Ophthalmologic Manifestation of Behçet’s Disease

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Loss of vision in Behçet’s disease is one of the most common, as well as one of the most serious, of its varied manifestations. Total blindness may often be the eventual outcome. The underlying problem in the eye, as well as in other organ systems, is an occlusive vasculitis. Although the most common ocular symptom is that of iridocyclitis, the presence of retinovascular lesions, especially necrotizing retinitis, is well known but often obscured by the severity of the anterior reaction, which precludes a good view of the retina. While Behçet’s disease is characterized by spontaneous remissions and relapses, no external factors have been found to explain the length of remissions. Blindness, which occurs in up to 25% of patients, is one of the major causes of permanent disability.

Key Words: Behçet’s disease, iridocyclitis, occlusive retinitis

Ocular findings

In a high percentage of cases, there is ocular involvement: 83 to 95% of men with BD and 67 to 73% of affected women will have associated ocular BD (Mishima et al. 1979). It is the manifestations of Behçet’s disease that frequently drive the patient to the doctor; ocular manifestations are reported in 70 to 85% of patients (Oshima et al. 1963; Nazzaro, 1965). In Korea, 24% of men versus 11% of women with BD showed ocular BD (Kang and Kim, 1992). The onset of ocular involvement is, on average, approximately 2 to 3 years after the first evidence of systemic BD has been noted, but can range up to 14 years. In one study, there was an average 3.6 years between the onset of ocular BD and the first evidence of systemic BD (Kang and Kim, 1992). Bilaterality is the rule when ocular symptoms are present, although delayed and asymmetrical involvement of the second eye ranges up to 2 years, with 38% of cases becoming bilateral within 1 month (Barra et al. 1991).

Ocular involvement is a major source of serious morbidity in BD. The ophthalmologist plays an important role in diagnosing this syndrome. Eye symptoms can be the presenting feature, with ocular findings being the initial manifestation in 25% of men. Further underscoring this is the association of ocular BD with neuro-Behçet’s disease, which predominantly accounts for mortality in this syndrome. Of patients with ocular BD, approximately 30% will have neuro-Behçet’s disease.

Anterior uveitis frequently accompanies ocular BD, but cases sparing the anterior segment are recognized (Barra et al. 1991). The sterile hypopyon described originally by Behçet actually is seen in only about one-third of cases and has likely decreased in incidence with more widespread strepoid treatment (Fig. 1). The presence of hypopyon depends on the severity of the intraocular inflammation. More commonly seen is a nongranulomatous iridocyclitis without hypopyon, which can be accompanied by decreased visual acuity, posterior and anterior synechiae formation (Fig. 2), inflammatory glaucoma, and cataract formation. Cataract is a common sequela of the administration of steroids for
Fig. 1. Chronic hypopyon of Behçet's patient demonstrating a profound anterior segment inflammation.

Fig. 2. Posterior synechiae formation in Behçet’s disease.

Fig. 3. Fundus photograph of typical retinal vasculitis in Behçet’s disease.

Fig. 4. Fluorescein angiograph of typical retinal vasculitis in Behçet’s disease.

Fig. 5. Fundus photograph of Behçet’s patient without fundoscopic abnormalities.

Fig. 6. Vasculitis showed dye leakage and vascular staining on fluorescein angiograph in Behçet’s patient without fundoscopic abnormalities (Fig. 5).
inflammation, or of the inflammation itself. Chronic anterior inflammation can lead to the formation of keratic precipitates and iris atrophy. Retinal hypoxia secondary to occlusive vasculitis can stimulate iris neovascularization and attendant neovascular glaucoma. Other less frequent anterior segment findings include episcleritis, keratitis, and subconjunctival hemorrhage. In Korea, the most frequent ocular symptoms in ocular BD are iritis (64%), occlusive vasculitis (34.2%)(Kang and Kim, 1992).

Fundus findings in BD, first noted by Gozcu 1 year after Behçet’s description, have been reported in 93% in a Turkish eye clinic series (Atmaca, 1989). Retinal vasculitis is the primary lesion, as in other organ systems, and is the hallmark funduscopic feature. Both retinal arteritis and phlebitis are seen with attendant perivascular sheathing. Macular edema, often in a cystoid pattern, accompanies the retinal vasculitis, as does the finding of yellow-white retinal exudates. The vasculitis can lead to retinal infarction, branch or central retinal vein occlusion, and optic atrophy.

Vasculitis is demonstrated by dye leakage and vascular staining on fluorescein angiography (Fig. 3, 4). Moreover, the earliest evidence of vasculitis, even in patients without visual complaints, may be fluorescein leakage from the vessels, sometimes in the absence of funduscopic abnormalities (Fig. 5, 6). For this reason, fluorescein angiography studies are of major importance in the initial evaluation of this entity and long-term follow-up. Edema and necrosis of the retina follow the vasculitic changes, and often the findings of retinal vascular obliteration and retinal necrosis are a mirror of central nervous system manifestations of the disease as well. Other angiographic features of Behçet’s retinitis include window defects due to chorioretinal degeneration, choroidal infarcts, and evidence of retinal and disc neovascularization. Additional posterior pole findings include retinal hemorrhage, chorioretinitis, and exudative retinal detachment. Optic disc hyperemia and papillitis may also result from vasculitis and can be confirmed with disc leakage and staining on fluorescein angiography. Inflammatory cells within the vitreous are also seen, but an isolated vitritis is not characteristic.

