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REVIEW

Ophthalmic manifestations in patients with inflammatory bowel disease: A review

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Abstract

Clinical manifestations of inflammatory bowel disease (IBD) are not locally restricted to the gastrointestinal tract, and a significant portion of patients have involvement of other organs and systems. The visual system is one of the most frequently affected, mainly by inflammatory disorders such as episcleritis, uveitis and scleritis. A critical review of available literature concerning ocular involvement in IBD, as it appears in PubMed, was performed. Episcleritis, the most common ocular extraintestinal manifestation (EIM), seems to be more associated with IBD activity when compared with other ocular EIMs. In IBD patients, anterior uveitis has an insidious onset, it is longstanding and bilateral, and not related to the intestinal disease activity. Systemic steroids or immunosuppressants may be necessary in severe ocular inflammation cases, and control of the underlying bowel disease is important to prevent recurrence. Our review revealed that ocular involvement is more prevalent in Crohn's disease than ulcerative colitis, in active IBD, mainly in the presence of other EIMs. The ophthalmic symptoms in IBD are mainly non-specific and their relevance may not be recognized by the clinician; most ophthalmic manifestations are treatable, and resolve without sequel upon prompt treatment. A collaborative clinical care team for management of IBD that includes ophthalmologists is central for improvement of quality care for these patients, and it is also cost-effective.

Key words: Inflammatory bowel disease; Crohn's

disease; Ulcerative colitis; Ocular complications; Eye manifestations

Core tip: Among all inflammatory bowel disease (IBD) patients, ophthalmic inflammatory disorders occur in 0.3% to 13.0% of cases, 1.6%-5.4% among the ulcerative colitis and 3.5%-6.8% among the Crohn's disease patients. Since asymptomatic inflammation of ocular tissues may occur, a routine ophthalmic follow-up is recommended in all IBD patients, mainly before changes in IBD therapy because some drugs may cause ocular adverse effects. Patients with chronic or recurrent use of systemic corticosteroids should be warned of the risk of cataracts and glaucoma. Patient awareness of possible eye involvement is important in improving understanding of their disease and health outcomes, supporting early diagnosis, which will contribute to success of the treatment.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, immune-mediated inflammatory gastrointestinal disease of unknown etiology[1-4]. Ulcerative colitis (UC) and Crohn's disease (CD) are the main types of IBD, with different pathophysiology and clinical features but both characterized by episodes of recurrent acute attacks[1,4-9].

The incidence and prevalence of IBD are highly variable, depending on the population studied[8,10-12], with an estimated global prevalence of 146.9 cases/100000 people. IBD has shown progressive increases in newly industrialized countries in Asia, South America and the Middle East, and has evolved into a global disease with a rising prevalence on every continent[13]. The highest worldwide prevalence of IBD is found in Europe, with 322 and 505 cases per 100000 people for CD and UC, respectively[3,8].

IBD is a chronic disease and requires chronic treatment. In addition, the disease has a great impact on the patient's quality of life, commonly requiring a lifetime of care. Ocular complaints can occur as an extraintestinal manifestation (EIM) of the disease or may be drug-related. These disorders can be non-specific, with no clinical relevance to the patient and/or the physician, but the risk of complications is a reality. Thus, early detection and treatment are necessary to prevent poor outcomes, as discussed in this review.

EIMs

Considering the underlying disease, the prevalence of EIM is variable and ranges between 12% to 35% in UC and 25% to 70% in CD[2,14-16]. Indeed, 6%-40% of patients with IBD have one or more EIMs that can be more debilitating than the underlying IBD itself[17]. Although the EIMs have a multifactorial pathogenesis, it is not well understood[16]. It seems to be related to an immune response against toxins and antigens that reach the bloodstream from the gastrointestinal tract, leading to an antigen-antibody complex deposition in different extraintestinal tissues[2,18-21].

Other complex mechanisms are speculated in some cases. It has been suggested that a human epithelial colonic autoantigen that is also present in the skin, bile ducts, eyes and joints triggers an antibody-mediated immune response[5,22,23] and that this is related to intestinal and extraintestinal symptoms in UC patients, but not in CD[5]. A higher incidence of HLA-B27 and HLA-DRB1*0103 positivity was demonstrated in IBD patients, and an association with extensive disease and the development of EIMs, mainly ocular and articular, has been reported[9,22,24]. However, Lanna *et al*[25] analyzed 96 IBD patients and found no association between HLA positivity and ocular or joint manifestations, suggesting that this finding could be justified by the great genetic heterogeneity in different global populations.

The frequency of EIMs in each type of IBD patient is controversial. Most studies show a higher frequency of EIMs in CD patients[2,20,26-28], while some report similar frequencies in both diseases[29]. EIMs may occur before an IBD diagnosis and even before recurrent intestinal episodes[3,30]. The diagnosis of IBD in those under 40 years old and of female sex are considered risk factors for the development of EIMs[2,31].

