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Pulmonary Sarcoidosis in Behçet's Disease Treated with Adalimumab

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ABSTRACT

TNF-α antagonists are used to treat various rheumatic diseases including sarcoidosis. However, there have been increasing reports of sarcoidosis in relation to treatment using these drugs. The pathogenesis of this reaction remains unknown.
This is a report of a clinical case of sarcoidosis in Behçet's disease (DB) with mucocutaneous and intestinal involvement in treatment using adalimumab, with improvement after anti-TNF suspension and corticosteroid therapy.

LEARNING POINTS

- This clinical case demonstrates the efficacy of the anti-TNFa adalimumab in the treatment of Behçet with intestinal manifestations and not responsive to other therapeutics.
- To our knowledge it is the first time it is described a case of sarcoid reaction in a patient with Behçet treated with adalimumab.
- It shows how two complications of the use of immunosuppressants (sarcoid reaction and *Legionella pneumophila* pneumonia) in the same patient can difficult the correct diagnosis because of the many and overlapping clinical manifestations.

KEYWORDS

Adalimumab, pulmonary sarcoidosis, Behcet's disease, *Legionella* pneumonia

INTRODUCTION

Tumor necrosis factor (TNF) is a proinflammatory cytokine produced by activated macrophages, CD4 + lymphocytes, NK cells, and other factors. Anti-TNF agents are used in the treatment of various inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis[1].
The use of anti-TNF in patients with Behçet's disease has been described in several patients with manifestations refractory to conventional medication, resulting in impressive remissions[1,2].
The most commonly used TNF-α antagonists include infliximab and adalimumab (monoclonal antibodies against TNF-α) and etanercept (a fusion protein that binds TNF-α mimicking its soluble receptor). These agents have also proved to be effective in the treating sarcoidosis and other inflammatory conditions. However, sarcoidosis-like paradoxical reactions have been reported in approximately 1/2800 patients treated with anti-TNF in inflammatory arthropathies[3].
A case of Behçet's disease treated using adalimumab is reported in which the patient was diagnosed with sarcoidosis 6 months after starting treatment, and also with *Legionella pneumophila* pneumonia. The patient improved after anti-TNF suspension and introduction of corticosteroids.

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CASE REPORT

A 47-year-old man with a 17-year history of Behçet's disease with mucocutaneous and intestinal involvement presenting incomplete response to colchicine, corticosteroids, azathioprine, and sulfasalazine.

Initially medicated with colchicine and corticosteroids without complete resolution of complaints and additionally medicated with thalidomide with a total resolution of the symptomatology that, unfortunately, had to be suspended due to the side effect of sensitive polyneuropathy of the lower limbs. Corticosteroid dosage was escalated and azathioprine was introduced but without complete control of the complaints – the patient maintained oral and genital ulcers as well as asthenia. Sulfasalazine was also introduced because of intestinal manifestations such as abdominal pain, diarrhea, and hematochezia but without satisfactory resolution of the complaints.

Faced with this resistance, the patient was treated with adalimumab resulting in a rapid and complete resolution of the symptoms. Six months after initiation of treatment and about three days after the administration of another dose of adalimumab, the patient started to complain of fever with night and evening predominance associated with flank, chest, and retrosternal myalgias and inflammatory arthralgia of the shoulders, elbows, knees, and metacarpophalangea joints. He also reported dizziness, headache, and mechanical neck pain. He had nausea without vomiting.

Physical examination revealed oropharynx without thrush or ulcers. No cervical or axillary adenopathies on palpation. No signs of arthritis. Lower limbs with slightly swollen knees. No alterations in ophthalmologic or neurological exams and in cardiopulmonary evaluation.

Blood test results: Creatinine 0.74 mg/dL, Sodium 142 mmol/L, Potassium 4.0 mmol/L, CK 29 U/L, PCR 8.74 mg/dL Leukocytes 7,200; Neutrophils 61.1%; Lymphocytes 22.0%; Hemoglobin 14.2 g/dL, VGM 91.3 fL, Platelets 270,000; SR 32 mm/h.

Chest X-ray: perihilar reinforcement.

