The eye in gastrointestinal disease

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INTRODUCTION

This article reviews disorders in which both gastrointestinal and ocular disease can occur. Gastrointestinal disease can affect the eye as part of the disease spectrum, and in other instances both the gastrointestinal system and the eye may be involved as part of a systemic disease process. The gastrointestinal system may be adversely affected by the treatment of an unrelated eye disease. Also, certain infections of the gastrointestinal system can have an adverse effect on the eye.

GASTROINTESTINAL DISEASES WITH EYE INVOLVEMENT

Inflammatory bowel disease

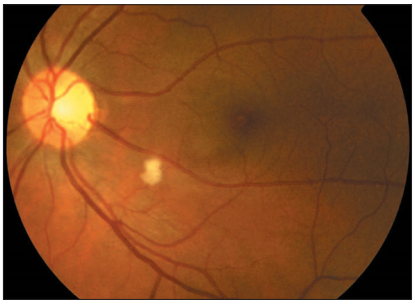
Ulcerative colitis and Crohn's disease are the two main types of inflammatory bowel disease (IBD). They are of presumed autoimmune aetiology and both are frequently associated with extra-intestinal manifestations. In a large study involving 700 cases of ulcerative colitis at least 4% of patients were reported to have some form of eye disease, including conjunctivitis, episcleritis and uveitis (Greenstein et al, 1976).

Uveitis is the commonest ocular complication (2–9% of patients with IBD) and appears to be closely related to the inflammatory activity of the underlying bowel disease, but episcleritis usually parallels the gastrointestinal activity more than uveitis when present (Greenstein et al, 1976; Lyons and Rosenbaum, 1997). Uveitis with IBD is more likely to be seen in female patients, is usually insidious in onset, bilateral, posterior (vitritis, retinal vasculitis and pars plana exudates) and patients are less likely to be HLA-B27 positive (Lyons and Rosenbaum, 1997). A few reports have shown decreased ocular inflammation after bowel resection for IBD (Hopkins et al, 1974; Knox et al, 1984). Crohn's disease is more common than ulcerative colitis in IBD patients presenting with uveitis. Fifty-nine per cent of patients with IBD present with uveitis before IBD is diagnosed, with an average time of 52 months between diagnoses (Lyons and Rosenbaum, 1997).

Arterial and venous thromboses are known complications of IBD. Any vascular system may be involved, including the retinal vasculature. Branch retinal artery occlusion, obliterative retinal arteritis and phlebitis, central retinal vein occlusion and retinal vasculitis with branch retinal artery occlusion have been reported in patients with Crohn's disease. Retinal periphlebitis (*Figure 1*) has been reported with cases of ulcerative colitis.

IBD can affect the cornea in many different ways. Corneal infiltrates and peripheral lesions can be seen and these tend to clear rapidly with topical steroids or systemic indomethacin. Geerards et al (1997) reported a case of ulcerative colitis in which the patient had progressive astigmatism as a result of inferior corneal thinning secondary to limbal vasculitis. The authors suggested the vasculitis could have caused malfunctioning of the limbal stem cells, which led to the production of a different type of epithelial cell and peripheral stromal thinning.

Figure 1. Cotton wool spot secondary to retinal vasculitis in a patient with Crohn's disease.



