Salmon patch-associated vitreous hemorrhage in non-proliferative sickle cell retinopathy masquerading as infectious uveitis

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ARTICLE INFO

ABSTRACT

Purpose: To report three cases of non-proliferative sickle cell retinopathy (NPSR) with vitreous hemorrhage masquerading as infectious uveitis.
Observations: Three patients were referred from ophthalmologists to our practices with clinical findings suggestive of infectious uveitis. The first patient was referred for new-onset floaters in both eyes, bilateral vitritis and dome-shaped lesions on B-scan ultrasound. He was initially treated for tuberculosis uveitis due to a positive purified protein derivative test. The second patient was referred with floaters and hazy vision in the setting of recent fever and headache and was also reported to have vitritis and unilateral yellow vitreoretinal lesions on fundoscopy. She was initially treated for toxoplasmosis and endogenous endophthalmitis. The third patient presented with flashes, floaters, and decreased vision four months after a ring-enhancing lesion was found on brain imaging, and was found to have unilateral vitritis with yellow vitreoretinal lesions. He was initially started on topical steroids and cycloplegics empirically for uveitis. All patients were ultimately diagnosed as having manifestations of NPSR, including vitreous hemorrhage, and dehemoglobinized salmon patch hemorrhages.
Conclusions and Importance: NPSR can occasionally masquerade as infectious uveitis. Obtaining a detailed history with relevant ancillary testing, along with performing a careful physical exam to recognize important clues, can help the physician arrive at the correct diagnosis in these equivocal cases.

1. Introduction

Retinal findings of sickle cell disease (SCD) include non-proliferative and proliferative changes. Non-proliferative sickle retinopathy (NPSR) is characterized by arteriolar and capillary occlusion, with accompanying signs such as salmon patch hemorrhages, iridescent spots, and black sunburst lesions. Salmon patches are usually asymptomatic, well-demarcated superficial intraretinal or preretinal hemorrhages in the mid-peripheral retina, whereas iridescent spots represent macrophages filled with blood breakdown products beneath the internal limiting membrane (ILM) in areas of old, resorbed hemorrhages. Sunburst lesions appear after resolution of the hemorrhages and reflect changes in the retinal pigment epithelium and pigment migration. With more advanced ischemia, proliferative sickle cell retinopathy (PSR) can occur. Sea-fan neovascularization may develop at the border of perfused and non-perfused retina, and overlying vitreoretinal traction may lead to sight-threatening complications such as vitreous hemorrhage or retinal detachment.[1,2] Less commonly, vitreous hemorrhage may occur when a salmon-patch hemorrhage leaks through the internal limiting membrane (ILM), despite the absence of neovascularization. The blood in salmon-patch hemorrhages may become dehemoglobinized over time and appear yellow.[2,3] This presentation may introduce a diagnostic challenge, as yellow salmon-patch hemorrhages may simulate infectious or inflammatory retinal or choroidal lesions, and dehemoglobinized vitreous hemorrhage may simulate vitritis. Additionally, because patients with hemoglobin SC disease often do not have a history of hospitalizations, in contrast to patients with SS disease, they may deny a history of sickle cell disease at time of presentation, further complicating the clinical picture.

We report three cases of NPSR masquerading as infectious uveitis.

Final diagnoses of NPSR were established after comprehensive history taking, meticulous examination, and review of ancillary testing. We also offer a clinical paradigm to help differentiate NPSR from other etiologies when the diagnosis is uncertain.

2. Findings

This retrospective clinical case series was conducted in accordance with the tenets of the Declaration of Helsinki and Institutional Review Board (IRB)/Ethics Committee approval was obtained at the Columbia University Irving Medical Center. IRB/Ethics Committee ruled that approval was not required by the Bascom Palmer Eye Institute. The study involved the chart review of two patients at the Bascom Palmer Eye Institute of the University of Miami and one patient at the Edward S. Harkness Eye Institute of the Columbia University Irving Medical Center. Clinical information obtained included patient history, best-corrected visual acuity (BCVA), pupillary reflexes, intraocular pressure (IOP), and findings from slit lamp biomicroscopy and dilated fundus exam. Results of B-scan ultrasound, fluorescein angiography (FA), and pertinent laboratory tests were also reviewed where available.

