Pulmonary Thromboembolism as a Complication in *Mycobacterium tuberculosis* Infection☆

Tromboembolismo pulmonar como complicación de infección por Mycobacterium tuberculosis

Dear Editor,

Respiratory infections are a well-known risk factor (RF) for the development of thromboembolic events, and tuberculosis has been shown to increase this risk. The prevalence of venous thromboembolism (VTE) in patients with active tuberculosis is 2%.[1] This may be explained by different mechanisms, including the Virchow triad: hypercoagulability due to the infection; venous stasis due to local compression of veins by lymphadenopathies and immobilization; and finally, endothelial dysfunction as a reaction induced by the *Mycobacterium tuberculosis* (*M. tuberculosis*) bacillus itself and by rifampicin.[2]

We report the case of a 74-year-old woman with a history of arterial hypertension, dyslipidemia, and hypothyroidism, who consulted initially due to a 1-month history of dyspnea on moderate exertion and edema. She had started diuretic treatment, but despite this the edema worsened, with the development of palpebral edema. The only finding of note on physical examination was the presence of bilateral pitting edema; cardiopulmonary auscultation was normal and there was no increase in jugular venous pressure. Initial clinical laboratory tests showed normal renal function, with potassium 3.07 mEq/l, LDH 279 U/l, proteins 5.05 g/dl, albumin 1.83 g/dl and NT-proBNP 718 pg/ml. Complete blood count and coagulation parameters were normal. Urine showed proteinuria in the nephrotic range (protein/creatinine ratio 18,749 mg). Chest X-ray showed only minimal bilateral clamping of the costophrenic angle and overall cardiomegaly. To determine the etiology of the nephrotic syndrome (NS), we requested ANA, anti-DNAds, ANCA, HCV, HBV and HIV serologies, all of which were negative. A renal biopsy was also performed, which showed immunofluorescence consistent with early membranous nephropathy and interstitial nephritis, with no granulomas. Membranous glomerulonephritis (MGN) in patients older than 65 years is frequently associated with cancer,[3] so we performed a chest-abdominal computed tomography (CT), that revealed inferior vena cava thrombosis and pulmonary thromboembolism with mediastinal lymphadenopathies. The study was completed with PET/CT. PET/CT showed diffuse hypermetabolic right prevascular paratracheal lymphadenopathies, and diffuse uptake in the left pulmonary hilum. Mediastinoscopy was used to biopsy the lymphadenopathies, reported by pathology to be lymph node extensively replaced by confluent granulomas of varying sizes with no necrosis. Culture isolated *M. tuberculosis*-complex with no resistance pattern on antibiogram (PCR and stain for mycobacteria were negative). The patient started treatment with isoniazid, rifampin, ethambutol and pyrazinamide. Studies were also performed to rule out associated causes of thrombophilia, including protein C, protein S, and antithrombin deficiencies, lupus anticoagulant and antiphospholipid antibodies, all of which were within the normal range.

The association of active tuberculosis and thrombosis has been previously established. Numerous cases of deep vein thrombosis in the limbs, hepatic and retinal vein thrombosis, and cerebral venous sinus thrombosis have been described. In contrast, few cases of arterial thrombosis have been described, and most of these involve the abdominal aorta.[4–6] Published studies report that patients with tuberculosis have a greater risk of VTE than patients without tuberculosis (OR=1.55), close to the risk in patients with neoplasms (OR=1.62).[1] Moreover, patients with tuberculosis and VTE have a significantly higher mortality than individuals with only one of these diseases.[1]

Even so, in populations like ours, tuberculosis is a relatively uncommon disease, so, unlike other RFs for VTE, it is often overlooked in the etiological study.[3]

Our patient presented another uncommon but significant RF for VTE, namely nephrotic syndrome associated with MGN. VTE is a complication that occurs in 7% of cases of MGN (74% of which appear during the first 2 years after diagnosis), and is even more often associated with nephrotic syndrome.[7] The presence of glomerular lesions in patients with tuberculosis is exceptional, and very few publications have appeared on this topic. The types of glomerular lesion vary, one being MGN. In most cases, tuberculosis develops before or at the same time as the renal lesions. Tuberculosis is the most common infectious cause of granulomatous interstitial nephritis.[8] These lesions seem to be caused by a T cell-mediated cellular immune response, but little literature is available on the different pathogenic mechanisms.[9,10] We believe that the presence of interstitial nephritis in our patient could have contributed to the appearance of a transient state of hypercoagulability mediated by the production of pro-inflammatory cytokines.

Having encountered this case, we believe that while tuberculosis is not necessarily one of the major diseases to be ruled out as a trigger for a thromboembolic event, it should be borne in mind. Moreover, a high index of suspicion must be maintained in patients with active tuberculosis who develop thromboembolic events, given the similar risk of such phenomena as in patients with tumor disease and the associated rise in mortality.

