Exudative Retinal Detachment in Ocular Inflammatory Diseases: Risk and Predictive Factors

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• PURPOSE: This study evaluated the risk and risk factors for exudative retinal detachment (ERD) in ocular inflammatory diseases.

• DESIGN: Retrospective cohort study.

• METHODS: Patients with noninfectious ocular inflammation had been followed longitudinally between 1978 and 2007 at 4 US subspecialty uveitis centers. The main outcome measurements were occurrences of ERD and predictive factors.

• RESULTS: A total of 176 of 14,612 eyes with ocular inflammation presented with ERD. Among uveitis cases, Vogt-Koyanagi-Harada syndrome (VKH) (odds ratio [OR] = 109), undifferentiated choroiditis (OR = 9.18), sympathetic ophthalmia (OR = 8.43), primary or secondary panuveitis (OR = 7.09), multifocal choroiditis with panuveitis (OR = 4.51), and "other" forms of posterior uveitis (OR = 16.9) were associated with a higher prevalence of ERD. Among the 9,209 uveitic or scleritic eyes initially free of ERD and followed, 137 incident ERD cases were observed over 28,949 eye-years at risk (incidence rate = 0.47% [0.40%-0.56%/eye-year]). VKH (HR = 13.2), sympathetic ophthalmia (HR = 5.82), undifferentiated choroiditis (HR = 6.03), primary or secondary panuveitis (HR = 4.21), and rheumatoid arthritis (HR = 3.30) were significantly associated with incident ERD. A significant dose-response relationship with the prevalence and incidence of ERD were observed for AC cells and vitreous cell activity. African Americans had significantly higher prevalence and incidence of ERD.

• CONCLUSIONS: Other ocular inflammatory conditions in addition to VKH syndrome and posterior scleritis were associated with increased risk of ERD, indicating that ERD does not necessarily dictate a diagnosis of VKH or posterior scleritis. In addition, the relationship between ERD and inflammatory severity factors implies that inflammation is a key predictive factor associated with developing ERD and requires early and vigorous control. (Am J Ophthalmol 2020;218:279–287. © 2020 Elsevier Inc. All rights reserved.)

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UVEITIS IS A MAJOR CAUSE OF VISUAL IMPAIRMENT worldwide and can cause devastating visual consequences. It has been estimated that, in the United States, 30,000 new cases of legal blindness occur annually as a result of uveitis, representing 10% of new cases of blindness in the United States.[1] Other studies have estimated that uveitis, including infectious causes, accounts for 25% of blindness worldwide.[1,2] Although these estimates may now be high in an era with more effective treatments for uveitis, it is clear that uveitis is an important cause of visual loss globally. Furthermore, uveitis may cause a disproportionately large decrease in workforce productivity as it

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TABLE 1. Prevalence of Exudative Retinal Detachment in the SITE Cohort Study

Characteristic (at Presentation)	Value	ERD Cases (%)	Adjusted OR of ERD (95% CI)[a]
Age	≥35	108 (61.36)	1.00
	<35	68 (38.64)	1.06 (0.72-1.58)
Sex	Males	78 (44.32)	1.00
	Females	98 (55.68)	0.72 (0.50-1.04)
Race	Whites	81 (46.02)	1.00
	African Americans	50 (28.41)	2.83 (1.80-4.44)
	Hispanics	32 (18.18)	4.90 (2.88-8.33)
Type of inflammation, compared with anterior uveitis[a,b]	VKH	69 (39.20)	109.4 (55.67-218.3)
	Retinochoroiditis	4 (2.27)	9.18 (1.52-29.65)
	Sympathetic ophthalmia	2 (1.14)	8.43 (0.60-32.64)
	Primary or secondary panuveitis	26 (14.77)	7.09 (3.16-14.65)
	Multifocal choroid panuveitis	5 (2.84)	4.51 (1.36-16.52)
	Other posterior uveitis	15 (8.52)	16.91 (5.63-35.73)
	Posterior scleritis	7 (3.98)	41.63 (10.04-104.7)
	Necrotizing scleritis	3 (1.70)	8.11 (0.96-27.35)
AC cells	No cell	91 (51.70)	1.00
	0.5+	30 (17.05)	1.54 (0.98-2.41)
	1.0+	14 (7.95)	1.07 (0.57-2.01)
	2.0+	25 (14.20)	2.31 (1.33-4.02)
	3.0+ and greater	16 (9.09)	2.64 (1.30-5.38)
Vitreous cells[a]	No cell	77 (46.39)	1.00
	1.0+	36 (21.69)	1.65 (0.99-2.77)
	2.0+	25 (15.06)	1.43 (0.80-2.55)
	3.0+ and greater	12 (7.23)	2.04 (0.89-4.69)
Vitreous haze[a]	None	117 (74.05)	1.00
	1.0+	29 (18.35)	1.57 (0.95-2.60)
	2.0+	8 (5.06)	1.14 (0.48-2.71)
	3.0+	4 (2.53)	1.18 (0.34-4.12)
Inflammation activity	Inactive	18 (10.34)	1.00
	Slightly active	22 (12.64)	2.93 (1.40-6.15)
	Active	134 (77.01)	5.06 (2.85-9.00)
Band keratopathy	No	164 (93.18)	1.00
	Yes	12 (6.82)	3.14 (1.59-6.22)

AC = anterior chamber.