Among EIMs, musculoskeletal conditions are most common, followed by mucocutaneous and ophthalmic diseases[15,32]. However, nearly any organ, including those of dermatologic, hepatopancreatobiliary, renal, pulmonary and endocrinological systems, can be involved, leading to a significant challenge to physicians who manage IBD patients[2,15,19]. Most IBD patients with EIMs have active colonic inflammation; although, they can occur prior to, or after, the onset of colonic symptoms[20,26,33-35]. Early recognition of EIMs is important as they may characterize subclinical inflammation in IBD patients, with a possible increased risk of morbidity and mortality[19,35,36].

The aim of this review was to evaluate the current literature about ocular EIMs, emphasizing inflammatory alterations that need prompt recognition to avoid irreversible visual impairment. Reference lists from the articles selected by electronic searching were manually reviewed to identify further relevant studies. Articles in each of these multiple searches were

reviewed, and those meeting the inclusion criteria, that is, publications providing data on the incidence, prevalence, clinical features and management of ophthalmologic manifestations in IBD, were recorded.

OCULAR INVOLVEMENT

The ocular system can be affected by several immune systemic diseases, including IBD[29,37-42]. Crohn[42] published the first report of ocular involvement in IBD in 1925, in which it was suggested that two patients he treated probably suffered from keratomalacia and xerophthalmia.

Since the first report, the main ocular findings have been related to inflammatory manifestations[20,25,27,29,43-45] that occur in the early years after an IBD diagnosis[2,15]. Although these findings can indicate disease activity[15,18], the association with the gastrointestinal tract-affected area is not well established[2,15]. It has been demonstrated that there is a greater tendency of ocular inflammation in CD patients, mainly with colitis or ileocolitis, and UC patients with pancolitis[2,34,46]. Zippi *et al*[28] corroborate the literature data in their retrospective study in Italian IBD patients, demonstrating a significant association between ocular EIM and CD.

The prevalence of ophthalmic inflammatory disorders is variable, according to the population studied, ranging from 0.3% to 13.0% among all IBD patients[14,20,25,27,29,34,45,47], 1.6%-5.4% among those with UC and 3.5%-6.8% among those with CD[25,29]. Although a greater frequency of ocular involvement has been demonstrated in CD *vs* UC patients[23,48], the results are controversial[25,27].

Considering the risk factors for developing ocular manifestation in IBD, an association has been reported with female sex[17,23,31], and the presence of arthritis or arthralgia in CD patients[23,46]. A paradoxical positive association has been demonstrated between smoking and ocular manifestation in UC patients[49], because it is well known that smoking exerts a protective effect against both the development and progression of UC[50,51].

The physiopathology of ocular EIMs remains unclear[2,25,29,52-54]. It has been suggested that local action of antigen-antibody complexes produced against the bowel wall vessels and transported *via* the bloodstream could be responsible for eye involvement[18,19]. However, Santeford *et al*[52] suggested a disturbance in physiological macrophage-mediated autophagy as a potential molecular link between systemic disease and uveitis. Lin *et al*[55], in a large retrospective analysis, suggested that a family history of IBD itself may confer an independent, increased susceptibility to the development of ocular inflammation, despite the absence of bowel disease or of known genetic susceptibility (HLA-B27).

The most common ocular manifestations related to IBD are episcleritis (2%-5%) and uveitis (0.5%-3.5%)[15,17,29,32], as listed in Table 1.

Karmiris *et al*[56] performed an important study due to the large number of subjects evaluated. They retrospectively analyzed 1860 (1001 with CD and 859 with UC) Greek IBD patients' medical reports. Arthritic, mucocutaneous and ocular (3% of IBD patients; 8.9% of all EIM occurrences) were the most common types of manifestations. Ocular EIMs were more frequent in women (54.55%) and CD patients (81.82%), with the exception of posterior uveitis, which had a predominance in UC patients. The authors mentioned episcleritis as the most frequent manifestation, although 31 cases of anterior uveitis and 16 cases of episcleritis were found. Disease activity was evaluated clinically in 346 participants, according to the treating physician's assessment (presence of symptoms associated with elevated inflammatory markers, mainly C-reactive protein and erythrocyte sedimentation rate, despite appropriate treatment at the time of the EIM diagnosis). They found 225 (65%) active IBD and 121 (35%) quiescent cases. The relationships between ocular EIM and IBD activity and extent, or behavioral and smoking habits were not clearly mentioned in the study.

Similarly, Bandyopadhyay *et al*[27] reported in their study of 120 Indian IBD patients an association between general EIMs and female sex, Hindu religion, severe gastrointestinal disease and steroid usage, but did not mention specific associations with ocular EIMs. The frequency of ocular EIM reported was similar to that among American and European populations. Manser *et al*[57] detected uveitis in 15.7% of patients with extraintestinal complications and 12.3% of all 179 UC patients evaluated. They suggested that the introduction of early mesalazine therapy, up to 2 mo after UC diagnosis, could be a protective factor against the development of EIMs[58].

