CASE REPORT

Tumour necrosis factor (TNF) inhibitor-induced isolated pleural granulomas: a rare adverse effect

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SUMMARY

A 53-year-old man with a history of Crohn's disease on infliximab, presented with several weeks of cough and dyspnoea. He had a right-sided pleural effusion, found to be exudative with lymphocytic predominance. He underwent right-sided video-assisted thoracic surgery (VATS) with biopsies and pleurodesis. Histopathology showed pleural-based non-caseating granulomas with unremarkable lung parenchyma. Cultures were only positive for *Propionibacterium acnes*. 8 months later, he was found to have a left-sided exudative, lymphocytic predominant pleural effusion. Left-sided VATS and biopsies again showed pleural-based non-caseating granulomas with normal lung parenchyma. Having ruled out an active infection and malignant lesions, we diagnosed infliximab-induced pleural granulomas. Infliximab was stopped. The patient continues to do well at 6 years of follow-up. We believe this is the first report of tumour necrosis factor (TNF) inhibitor-induced isolated pleural granulomas. *P. acnes* and cytokine imbalance might be responsible for the pathogenesis of TNF inhibitor-induced granulomas.

BACKGROUND

The use of tumour necrosis factor (TNF) inhibitors has been steadily increasing over the last few years for the treatment of various immune-mediated disorders. The increased use of these agents has led to a greater recognition of their potential adverse effects. Commonly recognised adverse effects include increased risk of tuberculosis and fungal infections and cancer. They can also worsen heart failure and multiple sclerosis. TNF inhibitors can also rarely induce granulomatous inflammation or a sarcoidosis-like illness. Such granulomas have previously been described in lung parenchyma, skin, eyes and central nervous system. We describe a case of isolated pleural-based granulomas due to infliximab. Based on our literature search (Ovid MEDLINE, PubMed and Google Scholar), this is the first such case reported in English literature.

CASE PRESENTATION

A 53-year-old man presented with several weeks of dyspnoea, cough and fatigue. His medical history was significant for Crohn's disease and papillary thyroid cancer. He had been diagnosed with Crohn's disease 14 years earlier, and his illness course had been severe, characterised by penetrating, fistulising and perianal disease. He had undergone multiple small bowel resections. His

most recent surgery was 2 years prior to the onset of respiratory symptoms and consisted of resection of 5 cm segment of distal ileum, followed by primary end-to-end anastomosis. During the 8 years prior to developing respiratory symptoms, after failing to control the Crohn's disease with aminosalicylates, methotrexate and steroids he was started on infliximab infusions. He initially was treated with 3 mg/kg of infliximab every 2 weeks, but after the bowel resection 2 years earlier given the active disease, the dose was increased to 7.5 mg/kg. Since then, his Crohn's disease was deemed under control. He had a history of stage 2 (T2, N0, M0) papillary thyroid cancer. He was treated with partial thyroidectomy and radiation therapy 2 years earlier and was now deemed to be in remission.

On examination, his vital signs were within normal limits. He had decreased breath sounds and dullness to percussion in the right lower hemithorax. Basic chemistry and complete blood counts were within normal limits. Chest X-ray showed a right-sided pleural effusion. This was followed by a chest CT scan, which redemonstrated a moderate right-sided pleural effusion (yellow arrow) with mild compressive atelectasis (red star) of the posterior right lower lobe (figure 1A). No other lung parenchymal pathology or lymphadenopathy was seen. The patient underwent ultrasound guided thoracentesis and 1 L of dark yellow pleural fluid was drained. Postprocedure chest X-ray revealed near complete resolution of the pleural effusion (figure 1B). The effusion was an exudate based on Light *et al*'s criteria.¹ It had $0.081 \times 10^9/L$ white cells, 88% of which were lymphocytes. Bacterial, fungal and mycobacterial cultures were negative. Cytology of the pleural fluid did not reveal any malignant cells. Serum quantiferon was negative.

Despite thoracentesis, the patient continued to complain of cough and dyspnoea. A few days later, he also started reporting fatigue and poor appetite. His examination suggested reaccumulation of the right-sided pleural effusion. Given the negative infectious workup, we suspected a malignant lesion. The patient was therefore referred for video-assisted thoracic surgery (VATS). Intraoperatively, 1 L of reddish brown pleural fluid was drained. Studding was noted on the apical and diaphragmatic pleura. Multiple pleural and right lower lobe wedge biopsies were taken. Talc pleurodesis was also performed. Histopathology revealed chronic inflammation of the pleura with non-necrotising epithelioid cell granulomas (figure 2). There was a marked cuff of mononuclear cells including plasma cells. The underlying lung parenchyma was

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Figure 1 (A) Prethoracentesis CT scan showing moderate right-sided pleural effusion (yellow arrow) and compressive atelectasis (red star). (B) Post-thoracentesis chest X-ray showing complete drainage of the effusion.

spared. Periodic acid-Schiff, Grocott's methenamine silver and acid-fast bacillus stains were negative. Cultures were only positive for *Propionibacterium acnes*. No Reed-Sternberg cells were seen. Immunohistochemical stains were also negative for kappa and lambda light chains and IgG4. No formal diagnosis could be reached at that point.

