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Sarcoidosis: A Different Disease or a Paradoxical Effect on Etanercept Treatment?

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INTRODUCTION

Sarcoidosis is a systemic condition with an unknown etiology characterized by the formation of noncaseating granulomas in various organs (1). In the vast majority of cases, patients do not show clinical symptoms, but there are situations in which it is necessary to initiate an immunosuppressive medication in addition to corticosteroid therapy (2). According to the European Respiratory Society guidelines regarding the treatment of sarcoidosis, therapy is initiated depending on the visceral impairment, the impact on the patient's quality of life, as well as the increase in mortality (3). The main immunosuppressive drugs used are either conventional synthetics such as: methotrexate, leflunomide, azathioprine or mycophenolate mofetil, or TNFα (tumor necrosis factor α) inhibitors: infliximab, adalimumab, B lymphocyte inhibitors: rituximab or even synthetic targeted medication: januskinase inhibitors (3). Data from the literature have shown that TNFα inhibitors may be associated with sarcoid-like reactions or even cause sarcoidosis in patients with rheumatic systemic autoimmune diseases such as ankylosing spondylitis (AS), psoriatic arthritis (PsoA) or rheumatoid arthritis (RA) (4-11).

TNFα inhibitors are a medication commonly used in autoimmune rheumatic diseases, being included in the treatment guidelines for RA or spondyloarthritis (AS, PsoA) (12-14). The safety of this biologic medication has been carefully considered in clinical trials, especially in terms of infection and malignancy risk (15-20). The onset of sarcoidosis following anti-TNFα therapy is considered by some authors to be a side effect of treatment (21); others argue that it is a paradoxical effect as TNFα inhibitors are used to treat sarcoidosis (22,23).

In this paper we present the case of a patient known to have PsoA and who, secondary to Etanercept therapy (ETN) - an extracellular domain of TNF receptor 2/IgG1-Fc fusion protein inhibitor, developed pulmonary sarcoidosis with significant clinical manifestations.

CASE REPORT

The 50-year-old patient presented to our clinic for the first time in March 2019, complaining of an altered general condition, inflammatory pain in the small joints of her left hand, right fist and bilateral forefoot, morning stiffness of over 60 minutes, swelling of the right carpal and bilateral metatarsophalangeal joints and finger III left hand dactylitis. The patient is an employee and denies alcohol and tobacco use. From the hereditary antecedents we point a sister diagnosed with psoriasis vulgaris, another sister who died of a gastric neoplasm and her father having cardiovascular diseases.

In 2003 the patient was diagnosed with palmoplantar pustulosis psoriasis confirmed by skin biopsy, and since March 2018, according to CASPAR (Classification criteria for psoriatic arthritis) criteria (24), with polyarticular PsoA. Treatment with methotrexate 10 mg per week was started in combination with folic acid, a therapy that she followed for 1 year until the current presentation.

The clinical examination in March 2019 highlighted grade 1 obesity (BMI = 31.22 kg / m^2), enlarged abdomen due to adipose tissue and palmoplantar pustulosis lesions, more pronounced at left plantar level. Moreover, swelling was observed in the right radiocarpal joint, pain in palpation of the bilateral radiocarpal line and in small joints of the hands and a limited mobility in the left hand. Swelling of the ankles and numerous dactylitis were observed at the level of the forefoot. The clinical images of the patient are presented in figure 1.

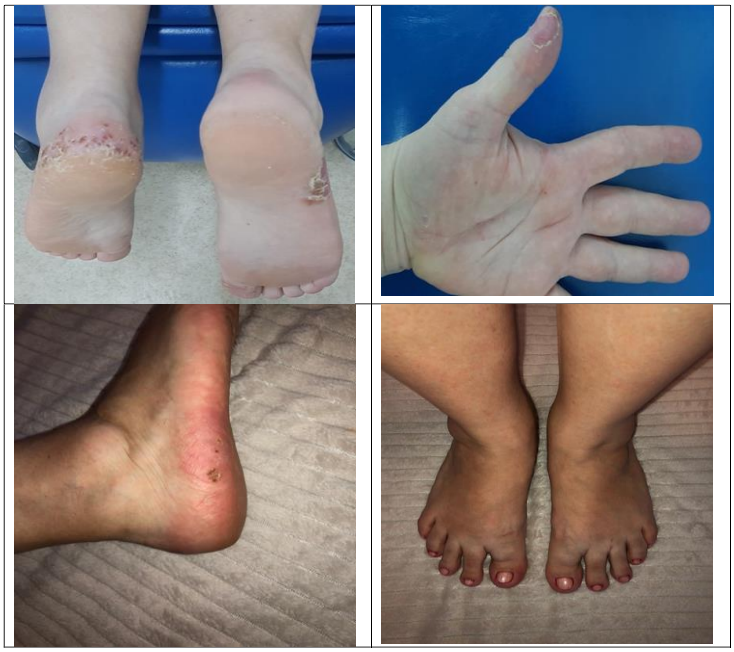

Fig.1. Clinical aspects of the patient: palmoplantar pustulosis lesions, second and third right toe dactylitis

