Anterior Granulomatous Uveitis: Differential Diagnosis

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Introduction

The term “anterior uveitis” is used for a group of inflammatory disorders involving primarily the iris and the anterior chamber of the eye. Granulomatous anterior uveitis is characterized by an insidious onset with a long course of symptoms and presence of iris nodules (both Koeppe’s and Busacca’s nodules). Medium-to-large keratic precipitates (KPs) are seen in patients with granulomatous anterior uveitis in contrast to fine and smaller KPs in non-granulomatous type of anterior uveitis.

Other features of granulomatous anterior uveitis include presence of hypopyon, synechiae, anterior segment neovascularization, iris atrophy, complicated (secondary cataract), irregular pupil (festooned pupil), occlusio pupillae, raised intraocular pressure, hypotony (due to ciliary body atrophy), and neovascular glaucoma (end-stage disease). The posterior synechiae may be broad-based or filiform.

There may be anterior synechiae leading to secondary angle-closure glaucoma. The grading of cellular reaction and flare in the anterior chamber helps in assessing activeness and severity of uveitis.

Multiple infective conditions such as tuberculosis (TB), Lyme’s disease, herpes simplex and zoster, cytomegalovirus (CMV), leprosy, toxoplasmosis, as well as non-infective conditions such as juvenile idiopathic arthritis (JIA), sarcoidosis, and multiple sclerosis, among others have been linked with granulomatous anterior uveitis. Hence, a complete systemic examination and laboratory tests may be required to reach the diagnosis. Other investigations such as contrast-enhanced computerized tomography (CECT) of the chest, radiography of the sacroiliac spine, Mantoux (tuberculin skin testing), venereal disease research laboratory (VDRL), and human leucocyte antigen (HLA) B-27, among others may be the relevant laboratory investigations needed.

Corticosteroids are the mainstay in the treatment of granulomatous anterior uveitis along with cycloplegic agents such as topical atropine 1% which helps in reducing the ciliary spasm. In refractory conditions where infectious etiologies have been adequately ruled out, immunomodulatory agents such as adalimumab, infliximab, and other biological agents or immunosuppressive therapies such as azathioprine,
cyclosporine, or methotrexate are used to reduce the ocular inflammation.

Work-Up of a Case of Anterior Granulomatous Uveitis

Prior to obtaining any diagnostic tests, it is important to exclude Fuchs’ uveitis syndrome (FUS) because this granulomatous condition, when sufficiently typical, does not need any work-up or treatment (Fig. 1). This condition usually presents with stellate KPs (Fig. 2). Furthermore corticosteroid treatment should be withheld in FUS to avoid the side effects of a treatment that usually has no impact on the inflammatory process. It is also relevant to exclude posterior segment involvement with spillover anterior segment inflammation. Spillover anterior granulomatous uveitis can occur in very inflammatory conditions such as toxoplasma retinochoroiditis.

Laboratory Evaluation for Anterior Granulomatous Uveitis

The first-line laboratory tests performed include serum angiotensin-converting enzyme (ACE) and lysozymes. ACE levels can be normally elevated in children, and serum lysozyme levels tend to be progressively more elevated in elderly persons. It is therefore important to perform both tests.

The second step is to differentiate between sarcoid, tuberculosis, and other granulomatous entities. In order to differentiate between tuberculosis and sarcoidosis, tuberculin skin test can be performed which indicates present or past infection with mycobacterium tuberculosis. Among patients with sarcoidosis, the tuberculin skin test may be negative. In addition, cutaneous anergy testing may be performed for sarcoidosis. For this purpose, serologies to four herpes viruses to which most of the adult population has been exposed (herpes simplex, herpes zoster, cytomegalovirus, and Epstein-Barr) are performed. ELISA serology detects exposure to these viruses, and complement fixation serology is done to establish whether the antibody titers are elevated. Polyclonal activation is an additional element for sarcoidosis.