DISEASES IN WHICH THE GUT AND THE EYE ARE INVOLVED

Behçet's disease

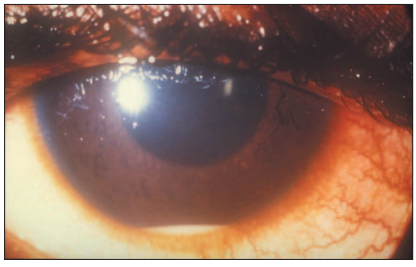
Behçet's disease is an occlusive vasculitis of unknown cause. It classically presents with a triad of genital ulceration, aphthous stomatitis and uveitis. Skin lesions, arthralgia and arthritis can also occur. Ulcerative haemorrhages that can mimic IBD may occur in the gastrointestinal tract. Both the anterior and posterior segments of the eye can be involved. The patient may present with acute anterior uveitis with hypopyon (*Figure 2*), which may occur in a white or red eye. The posterior segment of the eye is commonly involved and includes retinal vasculitis (occlusive arteritis and periphlebitis), retinal haemorrhages, vitritis, macular oedema, focal areas of retinal necrosis and ischaemic optic neuropathy. The incidence of HLA-B5 and subset B51 is increased among Behçet's patients, particularly those with ocular involvement.

Treatment is usually symptomatic and includes oral and topical corticosteroids, colchicine, cyclosporin, mycophenolate, azathioprine, thalidomide and interferon alpha (Goker and Goker, 2002).

Whipple's disease

Whipple's disease is a rare, chronic, multiorgan bacterial infection that primarily involves the gastrointestinal tract and its lymphatic drainage in middle-aged Caucasian men and can involve the eye. The most common presenting symptoms are weight loss, diarrhoea,

Figure 2. Acute anterior uveitis with a hypopyon in a patient with Behçet's disease.



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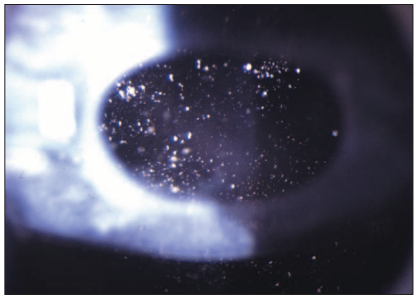
migratory, non-deforming seronegative polyarthralgias, and abdominal pain. Ocular manifestations, which often occur late in the course of Whipple's disease in patients with gastrointestinal or CNS involvement, include blurred vision or visual loss with one or more of the following: vitritis (*Figure 3*), retinitis, retinal haemorrhage, choroiditis, papilloedema, optic atrophy and keratitis. Neurological findings may include ophthalmoplegia, supranuclear gaze palsy, nystagmus, myoclonus and ptosis.

Whipple's disease is often difficult to diagnose because of the diverse clinical signs and symptoms, especially in patients with minimal or no gastrointestinal manifestations. Whipple's disease patients with uveitis may have a choroiditis-like picture similar to that seen in many different types of systemic disease associated with uveitis. Chan et al (2001) described the use of polymerase chain reaction to identify *Tropheryma whippelii* in vitreous samples for early definitive diagnosis of cases with suspected ocular Whipple's disease. Ocular Whipple's disease is very rare and was reported in 19 of 696 patients with systemic Whipple's disease (Chan et al, 2001).

Whipple's disease is difficult to treat, and the disease may be more amenable to antibiotic treatment earlier in the disease as compared to 'late' CNS Whipple's disease. The current empirically recommended treatment entails 1 year of double-strength trimethoprim/sulfamethoxazole (960 mg) twice a day after 2 weeks intravenous therapy. Ryser et al (1984) and Keinath et al (1985) suggested the current drug of choice, trimethoprim/sulfamethoxazole, for improved CNS penetration. However, trimethoprim/sulfamethoxazole is only bacteriostatic and no antibiotic is curative, leading to relapse with late CNS Whipple's disease.

Figure 3. Vitritis in a patient with Whipple's disease.