Paraclinically, we found a significant inflammatory syndrome: ESR = 110 mm/h, CRP = 347,2 mg/l and liver damage characterized by cytolysis and cholestasis; biological markers for hepatitis B and C were negative. The patient underwent an X-ray of the hands and feet that did not show any significant inflammatory lesions. The quantification of the disease activity was performed using the DASPSA score whose value was 73.7 which indicates a very active disease.

Given all these data: many painful and swollen joints, the presence of severe inflammatory syndrome, increased activity score, liver damage and mild intolerance of the patient to methotrexate (nausea), it was decided to change the therapy to leflunomide 20 mg/day.

After 7 months of treatment with leflunomide, the patient's condition worsened. The pain and swelling in the joints of the hands, feet and ankles bilaterally were accentuated. Although the inflammatory syndrome slightly decreased, the activity of the disease remained high. Liver damage has also persisted. Thus, anti-TNFα therapy was initiated with Etanercept 50 mg weekly subcutaneously, the clinical and biological evolution being favorable.

In October 2020, the patient presented for reassessment with severe physical asthenia, dry cough and moderate-intensity dyspnea. COVID19 infection was excluded by PCR test and a chest X-ray was performed showing reticular changes in the basal segments of the lower lobes (fig.2). Enlarged bilateral hilum, with uncertain etiological appearance. Absence of focal opacity. Normal size cord. Chest CT was recommended. In addition, a Quantiferon TB gold test and a sputum examination for tuberculosis were performed in the context of TNF inhibitor therapy, with negative results.

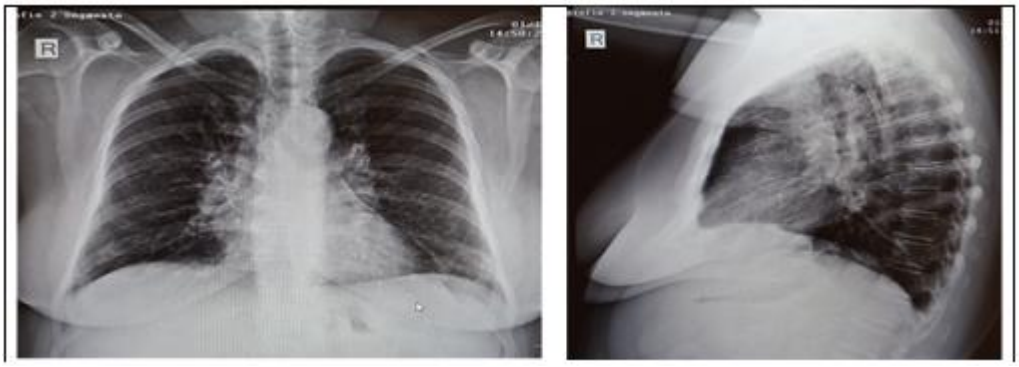

Fig.2. Chest X-ray: reticular changes in the basal segments of the lower lobes, enlarged bilateral hilum, absence of focal opacity, normal size cord

The patient underwent a pulmonary CT examination with contrast which showed: bilateral symmetrical mediastinal and hilar lymphadenopathy (multiple, having various sizes); moderate to massive adenomegaly, variable lymph node contour, some lymph nodes with a clear outline or a tendency to confluence into lymph node masses, especially paratracheal, subcarinar and hilar; in the lung parenchyma multiple micronodules or larger nodules; subpleural reticular and reticulo-micronodular aspects predominantly in the lower lobes (fig.3).