Cloché *et al*[59] evaluated 74 of 305 IBD patients with ophthalmological symptoms. Only one patient presented with scleritis and they concluded that ocular symptoms were neither specific nor associated with ocular inflammation. A limitation of the study was that only symptomatic patients underwent examinations. No subclinical occurrence was investigated; thus, it is not possible to determine the actual occurrence of ocular manifestations in the total sample. Even evaluating only symptomatic patients, a frequency of ocular manifestation of 1.4% was found, lower than that found in the literature. A possible explanation is based on the large number of patients receiving biological agents, about 50%, which may have treated the IBD and prevented ocular inflammation[60].

In an important prospective study, Felekis *et al*[61] performed complete eye examinations in 60 IBD patients, finding a high frequency of 43% of ocular EIMs. However, in some cases these findings could

Table 1 Studies evaluating ocular manifestations in inflammatory bowel disease patients

Ref.	Country	Study design	Ocular exam sample	Ocular manifestation frequency	Comment
Karmiris *et al*[56] (2016)	Greece	Prospective cohort	1860 (1001 CD; 859 UC)	55 (3%) (45 CD; 10 UC): 31 Anterior uveitis (25 CD; 6 UC); 16 Episcleritis (16 CD); 7 Posterior uveitis (3 DC; 4 UC); 1 Central serous retinopathy (CD)	Ocular EIMs represented the third most frequent group of EIM in the study All patients with episcleritis suffered from CD. There were patients with anterior and posterior uveitis
Manser *et al*[57] (2016)	Switzerland		140 UC patients with EIM or complications	22 (15.7%) Uveitis	Investigated prevalence of uveitis in patients with UC
Bandyopadhyay *et al*[27] (2015)	India		120 (62 CD; 58 UC)	16 (13%) (8 CD; 8 UC): 7 Uveitis (7 CD); 9 Episcleritis (1 CD; 8 UC)	Authors describe two cases of scleritis (2 CD) and one of endophthalmitis (CD) that were not accounted as ocular manifestations. Authors consider a selection bias, as most participants had severe intestinal disease
Isene *et al*[58] (2015)	Europe (Norway, Denmark, Netherlands, Spain, Italy, Greece, and Israel)	Prospective cohort	1145 (364 CD; 781 UC)	12 (1.0%) 10 (0.9%) Anterior uveitis; 2 (0.2%) Episcleritis	Authors concluded that familial IBD does not predict increased risk of immune-mediated EIM, as smoking does not seem to influence the risk
Zippi *et al*[28] (2014)	Italy	Retrospective	811 (216 CD; 595 UC)	26 Uveitis (3.2%) (16 CD; 10 UC)	It is not informed if other ocular manifestations have been investigated in addition to uveitis.
Cloché *et al*[59] (2013)	France		74 IBD (no underlying disease specification)	1 (1.4%): Scleritis	A large number of patients were receiving biological agents, approximately 50%, that may treat IBD and prevent ocular inflammation. Authors do not define the underlying IBD of the scleritis patient
Vavricka *et al*[22] (2011)	Switzerland	Prospective Cohort	950 (580 CD; 370 UC)	50 (5.3%) (36 CD; 14 UC): 50 Uveitis	Only uveitis was considered ocular EIM, and it was associated to active CD, but no relation was found to UC activity
Cury *et al*[60] (2010)	Brazil		88 (48 CD; 40 UC)	7 (6.25%) (no underlying disease specification): 1 Conjunctivitis; 3 Blepharitis; 1 Episcleritis; 2 Uveitis; 2 Cataracts	The study used a control group of 24. Considered also unspecific ocular abnormalities, as cataract and blepharitis
Felekis *et al*[61] (2009)	Greece	Prospective cohort	60 (23 CD; 37 UC)	26 (43%) (12 CD; 14 UC): 13 Dry eye; 8 Glucocorticoid-induced cataract; 3 Iridociclitis; 3 Retinal pigment epithelium disturbances; 2 Episcleritis; 2 Serous retinal detachment; 1 Conjunctivitis; 1 Choroiditis; 1 Vasculitis; 1 Optic neuritis	The study used a control group of 276. Authors conclude that ocular manifestations occur in UC patients as frequently as in CD patients; however, the results of the statistical analysis are not mentioned for any of the study variables
Lanna *et al*[25] (2008)	Brazil		96 (59 CD; 37 UC)	6 (6.2%) (4 CD; 2 UC): 4 Uveitis (2 bilateral; 2 CD; 2 UC); 1 Scleritis (CD); 1 Episcleritis (CD)	It was not possible to analyze the association between the HLA-B27 and ocular abnormalities because only 3 of the 6 patients had been tested for HLA-B27; all of them were negative for this antigen
Yilmaz *et al*[35] (2007)	Turkey	Prospective cohort	116 (20 CD; 96 UC)	28 (24.13%) (12 CD; 22 UC): 10 Conjunctivitis; 8 Blepharitis; 6 Uveitis; 6 Cataracts; 4 Episcleritis	Study considered unspecific ocular abnormalities, as cataract and blepharitis, which are very frequent in the general population

