Antiphospholipid syndrome and protein C deficiency in a patient with pulmonary tuberculosis

Maria Alejandra Velasquez Castañeda, Diana Carolina Concha Galan, Camilo Ernesto Barros Gutierrez

ABSTRACT
Tuberculosis is an infectious disease of long standing which has been described and typified looking for an effective treatment yet with an unusual presentation if it is expressed by hematological disorders concomitant with antiphospholipid syndrome in a person of the male gender. It can be considered that these two pathologies share a link in their pathophysiology. We present the case of a young adult patient with the presence of deep vein thrombosis of the extensive lower limb with subsequent finding of antiphospholipid syndrome and pulmonary tuberculosis with clinical improvement and resolution of the two conditions after treatment for tuberculosis and anticoagulation during treatment.

Keywords: Antiphospholipid syndrome, Pulmonary tuberculosis, Thrombosis

INTRODUCTION
Tuberculosis is a disease caused by alcohol-resistant bacillus *Mycobacterium tuberculosis* [1]. It remains endemic in Latin America despite medical work for treatment and cure [2]. In Colombia, during 2017, tuberculosis caused an estimated 1.3 million deaths worldwide, it is estimated that 10.0 million people developed tuberculosis disease [3], considered responsible for a large burden of disease and mortality [1]. Pulmonary tuberculosis is the main clinical presentation of tuberculosis worldwide. Approximately 20% of tuberculosis is extrapulmonary in the immunocompetent patient [4]. The presence of infection by the tubercle bacillus has been related to hematological alterations in some cases [5] with low prevalence, which conditions a limited knowledge about the relationship between these two entities.

CASE REPORT
We present a case of a 37-year-old patient who was admitted to the internal medicine unit for 15 days of: nocturnal diaphoresis and cough with expectoration and weight loss. He mentioned a history of extensive deep vein thrombosis of the external iliac, femoral, and calf in medical management with Dabigatran 110 mg every 12 hours for two months. Chest X-ray and tomography showed inferior right subpleural nodule and the presence of cavitary lung lesion in the left lower lobe (Figures 1 and 2). Clinical findings were compatible with pulmonary tuberculosis. A polymerase chain reaction was taken for *M. tuberculosis* in sputum. There was unfavorable progression of the patient, presenting hemoptysis, tachycardia, and high flow oxygen therapy requiring treatment intensive care unit. Pulmonary thromboembolism was suspected and confirmed with chest angiography.
Coagulopathy study was performed finding protein C deficiency and the presence of anticardiolipin antibodies (IgG), positive Beta 2 glycoprotein (IgG) (Table 1). Positive polymerase chain reaction report was received for multisensitive tuberculosis and chest computed tomography (CT) findings compatible with pulmonary tuberculosis (Figure 3). Enzyme-linked immunosorbent assay (ELISA) test for human immunodeficiency virus (HIV) was negative. Tetraconjugate treatment (isoniazid 75 mg + rifampicin 150 mg + pyrazinamide 40 mg + ethambutol 275 mg) was started for six months, as well as treatment with fondaparinux 7.5 mg/day, given the presence of severe thrombocytopenia, which resolved after the start of antituberculous treatment.

**DISCUSSION**

Tuberculosis is a systemic, ancient disease that dates from the beginning of the fifth century, reporting cases of blood-clogging patients described in clay tablets. Toward the 19th century Robert Koch describes the tubercle bacillus as a bacterium and its diagnosis through acid alcohol staining [6] diagnostic technique improved by Ziehl and Neelsen, staining that is used up to now. By the year of 1895 Conrad Roentgen provides another diagnostic method with the arrival of X-rays [5].

Its initial treatment was taking the patient outdoors, receiving the sunlight, and a balanced diet [7] after the development of drugs: streptomycin in 1943, isoniazid in 1952, and rifampicin in 1965. The concept of chemotherapy was established, showing an effective treatment for the eradication of the tubercle bacillus [5].

