SHORT REPORT

Adult-onset Still's disease preceding Crohn's disease

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Crohn's disease; Juvenile idiopathic arthritis; Adult onset Still's disease; Etanercept; Infliximab; Adalimumab

Abstract

Concomitant diagnosis of Crohn's disease and juvenile or adult-onset idiopathic arthritis is rare. It is possible that both conditions share some genetic or immunological defects although sufficient data are lacking.

We describe herein the first case of a patient with adult-onset Still's disease who was diagnosed on follow up with concomitant Crohn's disease.

A 38-year-old man diagnosed with adult onset Still's disease from the age of 24 was admitted in our hospital because of bloody diarrhea. On admission physical examination was unremarkable and all routine laboratory tests were normal except of Hg at 11.3 gr/dl, erythrocyte sedimentation rate at 27 mm/h and C-reactive protein at 14 mg/dl.

Ileocolonoscopy revealed small aphthoid ulcers in the terminal ileum and capsule endoscopy revealed the source of bleeding and small aphthoid ulcers starting from the distal jejunum up to the terminal ileum. Terminal ileum biopsies were diagnostic of Crohn's disease and patient had started on therapy with mesalamine 2 gr/day and azathioprine 2 mg/kg and is currently on multidisciplinary follow up.

We review all literature on co-existence of Crohn's disease with chronic idiopathic arthritis and we discuss the possible difficulties in diagnosis and therapy of those patients also in the view of the new biological agents.

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Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; JIA, Juvenile idiopathic arthritis; AOSD, Adult onset Still's disease.

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1. Introduction

Gastrointestinal involvement in connective tissue disorders appears almost regularly and gastrointestinal symptoms are frequent in patients with rheumatic and autoimmune diseases. Joint manifestations represent common extraintestinal symptoms in inflammatory bowel disease (IBD). Arthropathies in IBD may include ankylosing spondylitis, sacroiliitis, and juvenile idiopathic arthritis.1

Juvenile rheumatoid arthritis (JRA) was the older nomenclature of JIA. Juvenile idiopathic arthritis (JIA) is an umbrella term that refers to a group of disorders that have in common chronic arthritis. JIA is subdivided into seven categories: systemic (childhood onset Still's disease), polyarthritis rheumatoid factor positive, polyarthritis rheumatoid factor negative, oligarthritis, psoriatic arthritis, enthesitis-related arthritis and undifferentiated arthritis.

In patients with Crohn's disease (CD), polyarthritis and skin rash can easily be misdiagnosed as enteropathic arthritis and not as Still's disease of juvenile or adult onset. The diagnosis of adult-onset Still's disease (AOSD) requires the presence of all of the following: fever 39 °C, arthralgias or arthritis, rheumatoid factor <1:80 and antinuclear antibody <1:100. In addition, any two of the following are required: white blood cell count >15000 cells/mm³, Still's rash, pleuritis or pericarditis, hepatomegaly or splenomegaly or generalized lymphadenopathy.2 Concomitant diagnosis of CD and idiopathic arthritis is rare. It is possible that both conditions share some genetic or immunological defects although sufficient data are lacking.

We describe herein the first case of a patient with adult-onset Still's disease who was diagnosed on follow up with concomitant Crohn's disease.

2. Case report

A 38-year-old man diagnosed with adult onset Still's disease from the age of 24 was admitted in our hospital because of bloody diarrhea.

For the last three years the patient was admitted twice due to bloody diarrhea recurrent episodes. At that time, upper and lower gastrointestinal tract endoscopies with subsequent biopsies were repeated twice and were negative.

Patient's family history was unremarkable and patient was not smoking or drinking any alcohol. At the age of 20 he was admitted several times in many hospitals due to recurrent episodes of high fever of unknown origin up to 39 °C and arthralgias. Patient detailed clinical, endoscopic and laboratory investigation was unremarkable except of white blood cell count at 16,200/mm³ and Hg 12.3 gr/dl. Patient had started on various antibiotics but with no improvement of his fever or arthralgias. A peripheral lymphnode was surgically removed and based on pathology report suggestive of inguinal lymphadenitis of mycobacterial origin patient had started on clarithromycin and tuberculosis therapy. With that therapy fever subsided two weeks afterwards but relapsed again one month later.