[a]Analysis was adjusted for type of inflammation, bilateral inflammation, smoking status, age category, and sex. 95% confidence intervals (CI) were derived using Profile. Exudative retinal detachment (ERD), odds ratios (OR), CI, Vogt-Koyanagi-Harada (VKH) syndrome; Profile log likelihood ratio CI was computed using only 1 eye per patient. "Other posterior uveitis" includes acute posterior multifocal placoid pigment epitheliopathy (APMPEE), multiple evanescent white dot syndrome (MEWDS), serpiginous choroiditis, and neuroretinitis. Other forms of uveitis and scleritis not associated with significantly higher risk than anterior uveitis are not listed as potential risk factors but were included in the analysis.

[b]The remaining cases were kinds of inflammation unassociated with ERD, including 21 cases of anterior uveitis (11.93%), 11 cases of intermediate uveitis (6.25%), 4 cases of retinal vasculitis (2.27%), 8 cases of anterior scleritis (4.55%), and 1 case of "other" (0.57%).

often affects working age adult and younger individuals, leading to an economic impact exceeding the proportion of blindness caused.[3] Because structural complications of uveitis can give rise to ocular injury and visual loss, characterization of the risk of and risk factors for the various structural complications is valuable to identify high-risk individuals for clinical interventions.

Exudative retinal detachment (ERD) is potential complication of ocular inflammation. It is a classic feature of Vogt-Koyanagi-Harada (VKH) syndrome and has been known to occur in posterior scleritis.[1] The frequency with which it occurs under other conditions is unclear. This study reports the results of an evaluation of the risk of and risk factors for ERD in a large cohort of patients with ocular inflammatory diseases, including the association with various forms of ocular inflammatory diagnoses.

METHODS

• **DATA COLLECTION:** The Systemic Immunosuppressive Therapy for Eye Disease (SITE) cohort study was a large retrospective study of patients with noninfectious ocular

inflammation managed at 5 tertiary care academic ocular inflammation centers in the United States.[4] One of these centers was omitted from this analysis due to a consultative approach to patient management in which many follow-up visits were conducted at the referring center. The remaining centers primarily followed patients longitudinally. Patient data included in this analysis were derived from patient visits which occurred between 1978 and 2007 inclusively. Institutional review board (IRB) approval was obtained and maintained at all centers throughout the study under the governing IRB at the University of Pennsylvania, the Massachusetts Eye and Ear Infirmary, the Johns Hopkins University School of Medicine, the Oregon Health and Sciences University, and the National Eye Institute. IRB approval permitted data entry by medical record review and linkage to the National Death Index. Permission was granted for waiver of informed consent based on minimal risk with no patient contact. In order to avoid limiting the risk set according to presuppositions, all inflammatory conditions studied in the SITE cohort study were included in an initial investigation of at-risk ERD. These conditions included anterior, intermediate, posterior, and panuveitis (sites of uveitis defined according to the International Uveitis Study Group approach[4]), scleritis, mucous membrane pemphigoid with ocular involvement, inflammatory orbital disease, peripheral ulcerative keratitis, autoimmune cicatricial keratitis, and others. "Secondary" eye inflammation referred to inflammation in the presence of a systemic disease diagnosis, whereas "primary" eye inflammation was localized to the eye without a known associated systemic disease. Subsequently, categories with trivial numbers of ERDs were removed from further analysis. Patients with infectious ocular inflammatory diseases and human immunodeficiency virus infection had been excluded from the parent study. In addition, ERD associated with choroidal neovascularization (CNV) was excluded. All clinicians evaluating these patients had undergone an internal medicine residency, rheumatology fellowship, or an ocular immunology and inflammation fellowship training program, and the objective emphasized that a primary goal in the workup of ocular inflammatory diseases cases was the identification of systemic diseases that might have been associated with ocular inflammation.

The methodology for retrospective data collection and quality assurance has been described previously in detail.[5,6] Briefly, extensive demographic and clinical information was collected from all patients seen at all participating clinical sites, and patients were followed longitudinally over time. Systemic inflammatory diseases and certain markers for diseases (i.e., HLA-B27 and HLA-A29) were identified among these patients, who were tested when indicated according to clinical judgment. A database was developed with strict quality control measurements with data entered into a standardized form.[5] Trained and certified chart reviewers entered the data regarding each eye of every patient at every visit manually into a customized Access software (Microsoft, Redmond, Washington) database. Data included visual acuity, intraocular pressure, slit lamp and ophthalmoscopic clinical findings (including the presence or absence of complications described in Table 1, among others). Quality assurance techniques and cross-checks were used. ERD was ascertained primarily by ophthalmoscopic examination supplemented with diagnostic tests such as ultrasonography, optical coherence tomography, and/or fluorescein angiography when ophthalmoscopic diagnosis was uncertain. Anterior chamber (AC) cells and vitreous haze were graded using the standard numerical method, approximating the methods specified by the Standardization of Uveitis Nomenclature Group as closely as possible in a retrospective study.[7] Measurements of current ocular inflammation (AC cells, vitreous cells, vitreous haze, inflammation activity) were assessed in a time-updated manner for the incidence analysis in order to better capture the relationship between current inflammation and ERD risk. Overall activity of inflammation was graded as active, slightly active, inactive (no signs of inflammation), or missing (unable to tell from the medical record). "Active" was defined as "when there are recorded statements of observing clear signs of inflammation at that particular visit in the ocular tissues. Examples would be statements that the inflammation is "active," that AC or vitreous cells were observed (1+ or higher), the vitreous haze 1+ or higher was observed," and others. "Slightly active" was defined as "activity that is minimally present, described also by terms such as mild, few, trace" and so forth. "Inactive" was defined as having no signs of inflammation and/or explicitly stated as inactive.

