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Waldenström's Macroglobulinemia Masquerading as Birdshot Chorioretinopathy

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Abstract

Purpose—To describe Waldenström's macroglobulinemia (WM) as a masquerade syndrome.

Method—Case report.

Results—A 59-year-old human leukocyte antigen (HLA)-A29-negative Caucasian male presented with a seven-year history of floaters, progressive vision loss, and poor contrast sensitivity along with choroidal lesions suggestive of birdshot chorioretinopathy (BCR). Fluorescein angiography, fundus autofluorescence, and indocyanine green angiography showed multiple areas of hyperfluorescence and hypofluorescence. Electroretinography showed reduced cone and rod responses. Comprehensive work-up for infectious, paraneoplastic, and other causes including sarcoidosis was negative at the time. The patient was treated with multiple immunomodulatory agents without any significant improvement. Two years after initial presentation, the patient developed normocytic anemia and high levels of inflammatory markers. Further work-up yielded a diagnosis of WM. His choroidal lesions were significantly reduced after treatment with rituximab and bendamustine.

Conclusion—We report a case of WM masquerading as BCR. Other indolent diseases should be considered in the differential diagnosis for HLA-A29-negative patients presenting with birdshot-like lesions, especially if they are clinically unresponsive to multiple systemic immunosuppressive agents.

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Keywords

Birdshot chorioretinopathy; HLA-A29; lymphoplasmacytic lymphoma; macular edema; masquerade syndrome; rituximab; Waldenström's macroglobulinemia

Introduction

Waldenström's macroglobulinemia (WM) is a lymphoplasmacytic lymphoma characterized by overproduction of monoclonal immunoglobulin M (IgM).¹ Patients are often asymptomatic when diagnosed and are observed without treatment until anemia, thrombocytopenia, lymphadenopathy, hepatosplenomegaly, or serum hyperviscosity develops. Hyperviscosity syndrome occurs in up to 15% of patients and presents as blurred vision, headache, and epistaxis.² Funduscopy examination in these patients commonly reveals multiple retinal hemorrhages and venous dilatation with areas of focal constriction. Paraneoplastic retinopathy has also been previously described and attributed to WM,³ but no prior reports have shown WM to present with signs of birdshot chorioretinopathy in the absence of systemic symptoms. We report a case of HLA-A29-negative birdshot-like chorioretinopathy that was initially unresponsive to several immunomodulatory agents and was later diagnosed as WM.

Case

A 59-year-old Caucasian male suspected of having retinal degeneration was referred to the uveitis clinic at the National Eye Institute (NEI). He reported a seven-year history of floaters, progressive vision loss, and poor contrast sensitivity. His past medical history was significant only for a seizure disorder, which was controlled with lamotrigine.

On examination, visual acuity (VA) was 20/25 in both eyes, with normal intraocular pressures and no afferent pupillary defect. Anterior-segment examination was within normal limits. Posterior-segment examination showed trace vitreous cells in both eyes, but no vitreous haze. Funduscopy examination revealed multiple, oval, depigmented, creamy-appearing deep retinal/choroidal lesions scattered throughout both fundi (Fig. 1a, b). Larger, confluent lesions were also noted in the far periphery.

Fluorescein angiography (FA), fundus autofluorescence, and indocyanine green angiography showed hyperfluorescence, hypoautofluorescence, and hypofluorescence, respectively, in areas of choroidal lesions or scars, which were more numerous than seen on funduscopy (Fig. 1c–h). FA did not show leakage of the optic nerve or retinal vessels. Optical coherence tomography showed minimal intraretinal edema in both eyes. Humphrey visual field testing revealed superior defects with central scotomas bilaterally. Electroretinography indicated reduced cone and rod responses.

Laboratory testing, including complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum electrolytes, calcium, angiotensin-converting enzyme, lysozyme, rapid plasma reagin, syphilis immunoglobulin G (IgG), and Lyme IgG, was within normal limits. Human leukocyte antigen (HLA)-A29 testing was negative. Tuberculin

skin testing and chest radiograph were unremarkable. Age-appropriate malignancy work-up, including prostate-serum antigen, colonoscopy, computed tomography of the chest, abdomen, and pelvis, and magnetic resonance imaging of the brain, was also negative.

Based on clinical history and funduscopy findings in the absence of infectious, paraneoplastic, or other known causes including sarcoidosis, the patient was diagnosed with HLA-A29-negative birdshot-like chorioretinopathy and was started on immunomodulatory therapy (IMT). The patient was treated for relatively brief periods with mycophenolate mofetil (8 months in 2010, 5 months in 2012), methotrexate (5 months in 2012), and adalimumab (3 months in 2013), without significant improvement. While on IMT, the patient developed normocytic anemia and high ESR and CRP levels. These abnormal laboratory values persisted even after six months off all systemic treatment, and the patient was referred to a hematologist-oncologist. Bone marrow biopsy was performed, revealing a hypercellular marrow with lymphoplasmacytic infiltration. Further work-up, including serum protein electrophoresis, showed IgM to be monoclonal and highly elevated at 4630 mg/dL (normal range: 48–271 mg/dL). The patient was diagnosed with WM.