When the Mantoux test (tuberculin skin test) is positive, in the presence of compatible clinical signs such as granulomatous anterior uveitis, broad-based posterior synechiae, and mutton-fat KPs, this should raise the suspicion of a tuberculous granulomatous uveitis. An important test performed in addition to tuberculin skin testing is the gamma-interferon releasing assay (QuantiFERON® TB gold). In these tests, the lymphocytes of patients are tested in vitro in order to detect whether there are lymphocytes reacting in vitro when put in presence with specific proteins coming from mycobacterium tuberculosis. When the patient’s lymphocytes release interferon gamma, it means that the patient has been exposed to the bacteria, and tuberculosis should be actively researched.

Syphilis serology is performed either routinely or in case of a positive history among patients with anterior granulomatous uveitis. In case of undefined diagnosis, serology for Lyme borreliosis is performed with the known limitations of the value of a positive serology. Toxoplasma retinochoroiditis can sometimes present as a granulomatous (hypertensive) anterior uveitis. The presence of a retinal focus orients clearly into this direction.

It is relevant to keep in mind other infectious causes of anterior granulomatous uveitis such as viruses. In case of a negative ACE/lysozyme test and a noncontributory tuberculin skin test, viral causes of uveitis (especially herpetic uveitis) should be suspected in presence of raised
intraocular pressure and iris atrophy. Clinical signs that are very suggestive of herpes simplex/zoster uveitis are ocular hypertension and iris atrophy (found both in herpes simplex and varicella-zoster uveitis). Laboratory confirmation of herpes simplex/zoster anterior uveitis can be obtained by the detection of intraocular production of antibodies in the aqueous humor (Goldmann-Witmer coefficient). Aqueous paracentesis can be performed in these cases when in doubt to detect presence of viral DNA using polymerase chain reaction. A negative polymerase chain reaction effectively rules out viral infection.

Anterior granulomatous uveitis is characterized by KPs which has a "volume." Non-granulomatous KPs appear as "dusting" on the corneal endothelial surface. The medium and large-sized white granulomatous KPs are called mutton-fat KPs. Other characteristic features of granulomatous uveitis are Koeppe’s and Busacca’s nodules at the pupillary margin (Koeppe) or within the iris stroma (Busacca). Synechiae are common in more pronounced inflammation.

In FUS, the KPs are granulomatous in nature as they are medium sized, structured, and usually stellate shaped. The term granulomatous uveitis is in fact a misnomer because a histopathologic term is used to describe clinical conditions based on certain clinical features including specific KPs and iris nodules, among other clinical signs. Originally the clinical term of granulomatous uveitis was still based on the histopathologic presence of granulomatous lesions which today is no more always the case. It has become a clinical category, a clinical terminology for which in some cases an underlying granulomatous histopathology can be found such as in sarcoidosis and tuberculosis, but this clinical terminology has extended to other conditions where the underlying histopathology is not granulomatous such as in Fuchs’ uveitis.

Although this clinical distinction between granulomatous and non-granulomatous is a very useful classification, the subdivision is not an absolute one. A granulomatous uveitis may initially present as non-granulomatous before taking its granulomatous aspect. On the other hand, when dusty KPs are very numerous and thick, they may be mistaken as granulomatous.

Cases

Case 1: Tubercular Anterior Granulomatous Uveitis

Anterior uveitis that occurs due to presumed tubercular etiology has protean clinical manifestations. It usually presents with granulomatous inflammation with large mutton-fat KPs (Fig. 3) and iris nodules which can be either at the pupillary edge (Koeppe’s) (Fig. 4) or at the iris stroma (Busacca’s). Presence of broad-based posterior synechiae is highly predictive of tubercular anterior uveitis (Fig. 5). The sensitivity, specificity, and predictive values of various clinical signs of anterior segment involvement in tubercular uveitis are listed in Table 1.

