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UVEITIS RESOURCE CENTER
An ongoing series offering different perspectives on diagnosing and managing uveitis.

DIFFERENTIATING PRIMARY INTRAOCULAR LYMPHOMA FROM UVEITIS

How to diagnose and treat this rare disease.

BY J.W. HARBOUR, MD

The specific cause of uveitis in a given patient is often unclear. It is known that uveitis can be associated with other disease or infection in the body, which is why a good ocular and systemic workup can be essential to properly diagnosing and treating a patient who presents with ocular inflammation. Establishing the location of the inflammation is a critical part of the workup, as is identifying any possible associated systemic diseases.

Uveitis expert Thomas Albini, MD, serves as the moderator of the Uveitis Resource Center (retinatoday.com/uveitis-resource-center). He sits down with other uveitis specialists to gather their insights into the diagnosis and treatment of this condition. In this installment of the Uveitis Resource Center, J.W. Harbour, MD, director of ocular oncology at Bascom Palmer Eye Institute in Miami, Fla., reviews the differential diagnosis of primary intraocular lymphoma in patients who present with ocular inflammation.

Primary intraocular lymphoma (PIOL), or primary vitreoretinal lymphoma, is a rare form of non-Hodgkin lymphoma that occurs in the lymphoid tissues of the eye (ie, retina, vitreous, sub–retinal pigment epithelium (sub-RPE), and optic nerve head).[1] The disease is considered primary intraocular lymphoma if at the time of diagnosis it is limited to the eye and there is no intracranial involvement.[2] However, up to 80% of patients presenting with PIOL will eventually manifest intracranial malignancy.[3] Thus, preventing the spread of PIOL to the brain through early definitive diagnosis and treatment could reduce morbidity and mortality. The majority of patients with PIOL present with nonspecific visual symptoms, including floaters and blurry vision, which often leads to an initial incorrect diagnosis of uveitis or retinitis. This article explains what to do when you suspect that a patient has PIOL, how to diagnose it, and how to treat it.

FACTORS THAT RAISE SUSPICION OF PIOL

Patients who come to us with intraocular inflammation, vitritis, and anterior uveitis have often been diagnosed with intermediate uveitis or a similar entity and have accordingly been treated with steroids, which only worsened their inflammation. If a patient fits this profile and is over the age of 60 years, one should at least be thinking about intraocular lymphoma. This malignancy can occur in younger people, but for a patient older than 60 years, this diagnosis should be placed high in your differential.

In my experience, an older patient with significant vitritis in an eye that is white should have one thinking about intraocular lymphoma. Suspicions should be raised even more by the telltale sign of whitish-yellow infiltrates in the sub-RPE, but this sign is not always present. Often, optical coherence tomography will reveal bumps located in the RPE. These are a clue that one may be dealing with an infiltrate. I often order fluorescein angiography as well in these eyes because one might not see anything clinically, but the fluorescein may show a subtle RPE abnormality that is fairly diffuse.

Some patients develop central nervous system (CNS) lymphoma first and then ocular lymphoma later, and that is a different category of disease. If a patient starts with ocular disease and I am suspicious of lymphoma, I prefer to establish the diagnosis of intraocular lymphoma before

ordering a brain MRI, unless the patient demonstrates obvious neurologic signs such as slurred speech, change in personality, sudden loss of memory, or focal sensorimotor deficits.

Sometimes we see patients in the clinic who have been diagnosed with other types of lymphoma (eg, systemic lymphoma, non-CNS lymphoma). In these cases, the tumor tends to be more confined to the choroid, although there are exceptions to the rule. In general, if lymphoma is developing in the lymph nodes or in the viscera, and it involves the eye (iris or choroid), it is likely a metastasis similar to a metastatic carcinoma. Conversely, lymphomas that originate in the CNS tend to have a vitreoretinal presentation.

ESTABLISHING A DIAGNOSIS

The standard of care for diagnosis of PIOL is still cytology. Other tests such as flow cytometry, interleukin (IL)-10/IL-6 ratio, and immunoglobulin heavy chain gene rearrangement are all ancillary.

