Multimodal Imaging in Sympathetic Ophthamlma

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Multimodal Imaging in Sympathetic Ophthalmia

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ABSTRACT

Purpose: To show the current status of multimodal imaging and its role in supporting an early diagnosis of sympathetic ophthalmia.

Methods: The diagnosis is mainly clinical supported with ancillary investigations; mainly fluorescein angiography and others, including indocyanine angiography optical coherence tomography (OCT), OCT enhanced depth imaging, autofluorescence imaging, and ultrasonography.

Results: Various imaging modalities such as OCT, autofluorescence imaging and angiography are critical in the diagnosis and management of sympathetic ophthalmia. The clinician must make adequate use of such ancillary investigations in the management of the patients.

Conclusions: Sympathetic ophthalmia is a rare, bilateral inflammation of the uveal tract following penetrating trauma or surgery in one eye. The intraocular inflammation requires a prompt diagnosis so that the treatment can be initiated as early as possible.

Keywords: Autofluorescence, fluorescein angiography, indocyanine green angiography, OCT-enhanced depth imaging, sympathetic ophthalmia

Sympathetic ophthalmia (SO) is a rare, bilateral diffuse granulomatous uveitis that usually occurs following penetrating ocular trauma or surgery involving the uvea in one eye. The inflammation primarily involves the choroid to begin with presenting as posterior uveitis that may evolve to panuveitis. Rarely, the inflammation may involve iris and ciliary body initially, followed by panuveitis. The diagnosis of SO is usually based on the history and clinical signs of intraocular inflammation. The ancillary investigations are useful adjuncts to support the diagnosis, determine the severity and extent, as well as to evaluate the response to treatment during follow-up. Fundus fluorescein angiography (FFA) has been used most commonly in patients who present early with posterior segment manifestations, including optic disc edema, exudative retinal detachment, vitritis and Dalen-Fuchs nodules, and has characteristic findings seen during the acute phase. Since the inflammation primarily involves the choroid, indocyanine green angiography (ICG) too offers useful information and may be used during follow-up to monitor response to therapy. The improved imaging modalities to visualize the choroid with the enhanced depth imaging (EDI) OCT, is being used frequently for measuring changes in the choroidal thickness from the inflammatory process. However, the ultrasound B scan can still be used to demonstrate diffuse choroidal thickening in the posterior pole with or without exudative retinal detachment, in case EDI OCT is
unavailable or media is hazy.\textsuperscript{3,4} Autofluorescence imaging changes seen from the pathologic changes of retinal pigment epithelium, mostly take place during the chronic phase.

**FLUORESCEIN ANGIOGRAPHY**

At the onset of intraocular inflammation in sympathetic ophthalmia, the FFA features of retina and choroid differ from those observed during chronic or chronic-recurrent phases of this granulomatous inflammation. Initially, the clinical presentation of SO may be restricted to the ocular fundus in the form of posterior uveitis (Figure 1) with diffuse thickening of the choroid and or multifocal nodular changes in the choroid.\textsuperscript{1-4} The nodular changes may be from either Dalen-Fuchs nodules or foci of epithelioid histiocytic cell collections in the inner choroid. Subsequently, as the inflammation progresses, the posterior uveitis evolves into panuveitis. However, some patients with SO may present initially with posterior uveitis or anterior granulomatous uveitis that may evolve into panuveitis. The intraocular inflammation is known to be similar in the exciting eye and in the sympathizing eye. In the chronic phase of the inflammation, most patients present with panuveitis or anterior uveitis with extensive chorioretinal damage, including depigmentation of choroid in pigmented individuals and display of multiple nummular chorioretinal scars predominantly in the periphery of the fundus (Figure 2).

Two distinct types of abnormal angiographic features are known to occur in SO during initial presentation; initial pinpoint hyperfluorescent leaks or multiple hypofluorescent spots with dye pooling in the late phase. The pattern with initial pinpoint hyperfluorescent leaks is seen more frequently and is virtually identical to that seen in the acute phase of Vogt–Koyanagi–Harada (VKH) disease. Typically, hyperfluorescent multifocal leaks of the dye at the level of retinal pigment epithelium (RPE) are present. These leaks are commonly described as pinpoints leaks, which gradually increase in size and coalesce under focal retinal detachments (Figure 3) resulting in multilobular pooling of the dye with staining of the subretinal exudates.\textsuperscript{5} The focal leaks may represent disruption in RPE cell junctions or damage to RPE. However, there is no histopathologic confirmation of such RPE changes correlating with this angiographic finding.\textsuperscript{4} The choroid perfusion may be delayed focally or as patchy areas. Usually, the optic disc shows leaking of disc vessels or staining of the nerve head.

