Multimodal Imaging of Punctate Outer Retinal Toxoplasmosis

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BACKGROUND AND OBJECTIVE: To describe the multimodal imaging characteristics associated with punctate outer retinal toxoplasmosis (PORT).

PATIENTS AND METHODS: Multicenter, retrospective, observational case series of three patients who presented with PORT. Multimodal imaging was reviewed including optical coherence tomography (OCT), fundus autofluorescence, optical coherence tomography angiography, and conventional dye-based angiography.

RESULTS: Patient ages ranged from 13 years to 55 years. Each patient had multiple white, punctate outer retinal lesions in the affected eye at initial diagnosis. OCT showed both inner and outer retinal changes, including disruption of the ellipsoid and interdigitation zones and retinal pigment epithelium/Bruch’s membrane complex, as well as punctate, preretinal, hyperreflective lesions at the vitreoretinal interface, which regressed with treatment.

CONCLUSION: Multimodal imaging is useful in diagnosing and monitoring treatment response in PORT, an uncommon presentation of ocular toxoplasmosis that must be differentiated from white dot syndromes or other causes of unilateral retinitis.


INTRODUCTION

Although classic ocular infection by toxoplasmosis initially presents as focal retinochoroiditis and is associated with prominent vitreous cell and haze, the variant of punctate outer retinal toxoplasmosis (PORT), first described by Doft and Gass,1,2 is characterized by multifocal gray-white lesions at the level of the deep retina and retinal pigment epithelium (RPE) with minimal vitritis. With treatment, these lesions were described to resolve as fine, granular white dots, which were hypothesized to be outer retinal gliotic scars or infectious cysts. The purpose of the current report was to describe three cases of unilateral PORT using multimodal imaging, including swept-source optical coherence tomography (SS-OCT), to localize the location of the lesions on the surface of and within the neural retina.

PATIENTS AND METHODS

This study was approved by each governing institutional review board at the three separate study centers. It complies with the Health Insurance Portability and Accountability Act of 1996 and follows the tenets of the Declaration of Helsinki. Patients were evaluated at three centers. Multimodal imaging included color fundus photography, spectral-domain OCT angiography (SD-OCTA) and SS-OCTA, fundus autofluorescence (FAF), and fluorescein angiography (FA). The diagnosis of PORT was made based on clinical findings, positive serology, and a favorable response to treatment.
Case Summaries

The medical records and multimodal imaging of three patients diagnosed with and treated for PORT were reviewed. Ages ranged from 13 years to 55 years. All patients had unilateral findings of multiple punctate, white outer retinal lesions at initial diagnosis. Two of three patients were noted to have focal retinochoroidal scars at initial diagnosis. All cases involved the fovea. All lesions were hyperfluorescent on FA and were associated with punctate hypoautofluorescence on FAF. OCT showed both inner and outer retinal changes with disruption in the photoreceptor bands and retinal pigment epithelium (RPE), as well as punctate preretinal hyperreflective lesions that faded with treatment. SD-OCTA and SS-OCTA showed enlargement of the foveal avascular zone (FAZ).

Case 1: A 21-year-old woman with unremarkable medical and ocular histories presented with an acute decrease in visual acuity (VA) and vitreous floaters in her right eye. She was born in Cuba and immigrated to the United States as a child. She had a cat in her residence. Best-corrected VA (BCVA) was 20/100 in the right eye and 20/25 in the left eye. Slit-lamp examination showed quiet anterior chambers and 2+ vitreous cells in her right eye. Fundus examination revealed mild temporal pallor of the optic nerve and white, punctate macular deposits (Figure 1A). FA showed multiple perifoveal areas of punctate leakage, as well as mild staining at the nerve (Figure 1B). FAF showed multifocal areas of discrete hypoautofluorescence (Figure 1C). SD-OCT showed focal disruption of the ellipsoid zone (EZ) and interdigitation zone (IZ), as well as hyperreflective superficial retinal deposits and inner retinal involvement (Figure 1D) that largely resolved and became inactive following treatment (Figure 1E). SS-OCT demonstrated vitreous cells and multiple discrete hyperreflective lesions at the vitreoretinal interface with foveal thinning.