Other conditions included in this study as potentially predictive factors for ERD could be divided into specific diseases and classes of disease. Specific diseases included eye diseases (e.g., posterior scleritis, multifocal choroid with panuveitis, sympathetic ophthalmia) and systemic diseases (e.g., Behçet disease, VKH disease, polyarteritis nodosum, systemic lupus erythematosus, scleroderma, Sjögren syndrome, sarcoidosis, Crohns disease, ulcerative colitis, dermatomyositis, polymyositis, juvenile idiopathic arthritis, and relapsing polychondritis). Conditions that did not match established specific disease diagnoses were divided into classes of disease using descriptive names such as undifferentiated choroiditis, panuveitis, and necrotizing scleritis.

The project was conducted in accordance with the principles of the Declaration of Helsinki, with the approval of the governing IRB of each institution, each of which has recognized the protocol as a minimal risk retrospective study with no patient contact and approved waiver of informed consent, allowing all living and deceased patients to be included.

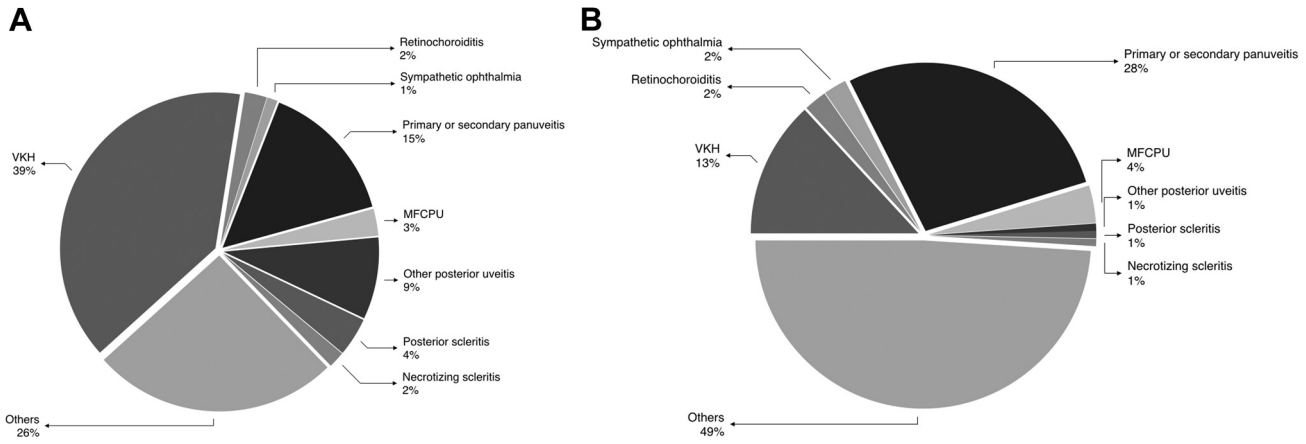

FIGURE 1. Pie chart indicates the percentage of prevalence (A) present at the initial visit and incident (B) exudative retinal detachments associated with various inflammatory disease diagnoses.

• **STATISTICAL METHODOLOGY AND OUTCOME MEASUREMENTS:** Simple and multivariate logistic regression models were used to determine risk factor associations for ERD at presentation by calculating crude and adjusted odds ratios (OR). Generalized estimating equations-derived methods were used to account for inter-eye correlation among the same patients. The prevalence of ERD at baseline was evaluated as the proportion within each at risk group using a per eye perspective.

The incidence of new ERDs was evaluated as the number of events per eye-year of time at risk of the event among those free of the event at the initial visit. Potential risk factors were evaluated using hazard ratios (HRs) and adjusted HRs with 95% confidence intervals (CI), which were calculated using univariate and multivariate Cox proportional hazard models. Smoking was hypothesized to be a risk factor and therefore was included as an adjustment covariate because it has been reported to be associated with an increased likelihood of bilateral ocular inflammation.[8] The outcomes of cases of ERD versus other cases of ocular inflammation from the same diagnostic groups were compared using summary statistics and comparison of incidence rates. The 95% CIs for the HRs and ORs are listed in a subscript form in the results section. As recommended for observational epidemiological studies,[9] *P* values and CIs reported are nominal (not adjusted for multiple comparisons). SAS version 9.3 software (SAS, Cary, North Carolina) was used for all statistical analyses.

