PEER REVIEWED

Acquired Toxoplasmosis Manifesting as Granulomatous Panuveitis

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Abstract

Diagnosing and treating panuveitis can be difficult with a variety of differential diagnoses. In this case report, a 62-year-old Caucasian male presented with a unilateral granulomatous panuveitis. His previous exams had revealed no signs of past inflammation. Although acquired toxoplasmosis is atypical, laboratory testing revealed positive IgM and IgG results, which would indicate a positive toxoplasmosis diagnosis. The patient responded to topical treatment with the addition of oral azithromycin and intravitreal clindamycin, followed by oral prednisone. He recovered three months later with only a mid-peripheral chorioretinal scar. Uveitis characteristics and lab test results were key indicators leading to the diagnosis of toxoplasmosis in this case.

Key Words: *uveitis, granulomatous uveitis, toxoplasmosis, posterior uveitis, panuveitis*

Background

This case report follows the diagnosis and management of a patient with unilateral granulomatous panuveitis including differential diagnosis, diagnostic lab testing and treatment. The case is an unusual presentation of uveitis, and it is a useful educational exercise to consider the differential diagnoses and potential treatment options. The intended audience is third- and fourth-year optometry students and residents.

Case Description

A 62-year-old Caucasian male presented in clinic with a chief complaint of seeing a spot in his right eye that appeared to move with the eye. He wasn't sure how long it had been there. He stated that he had noticed it when bowhunting season started approximately two weeks previously. He had not noted any pain, photopsia or decreased vision. The patient's medical history was significant for diet-controlled diabetes, hypertension, basal cell carcinoma, hypercholesterolemia, and bradycardia. His medications included simvastatin, baby aspirin and vitamin D. His last dilated fundus exam had been two years prior with unremarkable findings.

Figure 1. Yellow chorioretinal inflammatory lesion inferior to the optic nerve head in the right eye. Click to enlarge

Figure 2. OCT showing diffuse retinal thickening in the area of the inflammatory lesion.
Click to enlarge

The patient's best-corrected visual acuity (BCVA) on the day of presentation was 20/25- OD, 20/20 OS. Pupils showed a sluggish reaction in the right eye, a normal reaction in the left eye, and anisocoria, with pupils measuring 4 mm in the right eye and 2.5 mm in the left eye. There was no afferent pupillary

defect. Goldmann applanation tonometry measured 38 mmHg OD and 14 mmHg OS. The slit lamp exam was remarkable for 3+ mutton fat keratic precipitates on the corneal endothelium with mild corneal edema in the right eye and a moderate anterior chamber reaction with 2-3+ cells and mild to moderate flare. A very mild nuclear sclerotic and posterior subcapsular cataract were noted in each eye. All other anterior and posterior findings were normal OS. There was a poor view of the posterior pole OD, either due to the corneal edema or perhaps vitreal debris.

One drop each of brimonidine, timolol/dorzolamide, and cyclopentolate 2% were instilled in-office in the patient's right eye. It was suspected that posterior synechiae were forming OD due to the larger pupil size and the sluggish pupillary response. One hour after instillation of the drops, intraocular pressure (IOP) decreased to 24 mmHg, and the pupil dilated without signs of synechiae. The patient was started on prednisolone 1% q1h, cyclopentolate 2% bid, brimonidine bid and timolol/dorzolamide bid OD.

Follow-up 1: two days after initial presentation

The patient returned to the clinic two days later. He had noticed no change with his eyes. His BCVA was 20/50 OD. IOP was 14 mmHg, again measured with Goldmann applanation tonometry. Anterior chamber showed 2+ cells. The view of the posterior pole was much improved, and a 3-4 disc-diameter, slightly elevated, yellow inflammatory chorioretinal lesion was noted inferior to the optic nerve. **(Figure 1)** The optic nerve had a C/D ratio of 0.3 and appeared healthy and well-perfused. OCT showed diffuse retinal thickening in the area of the lesion that extended toward the macula. **(Figure 2)** Vitreal cells appeared mild. The patient reported a history of owning, taking care of, and interacting with cats on a long-term and regular basis. Fluorescent Treponemal antibody absorption (FTA-ABS) and Toxoplasma antibody tests were ordered, and the patient was referred to an ocular inflammatory specialist for further work-up.