The second type of the angiographic features is similar to that observed in patients with acute posterior multifocal placoid pigment epitheliopathy (APMPPE).\textsuperscript{4} These changes are less common and consist of hypofluorescent foci during the early phase of angiography and these foci become hyperfluorescent subsequently. Unlike APMPPE, these focal lesions are slightly elevated and may reveal a mild mottled appearance.\textsuperscript{3} It is postulated that the hypofluorescence could be from the obscuration of choroidal fluorescence by Dalen-Fuchs nodules or from focal

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**FIGURE 1.** A 15-year-old female with repaired full thickness anterior scleral laceration presented about 8 weeks later, with bilateral decreased vision. Fundus examination revealed bilateral hyperemic optic disc with multifocal serous detachments of retina seen in the posterior pole.

**FIGURE 2.** Wide-field fundus image of the left eye in a patient with chronic sympathetic ophthalmia, showing a depigmented choroid, juxta-papillary choroidal atrophy, and numerous nummular chorioretinal scars at the periphery.
obliteration of the choriocapillaris by the inflammatory cells extending from the choroid. The late hyperfluorescence represents staining of the lesions.

The chronic phase of SO is complicated by chorioretinal damage, nummular scars, choroidal atrophy, subretinal fibrosis, and choroidal neovascularization. These features result in variable angiographic changes reflective of the complications. Typically, the nummular scars reveal window defects from chorioretinal adhesions and focal RPE and inner choroidal damage. The subretinal fibrotic changes reveal a gradual increase in hyperfluorescence and staining. Histologically, the nummular scars may represent focal absence of RPE and photoreceptors cells, as reported in enucleated eyes of Vogt–Koyanagi–Harada disease. At these sites of RPE damage, retinal glial cells are seen in direct contact with Bruch’s membrane. The subretinal fibrosis reflects proliferated and metaplastic RPE cells devoid of melanin granules and these cells morphologically resemble fibrotic tissue localized to subretinal space. The choroidal and disc neovascularization is rare and these new vessels show leaking of the dye.

INDOCYANINE GREEN ANGIOGRAPHY

As SO primarily involves inflammation of the choroid, indocyanine green angiography (ICGA) can be a good imaging modality to evaluate the choroid and to look for the presence of choroidal infiltrates. The common findings on ICGA for patients with SO are multiple hypocyanescent spots, as against hyperfluorescent spots on corresponding FFA. These spots are likely to be due to cellular infiltration of the choroid and presence of Dalen-Fuchs nodules or overlying edema, based on studies that have correlated these findings histopathologically and found them to be consistent. The presence or absence of these hypocyanescent spots in each phase of ICGA may also give a clue to the type of lesion involved. Various studies have reported the pattern observed, however there are no consistent reports. Bernasconi et al. and Casella et al. described lesions in different stages of SO. While Casella and colleagues reported a pattern of ICG in acute stages of SO, Bernasconi reported two cases, one case each in the acute and chronic stage. Casella correlated the ICG changes in the acute stage with the histopathologic features of enucleated eye with sympathetic ophthalmia. Bernasconi et al. reported persistence of the hypocyanescent areas throughout the intermediate and late phases (Figure 4), with corresponding areas of hyperfluorescence on FFA and yellow atrophic areas on fundus examination, interpreted as likely to be due to chorioretinal atrophy. On the other hand, if the spots fade in the late phase, it was interpreted to be active choroidal space occupying lesions that resulted in late impregnation.
However, Casella et al. reported that, even though the ICGA showed hypocyanescent spots that persisted throughout the phases, correlation with histopathologic findings and FFA revealed that the spots were due to Dalen-Fuchs nodules and not chorioretinal atrophy as described by Bernasconi. Importantly, these hypocyanescent spots are noted to attenuate or disappear after corticosteroid treatment and are consistent with clinical improvement. However, Moshfeghi et al. reported that, even though the hypocyanescent spots disappeared in the intermediate phase, they reappeared in the late phase of ICGA.