The CIs for ORs or HRs were noted using subscript values in order to simplify the presentation of the many numbers reported. For example, "OR = 2.83; 95% CI: 1.80-4.44" was notated as (OR = $_{1.80}2.83_{4.44}$).

RESULTS

• **PREVALENCE OF ERD:** Among a total of 14,612 eyes in the SITE cohort seen for an initial visit, 176 eyes were identified as having ERD, yielding a crude prevalence of 1.2%. ERD cases were rare among cases of mucous membrane pemphigoid (0 of 898) and other forms of inflammation (1 of 323) compared to uveitis and scleritis, so these subpopulations of eyes of patients with ocular inflammation were not studied further.

The majority of patients with ERD in one or both eyes (61.4%) were older than 35 years of age and were female (Table 1). Racial distributions were as follows: white (46.0%), African American (28.4%), and Hispanic (18.2%), among others.

Factors associated with ERD at presentation included African American and Hispanic race/ethnicity (OR = $_{1.80}2.83_{4.44}$; $P < .0001$; and OR = $_{2.88}4.90_{8.33}$; $P < .0001$respectively, each with respect to white participants). Age and sex were not associated with prevalent ERD (OR = $_{0.72}1.06_{1.58;}$ $P = .76$; and OR = $_{0.50}0.72_{1.04}$; $P = 0.082$, respectively).

At the initial visit, among 265 cases of VKH syndrome, 69 cases (26%) had ERD (Table 1), and 196 did not. Similarly, 2 of 61 cases (3%) had sympathetic ophthalmia, 26 of 1,203 cases (2%) had primary or secondary panuveitis cases, 4 of 138 cases (3%) had retinochoroiditis cases, 5 of 356 cases (1%) had multifocal choroid panuveitis cases, 0 of 339 cases (0%) had birdshot retinochoroidopathy cases, 4 of 638 cases (1%) had retinal vasculitis, 8 of 1,488 cases (0.5%) had anterior scleritis, 3 of 106 cases (3%) had necrotizing scleritis cases, 7 of 54 cases (13%) had posterior scleritis, and 15 of 263 cases (6%) had other posterior uveitis, presented at the initial visit with ERD. The distribution of inflammatory conditions associated with ERD at the initial presentation is given in Figure 1, A.

Among uveitis cases, VKH (OR = $_{55.67}109.4_{218.3}$), undifferentiated choroiditis (OR = $_{1.52}9.18_{29.65}$), sympathetic ophthalmia (OR = $_{0.60}8.43_{32.64}$), primary or secondary panuveitis (OR = $_{3.16}7.09_{14.65}$), multifocal choroiditis with panuveitis (OR = $_{1.36}4.51_{16.52}$), and "other" forms

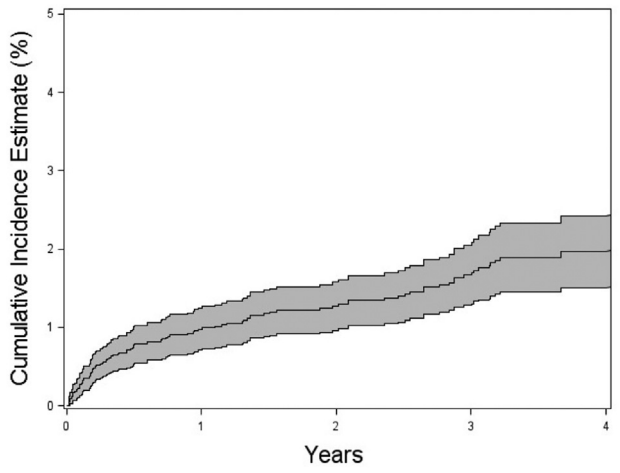

FIGURE 2. Cumulative incidence of exudative retinal detachment in patients with noninfectious uveitis and/or scleritis as a percentage over time; 95% confidence intervals are indicated in gray; 0.3 logMAR is equivalent to doubling of the visual angle. VKH = Vogt-Koyanagi-Harada syndrome.

of posterior uveitis (OR = $_{5.63}16.91_{35.73}$) were associated with a higher prevalence of ERD (Table 1). Posterior scleritis (OR = $_{10.04}41.63_{104.7}$) and necrotizing scleritis (OR = $_{0.96}8.11_{27.35}$) also were associated with a higher prevalence of ERD than anterior scleritis cases.

No significant associations were found between ERD prevalence and spondyloarthropathies (including HLA-B27+ status), Behçet disease, polyarteritis nodosum, granulomatosis with polyangiitis (previously known as Wegener's granulomatosis), other forms of arteritis, systemic lupus erythematosus, Sjogren syndrome, scleroderma, juvenile idiopathic arthritis, rheumatoid arthritis, polymyositis, and dermatomyositis. Additionally, no significant associations were found between ERD and other systemic conditions including Crohn's disease, ulcerative colitis, hypertension, diabetes, and smoking.