Follow-up 2: one week after initial presentation

The patient was seen five days later by the uveitis specialist. He reported having a history of a positive purified protein derivative test 15 years previously, and he had been treated with isonicotinylhydrazine for nine months. He stated that he had not traveled recently. His BCVA was 20/30-, his anterior chamber reaction had decreased to 1-2+ cells, and his IOP was 11 mmHg. His ocular findings were otherwise unchanged. His vitreal cell status was graded as 1-2+ with debris. A B-scan ultrasound test was performed and demonstrated questionable mild retinal thickening inferiorly OD.

Initially, due to the appearance of the lesion and the patient's prior history, the uveitis specialist considered tuberculoma to be the most likely diagnosis. Other possible etiologies included Toxoplasma, lymphoma, syphilis, Bartonella, sarcoidosis, human immunodeficiency virus (HIV), Lyme disease and metastasis. Tests for HIV, rapid plasma reagin (RPR), angiotensin-converting enzyme (ACE), quantiferon-gold, complete blood count (CBC), Bartonella and lyme disease were ordered. Prednisolone was tapered to qid, and cyclopentolate, brimonidine and timolol/dorzolamide were continued bid. An anterior chamber tap was not performed at this time, and oral azithromycin and oral prednisone were discontinued pending lab results and further monitoring of the patient.

Follow-up 3: eight days after initial presentation

The patient was seen again the next day, and his BCVA was 20/50 OD. Exam findings were unchanged from the previous day. The patient had discontinued timolol/dorzolamide on his own, but IOP remained acceptable at 9 mmHg. The labs for IgM and IgG toxoplasmosis came back positive. HIV testing was negative, and CBC was normal. Other labs were still pending. The patient was started on oral azithromycin 500 mg daily, and the topical medications were continued unchanged except for the discontinuation of timolol/dorzolamide.

Follow-up 4: 10 days after initial presentation

The patient returned two days later. His BCVA was 20/40 OD, and the anterior chamber reaction had decreased to 1+ cells, but exam was essentially unchanged. No additional lab results were available.

Follow-up 5: 16 days after initial presentation

The patient returned six days later. His exam was stable to slightly improved. His BCVA was 20/50, anterior chamber reaction was stable at 1+, vitreal reaction appeared slightly improved at 1+, the keratic precipitates were resolved, and the fundus lesion appeared stable to slightly smaller. The remainder of the lab results were as follows: Lyme disease negative, RPR/FTA negative, ACE 58 (and considered normal), quantiferon gold positive, and Bartonella negative. Due to the posterior location of the lesion and its relative stability and slow improvement, an intravitreal injection of clindamycin was administered.

Follow-up 6: three weeks after initial presentation

The patient returned five days later with a BCVA of 20/40- OD. He had inadvertently recently run out of prednisolone drops, but his overall ocular inflammation had decreased somewhat with slight improvement in anterior chamber and vitreous cells. The chorioretinal lesion appeared to be slightly smaller. The patient was started on oral prednisone 60 mg daily and resumed topical prednisolone 1% qid. He was to continue brimonidine bid and oral azithromycin 500 mg daily. Cyclopentolate was discontinued because the inflammation had improved significantly.

Follow-up 7: four weeks after initial presentation

The patient returned one week later. His general ocular inflammation had decreased and the chorioretinal lesion showed marked improvement. It was smaller and partially scarred at the site of the previous inflammation. His visual acuity was 20/25 OD. The patient was to begin tapering oral and topical prednisone. Brimonidine was discontinued because elevated IOP was no longer a concern.

Follow-up 8: two months after initial presentation

Figure 3. The lesion, 16 months after initial presentation, was inactive and atrophic.
Click to enlarge

The patient returned a month later. He had run out of azithromycin and had completed the oral prednisone taper. He was still taking topical prednisolone tid. His eye exam showed general improvement, and topical prednisolone was tapered to bid. He was to resume taking oral azithromycin 500 mg once daily.

Figure 4. OCT showing completely atrophic retina and choroid at the site of previous inflammation.
Click to enlarge

Follow-up 9: three months after initial presentation

The patient returned a month later. The ocular inflammation appeared resolved. A chorioretinal scar was visible at the site of previous inflammation. A retinal vein occlusion with several dot hemorrhages was noted peripherally, just anterior to the scarred area. Azithromycin was discontinued. The patient was released from the care of the uveitis specialist and instructed to return to his primary eyecare provider in

a year.