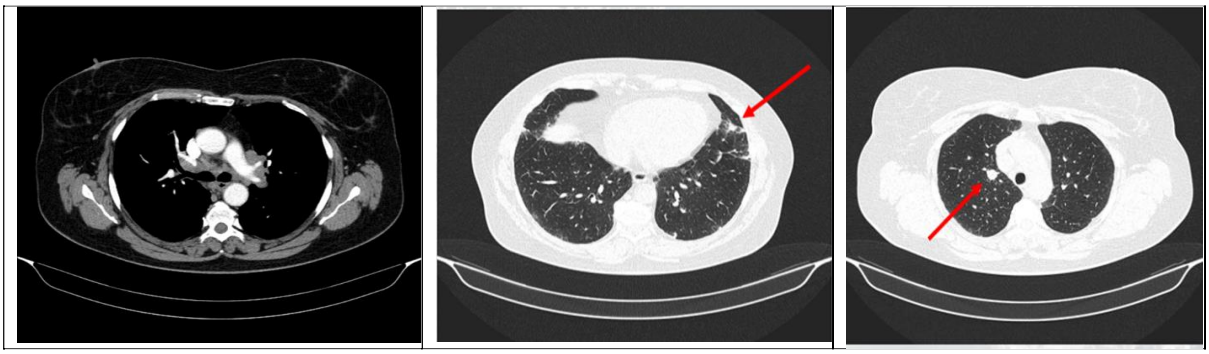

Fig.3. Chest contrast CT: bilateral symmetrical mediastinal and hilar lymphadenopathy (multiple, having various sizes); moderate to massive adenomegaly, variable lymph node contour, some lymph nodes with a clear outline or a tendency to confluence into lymph node masses, especially paratracheal, subcarinal and hilar; in the lung parenchyma multiple micronodules or larger nodules; subpleural reticular and reticulomicronodular aspects predominantly in the lower lobes.

The patient was referred to the pulmonology department where a bronchoscopy was performed and biopsy samples were taken. Bronchoscopic examination did not show any significant macroscopic changes. Histopathological examination of biopsy specimens highlighted rare well-defined microgranulomas without necrosis, with a sarcoidosis-compatible appearance. In addition, serum angiotensin convertase was measured, the values of which were slightly increased. Lung capacity was tested by spirometry - ventilatory parameters within normal limits and DLCO (Diffusing Capacity Of The Lungs For Carbon Monoxide) - normal transfer capacity.

In October 2020, corroborating the clinical manifestations and the results of paraclinical tests, the diagnosis of stage II sarcoidosis was supported. According to current sarcoidosis treatment recommendations, the pneumologist decided to stop therapy with Etanercept, considering the onset of sarcoidosis as a paradoxical reaction to TNFα inhibition. Returning to the rheumatology clinic, the treatment was changed to Adalimumab 40 mg every 2 weeks subcutaneously and a re-evaluation was recommended after 3 months. In February 2021 the patient presented with a good general condition, without respiratory symptoms. Chest X-ray showed some slightly thickened modifications around the hilum and in bibasal areas; pulmonary CT highlighted a favorable evolution namely the disappearance of mediastinal lymphadenopathy and of the changes in the lung parenchyma (fig.4). Unfortunately, in May 2021, the patient lost her therapeutic response to adalimumab. Joint symptoms worsened. Palmar and plantar psoriasis lesions have also worsened. X-rays of the hands and forefoot showed a rapid evolution of the joints towards destruction and periostitis. Chest X-ray showed no change from previous assessment. Thus, it was decided to change the class of therapy and the interleukin 17 inhibitor, Secukinumab 300 mg with the corresponding loading dose, was chosen. The response to this new therapy has been a rapid one and is maintained until present, the evolution of the patient being a favorable one both from the articular and pulmonary involvement.

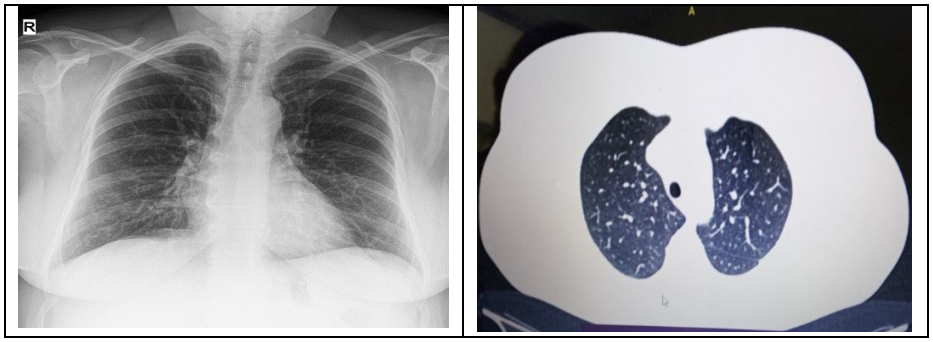

Fig.4. Chest X-ray: slightly thickened modifications around the hilum and in bibasal areas; pulmonary CT: disappearance of the changes in the lung parenchyma

DISCUSSION

We presented the case of a 50-year-old patient registered with PsoA since 2018; she followed various conventional synthetic treatment regimens such as methotrexate and leflunomide, then biological anti-TNFα therapy was started. Joint progression was favorable under etanercept therapy, but after approximately 12 months, the patient developed stage II pulmonary sarcoidosis, considered a paradoxical effect of TNFα inhibitor therapy.

