CASE REPORT

Schnitzler's syndrome: a diagnostic conundrum

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SUMMARY

A 63-year-old man was referred to the rheumatology unit with myalgia, arthralgia and a widespread rash. He was investigated for rheumatological disease; however, this did not yield any specific findings. His symptoms were attributed to statin use and newly started antihypertensives which were promptly discontinued. There was some subsequent improvement in his symptoms so he was discharged. He represented 3 years later with pelvic bone pain which had responded to a course of oral steroids started by the general practitioner, who was treating a presumed diagnosis of polymyalgia rheumatica. However, MRI of the pelvis showed bone marrow oedema and the diagnosis was changed to mastocytosis. He did not tolerate or respond to initial treatment. It was not until a second opinion was sought from the dermatologists that the diagnosis of Schnitzler's syndrome was made and treatment with anakinra (an interleukin-1 receptor antagonist) was started with almost complete resolution of his symptoms.

BACKGROUND

This is a very unusual diagnosis with only a few documented cases throughout the world. There are no diagnostic criteria and no randomised controlled trials to provide an evidence base for treatment. As with this case, there are often significant delays in diagnosis which can have major impact on the patient's quality of life and well-being.

Of the other case reports that exist, there have been many different treatment options trialed from steroids and thalidomide to disease modifying anti-rheumatoid drugs such as methotrexate. Very recently there is more emerging evidence to support interleukin-1 (IL-1) receptor antagonism as a treatment modality with very positive outcomes, as we have found. However, this is an expensive treatment that is not very widely available and there is not much long-term data available currently.

CASE PRESENTATION

In 2008, a 63-year-old man was referred to the rheumatology unit with a history of myalgia and an intermittent widespread rash (figure 1). His symptoms started several months earlier, following a trip to Australia when he developed flu-like symptoms, in particular myalgia. Soon after his return he had a routine appointment with his general practitioner (GP), who found him to be hypertensive and started him on lisinopril. Within a few days of starting the ACE inhibitor, he developed a widespread rash.

The rash was attributed to the ACEi and it was stopped; however, within a week or two of stopping it, the rash returned. There was associated disabling muscle ache, fatigue and joint pain and within 6 weeks of onset, he had lost half a stone in

weight. At the time, his autoimmune profile was negative apart from a mildly elevated rheumatoid factor at 23. His plasma viscosity was high at 1.94 but thyroid function, full blood count, liver function, U+E's, creatine kinase and calcium profile were all unremarkable. It was at this point that his GP referred him to a rheumatologist.

When seen by the rheumatologist, the symptoms of myalgia were initially attributed to simvastatin which he was taking for mixed hyperlipidaemia and was advised to discontinue it for 8 weeks. His rash was attributed to an urticarial response to lisinopril. Interestingly, the patient reported that symptoms of myalgia improved after stopping the statin but that the episodic rash continued.

As the rash failed to settle on follow-up, he was referred to a dermatologist. The rash was noted to be maculopapular, widespread and erythematous. It was mildly pruritic and faded without leaving any scarring. C1 esterase levels were normal. A diagnosis of chronic idiopathic urticaria was made and he was advised regarding antihistamine therapy and later discharged from follow-up from both dermatology and rheumatology units.

In 2010, he was re-referred to the rheumatology units with ongoing musculoskeletal pain, in particular, severe bone pain affecting the pelvic area and an episodic rash. In the interim he had been diagnosed with polymyalgia rheumatica by the GP and given a course of oral steroids which he failed to respond to in the typical fashion. He had reported ongoing arthralgia and muscle pain that affected the girdle area. However, the steroids, initially 15 mg once a day and weaned to 7.5 mg over 12 months, were noted to improve some of his symptoms, in particular the muscle ache.

Further review of the patient and investigations by the rheumatologist found that he had a persistent non-specific inflammatory response, without any evidence of connective tissue disease. He had negative extractable nuclear antigen, antinuclear antibody and antineutrophil cytoplasmic autoantibody with normal complement. However, his plasma viscosity remained persistently raised above 1.80 (normal range 1.50–1.72) along with a low but persistently raised C reactive protein (ranging from 6 to 10); he also had normal results of electromyography.

The new bone pain, which was predominantly over the pelvic area, was investigated with MRI (figure 2). This was reported as showing some patchy marrow oedema in the proximal right femur extending into the intertrochanteric region of the femoral neck. There was also a similar area in the right posterior iliac blade abutting the sacroiliac joint associated with sclerosis. Taking these

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Figure 1 Widespread non-pruritic rash.

findings into account, along with the clinical presentation, a diagnosis of mastocytosis was made.

A bone marrow biopsy was arranged to confirm this diagnosis, unfortunately the sample was taken from an area that was not radiologically affected and subsequently it did not add to the diagnosis. Arrangements were made to proceed to an open biopsy but while this was being organised, empirical treatment for mastocytosis was started.

A combination of oral sodium cromoglycate, hydralazine and ranitidine was started to help control his symptoms. MRI was repeated to decide where the biopsy should be taken from; however, it showed that the original changes had resolved, therefore open biopsy was abandoned.

