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Case Series

Title:

Orbital Inflammatory Complications of Crohn's disease: A Rare Case Series

Short Title:

Orbital involvement in Crohn's disease

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TMM wrote the manuscript. GA and LA advised on ophthalmological content. PK and JDT prepared the histological and radiological images respectively. LA and GWM were the primary clinicians in charge of the patients care. All authors contributed to critical review of the manuscript.

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Abstract

Orbital inflammatory disease is a rare ophthalmic manifestation of Crohn's disease. Inflammation is characteristically non-specific, involving one or multiple structures of the orbit. Mechanisms of disease and optimal methods of treatment are poorly understood. The aim of this report is to present three cases of orbital involvement in Crohn's disease. A retrospective case note review of patients with orbital inflammatory disease and Crohn's disease was performed at our academic centre to determine the clinical, imaging and histopathological features of this condition and its relationship to intestinal Crohn's disease. Three patients were identified with orbital inflammatory manifestations complicating Crohn's disease. All patients described were female with active intestinal disease and had a history of treatment with immunosuppressive therapies. Similarities were observed in clinical presentations with variance noted in radiological and histopathological findings. In all cases, symptoms improved with oral corticosteroids or non-steroidal drugs in combination with anti-tumour necrosis factor (anti-TNF) agents. Inflammatory bowel disease-related orbital complications are rare but potentially vision-threatening. It is important to consider mimics of orbital inflammatory disease such as systemic inflammatory disease, malignancy, congenital malformations, infection and trauma when formulating a comprehensive differential diagnosis. Therapeutic intervention is directed towards preservation of vision and orbital function and reducing the acute inflammatory process. Corticosteroids are typically the initial treatment of choice for moderate-to-severe disease, although several classes of immunomodulatory agents have been variably useful in treating this condition. Heightened awareness and close cooperation between gastroenterologists and ophthalmologists is mandatory.

Introduction

The reported incidence of ocular manifestations in patients with inflammatory bowel disease (IBD) is variable, ranging from 0.3-13% , 1.6%-5.4% among those with ulcerative colitis and 3.5%-6.8% among those with Crohn's disease,[1] and may be primary, secondary to treatment, effects of the intestinal disease or coincidental.[2-3] Ocular complications occur more frequently in patients with Crohn's disease [4-5]rather than ulcerative colitis and an association has been reported with female sex.[1,5] Patients with a colonic or ileocolonic disease location tend to have a higher incidence of ocular involvement compared to those with only a small bowel disease location.[6-7] The presence of other extraintestinal manifestations (EIM) such as arthralgia in Crohn's disease has been associated with ocular involvement.[8] Although episcleritis, scleritis and uveitis are the most common ocular-extraintestinal manifestations (O-EIM) in IBD,[2] orbital inflammatory disease (OID) has also been reported as a rare EIM. OID can present with an array of findings depending on the structures affected by the combined effects of inflammation, elevated orbital pressure and direct compression. Common findings include conjunctival injection, chemosis, eyelid swelling, proptosis, diploplia, pain with eye movement, ophthalmoplegia and impaired vision.[3] Important differentials to consider in OID include malignancies, congenital mass lesions, orbital cellulitis, and occult or distant trauma. Systemic inflammatory diseases associations of OID include autoimmune thyroid disease, sarcoidosis, granulomatosis with polyangiitis (GPA), systemic lupus erythematosis, and other connective tissue diseases.[9] Dacryoadenitis (localized inflammation of the lacrimal gland) is the rarest form of ocular adnexal involvement in IBD and typically presents with unilateral upper lid swelling, erythema, and pain in the superotemporal orbit.[10-12] Herein, we report a rare case series of 3 female patients with Crohn's disease developing heterogeneous manifestations of OID.

Case History 1

A 48-year-old woman was diagnosed with ileo-colonic non-stricturing, non-penetrating Crohn's disease at age 41. She described a 7-year history of joint pains and recurrent iritis preceding her diagnosis. Her prior treatments included 6-mercaptopurine, adalimumab, methotrexate and a polymeric diet. Whilst on a polymeric diet only due to previous drug intolerance issues and having stopped methotrexate 2 weeks prior to her presentation, she presented with a 2 month history of left lower eyelid swelling, diplopia and ptosis. An orbital mass was palpable inferiorly which was causing elevation of the globe with reduced movement. Blood analysis revealed a raised white cell count (WCC) of 16 x 10^9/L and a C-reactive protein (CRP) of 300 mg/L. Computed tomography (CT) and subsequent magnetic resonance imaging (MRI) of the orbits revealed a well-defined lesion in the inferior aspect of the left orbit, involving the inferior rectus, without any other orbital abnormality. [Figure 1 A-D]. Histopathological assessment showed multiple non-caseating granulomas, some of which containing multinucleate giant cells [Figure 2A]. Immunostaining was negative for Ziehl-Neelsen and IgG4. The patient was commenced on a 4 week reducing course of oral prednisolone, starting dose of 40 mg with recommencement of weekly 15 mg subcutaneous methotrexate. Two weeks following discharge, she was reviewed and noted to have made a full recovery with no recurrence of her luminal or orbital symptoms.

