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Anca-Negative Large-Vessel Vasculitis Masquerading As Seronegative Inflammatory Polyarthritis: A Case Series

Jethwa H
Shabbir S
Steuer A

Department of Rheumatology, Wexham Park Hospital, Slough, UK

Abstract

Aortitis is an umbrella-term describing inflammation of the aorta and is a form of large-vessel vasculitis. The clinical presentation is highly variable, but can include back pain, abdominal pain, fever or shortness of breath; some patients present with fatigue, limb pain or weakness, light-headedness, pre-syncope/syncope or headaches. Aortitis may be primary in origin (Takayasu's arteritis) or, less commonly, may be secondary to infection (such as syphilis or tuberculosis) or rheumatoid arthritis; aortitis associated with seronegative inflammatory arthritis is rare. We report two cases of aortitis in patients initially presenting withsymptoms of seronegative inflammatory arthritis. This report highlights the need for a high index of suspicion of large-vessel vasculitis in patients with inflammatory arthritis in whom raised inflammatory markers persist despite improvement in joint disease, and the value of positron emission tomography–computed tomography (PET-CT) in these instances.

Keywords

Aortitis; Large Vessel Vasculitis; Pet-Ct; Seronegative Arthritis; Inflammatory Arthritis

Introduction

Aortitis is a form of large-vessel vasculitis. The two major variants of large-vessel vasculitis are giant cell arteritis (GCA) and Takayasu's arteritis [1]. Less commonly, it may be secondary to infection (such as syphilis or tuberculosis) or other autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus and Behçet's disease [1].

The clinical presentation is highly variable, but can include back pain, abdominal pain, fever or shortness of breath; some patients present with fatigue, limb pain or weakness, light-headedness, pre-syncope/syncope or headaches. Due to the non-specific presentation, diagnosis is often aruduous. Complications of untreated aortitis include aortic anerurysms, rupture or dissection.

We report two patients who initially presented to the rheumatology clinic with features of seronegative inflammatory arthritis. Despite improvement in their joint disease with disease-modifying therapy, they continued to show systemic symptoms and raised inflammatory markers persisted. Following an extensive work-up, aortitis was diagnosed by positron emission tomography-computed tomography (CT-PET).

Case Presentations

Case 1

A 63 year old gentleman presented with a two week history of a symmetrical polyarthritis affecting the small joints of his hands. He had elevated inflammatory markers (C-reactive protein (CRP) 205 mg/L, erythrocyte sedimentation rate (ESR) 115 mm/hr, ferritin 3000 mcg/L) and raised liver enzymes (alanine aminotransferase (ALT) 100 units/L and alkaline phosphatase (ALP) 173 units/L). Serological tests were negative for rheumatoid factor (RF), anti-CCP antibodies, anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibody (ANCA (proteinase 3 (PR3) and myeloperoxidase (MPO)). Virology tests for hepatitis B and C, human immunodeficiency virus (HIV) and venereal disease research laboratory (VDRL) tests were negative. Urine and blood cultures were negative. A transthoracic echocardiogram and full body computed tomography (CT) scan were normal.

The presence of severe polyarthritis, mild liver dysfunction, and markedly raised ferritin without rash or fever led to a working diagnosis of adult-onset still's disease. Oral corticosteroid (prednisolone 30mg once daily) was started, and successfully weaned down with clinical improvement and resolving inflammatory markers (CRP 18 mg/L, ESR 29 mm/hr, ferritin 750 mcg/L).

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***Corresponding author:**

Jethwa H
Department of Rheumatology
Wexham Park Hospital, Slough, UK
E-mail: hannahjethwa@nhs.net

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On gradual weaning of prednisolone, the inflammatory arthritis flared. This settled with the introduction of methotrexate 15 mg once weekly.

18 months later, in view of clinical remission on methotrexate, the dose was reduced to 7.5 mg weekly. A rise in ESR coincided with the methotrexate dose reduction. The patient now complained of frontal headaches, dizziness, pre-syncope and new upper limb claudication. There was no temporal headache, visual disturbance, jaw claudication or scalp tenderness.

A PET-CT subsequently demonstrated aortitis with large vessel arteritis (Figure 1). He was recommenced on prednisolone 30mg and methotrexate dose was re-escalated to 15 mg. The patient's clinical response was dramatic, with a marked fall in his inflammatory markers: CRP 12 mg/L (from 88mg/L), ESR 34 mm/hr (from 103 mm/hr) and ferritin 707 mcg/L (from 1066 mcg/L). He remains under rheumatology follow up, and his condition is quiescent.

Case 2

A 75 year old gentleman presented to the emergency department with a seronegative polyarthritis. A full body CT was normal. Methotrexate 7.5mg once weekly was commenced, and he remained well for two years.

He then presented with an eight week history of increasing epigastric discomfort worse after eating. There was no active inflammatory arthritis at this time, however the patient had lost four kilograms of weight over a period of four months. Inflammatory markers showed a CRP 109 mg/L and ESR 77 mm/hr, with a normocytic anaemia (haemoglobin (Hb) 126 g/L). Urea and electrolytes, and liver function tests were normal, as were thyroid function tests, immunoglobulins and serum electrophoresis. Serological tests were negative for RF and CCP, ANA, ANCA (PR3 and MPO). Virology tests for hepatitis B and C, HIV and VDRL were negative. Urinary protein:creatinine ratio was normal.

Methotrexate was held whilst awaiting further investigations. An upper gastrointestinal endoscopy was normal. A transthoracic echocardiogram showed mild pulmonary hypertension only.