Figure 1. Multimodal imaging of the right eye in a 21-year-old woman with punctate outer retinal toxoplasmosis. (A) Color fundus photograph shows white, punctate, perifoveal retinal lesions. (B) Ultra-widefield fluorescein angiogram shows hyperfluorescence of the retinal lesions and optic nerve staining. (C) Fundus autofluorescence demonstrates punctate areas of hypoautofluorescence. The green line has been added to show the position of the B-scans in (D) and (E). (D) Optical coherence tomography shows findings of focal disruption of the ellipsoid and interdigitation zones. Within the hyporeflective pre-macular bursa, there are hyperreflective superficial retinal deposits that have largely resolved and become inactive (E) following treatment.
Table 1. Summary of case characteristics.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td>Sex</td>
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</tr>
<tr>
<td>Age</td>
<td>55</td>
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<tr>
<td>BCVA</td>
<td>20/100</td>
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<td>Cause of reduced vision</td>
<td>Toxoplasmosis of the retina</td>
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<td>Examination findings</td>
<td>Focal disruption of EZ and IZ</td>
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<tr>
<td>Treatment</td>
<td>Oral prednisone (30 mg/day) for 1 week</td>
</tr>
<tr>
<td>Outcome</td>
<td>Improvement to 20/80</td>
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Figure 2. Swept-source optical coherence tomography (SS-OCT) of the right eye in a 21-year-old woman with punctate outer retinal toxoplasmosis (same patient as shown in Figure 1) at initial presentation (A-C) and after treatment (D-F). (A) En face SS-OCT segmented at the level of the vitreoretinal interface shows an attached vitreous with punctate hyperreflective vitreous cells found mostly outside of the central hyporeflective pre-macular bursa. Within the bursa, there are hyperreflective superficial pre-retinal deposits (yellow arrows in A-D). (B) Structural OCT B-scan corresponding to the blue line in A. The dashed magenta lines show the segmentation slab. Adjacent to the focal preretinal deposits was also a larger, near-full-thickness hyperreflective lesion. (C) Structural OCT B-scan corresponding to the blue line in A demonstrates the location of the deposits at the vitreoretinal interface. (D) En face SS-OCT image segmented at the level of the vitreoretinal interface shows a reduction in superficial retinal deposits and partial resolution of the active lesions. (E) Structural OCT B-scan corresponding to the blue line in D. The dashed magenta lines show segmentation boundaries. (F) Structural OCT B-scan corresponding to the blue line in D shows inactive disease with a decrease in size of the lesions after treatment. There is thinning of the inner nuclear layer at the prior site of the lesion with an upwardly contracted outer plexiform layer.

and focal disruption of the EZ and IZ (Figure 2A-C). QuantiFERON-TB Gold (QIAGEN, Germantown, MD), angiotensin converting enzyme, rapid plasmin reagin, and fluorescent treponemal antibody absorbed returned negative. The patient was treated initially with oral prednisone (30 mg/day) for 1 week without clinical improvement as a diagnosis of an inflammatory white dot syndrome was considered. Additional laboratory investigations revealed negative *Bartonella henselae* and *B. quintana* immunoglobulin G (IgG) and IgM titers, positive *Toxoplasma gondii* IgG titers, and negative IgM titers. The patient was then treated with double-strength trimethoprim sulfamethoxazole twice daily and clindamycin 300 mg three times daily, and the oral corticosteroids were continued. One month after initiation of oral antibiotics, vision improved to 20/80. SD-OCT showed restoration of the EZ (Figure 1E). SS-OCT showed a resolution of the deposits at the vitreoretinal interface with now inactive lesions but resultant foveal thinning and atrophy (Figures 2D-2F).