A cholecystectomy was then decided due to cyst sludge and three years afterwards a splenectomy was performed due to splenomegaly and splenic infarcts. One year after splenectomy, at the age of 24, patient was diagnosed with adult-onset Still's disease and he had started on therapy with methotrexate and methylprednisolone 32 mg/d tapered to 2 mg/d as maintenance dose.

On current admission, physical examination was unremarkable. All routine laboratory tests were within normal limits except for Hg at 11.3 gr/dl, erythrocyte sedimentation rate at 27 mm/h and CRP at 14 mg/dl. Immunological tests were negative. Gastroscopy revealed H. pylori negative mild gastritis and duodenal biopsies were normal. Radiologic evaluation with abdominal computed tomography was normal. Ileocolonoscopy revealed small aphthoid ulcers in the terminal ileum and subsequent biopsies were taken. Biopsies were also taken from all parts of the proximal and distal colon that appeared normal.

Capsule endoscopy revealed small aphthoid ulcers starting from the distal jejunum up to the terminal ileum (Fig. 1). One of those jejunal aphthoid ulcers had red blood stigmata suggestive of the source of bleeding.

Biopsies from the terminal were diagnostic of Crohn's disease showing dense mucosal inflammatory infiltration with abscess formation and mucin depletion (Fig. 2a), ulceration of the overlying epithelium, loss of the normal architecture and lymphoid aggregation in the mucosa with inflammation extending to the muscularis propria (Fig. 2b).

Patient had started on therapy with mesalamine 2 gr/day and azathioprine 2 mg/kg and is currently followed up.

3. Discussion

Co-existence of adult onset Still's disease (AOSD) and Crohn's disease (CD) is extremely rare. This is the first case of AOSD preceding CD.

Another two cases with CD preceding AOSD have so far been described. The first case was that of a 31-year-old man with CD ileocolitis and severe schizophrenia that developed arthritis, fever, and skin rash followed by hepatosplenomegaly and pleural effusion later on. Patient was treated with mesalamine,

![Figure 1](image-url)
corticosteroids and total parenteral nutrition and because of intractable bowel disease a subtotal colectomy was performed. The second case was that of a 30-year-old woman with quiescent Crohn’s colitis who met all criteria for AOSD. Patient was successfully treated with corticosteroids.

In patient groups below 16 years of age, CD co-existence with juvenile idiopathic arthritis (JIA) is also rare. Of interest, in all JIA patients, CD diagnosis was always following arthritis diagnosis [Table 1].

In this AOSD patient reported herein many endoscopies were negative before CD diagnosis. In addition, except for his bleeding episodes this patient did not have any abdominal symptom. Abdominal symptoms and endoscopy findings in AOSD and JIA patients are not infrequent. However, the clinical significance of silent gut mucosa lesions frequently found in those patients remains to be elucidated. As small bowel lesions in this patient seemed to be very superficial, ulcerations related to therapy, mainly NSAID use has to be excluded as it was in this case.

In a prospective study in children with JIA it has been demonstrated that chronic gut inflammation was related to axial inflammatory complaints, inflammatory serum variables, thrombocytosis and sacroiliac radiological abnormalities. Furthermore in a study of late onset JIA and its relation to gut inflammation, ileocolonoscopy in 81% of the patients showed abnormalities that were classified as active chronic or CD-like lesions.

Finally, in a long follow-up study of 6 to 50 years of 24 patients who initially fulfilled criteria for JIA, diagnosis was revised in three patients: one suffered from mixed connective tissue disease, another from psoriatic arthropathy and the last one from Crohn’s disease.

In the new field of biological agents, treatment of both diseases is challenging. In some reports the immunodysregulatory and proinflammatory effects of etanercept have been underlined with a possible relation to CD occurrence and CD flares. In fact, in a retrospective study including 8 patients with JIA who developed IBD while under anti-TNF-alpha therapy all patients had been treated with etanercept before IBD onset. Five patients presented with Crohn’s disease (CD) and three with indeterminate IBD. Clinical remission of IBD was achieved in all patients after discontinuation of etanercept and initiation of IBD-specific therapy, including infliximab in six patients. According to the authors, IBD must be suspected in JIA patients treated with etanercept who develop intestinal symptoms. In another case, etanercept was discontinued and adalimumab was started on resulting in remission.