Mendoza *et al*[29] (2005)	Spain	Prospective cohort	566 (295 CD; 271 UC)	13 (2.3%) (6 CD; 7 UC): 8 Uveitis (2 CD; 6 UC); 5 Episcleritis (4 CD; 1 UC)	In 2 patients the ophthalmologic clinical presentation preceded the diagnosis of IBD, but its frequency is probably undervalued considering the high prevalence of asymptomatic uveitis
Ricart *et al*[47] (2004)	United States		243 IBD [47 familial IBD (25 CD; 22 UC); 196 sporadic IBD (114 CD; 82 UC)]	Familial IBD: 3 (2 CD; 1 UC) Sporadic IBD: 10 (7 CD; 3 UC) Authors don't specify which ocular EIM was found	Significant association between EIM and disease status (familial *vs* sporadic) was not detected. This suggests that susceptibility genes for the development of IBD and the susceptibility genes for the development of EIM are different
Lakatos *et al*[2] (2003)	Hungary	Prospective cohort	873 (254 CD; 619 UC)	28 (3.2%) (8 CD; 20 UC): 13 Conjunctivitis (4 CD; 9 UC), 10 Anterior uveitis (4 CD; 6 UC); 5 Scleritis (1 CD; 4 UC); 1 Orbital pseudotumor (female UC patient)	The prevalence was more frequent in women in both UC and CD. In UC more than half of the patients with ocular complication had pancolitis
Christodoulou *et al*[62] (2002)	Greece	Retrospective	248 (37 CD; 215 UC)	4 (1.61%) (1 CD; 3 UC): 4 Iridocyclitis	Evaluated only iridocyclitis as ocular EIM

CD: Crohn's disease; EIM: Extraintestinal manifestation; IBD: Inflammatory bowel disease; UC: Ulcerative colitis.

have been coincidental and not related to IBD, such as dry eye and blepharitis. According to the methodology, individuals with ocular symptoms were excluded from the control group, and half of the sample of IBD patients was selected during hospitalization (severe disease activity), suggesting selection bias. Even so, the article presents some ocular findings that are infrequent in the literature, because the subjects underwent complementary fundus examinations with fluorescein angiography, increasing the importance of the study.

Lanna *et al*[25] performed eye examinations in 96 of 130 IBD patients. Six patients (four with CD, two with UC) presented ocular manifestations. Uveitis was diagnosed in four patients, anterior nodular scleritis in a woman with CD, and episcleritis in a man with CD with recurrent peripheral arthritis and psoriasis. One of the two men with anterior uveitis also had ankylosing spondylitis.

Yilmaz *et al*[35] and Cury *et al*[60] considered all ocular findings as EIMs, including conjunctivitis, blepharitis, and cataracts. Some entities have a high prevalence in the general population, regardless of the presence of intestinal disease, what can be considered a confounding factor in the analysis. It is difficult to establish any relationship between these occurrences and IBD because they may be related to other factors, such as age and other underlying factors.

Cury *et al*[60] described a correlation between dry eye and the use of 5-aminosalicylates in IBD patients. Apparently, dry eye disease may be associated with IBD and also may be related to its treatment. Blepharitis was less common in IBD patients than controls (3% *vs* 33%)[60], suggesting a protective action of the drug used in IBD treatment.

Episcleritis

Episcleritis is a benign inflammation of the episclera, the thin blood-rich layer of tissue that covers the sclera. It is the most common ocular manifestation and causes moderate discomfort, acute redness in one or both eyes[34], and diffuse or localized episcleral edema, particularly surrounding the episcleral vessels[40]. Its classification as nodular or diffuse does not affect the prognosis[62-64].

Episcleritis seems to be more associated with IBD activity when compared with other ocular EIMs. It appears during flares of IBD, and its resolution occurs with effective treatment of the intestinal disease[20,32,41,46,54]. It is usually recurrent and can spread to the sclera, causing scleritis[40,43]. To an untrained observer and without a slit lamp examination, it is not easy to distinguish the two entities[65]. Differentiation from conjunctivitis, which is a frequent condition in the general population and may occur coincidently in patients with IBD, may also be difficult[43,66,67].

The differential diagnosis between episcleritis, uveitis, and scleritis is based on the absence of moderate-to-severe eye pain, photophobia, blurring, and low vision in the former[33]. Episcleral injection blanches with topical application of phenylephrine and softens with palpation[66]. As a benign condition, specific treatment is not always necessary; however, cool compresses, lubricant eye drops, topical non-steroidal anti-inflammatory drugs, and topical corticosteroids are occasionally required[20,33,34,54,66]. Figure 1 illustrates diffuse episcleritis.

