Case Report

Pulmonary eosinophilia associated to treatment with natalizumab

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Abstract:

Natalizumab (Tysabri®) is a leukocytes chemotaxis inhibitor that decreases the leukocytes passage through the hematoencephalic barrier and it is currently used in relapsing-remitting forms of multiple sclerosis (MS). We present a patient with allergic rhinoconjunctivitis diagnosed with MS who started treatment with natalizumab. She began to show mild asthmatic symptoms until she needed admission to the hospital due to respiratory insufficiency. Blood tests showed peripheral eosinophilia and the thoracic computed tomography scan demonstrated pulmonary infiltrates. The bronchoscopy with the bronchoalveolar lavage resulted in eosinophilic alveolitis. No evidence of bacterial, fungal and parasitic infection, connective tissue disease, or vasculitis were observed. After discontinuation of natalizumab, the patient improved without other treatments. As MS is a prevalent disease and the use of natalizumab is increasing, we consider important to point out that this drug can be associated with pulmonary eosinophilia, especially in patients with allergic rhinoconjunctivitis or asthma.

Key words:

Multiple sclerosis, natalizumab, pulmonary eosinophilia

Natalizumab (Tysabri®) is a leukocytes chemotaxis inhibitor that decreases the leukocytes passage through the hematoencephalic barrier and it is currently used in relapsing-remitting forms of multiple sclerosis (MS). We describe the potential association between natalizumab and the onset of pulmonary eosinophilia in a patient with MS.

Case Report

The patient is a 41-year-old woman without drug allergies and a current smoker with cumulative cigarette consumption of ten packages/year. Her family history includes a grandmother with asthma and her father had allergic rhinoconjunctivitis. She was also diagnosed with rhinoconjunctivitis and hypersensitivity to *Dermatophagoides pteronyssinus* as a child. Remittent-recurrent MS was detected in 1996 and treatment with interferon was initiated, changing to natalizumab in 2013 due to persistent activity of the disease.

In November 2014, she began to experience watery rhinorrhea, wheezing in the chest, coughing, and spitting up sputum. She consulted with her primary physician, who started treatment with amoxicillin/clavulanic acid, inhaled glucocorticoids, bronchodilator agents, and antihistamines resulting in moderate improvement. Three months later she consulted again, with dyspnea at rest and persistent cough the previous 48 h. The physical examination revealed oxygen saturation of 91% when breathing ambient air, with bilateral wheezing, and she was transferred to our tertiary referral hospital. Both times the administration took place in the previous 24 h.

A blood test on arrival to the emergency room showed leukocytosis 17,200 cells/mm^3 (13,670 cells/mm^3 neutrophils, 490 cells/mm^3 eosinophils) and arterial blood gas test (breathing oxygen at 0.24) showed: pH 7.47, PCO_2 34 mmHg, PO_2 66 mmHg, and HCO_3 25 mmol/L. The chest X-ray showed reticular opacities with basal predominance and a right perihilar condensation. Urine antigens for *Legionella* and *Streptococcus pneumoniae* were negative. Treatment with short-acting bronchodilators and piperacillin-tazobactam was started and she was admitted to the Pneumology Department.

During her hospital stay a thoracic computed tomography (CT) scan was done [Figure 1a],

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which showed "interstitial lung disease characterized by bilateral diffuse ground-glass attenuation in association with intralobular lines (crazy paving pattern) and some bronchiectasis."

The control blood test showed persistent leukocytosis (17,000 cells/mm^3) and eosinophilia (1,400 cells/mm^3). Tests for autoimmune disease, connective tissue disease, and vasculitis were negative; these included antinuclear antibodies, anticytoplasm of neutrophils, anti-DNA, anti-Sm, anti-ribonucleoprotein, anti-Ro, anti-La, anti-centromere, anti-SCL 70, anti-Jo 1, anti-citrullinated peptide, and rheumatoid factor. Immunoglobulins were also analyzed; all results were normal except IgE, (total value of 153 kU/L). Precipitins (*Aspergillus fumigatus*, excrement and serum of pigeon and parakeet) were also negative. Serial coprocultures ruled out parasites.

The bronchoscopy did not show endobronchial lesions, and the bronchoalveolar lavage resulted in eosinophilic alveolitis (83% macrophages, 4% lymphocytes, 1% neutrophils, and 12% eosinophils). Cultures for bacteria, mycobacteria, fungi, and studies for parasites and virus were negative. Lung function test detected a moderate airflow obstruction with a positive bronchodilator test and severe reduction of the carbonic monoxid (CO)-transference FEV_1/FVC 82%, FEV_1 53% ref., FVC 52% ref., TLC 85% ref., RV/TLC 60%, DLCO 48% ref., KCO 66%.ref.