Follow-up 10: 16 months after initial presentation

The patient returned for a follow-up appointment 16 months after his initial presentation. He was not taking any ocular medications. He reported that he had not noticed any floaters recently. His BCVA was 20/20 OD, 20/20 OS. He had no active ocular inflammation, and the chorioretinal scar in the posterior pole OD appeared inactive and atrophic. **(Figure 3)** OCT showed a completely atrophic retina and choroid in the area of the lesion. **(Figure 4)** Of note, there was a retinal vein occlusion anterior to the lesion, likely a result of the atrophy of the vessels overlying the lesion.

Education Guidelines

Key concepts

1. The first step in diagnosing uveitis must be to make careful observations about the patient's symptoms and clinical signs of the uveitis, information gathered from a thorough eye exam that includes a dilated fundus exam and IOP check
2. Classifying the uveitis according to location, laterality, chronicity and type (granulomatous vs. non-granulomatous) is an essential beginning step that aids in developing a list of differential diagnoses
3. Integrating the patient's uveitis symptoms and past history of the uveitis as well as the patient's medical history are another important aspect of considering possible diagnoses
4. Diagnostic testing should be ordered according to the list of possible diagnoses; the sensitivity and specificity of each lab test and the likelihood of disease should be considered
5. Infection or malignancy must be recognized and successfully treated before beginning steroid treatment

Learning objectives

1. To make careful observations about the signs of the uveitis: location, laterality, granulomatous vs. non-granulomatous, and chronicity (acute, chronic, recurrent)
2. To integrate facts about the uveitis symptoms, previous episodes of uveitis, the patient's demographic information and medical history
3. To analyze the observations and facts and develop a list of differential diagnoses
4. To tailor diagnostic testing according to the developed list of differential diagnoses:
    a. testing should be appropriately matched to the description of uveitis
    b. sensitivity and specificity of each laboratory test should be considered
    c. likelihood of disease should be assessed before ordering testing
5. To understand that infection or malignancy must be successfully treated before anti-inflammatory medications are started

Discussion questions

1. Why is it important to first note the location, laterality, type and chronicity of the uveitis as well as patient demographics? How will these observations assist in compiling a list of possible diagnoses?
2. Why is it important to order laboratory testing according to the patient's specific uveitis characteristics?
3. How do the sensitivity and specificity of lab tests and the likelihood of disease affect which testing should be ordered?
4. Why is it important to rule out or treat infection or malignancy before adding anti-inflammatory medication?

Discussion

On the day of presentation, the patient was diagnosed with a unilateral, granulomatous uveitis. The inflammation was clearly anterior, but it was unclear whether there was further involvement due to the poor view of the posterior pole, which was possibly due to the anterior chamber reaction, corneal edema or vitreal cells. Chronicity was uncertain because the patient was not sure how long the spot in his right eye had been present. He had noticed it a couple of weeks earlier, but that was perhaps due to his recent hunting activity with the opening of bow season. His last complete eye exam with dilation had been performed two years prior and was unremarkable. The patient was not symptomatic for pain or photophobia, implying that his condition may have been chronic. Also of note was the larger pupil, the sluggish pupillary response, and the increased IOP in the affected eye. This was likely due to synechiae beginning to form. Cyclopentolate easily dilated the eye without any signs of posterior synechiae remaining.

When he presented for his first follow-up visit, the posterior pole was much easier to view, and a yellow inflammatory chorioretinal lesion could be seen. As inflammation could be seen in the posterior pole as well as in the anterior chamber, this was classified as a case of panuveitis. The patient initially presented with a chief complaint of a spot moving around in his right eye. The symptomatic spot was likely the chorioretinal lesion. Alternatively, it could have been caused by vitreal cells. The chorioretinal lesion and the granulomatous nature of the uveitis could be associated with a number of conditions such as tuberculoma, lymphoma, syphilis, toxoplasmosis, Bartonella or sarcoidosis, most of which can present with variable ocular signs, locations in the eye, laterality and symptoms.