A 28-year-old female presented with decreased vision in her right eye for the past 2 months. She had no previous episodes in the past. She also complained of pain, redness, and watering. Assessment of best-corrected visual acuity...
(BCVA) was performed, which showed BCVA of 20/100 in the right eye and 20/20 in the left eye. Ocular examination revealed presence of anterior chamber cells 2+, flare 2+, and presence of posterior synechiae. There were large mutton-fat keratic precipitates on the corneal endothelial surface (Fig. 6). Systemic evaluation was performed which revealed a positive Mantoux test of 20 mm induration at 48 h. She had bilateral hilar and paratracheal lymphadenopathy which was suggestive of a previous inflammatory pathology (consistent with tuberculosis). Thus, a diagnosis of presumed tubercular anterior uveitis was made, and the patient was treated with antitubercular therapy with topical and oral corticosteroids.

**Case 2: Sarcoidosis**

A 39-year-old female (Asian Indian) presented with disturbance in vision in her left eye for the past 2 months. She had a previous episode of redness and pain in her left eye 10 years ago which was treated with topical corticosteroids. Ocular examination revealed a BCVA of 20/50 in the left eye and 20/20 in the right eye. Slit-lamp biomicroscopy revealed presence of mild anterior chamber reaction (cells 1+, flare 1+) and mutton-fat KPs in the inferior angle seen on gonioscopy (Figs. 7 and 8). At the time of this recurrence, she underwent a complete systemic evaluation. Her Mantoux testing revealed lack of any induration, and contrast-enhanced chest computerized tomography showed bilateral mediastinal lymphadenopathy. A diagnosis of presumed sarcoidosis was made, and the patient was started on oral corticosteroids and counselled regarding the need for systemic methotrexate.

**Case 3: Viral Granulomatous Anterior Uveitis**

A 28-year-old male presented with painful diminution of vision in the right eye for the past 15 days. He also complained of redness and watering. Examination revealed a BCVA of 20/50. The corneal sensations were slightly decreased in all the quadrants. The mean intraocular pressure measured 30 mm Hg in the right eye. Examination of the left eye revealed a normal visual acuity of 20/20 and intraocular pressure of 15 mm Hg. Slit-lamp examination revealed presence of 1+ cells and 1+ flare and granulomatous KPs (Fig. 9). There was evidence of mild iris atrophy involving the right eye compared to the left eye. Anterior chamber paracentesis was positive for herpes virus DNA. The patient was started on oral valaciclovir 1 g three times a day, topical corticosteroids, and cycloplegic agents.

**Conclusion**

Granulomatous uveitis is a well-defined group of entities determined by a set of clinical signs including small to large/mutton-fat granulomatous KPs, Koepppe and Busacca...
Table 1  Diagnostic accuracy of anterior segment features in tubercular uveitis

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
<th>Overall diagnostic accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutton-fat keratic precipitates</td>
<td>7</td>
<td>93</td>
<td>50</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>Broad-based posterior synechiae</td>
<td>32</td>
<td>93</td>
<td>79</td>
<td>60</td>
<td>47</td>
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<tr>
<td>Iris nodules</td>
<td>2</td>
<td>98</td>
<td>55</td>
<td>53</td>
<td>53</td>
</tr>
</tbody>
</table>

Fig. 6  Large mutton-fat keratic precipitates in a young girl with tubercular anterior uveitis

Fig. 7  Presence of iris nodules on the inferior iris angle in a young female with presumed sarcoid-related anterior uveitis

Fig. 8  Gonioscopic image of the patient in Fig. 7 diagnosed with sarcoidosis shows presence of iris nodules involving the inferior angle

Fig. 9  Pigmented granulomatous keratic precipitates in a young male with herpetic anterior uveitis
nodules, iris infiltration, and often increased intraocular pressure, which differentiates it clearly from non-granulomatous uveitis and orients toward specific clinical entities.

**Key Points**
1. An elaborate history taking and clinical work-up is the cornerstone of the management of a case of granulomatous anterior uveitis because of frequent association with rheumatological and infectious diseases.
2. Recurrent chronic course and presence of mutton-fat keratic precipitates and nodules in anterior chamber are suggestive of granulomatous type uveitis.
3. Corticosteroids (mainly topical) are the mainstay of therapy along with cycloplegic agents and antiglaucoma drugs (if required).

**Suggested Reading**