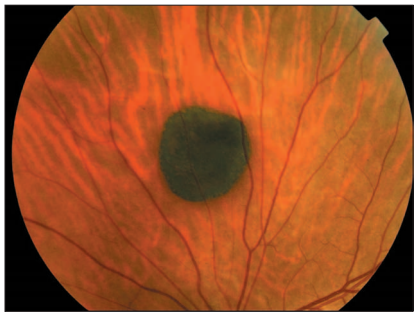
Pre-malignant

Familial adenomatous polyposis (FAP) is an autosomal dominant disease, the diagnosis of which is made in the presence of more than 100 adenomatous polyps in the colon and rectum. Adenomata generally appear in adolescence or early adulthood, and malignant change is unavoidable before the age of 50 years old unless prophylactic pancolectomy is undertaken. Colorectal polyps can be associated with several extracolonic manifestations, including upper gastroduodenal polyps, osteomas, epidermoid cysts of the skin, dental abnormalities, intra-abdominal desmoid tumours, and congenital hypertrophy of the retinal pigment epithelium (CHRPE) (Tiret and Parc, 1999).

CHRPE (*Figure 4*) is the most frequent extraintestinal manifestation associated with FAP. Multiple retinal lesions appear to be a phenotypic marker for FAP, with 70% sensitivity and close to 100% specificity (Traboulsi et al, 1987). Lesions associated with CHRPE are characterized by their number and bilaterality. The number of lesions is variable, from one to forty in the two eyes combined, with the average number being six per eye. Lesions are bilateral in 86% of cases (Tiret et al, 1997), and have been described in a premature infant born at 32 weeks gestation (Aiello and Traboulsi, 1993).

Lesions are often described according to Berk's classification, which divides them into four groups: oval, pigmented and surrounded by a halo (type A); round, small and pigmented (type B); round, large and pigmented (type C); and round, large and depigmented (type D). The most characteristic lesion is type A, but the most frequent lesions are type B (56%) (Berk et al, 1988). These punctate lesions can exist in the normal fundus, but there must be fewer than three. However, idiopathic solitary CHRPE has been described in 1–40% of the general population, which is a flat well-circumscribed benign lesion of the retinal pigment epithelium (Shields et al, 1992). When lesions are atypical or when there is no family history, colonoscopy should be considered.

Figure 4. Congenital hypertrophy of the retinal pigment epithelium (Berk type C).



Malignancy

Gastrointestinal carcinoma rarely causes ocular metastases. In one case series of 420 cases of metastatic uveal tumours, only 4% came from the gastrointestinal tract (Shields et al, 1997). In another case series involving 512 patients with uveal metastasis, the iris was involved in 7.8% of the cases and two patients had primary colonic carcinoma (Shields et al, 1995). Imamura et al (2001) described a case of iris metastasis of a gastric signet ring cell adenocarcinoma, which was the first sign of metastasis. This patient presented with uveitis and raised intraocular pressure not responding to medical treatment. Therefore, a trabeculectomy was performed and a peripheral iridectomy was done at the site of the metastasis. Histology confirmed the same type of carcinoma that was obtained from the specimen from the gastric mucosa 3 years ago.

Another case report of a gastric signet ring cell carcinoma showed metastasis to the optic nerve head (Sung et al, 1998). Metastasis to the optic disc is very rare and was reported as 5% of all intraocular metastases in one case series of 660 consecutive patients with intraocular metastasis from any source (Shields et al, 2000).

Burgueno and Lopez (2002) presented a case report of a 60-year-old male with metastatic adenocarcinoma of the rectum/sigmoid colon, who developed exophthalmos as a result of a tumour in the lateral rectus muscle. Metastasis in the extraocular muscles

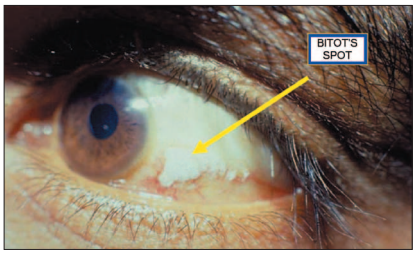
are very uncommon, but should form part of the differential diagnosis of any patient presenting with exophthalmos, since although the majority of patients with such metastasis have a previously diagnosed malignant tumour, there are cases where they lead to the diagnosis of the primary tumour.

