscopy with bronchoalveolar lavage and submit the specimens for cytological and bacteriological analysis and GeneXpert testing. The cytological examination excluded the presence of malignant cells, but the GeneXpert test confirmed the presence of *Mycobacterium tuberculosis*. Consequently, we confirmed the diagnosis of pulmonary tuberculosis and referred the patient to a pneumophthisiology clinic for specialized treatment.

3.DISCUSSION

The particularity of our clinical case is represented by the occurrence of pulmonary tuberculosis in an asymptomatic patient, exhibiting no pathological abnormalities on chest radiography, although contrast-enhanced chest CT identified a pulmonary nodule with malignant features in the right lower lobe. This

highlights the diagnostic difficulties presented by specific infectious lesions that may resemble cancer, especially in geographical areas with high tuberculosis endemicity.

The diagnosis and distinction of masses depend on parameters like location, size, form, lobulation, border features, density, and enhancement patterns. CT image analysis entails establishing a preliminary diagnosis based on mass characteristics; nonetheless, this method is significantly reliant on the clinician's expertise. The evaluation of these indications is subjective, often inconsistent, and lacking verified quantitative measurements, leading to disparate diagnosis accuracy. Thus, an unequivocal diagnosis generally requires pathological confirmation by biopsy [9].

Tuberculosis-induced lesions are typically situated in the apical lobes, which is a key imaging characteristic for diagnosis. Fibrous cords or protruding caseous nodules often fuse to form the mass's edge, and lobed structures are frequently visible. Tuberculosis tends to spread via the bronchi, with satellite foci often surrounding the nodules or masses. Calcification is a common complication, typically found around areas of caseous necrosis and the walls of cavities. The enhancement pattern generally exhibits no enhancement or minimal enhancement in the central necrotic region, whereas the granulation tissue presents as a ring surrounding it, with the inner margin of the necrotic area remaining smooth [9,11].

In the literature, there are many cases of both pulmonary and extrapulmonary tuberculosis where the infectious pathology resembled a tumor [12,13]. In about one-third of case reports tuberculosis and malignancies were misidentified during initial clinical evaluation [12]. Particular circumstances in which tuberculosis should be considered in the differential diagnosis encompass pulmonary nodules, pancreatic tumors, and ovarian lesions [12]. In addition to a singular neoplasm that may resemble a tuberculosis granuloma, there are case reports in the literature in whom tuberculosis had also imitated a Pancoast-Tobias tumor, presenting a range of symptoms attributable to the lesion's location, including tingling and pain in the shoulder, radiating to the scapula [14]. Nonetheless, these instances underscore the diverse clinical manifestations of this disease, necessitating comprehensive diagnostic evaluation.

While current imaging techniques like positron emission tomography (PET)/CT scans improve evaluation capabilities, they can also be misleading [12,15]. Therefore, a trained pathologist must conduct a histological examination for a defined diagnosis to prevent unnecessary extensive procedures and related postoperative complications [12]. Even histological and cytological findings must be interpreted cautiously, as active pulmonary tuberculosis can yield atypical sputum with inflammatory cells, small histiocytes, and occasionally giant cells with necrotic debris, while extrapulmonary tuberculosis may present with necrotic debris and neutrophils without granuloma formation [16-18]. Rapid diagnostic methods, such as polymerase chain reaction (PCR) for *Mycobacterium tuberculosis*, should be part of the diagnostic process. Rigorous histological verification and microbiological testing are essential to reduce the risk of misdiagnosis and subsequent incorrect treatment [12].

4.CONCLUSIONS

Contrary to widespread belief, tuberculosis is not exclusively a condition that affects individuals with a precarious socio-economic status. In medical clinics, the differential diagnosis between neoplasia and tuberculosis is often a matter of concern. Clinicians must maintain a high index of suspicion for cryptogenic inflammatory syndromes to minimize unnecessary medical interventions. Additionally, tuberculosis screening should be improved, as this ancient infectious disease does not discriminate based on socio-economic status.

Author Contributions:

V.A.I., G.G., A.B.D. were responsible for the diagnostic procedures, clinical diagnosis, and treatment decisions. A.M.B., A.B., E.R.B., A.A.B., M.A.B., I.M.B., A.B.D. and B.B. wrote the manuscript. V.A.I, C.L.T. and G.G. were

responsible for the data acquisition, collection and assembly of the articles. C.C.D. was responsible for the supervision. All authors have read and agreed to the published version 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. Informed consent was obtained from the patient included in the study"

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