Serologies were performed for Cytomegalovirus, Epstein-Barr Virus, Herpes simplex 1 and 2, *Chlamydia trachomatis*, *Coxiella burnetii*, *Mycoplasma pneumoniae*, *Clamydophila pneumoniae* which were negative. Mantoux test and IGRA were also negative. Bronchoalveolar lavage, bacteriological examination, and mycobacterial tuberculosis detection by polymerase chain reaction and cultures were negative. Negative hemocultures.

Therapy with adalimumab was suspended and empirical medicated with ceftriaxone and azithromycin started with initial improvement of complaints.

About 2-3 days after the end of the antibiotic therapy, the patient started complaining of a continuous right chest pain, grade 6/10, which aggravated with mobilization and with right lateral decubitus position. He reported dry cough and night sweats, without fever. Appearance of erythema nodosum in both lower limbs.

Chest radiography revealed bronchopneumonia of the right upper lobe. Analytically with PCR 38.5 mg/dL, SR 47mm/hr, and increased anti-*Legionella pneumophila* IgM antibody titer from 1/320 to 1/1000.

Because no imaging improvement occurred, a high-resolution chest CT was performed that demonstrated nodulation reaching the right upper lobe, middle lobe, and lower lobes. Central permeable tracheobronchial tree. Multiple mediastinal and hilar adenomegalies reaching about 15 mm short axis. There was a small volume of bilateral pleural effusion.

Legionella pneumonia was assumed and was treated with clarithromycin for 10 days. There was improvement in complaints, only right chest pain maintaining.

Thoracic CT was repeated one month later, which revealed a reduction in adenomegaly. Micronodulation was dispersed in both lungs. Analytically, it had ECA 132 U/L (8-52 U/L). A mediastinal ganglion biopsy was performed that revealed confluent, non-necrotizing epithelioid granulomas and multinucleated Langhans and Touton giant cells, suggesting the diagnosis of sarcoidosis.

He was medicated with methylprednisolone 40mg for 6 months. CT imaging showed complete resolution of nodular lesions and adenopathies.

DISCUSSION

A TNF-α induces macrophage differentiation of monocytes, essential for the induction and maintenance of granuloma integrity. It also plays an important role in host defense against infectious agents, especially in those with intracellular multiplication such as *Legionella pneumophila*. Cases of *L. pneumophila* pneumonia appear to be increasing in patients treated with TNF antagonists[4].

Pulmonary legionellosis may present as Legionnaires' disease, the most severe form, or as Pontiac Fever, the most moderate form, with fever and myalgias.

The patient presented in this article appears to have initially presented a more moderate form of the disease with fever and myalgias, and then subsequently progressed to pneumonia.

In this case, in spite of the directed treatment, the patient maintained right chest pain and pulmonary parenchymal alterations, with scattered micronodulations shown in imaging reevaluation. Sarcoidosis was evidenced by lymph node biopsy.

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It was difficult to distinguish the symptoms caused by sarcoidosis from the symptoms caused by *L. pneumophila* pneumonia since some are overlapping.

Reports of the association of Behçet's disease with sarcoidosis are rare[6,7]. However, there are a growing number of reports in the literature of sarcoidosis related to treatment with TNF antagonists[3,8,9]. The incidence of this adverse effect is estimated at 1/2800. The majority of the fewer than 40 cases reported to date have involved etanercept therapy. However, all three agents have been implicated[9]. The pathogenic mechanisms involved are unknown and it is considered to be a paradoxical effect, taking into account the mode of action of these agents since TNFα blockade suppresses granuloma formation.

It is thought that the phenomenon is independent of the underlying disease and has been reported in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, polyarticular juvenile rheumatoid arthritis, and polymyalgia rheumatic[8]. The duration of treatment before the diagnosis of sarcoidosis ranged from one month to five years. Pulmonary, ganglion, cutaneous, ocular, hepatic, parotid, and central nervous system involvement have all been reported.

In summary, the authors describe the occurrence of sarcoidosis in a subject with Behçet's disease which, due to the characteristics and temporal relationship, appears to be a direct consequence of the biologic treatment with adalimumab.

As described in the literature reviewed, the resolution of granulomas generally occurs one year after drug withdrawal. In some cases the treatment also involved the introduction of corticosteroids as was the case for the patient presented in this article. It is also reported that substitution by other anti-TNF resulted in resolution of the condition[8-10].

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