Published in final edited form as:

Retina. 2015 August ; 35(8): 1696–1703. doi:10.1097/IAE.0000000000000506.

Sympathetic Ophthalmia: Clinicopathologic Correlation in a Consecutive Case Series

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Abstract

Purpose—To correlate the clinical course of sympathetic ophthalmia (SO) with the histological and immunohistochemical characteristics of the enucleated inciting eye.

Methods—A consecutive case series with baseline clinical features and subsequent histopathologic findings.

Results—Evaluation of the 16 enucleated inciting eyes (blind and painful) disclosed that 9 of 16 had typical histology fulfilling the criteria for SO of diffuse granulomatous inflammation. Among the 16, 11 sustained previous penetrating trauma, 4 underwent previous eye surgery and one patient presented with an unknown etiology. Patients with atypical histology (7 of 7) were taking corticosteroids at the time of enucleation. Only 2 of 9 patients with typical histology were taking corticosteroids at time of enucleation. At 6 months after enucleation of the inciting eye, 4 of 7 patients with atypical histology had a visual acuity of 20/40 compared to 8 of 8 patients (100%) with typical histology. On a 4-point scale (0 - 3+) the choroidal infiltrate of the 9 histopathologically typical eyes showed an average of 2.5+ CD68 (macrophages), 2.5+ CD20 (B cells) and 1.5+ CD3 (T cells).

Conclusion—Histopathological findings had minimal correlation with the clinical course of SO. Corticosteroid treatment prior to enucleation may influence the pathological confirmation of SO. The predominance of B-lymphocytes and macrophages over T-lymphocytes may represent different stages of the disease process.

Keywords

Sympathetic Ophthalmia; Uveitis; Retina; Clinicopathologic Correlation; Pathology; Immunohistochemistry

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Disclosures: HAA – None

HWF – None

RCY – None

JLD – Santen, Xoma

SRD – None

Introduction

Sympathetic ophthalmia (SO) is a rare disease that manifests with bilateral, diffuse, non-necrotizing granulomatous uveal inflammation and typically occurs after penetrating ocular trauma or surgery. Although the pathogenesis is not completely understood, it is thought to be an autoimmune process that follows systemic exposure to sequestered uveal antigens.¹

Lubin et al reported that the severity of the inflammatory infiltrate in the enucleated correlated directly with the visual acuity of the sympathizing eye.² The cases with mild inflammation retained better vision while those with a more severe choroidal infiltrate had a worse visual outcome. Conversely, Reynard et al reported that histological severity did not correlate with the visual outcome.³ The clinical course of the sympathizing eye was then correlated with the histopathological and immunohistochemical characteristics of the inciting eye in sixteen patients clinically diagnosed with sympathetic ophthalmia. In the current study, all patients underwent enucleation secondary to a blind painful inciting eye.

Methods

The current study is a consecutive, comparative case series. The medical records and evaluation of specimens of enucleated blind painful inciting eyes of 16 patients clinically diagnosed with sympathetic ophthalmia (SO) at the Bascom Palmer Eye Institute between 1987 and 2009 were reviewed. The study was approved by the Internal Review Board at the University Of Miami Miller School Of Medicine, and all procedures were performed in accordance with the 1951 Declaration of Helsinki.

Paraffin sections (8 um) of the globes were obtained from the Florida Lions Ocular Pathology Laboratory and reassessed by ocular pathologist (SRD) for histologic characteristics. Slides were stained with hematoxylin and eosin (H&E) and periodic acid Schiff (PAS). Histologic confirmation was determined by diffuse granulomatous inflammation. Histopathological parameters that were evaluated included involvement of the choriocapillaris, presence of Dalen Fuchs nodules (histiocytes in the sub-RPE space), retinal detachment, scleral canal inflammation and atrophy of the optic nerve.