The resulting diagnosis was "pulmonary eosinophilia associated with natalizumab treatment in a patient with bronchial asthma" and the Neurology Department was asked for an alternative treatment. As the patient improved with inhaled corticosteroids and bronchodilators (without systemic corticosteroids), she was discharged a week later with the same treatment.

At the monitoring visit a month later, the patient was asymptomatic, the thoracic CT scan showed resolution of the pulmonary infiltrates [Figure 1b] and the respiratory function test had improved (FEV_1/FVC 83%, FEV_1 77% ref., FVC 74% ref., TLC 96% ref., DLCO 69% ref., and KCO 67% ref.). After 6 months, the asthma symptoms were under control, and the thoracic CT scan remained without infiltrates.

Discussion

Pulmonary eosinophilia is characterized by the presence of pulmonary infiltrates and eosinophilia in pulmonary tissue (evidenced by open or transbronchial biopsy) or in the bronchoalveolar lavage (>10% of the total cellularity), and may or may not be associated with peripheral eosinophilia.[1] The most frequent etiology is idiopathic (acute or chronic eosinophilic pneumonia, hypereosinophilic syndrome), known cause (parasites, drugs, and allergic bronchopulmonary aspergillosis) or associated to systemic vasculitis (Churg–Strauss syndrome, Wegener granulomatosis, and polyarteritis nodosa). Some clinical conditions are occasionally associated to pulmonary eosinophilia, such as infections (histoplasmosis, coccidiomycosis), neoplasm (Hodgkin's disease), and drugs abuse.[2]

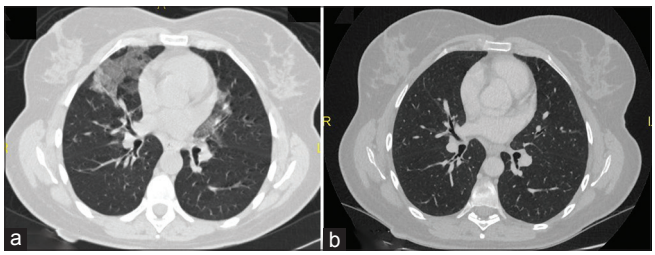

Figure 1: (a) Axial section of thorax computed tomography scan at lung window showing areas of bilateral ground-glass attenuation. (b) Axial section of thorax computed tomography scan at lung window showing resolution of the ground-glass areas

Drug toxicity is a frequent cause of pulmonary eosinophilia; therefore, a thorough analysis of the medicines taken by these patients is important. The most frequent medications involved are antibiotics, nonsteroidal anti-inflammatory drugs, and serotonin reuptake inhibitors. The clinical presentation varies, ranging from asymptomatic pulmonary infiltrate with or without associated cough, fever, and/or dyspnea, to severe cases with acute onset and respiratory failure. The usual treatment is the removal of the problematic drug; in some cases, systemic corticosteroids are necessary.[3]

Natalizumab[4] works by avoiding cellular recruitment. It binds the integrins that form the cellular adhesion molecules (specifically integrin VLA-4 o α4ß1) of the leukocytes, reducing their migration to the inflammatory tissue and inhibiting the interaction with the extracellular matrix, and therefore the activation of several signaling pathways. It is widely believed that the benefits of natalizumab in MS patients are based on blocking the passage of inflammatory cells through the hematoencephalic barrier, reducing the activity of the lesions. It is currently indicated in relapsing MS to avoid exacerbations and slow down the functional impairment. Adverse events are described as hypersensitivity, nonspecific reactions (such as headache, dizziness, nausea or vomiting, fever, and arthralgia), and infections (urinary or upper airway), and there is an increased risk of progressive multifocal leukoencephalopathy due to the JC virus.[5] Hypereosinophilia has been described in peripheral blood,[6] without lung involvement or opportunistic infections;[7,8] nevertheless, natalizumab has not been associated with pulmonary eosinophilia to date.

We describe a case of a patient with bronchial asthma, allergic rhinoconjunctivitis, and MS who developed a clinical profile compatible with medication-related pulmonary eosinophilia and improved after removal of natalizumab.

According to the classical criteria described by Naranjo *et al*.,[9] our case would be considered a probable adverse effect because we cannot rely on the re-exposure principle due to ethical considerations, or have serum levels of the drug. The prevalence of MS and the increasing use of natalizumab in these patients makes it important to report this previously unreported adverse event, which could be especially relevant in patients with a history of asthma or rhinoconjunctivitis that do not improve with symptomatic treatment.

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Conflicts of interest

There are no conflicts of interest.

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