Regarding clinical signs of inflammation, a dose-response relationship with the prevalence of ERD was observed for AC cells and vitreous cell activity. Slightly active (OR = $_{1.40}2.93_{6.15}$) and active inflammation (OR = $_{2.85}5.06_{9.00}$) also were associated with a higher prevalence of ERD. A similar pattern was seen when vitreous cells were examined. Higher levels of vitreous cells also tended to have similarly higher odds of ERD, but with the available power, there was no statistically significant association. The presence of band keratopathy also was associated with higher odds of presentation with ERD (OR = $_{1.59}3.14_{6.22}$). On the other hand, vitreous haze was not associated with ERD prevalence. Neither vitreous haze nor ERD were clinical complications of ocular inflammation, including macular edema, epiretinal membrane, iris synechiae, keratic precipitates, and preretinal neovascularization (data not shown) associated with increased prevalence.

• **INCIDENCE AND RISK FACTORS FOR DEVELOPING ERD:** Among the 9,209 uveitic or scleritic eyes that were followed that were initially free of ERD, 137 incident ERD cases were observed over 28,949 eye-years at risk (incidence rate = $_{0.004}0.0047_{0.0056}$%/eye-year) (Figure 2). African American race was significantly associated with a higher incidence of ERD (HR = $_{1.05}1.62_{2.48}$). However, patients younger than 35 years old (HR = $_{0.99}1.50_{2.28}$) and females versus males (HR = $_{0.71}1.09_{1.66}$, respectively) were not associated with an altered incidence of ERD.

The distribution of inflammatory conditions associated with ERD incidence is given in Figure 1, B. Among the ocular inflammatory diagnoses, only VKH (HR = $_{5.87}13.15_{29.47}$; $P < .0001$), sympathetic ophthalmia (HR = $_{1.73}5.82_{19.54}$; $P = .0012$), undifferentiated choroiditis (HR = $_{1.87}6.03_{19.46}$; $P = .0042$), and primary or secondary panuveitis (HR = $_{2.39}4.21_{7.40}$; $P < .0001$) were significantly associated with incident ERD. Other ocular diagnoses and clinical features, including scleritis, multifocal choroiditis, birdshot retinochoroiditis, retinal vasculitis, epiretinal membrane, choroidal neovascularization, retinal vascular sheathing, and retinal vascular occlusion were not significantly associated with incident ERD.

Among all the systemic inflammatory diagnoses examined, only rheumatoid arthritis (HR = $_{1.43}3.30_{7.63}$; $P = .0042$) was associated with a higher incidence of ERD, after adjusting for other factors, and this association was not replicated in the prevalence analysis. Further assessment of this issue is needed before determining this is a robust association. The spondyloarthropathies (including HLA-B27+ status), Behçet disease, polyarteritis nodosum, granulomatosis with polyangiitis, other forms of arteritis, systemic lupus erythematosus, scleroderma, Sjögren syndrome, sarcoidosis, Crohn's disease, ulcerative colitis, dermatomyositis, polymyositis, juvenile idiopathic arthritis, and relapsing polychondritis were not significantly associated with incident ERD; neither were hypertension, diabetes, and smoking significantly associated.

The incidence analysis demonstrated an even stronger relationship between (time-updated) inflammatory activity and ERD risk than the prevalent ERD analysis, with a clear dose-response relationship, with increasing ERD incidence observed with both increasing time-updated AC and vitreous cell grade (Table 2). Slightly active ($HR_{1.86}3.10_{5.18}$; $P < .001$) and active ($HR_{1.73}2.83_{4.64}$; $P < .0001$) inflammation, again both were associated with ERD when incidence was examined. In contrast with prevalent analysis results, vitreous haze (any level) (HR $_{1.67}2.75_{4.53}$; $P < .0001$) and macular edema (HR $_{1.18}1.97_{3.29}$; $P = .0007$) also were associated with a higher incidence of ERD.

TABLE 2. Incidence and Risk Factors for Exudative Retinal Detachment (ERD) in the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study[a]