All the patients were diagnosed with sympathetic ophthalmia based on acute and chronic signs and symptoms of bilateral intraocular inflammation, presence of focal choroidal infiltrates, thickening of the choroid and multifocal areas of leakage on fluorescein angiography and 15/16 had a compatible history of penetrating trauma or intraocular surgery. Treatments included corticosteroid therapy with the addition of one or more additional agents if needed (methotrexate, cyclosporine, cyclophosphamide, infliximab). Clinical data collected included ocular history, visual acuity at 6 months and last clinic examination after enucleation, and use of immunosuppressive drugs or corticosteroids.

Immunohistochemical stains included cell lineage markers CD-3, CD-20, CD-68; and cytokine receptors TNF- α , IL-4, INF- γ , IL-17. A 4-point scale (0 - 3+) was used to compare the intensity of the immunohistochemical stains to a positive control slide graded 3+ supplied by the manufacturer (Abcam: TNF- α , IL-4, INF- γ ; DAKO: CD-3, CD-20, CD-68 and eBioscience: IL-17).

Results

After enucleation, histopathologic evaluation of the 16 inciting eyes disclosed that 9 of 16 fulfilled criteria for sympathetic ophthalmia (Table 1). In these 9 eyes the characteristic histopathologic features were the following: inflammation involving the choriocapillaris was present in 4 of 9 eyes, Dalen-Fuchs nodules were present in 5 of 9 eyes, scleral canal inflammation was present in 7 of 9 eyes and eosinophils within the choroid were present in 9 of 9 eyes. All patients (7 of 7) with atypical histology were taking corticosteroids at the time of enucleation vs. 2 of 9 patients with typical histology. (Figures 1,2)

Clinical data of the 16 patients is summarized in (Table 2). The median follow-up after enucleation was 5.8 years (2 months to 16.2 years). Among the 16 patients 11 sustained previous penetrating trauma, 4 underwent eye surgery and one patient presented with an unknown etiology. At 6 months after enucleation, 4 of 7 patients with atypical histology had a visual acuity of 20/40 compared to 8 of 8 patients with typical histology. There was no correlation between the visual acuity and histological features of SO. At the 6 months follow-up examination, 11 of 11 remaining patients were receiving an immunosuppressive agent, of whom 4 were also receiving oral corticosteroids. The median times from inciting incident to diagnosis of SO and from diagnosis of SO to enucleation were 75 months (2-365 months) and 38.5 days (4 - 95 days) (excluding patient #6) in histopathologically atypical eyes and 25 months (2 - 127 months) and 47 days (1 -209 days) in histopathologically typical eyes respectively.

Results of the immunohistochemical stains are summarized in (Table 3, Figure 3). The infiltrate of the histopathologically typical eyes showed an average of 2.5+ CD68 (macrophages), 2.5+ CD20 (B cells) and 1.5+ CD3 (T cells). There was no consistent pattern of cytokine receptor staining.

Discussion

Treatment with immunosuppressive therapy prior to enucleation may lead to modification of the inflammatory infiltrate.⁴ In the current study, 7 of 7 (100%) patients clinically diagnosed with SO who had atypical histopathology were all treated with corticosteroids prior to enucleation. Two of these patients were treated for less than 2 weeks and still failed to show histopathological characteristics of SO. Thus, corticosteroid treatment prior to enucleation may make the pathological confirmation of SO diagnosis more challenging. Classically SO is described that as a granulomatous inflammation that spares the choriocapillaris. In the current study, and similar to the report by Croxatto et al,⁵ involvement of the choriocapillaris, presence of eosinophils and inflammation within the scleral canals are commonly seen on histopathology of SO.

Sympathetic ophthalmia is a clinical diagnosis based on history of penetrating injury in the inciting eye and presence of panuveitis in the sympathizing eye. Three cases had unusual circumstances regarding the acquisition of the enucleated globes. All three had clinical diagnoses of SO. Patient #2 had a history of a blind painful left eye secondary to trauma that underwent enucleation with atypical histology. One year later, the patient sustained a retinal

tear in the fellow eye that was treated with laser retinopexy. He developed focal lesions of sympathetic ophthalmia surrounding the laser marks. This suggests that the non-enucleated eye was the inciting eye, which is similar to a case report by Nussenblatt and Palestine.⁴ Patient #6 had a long duration of observation prior to enucleation because of parental refusal of enucleation despite a clinical diagnosis of SO. At 45 months, histology was atypical in the enucleated globe. Patient #10 had no known penetrating ocular injury or history of intraocular surgery. Extensive histopathological evaluation showed no evidence of intraocular trauma.