2.1. Case 1

A 17-year-old African American male presented to the eye clinic with a one-month history of floaters in both eyes. His medical history was only significant for undescended testicles. He also reported right eye trauma one month prior that resulted in subconjunctival hemorrhage. The patient had been referred to our practice by an ophthalmologist who had diagnosed the patient with tuberculosis uveitis based on a positive purified protein derivative (PPD) result. His medications included oral isoniazid, rifampin, pyrazinamide, and topical difluprednate 0.05% twice daily in both eyes.

On exam, BCVA was 20/30 in the right eye, and 20/40 in the left eye. His pupils were round and equally reactive to light without evidence of a relative afferent pupillary defect. His intraocular pressure (IOP) was 21 mm Hg in both eyes. Anterior segment exam was normal, including a deep and quiet anterior chamber in both eyes. On dilated fundus exam, there was marked vitreous haze with 3+ pigmented vitreous cells bilaterally. Multiple yellow vitreoretinal lesions were faintly visible in the mid-periphery of both eyes. B-scan ultrasonography demonstrated peripheral dome-shaped elevations in both eyes. There was no retinal detachment or choroidoscleral thickening in either eye.

Given his presentation, we took a more targeted medical history and found that his family history was notable for diabetes and a history of SCD, with his father having hemoglobin AS, mother AC, and brother AS variants. Complete blood count (CBC) demonstrated a minor decrease in platelet count but was otherwise unremarkable, and erythrocyte sedimentation rate (ESR) was within normal limits. Infectious workup for toxoplasmosis, cat-scratch disease, Lyme disease, syphilis, and cytomegalovirus was negative. Interferon gamma-release assay (IGRA) was also negative despite his previous positive PPD testing. However, hemoglobin electrophoresis testing was positive for hemoglobin SC, and vitreous hemorrhage secondary to sickle cell retinopathy was determined to be the final diagnosis. Anti-tuberculosis agents and topical steroids were discontinued, and he was observed for spontaneous resolution.

Four months later, the patient continued to have visual symptoms from non-clearing vitreous hemorrhages, ultimately requiring a 23-gauge pars plana vitrectomy in the right eye. Two weeks following surgery, he reported improvement in symptoms, with a BCVA of 20/20. On fundus exam, there were multiple dehemoglobinized salmon-patch hemorrhages and peripheral ischemic changes anteriorly associated with NPSR (Fig. 1). Fluorescein angiography after surgery showed peripheral nonperfusion without neovascularization.

2.2. Case 2

A 14-year-old African American female presented with a one-month history of photosensitivity associated with intermittent floaters. In addition, she reported an episode of fever with frontal headache ten days prior. Her ophthalmologist discovered a yellow lesion in the retina of the right eye and referred her for workup and treatment of infectious uveitis. Her medical history was significant for SCD (SS disease), with known NPSR in both eyes. She denied surgery or trauma to the eyes. Her medications included hydroxyurea, folic acid, cyproheptadine, and acetaminophen.

BCVA was 20/20 in both eyes, and her pupils were round and equally reactive to light without a relative afferent pupillary defect. Her IOP was 11 mm Hg in both eyes. Anterior segment exam was benign with a deep and quiet anterior chamber bilaterally. The right fundus exam was notable for focal vitreoretinal lesions with overlying vitreous haze inferiorly in the mid-periphery (Fig. 2). In the left eye, a black sunburst lesion was found in the superonasal quadrant.

Although she had a known history of NPSR, her recent symptoms of fever and headache, coupled with fundus findings concerning for a possible infectious etiology, led to empiric treatment and initiation of a
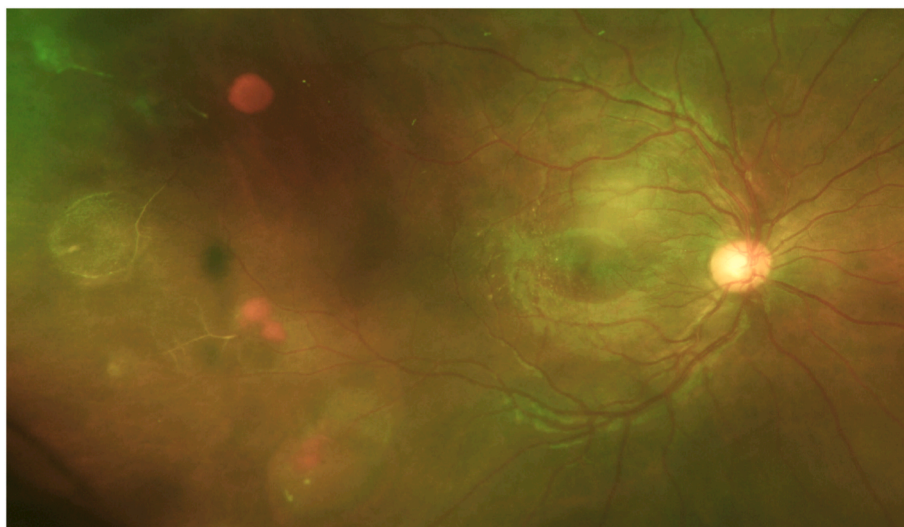

