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One Pleural Effusion, Two Diagnoses: Tuberculosis and Pleural CLL

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Abstract
Background: Pleural effusion in a patient with chronic lymphocytic leukemia (CLL) is a complex diagnostic problem, which may result from infection, pleural infiltration, lymphatic obstruction, or an intercurrent condition. Tuberculosis, frequent in immunocompromised patients, can coexist with lymphoproliferative pleural involvement and constitute a genuine diagnostic pitfall.
Methods: We report a case documented by pleural fluid analysis, two successive pleural biopsies with histological and immunohistochemical study, a GeneXpert MTB/RIF molecular test, CT pulmonary angiography, and clinical, biological and radiological follow-up over six months.
Results: A 62-year-old man, followed for chronic hepatitis B and CLL under surveillance, was admitted for a lymphocyte-predominant exudative left pleural effusion. A first biopsy showed a caseous granuloma, leading to a diagnosis of pleural tuberculosis and antituberculous treatment. At one and a half months, acute respiratory distress revealed a proximal right pulmonary artery embolism, bicytopenia (hemoglobin 8 g/dL, platelets 67,000/mm³), and progressing lymphadenopathy. A second biopsy showed a B-lymphoid infiltrate (CD20, CD5, CD23, BCL2) consistent with pleural CLL involvement, while GeneXpert remained positive, confirming persistent tuberculosis. Outcome was favorable at six months with continued treatment and anticoagulation, with complete radiological clearing.
Conclusion: A documented pleural tuberculosis should not lead to overlooking a second etiology in a patient with CLL. Any worsening despite well-conducted treatment requires rigorous diagnostic reassessment.

Keywords: *chronic lymphocytic leukemia; pleural tuberculosis; leukemic infiltration; GeneXpert; lymphocytic pleural effusion; diagnostic dilemma.*

I. Introduction

CLL, a clonal proliferation of mature B lymphocytes (CD19, CD5, CD23) that are functionally incompetent, is associated with progressive immunodeficiency (hypogammaglobulinemia, T-cell dysfunction, impaired innate immunity), exposing patients to an increased infectious risk, including tuberculosis (2- to 9-fold higher than the general population) [1,2]. Pleural effusion in the course of CLL may result from direct infiltration, lymphatic obstruction, infection, or a second cancer [1,3]. The coexistence of pleural tuberculosis and lymphoproliferative pleural involvement is rare but exposes clinicians to a genuine diagnostic pitfall, as either condition alone can account for the clinical picture.

II. Case Report

A 62-year-old man, followed for two years for chronic hepatitis B on tenofovir and for CLL under simple surveillance, with a known family tuberculosis contact, presented with progressively worsening mMRC grade IV dyspnea over three weeks, associated with a dry cough, left-sided pleuritic chest pain, and marked general deterioration. Imaging showed a large left pleural effusion; the fluid was a lymphocyte-predominant exudate. A first pleural biopsy showed an epithelioid and giant-cell granuloma with caseous necrosis: a diagnosis of pleural tuberculosis was retained and antituberculous treatment was started.

At one and a half months of treatment, the patient developed acute respiratory distress with a left "white lung" appearance (Figure 1); CT pulmonary angiography showed a proximal right pulmonary artery embolism associated with bilateral pulmonary nodules and micronodules (Figure 2). Biological worsening was also noted, with bicytopenia consisting of anemia at 8 g/dL and thrombocytopenia at 67,000/mm³, markedly more pronounced than at initial admission, together with clinical and radiological worsening and progression of lymphadenopathy, prompting reconsideration of the initial diagnosis. A second pleural biopsy revealed infiltration by a small B-cell lymphoid proliferation expressing CD20, CD5, CD23 and BCL2, consistent with pleural involvement by CLL. Xpert MTB/RIF performed on the same specimen

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remained positive, without rifampicin resistance, confirming the persistence of an active tuberculous component.

Figure 1. Chest radiograph: left "white lung" appearance.

