CASE REPORT

A case of IgG₄ oligoarthritis mimicking psoriatic arthritis

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SUMMARY

IgG₄-related disease (IgG₄-RD) is a rare but rapidly emerging immune-mediated fibroinflammatory condition that can affect almost any organ. It is typically associated with involvement of organs such as lymph nodes, submandibular glands, orbits, periaortic region and pancreas. However, IgG₄-RD presenting primarily as an inflammatory arthritis is much less recognised. We present a rare case of IgG₄-RD mimicking psoriatic arthritis. In spite of normal circulating IgG₄ plasma levels, a clinical index of suspicion was required to obtain a histopathological diagnosis. The patient's aggressive arthritis disease did not initially respond to typical disease-modifying agents such as methotrexate. Instead, we report a dramatic response to B cell depletion with rituximab. It is important to emphasise this case as a rare presentation of a rare disease. IgG₄-RD is a rapidly emerging condition and the diagnosis should be considered when the alternatives do not seem to fit.

BACKGROUND

IgG₄-related disease (IgG₄-RD) is a rapidly emerging immune-mediated fibroinflammatory condition that can affect almost any organ.¹ It is characterised by tumefaction or tissue infiltration by IgG₄-positive plasma cells, characteristic histological morphology and often, but not always, elevated serum IgG₄ concentrations.² The most commonly associated organs affected by IgG₄ disease include submandibular glands, lymph nodes, orbits, periaortic region in relation to retroperitoneal fibrosis³ and pancreas in the context of autoimmune pancreatitis.^{1,4} However, IgG₄-RD resulting in inflammatory arthritis is a much less recognised disease process.⁵ We present a case of an aggressive oligoarthritis related to IgG₄ that was difficult to treat but responded to B cell depletion with rituximab.

CASE PRESENTATION

A 30-year-old Caucasian man presented to our rheumatology clinic in June 2015 with right knee pain and swelling. He had a background of skin psoriasis and cerebellar medulloblastoma treated with debulking surgery and radiotherapy. He sustained trauma to his right knee 1 year prior, requiring intramedullary nail insertion. This was subsequently removed for concerns of infection, although no causative organism was identified and the pain and swelling persisted in spite of nail removal. He underwent a knee washout and was treated with a course of antibiotics, but the

symptoms persisted. In September 2015, he had an ultrasound-guided aspiration which revealed significant synovial thickening. Synovial aspirate was turbid with acute inflammatory infiltrate, 90% lymphocytes but no crystals on cytology or organisms grown on culture. Synovial biopsy was then performed and showed non-specific inflammatory infiltration but staining for IgG₄ plasma cells was not performed at that stage.

Over the course of 2015, he presented multiple times to hospital with rising inflammatory markers, spiking temperatures and nausea. He also complained of pain and swelling involving the contralateral left knee and right ankle. At presentation, his C-Reactive Protein (CRP) persisted above 250 mg/L and Erythrocyte Sedimentation Rate (ESR) above 100 mm/hour. He was treated with vancomycin for presumed osteomyelitis related to the previous intramedullary nail, but did not respond. Multiple blood, urine and synovial cultures did not reveal any organisms and mycobacteria culture was negative for all samples.

Blood tests at the time included complement that was within normal limits, raised IgA (5.28 g/L) and raised IgG (26.4 g/L). Serum IgG₄ level was not elevated at 0.95 g/L (NR <1.3 g/L). Ferritin was raised at 1266 µg/L. Serology was negative for anti-nuclear antibody, rheumatoid factor and anti-CCP antibody. Hepatitis B, C and HIV virology screens were negative. Syphilis and toxoplasmosis screen were also negative.

He went on to have an MRI scan of his knees which showed large bilateral joint effusions and anterior synovitis. Neither his symptoms nor his inflammatory markers responded to intramuscular methylprednisolone injection. We proceeded to administer 60 mg of methylprednisolone intra-articularly into both knees. This resulted in a dramatic improvement in his symptoms and his CRP normalised to 9 mg/L.

Concurrently, he was found to have haemoglobin of 54 g/dL associated with 15 kg weight loss and anorexia, but upper and lower gastrointestinal endoscopy did not reveal an underlying cause. Fluorodeoxyglucose positive emission topography (FDG-PET) was performed and reported to show several enlarged and metabolically active abdominal, pelvic, inguinal and popliteal lymph nodes. There was increased tracer uptake of both knee joints associated with large knee effusions (figure 1). Increased patchy distribution of tracer of axial and lower-limb skeleton was in keeping with increased bone marrow activity. Subsequently, bone marrow

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Figure 1 Fluorodeoxyglucose positive emission topography showing several enlarged and metabolically active abdominal, pelvic, inguinal and popliteal lymph nodes and increased tracer uptake of both knee joints associated with large knee effusions.

