SHORT REPORT

Recurrent posterior scleritis and orbital myositis as extra-intestinal manifestations of Crohn's disease: Case report and systematic literature review

Emma L. Culver a, John F. Salmon b, Peggy Frith b, Simon P.L. Travis a,*

a Department of Gastroenterology, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU, UK
b Department of Ophthalmology, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU, UK

Received 22 March 2008; received in revised form 23 June 2008; accepted 27 June 2008

Abstract

Background: Ocular episcleritis and uveitis are well-recognised extra-intestinal manifestations of Crohn's disease. Orbital myositis is rare: to our knowledge it has been associated with Crohn's disease in thirteen cases. Posterior scleritis, orbital myositis and Crohn's disease have been reported as coexisting in only two cases.

Methods and results: We describe a third case, that of a 31-year old female with Crohn's colitis for 8 years, complicated by enteropathic arthritis and pyoderma gangrenosum. She presented with intense and intractable periorbital pain, particularly at night and worse on eye movements. B-scan ultrasonography confirmed posterior scleritis and treatment with high dose oral steroids (up to 60 mg prednisolone) was initially effective, but subsequently failed to control the inflammation. There was only a partial response to infliximab. Five months after presentation, diplopia developed, with failure of abduction of the left eye. MRI scan of the orbits confirmed orbital myositis involving the left lateral and medial rectus muscles. Pulsed intravenous methylprednisolone and six cycles of intravenous cyclophosphamide over a three month period resulted in complete resolution of inflammatory symptoms.

Conclusions: This case highlights a rare combination of ocular abnormality secondary to Crohn's disease and reports successful resolution with aggressive immunosuppressive therapy.

© 2008 European Crohn's and Colitis Organisation. Published by Elsevier B.V. All rights reserved.

KEYWORDS
Crohn's disease; Orbital myositis; Posterior scleritis; Extra-intestinal manifestation; Cyclophosphamide

1. Introduction

Extra-intestinal manifestations of Crohn's disease (CD), characterised by inflammatory conditions outside the digestive tract, occur in about 15% of patients. They can relate to the underlying disease activity or be independent of it. Manifestations can coexist, with up to 30% of patients having multiple; the presence of one increasing the risk of others.
<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Initial presentation</th>
<th>Ocular involvement</th>
<th>Distribution of CD</th>
<th>Associated EIM or other disease</th>
<th>Therapy</th>
<th>Recurrent myositis</th>
<th>Follow-up</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>3</td>
</tr>
<tr>
<td>14 F</td>
<td>Ocular</td>
<td>Unknown</td>
<td>Terminal ileal</td>
<td>Unknown FH CD HLA-B15, B13</td>
<td>Oral antibiotics CS ileal resection IV Cefazolin CS</td>
<td>Yes</td>
<td>3 m</td>
<td>4</td>
</tr>
<tr>
<td>17 F</td>
<td>Ocular</td>
<td>Unilateral</td>
<td>Colonic</td>
<td>FH DM, RA HLA-B8, B22 HLA-BW6 HLA-CW3 HLA-DR3 + 4 HLA-MND. FH CD</td>
<td>CS</td>
<td>No</td>
<td>6 m</td>
<td>5</td>
</tr>
<tr>
<td>15 F</td>
<td>Ocular</td>
<td>Bilateral muscle cones</td>
<td>Terminal ileal</td>
<td>CS</td>
<td>No</td>
<td>3 m</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>12 F</td>
<td>Ocular</td>
<td>Bilateral</td>
<td>Ileocolonic</td>
<td>CS, Dexa, Diet</td>
<td>No</td>
<td>Yes</td>
<td>6 m</td>
<td>7</td>
</tr>
<tr>
<td>38 F</td>
<td>Gl</td>
<td>Unilateral</td>
<td>Ileocolonic</td>
<td>CS, 5-ASA, Colectomy CS, Salz, HLA-BW6 HLA-CW3 HLA-DR3 + 4 HLA-MND.</td>
<td>No</td>
<td>10 wk</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>44 M</td>
<td>Gl</td>
<td>Unilateral</td>
<td>Ileocolonic</td>
<td>CS, 5-ASA, Colectomy CS, Salz, Ileal resection</td>
<td>No</td>
<td>Yes</td>
<td>3 m</td>
<td>9</td>
</tr>
<tr>
<td>12 M</td>
<td>Gl</td>
<td>Bilateral</td>
<td>Ileocolonic</td>
<td>CS, 5-ASA, Colectomy CS, Salz, Ileal resection</td>
<td>Yes</td>
<td>2 m</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>48 F</td>
<td>Ocular</td>
<td>Bilateral</td>
<td>Ileocolonic</td>
<td>CS, 5-ASA, Colectomy CS, Salz, Ileal resection</td>
<td>No</td>
<td>1 yr</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>54 F</td>
<td>Gl</td>
<td>Bilateral</td>
<td>Ileal</td>
<td>CS, 5-ASA, Colectomy CS, Salz, Ileal resection</td>
<td>Yes</td>
<td>1 yr</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>34 F</td>
<td>Gl</td>
<td>Unilateral</td>
<td>Ileocolonic</td>
<td>CS, 5-ASA, Colectomy CS, Salz, Ileal resection</td>
<td>Yes</td>
<td>27 m</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>27 F</td>
<td>Ocular</td>
<td>Bilateral</td>
<td>Colonic</td>
<td>CS, 5-ASA, Colectomy CS, Salz, Ileal resection</td>
<td>Yes</td>
<td>27 m</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>14</td>
</tr>
</tbody>
</table>

