SHORT REPORT

A case of Crohn's disease complicated by Adult Onset Still's Disease

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Received 2 December 2009; received in revised form 24 February 2010; accepted 25 February 2010

Abstract

Arthritis and arthralgia are the most common extra-intestinal manifestations of Inflammatory Bowel Disease (IBD), occurring in up to a third of patients. These may affect the peripheral or axial skeletal system and may or may not reflect disease activity. As a result, it is challenging to identify an alternative diagnosis to account for joint manifestations in the setting of IBD. We describe a case of a 30 year old woman with quiescent Crohn's colitis who presented with 2 weeks of fever, flitting arthralgia, a sore throat and a nocturnal rash on her thighs. She denied any gastrointestinal symptoms to suggest a flare up of IBD. Investigations revealed a neutrophilia and a markedly elevated serum ferritin. The patient met all four major and several minor Yamaguchi criteria for Adult Onset Still's Disease (AOSD). She was treated with corticosteroids and analgesia with resolution of her symptoms and normalisation of her biochemical markers.

1. Introduction

Musculoskeletal manifestations are the most common extra-intestinal feature of IBD, occurring in up to a third of patients. Males and females are equally affected and involvement varies from arthralgia to acute arthritis with painful swollen joints. Both the peripheral and/or the axial skeletal systems may be affected. The prevalence of peripheral arthritis is reported to be between 5–10% in ulcerative colitis and 10–20% in Crohn's disease. There are two types of peripheral arthritis in IBD. Type 1 is pauciarticular, involving less than five large joints. This sub-type predominantly affects the lower limb, is usually self-limiting and is related to luminal disease activity. Type 2 is a symmetrical polyarthritis involving five or more small joints (predominantly the hands) and is independent of luminal disease activity. Both types 1 and 2 are typically non-erosive in nature.

In addition, patients with IBD may develop other autoimmune arthritides and population-based studies have

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doi:10.1016/j.crohns.2010.02.010
demonstrated an increased risk of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthropathy. It has been suggested that these disorders may share common pathogenic pathways. Herein we report a case of quiescent Crohn’s disease presenting with an acute arthritis, fever and a skin rash that was subsequently diagnosed with Adult Onset Still’s Disease.

2. Case report

A 30 year old woman diagnosed with left sided Crohn’s colitis, following a colonoscopy with suggestive histology on colonic biopsies in 2002, presented to the emergency department with a 2-week history of intense flitting arthralgia involving both of her large and small peripheral joints, fever, sore throat and a nocturnal rash on her thighs. She did not describe any gastrointestinal symptoms to suggest a flare and did not report any insect bite or relevant travel history. She had previously been treated for acute flare four months prior to this presentation as an outpatient with corticosteroid enemas and was maintained on oral mesalazine with good response.

On examination she was pyrexial, with a temperature of 38 °C and tachycardic (100 beats per min). Her pharynx was injected and examination of her left wrist revealed an active synovitis. She had an erythematous macular rash on her thighs (Fig. 1). The rest of the examination was normal. A full blood count demonstrated a neutrophilia of 19×10⁹/L (normal range 4.0–10.0) and a mild thrombocytosis of 470×10⁹/L (normal range 178–400), with a normal haemoglobin of 12.4 g/dl. Urea and electrolytes were normal. However, liver function tests were deranged: alkaline phosphatase 146 U/L (normal range 40–120), gamma-glutamyl transferase 66 U/L (normal range 0–35), aspartate transaminase 66 U/L (normal range 5–40). Inflammatory markers were significantly elevated with an Erythrocyte Sedimentation Rate of 100 mm in 1 h (normal range 0–15) and a C-reactive protein of 190 mg/l (normal range 0.0–5.0). The latter remained significantly elevated during the course of her admission. Creatinine kinase was normal. Chest X-ray (Fig. 2) revealed a left sided pleural effusion. There were no abdominal collections or lymphadenopathy on abdominal ultrasound scan. A septic screen including urine, blood and sputum cultures, pleural tap, lumbar puncture and bone marrow biopsy were all negative. Similarly, viral serology for hepatitis A, B and C as well as cytomegalovirus and Epstein–Barr virus were negative for active disease. Further radiology in terms of an abdominal computed tomography scan was unremarkable. A colonoscopy with terminal ileal intubation demonstrated quiescent Crohn’s disease.

During the course of her admission she was empirically treated with broad spectrum intravenous antibiotics, pending the results of the above investigations. Oral mesalazine was continued. She also received paracetamol as an analgesic and anti-pyretic agent. Despite these interventions, her pyrexia persisted, registering temperatures above 40 °C over several weeks. In consultation with our rheumatology colleagues, the following investigations were performed: rheumatoid factor, antinuclear antibodies, uric acid, anti-cyclic citrullinated peptide and a procalcitonin. These were all negative. However, a markedly elevated serum ferritin of 20 380 µg/L (normal 15–150) was noted.

