

Occurrence of pulmonary rheumatoid nodules following biological therapies

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Abstract In rheumatoid arthritis (RA), disease activity is generally determined by the joint involvement, but the treatment outcome is often influenced by extra-articular manifestations. Authors present a 74-year-old female patient's case history, who was treated with seropositive RA. Marked disease activity was observed even following combined traditional disease-modifying antirheumatic drug (DMARD) treatment (disease activity score in 28 joints (DAS28)=6.6). Therefore, the patient received TNF- α antagonist therapy. Golimumab was administered subcutaneous (SC) once monthly which resulted in significant improvement in both clinical and laboratory signs (DAS28=3.43). However, the follow-up chest x-ray indicated multiple intrapulmonary foci and enlarged lymph nodes. Biopsies and histology excluded malignancy; rheumatoid nodules were confirmed. Anti-TNF therapy was discontinued and tocilizumab treatment was initiated. The IL-6 receptor inhibitor suppressed arthritic activity, and 2 months later, the follow-up chest x-ray showed a regression of chest nodules. Our cases, as well as reports from other centers, suggest that TNF blockade may induce rheumatoid nodulosis and the use of alternative biologics may be feasible as further treatment of RA.

Keywords Golimumab · Pulmonary rheumatoid nodules · Rheumatoid arthritis · TNF- α inhibitor · Tocilizumab

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive inflammatory disease involving multiple joints that leads to painful limitation of motion, disability, and a significant deterioration of the patients' quality of life. The process usually affects the joints, but sometimes, other organ systems can also be affected [1]. Extra-articular manifestations, such as vasculitis, atlanto-axial subluxation, polyneuropathy, carpal tunnel syndrome, pleuritis, pneumonitis, keratoconjunctivitis sicca, lymphadenomegaly, and others often occur in patients with high disease activity and may result in unfavorable prognosis.

In about 20–30 % of patients, seemingly harmless rheumatoid nodules may develop, which are usually present in the limbs; however, these may also occur within the bones or internal organs. Rheumatoid nodules may also cause differential diagnostic difficulties. Their size may vary from that of a grain of rice to that of a walnut. Their histological picture is very typical: the centrally located fibrinoid necrosis is surrounded by a palisade of multinucleated giant cells and by infiltrates of lympho-plasmocytoid cells on the outside.

Of all rheumatoid nodules appearing within internal organs, pulmonary nodules may cause significant differential diagnostic issues. Intrapulmonary nodules may occur in <1 % of RA patients. The presence of multiple rounded masses is usually detected by routine chest x-ray. The following conditions should be excluded: primary or metastatic solid tumors, lymphomas, granulomatous diseases, such as tuberculosis, granulomatosis vasculitis (Wegener's), aspergillosis, as well as infectious lesions including multiple pulmonary abscesses or fungal infection [1, 3, 4].

Clinical experience and literature data indicate that of all traditional disease-modifying antirheumatic drugs (DMARDs), the use of methotrexate and leflunomide contributes to the growth of nodules, while antimalarials, sulfasalazine, and corticosteroids may exert opposite effects

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[2, 3]. No review articles have yet been published on the possible effects of biologic DMARDs on rheumatoid nodules, however, a few case reports have been published suggesting that such nodules may develop during anti-TNF, primarily adalimumab, infliximab, or etanercept treatment [4, 5]. Also, no reports have become available with respect to golimumab and rheumatoid nodulosis.

Case report

We present the case of a 74-year-old female patient with a history of tonsillectomy, hemorrhoidectomy, cholecystectomy, gynecological plastic surgery, and endarterectomy due to left-side internal carotid artery stenosis. She also has controlled hypertension and bronchial asthma and she undergoes regular neurological check-ups due to trigeminal neuralgia.

Her arthritic symptoms developed in the summer of 2010, initially only presenting as swelling of both ankles. By April 2011, arthritis extended to the shoulders, wrists, and small joints of the hands. Laboratory tests revealed systemic inflammation (ESR=76 mm/h, CRP=20.5 mg/l) and seropositivity (IgM RF=45 IU/ml, anti-CCP=36 U/ml). According to the 2010 classification criteria, the diagnosis of seropositive RA was established. Low-dose corticosteroid and traditional DMARD (tDMARD) treatment was initiated but this was often insufficient due to the patient's individual intolerance and poor compliance. Corticosteroid therapy (12 mg/day methylprednisone tapered to 4 mg/day) exerted a favorable impact on disease activity; however, most tDMARDs cause various adverse effects. Methotrexate (15 mg weekly) resulted in unbearable itching. During leflunomide treatment (20 mg daily), a left-side bronchopneumonia developed thus the treatment had to be interrupted. When leflunomide was re-administered, itchy rashes appeared which could be controlled by antihistamines. Finally, the combination of leflunomide with 250 mg/day chloroquine was ineffective, as disease activity score in 28 joints (DAS28) was 6.31 in June 2011. Therefore, the initiation of biological therapy became necessary. During pre-screening, chest x-ray was negative. In October 2011, golimumab SC once monthly was administered. This therapy resulted in significant reduction in disease activity (DAS28: January 2012=4.66, April 2012=4.06), however, a number of subjective adverse events including undue chills not followed by fever, hand tremor, and mild itching occurred.