Scleritis

Scleritis is an inflammation of the sclera, the opaque and protective outer layer of the eye, that causes

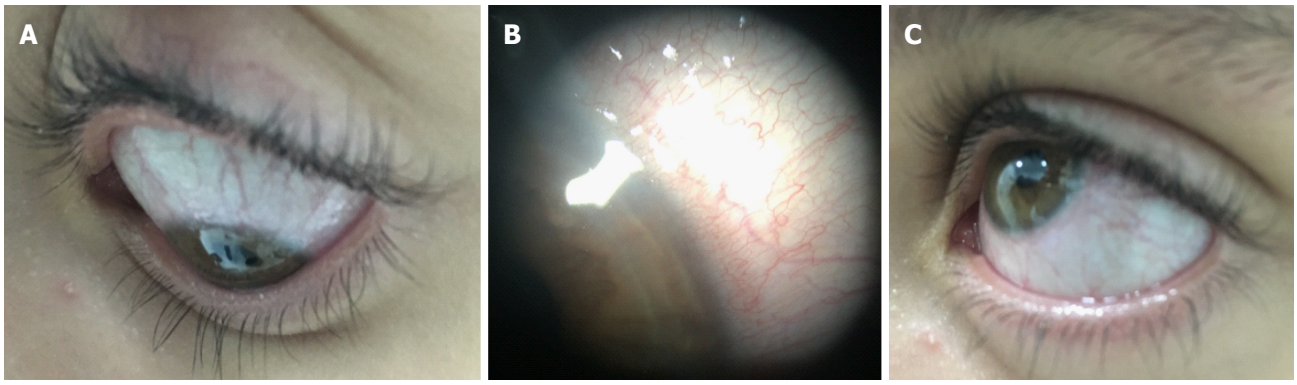

Figure 1 Diffuse episcleritis. A: Superior view; B: Episcleral injection at slit lamp exam; C: Inferior view. Personal archive.

Table 2 Uveitis classification

SUN classification	Primary site of inflammation	Manifestation
Anterior uveitis	Anterior chamber	Iritis, iridocyclitis, anterior cyclitis
Intermediate uveitis	Vitreous	Pars planitis, posterior cyclitis, hyalitis
Posterior uveitis	Retina or choroid	Focal, multifocal or diffuse choroiditis, chorioretinitis, retinochoroiditis, retinitis, neuroretinitis
Panuveitis	Anterior chamber, vitreous, and retina or choroid	

Adapted from Standardization of Uveitis Nomenclature Working Group[70]. SUN: Standardization of Uveitis Nomenclature Working Group.

ocular pain, which radiates to the face and scalp. Characteristically, it worsens at night, and is associated with ocular hyperemia and visual loss[34,40]. It can present with a deep scleral injection that does not blanch with phenylephrine[66].

Scleritis and intermediate or posterior uveitis are much rarer than episcleritis and anterior uveitis in IBD, occurring in less than 1% of cases, but should be evaluated with caution because, if left untreated, it may progress to permanent visual loss[33]. Scleritis classification is important because it is related to severity and prognosis. Watson and Hayreh[63] classified scleritis as anterior (diffuse, nodular, or necrotizing, with or without inflammation) and posterior. Involvement of the anterior part of the sclera is more common and posterior scleritis is not associated with ocular hyperemia. A modified classification of scleritis was proposed by Watson *et al*[64] (Figure 2) in accordance with location (anterior or posterior), and clinical presentation (diffuse, nodular, or necrotizing). The necrotizing anterior scleritis was classified according to its etiology, as vaso-occlusive, granulomatous, surgically induced, and scleromalacia perforans. Figure 3 illustrates the different types of scleritis.

Systemic treatment is necessary in all cases, usually with oral non-steroidal anti-inflammatory drugs but they should be used with great caution in active IBD[68]. Systemic steroids or immunosuppressants may be necessary in severe cases, and control of the underlying bowel disease is important to prevent recurrence[34,68]. To avoid side effects of long-standing corticosteroids use, immunosuppressive therapy is required[40], which will be discussed regarding uveitis treatment.

Uveitis

Uveitis is the third leading cause of irreversible blindness in developed countries[37,52,69]. It is defined as inflammation of the uveal tract, the middle layer of the eye, which includes the iris, ciliary body, and choroid[70]. It is classified according to the primary site of inflammation as anterior, intermediate, posterior, or panuveitis[70] (Table 2).

Uveitis is characterized by vascular dilation, leading to conjunctival injection, aqueous flare related to increased vascular permeability, and aqueous and vitreous inflammatory cells[69]. Uveitis can be idiopathic[38,71], drug-related[72,73], or systemic disease-related[37,38,74]; in approximately 50% of cases, an underlying disease can be identified[38]. Anterior uveitis is the most common pattern, related to seronegative spondyloarthropathies[40,55,74]. Figure 4 shows the clinical signs of anterior uveitis.

In IBD patients, anterior uveitis has an insidious onset, it is longstanding and bilateral[25,33,46,75], and not related to the intestinal disease activity[32,54,68,76]. In contrast, Vavricka *et al*[22], after prospectively evaluating a large sample of IBD patients, demonstrated an association between uveitis and CD activity, but not with UC.