In the current series, patients with atypical histopathological findings did not have less time from diagnosis to enucleation, better final visual acuity or a reduced course of immunosuppressive therapy. Although the histopathological findings had minimal correlation with the clinical course of SO in the cases studied, the ability to detect such changes was limited by small sample size and variable length of follow-up.

Typically, sympathetic ophthalmia is believed to be a T-cell mediated inflammation.⁵ There are reports of predominance of B-lymphocytes within the infiltrates.⁷⁻⁹ In the current study, B-lymphocytes and macrophages were more abundant than T-lymphocytes. This may represent different stages of the disease process and the time at which the enucleation was performed relative to the onset of disease.

T-helper (Th) a subset of T-lymphocytes is further subdivided into Th1, Th2 and Th17 each producing unique cytokines (Th1: IL-2, IFN- γ ; Th2: IL-4, IL-5, IL-13; Th17: IL-17). Furusato et al reported high levels of macrophages (CD68) and Th17 (IL-17) within the granulomatous inflammation and predominance of Th1 cells (IFN- γ) within the non-granulomatous infiltrate.¹⁰ An attempt was made to characterize the inflammatory infiltrates by staining for cytokine receptors for TNF- α , IL-4, INF- γ , IL-17. However, no specific pattern was detected. This was consistent with the predominance of B-lymphocytes and the scarcity of T-cells within the infiltrate. Additionally this may be secondary to staining of cytokine receptors rather than cytokine production.

The limitations of the current study include the small number of patients, the retrospective collection of clinical data, the lack of a control group and the lack of a prospective treatment protocol during this 22-year study. However, the strengths of the study include continued follow-up clinical data on a relatively large cohort of study patients. Additionally, the availability of the corresponding histopathology in SO where enucleation is done infrequently due to advanced modern imaging and treatment options.

In summary, the current study does demonstrate that histopathological findings had minimal correlation with the clinical course of SO. Corticosteroid treatment prior to enucleation may make the pathological confirmation of SO diagnosis more challenging. Involvement of the choriocapillaris, presence of eosinophils and inflammation within the scleral canals are commonly seen on histopathology of SO. B-lymphocytes and macrophages were more abundant than T-lymphocytes. This may represent different stages of the disease process and the time at which the enucleation was performed relative to the onset of disease.

Acknowledgments

Supported in part by Florida Lions Eye Bank, Miami, FL, Center Core Grant P30EY014801 from the National Institutes of Health, Bethesda, Maryland, and an unrestricted grant from Research to Prevent Blindness Inc, New York, New York.

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Figure 1.

Patient # 10. Clinicopathological correlation of sympathetic ophthalmia. (Top left) Early venous phase ICG angiogram (45 seconds) of the right eye showing focal areas of choroidal hypofluorescence consistent with choroidal inflammatory infiltrates. (Top right) Later phase ICG angiogram (15 minutes) showing blockage of underlying choroidal and retinal fluorescence by subretinal fluid, which produces a dark shadow in the Heidelberg angiographer. The focal defects in choroidal staining are still visible. (Middle left) Early fluorescein angiogram (25 seconds) showing pinpoint leaks. There is a suggestion of focal choroidal infiltrates with irregular choroidal filling. (Middle right) Later stage fluorescein angiogram (10 minutes) showing progressive leakage and optic nerve hyperfluorescence. (Bottom left) Histologic section of the left eye with Dalen Fuchs nodules (arrow) located between Bruch's membrane and the retinal pigment epithelium. (H&E 200×) (Bottom right) Histologic section (H&E 200×) of the left eye reveals a thickened choroid composed of lymphocytes, macrophages, epithelioid cells and giant cells.

