Sarcoidosis-like reaction secondary to adalimumab treatment in a patient with axial spondyloarthritis

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Abstract

Anti-TNF agents, namely adalimumab, are safe drugs that play an important role in the treatment of immune-mediated inflammatory diseases. However, "paradoxical effects" have been described with their use. A "sarcoidosis-like" reaction induced by these agents is rare and is characterized by a systemic granulomatous reaction indistinguishable from sarcoidosis. We present a 55-year-old male patient, with axial spondyloarthritis, treated with adalimumab. At 17 months ofadalimumab, he complained of dry cough and wheezing. Chest CT showed a peri-lymphatic and pericisural micronodular pattern and hilo-mediastinal lymph nodes, suggestive of sarcoidosis. Angiotensin converting enzyme was increased. Assuming the hypothesis of a sarcoidosis-like reaction secondary to adalimumab, this therapy was discontinued with progressive clinical and radiological improvement.

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Introduction

Tumor necrosis factor (TNF, also known as TNF-α) was identified in 1975. It is produced predominantly by activated macrophages and T lymphocytes and plays an important role in inflammation [1].

Anti-TNF agents are safe drugs and currently represent an important weapon in the treatment of immune-mediated inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis and ankylosing spondylitis [2,3].

Adalimumab is a non-chimeric IgG1 recombinant anti-TNF human monoclonal antibody [4,5]. It appears to be effective in treating sarcoidosis; however, evidence of its efficacy is limited to several small studies performed in four populations: refractory pulmonary sarcoidosis with or without prior treatment with infliximab; cutaneous sarcoidosis; sarcoid uveitis and cardiac sarcoidosis [5]. "Paradoxical effects" related to the use of these agents have been described, defined as the resumption or exacerbation of a condition (symptom/disease) usually improved by their use [2].

A drug-induced sarcoidosis-like reaction ("sarcoidosis-like" reaction) is a systemic granulomatous reaction, indistinguishable from sarcoidosis, and occurs in a temporal relationship with the onset of the offending drug [6]. This reaction usually improves or disappears after discontinuing the drug, requiring no specific treatment. There are four categories of drugs that have been associated with the development of this reaction: immune checkpoint inhibitors, antiretroviral drugs, interferon and TNF-α antagonists, namely adalimumab.

Case Report

We present a 55-year-old male patient, former smoker, currently retired (previously worked in construction). He had a personal his-

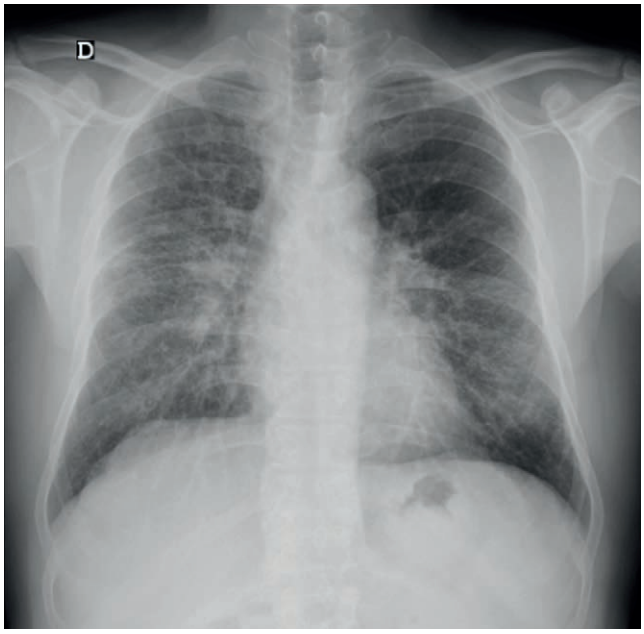

Figure 1. Chest X-ray (July 2020): marked reticular pattern, globose hila, suggestive of increased mediastinal adenopathies.