Jacobson and Adamus (2001) described a case of colon cancer-associated retinopathy presenting as a unique paraneoplastic condition. The patient had progressive visual glare for 1 year with normal visual acuity and colour vision, paracentral scotomas and a normal-appearing retina. Electroretinography revealed no responses of the right eye and attenuated responses of the left eye, especially those recorded under scotopic conditions. Anti-bipolar antibodies were detected and subsequent evaluation uncovered an adenocarcinoma of the colon. Several months after resection of the tumour and chemotherapy, there was no evidence of the cancer or the anti-bipolar cell antibodies, and electroretinography responses were markedly improved.

Malabsorption

Xerophthalmia, the eye manifestation of vitamin A deficiency, is one of the main causes of blindness in developing countries as a result of malnutrition, but is rare in industrial countries (Horwath et al, 2000). Vitamin A deficiency can lead to nyctalopia or night blindness, conjunctival (*Figure 5*) and corneal xerosis (*Figure 6*). Patients may develop vitamin A deficiency as a result of short bowel syndrome resulting from gastroschisis or bowel resection, with subsequent malabsorption. Electroretinograms can confirm the diagnosis of vitamin A deficiency and should be used to confirm suspected cases. Symptoms usually improve after vitamin A substitution. Although rare in developed countries, ophthalmologists should consider xerophthalmia as differential diagnosis in night blindness and conjunctival and corneal xerosis. Also, malabsorption can occur in IBD and vitamin A should be supplemented to avoid these complications. Early diagnosis and adequate treatment can prevent permanent visual loss.

Figure 5. Arrow showing Bitot's spot secondary to vitamin A deficiency.

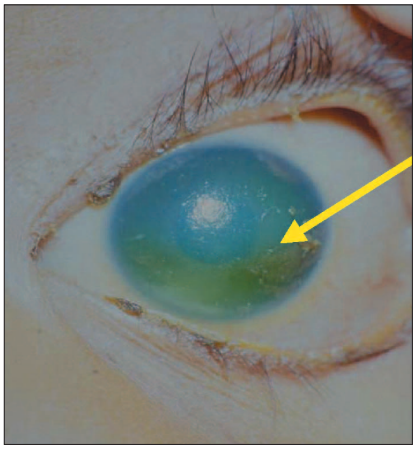


Acute corneal ulceration in malnourished children is the commonest cause of childhood blindness in Northern Nigeria and usually develops after measles (Sandford-Smith and Whittle, 1979). Measles is known to have a depressive effect on vitamin A levels. Inua et al (1983) reported a 20–30% decrease in normal serum retinol level in children with post measles corneal ulceration whereas malnourished children had a 4–12% decrease. However, other severe diseases in malnourished children rarely precipitate corneal ulceration even though retinol levels are very low. Thus a specific deficiency of vitamin A does not appear to be the primary cause of these ulcers but may be a contributory one.

GASTROINTESTINAL INFECTIONS WITH EYE INVOLVEMENT

Reiter's syndrome usually affects young adult males who may be HLA-B27 positive and present with urethritis, conjunctivitis or uveitis, polyarthritis and occasionally keratitis. Patients may have an elevated erythrocyte sedimentation rate and may develop recurrent episodes. Uveitis is usually unilateral, acute in onset, anterior and may or may not persist. Patients with reactive arthritis, sacroiliitis, spondylitis or Reiter's syndrome following intestinal infection from *Yersinia*, *Salmonella*, *Shigella*, *Klebsiella* or *Campylobacter* organisms have been reported from endemic areas and after epidemic dysenteries (Kuntz et al, 1982; Herman et al, 1988). Possession of the antigen HLA-B27 affects severity and prognosis of the arthritis and is more often associated with spondylitis and Reiter's syndrome (Herman et al, 1988). Aseptic arthritis can occur following intestinal infection caused by *Clostridium difficile* and generally have a favourable prognosis (Lemaire, 1983).

Figure 6. Arrow showing corneal xerosis secondary to vitamin A deficiency.