Figure 2.

Patient #5. Clinicopathological correlation of sympathetic ophthalmia. (Top left) Montage color fundus photo of the right eye with discrete well circumscribed peripheral hypopigmented chorioretinal lesions. (Top right) Histological section of the left globe discloses a mild chronic lymphocytic infiltrate within the choroid. No granulomatous inflammation is identified. (H&E 200×). (Bottom left) Patient #4. Montage color fundus photo of the right eye with peripapillary subretinal whitening and macular exudation with foci of hyperpigmentation. Multiple, peripheral hypopigmented areas are present. (Bottom right) Histological section of the left globe discloses a diffuse mild choroidal lymphocytic infiltrate with no evidence diffuse granulomatous inflammation (H&E 200×).

Figure 3.

Patient #15. Immunohistochemical findings of sympathetic ophthalmia. (Top left) Mild immunohistochemical staining of choroidal T-lymphocytes with CD3. (Top right) Moderate to marked immunohistochemical staining of choroidal B-lymphocytes with CD20. (Bottom left) Moderate to marked immunohistochemical staining of choroidal histiocytes and giant cells with CD68. (Bottom right) Moderate immunohistochemical staining of the retinal photoreceptors with TNF-alpha. (All photos are original magnification $\times 200$.)

Table 1

Histopathological features of sympathetic ophthalmia cases and duration of treatment prior to enucleation.

Patient	Histo-pathology	Diffuse granulomatous Inflammation	Duration of corticosteroid treatment prior to enucleation	Sparing of chorio-capillaries	Presence of eosinophils	Dalen Fuchs Nodules	Scleral canal inflammation	Optic nerve atrophy
1	negative	1	44 days	Yes	No	No	No	Yes
2	negative	0	1 day	Yes	No	No	No	Yes
3	negative	1	6 days	Yes	No	No	No	Yes
4	negative	1	8 months	Yes	No	No	No	Yes
5	negative	1	15 days	Yes	No	No	No	No
6	negative	1	1 month (+MTX)	Yes	No	No	No	Yes
7	negative	1	2 months	Yes	No	No	No	No
8	positive	3	2 days	Yes	Yes	Yes	No	No
9	positive	3	N/A	Yes	Yes	No	No	No
10	positive	3	1 day	No	Yes	Yes	Yes	Yes
11	positive	3	N/A	No	Yes	No	Yes	No
12	positive	3	N/A	No	Yes	Yes	Yes	No
13	positive	2	N/A	Yes	Yes	No	Yes	No
14	positive	2	N/A	Yes	Yes	No	Yes	Yes
15	positive	3	N/A	No	Yes	Yes	Yes	No
16	positive	3	N/A	Yes	Yes	Yes	Yes	No

MTX: Methotrexate

Table 2

Clinical features of sympathetic ophthalmia cases and follow up clinical data.

Patient	Age at SO Diagnosis (years)	Sex	Inciting event	Time from inciting incident to diagnosis of SO (months)	Diagnosis of SO to enucleation (days)	VA at presentation	VA at 6 months	VA at last visit	Post-enucleation treatment	Duration in months	Dose of treatment (if available)	Months of follow up
1	76	M	Trauma	116	59	20/50	20/50	20/400	Corticosteroids	12 m	80 mg taper	12
2	42	M	Laser retinopexy	13	4	20/20	20/15	20/15	Corticosteroids Azathioprine	6 m 12 m	60 mg taper N/A	22
3	68	M	Trauma	365	6	20/25	20/25	20/25	Corticosteroids Azathioprine	3 m 3 m	20 mg taper 100 mg	7
4	53	M	Trauma	9	50	20/40	20/25	20/50	Corticosteroids	18 m	60 mg taper	28
5	77	F	Surgery (PPV)	15	17	20/400	20/200	20/400	Corticosteroids Azathioprine Cyclophosphamide	61m 4 m 32 m	60 mg taper 100 – 125 mg 12.5 – 100 mg	83
6	11	M	Surgery (PPV)	7	1362	20/20	20/20	20/20	Corticosteroids Methotrexate	3m 1m	5 mg taper 2.5 mg	12
7	9	M	Trauma	2	95	20/25	20/30	20/20	Corticosteroids Methotrexate Cyclosporine Infliximab	36 m 82 m 60 m 60 m	25 mg taper 10 – 25 mg 150 – 250 mg 5 mg	144
<i>Overlapping immunosuppression treatment</i>												
8	6	F	Trauma	2	209	CF 6ft	N/A	20/200	Corticosteroids	2 m	40 mg taper	2
9	20	M	Trauma	127	115	20/20	20/20	20/20	Corticosteroids	9 m	80 mg taper	101

