Behçet syndrome with eye involvement

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Abstract:

Behçet's uveitis (BU) is a significant form of major organ involvement in Behçet syndrome and is associated with considerable morbidity. Ocular examination is crucial for diagnosing BS and detecting vitreous cells, even in asymptomatic patients. The primary goals in managing BU are to rapidly suppress ocular inflammation and prevent relapses. Initial treatment for posterior segment involvement in BU typically involves immunosuppressive agents combined with glucocorticoids. Biologic agents are increasingly used in BU management, including as first-line treatments for patients with poor prognostic risk factors or sight-threatening uveitis. There is no established consensus on when to discontinue or taper immunosuppressive therapy. Once remission is achieved, the absence of retinal vasculitis should be confirmed with fluorescein angiography, which should be utilized throughout the process of tapering immunosuppressive therapy. In addition to monoclonal tumor necrosis factor-alpha antagonists and tocilizumab, Janus kinase inhibitors may offer the potential for managing BU in the future.

Keywords:

Behçet syndrome, treatment, uveitis

Introduction

Behçet syndrome (BS) is a variable vasculitis that can affect blood vessels of all sizes and types.[1] The most common clinical findings include mucocutaneous manifestations such as oral aphthous ulcers, genital lesions, papulopustular lesions, and erythema nodosum-like lesions, which tend to appear in the early stages of the disease.[2] Arthritis in BS is characterized by mono-oligoarticular, nonerosive, and recurrent attacks.[3] Some patients may experience inflammatory arthralgia and/or back pain without any objective signs of inflammation. The mucocutaneous manifestations and joint involvement in BS significantly impact patients' quality of life. Major organ involvement, including ocular, nervous system, vascular, and gastrointestinal involvement, contributes to the morbidity and mortality associated with BS. Although both females and males are equally affected, the disease tends to be more severe in males and younger individuals.[4]

There is no single clinical, laboratory, or imaging biomarker for the diagnosis of BS; instead, the diagnosis is based on a combination of available diagnostic data and the exclusion of other potential diagnoses. The pathergy test, which has been considered a highly specific diagnostic tool for BS, has shown decreased positivity rates in both nonendemic countries and endemic regions over the past few decades.[5,6] Diagnosing BS can be challenging due to several factors: genital ulcers may heal without leaving scars and may only be present in a patient's medical history; oral aphthous lesions and papulopustular lesions are nonspecific and can also occur in the general healthy population; and these lesions, along with articular symptoms, are common in other inflammatory rheumatic diseases. In addition, the hallmark oral aphthous lesions may be absent in about 1%–10% of BS patients, particularly in those presenting with major organ involvement such as ocular and vascular complications.[7,8] Treatment for BS is individualized based on the patient's demographics, disease duration, active manifestations, accompanying disease features, and overall disease severity.[9] This review specifically focuses on Behçet's uveitis (BU), which is the most common type of major organ involvement in the disease. It covers the manifestations, diagnosis, imaging modalities, and treatment approaches related to ocular involvement in BS.

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Behçet's Uveitis

BU progresses with attacks, has a spontaneous resolution, and is characterized as a nongranulomatous uveitis and retinal vasculitis. Spontaneous recovery is an important aspect of the disease, but each attack has the potential to cause sequelae and poses a risk to visual prognosis. Although BS affects both genders equally, ocular involvement is more frequent and severe in men, particularly during the third and fourth decades of life.[10] The most common manifestation is panuveitis, followed by posterior uveitis, with isolated anterior uveitis being rare. The disease may initially present as panuveitis or begin as anterior or posterior uveitis and progress to panuveitis over time. It usually affects both eyes, either starting bilaterally or beginning unilaterally and later involving both eyes. Eye involvement typically occurs within 5 years of a BS diagnosis. However, in approximately 10%–15% of cases, ocular involvement may present as the first symptom, even before the development of other manifestations, including oral aphthous ulcers. Therefore, a thorough understanding of ocular findings is crucial for the early diagnosis of BS, which can help prevent delays in treatment, recurrent attacks, and loss of visual function.[11-13]