With the patient's history of owning and interacting with cats and the positive toxoplasmosis lab results, that diagnosis moved to the top of the list of possibilities. Due to the patient's history of a positive purified protein derivative test 15 years prior, tuberculoma was also high on the list. The patient was started on azithromycin at that point, one of several possible treatments for toxoplasmosis. After a week on azithromycin, the ocular inflammation appeared stable to slightly improved. The remaining lab results came back negative, decreasing the likelihood that other conditions were the cause of the panuveits. The only other positive lab result was the quantiferon gold, which is likely to remain positive in patients who have a history of tuberculoma. Because the toxoplasmosis diagnosis seemed even more likely, and because the chorioretinal lesion had not appeared to improve much with treatment, an intravitreal injection of clindamycin was administered at that visit. Five days later, when the infection appeared to be resolved or nearly resolved, oral prednisone was started to help decrease the posterior segment inflammation.

Choosing appropriate laboratory testing in uveitis

Table 1.
Click to enlarge

Diagnostic testing should be chosen according to the most likely differential diagnoses. Ordering nonspecific laboratory testing is inefficient, expensive and can provide useless and even misleading information. This can be a challenging process, but it is important to carefully consider which tests would be most helpful in diagnosing the patient. One important concept is estimating the likelihood of disease based on the patient's signs, symptoms and history. Another important factor is understanding the sensitivity and specificity of each test in order to determine how much weight a test result should have in the overall picture of the patient's case. Some individual research may need to be performed by the provider before laboratory testing is ordered, especially when considering a more complicated uveitis. **Table 1** provides a summary of differential diagnoses that were considered in this case along with their specific characteristics and lab tests ordered.[1]

Serology testing for toxoplasmosis

When the lab results were received, the positive IgG and IgM results strongly supported the diagnosis of toxoplasmosis. Ocular toxoplasmosis is the most common cause of posterior uveitis.[2-4] A case of acquired toxoplasmosis in a 62-year-old patient, however, is unusual. It is thought that the majority of cases of toxoplasmosis are congenital with later reactivation, especially if ocular disease is present.[5] It is more common for acquired toxoplasmosis to present unilaterally, while congenital toxoplasmosis infections more often present bilaterally.[4]

The presence of IgM antibodies on serology testing indicates an acute infection and levels remain elevated for about one year following the initial exposure.[2] On the other hand, IgG antibodies indicate a previous exposure and are detectable for life.[2] If IgM antibodies against Toxoplasma gondii are present, it signals an active infection. While doctors had no previous IgM or IgG testing for this patient to aid in definitively determining whether this case was congenital or acquired, due to the patient's age and the positive IgM results, it was concluded that this was an acquired case. In addition, the patient's previous eye exam showed no remarkable findings, including no signs of past inflammation. The other indication that this case was acquired was the absence of chorioretinal scars, which would indicate a previous episode. Therefore, the patient was diagnosed as having presumed primary acquired toxoplasmosis. An exact mode of transmission for acquiring the toxoplasmosis remained uncertain after discussion with the patient, but interaction with his cats seems quite possible.

Transmission

Toxoplasmosis can be transmitted to humans through a number of avenues. Oocytes are found only in the intestines of cats and may be transmitted to humans or other animals through cat feces. The oocytes develop into tachyzoites and rapidly divide in cells, causing destruction of tissue and spreading the infection. Tachyzoites can also infect the fetus of a pregnant woman. Tachyzoites can form cysts called bradyzoites containing thousands of organisms and are typically found in muscle or neural tissue. Ingestion of undercooked meat contaminated with these cysts is another possible mode of transmission, as is drinking water contaminated with oocytes.[1,3,5,6]

Signs and symptoms of toxoplasmosis

Ocular symptoms of toxoplasmosis often include floaters, caused by vitreous cells and debris, and decreased vision, typically caused by inflammatory lesions in the macula.[5,7] Ocular signs include anterior chamber inflammation, elevated intraocular pressure, vitritis, retinitis, vasculitis, disc edema secondary to peripapillary retinitis and, in rare cases, hard exudates in the macular area.[7] The location of chorioretinal lesions has a significant impact on visual acuity, with macular lesions being the most sight-threatening.[6] In a study of 248 patients, an outbreak of T gondii retinitis was discovered in the residents of Coimbatore, India, in 2004-2005. Among those 248 patients (254 eyes), 230 eyes were found to have unifocal retinitis. The retinal lesions were all raised and yellow with poorly defined borders. They healed over time and resulted in retinal scarring.[7]