Case 2: A 13-year-old girl with unremarkable medical and ocular histories presented with reduced vision in her right eye for 3 months. BCVA was 20/250 in the right eye and 20/20 in the left eye. There was a mild afferent pupillary defect in the affected right eye. Slit-lamp examination showed no anterior chamber or vitreous cells. Fundus examination of the right eye
revealed a retinochoroidal scar in the superior macula with surrounding retinal whitening and punctate and superficial white lesions. There was mild temporal pallor of the optic nerve (Figure 3A). SD-OCT through the fovea showed hyperreflective round discrete lesions at the inner fovea with loss of the EZ and IZ and obscurcation of the RPE (Figure 3B). There were mid-posterior vitreous cells visible by OCT. FA showed hypofluorescence in the area of the retinochoroidal scar surrounded by speckled hyperfluorescence (not shown). A diagnosis of diffuse unilateral subacute necrotising neuritis (DUSN) was suspected and the patient was treated with albendazole (Albenza; Impax Laboratories, Fort Washington, PA) for 1 month without improvement. No worm was visualized on serial examinations. Serologies for T. gondii revealed positive IgG titers. The patient was treated with trimethoprim sulfamethoxazole and oral prednisone taper. Three
years later, the patient developed more punctate white lesions (Figure 3C), and SD-OCT showed superficial hyperreflective deposits at the fovea along with mild disruption of the EZ and focal splitting of the RPE/Bruch’s membrane complex (Figure 3D) and was treated for recurrent toxoplasmic retinochoroiditis with trimethoprim/sulfamethoxazole double strength twice daily for 4 weeks. Five years after initial presentation, the patient developed more confluent white macular lesions. SD-OCT showed thickening of the perifoveal retina, vitreous cells, and foveal thinning consistent with an evolution into full-thickness retinitis (Figures 3E and 3F), and the patient was again treated with trimethoprim/sulfamethoxazole double strength twice daily for 4 weeks. The choroid appeared mildly thickened and there was partial anterior bowing of the RPE/Bruch’s membrane complex. At last follow-up 6 years after initial presentation, the perifoveal lesions had progressed to atrophy with pigment clumping. There was an atrophic appearance on SD-OCT with diffuse photoreceptor loss, a mild epiretinal membrane, and prominent foveal thinning (Figures 3G and 3H). FAF at last follow-up revealed diffuse hypoautofluorescence associated with loss of the RPE, which correlated with the appearance on en face SD-OCT at the level of EZ-RPE (Figure 4). BCVA at last examination was 20/160 in the affected eye.

**Case 3:** A 55-year-old woman with a history of hyperopia and an unremarkable medical history presented with decreased vision in her left eye for 2 days. Travel history included a recent trip to South Africa. BCVA was 20/20 in the right eye and 20/50 in the left eye. Slit-lamp examination in the affected left eye showed no anterior chamber cells and a 1+ vitreous cells. Fundus examination of the left eye revealed perifoveal white lesions, as well as a larger atrophic lesion in the inferior macula (Figure 5A). FAF showed mottled hypoautofluorescence perifo-
veally and a discrete area of hypoautofluorescence in the inferior macula (Figure 5B). FA demonstrated hyperfluorescence perifoveally and of the inferior macula lesion, as well as late leakage of the optic nerve (Figures 5C). SD-OCTA of the central macula showed an enlarged foveal capillary ring (Figures 5D and 5E). At initial presentation, SD-OCT of the left eye revealed disruption of the EZ and IZ with hyperreflectivity at the level of the RPE and generalized foveal thinning (not shown). Enhanced depth imaging OCT (EDI OCT) showed a mildly thickened choroid (not shown). Blood serology returned positive for *T. gondii* IgG and IgM. The patient was treated with double-strength trimethoprim sulfamethoxazole twice daily and azithromycin. SD-OCT at 6 months showed superficial punctate hyperreflective deposits, mild vitreous cells, and continued hyperreflectivity at the fovea with generalized atrophy and loss of the EZ and IZ (Figures 5F and 5G). VA remained stable at 20/50.
DISCUSSION

Twenty-four years after the initial description by Doft and Gass, de Souza and Casella described five cases of PORT imaged by time-domain OCT and hypothesized that the outer retinal lesions were a granulomatous immune response to infection. The cases described by de Souza et al. showed mild exudation associated with the lesions as they regressed. Of note, the authors felt that the outer retinal variant may represent a successful immune response to disease and might be early pathological findings in a spectrum of disease leading to extension of the infectious organism into the inner retina (resulting in punctate inner retinal toxoplasmosis) followed by fulminant expansion into the inner retina and vitreous (causing the “light in the fog” presentation).