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Sarcoidosis-Like Granulomatous Reaction Associated with Pembrolizumab Immunotherapy☆

Reacción granulomatosa sarcoidosis-like asociada al tratamiento con inmunoterapia (pembrolizumab)

Dear Editor,

The recent introduction of immunotherapy in the treatment of cancer has revolutionized the management of some tumors, including lung cancer,[1] and this treatment is being progressively included in the various therapeutic guidelines. Pembrolizumab is a humanized anti-PD1 monoclonal antibody that is approved in Spain for the treatment of non-small cell lung cancer, in both first and second-line treatment in selected patients,[2] and in metastatic melanoma. We report the case of a patient with a diagnosis of metastatic melanoma treated with pembrolizumab, who developed a granulomatous sarcoidosis-like reaction to this treatment, a little-known adverse effect that is rarely described in the literature.

This was a 72-year-old man, former smoker of 50 pack-years, with no respiratory history, diagnosed with a superficial melanoma after excision of a mole from the lower left limb in 2014, with subsequent widening of surgical borders. After 2 disease-free years, metastases were detected in the left inguinal lymph nodes, and lymphadenectomy was performed. Unresectable mesenteric lymphadenopathies subsequently appeared, so treatment began with pembrolizumab every 3 weeks.

After 6 months of treatment, with partial response of the lymphadenopathies, the respiratory medicine department was consulted due to the appearance on a follow-up chest CT of septal thickening, nodules predominantly in the subpleural and fissure regions, and hilar and mediastinal lymphadenopathies measuring up to 15 mm, changes highly suggestive of a sarcoidosis-like granulomatous reaction (Fig. 1). Chest CT before starting treatment showed no changes in the pulmonary parenchyma and no mediastinal lymphadenopathies.

The patient was asymptomatic at all times, with no respiratory symptoms, cough, dyspnea or fever, nor did he present new skin lesions. The examination revealed bibasal crackles and edema of the lower limbs (secondary to lymphadenectomy), and basal pulse oximetry was 95%. Angiotensin-converting enzyme was 54 U/l and functional respiratory tests were normal. Fiberoptic bronchoscopy was performed, and no endobronchial changes were visualized. Bronchoalveolar lavage was consistent with lymphocytic alveolitis, with a CD4/CD8 ratio of 1.1. Five transbronchial biopsies were obtained that showed non-caseifying epithelioid granulomas (Fig. 1). All microbiological analyses of lavage and biopsy material were negative, including mycobacteria testing.

Given the consistent radiological and histological findings and the correlation in time with the treatment, the patient was diagnosed with sarcoidosis-like granulomatous reaction associated with pembrolizumab. As he was asymptomatic and lung function was normal, we decided, in consultation with the oncology department, to discontinue pembrolizumab and to monitor the patient. In the chest CT performed 1 month after withdrawing treatment, partial radiological improvement was seen, both in parenchymal involvement and in the size of the lymphadenopathies, so this approach was maintained. Six months after discontinuing the drug, the follow-up CT showed that the radiological changes had resolved almost completely. The good response to merely discontinuing pembrolizumab confirmed that the sarcoid reaction was directly related to the treatment.

Immunotherapy is defined as the set of treatments aimed at strengthening the immune system to promote the development of antitumor activity. These drugs act by unblocking key inhibitory lymphocyte pathways, such as the CTLA-4 or PD-1/PDL-1 pathway, resulting in the stimulation of T cell activity.[3] This activation helps the immune system to attack tumor cells, although it can also increase the chance of host tissue reactions. For this reason, adverse effects associated with these treatments are often autoimmune events, the most common being skin rashes, colitis, liver disease, pneumonitis, and endocrine diseases. The respiratory adverse effects reported in clinical trials include cough, dyspnea, bronchitis, organizing pneumonia, hoarseness, pulmonary fibrosis, and particularly, pneumonitis, which is potentially the most serious.[4,5] A meta-analysis of 653 patients treated with pembrolizumab estimated a rate of pneumonitis of 6%, and described 5 typical radiological patterns: cryptogenic organizing pneumonia, ground glass pattern, hypersensitivity type, interstitial, and nonspecific.[6]

Sarcoidosis-like granulomatous reactions have already been described in association with other cancer treatments, such as alpha-interferon or cisplatin,[7] or monoclonal antibodies, such as anti-tumor necrosis factor or anti-CD20. These reactions have also been described recently in some cases in association with immunotherapy. In 2008, the first case of sarcoidosis-like granulomatous reaction associated with ipilimumab (anti-CTLA-4) was reported in a patient with metastatic melanoma.[8] Another 13 cases with this drug were subsequently published, 12 in the treatment of melanoma and 1 in prostatic adenocarcinoma. Three cases associated with nivolumab (anti-PD1), also in melanoma, have been published, the first in 2016.[9] With regard to treatment with pembrolizumab, only 5 confirmed cases have been described, 4 in melanoma[10–12] and 1 in metastatic leiomyosarcoma.[13] Another 3 cases of reactivation of granulomatous disease prior to initiating immunotherapy (2 treated with pembrolizumab[14] and 1 with a combination of ipilimumab and nivolumab) have been published.

These reactions are treated by discontinuing the drug and administering corticosteroids, depending on the degree of involvement. According to guidelines for managing immune-mediated adverse effects,[5,15] asymptomatic cases can be managed simply with close monitoring, while corticosteroids should be reserved

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