A 6-year-old Girl with ‘Pink Eye’ for Several Months

Robert Listernick, MD

This 6-year-old girl was first seen 6 months ago for evaluation for “pink eye” of several months duration. An optometrist made the diagnosis of uveitis, and she was referred for further evaluation. She had never complained of vision loss or eye pain. Her past medical history, family history, and review of systems were unremarkable. In particular, there was no family history of inflammatory bowel disease, lupus, rheumatoid arthritis, or thyroid disease. There was no significant travel history or animal exposure.

Her weight was in the 25th percentile, height in the 10th percentile. Vital signs were unremarkable. Her general physical examination was normal. On ophthalmologic exam, she had 20/15 vision in the right eye and no light perception in the left eye. There was marked uveitis in the left eye and a possible retinal detachment.

Robert Listernick, MD, moderator: This girl’s vision in her left eye had been wiped out, but she never complained of vision loss.

Marilyn Mets, MD, pediatric ophthalmologist: Young children rarely complain of insidious loss of vision, regardless of the magnitude of the loss. On initial evaluation here, her right eye was normal. However, she had panuveitis of the left eye, meaning that there was inflammation of the anterior chamber, the vitreous, and the retina or choroid. The uvea consists of the iris, ciliary body, and the choroid, which lines the inner globe. Inflammation of any of these layers is termed “uveitis.” In addition, there was a retinal detachment.

Dr. Listernick: Why is there a retinal detachment?

Dr. Mets: In this case, the inflammatory process leads to the accumulation of fluid from leaky vessels underneath the retinal layer, which eventually builds up and causes the detachment.

Dr. Listernick: Could you estimate how long the inflammatory process had been occurring?

Dr. Mets: At least several months because of the appearance of the retinal detachment.

Dr. Listernick: What were your initial thoughts about etiology?

Dr. Mets: Our initial concern was the possibility of retinoblastoma, even though we didn’t see a mass on ophthalmoscopy. Once ultrasonography ruled this out, the biggest concern was a rheumatologic disease, such as juvenile idiopathic arthritis (JIA), sarcoidosis, inflammatory bowel disease, or any other vasculitic syndrome. The uveitis of JIA is usually predominantly in the anterior chamber, making that diagnosis less likely. Infection was also a remote possibility, such as visceral larva migrans.

Ellen Chadwick, MD, pediatric infectious disease physician: As far as infections go, Toxocara canis (visceral larva migrans), toxoplasmiosis, and Bartonella henselae (cat scratch disease) are the most common infectious agents associated with uveitis. Certainly, viruses, such as varicella zoster virus or CMV, could also cause uveitis but not in this clinical setting.
Dr. Listernick: As a rheumatologist, when you’re called about a young girl with uveitis, what goes through your mind?

Marisa Klein-Gitelman, MD, pediatric rheumatologist: Isolated uveitis as part of pauciarticular JIA before the onset of arthritis is common. Unfortunately, a great deal of silent damage may occur before the patient comes to medical attention. After that, virtually any vasculitic syndrome can be associated with uveitis, such as sarcoid, lupus, Behcet’s disease, or polyarteritis nodosa.

Dr. Listernick: I noticed that at presentation she had an elevated level of angiotensin converting enzyme (ACE).

Dr. Klein-Gitelman: An elevated ACE level is consistent with, but not diagnostic, of sarcoidosis. ACE can be elevated in other inflammatory diseases. It is useful in following disease activity of sarcoidosis once a histologic diagnosis has been made.

Dr. Mets: She was treated with prednisolone ophthalmic drops in the left eye. We felt that her vision was irretrievably lost. However, we were trying to quell the inflammatory process, which can lead to an increase in intraocular pressure and intense pain and damage to the globe itself. Subsequent examinations revealed the beginning of the same inflammatory process in the right eye as well, despite the addition of systemic steroids. There were perivascular exudates and hemorrhages developing in the retina, consistent with an active vasculitic process. Although there was no histologic diagnosis, sarcoid was high on the list because the fundoscopic findings were highly reminiscent of the “candle wax drippings” seen in sarcoid. The pathologic findings in the right eye improved markedly on high dose systemic steroids.

Dr. Listernick: Around the time of the last eye exam, she developed daily fevers with fatigue and night sweats. There was no history of arthritis, rash, or other symptoms. On examination, she was alert and healthy appearing. Temperature was 39.3°C, but her vital signs were otherwise unremarkable. She had multiple bilateral firm, mobile, nontender, posterior cervical lymph nodes measuring 1 to 2 cm. Lungs were clear. Heart exam was normal. Liver was palpable 5 cm below the right costal margin, and the spleen was palpable at the iliac crest. Neurologic exam was unremarkable.