A clinical overlap of anterior uveitis, dermatologic manifestations (erythema nodosum)[43], and musculoskeletal symptoms (arthritis and sacroileitis)[18,75,77] in CD was reported. It was proposed that a common antigen (an isoform of tropomyosin) in the non-pigmented ciliary epithelium of the eye, the keratinocytes, chondrocytes and the gut triggered an autoimmune reaction[22,23]. Thus, in IBD patients with eye complaints and others EIMs, the presence of uveitis

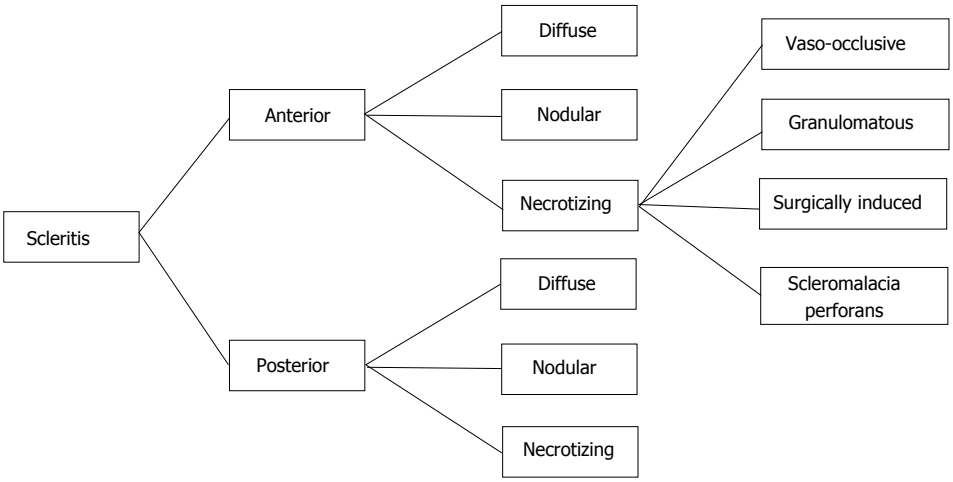

Figure 2 Classification of scleritis[64].

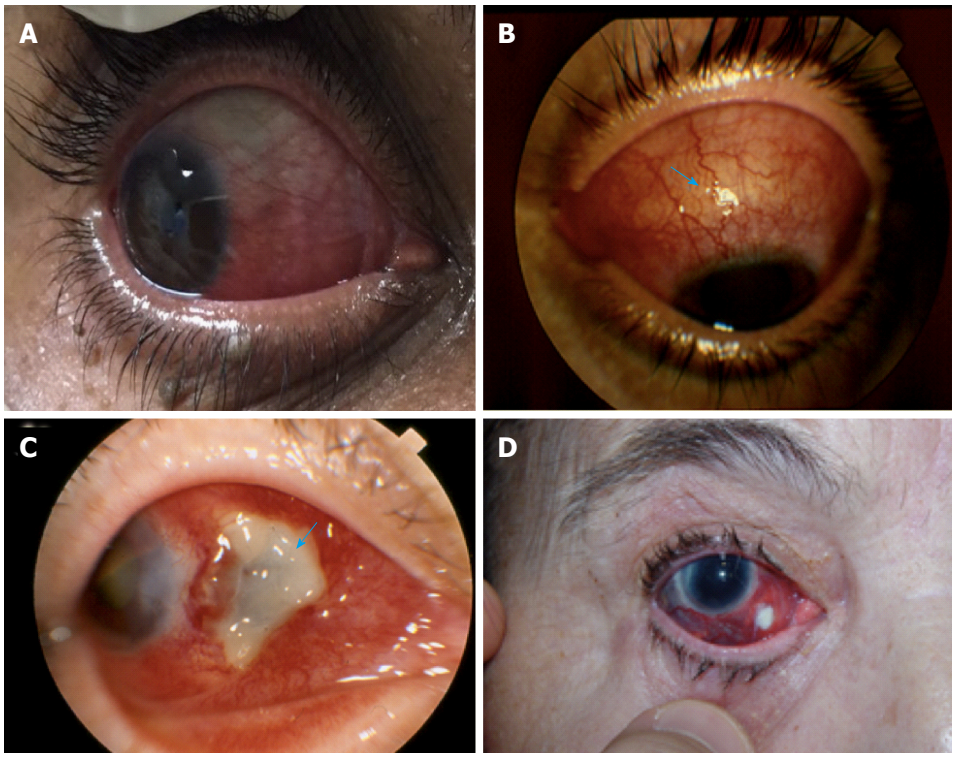

Figure 3 Clinical presentation of scleritis. A: Anterior diffuse scleritis (personal archive); B: Anterior nodular scleritis (personal archive). The differential diagnosis is based on the presence of a sclera nodule (arrow); C: Anterior necrotizing scleritis, showing the avascular area of necrosis (arrow) (personal archive); D: Anterior necrotizing surgically-induced scleritis, induced by scleral biopsy (courtesy of Prof. Andre Curi).

must be considered[34,68]. Because uveitis has a variable chronicity and severity, it may be complicated, according to its primary site of inflammation, by cataracts, glaucoma, band keratopathy, hyphema, vitreous hemorrhage, cystoid macular edema, retinal detachment, retinal ischemia, optic atrophy, chronic eye pain and blindness[69].