The current report describes the multimodal imaging characteristics of PORT. All patients had only a mild vitritis, which did not obscure the ophthalmoscopic details, and punctate, multifocal white lesions, associated, but not contiguous with, a retinochoroidal scar in two of three cases. All three patients displayed angiographic findings of optic nerve leakage and hyperfluorescence of the active macular lesions. Furthermore, all patients had hyperreflective inflammatory deposits at the vitreoretinal interface that also extended to the inner retina and were associated with outer retinal changes including disruption of the EZ, IZ, and RPE/Bruch’s membrane complex. One of the three cases showed a chronic and recurrent course, whereas the other two cases showed a moderate response to treatment. However, all three cases, despite appropriate treatment, developed foveal thinning and persistent visual changes. PORT may occasionally be associated with choroidal neovascularization, yet none of the three cases in this series had developed choroidal neovascularization at their most recent follow-up.

A report by Lujan described a case of PORT where SD-OCT disclosed surrounding intraretinal and subretinal fluid at initial presentation that resolved, leaving a retinochoroidal scar with alternating hypertrophy and atrophy of the RPE and a defect in Bruch’s membrane. None of our cases had prominent intraretinal or subretinal fluid. With SS-OCT, Chen et al. described a case of conventional acute toxoplasmosis chorioretinitis that showed thickening of the posterior hyaloid, vitreous cells emanating from retinal blood vessels, thickening and disorganization of all retinal layers, and increased choroidal thickening under the lesion. SS-OCT was useful in the current report to visualize the inflammatory deposits at the level of the vitreoretinal interface. The cells appeared suspended in the formed vitreous outside of the pre-macular bursa but may have collected at the vitreoretinal interface within the bursa. All of these patients were young and had an attached hyaloid.

Though highly speculative, perhaps the presence of the bursa influences this particular central presentation of toxoplasmosis. Furthermore, these deposits could also potentially be followed to assess for response to treatment.

In summary, the current report describes three cases of PORT, an uncommon but important variant of toxoplasmosis that may masquerade as an idiopathic white dot syndrome or DUSN. For instance, both DUSN and PORT may exhibit multifocal deep inflammatory lesions: outer retinal in PORT and choroidal in DUSN. PORT also tends to show disruption of multiple retinal layers, whereas DUSN tends to be photoreceptors and RPE/Bruch’s complex. Last, PORT, which is hyperacute, often produces serous retinal detachment, which is uncommon in DUSN. Other uveitic conditions such as sarcoidosis, tuberculosis, and cat-scratch, may also show overlapping features with PORT.

Multimodal imaging and, in particular, OCT, may be extremely useful in localizing the active lesion and obtaining a diagnosis. The detection of more superficial retinal involvement is pathognomonic of this condition and helps clinicians rule out other diseases such as multifocal choroiditis, punctate inner choroiditis, or DUSN, where there is no superficial retinal involvement. It is important to note that although all three cases in this series were consistent with a clinical diagnosis of PORT, as it has been described classically, multimodal imaging revealed that there was evidence of involvement and disruption of both outer and inner retinal layers at various points in the disease process.

The lesions in PORT may be small but come to medical attention because of visual symptoms and their macular location. Small scars of this type in other fundus locations might be easily passed over as inconsequential. Despite the subtleties of this clinical presentation, it is important to note that PORT is still treated the same as classically appearing toxoplasmosis and may have a similar response to therapy.

REFERENCES