Eight months later, the patient again presented with 2–3 weeks of cough and dyspnoea. Workup revealed a left-sided pleural effusion (figure 3). Thoracentesis was performed, and 1.2L of serosanguinous pleural fluid was drained. Further analysis revealed that it was an exudate with lymphocytic predominance. Cultures and cytological examination of the pleural fluid were negative. Given this and the histopathology report from right-sided VATS, the main diagnostic considerations were pleural granulomas due to underlying Crohn's disease versus infliximab-induced granulomas. The former was ruled out with upper and lower gastrointestinal endoscopies showing no evidence of active Crohn's disease. Given the possibility of infliximab-induced granulomas, infliximab's dose was halved. Initially, the patient did well, but 7 months later, the left-sided effusion recurred. The patient underwent left-sided VATS, drainage of the pleural effusion, pleural and left lower lobe wedge biopsies. Talc pleurodesis was also performed. The pathology results were similar to the ones from the right-sided VATS with pleural-based non-necrotising granulomas. No evidence of malignancy or infection was found. Having ruled out alternative aetiologies, we diagnosed infliximab-induced pleural granulomas. Infliximab was discontinued. At 6 years of follow-up, the patient continues to do well, without any recurrence of pulmonary symptoms. Crohn's disease required maintenance therapy and has remained well controlled with tacrolimus and vedolizumab.

Figure 2 (A) Low power: parietal pleura and adjacent chest wall soft tissue with granulomatous pleuritis (yellow arrow). Lung parenchyma is unremarkable (green arrow). (B) Low power: visceral pleura with occasional granulomas (yellow arrow). (C) High power: pleural granulomas (yellow arrow).

Figure 3 Chest X-ray showing left-sided pleural effusion.

DISCUSSION

Pulmonary granulomatosis and sarcoidosis-like illness have been well described with the use of anti-TNF agents.^{2–7} One of the largest case series was reported by Daïen *et al*,⁸ who reported their experience of 10 patients developing sarcoidosis while on anti-TNF therapies.⁸ Five patients had received etanercept, and three each received infliximab and adalimumab. Indications for therapy were ankylosing spondylitis in five patients, rheumatoid arthritis in four and psoriatic arthritis in one patient. Median time to the onset of symptoms from the initiation of therapy was 18 months (range 1–51 months). Median time to resolution of symptoms after discontinuing anti-TNF therapy was 6 months. TNF inhibitor-induced granulomas have also been reported in skin,⁹ eyes,^{5 10} liver¹⁰ and central nervous system.¹¹

However, two aspects make our case unique. First, all prior reports of TNF inhibitor-induced pulmonary granulomas/sarcoidosis were characterised by hilar lymphadenopathy and lung parenchymal lesions. Although pleural involvement has been described, it has always been in conjunction with hilar lymphadenopathy and lung parenchymal changes.¹² Our case is the first report of isolated pleural granulomas and effusions due to anti-TNF therapy. Second, our patient had been on infliximab for 8 years before the onset of symptoms. Based on our review of the past reported cases, this is the longest interval between the start of anti-TNF therapy and the onset of granulomas/sarcoidosis-like illness.

The mechanisms behind anti-TNF therapy-induced granulomas are not completely understood. In fact, this phenomenon appears to represent a paradox, since TNF inhibitors are often used in the treatment of refractory sarcoidosis.^{13–15} T-helper (TH) cells interact with the antigen presenting cells, which initiates the formation and maintenance of granulomas.⁸ TNF- α production is stepped up, which along with interleukin (IL) 2, IL-8 and interferon- γ (INF- γ), plays an important role in the progression of granulomas. Yet, TNF inhibitors appear to stimulate the granulomas formation process by increasing the ratio of TH-1 to TH-2 cells.^{16 17} They also increase the levels INF- γ , which further promotes granuloma formation.¹⁸

Infection-mediated theory has also been postulated to explain TNF inhibitor-induced granulomas. Abe *et al*¹⁹ found a significantly higher prevalence of *P. acnes* in lymph nodes of patients with sarcoidosis as compared with controls.¹⁹ This finding has led to multiple authors speculating that *P. acnes* may be the causative agent stimulating granulomatous inflammation and development of sarcoidosis.^{20–22} We hypothesise that anti-TNF agents, by virtue of their immunosuppressive properties,

decrease the clearance of *P. acnes*. This, in turn, may stimulate a granulomatous inflammatory response, as seen in our patient. However, more research is needed to better understand these mechanisms.

Looking back at our case, had we recognised this rare adverse effect earlier, we could have discontinued infliximab therapy sooner. This could have potentially spared our patient from disease recurrence on the left side and repeat VATS. The fact that isolated pleural-based granulomas due to TNF inhibitors had never previously been reported was the main factor behind the delay in recognition of this adverse effect.