Treatment

Prompt treatment can avoid complications and visual impairment[38,40,76]. Treatment of anterior uveitis is based on topical steroids, to reduce inflammation, and topical cycloplegics, to prevent ciliary body and pupillary spasms related to ocular pain. Also, cycloplegics prevent posterior synechiae because they dilate the pupil and stabilize the blood-aqueous barrier, avoiding protein leakage (flare)[33,34,68]. According to the gravity of uveitis, periocular corticosteroid injections or systemic corticosteroids may also be necessary[37,53]. Uveitis with a chronic course requires immunosuppressive therapy to spare the prolonged use of corticosteroids and their side effects[38,53]. However, the choice of immunosuppressive therapy requires a multidisciplinary decision, especially if there

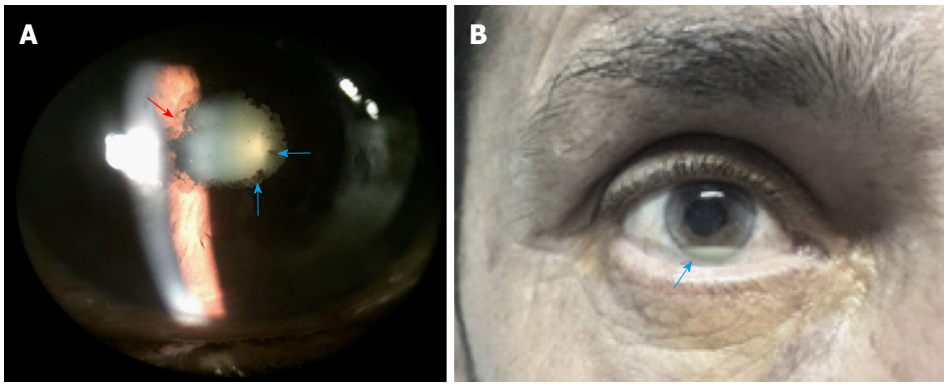

Figure 4 Anterior uveitis. A: Slit lamp exam revealed posterior synechiae (red arrow) and pigment deposits on the anterior lens capsule (blue arrow) (personal archive); B: Inflammatory cells in the anterior chamber of the eye causing hypopyon (arrow) (personal archive).

is another associated EIM[20].

Cyclosporine, a T-cell inhibitor[24,32,41], thiopurines (antimetabolites)[33,41,66,78], methotrexate[33,41,79], sulfasalazine (5-ASA derivate)[68,80], and biological anti-tumor necrosis factor (TNF) agents (mainly infliximab and adalimumab)[33,81] are effective in treating both the IBD and the inflammatory IBD-related ocular impairment[6,34,44,53,82-85]. Although vedolizumab and certolizumab pegol have been introduced more recently in the therapy of CD[8,82,83], their efficacy in ocular inflammation is unknown. Despite the fact that the anti-metabolite mycophenolate can be used to treat uveitis[68,78,86,87], it is not indicated as an IBD treatment[81].

Patient awareness of EIMs is important in improving patient understanding of their disease and health outcomes[88]. It also increases the likelihood of early diagnosis, contributing to success of the applied treatment.

Other ophthalmic manifestations

Other ophthalmic manifestations have been described in relation to IBD. Table 3 presents observational case reports, interventional case reports, and case series describing other ocular disorders in IBD patients. Some of these manifestations can be debilitating if not recognized and treated at an early stage.

Ocular complications

Ocular impairment may be related to IBD, drug therapy or to other factors, such as age, genetics and other concomitant diseases[34,38]. Cataracts and open-angle glaucoma are complications of long-standing ocular inflammation or the prolonged use of corticosteroids[34,37,41,43]. Some ocular manifestations have been related to drugs used in the treatment of IBD, such as corneal immune infiltrates[121] and diffuse retinopathy[122] related to adalimumab, anterior optic neuropathy[123] and retinal vein thrombosis[124,125] developing after infliximab, and cyclosporine, used in CD, causing rare optic neuropathy[66]. Levels of methotrexate in tears approximate serum levels after short-term use, which may lead to irritation of the conjunctiva, cornea, and eyelids[67].

Uveitis has been associated with the use of biological anti-TNF drugs. It has been described in association with etanercept, infliximab, adalimumab, and rifabutin[72,73]. Inflammation declines with drug withdrawal, which is recommended, and the use of topical corticosteroids may be necessary to complete the remission of the inflammatory condition[38,72]. Furthermore, neurological side effects from drug therapy can cause visual impairment without directly affecting the eyes[126].