Attacks of ocular BD generally persist for 2 to 3 weeks but tend to have a relapsing-remitting course. However, the average frequency of ocular inflammatory attack was 1.2 per year and the duration of attack was 2.1 months in Korea (Choi and Chung, 1995). These cumulative events can lead to late findings of vitreous condensation, tractional retinal detachment, macular holes, and pigment epithelial atrophy. Retinal and disc neovascularization may require panretinal photocoagulation therapy. Other late posterior findings include optic atrophy and phthisis bulbi. In the later stages of ocular disease, the permanent loss of visual acuity (in 70-80% in both sexes) may be due to atrophy of the optic nerve secondary to inflammatory glaucoma (Michelson and Chisari, 1982).

Histopathological features

The histopathological findings of the ocular lesions are diverse, but the basic mechanism is observed in the characteristic occlusive necrotizing nongranulomatous vasculitis and perivasculitis, as in other organ systems. The vasculitic changes are found most frequently in the retina, but uveal vasculitis is also a component. Both the arterial and venous systems may be affected, with lymphocytic inflammation giving rise to perivascular cuffing, intraluminal inflammation and thrombi, or inflammation of the vessel wall. Typically, the vasculitis has an obliterative and hemorrhagic pattern, with secondary necrotic changes. Chronic lymphocytic infiltration is found throughout the eye in the corneal stroma, iris vessels, ciliary body, vitreous, and choroid. Nongranulomatous uveitis is a common feature, and additional findings include focal necrosis of the iris, perivascular lymphocytic infiltration of the optic nerve, and secondary degeneration and gliosis of the retina (Fenton and Easom, 1964).

Management

A number of treatment options are used in BD, and the therapeutic regimen is tailored to the course and severity of the disease. Certain factors, including ocular, neurological, and vascular involvement, as well as recurrent episodes are an indication for more aggressive approaches.

Corticosteroids are an important first-line treatment of ocular BD. Anterior uveitis can be treated
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with topical steroid medications or, for more severe or recalcitrant iridocyclitis, corticosteroid can be administered periocularly with subconjunctival, sub-Tenon's capsule or transepithelial injections. Patients with involvement of the posterior segment require systemic administration of steroids in oral or intravenous form. Although long-term visual loss can occur despite chronic steroids therapy, this remains a mainstay of treatment of the acute phase of the disease and is an adjunctive treatment modality in patients requiring systemic chemotherapeutic treatment, as will be discussed next.

A variety of cytotoxic agents have been used in the treatment of BD, but thus far no agent has emerged as a standard treatment for all patients. Chlorambucil is considered by some to be the most effective immunosuppressive treatment agent; patients have been seen to attain long-term remissions after chlorambucil therapy (Foster et al. 1991). Azathioprine, in a controlled, prospective trial, has been demonstrated to be effective in preventing new eye lesions and the progression of existing eye disease as well as in treating nonocular symptoms (Yazici et al. 1990). Cyclophosphamide is also used in the treatment of ocular BD and is advocated for treating the neurological manifestation. Cyclosporin A has been reported to be dramatically effective in the treatment of BD (Nussenblatt et al. 1985). Cyclosporin A does have the problem of nephrotoxicity, which occurs to some degree in nearly all patients if high doses (10 mg/kg/day) are used (Palestine et al. 1986). Lower doses (5 mg/kg/day) are now often used in conjunction with systemic corticosteroids. In another study comparing Cyclosporin A to a combination of cytotoxics and steroids, Cyclosporin A was found to be more effective at preventing recurrences (Benezra et al. 1988). In Korea, there were reports that Cyclosporin A was effective in the treatment of patients with refractory ocular involvement (Kim et al. 1990; Kang and Kim, 1992). Other therapeutic agents in the armamentarium for this disease include, colchicine, bromocriptine, indomethacin, levamisole, and fibrinolytic agents. As no single agent is uniformly effective, combination therapy with 2 cytotoxic drugs is a common approach, with the option of treating concurrently with systemic corticosteroids. The potential serious toxicities of these agents and the chronicity of their administration mandate that such treatment be managed by physicians with expertise in chemotherapeutics.

Another treatment modality that has been employed in the acute stages of BD is plasma exchange, which interrupts acute episodes in the face of resistance to medical therapy but does not alter the long-term course of the disease (Raizman and Foster, 1989). Recently, treatment of the dermatological manifestations of BD using interferon has been reported; but the efficacy of this agent for ocular symptoms has yet to be completely demonstrated (Durand and Soubeyrand, 1994).

Prognosis

Significant morbidity and mortality in BD are primarily associated with its effects on the eyes, CNS, gastrointestinal tract, and large vessels. The remaining multisystemic attacks in BD, such as dermatological and genital lesions, follow an episodic course and usually resolve without serious sequelae. The disease follows a relapsing-remitting course for many years, with the natural course of each episode resolving after several weeks. It is believed that after a chronic course, the disease eventually reaches an end-point of diminished or extinguished activity.

Loss of vision is the most common serious complication in BD; even with treatment, the frequency of visual loss is high. Visual loss occurs, on average, approximately 3 years after the onset of ocular BD (Mamo, 1970). In one study, 74% of treated patients lost useful vision 6 to 10 years after the onset of symptoms (Benezra and Cohen, 1986). In a Japanese study, 50% had vision poorer than 20/200 after 5 years (Mishima et al. 1979).

Mortality in BD generally is associated with CNS involvement, particularly of the brainstem, and is seen also with perforation of gastrointestinal tract ulcers, particularly of the ileocecal region, and with large-vessel pathology such as aortic aneurysm or vena caval obstruction.

REFERENCES

Atmaca LS: Found change associated with Behçet's