tory of HLA B27+ axial spondyloarthritis for which therapy with adalimumab was instituted in February 2019, with consequent symptomatic control of joint complaints. In July 2020 (17 months after starting therapy with adalimumab) the patient reported complaints of dry cough, dyspnea, asthenia and wheezing. He performed a chest X-ray (Figure 1), which showed marked reticular pattern and globose hila, suggestive of increased mediastinal adenopathies. Chest computed tomography (CT) scan (Figure 2) showed a perilymphatic and pericisural micronodular pattern, and hilar, mediastinal, and abdominal lymph nodes, suggestive of sarcoidosis. Laboratory tests showed an increased angiotensin converting enzyme (ACE): 77 U/L and mycobacterial infection was excluded. The case was analyzed in a multidisciplinary meeting. Clinical findings, analytic and imaging results raised the hypothesis of a sarcoidosis-like reaction related to adalimumab treatment. Fiberoptic bronchoscopy was proposed to perform bronchoalveolar lavage and bronchial biopsies, which the patient refused. Considering this diagnostic suspicion, therapy with adalimumab was interrupted in July 2020, with consequent improvement of the patient's complaints. In April 2021 (10 months after discontinuation of adalimumab), imaging reassessment with chest CT was performed (Figure 3), showing a clear improvement in the pre-existing changes in the lung parenchyma, with resolution of a large part of the micronodular pattern, dimensional reduction of the bilateral mediastinal and hilar lymph nodes. He repeated laboratory tests that showed ACE values

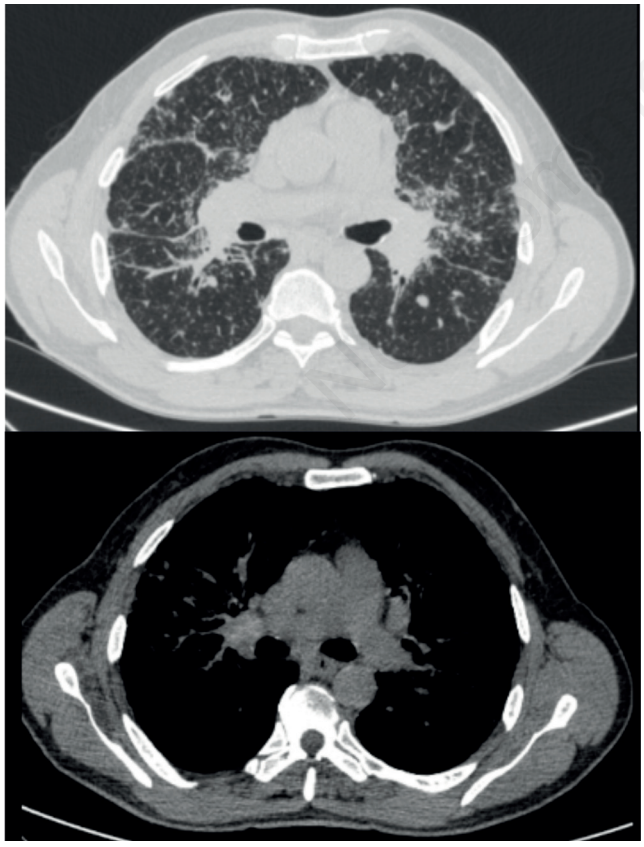

Figure 2. Chest CT (July 2020): perilymphatic and perisural micronodular pattern; presence of hilar mediastinal adenopathies.