The exceptional case of co-existence of JIA, CD and Turner’s syndrome implicates a possible genetic link of those diseases. In fact, JIA shares many susceptibility loci with other autoimmune diseases.

In general it seems that medical treatment in AOSD is mostly empirical with relatively low efficacy of biologic agents but with a promising action of the anti-interleukin-6 receptor.

In an intestinal biopsy specimen from a JIA or AOSD patient it is difficult to distinguish a real CD lesion from a CD-like lesion, especially in the absence of granulomas. Though the typical histological findings of CD are easily recognizable, other lesions such as bacterial infection, ischemia and autoimmune diseases can mimic CD morphology.

The pathological changes of infectious diseases are specific, depending on bacteria that infect the bowel. In general, acute self-limiting colitis demonstrates with edema, prominent neutrophilic infiltration, cryptitis and crypt abscesses, but there are no gland distortion and basal plasmacytosis. Ischemic enteritis is a result that many situations can cause, including systemic diseases, vasculitides, vasculopathies, drugs and mechanical reasons.

Some autoimmune diseases including rheumatoid arthritis, scleroderma and systemic lupus erythematosus, can cause bowel damage through systemic vasculitis. In those patients non-steroid anti-inflammatory drug use as a therapeutic agent can cause drug related intestinal involvement. On the other hand it has been also suggested that intestinal inflammation may represent a primary abnormality in patients with RA. Nevertheless, still there are no disease-specific changes described in the gut.

We believe that patient personal and family history, laboratory and endoscopic evaluation combined with multidisciplinary long-term follow up may finally provide the definite diagnosis. In addition some recent advances in imaging techniques such as capsule endoscopy may aid making the definite diagnosis, i.e. in children presenting with adult-onset Still’s disease.
Table 1  Overview of patients with Crohn’s disease (CD) and adult onset Still’s disease (AOSD) or juvenile idiopathic arthritis (JIA). [ERA = ethesitis-related arthritis, AS = ankylosing spondylitis].