**AUTOFLUORESCENCE IMAGING**

Autofluorescence (AF) can be a useful non-invasive imaging modality in patients with SO. AF is a simple and non-invasive procedure, based on the detection of fluorophores, which is mainly represented by lipofuscin in the RPE. Lipofuscin is a byproduct of phagocytosis with accumulation of incompletely degraded products of photoreceptor outer segments and is therefore indicative of the metabolic activity of the RPE in relation to its phagocytic function. It has also been shown to produce oxygen radicals that can cause apoptosis of the RPE cells. Thus, the amount of lipofuscin is a likely indicator of the disease activity and viability of the RPE. As the amount of lipofuscin is positively related to the intensity of AF, hyperautofluorescence represents increased metabolic activity of the RPE, thus predicting dysfunction of the RPE, while hyperautofluorescence typically occurs with the loss of RPE cells. Furthermore, not only can AF aid in the early detection of disease activity, it also allows for the evaluation of the extent of damage, the identification of sequelae such as choroidal neovascularization secondary to inflammation, as well as understand the pathophysiology of the disease.

In a study of a patient with clinically diagnosed SO, Fleischman et al. reported that a petaloid pattern of hyperautofluorescence centered on the optic nerve corresponding to areas of exudative retinal detachment on fundus examination was seen in this patient prior to treatment (Figure 5). Following resolution, speckled areas of hyper- and hypoautofluorescence resembling leopard spots were seen in the previous areas of exudative detachment (Figure 6). This patient underwent enucleation for the contralateral eye and the histology confirmed the diagnosis of SO. However, there are limited studies reporting the application of AF in SO. Nevertheless, various studies have been done regarding the use and pattern of AF in posterior uveitis and specifically VKH disease, which is histopathologically similar to SO. Characteristic patterns of each disease are gradually being observed, however, further studies are required to establish the pattern of AF in posterior uveitis, especially that of SO. The wide-field AF allows for detection of lipofuscin in the periphery that corresponds to RPE health in that area.

![Image of fundus fluorescein angiography and indocyanine green angiogram](image-url)
ULTRASOUND B SCAN

B-scan ultrasonography in SO typically shows diffuse choroidal thickening (in >60% of cases) and in some cases, serous retinal detachment at the posterior pole. Cases of SO have been reported in the literature, where there has been no history of antecedent trauma. The only inciting factor has been some surgical procedure, most commonly vitreoretinal surgery. B-scan ultrasonography also becomes an essential tool in the management of cataract in SO prior to surgery in cases where the retina cannot be visualized due to posterior synechiae or dense cataract (Figures 7 and 8).
In the last few years, technological disconnection from the RPE, the shedding of the outer segments appear elongated (white arrows). A distinctive feature only reported in SO and VKH is the presence, in some cases, of hyperreflective septa (likely fibrin made) crossing the detachment and dividing it in pockets (Figure 7A). As a consequence of the photoreceptors’ disconnection from the RPE, the shedding of the outer segments can be interrupted in the area of fluid accumulation resulting in photoreceptors outer segment elongation (Figure 7B). Such alterations can regress and completely disappear if prompt therapy is started. On the contrary, longstanding fluid leads to irreversible damage of the overlying retina, resulting in cystoid macular edema formation and loss of photoreceptors function, similar to that described in chronic central serous chorioretinopathy. A case of persistent subretinal fluid in SO secondary to a RPE tear has been recently described by the use of SD-OCT.

Although reported just in single cases, choroidal features in the acute phases of SO resemble the widely described alterations found in VKH, including folds, massive thickening and loss of the physiologic architecture of the choroidal layers. During the chronic stage of the disease, atrophic changes have been reported in the choroidal structure, regardless the inflammatory status of the patient. Choroidal thickness has been shown to be a good biomarker for monitoring disease activity in VKH, especially during the chronic stage of the disease. Considering the similarities existing between VKH and SO, a possible role of EDI-OCT-based choroidal thickness assessment in the management of SO patients should hence be speculated, although follow-up studies focusing on the correlation between choroidal changes and SO activity have not been reported in the literature so far.