Learning points

- ▶ Tumour necrosis factor (TNF) inhibitors can cause granulomas and sarcoidosis-like illness, typically involving lungs, skin, eyes and central nervous system.
- ▶ Rarely, TNF inhibitors can cause isolated pleural granulomas and effusions.
- ▶ This rare adverse effect should be considered when working up exudative lymphocytic pleural effusions after infectious and malignant lesions have been ruled out.
- ▶ Cessation of TNF inhibitor therapy leads to complete resolution of symptoms within a few weeks.
- ▶ TNF inhibitor-caused granulomatous inflammation is likely mediated by *Propionibacterium acnes* infection and an imbalance between T helper (TH)-1 and TH-2 cells.

Contributors MSA, RF and DD were involved in the planning, conception and design of this project. MSA and DD collected the history. MSA and RF did the literature search. NR evaluated and provided description regarding the histopathology.

Competing interests None declared.

Patient consent Obtained.

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REFERENCES

- 1 Light RW, Macgregor MI, Luchsinger PC, *et al.* Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med* 1972;77:507–13.
- 2 Almodóvar R, Izquierdo M, Zarco P, *et al.* Pulmonary sarcoidosis in a patient with ankylosing spondylitis treated with infliximab. *Clin Exp Rheumatol* 2007;25:99–101.
- 3 Farah RE, Shay MD. Pulmonary sarcoidosis associated with etanercept therapy. *Pharmacotherapy* 2007;27:1446–8.
- 4 Ishiguro T, Takayanagi N, Kurashima K, *et al.* Development of sarcoidosis during etanercept therapy. *Intern Med* 2008;47:1021–5.
- 5 Louie GH, Chitkara P, Ward MM. Relapse of sarcoidosis upon treatment with etanercept. *Ann Rheum Dis* 2008;67:896–8.
- 6 Massara A, Cavazzini L, La Corte R, *et al.* Sarcoidosis appearing during anti-tumor necrosis factor alpha therapy: a new "class effect" paradoxical phenomenon. Two case reports and literature review. *Semin Arthritis Rheum* 2010;39:313–9.
- 7 Peno-Green L, Lluberas G, Kingsley T, *et al.* Lung injury linked to etanercept therapy. *Chest* 2002;122:1858–60.
- 8 Daïen CI, Monnier A, Claudepierre P, *et al.* Sarcoid-like granulomatosis in patients treated with tumor necrosis factor blockers: 10 cases. *Rheumatology* 2009;48:883–6.
- 9 Bachmeyer C, Blum L, Petitjean B, *et al.* Granulomatous tattoo reaction in a patient treated with etanercept. *J Eur Acad Dermatol Venereol* 2007;21:550–2.
- 10 Hashkes PJ, Shajrawi I. Sarcoid-related uveitis occurring during etanercept therapy. *Clin Exp Rheumatol* 2003;21:645–6.
- 11 Sturfelt G, Christensson B, Bynke G, *et al.* Neurosarcoidosis in a patient with rheumatoid arthritis during treatment with infliximab. *J Rheumatol* 2007;34:2313–4.
- 12 O'Shea FD, Marras TK, Inman RD. Pulmonary sarcoidosis developing during infliximab therapy. *Arthritis Rheum* 2006;55:978–81.
- 13 Baughman RP, Drent M, Kavuru M, *et al.* Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med* 2006;174:795–802.
- 14 Doty JD, Mazur JE, Judson MA. Treatment of sarcoidosis with infliximab. *Chest* 2005;127:1064–71.
- 15 Saleh S, Ghodsian S, Yakimova V, *et al.* Effectiveness of infliximab in treating selected patients with sarcoidosis. *Respir Med* 2006;100:2053–9.
- 16 Maurice MM, Van Der Graaff WL, Leow A, *et al.* Treatment with monoclonal anti-tumor necrosis factor alpha antibody results in an accumulation of Th1 CD4+ T cells in the peripheral blood of patients with rheumatoid arthritis. *Arthritis & Rheumatism* 1999;42:2166–73.
- 17 Kawashima M, Miossec P. Effect of treatment of rheumatoid arthritis with infliximab on IFN gamma, IL4, T-bet, and GATA-3 expression: link with improvement of systemic inflammation and disease activity. *Ann Rheum Dis* 2005;64:415–8.
- 18 Furst DE, Wallis R, Broder M, *et al.* Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. *Semin Arthritis Rheum* 2006;36:159–67.
- 19 Abe C, Iwai K, Mikami R, *et al.* Frequent isolation of *Propionibacterium acnes* from sarcoidosis lymph nodes. *Zentralbl Bakteriol Mikrobiol Hyg A* 1984;256:541–7.
- 20 Esteves T, Aparicio G, Garcia-Patos V. Is there any association between sarcoidosis and infectious agents?: a systematic review and meta-analysis. *BMC Pulm Med* 2016;16:165.
- 21 Werner JL, Escolero SG, Hewlett JT, *et al.* Induction of pulmonary granuloma formation by *Propionibacterium acnes* is regulated by MyD88 and Nox2. *Am J Respir Cell Mol Biol* 2017;56:121–30.
- 22 Zhou Y, Hu Y, Li H. Role of *Propionibacterium acnes* in sarcoidosis: a meta-analysis. *Sarcoidosis Vasc Diffuse Lung Dis* 2013;30:262–7.

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