Figure 2 A histology section from the patient's lymph node biopsy demonstrating plasma cells staining positive for IgG₄ immunostain. Magnification x4.

and lymph node biopsy did not reveal any malignant cells, but rather confirmed changes in keeping with inflammation. Lymph node biopsy showed a predominance of plasma cells. With no underlying malignancy or lymphoproliferative disorder identified, a provisional diagnosis of seronegative inflammatory arthritis was made and the patient was discharged home with oral prednisolone 20 mg daily.

One month later, he represented with a recurrence of his bilateral knee effusions and pain in both knees and right ankle associated with a flare of scalp psoriasis. CRP had increased once more to 131 mg/L. He was then started on methotrexate 15 mg orally weekly but soon discontinued this due to severe nausea. His inflammatory arthritis progressed and did not respond to an intra-articular steroid injection. He went on to have pulsed intravenous methylprednisolone 1 g over 3 days, which terminated his arthritis and normalised his CRP to 12 mg/L.

He remained dependent on oral prednisolone, not managing to reduce the dose below 15 mg daily. Steroid sparing therapy with methotrexate 15 mg weekly was administered without clinical improvement.

Additional stains were then performed on the previous synovial and lymph node biopsies (figure 2). These showed that the plasma cells were IgG positive, and significant proportion were positive for IgG₄ (>50/high power field (hpf) to >30/hpf is highly suggestive).⁶

TREATMENT

On the basis of these findings, our patient was diagnosed with IgG₄-related inflammatory arthritis. He then received B cell depletion therapy with rituximab and successfully managed to wean off his prednisolone.

OUTCOME AND FOLLOW-UP

At the latest follow-up, he was managing his disease with maintenance oral methotrexate.

DISCUSSION

Our case demonstrates that IgG₄-RD can be a rare cause of inflammatory arthritis and should be considered as a cause of aggressive inflammatory arthritis. Although our patient demonstrated definite scalp psoriasis, the severity of inflammation and

lack of response to conventional treatment for psoriatic arthritis led us to consider an alternative diagnosis. The patient's general deterioration with significant weight loss reminds of importance of screening for malignancy, which was mimicked by an aggressive inflammatory process. IgG₄-RD presenting with arthritis is rare—only four previous cases have been described.^{5–9} Of these, three out of four demonstrated organ infiltration typically found in IgG₄-RD (sialadenitis, pancreatitis and nephritis). The one case with arthropathy only occurred in a 74-year-old woman with significantly elevated plasma IgG₄ levels who responded to a 12-week course of low-dose prednisolone (15 mg).⁸ In contrast, our patient was younger and exhibited a more aggressive inflammatory response, requiring higher doses of corticosteroids with a failure to wean below 15 mg prednisolone.

The absence of elevated serum IgG₄ levels should not detract from the diagnosis as only 51% of patients from a large case series demonstrated this.¹ Also noted were elevations in other IgG subclasses in patients with IgG₄-RD with normal IgG₄ levels. Our patient did not demonstrate these findings, nor did he demonstrate low complement, also a feature in 25% of patients with active disease.¹

Evaluating the extent of organ involvement in IgG₄-RD and assessing for malignancy can be achieved by FDG-PET scanning.¹⁰ The prevalence of multiorgan involvement has been found to be up to 97% with appreciable differences in appearance from metastatic malignancy.¹¹ In our case, an FDG-PET only demonstrated active synovitis in the knees and multiple metabolically active lymph nodes in the abdominal and pelvic areas. Unusually, there was no evidence of IgG₄-RD multiorgan involvement. The distinction between lymphoma and IgG₄-RD in this case was impossible to make on FDG-PET and we were aware of the association of malignancy preceding IgG₄ disease or the possibility of a paraneoplastic phenomenon.¹²

Our case demonstrates the importance of B cell depletion therapy in treating IgG₄-RD. Our patient responded dramatically to rituximab given at the standard inflammatory arthritis dose of 2×1g

infusions administered 2 weeks apart. Previous cases of IgG₄-RD have responded well to rituximab with an appreciable decline in serum IgG₄ levels due to peripheral B cell depletion.¹³ However, a separate mechanism of action of rituximab such as inhibition of differentiation of IgG₄+ B lymphocytes into plasma cells may explain the improvement in our patient. Rituximab therapy can lead to rapid and sustained responses in IgG₄-RD and should be considered for reduction in corticosteroid burden.¹⁴ Finally, it is important to emphasise this case as a rare presentation of a rare disease. Knowledge of IgG₄-RD is evolving and the diagnosis should be considered when nothing else seems to fit.

Contributors Both authors managed the patient in clinic and on the ward during his admission. Both authors summarised the case, performed a literature review and wrote the case report. ZF is the corresponding author and NM is the senior author of this submission.

Competing interests None declared.

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Learning points

- ▶ IgG₄-related disease (IgG₄-RD) is a rare but rapidly emerging immune-mediated fibroinflammatory condition that can affect almost any organ.
- ▶ IgG₄-RD can present as an aggressive seronegative oligoarthritis.
- ▶ In spite of normal circulating IgG₄ plasma levels, a clinical index of suspicion is required to obtain a histopathological diagnosis.
- ▶ B cell depletion with rituximab is an important therapeutic option in treating IgG₄-RD.

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