CASE REPORT

Successful treatment of recurrent pleural and pericardial effusions with tocilizumab in a patient with systemic lupus erythematosus

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SUMMARY

A 22-year-old Caucasian man presented to hospital with pleuritic chest pain. He had had a history of a sun-sensitive rash a year prior. Workup revealed normal cardiac enzymes and chest X-ray. However, electrocardiogram revealed ST elevation and PR depression, and echocardiogram revealed a slight pericardial effusion without other findings. A diagnosis of pericarditis was made. Subsequently, he was found to be positive for antinuclear antibodies (ANAs), as well as antibodies to SSA, SSB and double-stranded DNA; C3 was low, and C4 was undetectable. A diagnosis of systemic lupus erythematosus was made. The patient initially responded to high-dose ibuprofen. One month later, he developed a new pericardial effusion, this time with concomitant massive left-sided pleural effusion, requiring three separate thoracenteses draining a total of 6 L of pleural fluid. The recurrent effusion failed to respond to high-dose corticosteroid treatment. Owing to the severity and rapidity of the recurrence of pleural and pericardial effusion, intravenous tocilizumab was administered. The patient had excellent clinical and radiographic improvement. This case shows that tocilizumab may have a role in the treatment of intractable pleuropericardial effusion and other forms of lupus-associated serositis.

BACKGROUND

SLE is a chronic autoimmune disease characterised by the production of autoantibodies, which deposit within tissues and fix complement, leading to disease manifestations.¹ However, a variety of immunopathogenic mechanisms are involved, including TH1 and TH17 cell-mediated immunity and acute inflammation.² Serositis is a frequent manifestation in SLE and can be the presenting feature.³ The pleura is involved more commonly in SLE than in any other connective tissue disease. There is a reported cumulative incidence between 16% and 55% and a prevalence around 17%,^{4 5} with pleuritis occurring more commonly in men than in women.⁶

Pleural and pericardial effusions in SLE are usually bilateral, small in size, often asymptomatic and may not require specific therapy;⁷ however, symptomatic or otherwise significant effusions require therapy. We present a case of massive, recurrent pleural effusion with associated pericarditis responding to the IL-6 inhibitor tocilizumab.

CASE PRESENTATION

We present a case of a previously healthy 22-year-old Caucasian man, on no regular medications, who presented to hospital with pleuritic chest pain. Review of systems revealed a history of malar rash and separate photosensitive rash. With the exception of prevalent cigarette smoking, further review of systems and medical history were unremarkable. The remainder of social and family history was unremarkable. On initial presentation, vital signs were normal. General physical examination revealed mild distress but was otherwise within normal limits. Chest X-ray and cardiac enzymes were normal. Electrocardiogram, however, revealed ST elevation and PR depression. Echocardiogram revealed a slight pericardial effusion; a diagnosis of pericarditis with effusion was made. Ultimately, laboratory data revealed normal complete blood count, electrolytes, creatinine, albumin, liver enzymes and function, and thyroid-stimulating hormone. However, C reactive protein (CRP) was elevated at 24 and ESR at 37. Ultimately, connective tissue disease workup was positive for antinuclear antibodies (ANAs) at 1:1280, as well as antibodies to SSA, SSB and DNA at 1361. C3 was low at 0.69, and C4 was undetectable. The patient met the 1997 modified ACR criteria, as well as the 2012 SLICC criteria, for SLE. Initial therapy included ibuprofen 800 mg po three times a day and pantoprazole, with hydroxychloroquine 200 mg po two times a day subsequently added. Two months later, he returned to the emergency room with pleuritic chest pain. There was decreased air entry and dullness at the left lung base. A chest X-ray revealed a large left-sided pleural effusion. Thoracentesis was performed, and 2 L of pleural fluid was drained. Pleural fluid culture was negative for bacterial, mycobacterial and fungal infections. Cytology was negative for malignancy. Despite the treatment with corticosteroids, the effusion recurred requiring a second thoracentesis within 2 weeks and a third another week later.