Clinical Signs of Behçet's Uveitis

Anterior segment involvement

Anterior segment involvement in BU presents as acute uveitis. The findings include nongranulomatous anterior chamber cells, keratic precipitates, and posterior synechiae, but the characteristic sign of anterior segment involvement is a white, mobile hypopyon. Hypopyon is a severe form of anterior uveitis and almost always indicates significant posterior segment involvement in BU. The term "white uveitis" refers to the relatively whiter appearance of the eye compared to other forms of acute uveitis. Since the anterior chamber reaction lacks fibrin, the hypopyon is easily displaced, hence the term "mobile hypopyon." Hypopyon attacks have decreased significantly, especially after the widespread use of biological treatments since the 2000s. Today, the most common anterior segment involvement observed is mild-to-moderate nongranulomatous anterior uveitis. Isolated anterior segment involvement is the rarest type of BU, occurring in about 10% of cases, and is typically seen in older female patients. Anterior segment inflammation is more commonly part of panuveitis, the most prevalent type of BU.[11,13] Recurrent anterior uveitis attacks may be complicated with cataract, glaucoma, and posterior synechiae.[11]

Posterior segment involvement

Posterior segment involvement in BU can manifest in two forms: diffuse retinal vasculitis and occlusive vasculitis, or a combination of both. The most common type is diffuse retinal vasculitis, often accompanied by diffuse vitreous inflammation. This condition can occur alone or alongside other fundus abnormalities. While veins are more commonly affected, arteries or a combination of both veins and arteries may also be involved. Other posterior segment abnormalities include retinitis, hemorrhage, optic disc inflammation, vascular obstruction, and inflammation-induced neovascularization. Retinitis and hemorrhage can occur together or separately, in varying sizes, numbers, or locations within the fundus [Figure 1]. These are indicators of active inflammation. Retinitis may resolve with or without treatment, but it often leads to atrophy in the inner layers of the retina, which can impair visual function by disrupting the retinal architecture, especially in the posterior pole. Therefore, prompt treatment is essential for both anatomical and functional recovery. Vitreous inflammation is a significant finding associated with retinal vasculitis, and its severity varies according to the level of inflammation. A reduction in the grade of vitreous inflammation is a positive sign of treatment effectiveness.

The most common manifestation of occlusive vasculopathy is retinal branch vein occlusion, though central vein occlusion, branch or central artery occlusion, and widespread peripheral vaso-occlusion may also occur. This type of vasculopathy can be recurrent. Unlike diffuse retinal vasculitis, occlusive vasculopathy is not typically accompanied by vitreous inflammation; however, vitreous inflammation may be present when diffuse retinal vasculitis coexists. Recurrent attacks can lead to long-term posterior segment complications such as localized or generalized retinal atrophy, pigmentary retinal changes, empty (ghost) vessels, optic atrophy, perivascular sheathing, and macular complications.[14]

Imaging

Color fundus photography

Repeated imaging is useful for documenting and monitoring the severity of vitreous inflammation and other fundus abnormalities. It can also track changes over time during routine examinations. However, it is not sufficient on its own to assess complete control of inflammation.

Fundus fluorescein angiography

The gold standard imaging method for detecting active retinal vasculitis and monitoring BU is fundus fluorescein

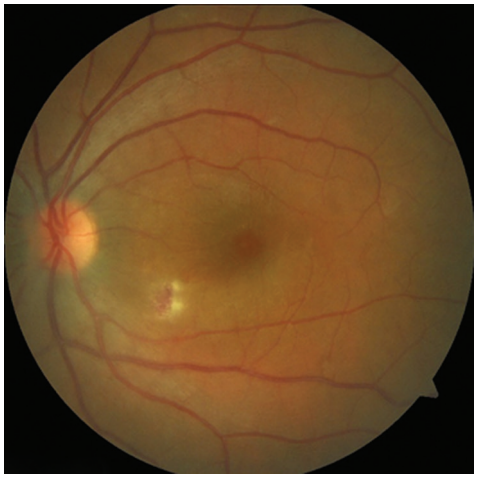

Figure 1: Retinitis with hemorrhage in a patient with Behçet's uveitis

angiography (FA). The characteristic angiographic appearance of BU is a fern-like pattern caused by diffuse capillary leakage [Figure 2]. Depending on the form and severity of involvement, other FA findings may include staining in large vessels and/or the optic disc, ischemia, macular edema, and neovascularization.[15] FA can be used for diagnosis to detect characteristic findings in suspicious cases. The purposes of FA in monitoring are as follows:

1. To assess treatment effectiveness
2. Periodically to evaluate the maintenance of complete remission.
3. To evaluate before reducing or discontinuing treatment.