Characteristic	Value	ERD Cases	Incidence rate per Eye-Year (95% CI)	Adjusted HR of ERD (95% CI)[b]
Age	≥ 35	72	0.0038 (0.0030-0.0048)	1.00
	< 35	65	0.0065 (0.0050-0.0083)	1.50 (0.99-2.28)
Gender	Male	46	0.0045 (0.0033-0.0061)	1.00
	Female	91	0.0048 (0.0039-0.0059)	1.08 (0.71-1.65)
Race	White	84	0.0039 (0.0031-0.0049)	1.00
	African American	43	0.0086 (0.0062-0.0116)	1.62 (1.05-2.48)
	Hispanic	6	0.0060 (0.0022-0.0131)	0.99 (0.37-2.64)
Type of inflammation[b,c]	VKH	18	0.0460 (0.0272-0.0726)	13.15 (5.87-29.47)
	Sympathetic ophthalmia	3	0.0172 (0.0036-0.0504)	5.82 (1.73-19.54)
	Retinochoroiditis	3	0.0165 (0.0034-0.0483)	6.03 (1.87-19.46)
	Primary or secondary panuveitis	38	0.0132 (0.0093-0.0181)	4.21 (2.39-7.40)
	Multifocal choroid panuveitis	5	0.0057 (0.0019-0.0133)	2.25 (0.76-6.68)
	Other posterior uveitis	1	0.0028 (0.0001-0.0158)	1.05 (0.14-7.97)
	Posterior scleritis	1	0.0093 (0.0002-0.0519)	3.03 (0.56-29.05)
	Necrotizing scleritis	1	0.0043 (0.0001-0.0241)	1.47 (0.20-10.96)
AC cells	No cell	67	0.0029 (0.0022-0.0037)	1.00
	0.5+	30	0.0099 (0.0067-0.0141)	2.54 (1.56-4.13)
	1.0+	22	0.0135 (0.0084-0.0204)	3.46 (1.97-6.06)
	2.0+	13	0.0165 (0.0088-0.0282)	3.61 (1.72-7.59)
	3.0+	3	0.0116 (0.0024-0.0339)	2.63 (0.76-9.17)
	4.0+	2	0.0694 (0.0084-0.2506)	13.59 (3.22-57.28)
Vitreous cells[c]	No cell	63	0.0028 (0.0022-0.0036)	1.00
	0.5+	26	0.0117 (0.0076-0.0171)	2.53 (1.45-4.39)
	1.0+	17	0.0085 (0.0049-0.0136)	1.86 (1.00-3.47)
	2.0+	15	0.0145 (0.0081-0.0239)	2.70 (1.35-5.39)
	3.0+	6	0.0273 (0.0100-0.0594)	4.77 (1.83-12.43)
	4.0+	2	0.0646 (0.0078-0.2333)	13.73 (3.98-47.35)
Vitreous haze[c]	No	89	0.0035 (0.0028-0.0043)	1.00
	Yes	36	0.0159 (0.0111-0.0220)	2.75 (1.67-4.53)
Inflammation activity	Inactive	57	0.0026 (0.0019-0.0033)	1.00
	Slightly active	30	0.0116 (0.0078-0.0165)	3.10 (1.86-5.18)
	Active	50	0.0123 (0.0091-0.0162)	2.83 (1.73-4.64)
Rheumatoid arthritis	Yes	10	0.0088 (0.0042-0.0161)	3.30 (1.43-7.63)
Macular edema	Yes	27	0.0143 (0.0094-0.0208)	1.97 (1.18-3.29)

AC = anterior chamber; SITE = Systemic Immunosuppressive Therapy for Eye Diseases; VKH = Vogt-Koyanagi-Harada syndrome.

[a]All values are those present at cohort entry, except for AC cells, vitreous cells, vitreous haze, and inflammation activity were updated to better assess the relationship between current inflammation and exudative retinal detachment risk.

[b]Analysis was adjusted for type of inflammation, bilateral inflammation, smoking status, age category, and sex. The 95% confidence interval (CI) was derived using the Profile Likelihood CI method. Exudative retinal detachment (ERD); hazard ratio (HR), CI, and AC. "Other posterior uveitis" includes acute posterior multifocal placoid pigment epitheliopathy (APMPEE), multiple evanescent white dot syndrome (MEWDS), serpiginous choroiditis, and neuroretinitis.

[c]Adjusted analysis adjusts for: type of inflammation, bilateral inflammation, smoking status, age category, and gender. 95% CI produced using Profile Likelihood CI method. Exudative retinal detachment (ERD); Hazard ratio (HR), Confidence interval (CI), Anterior chamber (AC). "Other posterior uveitis" includes acute posterior multifocal placoid pigment epitheliopathy (APMPEE), multiple evanescent white dot syndrome (MEWDS), serpiginous choroiditis, and neuroretinitis.

• **IMPACT OF ERD ON VISUAL ACUITY:** From the visit preceding to the first visit with ERD, mean visual acuity dropped 2.8 Early Treatment Diabetic Retinopathy Study (ETDRS)-equivalent lines, and then improved 1.9 lines at the first visit following resolution (Figure 3).These changes were noted to be statistically significant ($P < .0001$).

DISCUSSION

THESE RESULTS INDICATE THAT ERD IS A RARE FINDING IN patients with ocular inflammatory disease, which occurs almost exclusively in the setting of posterior uveitis, panuveitis, and/or scleritis. As expected, presentation with ERD

is most strongly associated with VKH and posterior scleritis and is strongly associated with active inflammation, generally following a dose-response relationship with increasing inflammation. However, several other forms of uveitis and scleritis also are associated with ERD to a lesser degree, and other demographic and clinical characteristics are associated with this finding. Thus, an important number of ERD cases are unrelated to VKH or posterior scleritis, especially ERD cases following initial presentation. The results also confirm the importance of controlling inflammation to avoid or resolve ERD.

Exudative retinal detachments tend to be less common and often have a better prognosis than other types of retinal detachment.[10] ERD is caused by fluid accumulation underneath the sensory retina leading to detachment, providing a straightforward explanation as to why ERD is associated with inflammation in or around this region of the eye. Retinal detachments caused by traction or a retinal break tend to have a poor prognosis if the macula is involved, which is less true for ERD involving the macula. In contrast to ERD, treatment of rhegmatogenous or traction retinal detachment typically is surgical rather than medical. Medical treatment of ERD is possible due to the underlying pathophysiology of ERD, which occurs when either retinal blood vessels or retinal pigment epithelium have been damaged, allowing fluid to accumulate underneath the retina. This is generally due to inflammatory or occasionally neoplastic diseases.[10]