Key: CS (high dose oral prednisolone); MeP (pulsed intravenous methylprednisolone); Dexa (IV dexamethasone); Salz (Salazopyrine); AZA/MP (azathioprine/mercaptopurine); MTX (methotrexate); CP (cyclophosphamide); RT (radiotherapy); IFX (infliximab); MR (medial rectus muscle); LR (lateral rectus); SR (superior rectus); RM/RL (rectus medialis and rectus lateralis); FH (family history); NSAID (non-steroidal anti-inflammatory).
Ocular manifestations have been reported in up to 10% of patients with CD, including uveitis, episcleritis, scleritis and chorioretinitis, although this is likely to be an overestimate based on a referral population. Orbital involvement and orbital myositis, defined as orbital inflammation confined to one or more of the extraocular muscles, is exceptional. In a review of 700 patients with inflammatory bowel disease (498 with CD), only one had orbital myositis (0.14%). Nine cases have subsequently been reported, describing the association of isolated orbital myositis with CD (Table 1). The coexistence of scleritis with orbital myositis in CD has been documented in just two patients.

We present the case of a patient with CD, recurrent posterior scleritis and orbital myositis. This case highlights a rare combination of ocular abnormalities secondary to CD and describes the excellent response to aggressive immunosuppressive therapy.

2. Case report

A 23-year old woman presented in August 1999 with a five-week history of loose stools, urgency and abdominal pain. On examination there was localised peritonism in the right iliac fossa. Laboratory investigations revealed a normocytic anaemia, raised inflammatory markers and thrombocytosis. Terminal ileal CD was diagnosed at laparoscopy and confirmed by small bowel enema. Colonoscopy showed no evidence of distal colonic CD. She failed to settle with high dose oral steroids and underwent ileocaecal resection with anastomosis in November 1999. She remained asymptomatic on no maintenance treatment for six months. In May 2000 she presented with recurrent disease in the neoterminal ileum, treated with corticosteroids. She was intolerant of thiopurines (azathioprine and 6-mercaptopurine). Methotrexate was well tolerated and provided good control of her bowel symptoms. She remained symptom-free for two years.

In October 2002 she presented with a peripheral asymmetric oligoarthritis, affecting the large joints of the lower limbs. Her intestinal disease was active. Autoimmune screen and rheumatoid factor were negative. Exacerbations of arthritis were controlled by local intra-articular steroid injections, systemic corticosteroids and increased doses of methotrexate. Two years later, she developed skin ulceration characteristic of pyoderma gangrenosum. Her bowel symptoms were quiescent. She was treated with infliximab (5 mg/kg), which induced a positive response of up to two months. Infliximab was continued every 2 months for 1 year. She discontinued methotrexate in May 2005 as she wanted to become pregnant.

In January 2006, she presented with a two-week history of a painful right eye, particularly at night and exacerbated by eye movement. Visual acuity was normal (6/6 right, 6/5 left). There was mild chemosis and reproducible pain elicited by horizontal gaze. Slit lamp and fundal examinations were unremarkable. Hess chart analysis showed no evidence of extraocular muscle defects. TSH was within the normal range and thyroid autoantibodies were negative. A B-scan ultrasound of the right eye showed evidence of posterior scleral thickening and a ‘T’ sign, typical of posterior scleritis (Fig. 1). A non-steroidal (flurbiprofen 150 mg/day) was initiated, with little relief. High dose oral steroids (prednisolone 40 mg/day) were started and achieved an immediate response and were tapered gradually over six weeks. Over the next three months she experienced three episodes of symptomatic posterior scleritis, affecting first the right then the left eye, confirmed on B-scan ultrasonography. The pain responded to prednisolone 40 mg/day, but recurred as the dose was reduced below 20 mg/day. Her
intestinal disease was active: colonoscopy demonstrated moderately active segmental colitis with inflammation of the ileocaecal anastomosis, confirmed by histopathology. She was given infliximab for the intestinal activity, and the ocular pain resolved immediately. She became pregnant later that year and was given infliximab infusions in the second and third trimesters for symptomatic intestinal disease. She had an uncomplicated caesarian section and the healthy newborn followed the usual vaccination programme.