SD-OCT can also be used to image and follow the evolution of Dalen-Fuchs nodules. These peculiar SO lesions appear as round-shaped hyperreflective areas located at the level of the outer retina and disrupting the RPE, as well as the outer retinal bands (Figure 8A). In response to therapy, the lesions usually regress but RPE disruption can persist (Figure 8B,C).

**OPTICAL COHERENCE TOMOGRAPHY**

Spectral domain optical coherence tomography (SD-OCT) is a non-invasive imaging technique that allows collecting tomographic quasi-histologic scans of the retina and RPE. In the last few years, technological improvements in the SD-OCT technology have overcome the limitations of the technique in penetrating ocular tissues and nowadays enhanced depth imaging (EDI-OCT) is available for the study of ocular structures deeper than the RPE such as the choroid and the sclera. Today, SD-OCT and EDI-OCT are widely used in the diagnosis and the management of several retinal diseases and uveitis allowing the detection of generic inflammatory changes, such as cystoid macular edema or choroidal thickening as well as distinct features of specific uveitis entities.

SO shows peculiar findings on SD-OCT and EDI-OCT during the whole course of the disease. The acute phase is characterized by multiple serous detachments of the neurosensory retina similar to those described in VKH disease. Such fluid accumulations appear on SD-OCT as empty spaces between the neurosensory retina and the underlying RPE (Figure 7). A distinctive feature only reported in SO and VKH is the presence, in some cases, of hyperreflective septa (likely fibrin made) crossing the detachment and dividing it in pockets (Figure 7A). As a consequence of the photoreceptors’ disconnection from the RPE, the shedding of the outer segments can be interrupted in the area of fluid accumulation resulting in photoreceptors outer segment elongation (Figure 7B). Such alterations can regress and completely disappear if prompt therapy is started. On the contrary, longstanding fluid leads to irreversible damage of the overlying retina, resulting in cystoid macular edema formation and loss of photoreceptors function, similar to that described in chronic central serous chorioretinopathy. A case of persistent subretinal fluid in SO secondary to a RPE tear has been recently described by the use of SD-OCT.

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**Optical Coherence Tomography Angiography**

The latest generation of OCT, named angio-OCT (OCTA), allows the visualization of vascular structures without dye injection. Up to now, there are no reports in the literature describing OCTA findings in SO. OCTA cannot visualize retinal barriers (inner/outer) breakdown, thus it could be less useful than fluorescein or indocyanine green angiography for the detection of inflammatory changes. Nevertheless, the capability of OCTA in visualizing occlusive and inflammatory alterations of the choriocapillaris has been recently reported in VKH disease. This study has reported 10 eyes of patients with acute VKH disease who underwent multimodal imaging including OCTA to evaluate retinochoroidal vasculature. They
observed multiple foci of choriocapillaris flow-void that correlated with ICGA and showed a decrease in size and number on treatment. Similar lesions had been described in SO by invasive imaging techniques in the past, thus a possible role of OCTA in the identification of such alterations could be considered, as SO resembles VKH very closely.

Besides the areas of capillary flow-void, OCTA is also useful in detecting accompanying choroidal neovascularization that may occur as a complication during the chronic stage of the disease. In a recent study, OCTA has been reported to be more sensitive than conventional imaging techniques including fluorescein angiography and OCT in detecting choroidal neovascularization in patients with punctate inner choroidopathy and multifocal choroiditis. Thus, it may also be useful for detection of the choroidal neovascularization in SO.

In conclusion, the diagnosis of sympathetic ophthalmia is generally based on the clinical impression and supported by multimodal imaging. SO is suspected in a patient who presents with inflammation in the opposite eye following ocular trauma or surgery. The initial presentation may be in the form of serous retinal detachments with minimal/absent anterior segment inflammation. Fluorescein angiography features are characteristic and may help in making the diagnosis. Enhanced depth imaging on OCT, showing thickened choroid with overlying serous detachment, substantiates the diagnosis. Both these features can also be seen on an ultrasound B scan. In patients with typical presentation, the treatment may be initiated based on fundoscopy, fluorescein angiography, and OCT. The disease may be monitored on repeat fundoscopy and OCTs that document reduction of serous detachment, as well as choroidal thickening. OCTA is a newer modality, which appears promising during the acute phase of SO, as well as for monitoring.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.
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