As also previously reported by Rao and associates,[11] VKH syndrome had a strong association with ERD when prevalence was examined. To a lesser extent, there is an association with incident ERD after initial presentation as well. VKH is a multisystem disease which is thought to result from an immune trigger and genetic predisposition leading to an attack on pigment, resulting in diffuse choroiditis, typically with accompanying intraocular inflammation. The severe effect on the posterior segment leads to nonrhegmatogenous exudative or serous retinal detachment, vitreous inflammation, and changes in the retinal pigment epithelium, including focal leakage. Localized ERD results from subretinal fluid accumulation and can be the presenting sign in the acute phase in a large percentage of patients, as confirmed in the present study.[12,13] Histopathological analysis showed lymphocytes underneath the retinal pigment epithelium, epithelioid histiocytes, and multinucleated giant cells.[14] It is important to differentiate true serous retinal detachments from intraretinal fluid accumulation or neurosensory retinal detachment, all of which are well demonstrated by optical coherence tomography, because this distinction has important treatment implications. Anti-inflammatory treatments lead to resolution of intraretinal fluid earlier than subretinal fluid.[15,16] Given the presence of an exudative phase soon after onset of the disease, most VKH cases are diagnosed at presentation as a result of the presence of ERD and the accompanying signs and visual symptoms. The pattern of having an early exudative phase followed by a chronic phase usually without ERD presumably explains the much higher risk of prevalence than incidence of ERD in VKH patients that was observed in the present results.

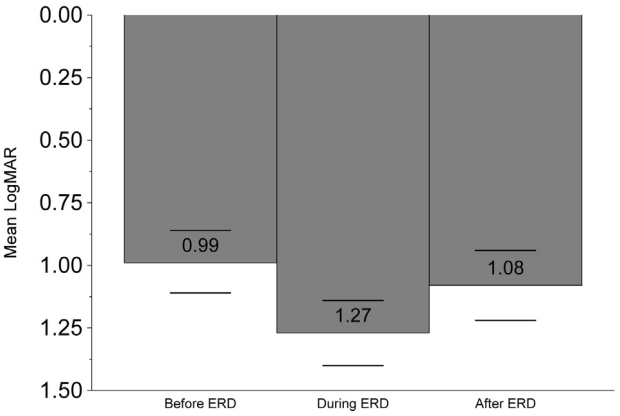

FIGURE 3. Mean logMAR visual acuity in cases of noninfectious uveitis and/or scleritis were given at the visit preceding the incident exudative retinal detachment, at the time exudative retinal detachment was diagnosed, and at the visit following exudative retinal detachment diagnosis.

Sympathetic ophthalmia, a condition sharing many attributes with VKH syndrome, also was associated with lesser degree of excess risk of ERD. Sympathetic ophthalmia is an immune mediated disease.[17] It results from a diffuse granulomatous non-necrotizing inflammatory response that involves the entire uveal tract, which leads to thickening of the posterior choroid. This choroidal, as well as retinal, inflammation presumably leads to ERD in a minority of cases,[18–20] perhaps less often than in VKH because the onset may be less abrupt.

Inflammation in posterior scleritis can extend anteriorly and has been reported to cause several chorioretinal sequelae including cilioretinal artery occlusion, retinochoroidal infarction, and serous retinal detachment.[21,22] Leakage in the retinal pigment epithelium can lead to subretinal fluid and resulting ERD; breakdown of the blood-retinal barrier also may contribute.[23] Presumably a more exuberant inflammatory response in necrotizing scleritis explains the increased prevalence of ERD in necrotizing scleritis cases.

A dose-response relationship between most clinical markers of inflammatory activity and risk of ERD was observed, confirming the expectation that ERD is associated with active inflammation and suggesting that it is likely to improve with control of inflammation (which validates clinical impressions).This pattern also was noted in a previous study in which the authors concluded that a shorter duration of systemic corticosteroids and/or immunosuppressive drug therapy at first and second recurrences of VKH was associated with more clinical features of ERD.[24]

The present study also found that the site of inflammation was important in predicting the risk of presenting ERD with inflammation around the subretinal area as it is associated with a higher risk. For example, posterior scleritis, posterior uveitis, and panuveitis, which involves the posterior uvea, had a high association with ERD. Necrotizing scleritis was also highly associated. Although smoking has been reported to be associated with an increased likelihood of bilateral ocular inflammation, no association was found between smoking status and the prevalence or incidence of ERD.[8] Finally, certain systemic diseases, such as rheumatoid arthritis (associated with scleritis), and markers of severe intraocular inflammation, such as band keratopathy, also were associated with increased risk of ERD in some analyses, which other studies have demonstrated as well.[25] The association between rheumatoid arthritis and ERD may reflect a higher risk of severe scleritis in rheumatoid arthritis representing some residual confounding upon adjustment for scleritis.

The observations of an average drop by nearly three EDTRS lines in visual acuity in association with incident ERD (Figure 3) and the nearly 2 line improvement in visual acuity on average at the visit after ERD was first diagnosed (after anti-inflammatory treatment in most cases) is consistent with the existing concept that ERD is a clinically important complication of inflammatory eye disease that benefits substantially from treatment.