DIFFERENTIAL DIAGNOSIS

Pleural effusions in patients with SLE can also be secondary to renal failure, pulmonary embolism, infection or congestive heart failure. Lupus pleuritis in SLE is thought to result from immune complex deposition, complement activation and direct binding of anti-dsDNA antibodies to mesothelium.^{8 9} Pleural effusions tend to develop during

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flares are usually characterised by an exudate with either lymphocytic or neutrophilic predominance and are often bilateral.¹⁰ Other causes of effusions include malignancies, pancreatitis, tuberculosis and rheumatoid arthritis (RA).

TREATMENT

Following the first thoracentesis, the patient was treated with 30 mg of prednisone daily with a taper. Thirteen days later, the patient presented for a third time to hospital with recurrent left-sided pleural and pericardial effusion. At that time, rheumatology/immunology was consulted to see the patient in hospital. CT scan revealed a massive left-sided pleural effusion, with basal consolidation, a small pericardial effusion and a non-specific ground glass density in the left upper lobe (figure 1A,B). Plan was made for 3 days of pulsed intravenous methylprednisolone. However, following a single dose of 500 mg intravenous methylprednisolone, the patient had a severe anxiety-type reaction. Hence, the steroid regimen was changed to prednisone 60 mg po two times a day; hydroxychloroquine 200 mg po two times a day was continued. The patient left hospital against medical advice. Despite this ongoing high-dose corticosteroid treatment, a week later the patient returned to hospital with recurrent left-sided pleural plus pericardial effusion. Again, 2 L

of pleural fluid was drained for a total of 6 L over the span of 3 weeks.

The addition of immunosuppressive therapy and/or colchicine was considered. However, given the severity and rapidity of the recurrence of pleural fluid in this case despite 60 mg of prednisone po two times a day, it was suspected that none of these strategies were likely to resolve the situation in a satisfactory time frame.

At that point, based on the known biology of lupus-associated pleuritis, and a previous case report of successful tocilizumab treatment of a patient with intractable pericardial effusion,¹ treatment with intravenous tocilizumab, 8 mg/kg q4 weeks, was initiated. Eight days following the third thoracentesis, chest X-ray revealed persistent pleural and pericardial effusion. The first dose of intravenous tocilizumab was administered 4 days later. Other treatments were not changed. Two days following the first infusion of tocilizumab, chest X-ray revealed total regression of the pleural and pericardial effusion (figure 2). The patient was completely asymptomatic.

With documented resolution of the pleural fluid, the prednisone was reduced to 50 mg po two times a day, and then 1 week later to 50 mg po daily with a plan to taper by 5 mg per day per week towards 25 mg daily, then by 2.5 mg per day per week towards 10 mg daily, as tolerated. Within 4 months, the patient successfully tapered to 10 mg of prednisone daily. Mycophenolate was prescribed following the third dose of tocilizumab with uptitration to 720 mg two times a day. The patient, however, did not initiate this medication for an additional 5 months.

OUTCOME AND FOLLOW-UP

In the subsequent 14 months of follow-up, on tocilizumab, the patient had no recurrence of pleural or pericardial effusion, with two exceptions. At month 8, a missed tocilizumab infusion resulted in recurrent pleuritic chest pain despite the aforementioned background medications. Furthermore, following transition to subcutaneous administration of tocilizumab 162 mg qweekly from intravenous dosing at month 16, an attempt to decrease dosing interval to every 2 weeks at month 21 led to another recurrence of pleuritic chest pain that resolved with

Figure 1 (A) CT chest demonstrating pericardial effusion. (B) CT chest demonstrating left-sided pleural effusion.

Figure 2 Chest radiograph (PA view), demonstrating marked regression of the recurrent left-sided pleural effusion.

resumption of weekly dosing. These events support the role of tocilizumab in controlling serositis in this patient.

DISCUSSION

SLE is characterised by increased T-cell and B-cell activation and abnormal distribution of lymphocyte subsets.¹¹ A hallmark of lupus is the presence of hyperactive B cells and loss of B-cell tolerance. Immune complexes containing nucleic acid autoantigens can engage and activate endosomal toll-like receptors (TLRs) and promote inflammation in SLE. Plasma cell expansion and the production of autoantibodies are also features, although the autoantibodies are benign unless generated in an inflammatory milieu, where class-switching to pathogenic isotypes occurs. Proinflammatory cytokines not only drive T-cell activation and dendritic cell maturation, but they can also stimulate extramedullary haematopoiesis, leading to expansion of innate immune cells which can induce the production of acute-phase proteins.¹²