Optical coherence tomography

The most common application of optical coherence tomography (OCT) is to detect macular edema caused by inflammation and to monitor the patient's condition after therapy [Figure 3]. Other applications include differentiating retinitis from other causes such as toxoplasmosis, viral retinitis, and Bartonella, as well as detecting and monitoring macular issues such as epimacular membranes, macular holes, and macular atrophy.

In retinitis due to BS, OCT findings typically show increased thickness and hyperreflectivity in the inner layers of the retina, along with back shadowing. After these lesions have healed, OCT may reveal localized defects in the retinal nerve fiber layer in the inner layers. OCT scans of the optic disc in Behçet's neuroretinitis may display a "smoking volcano" appearance or a "mushroom-shaped cloud that caps the plume."[15]

Optical coherence tomography angiography

OCT angiography (OCTA) is a rapid, noninvasive imaging technique that provides high-resolution, depth-resolved images of the retinal and choroidal microvasculature by calculating motion contrast from repeatedly obtained OCT B scans at the same site. OCTA has been shown to be more effective than FA in detecting microvascular changes in the macular region, such as retinal capillary nonperfusion, enlargement of the foveal avascular zone, and disruption of the normal capillary network. The deep capillary plexus appears to be more affected than the superficial capillary plexus.[16-18]

However, OCTA is not yet used routinely in BU due to its inability to show vessel leakage, the current limitations in wide-field imaging, the need for clear optical media to obtain acceptable images, and issues with artifacts. As technology advances in the coming years, the potential applications of OCTA in BU are likely to expand.

Choroidal imaging

Although there are articles in the literature with inconsistent results regarding choroidal involvement in BU, both the literature and clinical practice suggest that the choroid is generally unaffected. As a result, neither enhanced depth imaging-OCT nor indocyanine green angiography is routinely used in the diagnosis and management of BU.[19]

Screening in Behçet's Uveitis

Ocular screening is crucial for evaluating patients with BS to detect ocular inflammation, even in asymptomatic individuals, and for assessing those with a suspected diagnosis of BS. Some patients with BS may present with vitreous cells without other eye involvement or ocular symptoms at diagnosis.[20,21] These patients require close follow-up, as 22% may develop posterior segment involvement within 2 years.[20] Detecting vitreous cells is also helpful for diagnosing BS, as they are included among the ocular manifestations in the International Study Group Criteria for Behçet's disease.[22] Therefore, in

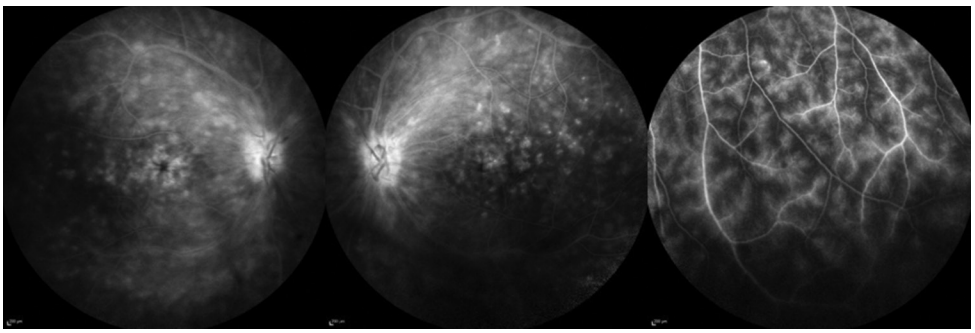

Figure 2: Diffuse capillary leakage, optic disc staining and peripheral fern-like appearance in a patient with Behçet's uveitis

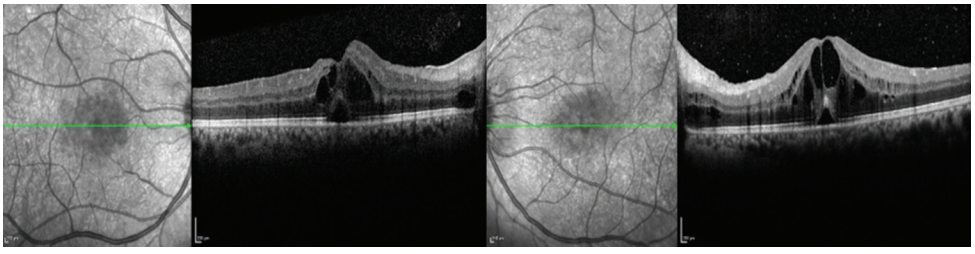

Figure 3: Bilateral macular edema in optical coherence tomography in a patient with Behçet's uveitis

BS patients with no signs of ocular inflammation at the time of diagnosis, regular ophthalmologic evaluations (at least once a year, though this may vary based on the patient's risk status) should be performed to identify subclinical ocular inflammation.