A diagnosis of Adult Onset Still’s Disease (AOSD) was made as our patient fulfilled all four major Yamaguchi criteria for this disorder: fever more than 39 °C, arthralgia lasting more than two weeks, a maculo-papular salmon-pink rash and a white cell count of more than 10 ×10⁹/L. In terms of minor criteria, she had a sore throat, abnormal liver function tests and a normal rheumatoid factor and antinuclear antibody level. She was commenced on non-steroidal anti-inflammatory drugs (NSAIDs) and prednisone at 1 mg/kg. This resulted in a rapid recovery of her joint pain over the ensuing
days and a normalisation of her body temperature, skin rash and biochemical markers. Moreover, there was a 10 fold decrease in the serum ferritin level on discharge. Prednisone was subsequently weaned and stopped while mesalazine was replaced with sulphasalazine in order to take advantage of the anti-arthritic effect of the sulphasalazine component.\(^3\) She remains asymptomatic at follow up visits, both in terms of the Crohn’s colitis and AOSD.

### 3. Discussion

AOSD, also known as adult-onset juvenile rheumatoid arthritis, is a rare immune-mediated multi-systemic inflammatory disorder characterised by daily spiking high fevers, arthritis or arthralgia and a salmon-pink evanescent rash. In 1897, George Still described signs and symptoms of the disease in 22 children and in 1971, Eric Bywaters identified 14 adults with a disorder similar to paediatric Still’s disease, thereby establishing a new disease entity named AOSD.\(^9\) The aetiology of AOSD is unknown but infectious triggers either bacterial or viral, as well as genetic factors are thought to play a role.\(^9\) The most sensitive set of criteria was proposed by Yamaguchi et al. and include four major and four minor criteria as listed in Table 1.\(^7,8\) The presence of five or more criteria of which at least two are major criteria yield a sensitivity of 96.2% and a specificity of 92.1%.\(^7\) Additional clinical features of AOSD include pleural effusion, pericarditis, transient pulmonary infiltrates and haematological manifestations such as pancytopenia and thrombotic thrombocytopenic purpura (which in turn may manifest as renal failure, cerebral infarction or encephalopathy).\(^11,12\) Our patient fulfilled all four major and three minor Yamaguchi criteria. In addition, she also had evidence of a left sided pleural effusion which has been described in AOSD.\(^12\)

Although this patient had a long standing, confirmed diagnosis of Crohn’s disease, we were compelled to search for another explanation for her symptoms, given the atypical presentation and disease course, in particular, arthralgia affecting multiple joints, the presence of an atypical rash and an unremitting fever, in the absence of active IBD. A thorough search for sepsis and neoplastic disease, such as lymphoma, proved to be negative as were serological markers for several other rheumatological conditions. A raised serum ferritin of greater than 20 000 µg/l led us to consider a diagnosis of AOSD, complicating inactive Crohn’s colitis.\(^13\)

Ferritin is an acute phase reactant that is cytokine driven; it is closely linked to the inflammation generated by the histiocyte-macrophage system in AOSD and is also released from damaged hepatocytes.\(^8\) Fautrel et al. found serum ferritin and glycosylated ferritin to be powerful diagnostic markers for AOSD in their retrospective review of 49 patients with AOSD.\(^14\) Glycosylated ferritin is not available in our country and was not performed on our patient.

Our patient was commenced on NSAIDs and prednisone simultaneously given that the efficacy of monotherapy with NSAIDs is only 7–15% in this condition.\(^8\) In contrast, the reported efficacy of glucocorticoids in AOSD varies between 76 and 95%.\(^8\) Although NSAIDs can precipitate a flare of inflammatory bowel disease, in this case there was a favourable response to the above combination therapy, both clinically and in terms of her biochemical markers. Methotrexate is considered second line therapy in patients with AOSD who are steroid dependent and as with Crohn’s disease, refractory AOSD has been successfully treated with agents targeting Tumour Necrosis Factor Alpha (TNF-α) and Interleukin-6 (IL6).\(^10\) This is not surprising given that Crohn’s disease and AOSD are both thought to be Th1 predominant conditions where pro-inflammatory cytokines such as IL1, IL6, IL8 and TNFα dominate the milieu.\(^10,15\)

On the other hand, AOSD has been described to share several clinical and pathophysiological features with autoinflammatory syndromes, favouring its distinction from chronic inflammatory joint diseases.\(^16\) The lack of identifiable microorganisms, autoantibodies, or autoantigen-specific T cells is a common feature shared by both AOSD and autoinflammatory syndromes. IL1, together with IL6 and IL6 receptor play a central role in exacerbations of AOSD and autoinflammatory syndromes. Agents that target IL1 and IL6 receptors have proven to be efficacious in the treatment of both severe AOSD and certain autoinflammatory syndromes. This further lends support to likening AOSD to an autoinflammatory syndrome as opposed to an autoimmune condition and may therefore explain the paucity of cases of Crohn’s disease complicated by AOSD.

This is only the second reported case of AOSD complicating Crohn’s colitis. Kono et al. reported on a case of Crohn’s disease complicated by AOSD in 2003.\(^15\) Similar to our experience they found that AOSD is a challenging diagnosis to make in the setting of IBD. Although rare, AOSD should be considered in the differential diagnosis of IBD arthropathy, particularly if the presentation is atypical.

### Authors’ contribution

Rajabally M.N. and Levin D. were involved in the patient care. Rajabally M.N. drafted the manuscript which was then reviewed individually by Levin D. and Watermeyer G.

All authors read and approved the final manuscript.

### Conflict of interest

The authors declare that there was no conflict of interest.
References