Okhravi et al (1997) reported a case of metastatic fungal enophthalmitis with secondary keratitis caused by *Paecilomyces lilacinus* and *Aspergillus fumigatus*. The patient was on holiday in Ecuador and developed severe diarrhoea associated with neutrophilia and an elevated erythrocyte sedimentation rate (41 mm/hr). Ocular symptoms commenced 2 days after the diarrhoea; and at 10 days the patient was severely symptomatic with pain, redness, photophobia and blurred vision in the left eye. Ocular examination at this time revealed a left-sided conjunctivitis, anterior uveitis, hypopyon, a discrete focus of inflammation on the iris, and no corneal or posterior segment involvement. This infection was resistant to treatment and progressed to involve the crystalline lens and the cornea, requiring multiple surgical procedures and eventually having a poor visual outcome.

Hepatitis C infection is associated with ocular diseases such as Sjögren's syndrome, Mooren's ulcer and retinal pigment epitheliitis. The role of hepatitis C infection in Sjögren's syndrome has been established, whereas its role remains obscure in the other two diseases (Tahri et al, 1997). Moazami et al (1995) and Wilson et al (1994) reported resolution of Mooren's type ulcer using interferon alpha-2b treatment in patients

with chronic hepatitis C virus infection. The improvement of the corneal ulcer usually parallels the return of serum liver enzyme levels to the normal range, however, relapse is common and continued follow up is necessary.

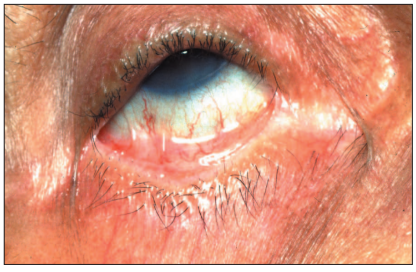
GASTROINTESTINAL DISEASES AS A COMPLICATION OF EYE TREATMENT

Many ocular conditions are caused by a chronic inflammatory process requiring long-term anti-inflammatory treatment. These treatments are usually administered orally and can have devastating effects on the gastrointestinal system. Treatment varies from non-steroidal anti-inflammatory agents to corticosteroids and other immunosuppressant agents.

Tamesis et al (1996) reviewed 602 patients with ocular inflammatory disease treated with immunosuppressive drug therapy and/or systemic corticosteroids, comparing the relative toxicities of six immunosuppressive drugs to prednisolone. Patients on prednisolone had a higher incidence of gastrointestinal symptoms and, unlike the immunosuppressive agents, these symptoms were unlikely to subside upon discontinuation of long-term treatment.

Ocular cicatricial pemphigoid (*Figure 7*) is an autoimmune disease that, untreated, progresses to conjunctival scarring and blindness; systemic immunosuppression is required to control it. Long-term systemic treatment and more than one drug are frequently necessary to avoid recurrences, exposing elderly patients to a higher risk of drug toxicity. Miserocchi et al (2002) reviewed sixty-one patients with biopsy-proven ocular cicatricial pemphigoid treated with chemotherapy and/or corticosteroids. Dapsone is one of the first-line immunosuppressants used to treat ocular cicatricial pemphigoid. This is associated with the most gastrointestinal side effects as compared to methotrexate, azathioprine or cyclophosphamide, which are the alternatives.

Figure 7. Lid and conjunctival scarring with forniceal shortening in a patient with ocular cicatricial pemphigoid.



Lim et al (2003) reported two cases of transient paralytic ileus following the use of cyclopentolate and phenylephrine drops in preterm infants. Cyclopentolate and phenylephrine drops are commonly used to induce mydriasis during routine screening for retinopathy of prematurity in preterm infants. Thus an adequate history can reveal the use of these medications, avoiding unnecessary investigations and treatment in symptomatic preterm infants experiencing this temporary side effect secondary to systemic absorption. HM

Figures 5 *and 6 are reproduced courtesy of Professor Allen Foster.*

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