Ocular screening is also important for patients with a suspected diagnosis of BS and those with vitritis, especially if they have few extraocular symptoms or only nonspecific symptoms such as oral aphthous lesions and papulopustular lesions. In a masked study, Turkish uveitis experts were able to differentiate BU from other uveitides in up to 80% of clinical photographs, demonstrating that experienced ophthalmologists can recognize certain features of BS.[23] A newly proposed diagnostic algorithm, incorporating ocular findings detected by biomicroscopy, fundus examination, and FA, has demonstrated an area under the curve of 0.92 (95% confidence interval, 0.89–0.96).[24]

Assessment of Ocular Activity and Damage

There are few scoring systems developed to define inflammation features in BU. The only existing score for vitreous haze related to activation was initially created by Nussenblatt *et al*.[25] and later revised by Davis *et al*.[26] In addition, the Behçet Disease Ocular Attack Score 24, developed by Japanese ophthalmologists, assesses the intensity of ocular activation.[27] This system typically uses terms such as "severe," "moderate," or "mild" to characterize inflammation severity and observable tissue damage through ophthalmoscopy.

We have recently introduced a new tool for assessing damage in BU, known as the Cerrahpasa Ocular Damage Grading System, created by Ozyazgan *et al*.[28] This new system provides detailed descriptions for grading damage from stage 1 to stage 5, ensuring consistent evaluation by ophthalmologists. By employing this tool, we aim to offer a more objective representation of damage at any stage of the disease, moving beyond subjective terms like "severe" or "mild." The system is currently awaiting validation through internal and external diverse cohorts.

Treatment

The primary goals in managing BU are to control acute attacks rapidly and intensively, similar to approaches used in other types of uveitis, and to implement long-term immunosuppressive therapy to prevent relapses, known as maintenance treatment. While isolated anterior uveitis may be managed with topical agents if no risk factors are present, systemic immunosuppression is required for all patients with posterior segment involvement.[9]

Management should be personalized, considering factors such as the patient's age, gender, history of previous attacks, the location and severity of past and current eye involvement, the severity of the current attack, and whether it threatens the patient's vision. Risk factors include male gender, young age, posterior involvement, sight-threatening attacks, and low visual potential. Patients with these risk factors require more intensive immunosuppressive treatment and closer follow-up.[9]

Glucocorticoids (pulse, oral, or topical) remain crucial for treating acute BU attacks. Even with the advent of biologics, pulse steroids are still used for severe posterior involvement that threatens vision. However, glucocorticoids are unsuitable for long-term maintenance due to the recurrent nature of BU. To prevent relapses over the long term, glucocorticoids should be combined with conventional immunosuppressive agents, biologics, or interferon-alpha, depending on the severity of the attack and risk factors. Systemic glucocorticoid therapy should be tapered to 10 mg or less within 3 months to reduce systemic and ocular glucocorticoid toxicity. If this reduction is not possible due to persistent ocular inflammation, intensifying immunosuppressive therapy is necessary.[9]

For moderate cases with posterior involvement, especially if the patient is not in a high-risk group, conventional immunosuppressive therapy with azathioprine (AZA) and/or cyclosporine A (CsA) is usually the first choice. AZA at a dose of 2–2.5 mg/kg takes approximately 3 months to become effective, so it should be used in conjunction with glucocorticoids to taper the glucocorticoid dose to 10 mg or less within 3 months. Regular monitoring of liver function and blood counts is required, and gastrointestinal side effects are the most common reasons for discontinuation.[4,29] CsA has a rapid onset of activity and is used at a dose of 2–5 mg/kg/day. It can be effective alone or in combination with AZA for mild-to-moderate inflammation but requires caution regarding hypertension and nephrotoxicity,[30] and should not be used in patients with nervous system involvement.[31] In patients intolerant to AZA or CsA, mycophenolate may be preferred, especially for maintenance therapy.[32]

