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CASE BASED REVIEWS

Pulmonary rheumatoid nodules in a patient treated with golimumab

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ABSTRACT

Introduction: Pulmonary rheumatoid nodules are a relatively uncommon extra-articular manifestation of rheumatoid arthritis. We report a case occurring after therapy with golimumab.
Case report: A 79-year-old woman, with a seropositive rheumatoid arthritis diagnosis since the age of 55, was under treatment with methotrexate 20mg/week since diagnosis, in combination with golimumab for the past 8 years. High-resolution computed tomography (HRCT) of the chest revealed over 60 bilateral lung nodules, multifocal, the majority with a diameter range 5-7 mm and with central cavities. A video bronchoscopy was performed: histopathology was negative for neoplastic cells, and bacteriologic, fungal and mycobacterial cultures were negative. Golimumab was suspended, maintaining only methotrexate. Chest HRCT at six months showed complete resolution of the lesions.
Discussion: A diagnosis of rheumatoid nodules was made based on the clinical setting, radiographic features, cultural exams and histopathology findings. There have been reports suggesting they may develop during TNF inhibitors therapy, mainly observed with etanercept. Only one other case has been described with golimumab. Treatment discontinuation resulted in regression/stability of the lesions in most patients, as happened in our case.

Keywords: Side effects; Biological therapies; Rheumatoid arthritis; Anti-TNF agents; Respiratory; Rheumatoid nodules.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory disease characterized by symmetric polyarthritis, but it can also affect other organs. Rheumatoid nodules are the most common cutaneous manifestation of RA (30-40% of the patients during the disease course), but pulmonary rheumatoid nodules are a relatively uncommon extra-articular manifestation[1]. Their differential diagnosis includes opportunistic infections (e.g., pulmonary abscesses and fungal infections), granulomatous diseases such as tuberculosis and granulomatous vasculitis, and malignancies.

Several reports show that TNF blockade may induce rheumatoid nodulosis, mainly etanercept, adalimumab and infliximab[2]. We present the second reported case of pulmonary rheumatoid nodulosis following therapy with golimumab.

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CASE REPORT

A 79-year-old woman with seropositive, erosive RA (rheumatoid factor 430 IU/mL and anti-cyclic citrullinated peptide antibodies 1249 IU/mL), diagnosed at age 55, had been receiving oral methotrexate 20mg/week (supplemented with folic acid 20 mg/week) since diagnosis, in combination with subcutaneous golimumab 50mg every 4 weeks for the past 8 years. Her only other relevant medical history was dyslipidemia.

Over the preceding year, she had experienced a sporadic productive cough without dyspnea or fever. She had no history of smoking, and no relevant occupational or environmental exposures were identified.

At her most recent appointment, she was in clinical remission. Physical examination was unremarkable, with no tender or swollen joints and normal cardiac and pulmonary auscultation. No subcutaneous rheumatoid nodules were observed. Laboratory studies showed an erythrocyte sedimentation rate (ESR) of 35 mm/1st hour and C-reactive protein (CRP) of 0.015 mg/dL, corresponding to a Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP) of 1.39.

A chest radiograph showed increased interstitial markings, prompting further evaluation with high-resolution computed tomography (HRCT). HRCT revealed more than 60 bilateral pulmonary nodules, multifocal,

the majority subpleural and with a diameter range from 5 to 7 mm, and some with central cavitation (Figure 1). For further investigation, a bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial lung biopsies was performed. BAL was negative for malignant cells, and the biopsies revealed normal fragments of lung parenchyma. It was not possible to obtain a nodule biopsy. Bacteriologic, fungal and mycobacterial cultures were negative. BAL differential showed increased neutrophils (48%), no eosinophilia or lymphocytosis (2%), with a CD4/CD8 ratio of 1, a profile most consistent with a nonspecific neutrophilic alveolitis, which argues against hypersensitivity pneumonitis or sarcoidosis (typically lymphocytic with elevated CD4/CD8), and does not support eosinophilic pneumonia.[3] Laboratory testing showed negative interferon gamma release assay (IGRA) and antineutrophil cytoplasmic antibodies and normal angiotensin-converting enzyme levels.

Golimumab was discontinued, and the patient maintained only methotrexate at the same dose. A follow-up chest HRCT two months later showed a reduction in both the number and size of the micronodules, and at six months, the lesions had completely resolved (Figure 2). However, after six months of golimumab interruption, her inflammatory arthralgias recurred, so rituximab was started with clinical improvement.