Laboratory evaluation included hemoglobin 7.7 g/dL with MCV 67; white blood cell count 2,200/μm³ with 64% lymphocytes, 24% neutrophils, 9% monocytes; platelet count 49,000/μm³ and reticulocyte count 2.1%. Complete blood count performed 3 months earlier had been normal. Erythrocyte sedimentation rate and C-reactive protein were minimally elevated. Chemistries were normal save for albumin 2.7 g/dL. Ferritin and triglycerides were normal, but the serum neopterin was markedly elevated. Serum ACE level was still elevated.

Robert Liem, MD, pediatric hematologist: She’s pancytopenic with a microcytic anemia and an inadequate reticulocyte response. The first question is whether this is a primarily oncologic process or is secondary to a systemic vasculitis. Given her previous history, my first thought was that her laboratories might be indicative of immune dysregulation and immune-related cytopenias. However, given the complex history and massive hepatosplenomegaly, bone marrow examination looking for an oncologic process was certainly reasonable. Her massive splenomegaly may have contributed significantly to the cytopenias by causing hypersplenism.

Dr. Listernick: What were the rheumatologists’ initial thoughts?

Dr. Klein-Gitelman: Certainly, sarcoid had to be a prominent consideration, given the history of uveitis, elevated ACE levels, and the prominent hepatosplenomegaly and cytopenias. However, in order to confirm that diagnosis, we need to document the presence of noncaseating granulomas in a body tissue. Other thoughts included hemophagocytic syndrome, what the rheumatologists call macrophage activation syndrome (MAS).

Dr. Listernick: How does sarcoidosis generally present in children?

Dr. Klein-Gitelman: Certainly, sarcoid had to be a prominent consideration, given the history of uveitis, elevated ACE levels, and the prominent hepatosplenomegaly and cytopenias. However, in order to confirm that diagnosis, we need to document the presence of noncaseating granulomas in a body tissue. Other thoughts included hemophagocytic syndrome, what the rheumatologists call macrophage activation syndrome (MAS).

Dr. Listernick: How does sarcoidosis generally present in children?

Dr. Klein-Gitelman: Children who have sarcoidosis may present in the same way that adults do with lung disease, arthritis, uveitis, and hepatosplenomegaly. However,
children may develop a very specific pediatric disorder called Blau syndrome or familial juvenile systemic granulomatosis. This is caused by mutation in the nucleotide-binding oligomerization domain protein 2 gene (NOD2/CARD15). It’s an autosomal dominant condition characterized by severe uveitis, granulomatous arthritis with contracture formation, and granulomatous dermatitis, leading to a variety of rashes, including skin ulceration. These children don’t get systemic organ involvement as our child has. Also, the patients whom I’ve seen have had severe anterior uveitis with only minimal posterior disease at most.

**Dr. Listernick:** How is the diagnosis of sarcoid made?

**Maria Proytcheva, MD, pediatric hematopathologist:** You need to find non-necrotizing granulomata on histologic examination. They have a characteristic appearance; in general, they are tight and usually have no necrosis. Most importantly, before making the diagnosis of sarcoidosis, we need to exclude a variety of infectious agents, such as mycobacteria or *Bartonella henselae* using special stains and by serology.

**Anthony Mancini, MD, pediatric dermatologist:** As an aside, when we biopsy the skin looking for sarcoid, we are taught to look for “naked granulomas,” which are not only noncaseating but also noninflammatory, with little or no lymphocytic or plasma cell infiltrate.

**Dr. Listernick:** Lymph node and bone marrow biopsies were performed.

**Dr. Proytcheva:** The architecture of the lymph node is preserved, and there is a variable expansion of the paracortical areas due to proliferation of variable sized lymphocytes and histiocytes. There is minimal focal single cell necrosis. This is clearly a non-neoplastic process. In neoplastic proliferations, you would see a uniformly monotonous population of cells. Immunohistochemical stains also show a mixture of B and T lymphocytes and histiocytes. The number of T cells is higher than B cells and most of the T cells are positive for CD8. Some of the histiocytes have abundant cytoplasm and eccentric “C” shaped nuclei. There is overt necrosis and no granulomata are present. The presence of preserved nodal architecture, heterogeneity of the inflammatory infiltrate with predominance of CD8 positive T cells, and single cell necrosis are characteristic of Kikuchi-Fujimoto disease (KF).

**Dr. Proytcheva:** What is KF?

**Dr. Proytcheva:** KF, also known as histiocytic necrotizing lymphadenitis, is generally a self-limited lymphadenitis found on lymph node biopsy in a child or adult who has asymptomatic lymph node enlargement. Originally described in Japan, it has been identified in all ethnic groups. More frequently, KF is mild associated and is associated with such symptoms, such as fever, fatigue, or rash. Association with severe disease, such as hepatosplenomegaly or encephalitis, is rare but has been described. These patients may also have associated mild anemia, leukopenia, and elevated ESR.