In April 2012, the chest x-ray performed at the six-month check-up indicated enlarged hilar lymph nodes and multiple intrapulmonary rounded masses (Fig. 1); therefore, golimumab treatment was suspended. Malignancies could not be confirmed nor ruled out by chest CT, therefore a series of investigations were performed. Abdominal CT, mammography, and gynecological



Fig. 1 Chest x-ray indicating enlarged hilar lymph node and multiple rounded masses

examination did not confirm malignancies and the repeatedly negative IGRA test ruled out tuberculosis. In June 2012, the patient underwent VATS surgery in order to obtain tissue samples. Yet, histology revealed no malignancy; on the other hand, the classic histological picture of rheumatoid nodules was observed (Fig. 2). The repeated chest x-ray in August 2012 described the same picture; the number and size of nodules remained unchanged. In the meantime, the patient's disease activity increased (DAS28=7.04).

In September 2012, tocilizumab treatment was initiated. It was well tolerated by the patient. Chest x-ray performed in October 2012 showed significant regression of the rounded masses. Fibrotic bundles developed at the former location of

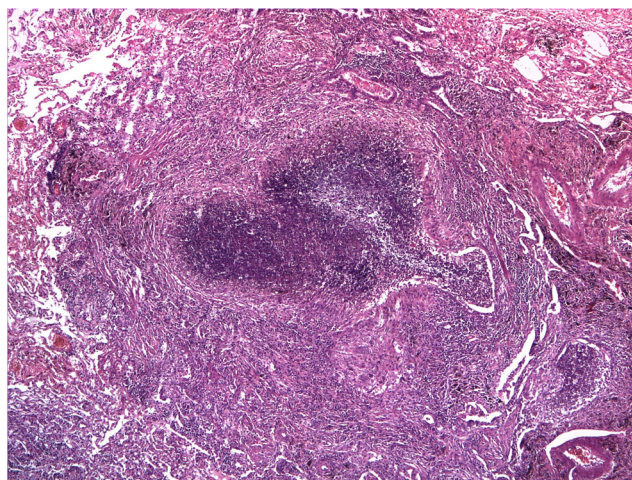


Fig. 2 Histology indicating a classical histological picture of a rheumatoid nodule (hematoxylin-eosin, $\times 100$)

nodules (Fig. 3). Tocilizumab also resulted in significant improvement in disease activity (DAS28 in January 2013=3.43) eventually resulting in clinical remission (DAS28 in April 2013=1.75, in September 2013=2.28). In April 2013, the chest x-ray had no recent pathological lesions. The patient has been successfully treated by tocilizumab to date.

Discussion

Pulmonary rheumatoid nodule is a rare extra-articular manifestation of RA; however, it may cause serious difficulties in differential diagnosis. For example, lung cancer is 1.43 to 1.63 times more likely to occur in RA patients compared to the general population [6, 7]. The possibility of malignancy is more likely if the patient is a smoker and/or has a higher disease activity. Infections with atypical manifestations are not at all rare in immunosuppressed patients [1, 3, 4].

Histological sampling is often needed for the final diagnosis. Japanese authors report that differential diagnosis can be facilitated by a fluorodeoxyglucose PET/CT scan of the nodules, but on the basis of their own two case reports, they warn that a well-differentiated adenocarcinoma may give false negative results or a granuloma with an active inflammation may give false positive results [8]. The selection of the right treatment requires a well-founded exclusion of malignancy, and this is only possible after histology is performed. This is especially important due to the fact that since 1972, four cases have been reported where malignant foci were present within rheumatoid nodules. Spina et al. [9] observed malignant cells at the periphery of a confirmed rheumatoid nodule,



Fig. 3 Post-treatment x-ray shows significant regression

which included small cell anaplastic parts, adenocarcinoma, and squamous cell carcinoma. According to the authors, the development of this rare combination was due to cytokines abundantly produced in RA that may cause heterogeneous mutations.