DISCUSSION

The prevalence of pulmonary rheumatoid nodules ranges from <1% in radiological studies to 32% in lung biopsies series.[4] They are more frequent in male patients, seropositive RA, and smokers[5]. These nodules are frequently multiple and rounded; with up to 50% demonstrating cavitation[6]. Though usually asymptomatic, they can lead to several complications, including pleural effusion, pneumothorax, bronchopleural fistulas, hemoptysis, and secondary infections, particularly in cavitary lesions[7,8]. Their differential diagnosis is crucial for treatment selection and requires the exclusion of infection and malignancy.

In this case, the diagnosis of pulmonary rheumatoid nodules was supported by the clinical context (seropositive erosive RA), typical radiographic features (multiple, predominantly subpleural, some cavitated nodules), absence of systemic symptoms, and spontaneous resolution after discontinuation of golimumab. Although a nodule biopsy was not obtained, BAL and transbronchial biopsies showed no evidence of infection or malignancy. Negative cultures substantially reduced the likelihood of bacterial, mycobacterial, or fungal infections, though these cannot be completely excluded.

PET–CT was considered but not performed, as the small size of the nodules (5-7mm) limited its diagnostic yield and the patient preferred to avoid additional testing. Moreover, since rheumatoid nodules may exhibit FDG uptake, PET–CT cannot reliably distinguish them from malignancy or infection[9].

Treating these lesions consists of controlling inflammatory activity and, in most cases, eliminating the potential triggering agent. A few case reports have been published suggesting that rheumatoid nodules may develop during TNF inhibitors (TNFi) therapy, mainly observed with etanercept[2,10–13]. There are cases reported with monoclonal antibodies, but only one case with golimumab: a 74-year-old female patient with seropositive RA in which multiple intrapulmonary nodules were diagnosed 6 months after the initiation of goli-

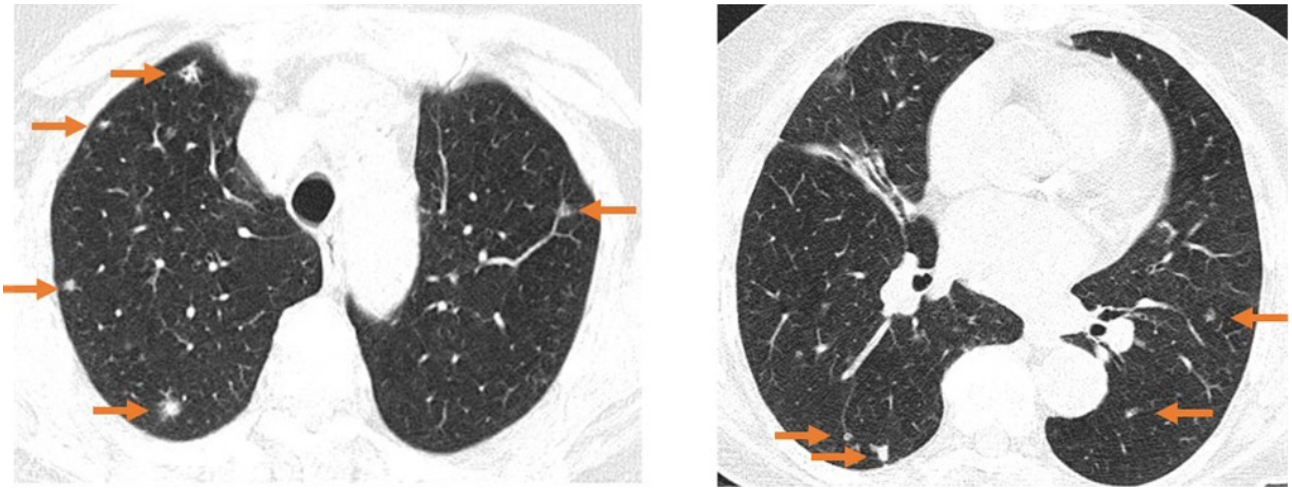

Figure 1. Chest high-resolution computed tomography (HRCT) showing multiple lung nodules in different locations (arrows).