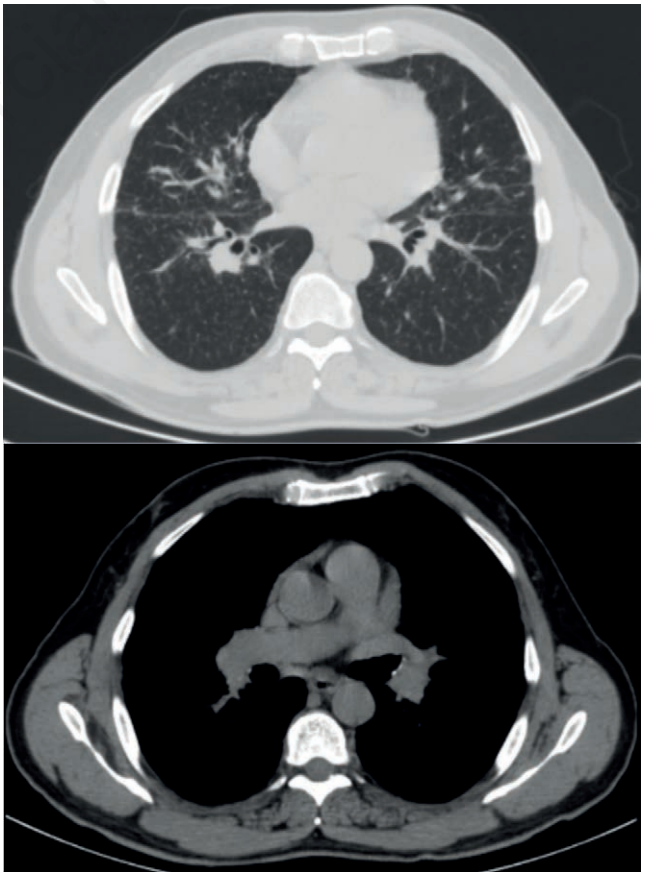

Figure 3. Chest CT (April 2021): improvement of pre-existing changes in lung parenchyma, resolution of the micronodular pattern of perilymphatic and perisural distribution; dimensional reduction of bilateral mediastinal and hilaradenopathies.

within the normal range (ACE: 34 U/L). At the time of writing the patient remained asymptomatic.

Discussion

Sarcoidosis is a granulomatous disease that can affect a wide variety of organs. The exact immunopathogenesis of sarcoidosis is still unknown, and the diagnosis of sarcoidosis currently requires the subjective criteria of a clinical presentation consistent with sarcoidosis [6]. It is thought to have a multifactorial origin in which environmental factors, genetic susceptibility and microorganisms can play a role [7,8]. Non-caseating granulomas are essential.

TNF-α plays an important role in the formation and maintenance of sarcoid granuloma, therefore TNF-α antagonists are used to treat sarcoidosis. Despite data supporting the use of these drugs in sarcoidosis, paradoxical sarcoidosis-like reactions induced by TNF-α antagonists have been described. These reactions, although rare [9], are more frequent with the use of etanercept, but can occur with any TNF-α antagonist, namely adalimumab, usually around 24 months after starting therapy [8]. Although the molecular mechanism is still unknown, there are several hypotheses to explain this paradoxical reaction [3,8]. Firstly, etanercept was thought to be the only responsible drug. However, by evaluating the case reports in literature, we might conclude that the development of sarcoidosis-like lesions under anti-TNF is a class effect [10]. Cytokine imbalance due to long term TNF-α suppression could lead to paradoxical reactions. TNF inhibitors may lead to excess interferon-alpha (INF-α) production in dendritic cells. The imbalance of INF-α and TNF-α can support the production of autoantigens which leads to paradoxical reactions. No specific treatment is described for these patients [11]. Only case reports or small studies were described, but not replicated in larger studies.

This article presents a patient who developed a sarcoidosis-like reaction secondary to treatment with adalimumab. Symptoms including cough, dyspnea, asthenia and wheezing appeared about 17 months after starting adalimumab. The chest imaging studies showed mediastinal adenopathies, perilymphatic and perisural micronodules. After excluding infectious causes, the most likely hypothesis was sarcoidosis-like secondary to treatment with adalimumab. Discontinuation of the drug led to clinical resolution and imaging improvement.

Conclusion

Sarcoidosis-like lesions during anti-TNF therapy are uncommon. The etiology of this manifestation remains unknown and difficult to explain. It is recommended that practitioners using anti-TNF therapy are vigilant when patients present with asthenia, unexplained fever, dyspnea, cough, skin lesions. When new granulomatous lesions are detected, it is recommended to exclude mycobacterial infections. However, when these investigations are negative, sarcoidosis-like reaction must be considered.

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