The current treatment is directed according to the pattern of resistance of the pathogen, which is divided into two phases, the first phase where treatment with rifampicin, isoniazid, pyrazinamide, and ethambutol is indicated. The second phase of the treatment lasts six months. It is important to ensure adherence by the patient. If resistance to isoniazid is noticed, this medication should be replaced by last-generation quinolones (levofloxacin or moxifloxacin). Multiresistant tuberculosis refers to the resistance of rifampicin and isoniazid, the treatment will be oriented according to the resistance patterns in association with pyrazinamide [7].
Although the main presentation of tuberculosis is pulmonary, in the immunosuppressed patient, tuberculous lymphadenitis is the most common [8]. The relationship with hematological cases is rare [6], however, there are cases in the literature where the presentation of tuberculosis disease interferes with the coagulation cascade, causing thrombotic phenomena due to the increase in plasma fibrinogen, prolongation of coagulation times, as well as protein deficiency that finally concludes in an imbalance of pro- and anticoagulant factors presenting thrombosis [9].

In the case presented, there is evidence of a deficiency of protein C and positive antiphospholipid syndrome. Although they alone generate a state of hypercoagulability, it is known that the activation of the pro-inflammatory cascade caused by tuberculosis infection causes vascular endothelial injury, this being related to the triad of Virchow, increases the thrombotic phenomena. Acute phase cytokines promote an altered liver response, which in turn generates a deficiency in the production of proteins related to coagulation [10].

Regarding the antiphospholipid syndrome, it is defined as a systemic pathology with compromise of the immune system that conditions thrombotic or obstetric phenomena in the presence of a positive antiphospholipid antibody. It was described as a syndrome by Dr. Graham Hughes toward the year of 1983, in relation to the presence of antiphospholipid antibodies, thrombotic phenomena, and gestational losses [11], its diagnosis was developed over time through the holding of international workshops and symposia, the last documented in 1982 in Sapporo, Japan, where it was considered that the disease occurs if it meets clinical and laboratory criteria [12] (Table 2).

The development of the antiphospholipid syndrome increases oxidative stress which leads to an overexpression of the B2 glycoprotein, increasing its oxidation and its free expression in the circulation. Two hits are described to represent the pathophysiology, the first hit develops due to endothelial injury and the second hit is where the thrombus is established [14]. The relationship of protein C with the expression of glycoprotin B2 has been described as well as a subsequent activation of the coagulation cascade with the consequent result of thrombotic phenomena [15].

**CONCLUSION**

Tuberculosis is a pathology that occurs more frequently at a pulmonary level, in some cases with a hematological compromise that conditions thrombotic phenomena, describing in the literature with the presence of pulmonary thromboembolism and deep vein thrombosis, with resolution of the coagulopathy disorder after completion of antituberculous treatment. However, given the low frequency of the clinical course of these findings, anticoagulation is still not necessary as prophylaxis in patients with tuberculosis.

In this patient, the coagulopathic profile was followed, however, with a persistent positive profile, which concludes that in this case there is no cause–effect relationship between tuberculosis, antiphospholipid syndrome, and protein C deficiency.

**REFERENCES**

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**Table 2: Sapporo classification criteria [13]**

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<th>Clinical criteria</th>
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<td>Presence of arterial or venous thrombosis</td>
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<td>One or more deliveries before week 34 with morphologically normal fetuses due to preclampsia, eclampsia, or placental insufficiency</td>
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<td>Three or more consecutive abortions not explained before week 10 of pregnancy</td>
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<th>Laboratory criteria</th>
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<td>Anticardiolipin antibodies (IgM, IgG) with a moderate to high titer</td>
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<tr>
<td>Positive B2 glycoprotein</td>
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<td>Positive lupus anticoagulant</td>
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Author Contributions
Maria Alejandra Velasquez Castañeda – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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All relevant data are within the paper and its Supporting Information files.

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