In the treatment of pulmonary rheumatoid nodules it is highly important to reduce clinical activity of the disease and eliminate the potential triggering agent. Literature data and clinical evidence show that the administration of leflunomide and methotrexate contributes to the growth of both the number and the size of nodules; however, no reviews have yet been published with respect to the effects of biologic DMARDs. Scattered case reports suggest that pulmonary rheumatoid nodules may develop during anti-TNF therapy. These nodules were resolved after the suspension of treatment. Toussirot et al. [5] published a report on 11 French patients, who developed pulmonary rheumatoid nodules upon anti-TNF therapy. Etanercept, adalimumab, and infliximab were administered to six, three, and two patients, respectively. Treatment discontinuation resulted in regression of the nodules in nine cases, while two patients were subsequently treated with rituximab. Derot et al. [10] reported definitive regression of rheumatoid nodules after the suspension of etanercept therapy. Andres et al. [11] report a case where pulmonary nodules were successfully treated by tocilizumab. Glace et al. [12] report ten cases with pulmonary rheumatoid nodules that developed during the administration of traditional DMARDs and/or TNF- α inhibitors. Here, rituximab was administered to all patients. In eight patients, the nodules disappeared or the size was reduced significantly. Methotrexate or leflunomide therapy was not discontinued after starting rituximab treatment.

Our case may be the first reported one, where pulmonary rheumatoid nodules developed upon golimumab treatment. The nodules, similarly to the case of Andres et al. [11], resolved after tocilizumab therapy. In conclusion, multiple rounded masses seen on the chest x-ray image of patients with RA are often pulmonary manifestations of the underlying disease; however, one must not rule out malignancies or infections. Correct diagnosis requires biopsy and histology. Furthermore, if these multiple rounded masses develop during anti-TNF therapy, it is advised to switch to another biological DMARD with different mode of action.

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Disclosures None

References

1. Myasoedova E, Davis JM, Crowson CS, Gabriel SE (2010) Epidemiology of rheumatoid arthritis: rheumatoid arthritis and mortality. *Curr Rheumatol Rep* 12:379–385
2. Kerstens P, Boerbooms AM, Jeurissen ME et al (1992) Accelerated nodulosis during low dose methotrexate therapy for rheumatoid arthritis; an analysis of ten cases. *J Rheumatol* 19:867–71
3. Braun MG, Van Rhee R, Becker-Capeller D (2004) Development and/or increase of rheumatoid nodules in rheumatoid arthritis patients following leflunomide therapy. *Rheumatology* 63:84–87
4. Kekow J, Welte T, Kellner U et al (2002) Development of rheumatoid nodules during anti-ecrosis factor alpha therapy with etanercept. *Arthritis Rheum* 46:843–844
5. Toussirot E, Berthelot JM, Pertuiset E et al (2009) Pulmonary nodulosis and aseptic granulomatous lung disease occurring in patients with rheumatoid arthritis receiving tumor necrosis factor alpha-blocking agent: a case series. *J Rheumatol* 36:2421–2427
6. Khurana R, Wolf R, Berney S (2008) Risk of development of lung cancer is increased in patients with rheumatoid arthritis: a large case control study in US veterans. *J Rheum* 35:1704–1708
7. Smitten AL, Simon TA, Hochberg MC et al (2008) A metaanalysis of the incidence of malignancy in adult patients with rheumatoid arthritis. *Arthritis Res Ther* 10:R45
8. Saraya T, Tanaka R, Fujiwara M et al (2013) Fluorodeoxyglucose (FDG) uptake in pulmonary rheumatoid nodules diagnosed by video-assisted thoracic surgery lung biopsy: two case reports and a review of the literature. *Mod Rheumatol* 23:393–396
9. Spina D, Ambrosio MR, Rocca BJ et al (2011) Rheumatoid nodule and combined pulmonary carcinoma: topographic correlations; a case report and review of the literature. *Histol Histopathol* 26:351–356
10. Derot G, Marini-Portugal A, Maitre B et al (2009) Marked regression of pulmonary rheumatoid nodules under etanercept therapy. *J Rheumatol* 36:437–439
11. Andres M, Vela P, Romera C (2012) Marked improvement of lung rheumatoid nodules after treatment with tocilizumab. *Rheumatology* 51:1132–1134
12. Glace B, Gottenberg JE, Mariette X et al (2012) Efficacy of rituximab in the treatment of pulmonary rheumatoid nodules: findings in 10 patients from the French Auto Immunity and Rituximab/Rheumatoid Arthritis registry (AIR/PR registry). *Ann Rheum Dis* 71:1429–1431