The patient continued to report progressive eye symptoms and was treated with rituximab and bendamustine based on the presumed relation of both systemic and ocular findings to WM. With this regimen, the patient's inflammatory markers normalized, and his choroidal lesions reduced substantially from baseline (Fig. 1i, j). However, the patient developed clinically significant macular edema, which did not improve with a trial of topical prednisolone acetate and topical ketorolac or oral prednisone, but improved with oral acetazolamide.

Discussion

Birdshot chorioretinopathy (BCR) is a rare form of posterior uveitis most commonly seen in middle-aged Caucasian females and strongly associated with HLA-A29 seropositivity.⁴ It presents insidiously with symptoms of blurred vision, floaters, decreased night or color vision, and photopsias, which can be out of proportion to VA. BCR is largely a clinical diagnosis and is best characterized by its multiple, discrete, oval or round, often depigmented choroidal lesions that appear to radiate from both optic discs. Despite strong HLA-A29 association, HLA-A29 has low positive predictive value because of its presence in up to 7% of Caucasians,⁴ but its high negative predictive value still makes it clinically useful.⁵ Based on our clinical experience, HLA-A29 seronegativity in a patient suspected of BCR should raise clinical suspicion of other etiologies, such as infections, intraocular lymphomas, and other masquerade syndromes.

Our patient presented with a long history of progressive visual disturbances and choroidal lesions highly suggestive of BCR despite being HLA-A29-negative. Comprehensive work-up at the time was negative; systemic signs of WM first became evident only two years after initial presentation to our clinic or nine years after onset of visual symptoms. Although it is possible that even short courses of IMT could have uncovered or hastened the systemic manifestation of his underlying WM, it is unlikely that such brief periods of IMT induced a lymphoplasmacytic lymphoma in this patient, especially given that BCR-like infiltrates

preceded IMT and were likely early manifestations of this smoldering, indolent disease. Furthermore, previous reports have identified IgM deposits in the retina and/or choroid in WM and multiple myeloma.⁶ Given the marked response to rituximab and bendamustine, we believe that the patient's choroidal lesions were secondary to WM. Fortunately, despite the delay in diagnosis, this patient's VA remained unchanged, until macular edema developed after starting rituximab. The development of macular edema several weeks following rituximab infusion has also been previously reported in two scleritis cases despite resolution of scleritis.⁷ The mechanism by which rituximab causes macular edema is unclear, but interestingly, acute exacerbations in scleritis and idiopathic orbital inflammation shortly after rituximab administration have also been reported.^{8, 9}

Mashayekhi *et al.* have previously described the clinical features and differences between primary and secondary choroidal lymphomas, including two cases of WM.¹⁰ Compared to patients with primary choroidal lymphoma, patients with secondary choroidal lymphoma were more likely to have bilateral disease, poor VA at presentation (20/200), rapid progression of visual symptoms, as well as anterior segment inflammation with vitreous cellular reaction and/or infiltration. All patients with secondary choroidal lymphoma in this study had pre-existing or concurrently diagnosed systemic lymphoma, and the authors state that although there have been rare reports, any patient with choroidal lymphoma in the absence of existing or concurrently diagnosed systemic lymphoma are at minimal-to-no risk of developing systemic lymphoma. Our patient, however, first developed visual symptoms and deep retinal/choroidal lesions years prior to developing systemic manifestations of WM. While it is certainly possible that this patient could have developed both primary choroidal lymphoma and WM, a primary choroidal lymphoma in a patient with deep retinal/choroidal lesions and vitreous cellular reaction in both eyes is less likely, given the unilateral nature of primary choroidal lymphoma.

To the best of our knowledge, this is the first report of WM masquerading as BCR in the absence of systemic signs or symptoms and highlights the importance of considering other indolent diseases like WM in the differential diagnosis of birdshot-like lesions in HLA-A29-negative patients, especially when they do not respond to treatment as expected or when the clinical picture evolves.

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Figure 1.

Montage of color fundus photographs at presentation (**a**, right eye; **b**, left eye) shows multiple, oval, depigmented, creamy-appearing deep retinal/choroidal lesions scattered throughout the fundus bilaterally. Similarly appearing but larger, confluent lesions are seen in the far periphery. Fluorescein angiography (FA) (**c**, right eye; **d**, left eye) shows retinal pigment epithelium (RPE) window defects without significant optic nerve or retinal vascular leakage. Fundus autofluorescence (FAF) (**e**, right eye; **f**, left eye) shows multiple areas of hypoautofluorescence in both eyes, many of which correspond to RPE window defects on

FA. Late indocyanine green (ICG) angiography (**g**, right eye; **h**, left eye) also shows multiple hypofluorescent spots, which correspond to choroidal lesions. Montage of color fundus photographs 3.5 months post-treatment with rituximab and bendamustine (**i**, right eye; **j**, left eye) shows marked reduction of the patient's birdshot-like lesions. These lesions also appeared flat and inactive on exam.

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