Treatment of toxoplasmosis

There are several treatment options for managing toxoplasmosis, with some controversy regarding one antibiotic vs. another, and when corticosteroids should be initiated. Typically prescribed medications include pyrimethamine, sulfadiazine, clindamycin, trimethoprim/sulfamethoxazole, azithromycin and corticosteroids. None of the T gondii-specific antibiotics are able to penetrate the cyst walls of the bradyzoite form, but they are thought to limit proliferation of the tachyzoites during active disease. Corticosteroids are used to decrease inflammation and scarring, but due to the risk of increasing parasite proliferation, they must be used in conjunction with antibiotics. In addition, there is some question as to

whether corticosteroids could increase the chance of future recurrence of the disease.[7,8]

Differential Diagnosis

In this particular case, other conditions involving chorioretinitis with corresponding panuveitis that were considered were tuberculoma, lymphoma, syphilis, Bartonella, and sarcoidosos.

Tuberculosis

Ocular tuberculosis most commonly presents as a posterior uveitis, although it can also manifest as granulomatous anterior, intermediate or panuveitis.[9] If posterior uveitis is present, it often indicates choroidal involvement, which can include subretinal abscess, tubercles and tuberculomas.[9] Choroidal tubercles are small nodules, less than 1/4 disc diameter, and result in a scar when healed.[9] Tubercles can also develop into a choroidal tuberculoma that is often associated with an exudative retinal detachment.[9] The quantiferon gold result was positive in this case, which is consistent with the patient's history of previously testing positive for tuberculoma and undergoing treatment. Our patient was not experiencing any systemic symptoms of active tuberculoma at the time of presentation.

Lymphoma

Primary intraocular lymphoma can also present as a uveitis and vitritis. As with toxoplasmosis, patients often complain of blurred vision and floaters.[10] Fluorescein angiography (FA) is useful in the diagnosis of primary intraocular lymphoma.[10] Window defects on FA indicate tumor infiltrates, and leakage on FA, which indicates inflammation, is not usually present.[10] In this case, an FA was not performed. Once the IgM and IgG test results were known to be positive, the CBC was normal, and the clinical course proceeded as expected, this case was determined to be toxoplasmosis.

Syphilis

Ocular syphilis can present as uveitis, vitritis, retinitis, retinal vasculitis, papillitis or neuroretinitis.[11] The uveitis associated with syphilis may present as granulomatous or non-granulomatous.[11] Serology testing for syphilis involves both Treponema-specific and non-Treponemal tests.[11] The Treponema-specific test, FTA-ABS, was ordered. In this case, the FTA-ABS was negative, so ocular syphilis was ruled out.

Bartonella

Another differential diagnosis considered was Bartonella. The mode of transmission of the bacteria Bartonella to humans is largely through cat fleas.[12] Cats' claws can become contaminated with the Bartonella species via the cat flea feces, and transmission to humans can occur through a cat scratch, bite or cat saliva at an open wound.[12] The different species of Bartonella, of which there are more than 20, have varying ocular manifestions. The most common ocular manifestions of Bartonella include Parinaud oculoglandular syndrome, choroiditis, retinitis, neuroretinitis, vasculitis and anterior and intermediate uveitis.[12] In this case, the lab testing for Bartonella was negative, and the clinical appearance of the uveitis was more consistent with toxoplasmosis than Bartonella.

Sarcoidosis

Sarcoidosis is an inflammatory disease that affects many organs in the body, including the eyes. Its etiology is unknown, and it is characterized by non-caseating granulomas.[13] Sarcoidosis manifests ocularly as a granulomatous uveitis. It often presents posteriorly and typically presents bilaterally.[13] In this case, the ACE level was not considered elevated, and the patient did not show systemic signs or symptoms of sarcoidosis, so it was ruled out.

Conclusion

This teaching case report illustrates a case of unilateral granulomatous panuveitis. While uncommon, this case was determined to be one of acquired ocular toxoplamosis. One valuable point in this case is the importance of dilation in general, and specifically in this episode of panuveitis. Viewing the posterior pole was not only critical for diagnosis but also for follow-up appointments for determining if and how well the patient was responding to treatment. Lab results also played an important role in the diagnosis in this case. This patient was seen in a hospital setting, but if laboratory testing is not readily available at a clinic site, referrals can easily be made. With treatment consisting of topical prednisolone, cyclopentolate, oral azithromicin, intravitreal clindamycin and the later addition of oral prednisone, this patient's chorioretinitis eventually resolved with minimal ocular complication.

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