Patient	Age at SO Diagnosis (years)	Sex	Inciting event	Time from inciting incident to diagnosis of SO (months)	Diagnosis of SO to enucleation (days)	V/A at presentation	V/A at 6 months	V/A at last visit	Post-enucleation treatment	Duration in months	Dose of treatment (if available)	Months of follow-up
et al.												
10	19	F	Unknown	N/A	14	20/100	20/30	20/30	Corticosteroids Methotrexate	6 m 1 m	80 mg taper 15 mg	12
11	28	M	Trauma	2	12	3/200	20/20	20/200	Corticosteroids	190 m	100 mg taper	206
12	38	F	Trauma	50	22	20/70	20/20	20/25	Corticosteroids Methotrexate Mycophenolate	60 m 60 m 48 m	60 mg taper 7.5 -20 500-1000	156
13	12	M	Trauma	2	30	20/50	20/20	20/20	Corticosteroids	1 m	40 mg taper	197
14	84	M	Surgery (PPV)	8	10	20/200	20/40	20/40	Corticosteroids Azathioprine Mycophenolate	7 m 6 m 2 m	60 mg taper N/A N/A	7
Overlapping immunosuppression treatment												
15	32	F	Trauma	2	1	20/20	20/15	20/15	Corticosteroids Methotrexate Cyclosporine Cyclophosphamide	6 m 48 m 18 m 18 m	80 mg taper 12.5 – 25 mg 200 – 400 mg 50 – 150 mg	73
Overlapping immunosuppression treatment												
16	19	M	Trauma	7	6	20/400	20/20	20/20	Corticosteroids Cyclosporine Methotrexate	36 m 60 m 7 m	100 mg taper 150-300 mg 12.5 – 20 mg	65
Overlapping immunosuppression treatment												

m: months; N/A: not available; PPV: pars plana vitrectomy; VA: visual acuity Trauma = open globe injury

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Table 3

Grade of immunohistochemical staining in enucleation specimens from sympathetic ophthalmia patients compared to a standard grade 3+ control slide.

Patient	Presence of diffuse granulomatous inflammation on histopathology	Steroid at time of enucleation	CD 68	CD 3	CD 20	TNF- α	INF- γ	IL-4	IL-17
8	positive	Yes	2	2.5	3	2	0.5	0.5	0
9	positive	No	2.5	2	3	2	0	0	0
10	positive	Yes	2	1	2.5	1	0.5	0.5	0
11	positive	No	3	1	2.5	2.5	0.5	0	0
12	positive	No	2	1	2	2	0	0.5	0
13	positive	No	2	3	3	2	0.5	0.5	0
14	positive	No	2.5	0.5	1	0	0	0	0
15	positive	No	3	1.5	2.5	3	1.5	0	0
16	positive	No	2	1	2	1	0.5	0.5	0

A standard 4-point scale (0 - 3+) was used to compare the intensity of the immunohistochemical stains to a positive control slide graded 3+ supplied by the manufacturer.

CD 68: marker for macrophages, CD3: marker for T cells, CD20: (marker for B cells), TNF- α : tumor necrosis alpha (marker for non-specific inflammation and necrosis), INF- γ : interferon gamma (marker for T-helper 1), IL-4: interleukin-4 (marker for T2 helper cells), IL-17: interleukin-17 (marker for T-helper 17)