Short Report

Sarcoidosis-Like Lesions: Another Paradoxical Reaction to Anti-TNF Therapy?

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Abstract

Background: Since the introduction of anti-tumour necrosis factor [TNF] therapy in inflammatory diseases, paradoxical reactions are increasingly being reported. One of these paradoxical reactions is the development of sarcoidosis-like lesions. This presentation is paradoxical since anti-TNF therapy can also be therapeutic in refractory cases of sarcoidosis.

Methods: We report two cases of sarcoidosis-like lesions under anti-TNF therapy. Both were patients with inflammatory bowel disease [IBD], treated successfully with adalimumab. Next, we reviewed the literature for similar cases. Medical subject heading terms ‘adalimumab’, ‘infliximab’, ‘etanercept’, ‘golimumab’ or ‘certolizumab’, and ‘sarcoidosis’ were used to perform key word searches of the PubMed database.

Results: We identified 90 reported cases of sarcoidosis-like lesions, which developed during anti-TNF therapy. In most cases, the anti-TNF drug involved was etanercept. The median age was 43 years and there was a predominance of female patients. The underlying disease was rheumatoid arthritis in most cases, followed by ankylosing spondylitis and psoriasiform arthritis. In six cases, the underlying disease was IBD. In 71 cases there was at least a partial resolution by discontinuation of the anti-TNF treatment, initiation of steroids or both. Re-initiation of anti-TNF therapy gave relapse in seven out of 20 cases.

Conclusion: Sarcoidosis-like lesions are increasingly reported during anti-TNF treatment. Vigilance is appropriate when patients present with symptoms compatible with sarcoidosis.

Key Words: Inflammatory bowel disease; sarcoidosis; tumour necrosis factor antagonists and inhibitors

1. Introduction

Anti-tumour necrosis factor [TNF] agents have been shown to be well-tolerated and efficacious in the treatment of inflammatory diseases such as rheumatoid arthritis [RA], psoriasis, psoriasiform arthritis [PA], ankylosing spondylitis [AS] and inflammatory bowel disease [IBD]. However, the increasing use has led to a growing awareness of paradoxical reactions. A paradoxical reaction under anti-TNF therapy can be defined as the development or worsening of a condition that normally can be treated by this therapy. The most frequently reported paradoxical reactions are psoriasiform skin lesions. Other similar manifestations are uveitis, ileitis or colitis, joint manifestations, vasculitis and autoimmune diseases such as lupus and myositis. Since all kinds of paradoxical reactions are already observed during infliximab, adalimumab as well as etanercept therapy, a class effect is suggested. A less frequently described paradoxical reaction is ‘sarcoidosis’. We report two cases of patients with Crohn’s disease [CD] developing sarcoidosis-like lesions during adalimumab treatment. Next, we review the available literature.
2. Case History 1

A 30-year-old man was diagnosed with CD at the age of 17. He was treated with infliximab, which had to be discontinued due to a paradoxical psoriasiform reaction. Three months later, adalimumab was initiated for a serious CD relapse. After more than 5 years without any adverse events, he developed a bilateral intermediate uveitis with an anterior component, diagnosed by slit-lamp and dilated fundus examination. Differential diagnosis included an infection, CD-related uveitis and adalimumab-induced uveitis. Adalimumab was discontinued. Five months later, he presented with significant weight loss, fatigue, increased stool frequency and urgency. A computed tomography (CT) scan of chest and abdomen showed bilateral mediastinal and hilar lymphadenopathies, as well as multiple nodular lung lesions [Figure 1a], an enlarged spleen and multiple mesenterial lymphadenopathies. Blood analysis showed a C-reactive protein of 15 mg/l [normal <5 mg/l] and an angiotensin-converting enzyme [ACE] of 78 U/l [18–55 U/l]. Bronchoscopy and endobronchial ultrasounds with biopsies were performed. Mycobacterium tuberculosis and atypical mycobacteria were excluded. Histology showed non-necrotizing granulomas. Positron emission tomography combined with CT-scan [PET-CT] showed hypermetabolic lung lesions, multiple lymphadenopathies and elevated tracer uptake in rectum and sigmoid [Figure 1b]. The diagnosis of a novel onset sarcoidosis in combination with active CD was made. The patient was started on oral steroids [32 mg methylprednisolone]. Two months later, he felt better and regained his weight. Ophthalmological evaluation showed a decreased inflammation.