Case History 2

A 27-year-old woman was diagnosed with ileo-colonic non-stricturing, non-penetrating Crohn's disease at the age of 17 years. Other co-morbidities included osteopenia, previous erythema nodosum, sinusitis and a positive lupus anticoagulant result. Her family history

included autoimmune haemolyic anaemia, granulomatosis with polyangiitis (GPA) and tuberculosis. In the 4 years following diagnosis, her Crohn's disease followed a steroid-refractory course complicated by stricturing of the large intestine, leading to a segmental transverse colon resection and right-sided double-barrelled colostomy. One year later, she underwent a loop ileostomy for a perforated internal hernia. In the subsequent 5 years, additional surgeries were also performed for reversal of the loop ileostomy and subsequent refashioning of the colostomy. Her treatments included several courses of corticosteroids, azathioprine (developed intolerance), infliximab (anaphylaxis) and later adalimumab with addition of methotrexate. Whilst off adalimumab for one week (recurrent viral infections), she presented with a 2 day history of acute onset of bilateral painful S-shaped periorbital swelling, moderate erythema and chemosis worse on the left with diplopia [Figure 3A]. Ocular movements were restricted and episcleritis was evident. A computed tomography (CT) scan of head, orbits and sinuses revealed bilateral lacrimal gland enlargement. Lateral and superior recti were also enlarged [Figure 1 E-F]. Blood analysis showed raised inflammatory markers with a white cell count of 21.6 x 10^9/L and a C-reactive protein of 166 mg/L, normal serum angiotensin converting enzyme (ACE) levels and thyroid function. Immunological tests showed positive perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) and low proteinase 3 (PR3). Neither pulmonary nor renal involvement was present. Histology showed a chronic dacryoadenitis, acute vasculitis of medium sized vessels and necrotising histiocytic granulomas [Figure 2B]. Stains for Periodic acid-Schiff-diastase (DPAS), Ziehl-Neelsen and IgG4 were negative and pus collected from the lacrimal gland during the biopsy did not reveal any microbial growth. The patient was started on a 2-day course of intravenous Co-amoxiclav (1.2 g three times daily) and an 8-week reducing course of high dose oral prednisolone (commencing at 60 mg daily) for presumed OID complicating

Crohn's disease. Following re-commencement of weekly 25 mg subcutaneous methotrexate and biweekly adalimumab, her symptoms and signs had completely resolved at ophthalmological assessment one week later [Figure 3C].

Case History 3

A 33-year-old woman was diagnosed with colonic non-stricturing, non-penetrating Crohn's disease at age 21. Co-morbidities included previous sinusitis. The patient was treated with azathioprine and subsequently infliximab 5mg/kg every 7 weeks. Recently she had experienced a relapse of her Crohn's disease symptoms with endoscopic findings in keeping with active left-sided colonic disease. The patient presented with a 4-month-history of left-sided swelling in the lacrimal gland area with typical S-shaped configuration, which had become more obvious over the preceding few days prior to hospitalization. On examination, there was an S-shaped deformity of the left upper eyelid along with mild eyelid oedema and a lobulated swelling of the lacrimal gland. CT of the orbits showed an enlarged left lacrimal gland, which enhanced uniformly post-contrast [Figure 1 G, H]. Blood analysis showed a raised CRP of 55 mg/L. Histology revealed a dacryoadenitis featuring numerous, well-circumscribed non-caseating granulomas, some of which contained multinucleate giant cells. Special stains for microrganisms (Gram, Grocott, PAS and Ziehl-Neelsen) and IgG4 were negative. The presence of dacryoadentis in the absence of a raised serum ACE level favored a diagnosis of an extra-intestinal manifestation of Crohn's disease rather than sarcoidosis. The patient was commenced on a 2-day course of 100 mg twice daily flurbiprofen due to a previous psychotic reaction to corticosteroids followed by infliximab.

Subsequent follow-up revealed complete resolution of symptoms aside from some residual scar tissue at the biopsy site.