Fig. 1. Case 1. Fundus photograph of the right eye following vitrectomy. Salmon patch hemorrhages, iridescent spots, sunburst lesions, and peripheral ischemic vessels are visualized in the temporal retina.
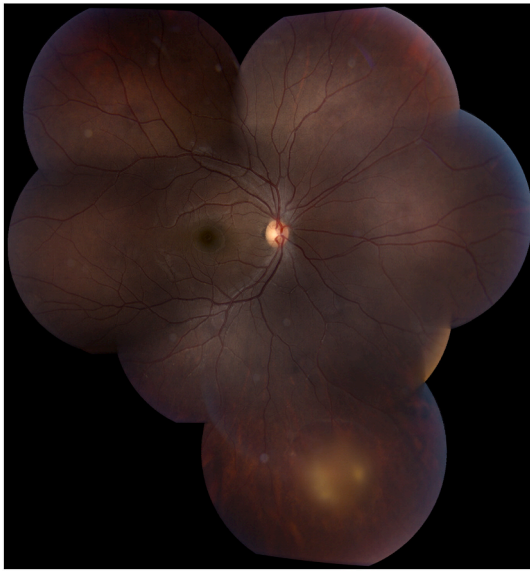
Fig. 2. Case 2. Fundus photograph of the right eye demonstrating focal vitreoretinal lesions inferiorly. There is focal haze that is isolated below the posterior hyaloid and directly over the yellow lesions. However, the remainder of the vitreous is clear. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

broad workup. The patient was placed on sulfamethoxazole-trimethoprim and clindamycin for possible toxoplasmosis and fluconazole for coverage of Candida species. Labs for toxoplasmosis, tuberculosis, and syphilis were negative, and CBC demonstrated only a hemolytic anemia. Antimicrobials were subsequently discontinued as the patient's presentation was found to be secondary to a dehemoglobinized salmon patch with overlying vitreous hemorrhage. Her symptoms gradually resolved, and the fundus lesions in the right eye gradually progressed to a black sunburst morphology (Fig. 3).

One year after her initial presentation, she presented with new,

Fig. 3. Case 2. Fundus photograph of right eye, demonstrating black sunburst lesion inferiorly in area of prior vitreoretinal lesions (asterisk). Close inspection reveals the margins of the elevated internal limiting membrane, which was previously occupied by the salmon patch hemorrhage.

similar yellow vitreoretinal lesions in both eyes. There was again concern for a possible infectious process based on appearance, although she was asymptomatic with BCVA of 20/20 bilaterally. Systemic anti-microbials were empirically started a second time, but after two weeks her exam remained stable with no new symptoms. These findings were consistent with NPSR as before, rather than infectious lesions, and they evolved to a black sunburst appearance.

2.3. Case 3

A 15-year-old African American male was initially referred to our eye clinic to rule out ocular neurocysticercosis. The patient had presented with seizures, and brain magnetic resonance imaging (MRI) showed a ring-enhancing lesion that was concerning for neurocysticercosis. The patient had a past medical history of seizures and known hemoglobin SC disease, with no known past ocular history. On initial exam he was asymptomatic, with BCVA of 20/20 in both eyes. Pupils, IOP, and anterior exam were normal. On dilated exam, the vitreous was clear, and there were a few areas of chorioretinal scarring in the periphery of both eyes. FA showed peripheral nonperfusion but no leakage, consistent with NPSR. The patient was subsequently lost to follow-up.