3. Case History 2

A 21-year-old man was diagnosed with CD when he was 10. He was treated with infliximab successfully for 6 years. Due to a delayed hypersensitivity reaction, therapy was switched to adalimumab. Eighteen months later he presented with a nodular skin lesion [Figure 2a]. Biopsy revealed a non-caseating granulomatous inflammatory process [Figure 2b]. Chest X-ray revealed hiliar lymphadenopathies. High-resolution CT confirmed these findings and demonstrated mediastinal lymphadenopathies and multiple small nodules. Laboratory analysis showed elevation of ACE [114 U/l]. No gastrointestinal or cardio-pulmonary symptoms were present. Adalimumab was discontinued. Retrospectively, serum analysis showed a complete absence of adalimumab. Broncho-alveolar lavage did not reveal an infectious cause. The diagnosis of sarcoidosis-like lesions was made. Four months after application of topical steroids and hydroxychloroquine, there was a deterioration of lung function tests. Furthermore, magnetic resonance imaging suggested cardiac involvement. High doses of oral steroids [64 mg methylprednisolone] were administered. After 1 month, there was an improvement of cutaneous lesions and lung function test results.

4. Discussion

We searched PubMed for case reports about sarcoidosis-like lesions under anti-TNF therapy by the combination of medical subject heading terms ‘adalimumab’, ‘infliximab’, ‘etanercept’, ‘certolizumab’ or ‘golimumab’, combined with ‘sarcoidosis’. This combination gave us 46 relevant articles. By studying the reference lists of the selected articles, ten additional articles were selected. The 56 articles reported in total 90 cases [details in Supplementary Table S1]. In all except two cases, there was a histological confirmation of sarcoidosis-like lesions. The median age was 43 years [range 7–72]. There was a predominance of females [61%]. The underlying anti-TNF therapy was etanercept [n=53, 59%], adalimumab [n=21, 23%] and infliximab [n=16, 18%]. Median duration between initiation of anti-TNF therapy and diagnosis was 22.5 months [range 1–84 months]. Underlying diseases were RA [n=51, 56.6%], AS [n=15, 16.6%], psoriasis or PA [n=13, 14.4%], IBD [n=6, 6.6%], juvenile idiopathic arthritis [JIA, n=4, 4.4%] and SAPHO-syndrome [synovitis-acne-pustulosis-hyperostosis-and-osteitis, n=1, 1.1%]. In 43 cases, the anti-TNF therapy was discontinued and steroids were started, with an improvement or resolution in 41 cases [95%]. In 37 cases, anti-TNF discontinuation was the only intervention, giving improvement in 32 cases [86%]. In five cases, addition of steroid therapy alone gave improvement in four cases [80%]. In one out of three cases improvement was observed without any intervention [33%]. Most frequently affected organs were lungs [n=67, including hiliar and mediastinal lymphadenopathies], skin [n=31] and eyes [n=12]. In 20 cases, there was a reinitiation of anti-TNF therapy. In six cases, the same drug was used, which gave recurrence in four cases. In 14 cases, another anti-TNF was initiated with relapse in three cases.

We reported two cases of sarcoidosis-like lesions, which developed during or shortly after anti-TNF treatment for CD. The development of sarcoidosis-like lesions during anti-TNF therapy can be seen as paradoxical since some anti-TNF agents are also used in refractory sarcoidosis. The development of sarcoidosis-like lesions

Figure 1. [a] Chest CT-scan showing mediastinal and hilar lymphadenopathies, as also multiple nodular lung lesions. [b] PETCT compatible with sarcoidosis combined with active Crohn’s disease.
Figure 2. [a] Brown reddish infiltrated skin nodule with apple jelly appearance on diascopy. [b] Granulomata with epithelioid histocytes, giant cells and lymphocytes.

Patient under anti-TNF therapy presenting with:
- Fever
- Dyspnee
- Skin lesions
- Uveitis

Consider work up in function of symptoms:
- Radiology (chest X-Ray, chest CT-scan, PET/CT-scan if necessary).
- Pulmonary work up: broncho-alveolar lavage, bronchoscopy with biopsy?
- Stain/culture/PCR for micro-organisms
- Cardiac investigation, Dermatologic investigation, Ophthalmologic investigation, Neurologic investigation if necessary
- Tissue biopsy

Result compatible with sarcoidosis-like lesions?*

Yes

Is a mycobacterial infection excluded?

Yes

Diagnosis of sarcoidosis-like lesions

Severity

Mild
- Cutaneous lesions
- Asymptomatic chest findings
- Cutaneous lesions
- No functional impairment of vital organs

- Discontinue anti-TNF therapy
- Local therapy
- Consider Steroids if no improvement

Severe
- Functional organ impairment
- Uveitis
- Decrease in lung function test results
- Cardiac involvement
- Neurologic involvement

- Discontinue anti-TNF therapy
- Associate steroid treatment

No

Further work-up

Figure 3. Proposed diagnostic algorithm and treatment strategy. *Non-caseating granulomas on biopsy or clinical diagnosis of sarcoidosis organ involvement. To make a clinical diagnosis of sarcoïd organ involvement we can refer to the WASOG sarcoidosis organ assessment instrument, a clinical tool based on expert opinion to make a diagnosis of sarcoidosis without biopsy. They suggest that for an adequate diagnosis, ‘highly probable’ or ‘at least probable’ involvement is necessary. In the case of a ‘possible’ involvement, an adequate clinical diagnosis of sarcoidosis needs additional findings.
under anti-TNF therapy is rare. Daen et al. estimated a frequency of 1:2800 [0.04%].