Due to the unexplained persistent chronic inflammatory response, a PET-CT was organized, which showed a large vessel vasculitis and aortitis (Figure 2). The patient was commenced on prednisolone 30mg.

After just one week of corticosteroid therapy, the inflammatory markers had reduced: CRP 5 mg/L and ESR 17 mm/hr, with resolution of the anaemia. The prednisolone was slowly weaned and methotrexate 7.5mg re-introduced. The patient remains symptom free, under regular rheumatology follow up.

Discussion

Inflammatory polyarthritis is a common condition seen in rheumatology clinics and, although raised inflammatory markers and systemic systems can be associated with the underlying joint inflammation, these features tend to subside upon commencement of effective disease-modifying therapies. In view of the vague symptomatology associated withaortitis, a high index of suspicion is required in patients who demonstrate an atypical response to treatment. In these reported cases, we suspect the symptoms of polyarthritis were the initial manifestation of the ANCA-negative large vessel vasculitis.

In addition to the more common causes of large vessel vasculitis, cases have been reported of aortitis related to paraneoplastic disorders [2], sarcoidosis [3] and IgG4-related diseases [4].Neither of our patients fulfilled the criteria for giant cell arteritis, therefore temporal artery biopsies were not performed. Given the arthropathic presentation, IgG4 disease was not considered and full body CT scans in both patients did not demonstrate underlying malignancy.

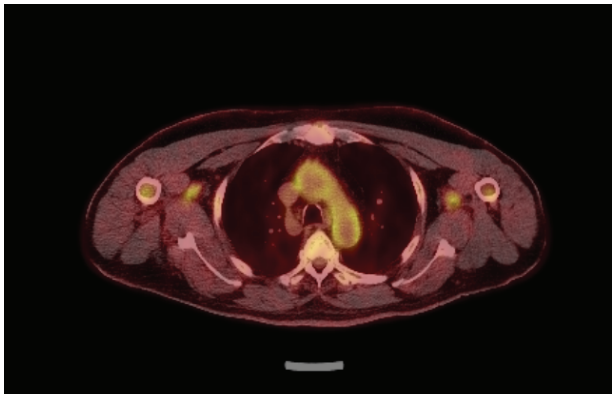

Figure 1: CT-PET image showing increased uptake of tracer (fluorine-18 (F-18) fluorodeoxyglucose (FDG)) in the aortic arch of patient one.

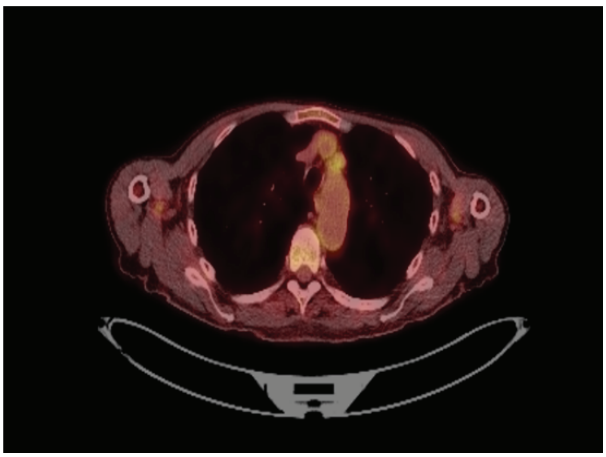

Figure 2: CT-PET image showing increased uptake of tracer (F-18 FDG) in the aortic arch of patient two

Rheumatoid vasculitis is rare and thought to affect only 1-5% of patients with RA, and occurs almost exclusively in patients with seropositive nodular RA [5]. Although this can affect any organ in the body, the skin or peripheral nerves are involved in more than 80% of patients [5].

A handful of case reports exist on patients with RA with aortitis, for example Kaneko et al. [1] report a 69 year old female who initially presented with symmetrical inflammatory polyarthritis and was found to have a positive rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) levels (215.4 and 51.1 IU/mL, respectively). Diagnosis of seropositive RA was made and she was commenced on Sulphasalazine, which was later supplemented with Tacrolimus due to ongoing active disease. Four years later, she developed a one week history of fever, cough and back pain and, following extensive investigations, was diagnosed with aortitis on PET-CT.

Kaneko et al. [2014] [1] also performed a systematic review of patients with RA aortitis and, of the 24 other cases identified, only three of these patients had seronegative disease (note: serology was not documented in two of these cases).

In 1989, Gravallese et al. [6] reviewed 188 autopsy cases of patients with RA and identified features of aortitis in ten of these, nine of whom had seropositive disease [7]. Although involvement of the thoracic aorta was most common, involvement of both the thoracic and abdominal aorta was present in four cases. Interestingly, the diagnosis of aortitis was not made until autopsy in all ten cases;

furthermore, six of these patients died due to complications of their vasculitis, including four patients with coronary arteritis and associated myocardial infarction.

Conclusion

The patients we report presented with features of seronegative inflammatory arthritis and although their disease was initially well-controlled with disease-modifying treatment, the development of systemic symptoms associated with persistence in elevated inflammatory markers lead to a suspicion of large-vessel vasculitis. Although vasculitis is only rarely associated with patients who have seronegative inflammatory disease, a high index of suspicion is needed to make prompt diagnosis and initiate timely management to avoid associated complications.

Conflict of Interest

There are no conflicts of interest to declare.

For the purposes of this case report, patient details have been anonymised and informed verbal consent has been obtained from each patient.

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