In February 2007, she presented with a frontal headache and severe left periorbital pain, resistant to high dose oral steroids (60 mg prednisolone). Her intestinal disease was active with increased bowel frequency and elevated inflammatory markers. Infliximab infusions (5 mg/kg) provided only partial relief from periorbital pain (two weeks) and had no impact on intestinal symptoms; they were subsequently discontinued. The pain intensified and she developed diplopia. On examination there was evidence of conjunctival injection, chemosis and failure of abduction of the left eye. Hess chart analysis revealed under-activity of the lateral rectus and over-activity of the medial rectus muscle on horizontal gaze. MRI of the orbits with gadolinium contrast delineated enlarged left medial rectus and lateral rectus muscles and their tendinous insertions consistent with orbital myositis (Fig. 2). There was no localised inflammatory mass and the right eye was unaffected.

She was admitted to a hospital for pulsed methylprednisolone (1 g on three consecutive days) and intravenous cyclophosphamide (15 mg/kg every two weeks, six doses). Oral corticosteroids were continued for twelve weeks (prednisolone 15 mg/day). Within 1 h of the first intravenous infusions her pain was markedly reduced and after the second infusion of cyclophosphamide her eye movements returned to normal. Hess chart plots confirmed normal activity of the muscles after treatment. After the third infusion of cyclophosphamide she reported symptomatic improvement in intestinal activity, there was no endoscopic evaluation. There were no complications.

Two months after completion of the cyclophosphamide infusions, she experienced a recurrence in symptomatic CD. She was commenced on adalimumab (80 mg, 40 mg, 40 mg subcutaneous injections at two-week intervals) with good effect. She has continued on maintenance treatment every two weeks and remains in remission. At nine-month follow-up there have been no further episodes of orbital inflammation.

3. Systematic literature review

We used Pubmed database, Medline database and Ovid search engine to identify studies and cases relevant to this article. The keywords used in our search were orbital myositis; ocular myositis; orbital pseudotumour; inflammatory bowel disease; Crohn's disease; ulcerative colitis.

Fifteen cases of orbital myositis associated with inflammatory bowel disease (thirteen with CD,13,14 two with UC15,16) have been reported (Table 1). In two of these cases, both scleritis and orbital myositis were associated with CD.13,14 Three quarters (11/15 with details available) were female and two thirds (10/15) had colonic or ileocolonic disease. In a quarter (4/13 with CD) a family history of CD and other associated autoimmune diseases were present. There was no record of other extra-intestinal manifestations in the reports.

In half (6/13) ocular myositis presented before the onset of CD. In half (7/13) the myositis was bilateral. Visual compromise in the form of diplopia and blurred vision affected three quarters (9/13), and in all but one patient these features resolved with treatment. Persistent diplopia and pain was reported in one patient at 27-month follow-up.13 There were no incidences of blindness or permanent visual loss.

4. Discussion

Orbital myositis represents a subgroup of the 'orbital pseudotumour syndrome', which defines inflammation within any structure in the confines of the orbit.17 It can involve a single muscle or the entire orbital musculature and can be acute or recurrent and chronic. It is most often described as idiopathic, but has been associated with a number of systemic inflammatory diseases.14,18 Diagnosis is based upon typical clinical presentation and radiological appearances on contrast-enhanced MRI.19 Biopsy is only indicated for an atypical presentation, rapid progression of neurological deficit or if there is evidence of a localised orbital mass.20

The mainstay of treatment is high dose corticosteroids (prednisolone up to 100 mg/day, tapered accordingly) and the response is typically rapid; pain resolving within 24 h.19 Chronic and recurrent disease may be attributed to delays in diagnosis, treatment or insufficient doses of steroid. Recurrences can be bilateral, extend beyond the orbital musculature and may lead to diffuse systemic muscle inflammation.21 In aggressive disease, pulsed intravenous...
methylprednisolone can be effective. In steroid-refractory cases, immunomodulators including methotrexate and ciclosporin, cytotoxic agents such as cyclophosphamide, anti-TNF therapy, and radiotherapy have been tried with variable benefit.\(^{20,22}\)