IL-6 is a multifunctional cytokine that plays several critical roles in host defence.¹³ It can influence lymphocyte growth and differentiation and antibody production, and it mediates the acute-phase inflammatory response. Overexpression of IL-6 has been associated with coronary artery disease,¹⁴ proliferative mesangial cell glomerulonephritis,¹⁵ malignancy¹⁶ and haematological abnormalities.¹⁷ Given its pleiotropic characteristics, it has been implicated in the pathogenesis of many inflammatory and autoimmune diseases,¹⁸ including the cellular abnormalities seen in SLE.¹⁹ It has a critical role as a B-cell differentiating factor as well, and it is required for normal plasmablast and plasma cell survival.

In lupus patients, B cells pathologically secrete large amounts of IL-6 and continuously express IL-6 receptors, leading to cell hyperactivity that mediates organ damage.²⁰ Moreover, some studies have demonstrated that IL-6 correlates with disease activity and might even be useful as biomarker of SLE.^{21–22} Eilertsen *et al*²³ concluded that IL-6 could be the main driving cytokine in SLE arthritis. Their group performed a cross-sectional study measuring proinflammatory cytokines (IL-1, IL-2, IL-6, IL-8 and TNF- α) and the presence or absence of synovitis and joint deformities in 47 SLE patients. All cytokine levels were significantly elevated in SLE patients compared with controls, but they found that SLE patients with ongoing synovitis (19%) and joint deformities (11%) had increased erythrocyte sedimentation rate (ESR), IL-6 and anti-dsDNA Ab levels, and that IL-6 levels correlated with high ESR, anti-dsDNA Ab and reduced haemoglobin levels. In 2014, a study by Maier-Moore *et al*²⁴ showed that IL-6 deficiency corrects nephritis, lymphocyte abnormalities and secondary Sjögren's syndrome in SLE-prone mice.

Thoracic involvement occurs more frequently in SLE than in any other connective tissue disease, with more than half of SLE patients exhibiting some degree of involvement.²⁵ The clinical manifestations of pleural and pericardial disease in SLE include pleuritic chest pain, often accompanied by dyspnoea, cough and fever, and may occur with or without effusion. Asymptomatic pleural involvement may be even more common; pathological changes consistent with pleuritis or pleural fibrosis have been demonstrated at necropsy in 50–83% of patients.²⁶

Pleuritis-related pleural effusions are usually small or moderate (400–1000 mL) and may be asymptomatic, and massive pleural effusions are uncommon.²⁷

Tocilizumab is a humanised murine monoclonal antibody against the IL-6 receptor that prevents IL-6 activation.²⁸ It binds to receptors present in serum and joint fluid as well as membrane-bound IL-6 receptor (IL-6R) on the surface of cells (macrophages, B and T lymphocytes and dendritic cells),

leading to suppression of various previously mentioned immunological functions.²⁹

Tocilizumab is yet to be assessed in later-phase clinic trials in SLE, but a phase I trial demonstrated that tocilizumab is well tolerated in SLE patients; however, a temporary, dose-dependent neutropenia was observed.³⁰ Neutropenia was not a complication in our patient. A recent study in SLE patients showed that tocilizumab treatment can reduce B-cell and T-cell activation, memory B cells and autoantibody-producing plasma cells without impacting naive B cells populations.³¹

There are three case reports successfully using tocilizumab to treat pericardial effusions associated with RA^{32–34} and a single case of successful treatment with tocilizumab in a patient with SLE and intractable pericardial effusion.³⁵ In most of these cases, there was demonstration of high levels of IL-6 in the pericardial fluid compared to serum, suggesting that IL-6 is secreted from infiltrated macrophages in the pericardium, and tocilizumab inhibits activated macrophages and IL-6 in pericarditis.^{32–33–35}

To the best of our knowledge, this is the first reported case of the successful treatment of SLE-associated pleuritis and pleural effusion with tocilizumab.

Learning points

- This case highlights the important (and yet to be further investigated) role of IL-6 in the inflammatory response seen in SLE pathophysiology.
- Targeted therapy against IL-6 with tocilizumab or other anti-IL-6 strategies may be an important therapy for patients with SLE-associated pleural and pericardial effusion and other forms of SLE-associated serositis. Further investigation is warranted.

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Competing interests None declared.

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