Katsanos *et al*[48] performed a review of orbital and optic nerve involvement in IBD. It was found that optic nerve impairment can occur as a result of damage of the optic nerve tissue *per se*, as a result of inflammation and/or ischemia, due to intracranial hypertension, and secondary to anti-TNF agents. In some cases, it was difficult to determine the exact cause of ocular involvement in IBD.

After bowel resection in the IBD context, short bowel and malabsorption syndromes can lead to vitamin A deficiency, which may result in night blindness (nyctalopia) and keratoconjunctivitis sicca[127,128]. Vomiting and unilateral painful red eye lead to a suspicion of acute angle closure glaucoma[67], a threatening ophthalmological urgency that has not been described in IBD but which may confound the clinician.

Finally, an association between the use of latanoprost eye drops for glaucoma treatment and IBD relapse has been reported[129]. It was concluded that the systemic absorption of the prostaglandin analog could have caused an increase in intestinal inflammation in IBD patients.

CONCLUSION

Physicians must remember that ocular involvement is more prevalent in CD and in active IBD, primarily in the presence of others EIMs. The ophthalmic symptoms in IBD are mainly non-specific and their relevance may not be recognized by the clinician. Moreover,

Table 3 Case reports and case series of other ocular manifestations associated with inflammatory bowel disease

Ref.	Country	Ocular impairment	IBD
Hwang *et al*[89] (2001)	Canada	Dacryoadenitis	CD
Mochizuki *et al*[90] (2010)	Japan		UC
Boukouvala *et al*[91] (2012)	United Kingdom		CD
Jakobiec *et al*[92] (2014)	United States		2 CD
Ruiz Serrato *et al*[15] (2013)	Spain	Palpebral ptosis	CD
Diaz-Valle *et al*[93] (2004)	Spain	Lid margin ulcers	CD
Leibovitch *et al*[94] (2005)	Australia	Pyodermatitis-pyostomatitis vegetans of eyelids	UC
Garrity *et al*[95] (2004)	United States	Orbital myositis	2 CD
Verma *et al*[96] (2013)	Canada		CD
Foroozan *et al*[97] (2003)	United States	Ocular miasthenia graves	UC
Pham *et al*[31] (2011)	United States	Peripheral ulcerative keratitis	3 CD
Roszkowska *et al*[98] (2013)	Italy	Salzmann nodular corneal degeneration	CD
Zullow *et al*[99] (2017)	United States	Central serous	UC
Geyshis *et al*[100] (2013)	Israel	chorioretinopathy	UC
Assadsangabi *et al*[101] (2010)	United Kingdom		CD
Ugarte *et al*[102] (2002)	United Kingdom	Serpiginous chorioretinopathy	CD
Casalino *et al*[103] (2014)	Italy	Choroidal	CD
Thomas *et al*[104] (2014)	United States	neovascularization	CD
Unal *et al*[105] (2008)	Turkey		CD
Saatci *et al*[106] (2002)	Turkey	Retinal vasculitis	CD
Larsson *et al*[107] (2000)	Sweden	Retinal vein occlusion	1 CD, 1 UC
Buchman *et al*[108] (2006)	United States		UC
Unal *et al*[105] (2008)	Turkey		CD
Yamane *et al*[109] (2007)	Brazil		CD
Vayalambrone *et al*[110] (2011)	United Kingdom		UC
Falavarjani *et al*[111] (2012)	Iran	Retinal artery	CD
Abdul-Rahman *et al*[112] (2010)	New Zealand	occlusion	CD
Saatci *et al*[106] (2002)	Turkey		CD
Siqueira *et al*[113] (2016)	Brazil		CD
Saatci *et al*[106] (2002)	Turkey	Retinal neovascularization	CD
Fuentes-Páez *et al*[114] (2007)	Spain	Subretinal fibrosis and uveitis syndrome	UC
Munk *et al*[115] (2016)	United States	Acute macular neuroretinopathy	UC
McClelland *et al*[116] (2012)	United States	Optic perineuritis	CD
Felekis *et al*[117] (2010)	Greece	Anterior ischemic optic neuropathy	CD
Mason *et al*[118] (2002)	United States	Macular edema	CD
De Franceschi *et al*[119] (2000)	Italy	Dystrophy of the retinal pigment epithelium	CD
Villain *et al*[120] (2002)	France	Pseudotumor cerebri	CD

CD: Crohn's disease; IBD: Inflammatory bowel disease; UC: Ulcerative colitis.

asymptomatic inflammation of ocular tissues may occur, so a routine ophthalmic follow-up is recommended in all IBD patients (with or without ocular symptoms), mainly before changes in IBD therapy, because some drugs may cause ocular adverse effects. It is important to remember that most ophthalmic manifestations are treatable without sequel if recognized promptly.

Ophthalmologists must consider that ophthalmic manifestations of IBD may precede the systemic disease, and systematic anamnesis must be done in chronic uveitis of unknown etiology. Patients with chronic or recurrent use of systemic corticosteroids should be warned of the risk of cataracts and glaucoma. A collaborative clinical care team for management of IBD that includes ophthalmologists is central for improvement of the quality care for these patients, and is also cost-effective.

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