There is significant relapse risk reported with most modalities of treatment for recurrent orbital myositis.\(^{22}\) Cyclophosphamide has been used for refractory orbital pseudotumours, with the advantages of avoiding long-term steroid therapy and the malignant potential of radiation treatment.\(^{24,25}\) Leone and Lloyd, based on their experience of 45 patients with orbital inflammatory disease, found that the two most refractory cases responded to oral cyclophosphamide (200 mg/day for 15–18 months) as adjunctive therapy to prednisolone (up to 80 mg/day for 18 months), establishing control of orbital inflammation at one year off all medication.\(^{24}\) Paris et al., found that high dose prednisolone (100 mg/day) plus intravenous pulsed cyclophosphamide (100 mg/day, five-day pulses, two cycles at three-week intervals) given to five patients with orbital pseudotumour refractory to steroids and radiotherapy, caused remission of symptoms maintained for up to 11 years.\(^{25}\) Nevertheless, the decision to initiate cytotoxic therapy should be made by experienced specialists, taking account of the severity and refractory nature of the inflammatory process, the potential for visual compromise and response to other therapy.

Evidence for the use of cyclophosphamide in CD is limited. There are isolated case reports and small prospective uncontrolled trials evaluating safety and efficacy of intravenous cyclophosphamide in steroid-refractory luminal CD. There is no current evidence for use in fistulating CD. The largest of these trials (16 patients),\(^{27}\) reported an 81% (13/16 patients) remission in symptomatic disease (defined by reduction in the CD activity index) within 8 weeks after 2 pulses of cyclophosphamide and maintenance with azathioprine or methotrexate. This response was sustained for a median of 19 months (range 1–45). The non-responders had a longer duration of disease (mean 16 years), more intense pre-treatment with immunosuppressives and a larger number of prior surgical interventions. Over one-third of patients (38%, 6/16 patients) experienced infectious side effects; urinary tract infection, Candida spp. oesophagitis, neutropenic sepsis, central venous catheter infection complicated by pneumonia. There were no deaths. Cyclophosphamide is not currently recommended for use in inflammatory bowel disease.

Orbital myositis has been associated with other inflammatory conditions of the eye, such as uveitis and scleritis.\(^{23}\) The clinical presentation of posterior scleritis and orbital myositis are similar, but important to differentiate, as orbital myositis may be associated with increased risk of ocular complications and requires more intensive treatment.\(^{14,19}\) This was illustrated in a retrospective case series of 103 patients (76 with scleritis, 27 with episcleritis) managed at an ophthalmology centre.\(^{14}\) Eleven patients had evidence of both orbital myositis and scleritis, with involvement of the posterior sclera. Ocular complications such as cataract, keratitis, uveitis, high intraocular pressure and glaucoma occurred in two thirds (64%) of those with both myositis and scleritis compared to a third (30%) with scleritis alone. Loss of visual acuity at presentation affected a quarter (27%) of patients with myositis and scleritis and persisted despite treatment. Loss of visual acuity resolved with treatment in three quarters (77%) of those without myositis.\(^{14}\)

The coexistence of scleritis, orbital myositis and CD is exceptional, and has been reported in just two patients. In the retrospective case series detailed above, one patient was reported to have scleritis, orbital myositis and CD (there were no further details about this patient). In a retrospective observational series of seven patients reporting the response of refractory orbital myositis to infliximab,\(^{13}\) there were two patients with CD, one with scleritis and orbital myositis. This patient received treatment in the form of oral corticosteroids, retrobulbar triamcinolone injections, radiotherapy and methotrexate, before scheduled infliximab every two months relieved symptoms with no evidence of recurrence at 27-month follow-up.\(^{13}\)

This third reported case of posterior scleritis, orbital myositis and CD establishes a sufficient pattern for it to be considered an exceptional ocular extra-intestinal manifestation of CD. This combination occurs in female patients with colonic CD, activity-associated extra-intestinal manifestations (such as large joint arthropathy and pyoderma) and is refractory to standard therapy. The pattern, once recognised, should prompt early specialist referral so that biological or cytotoxic therapy can be considered at an early stage in the hope that the course of the disease can be modified.

Acknowledgements

EC was responsible for writing the draft manuscript, the literature search, and collection and preparation of images and tables. JFS was responsible for critical review and editing the manuscript. PF was responsible for editing the manuscript. SPLT was responsible for obtaining patient consent, critical revision and editing the manuscript. All authors read and approved the final manuscript. SPLT is also the guarantor of the article.

References