**Dr. Listernick:** Is treatment necessary?

**Dr. Proytcheva:** No, the illness is usually self-limited. However, a proportion of patients with KF may develop systemic lupus erythematous (SLE). The relationship between the two disorders is unclear.

**Dr. Listernick:** What about uveitis?

**Dr. Mets:** For what it’s worth, there are several reported cases of uveitis associated with KF. In general, the uveitis in KF was anterior, although there have been two cases of posterior uveitis. However, at best, it’s an extremely uncommon association.

**Dr. Listernick:** We’re not finished! We have to hear about the bone marrow biopsy.

**Dr. Klein-Gitelman:** While we were trying to interpret the results of the bone marrow biopsy, we were aggressively treating the retinal vasculitis, first with high dose corticosteroids and then with methotrexate. The working diagnosis was uveitis associated with KF.

**Dr. Proytcheva:** The most striking bone marrow finding was the presence of a hypercellular marrow with numerous histiocytes displaying erythrophagocytosis. Immunohistochemical stains did not reveal any other abnormal population of cells although the number of lymphocytes was increased. Although hemophagocytosis is a non-specific finding in the marrow and can be seen in a number of conditions, the extent of hemophagocytosis is quite striking and is highly suggestive of hemophagocytic syndrome. Cerebrospinal fluid examination also showed marked hemophagocytosis similarly to the bone marrow.

**Dr. Klein-Gitelman:** Hemophagocytic syndrome is a heteroge-
neous group of disorders characterized by fever, hepatosplenomegaly, lymphadenopathy, and variable degrees of end organ failure that can involve any organ, most commonly the liver, central nervous system, and bone marrow. International criteria used by hematologists require the presence of all five of the following: 1) fever, 2) splenomegaly, 3) cytopenia involving at least 2 cell lines, 4) hypertriglyceridemia or hypofibrinogenemia, and 5) hemophagocytosis demonstrated in the bone marrow, liver, or lymph node. Additional laboratory findings include a markedly elevated serum ferritin, low or absent natural killer cell activity, and elevated serum soluble IL-2 receptor.

Dr. Listernick: What is the etiology of hemophagocytic syndrome?

Dr. Klein-Gitelman: It can be secondary to any number of infections or rheumatologic diseases, most notably systemic JIA. Alternately, defects in at least four identified genes have been shown to be a cause of familial hemophagocytic syndrome, also known as familial hemophagocytic lymphohistiocytosis (HLH).

Dr. Listernick: How does this relate to KF?

Dr. Klein-Gitelman: The two have been reported together. However, it isn’t clear in those cases if the KF is the etiology of the hemophagocytic syndrome or if KF is simply one manifestation of the disease.

Dr. Listernick: How did you approach her care?

Dr. Klein-Gitelman: Once the diagnosis of hemophagocytic syndrome was suspected, we performed testing for all the known genetic causes of familial hemophagocytic lymphohistiocytosis. She had homozygous mutations in RAB27A, establishing the diagnosis of familial hemophagocytic lymphohistiocytosis. A lumbar puncture was abnormal with an elevated number of white blood cells indicating central nervous system involvement. Her initial therapy was a combination of dexamethasone, cyclosporine, and VP-16. Because of the CNS involvement, she was also given intrathecal methotrexate and alemtuzumab, a monoclonal antibody directed against a specific surface antibody on mature lymphocytes. Treatment is ongoing.

Dr. Listernick: Thank you, everyone.

Key Learning Points

1. Young children rarely complain of insidious loss of vision, regardless of the magnitude of the loss.
2. Uveitis can be associated with a number of vasculitic syndromes (eg, juvenile idiopathic arthritis, sarcoid, Behçet’s disease) and infections (eg, toxoplasmosis, Bartonella henselae, cytomegalovirus, varicella-zoster virus).
3. An elevated angiotensin converting enzyme (ACE) level is consistent with, but not diagnostic, of sarcoidosis. It is more useful in following disease activity of sarcoidosis once a histologic diagnosis has been made.
4. Hemophagocytic syndrome requires the presence of all five of the following criteria: 1) fever, 2) splenomegaly, 3) cytopenias involving at least two cell lines, 4) hypertriglyceridemia or hypofibrinogenemia, and 5) hemophagocytosis demonstrated in the bone marrow, liver, or lymph node. Additional laboratory findings include a markedly elevated serum ferritin, low or absent natural killer cell activity, and elevated serum soluble IL-2 receptor.