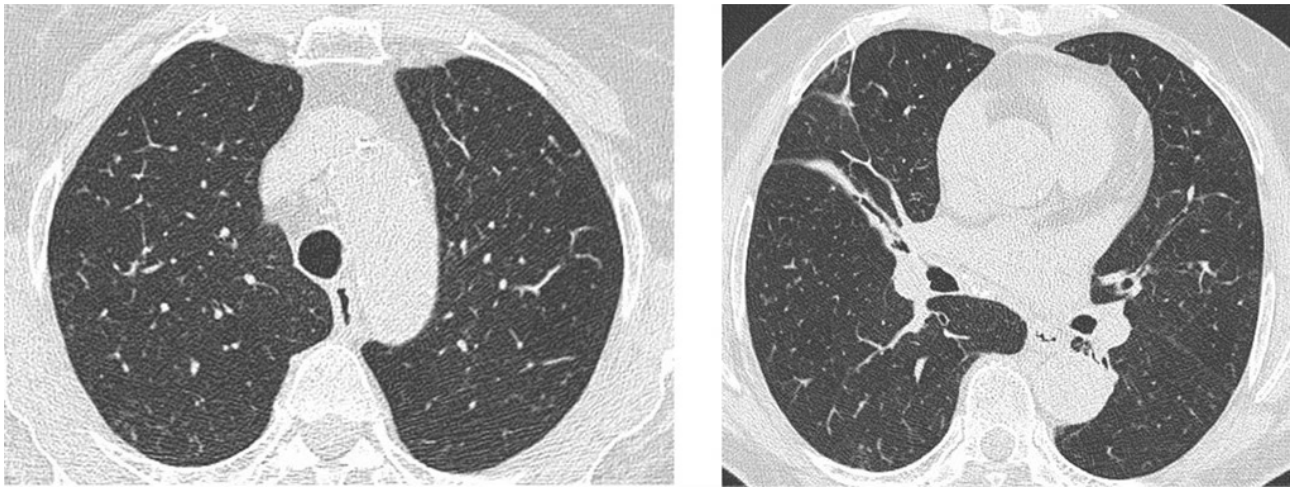

Figure 2. Chest HRCT 6 months after the suspension of golimumab showing resolution of the nodules.

mumab [14]. Prior to starting golimumab, she was being treated with a combination of leflunomide and chloroquine, as methotrexate was not tolerated. Treatment discontinuation of TNFi resulted in regression/stability of the lesions in most patients, as in our reported case[2]. Contrarily, there was one case where preexistent pulmonary rheumatoid nodules shrinkage was observed during etanercept therapy[15].

The mechanisms behind the nodules' formation are unclear. One known mechanism is drug-induced vasculitis by TNFi[16]. Alternatively, since TNFi reduce cell trafficking to inflamed joints, it has been suggested that they may favour the cellular infiltration of other tissues leading to rheumatoid nodules[10]. Immune dysregulation, particularly Th1 polarization and interferon (IFN)-γ/α overexpression, has also been implicated[17]. However, as in all the reported cases, a causal relationship with TNFi cannot be confirmed.

Accelerated rheumatoid nodulosis is also a well-known complication of methotrexate[18]. This is hypothesized to involve purine metabolism interference, adenosine A1 receptor-mediated macrophage activation, and subsequent immune-complex vasculitis, which may amplify granuloma formation in the presence of TNF-α suppression. In this case, methotrexate was initially maintained based on clinical reasoning — it had been well tolerated for over 20 years without previous evidence of pulmonary involvement, and we aimed to discontinue only one drug at a time to better assess causality while minimizing the risk of disease flare. The long-standing use of methotrexate without dose change, along with lesion resolution despite continued therapy, argues against its sole responsibility.

Glace *et al.* reported ten cases that had been treated previously with TNFi (etanercept or adalimumab), six of whom developed new or enlarging pulmonary rheumatoid nodules[19]. Rituximab was administered to all 10 patients, resulting in size reduction or disappearance of the nodules. The authors suggest that the probable efficacy of rituximab is supported by the presence of B lymphocytes in the periphery of the pulmonary nodules. Considering these findings, we decided that rituximab was the better option for our patient when disease activity recurred. Another possible treatment would be tocilizumab, which has also shown favourable effects, including in the previous case described with pulmonary nodules associated with golimumab[14]. However, exacerbation of rheumatoid subcutaneous nodulosis with tocilizumab has also been reported, highlighting the need for individualized therapeutic decisions[20].

Emerging evidence indicates that Janus kinase inhibitors (JAKi) may also represent a promising therapeutic option for rheumatoid nodules, both subcutaneous and pulmonary[21]. As oral small molecules that target the intracellular JAK–Signal Transducer and Activator of Transcription (STAT) pathway, they provide a relatively rapid onset of action, allow flexible dose adjustment and have the additional advantage of being effective in monotherapy, simplifying the treatment regimen, reducing sides effects and drug interactions[22].

CONCLUSION

Pulmonary rheumatoid nodules may occur as a complication of RA treatment, including with TNFi - we report the second case with golimumab. Following the exclusion of infection and malignancy, management typically involves discontinuing the TNFi and, if needed, switching to a biologic with a different mechanism of action. We suggest two future research directions: (1) single-cell transcriptomic profiling of nodule tissue to identify novel therapeutic targets, and (2) longitudinal

imaging cohorts to monitor nodule dynamics in relation to specific RA therapies.

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