For refractory cases, sight-threatening initial attacks, patients with risk factors for poor prognosis, or those who cannot tolerate conventional treatments, monoclonal tumor necrosis factor-alpha (TNF-α) antagonists, or interferon-alpha should be considered. Interferon-alpha is highly effective in BU, often providing long-term remission after treatment cessation.[33] Common side effects include flu-like symptoms, managed with paracetamol, as well as potential adverse effects such as elevated liver function tests, alopecia, leukopenia, thrombocytopenia, weight loss, depression, and autoimmune thyroiditis. These side effects are dose-dependent and generally decrease with dose reduction.[34] However, interferon-alpha is not available in many parts of the world. Monoclonal TNF-α antagonists, such as infliximab and adalimumab, are increasingly used for BU and have shown effectiveness in rapidly controlling the condition, improving visual acuity, reducing attack frequency, and achieving long-term remission.[35-38] The most concerning adverse event is infection, particularly tuberculosis, for which BS patients appear to be at higher risk.[39] Therefore, patients should be screened for tuberculosis and hepatitis before starting treatment and monitored regularly.

Infliximab is usually administered as an infusion of 5 mg/kg every 8 weeks, following initial doses at weeks 0, 2, and 6. For BU, more frequent dosing, such as every 4 weeks, and higher doses up to 10 mg/kg may be necessary. Adalimumab is typically given as 40 mg in the 1st week following an 80 mg loading dose, then 40 mg every 2 weeks for patients over 30 kg. For those under 30 kg, the dose should be halved. Other monoclonal TNF-α antagonists, such as golimumab and certolizumab, have been reported to be effective in refractory BU in small case series but are less commonly used.[40-42]

In patients who are refractory or intolerant to monoclonal TNF-α antagonists, tocilizumab may be considered.[43-45] Recently, Janus kinase inhibitors have shown promising results for managing various types of organ involvement in BS.[46-50]

The effectiveness of inflammation control should be assessed using FA. After achieving remission, gradual extension of treatment intervals may be considered.[51] While there is no consensus on when and how to discontinue treatment, once effective inflammation control is achieved, treatment should continue for at least two additional years (or longer if the patient is in a high-risk group) before tapering and eventually stopping. There is also no consensus on whether conventional immunosuppressive agents should be combined with monoclonal TNF-α antagonists. Immunogenicity does not seem to be a concern in BS,[52] and previous observations suggest no benefit in adding an immunosuppressive agent to monoclonal TNF-α antagonists in BS management.[53,54] However, we prefer combination therapy to maintain background immunosuppression, as some patients may not adhere to biological treatments due to infections or other reasons. During the tapering phase, patients should be closely monitored, and inflammation should be controlled using FA before each dose reduction.

Prognosis

Ocular involvement affects approximately 50% of patients with BS and significantly contributes to morbidity. A long-term outcome study of patients from 1977 to 1983 revealed that, after 20 years, 44% of male patients and 21% of female patients experienced significant vision loss (visual acuity ≤0.1).[7] Another retrospective study of 880 patients seen between 1980 and 1998 found that the risk of blindness at 1, 5, and 7 years was 9%, 26%, and 30%, respectively, for patients admitted in the 1980s, whereas this risk decreased to 5%, 16%, and 21% for those admitted after 1990.[13] Comparing visual outcomes from the 1990s to the 2000s, there was a notable reduction in the risk of vision loss, from 27.6% in the 1990s to 12.9% in the 2000s.[55] The prognosis for BU has improved over the decades, likely due to advancements in immunosuppressive treatments, particularly biologics. Furthermore, we did not observe any new cases of uveitis among 282 BS patients receiving infliximab,[56] and only two new cases of isolated anterior uveitis among 335 BS patients receiving adalimumab.[57] This suggests that biological agents can modify the disease course of BS.

Conclusion

Ocular screening is crucial for diagnosing patients with BS and for those suspected of having it. The presence of vitreous cells is vital for diagnosis and necessitates close follow-up. BU has distinct ocular findings that experienced ophthalmologists can identify through ocular examination, with FA remaining the gold standard for diagnosing and monitoring disease activity. Immunosuppressive therapy, along with glucocorticoids, is fundamental to managing BU. The prognosis for BU has improved, likely due to advancements in diagnosis, increased awareness leading to earlier detection, and the use of immunosuppressive and biologic agents.

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Conflicts of interest

S.N.E has received honorariums for presentations from Celltrion. D.U has no conflict of interest to declare.

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