Unfortunately, the empirical treatment for mastocytosis was not tolerated by the patient; and by December 2011 they had all been discontinued as the patient reported that the sodium cromoglycate and hydralazine worsened his rash and the ranitidine caused him to have diarrhoea. He also reported that his symptoms had generally worsened on a reduced dose of prednisolone from 7.5 to 5 mg daily.

He was referred back to the dermatology unit for a second opinion in early 2012 with ongoing intermittent severe urticarial eruptions. It was at this point that the diagnosis of

Figure 2 MRI of hips and pelvis. Short TI inversion recovery sequence: marrow oedema within the right femur and femoral neck.

Schnitzler's syndrome was established. An incisional elliptical skin biopsy was taken to exclude urticarial vasculitis and immunoglobulins were checked as well as protein electrophoresis and early morning Bence-Jones protein. He was found to have an IgM paraprotein which further supported the diagnosis of Schnitzler's syndrome. The skin biopsy did not show evidence of urticarial vasculitis.

TREATMENT

After agreement from the Primary Care Trust, he was started, on exceptional grounds, on daily subcutaneous injections of anakinra (kineret), an IL-1 receptor antagonist. Within 24–48 h his symptoms started to improve and within several months he was off all oral steroids without any recurrence of his rash, myalgia and lethargy. His blood tests confirmed resolution of his raised inflammatory markers.

OUTCOME AND FOLLOW-UP

The patient is being monitored regularly by the dermatologists and the rheumatologists and he now has haematology follow-up for his paraproteinaemia.

DISCUSSION

Schnitzler's syndrome is a rare acquired systemic autoinflammatory disease that runs a chronic but usually benign course. There have not been any documented cases of spontaneous remissions.¹ A small proportion of patients will go on to develop a lymphoproliferative disorder such as lymphoplasmacytic lymphoma, Waldenstrom macroglobulinaemia or IgM myeloma.^{1 2} The original patient in whom the disease was first reported died at the age of 88 with lymphoplasmacytic infiltration of his liver.¹

The pathogenesis of Schnitzler's syndrome is unknown; however, it is described as a chronic, non-pruritic urticaria, associated with intermittent fevers, bone pain, arthralgia or arthritis, skeletal hyperostosis, lymphadenopathy and a low concentration monoclonal immunoglobulin M (IgM) gammopathy.^{1 2} Depending on the literature, between 10% and 45% of cases go on to develop haematological malignancy usually in the form of a lymphoproliferative disorder.^{3 4} Two main hypothesis of pathophysiology have been proposed, the first is that the deposition of the IgM paraprotein leads to the formation of immune complexes and the activation of the complement cascade, which results in the cutaneous manifestations of the syndrome. The second is that there is uncontrolled activation of IL-1- α , this is supported by the fact that the condition generally responds well to IL-1 pathway inhibition.^{2 4}

There is strong emerging evidence that anakinra, a recombinant form of human IL-1 receptor antagonist causes rapid improvement of clinical symptoms. Anakinra competitively inhibits the binding of IL-1- α and IL-1- β to the IL-1 receptor type 1.⁴ IL-1 is a proinflammatory cytokine mediator of cellular response during the inflammatory process. There is growing evidence of the use of anakinra in inflammatory diseases such as rheumatoid arthritis (RA).⁴

Our patient (as is documented in other case reports) demonstrated a dramatic response to anakinra which would support the role of IL-1 in the pathogenesis of Schnitzler's syndrome.^{3 5} Thalidomide has also been trialled as a treatment for Schnitzler's syndrome without the same improvement as seen in anakinra. In one case report thalidomide had to be discontinued due to polyneuropathy in a patient, although thalidomide (50 mg) with low-dose corticosteroid induced a partial response.⁴

Anakinra is licensed for the treatment of RA in combination with methotrexate in patients who have had an inadequate response to methotrexate alone.^{6–8} Four randomised, double-

Learning points

- ▶ In rare diseases, the time from presentation to diagnosis can be significantly delayed. When faced with such a difficult case it can be helpful to revisit the history and to seek second opinions which may provide a different perspective.
- ▶ Deciding what treatment to offer a patient when evidence base is limited is extremely challenging and lack of evidence base can prove a barrier to more experimental or restricted treatments.
- ▶ Although rare, the clinical features of Schnitzler's syndrome are very well documented and relatively straightforward to identify. Therefore, better awareness of its existence may help to improve diagnosis and might lead to the development of rigorous diagnostic criteria.

blind placebo-controlled trials have been completed to assess its short-term efficacy in adults with RA whereas its use in Schnitzler's syndrome is limited mainly to case discussions.⁷

The results of the RCTs found significant improvement in the American College of Rheumatology 20% response (ACR20) with 100 mg/day of anakinra compared with placebo. The most common side effect recorded was injection site reactions including bruising, inflammation and pain. Serious infections were less frequently reported and included bacterial infections such as cellulitis, pneumonia and bone and joint infections, 2.1% of patients treated with anakinra 100 mg/day for 6 months

compared with 0.4% of placebo-treated patients, although this was not a significant difference. Neutropaenia was reported in some patients on anakinra.^{7–9}

Contributors CF wrote the case report. AD contributed by proofreading and editing the manuscript, made the final diagnosis and was involved in patient's ongoing care.

Competing interests None.

Patient consent Obtained.

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