Discussion

We report a case series of OID developing in 3 immunosuppressed female patients with active Crohn's disease. Orbital inflammatory disease is a rare EIM of IBD. Consequently, its exact association with clinical characteristics of the intestinal disease and patient demographics is uncertain.[5] In a review of 24 patients with biopsy proven non-specific OID, the lacrimal gland was affected in 54.2% of the time, extraocular muscles 50%, orbital fat 75%, sclera 4.2%, optic nerve 20.8% and other structures in 8.3%.[13] The histopathologic spectrum of non-specific OID is typically non-diagnostic secondary to a wide range of presentations ranging from diffuse polymorphous infiltrate to lymphoid, granulomatous, sclerosing, eosinophilic or vasculitic inflammation.[14]

In our first and third cases we observed unilateral orbital inflammatory changes. However, in case 2, bilateral orbital inflammation and a family history of vasculitis prompted an evaluation of systemic causes such as GPA, sarcoidosis, lymphoma and IgG4 related disease. Whilst p-ANCA antibodies were detected in case 2, patients with IBD are more likely to be p-ANCA positive than the general population, as are patients with idiopathic ocular inflammation with a family history of IBD.[15] pANCA is detected in 60-70% of ulcerative colitis cases, 10-15% of Crohn's disease cases, and less than 5% of non-IBD colitis cases.[16-17] Moreover, although histology demonstrated an acute necrotizing granulomatous vasculitis,

this was not typical of a primary vasculitis and has been previously reported in OID.[14] However, association between GPA and Crohn's disease has previously been described,[18] albeit in the absence of orbital involvement.

Pathophysiological mechanisms of EIMs in IBD are not clearly understood and warrant further study. Proposed pathogenetic autoimmune mechanisms include genetic susceptibility, antigenic display of autoantigen, aberrant self-recognition and immunopathogenetic autoantibodies against organ-specific cellular antigens shared by colon and the extraintestinal organs.[19] An immune response to a colonic antigen may explain why ocular manifestations occur more commonly with a colonic involvement.[20] In cases 2 and 3, granulomatous dacryoadenitis may have arisen due to antigenic overlaps between gastrointestinal and lacrimal tissues or alternatively, a gastrointestinal antigen may have localized haematogenously to the lacrimal glands location and incited a T-cell response, which produced an accompanying granulomatous reaction.[12] In relation to genetic susceptibility, one study found that the prevalence of a family history of IBD is three to fifteen-fold higher in patients with ocular inflammation than the general population.[21] Other studies have reported major histocompatibility complex (MHC) associations with O-EIMs including human leucocyte antigen haplotypes (HLA)-B27, B58 and HLA-DRB1 0103.[22]

Treatment of OID will depend on the extent of concomitant intestinal disease and additional EIMs. Although resolution may occur with observation alone or with antibiotics, corticosteroid treatment as seen in cases 1 and 2 generally results in much faster resolution of symptoms, and is reserved for moderate-to-severe disease.[10] Treatment of IBD-associated ocular inflammation can also be achieved with immunosuppression such as

azathioprine and methotrexate, and when refractory, responds well to anti-TNF therapy.[2] There are no reports on the efficacy of other licensed biological agents. It is therefore noteworthy that immunosuppression had been stopped in both cases 1 and 2 prior to developing orbital complications, which may have precipitated OID.

In conclusion, it is important to consider OID in the differential diagnosis of patients with Crohn's disease, presenting with periorbital swelling and ocular motility dysfunction. Care should be taken to exclude orbital cellulitis, thyroid eye disease, IgG4-related disease (with dacryoadenitis), lymphoproliferative and metastatic disease, sarcoidosis and GPA. Patients presenting with ocular complications of their IBD should be managed through the combined care of gastroenterology and ophthalmology services where clinical evaluation should include careful history, physical examination, appropriate laboratory and radiographic orbital investigations, as well as need for diagnostic biopsy.

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Figure legends

Figure 1. Orbital imaging in the 3 cases. Arrows indicate the site of the inflammatory masses. (A, B) Axial and coronal CT reformats of case 1. (C, D) Axial and coronal MRI of case 1. (E, F) Axial and coronal CT reformats of case 2. (G, H) Axial and coronal CT reformats of case 3.

Figure 2. Photographs of the patient in case 2 demonstrating the presenting signs and post-operative recovery. (A). At diagnosis (B) Immediately post-operatively (C) Patient at 1 week post-discharge.

Figure 3. Representative histology. Small arrow indicates granuloma, large outline arrow indicated vasculitis (A) Orbital granuloma. (B) lacrimal granuloma with prominent vasculitis