Numerous data in the literature support the development of this paradoxical effect of anti-TNFα therapy, namely sarcoidosis (25-30). Recently, in 2022, the data of a study conducted on a large cohort of 2492 RA cases were published. Of these patients, 697 received treatment with TNF inhibitors. There were only 4 cases of medication-induced sarcoidosis, patients presenting with various clinical manifestations ranging from pulmonary sarcoidosis with hilar lymphadenopathy, incomplete Heerfordt syndrome or sarcoid-like granulomatosis (31). Of these 4 cases, 3 were on etanercept and one on infliximab. The mean duration of clinically manifest sarcoidosis varied considerably, ranging from 7 to 123 months after exposure to the TNF inhibitor (31).

The pathogenic mechanism underlying this paradoxical clinical manifestation is not yet known. Several theories have been put forward regarding the mechanism of paradoxical sarcoidosis: TNFα inhibits transforming growth factor (TGF)-β and the secretion of interferon (IFN)-γ and interleukin (IL)-12; TNFα activates nuclear factor (NF) -kB which causes leukocyte recruitment and also induces apoptosis. Inhibiting TNFα, it decreases the secretion of TGF-β which stimulates the secretion of Th1 cytokines, favoring the development of sarcoidosis. In addition, inhibition of apoptosis appears to play an important role in the appearance of sarcoid lesions (32).

Regarding etanercept, the TNFα inhibitor most commonly associated with the development of paradoxical sarcoidosis, it causes a partial neutralization of TNFα, which favors the redistribution of this cytokine to low-concentration areas such as the lungs. Moreover, etanercept binds only to the soluble TNF receptor, which does not result in complement-induced cytotoxic cell lysis (26).

Although there is relatively few published data, the information is consistent and significant, having much evidence regarding sarcoidosis as a paradoxical effect after TNFα inhibition. Reinforcing this, an analysis of ten cases of RA, AS and PsoA highlighted the characteristics of the patients who developed sarcoid-like granulomas after anti-TNFα therapy. 50% of cases were treated with etanercept, followed by adalimumab and infliximab therapy. The average time from the initiation of the medication and the development of granulomatous lesions was 18 months. Most patients presented with cutaneous and pulmonary clinical manifestations, the latter being evidenced by chest CT – most frequently lymphadenopathy and parenchymal lesions. The management of these cases included stopping anti-TNFα medication with or without steroids. Both the clinical and the biological and radiological remission were obtained after an average of 6 months after drug discontinuation (33).

In the case of the presented patient, etanercept treatment was used in the context of an active PsoA that did not respond to conventional therapy. The evolution of the articular manifestations was favorable, but after 12 months the patient developed a pulmonary involvement clinically manifested by cough and dyspnea. The final diagnosis was made following a lung biopsy. Because there were no clear international case management recommendations for paradoxical sarcoid lesions after TNFα inhibitors and in the context of an aggressive joint and skin condition, we decided to discontinue etanercept therapy and switch to adalimumab. After 6 months of adalimumab, the patient's progress was good, reaching the remission of both the clinical and paraclinical lung disease (radiographic and CT improvement). The same did not happen with the articular and cutaneous manifestation, which showed an exacerbation. In this context, we decided to stop adalimumab and initiate secukinumab, the subsequent evolution being favorable.

Managing these particular situations is challenging. Some authors recommend stopping anti-TNFα medication that

has induced sarcoid manifestations (33). Others have chosen, in addition to stopping anti-TNFα therapy, the administration of systemic steroid treatment (31). All these take into account the clinical manifestations and the severity of the symptoms, most of the times the resolution being spontaneous without requiring another adjuvant therapy. Other data, in accordance with the presented case, indicate the possibility of restarting anti-TNFα treatment, this fact being followed by some relapses (34).

CONCLUSIONS

The emergence of new therapies brings new challenges. In addition to the favorable effects attributed to anti-TNFα medication, we must not forget the possible "surprising" events such as paradoxical manifestations. Whether we are talking about psoriatic or sarcoid lesions, we are facing new diagnostic and management challenges. An early and correct diagnosis, as well as the multitude of therapeutic options, help us to properly manage these particular situations.

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