The exact etiology of the concomitant presentation is unclear, as well as the exact etiology of sarcoidosis itself.

Sarcoidosis is a granulomatous disease that can affect a wide variety of organs. It is thought to have a multifactorial origin in which environmental factors, genetic susceptibility and microorganisms can play a role. Non-caseating granulomas are the cornerstone.

There are several hypotheses to explain this paradoxical reaction. The oldest suggests etanercept to be the drug responsible. However, by evaluating the listed case reports, we might conclude that the development of sarcoidosis-like lesions under anti-TNF is a class effect. According to Massara et al., cytokine imbalance due to long-term TNF-α suppression could lead to paradoxical reactions. As reported by Cleynen & Vermeire, 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 auto-antigens which leads to paradoxical reactions. Another hypothesis is the role of an underlying infectious agent. Infection is suggested to be one of the underlying causes of sarcoidosis and treatment with anti-TNF therapy increases the infection risk. Toussirot et al. hypothesized a pre-existing latent sarcoidosis which comes overt by interrupting previous steroid therapy.

However, since the etiology of sarcoidosis is not yet fully explained, it is difficult to prove that the detected lesions are effectively sarcoidosis. We may perhaps have two manifestations of the same underlying disease. Both are chronic inflammatory diseases, characterized by formation of non-caseating granulomas. They also share other similarities, such as erythema nodosum, uveitis and arthralgia. Over 30 cases report an overlap between CD and sarcoidosis. CD and sarcoidosis may share a common pathogenesis and common genetic ground. The nucleotide oligomerization domain [NOD2] is well known as a susceptibility gene for CD, but is also reported in early-onset sarcoidosis and Blau-syndrome. A mutation in the caspase recruitment domain [CARD] 15 gene, coding for NOD2, can bring more insights in the underlying pathophysiology of CD. NOD2 is found in high concentrations in the ileum and the Paneth cells. A leucine-rich domain of NOD2 recognizes muramyl dipeptide, the essential structure of bacterial peptidoglycan. For the mutations associated with CD, there is a loss-of-function, leading to an increased bacterial translocation and production of antibodies against bacterial components. The mechanism for NOD1/CARD4 is similar.

In Blau-syndrome and early-onset sarcoidosis, however, there is rather a gain-of-function mutation in the same genes with an increased NF-kB activity. Sato et al. reported an association between two NOD2 polymorphisms and a severe pulmonary sarcoidosis subtype, whereas others could not find an association between the gene variants associated with CD and sarcoidosis. Further investigation is needed and may provide more insights into the pathogenesis and common ground of both diseases. Genome-wide association analysis revealed also other common susceptibility loci, e.g., 10p12.2. Coincidence between RA or PA and sarcoidosis are also reported. In several cases, anti-TNF therapy was used to treat both sarcoidosis and RA or PA. Chebib et al. reported also a case of concomitant CD and sarcoidosis in which both responded well to infliximab.

In our first case, the therapy with adalimumab had already been discontinued for 5 months when the patient presented. In the second case, the sarcoidosis-like lesions were first observed under adalimumab therapy, but a pulmonary deterioration occurred 4 months after discontinuing adalimumab. Moreover, adalimumab serum levels were absent at the moment of symptom onset. These findings demonstrate the difficulty to differentiate true sarcoidosis from sarcoidosis-like lesions. We propose an algorithm for diagnosis and treatment [Figure 3].

In conclusion, sarcoidosis-like lesions during anti-TNF therapy are not uncommon. The etiology of this manifestation remains unknown and difficult to explain. It is recommended to practitioners using anti-TNF therapy to be vigilant when patients present with asthenia, unexplained fever, dyspnoea, uveitis or skin lesions. When new granulomatous lesions are detected, it is recommended to exclude mycobacterial infections. However, when these investigations are negative, sarcoidosis-like lesions must be considered.

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Author Contributions
AD: acquisition of data, analysis and interpretation of data, drafting the article. MF: conception and design of the study, analysis and interpretation of data, revising critically for important intellectual content. SV, GVA, WW: revising critically for important intellectual content.

References
9. Massara A, Cavazzini L, La Corte R, Trotta F. Sarcoidosis appearing during anti-tumor necrosis factor alpha therapy: a new “class effect” paradox-
Anti-TNF and sarcoidosis-like lesions