Four months later, the patient returned complaining of flashes and floaters in the left eye for two weeks. BCVA was 20/20 in both eyes, pupils were round and reactive without a relative afferent pupillary defect, and IOP was 14 and 10 in the right and left eyes, respectively. Anterior exam was notable for a fine 1+ anterior chamber reaction in the left eye, mild vitreous haze, and a new yellow vitreoretinal lesion in the temporal quadrant (Fig. 4A). Optical coherence tomography through the lesion demonstrated a sub-ILM location. Fluorescein angiography showed localized blockage of fluorescence (Fig. 4B). Infectious workup was negative for tuberculosis, syphilis, Lyme disease, and toxoplasmosis. Blood cultures, parasitology, and cysticercosis antibody were also negative. Autoimmune labs were unremarkable. The patient was started on topical steroids and cycloplegics empirically for uveitis. The symptoms and vitreous haze gradually resolved without any additional treatment, and the drops were discontinued because the anterior chamber reaction was determined to be fine, pigmented hemorrhagic cells migrating from the vitreous cavity rather than inflammatory cells. The yellow lesion itself evolved to a sub-ILM cavity, consistent with a salmon patch hemorrhage with clearing of the dehemoglobinized blood (Fig. 4C).

3. Discussion

Our series depicts three cases of NPSR that were initially treated as cases of infectious uveitis, but were ultimately determined to be the specific presentation of dehemoglobinized salmon patch hemorrhages leaking into the vitreous, simulating inflammation. These cases illustrate the diagnostic challenge that a clinician may face when encountering a new patient presenting with anterior chamber cell, floaters, vitreous haze, and discrete yellow vitreoretinal lesions in the periphery.[4] Further complicating the clinical picture is that some patients with sickle cell retinopathy are unaware of their diagnosis of SCD. These patients tend to be those with milder systemic manifestations (e.g. SC disease or sickle-beta thalassemia) but more severe retinopathy.[5]

In these instances, a high index of suspicion paired with a thorough history, negative systemic workup, and a careful clinical exam can lead to accurate diagnosis. While vision loss in SCD from vitreous hemorrhage has typically been described in the context of PSR,[6] many clinicians are not aware that vitreous hemorrhage may also be a component of NPSR, and therefore, they may not consider this possibility on the differential diagnosis. In these cases, blood sequestered in salmon patch hemorrhages becomes dehemoglobinized over time and may pass through the ILM and leak into the vitreous. These focal salmon-patch hemorrhages become yellow and can closely resemble infectious fungal lesions or inflammatory granulomas.[2,3,7] Because the vitreous is

Fig. 4. Case 3. (A) Fundus photograph of left eye demonstrating a vitreoretinal infiltrate and surrounding vitreous haze. (B) Corresponding fluorescein angiography in recirculation phase demonstrating hypofluorescence caused by blockage from the lesion in the late phase, with no surrounding leakage to suggest a neovascular process. (C) Fundus photograph of same lesion six weeks later with clearing of most of the dehemoglobinized blood and the residual sub-ILM cavity.

variably hazy, a detailed retinal exam may be challenging. Hemorrhage is often not suspected because of the yellow-white coloration. In our experience, the following are the most important factors to distinguish salmon patch-associated vitreous hemorrhages from infectious uveitis:

1. Eyes in salmon-patch-associated vitreous hemorrhages are typically not injected, in contrast to eyes that have active infectious uveitis with inflammatory cells.
2. Anterior chamber cells may be present in eyes with vitreous hemorrhage, but in these cases the cells will be finer and pigmented; keratic precipitates and posterior synechiae are typically absent.
3. The vitreous cells in salmon patch-associated vitreous hemorrhages are pigmented and finer than the larger white cells that accompany infectious or noninfectious uveitis.
4. Salmon patches are located superficially compared to the subretinal or choroidal location of infectious (i.e. fungal) lesions in early stages. In later stages, dehemoglobinized salmon patch hemorrhages have more discrete borders compared to the fluffier borders seen in infectious lesions.
5. In cases of unilateral salmon-patch-associated vitreous hemorrhage, fundus examination of the fellow eye often reveals signs of sickle cell retinopathy.
6. With fungal endophthalmitis, there is usually a clear patient risk factor such as immunosuppression, malignancy, or recent hospitalization or surgery. Additionally, systemic blood cultures are usually positive in cases of fungal endophthalmitis.

4. Conclusions

The presence of fine, pigmented anterior or vitreous cells and peripheral yellow vitreoretinal lesions in a patient with a past medical or family history of SCD should trigger a high suspicion for salmon-patch associated vitreous hemorrhage and sickle cell retinopathy. In the right clinical context, this diagnosis should also be considered in the differential even in the absence of a known history of SCD, and may warrant hemoglobin electrophoresis testing. Being able to distinguish salmon-patch associated vitreous hemorrhage in NPSR from infectious uveitis may spare the patient costly investigations and unnecessary medical interventions.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

Declaration of competing interest

The following authors have no financial disclosures: TRC, BDK, JL, ECW, TAA, JD, IS, RWSC.

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