For me to be convinced that a patient has lymphoma, I need an experienced cytologist to tell me that he or she saw large B-cells in the specimen, which requires a vitrectomy specimen. Therefore, I recommend vitrectomy. For the purpose of collecting a specimen, I recommend using a low (200-300 cpm) cut rate and manual aspiration of the sample into a tuberculin syringe with a 25-gauge needle. The infusion may have to be turned on temporarily to keep the eye inflated, but one should be able to obtain several primary samples this way.

Lymphoma cells are fragile and tend to rupture and degenerate quickly, so I alert the pathology lab that the samples are on their way, then I put them on ice and walk them to the lab myself. This way I know they will not sit on a shelf for 3 or 4 hours before someone processes them. Once the primary sample is retrieved, I turn the cut rate up to about 600 cpm for a nice core vitrectomy. The process can be finished with normal settings.

THE MYD88 CONNECTION

There has been a potentially important diagnostic breakthrough recently. It turns out that myeloid differentiation primary response gene 88 (MYD88) mutations were identified in 69% to 82% of vitreoretinal lymphoma cases[4,5] and in 87% of primary vitreoretinal lymphoma cases.[5] Because only a small sample is needed to test for this mutation, a vitreous tap could potentially take the place of standard vitrectomy.

The mutation can be detected using a polymerase chain reaction–based method. If the mutation is present, the diagnosis is established. But if the mutation is absent, then vitrectomy is still necessary because, as noted above, about 15% to 30% of cases do not have the mutation.

The MYD88 mutation is specific enough that one could take it as being diagnostic without cytology, but at this time we really should not rely solely on the presence or absence of the mutation. Additional studies are needed before this becomes standard of care. At the Bascom Palmer Eye Institute we plan to start doing the MYD88 test and comparing it with cytology in a prospective manner to determine whether we can replace vitrectomy with vitreous tap.

WATCH THE VIDEO

A video of Thomas Albini, MD, interviewing Dr. Harbour on the differential diagnosis of primary intraocular lymphoma in patients who present with ocular inflammation can be viewed at: bit.ly/2016harbour.

THERAPEUTIC OPTIONS

There are two main options for treatment of PIOL: external-beam radiotherapy (EBRT) with a relatively low (30-35 Gy) dose or intravitreal chemotherapy.

The chemotherapy options are generally methotrexate and rituximab. In my hands, methotrexate works better than rituximab, and I have not seen toxicity with methotrexate, so I prefer to use it until the patient develops resistance. When that happens, I switch to rituximab.

Systemic chemotherapy by itself for the treatment of patients with isolated ocular disease is not effective. I prefer to treat patients, even those with only ocular involvement, both systemically and locally. In our hands, many of these patients never develop CNS lymphoma. We have published that data.[6]

Ocular therapy is always needed in patients with PIOL. I have had patients referred who have already gone through several rounds of systemic chemotherapy, yet they still have active disease in their eyes, so these patients need local therapy. The choice between EBRT and intravitreal chemotherapy is a multifactorial decision. The common argument against EBRT is the associated retinal radiation toxicity, but I do not think that is a good enough argument. At 30 Gy to 35 Gy, most patients do not get significant radiation retinopathy.

I prefer EBRT for patients who present with bilateral disease, particularly if they travel a long distance to my office. This therapy option takes only a couple of weeks and then the patient is done with it. Also, the local recurrence rate is low if the EBRT is done by a good radiation oncologist.

I prefer intravitreal chemotherapy for patients who present with unilateral disease, or for those who have had a vitrectomy in one eye and I plan a vitrectomy in the other eye; therefore, I know both eyes have been debulked quite a

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bit. In these patients, their disease can usually be controlled with a few injections of methotrexate. I tend not to use the intensive protocol of twice-a-week treatment for 1 month and then once-a-month thereafter. I treat patients once a month until I no longer see these cells on slit-lamp examination of the anterior chamber, anterior vitreous, and posterior vitreous and that has worked effectively for me.

PATIENT PROGNOSIS

Data on the prognosis for patients with PIOL in light of recent improved diagnostics and the latest approaches to treatment are lacking. There have been admirable efforts to compile data from multiple centers, but if these centers are managing patients differently, it makes it hard to compare data. I have several patients with CNS disease who were well-controlled with systemic chemotherapy using the agents discussed above, and some of these individuals are now 10 and 15 years out from treatment. ■

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