<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Year</th>
<th>Number of patients (n=20)</th>
<th>Age/sex</th>
<th>Rheumatology diagnosis</th>
<th>Crohn’s disease location</th>
<th>Timing of diagnosis</th>
<th>Therapy</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current report</td>
<td>2011</td>
<td>1</td>
<td>38/M</td>
<td>AOSD</td>
<td>Jejunum and ileum</td>
<td>AOSD preceding (14 years) CD preceding (8 years)</td>
<td>Mesalazine, methylprednizolone azathioprine Sulphasalazine, Prednisone 1 mg/kg (tapered) NSAIDS (acute phase) Surgery, oral cyclophosphamide (50 mg x1/week), methylprednizolone -Infliximab (3.1 mg/kg/8 weeks) (etanercept previously)</td>
<td>Recurrent GI bleeding splenectomy Both diseases responded well to therapy</td>
</tr>
<tr>
<td>Rajabally et al.</td>
<td>2010</td>
<td>1</td>
<td>30/F</td>
<td>AOSD</td>
<td>Left sided colitis</td>
<td>CD preceding (8 years)</td>
<td>Sulphasalazine, Prednisone 1 mg/kg (tapered) NSAIDS (acute phase)</td>
<td>Both diseases responded well to therapy</td>
</tr>
<tr>
<td>Kono et al.</td>
<td>2003</td>
<td>1</td>
<td>31/M</td>
<td>AOSD</td>
<td>Ileocolitis and umbilical fistula</td>
<td>CD preceding (9 years)</td>
<td>Surgery, oral cyclophosphamide (50 mg x1/week), methylprednizolone -Infliximab (3.1 mg/kg/8 weeks) (etanercept previously)</td>
<td>Severe schizophrenia two years after CD Subtotal colectomy</td>
</tr>
<tr>
<td>Tarkiainen et al.</td>
<td>2011</td>
<td>2</td>
<td>9/M</td>
<td>-ERA</td>
<td>Ileocolitis</td>
<td>-JIA preceding (3.6 years) -JIA preceding (1.4 years)</td>
<td>Adalimumab (previously etanercept, infliximab allergic)</td>
<td>-Mother: JIA</td>
</tr>
<tr>
<td>Oikonomou et al.</td>
<td>2010</td>
<td>1</td>
<td>4/F</td>
<td>-Seronegative polyarthritis</td>
<td>Ileocolitis</td>
<td>JIA preceding (15 years)</td>
<td>-Infliximab (most patients)</td>
<td>Both diseases responded well to adalimumab causative role of etanercept in CD occurrence?</td>
</tr>
<tr>
<td>Dallochio et al.</td>
<td>2010</td>
<td>5</td>
<td>All 5 F &lt;18 years (3 more patients indeterminate IBD)</td>
<td>-Systemic-Oligoarticular-Polyarticular</td>
<td>-Left colon, anal abscess-Pancolitis, anal abscess-Stomach, duodenum, pancolitis</td>
<td>-11 years -9.5 years -10 years</td>
<td>Infliximab (most patients) Azathioprine (two patients) Mesalazine (three patients)</td>
<td>All patients on etanercept 11–78 months before CD onset Etanercept discontinuation in all Two patient anterior uveitis</td>
</tr>
<tr>
<td>Year</td>
<td>Age</td>
<td>Gender</td>
<td>JIA Form</td>
<td>JIA Duration</td>
<td>Associated Features</td>
<td>Treatment</td>
<td>Other Relevant Information</td>
<td></td>
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<tr>
<td>2010</td>
<td>11/F</td>
<td>JIA oligoarthritis</td>
<td>ileocolitis</td>
<td>JIA preceding 7.5 years</td>
<td>[No detailed therapy per patient]</td>
<td>Adalimumab (previously etanercept for 1 year)</td>
<td>Chausative role of etanercept in CD occurrence?</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>18/F</td>
<td>JIA polyarthritis</td>
<td>ileocecal valve</td>
<td>JIA preceding 11.9 years</td>
<td>Mesalazine</td>
<td>Uveitis operated for mandibular hypoplasia Turner syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>16/F</td>
<td>JIA oligoarthritis</td>
<td>Transverse colon</td>
<td>JIA preceding 2 months</td>
<td>Mesalazine 2.4 gr/d</td>
<td>Causative role of etanercept in CD occurrence and relapse?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>6/M</td>
<td>JIA oligoarthritis</td>
<td>ileocolitis and perianal fistula</td>
<td>JIA preceding 4 years</td>
<td>Infliximab (5 mg/kg every 8 weeks) (previously etanercept 0.4 mg/kg twice a week)</td>
<td>Causative role of etanercept in CD occurrence and relapse?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>14/M</td>
<td>JIA (childhood Still's)</td>
<td>Colitis (with skip lesions and strictures)</td>
<td>JIA preceding (only by two months)</td>
<td>Azathioprine, prednisone</td>
<td>Both diseases responded well to therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td>22/M</td>
<td>JIA</td>
<td>Not mentioned</td>
<td>JIA preceding (7 years)</td>
<td>NSAIDS and sulfasalazine</td>
<td>Family history of Crohn’s and ankylosing spondylitis 1 additional patient with Crohn’s like lesions (not Crohn’s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>23/M</td>
<td>JIA (both Bw62-B27)</td>
<td>Not mentioned</td>
<td>JIA preceding (10 and 8 years respectively)</td>
<td>NSAIDS (CD therapy not mentioned)</td>
<td>From 32 pts, 26 (81%) with histology of gut inflammation and 19/26 classified as active chronic or Crohn-like lesions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1981</td>
<td>M (age unknown)</td>
<td>JIA</td>
<td>Not mentioned</td>
<td>JIA diagnosis revised on follow up to AS</td>
<td>Not mentioned</td>
<td>From 24 JIA pts aged 17–55 years followed for 6 to 50 years</td>
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</tbody>
</table>
with arthropathy and suspected IBD. To conclude, concomitant diagnosis of Crohn’s disease and idiopathic arthritis is rare and requires expertise. Treatment is defined on a personalized basis.

**Conflict of interest**

None.

**Acknowledgment**

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**References**