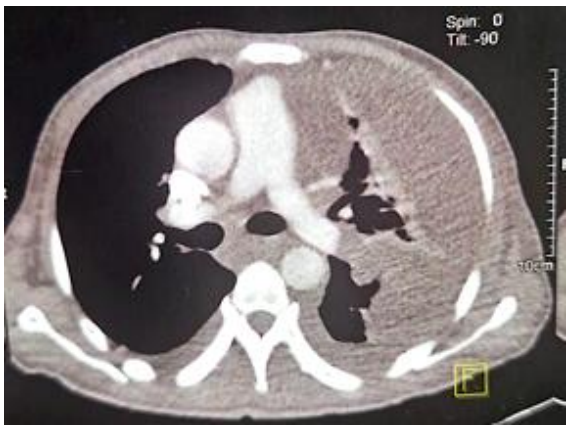
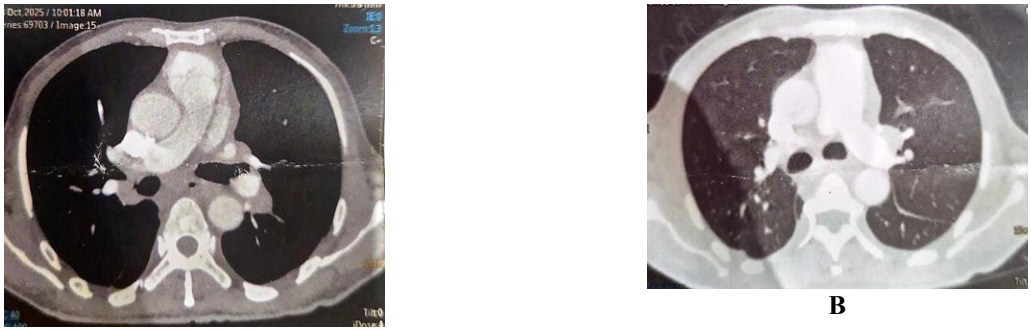


Figure 2. CT angiogram: right pulmonary artery embolism and left pleural effusion.

Antituberculous treatment was continued and therapeutic anticoagulation was started for the pulmonary embolism. At six months, the outcome was favorable: complete resolution of the pleural effusion, disappearance of the pulmonary nodules, and complete radiological clearing (Figure 3).



A **B**

Figure 3. Follow-up chest CT (A, B): complete radiological clearing.

III. Discussion

This observation must first be placed in its epidemiological context. In a tuberculosis-endemic area such as Morocco, where the incidence of all forms is close to 98 cases per 100,000 population [5], and in a patient whose hematologic malignancy raises the risk of active tuberculosis two- to nine-fold [2], this diagnosis was a priori the most probable hypothesis for a lymphocyte-predominant exudative pleural effusion. Direct pleural involvement by CLL is, conversely, a rare event, affecting only about 4% of patients during their disease course [4], far below the 20–30% reported in lymphomas [3]. It is precisely this asymmetry in frequency that makes the coexistence of the two conditions, confirmed here on a single specimen, so remarkable: to our knowledge, the literature reports no formally documented equivalent for CLL, comparable tuberculosis–lymphoid malignancy associations being limited to rare cases involving Hodgkin lymphoma [6,7].

The decision to perform a second pleural biopsy, rather than a repeat thoracentesis, followed a precise diagnostic rationale. Xpert MTB/RIF, poorly sensitive on pleural fluid owing to the paucibacillary nature of the effusion (pooled sensitivity of around 20%), performs markedly better on tissue, where sensitivity can exceed 80% [8,9]. The clinical and biological worsening despite well-conducted treatment therefore warranted rebiopsying the pleura rather than repeating fluid sampling, which allowed simultaneous molecular and histological confirmation of both conditions on the same specimen.

This dual etiology had a major therapeutic consequence: despite progression of the hematologic malignancy, no CLL-specific treatment could be

introduced as long as rifampicin was being administered. As a potent CYP3A4 inducer, rifampicin reduces ibrutinib exposure by a factor of ten to thirteen [10] and formally contraindicates the initiation of venetoclax [11] — two agents that are nonetheless central to first-line CLL therapy. The pulmonary embolism that occurred during the course of the disease, for its part, illustrates the convergence of two independent prothrombotic states: the well-documented one linked to the systemic inflammation of active tuberculosis [12], and the one intrinsic to CLL itself, recognized as an independent risk factor for venous thromboembolism [13]. Overall, this observation is a reminder that a diagnosis, however solidly established, never dispenses with sustained clinical vigilance, which alone can uncover an underlying second pathology.

IV. Conclusion

In a patient with CLL, a documented pleural tuberculosis should not lead to overlooking a second etiology. Any clinical, biological, or radiological worsening despite well-conducted antituberculous treatment requires a rigorous diagnostic reassessment, if necessary through a new tissue biopsy.

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