The limitations of this study are related mostly to its retrospective design. Misclassification of ERD may have occurred, and if so, misclassification would have tended to dilute true associations, which would lead to underestimates of risk ratios with true risk factors. Particularly, CNV may lead to localized retinal detachment, which could be confused with inflammatory ERD. In the present study, ERD associated with CNV was excluded. Furthermore, CNV was not associated statistically with ERD in a sensitivity analysis of this study (data not shown), suggesting that inflammatory ERD indeed was identified correctly in most cases, such that misclassification was unlikely to have led to qualitatively inaccurate conclusions. Confusion of ERD with central serous chorioretinopathy could have happened in a small number of cases, but as the 2 entities typically have different findings, it is unlikely that such misdiagnosis happened to a degree sufficient to qualitatively affect results. However, when ERD cases do not respond as expected to corticosteroid therapy, the possibility of central serous chorioretinopathy should be considered. Also, in a retrospective study, subtle cases of ERD may have been missed occasionally, which (if so) would lead to a slight underestimate of the absolute risk of ERD but was not likely to affect predictive factor associations given that false negatives would be very few compared to true negatives. Losses to follow-up also can lead to bias for longitudinal analyses if loss to follow-up is more or less likely in cases at higher risk than other cases. However, given that associations were mostly similar in the incidence and prevalence analyses, it is unlikely that differential follow-up played an important role for qualitative interpretation of results. The results are derived from a tertiary center-based cohort, so results may be more representative of a tertiary than a primary ophthalmology practice experience; however, most ERD cases would be referred for tertiary care. Although the present authors did not directly assess the effects of corticosteroid and other anti-inflammatory treatment on the incidence of ERD, it may be inferred that treatments sufficient to suppressive active inflammation would be beneficial in avoiding ERD. Older retrospective observations may have underestimated disease activity given that newer imaging technologies were not used in the early periods of the study, which might have led to underestimation of the extent of the significant disease activity-outcome associations. Finally, the disease definitions in this cohort were based on earlier description and may not include the latest consensus about defining these diseases.

In summary, ERD, although rare, is an important finding in patients with uveitis and scleritis, which are often associated with substantially reduced visual acuity. Fortunately, however, it is also prone to substantial visual recovery with treatment. This study found that, in addition to VKH and posterior scleritis (the diagnoses most commonly associated with ERD), also sympathetic ophthalmia, undifferentiated choroiditis, primary or secondary panuveitis, necrotizing scleritis, multifocal choroiditis with panuveitis, and "other" forms of posterior uveitis were associated with a higher prevalence of ERD at presentation for tertiary care, indicating that ERD does not necessarily dictate a diagnosis of VKH or posterior scleritis (although ERD is more common in the latter entities). On the other hand, among the ocular inflammatory diagnoses, only VKH, sympathetic ophthalmia, undifferentiated choroiditis, and primary or secondary panuveitis were significantly associated with incident ERD, perhaps because first attacks of inflammatory eye disease may be more severe and/or because inflammation tends to be better managed after initial presentation for tertiary care. African American and Hispanic race/ethnicity also were associated with higher risk of ERD after adjusting for other variables, which requires further investigation. In addition, a dose-response relationship with the prevalence of ERD and incidence was observed for AC cells and vitreous cell activity and also a higher risk of presentation with ERD in association with band keratopathy, confirming a strong relationship of ERD with inflammatory severity. Thus, the study demonstrates that inflammation is a key predictive factor associated with developing ERD and early and that vigorous control of inflammation is necessary to reverse ERD and prevent sequelae as much as possible.

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REFERENCES

1. Nussenblatt RB. The natural history of uveitis. *Int Ophthalmol* 1990;14:303–308.
2. Bodaghi B, Cassoux N, Wechsler B, et al. Chronic severe uveitis: etiology and visual outcome in 927 patients from a single center. *Medicine (Baltimore)* 2001;80:263–270.
3. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. *Br J Ophthalmol* 1996;80:332–336.
4. Bloch-Michel E, Nussenblatt RB. International Uveitis Study Group recommendations for the evaluation of intraocular inflammatory disease. *Am J Ophthalmol* 1987;103:234–235.
5. Kempen JH, Daniel E, Gangaputra S, et al. Methods for identifying long-term adverse effects of treatment in patients with eye diseases: the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) cohort study. *Ophthalmic Epidemiol* 2008;15:47–55.
6. Pasadhika S, Kempen JH, Newcomb CW, et al. Azathioprine for ocular inflammatory diseases. *Am J Ophthalmol* 2009;148:500–509.
7. Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol* 2005;140:509–516.
8. Galor A, Feuer W, Kempen JH, et al. Adverse effects of smoking on patients with ocular inflammation. *Br J Ophthalmol* 2010;94:848–853.
9. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine–reporting of subgroup analyses in clinical trials. *N Engl J Med* 2007;357:2189–2194.
10. American Academy of Ophthalmology (2009). Basic and Clinical Science Course. 12. San Francisco: American Academy of Ophthalmology; 2009-2010:292–299.
11. Rao NA, Gupta A, Dustin L, et al. Frequency of distinguishing clinical features in Vogt-Koyanagi-Harada disease. *Ophthalmology* 2010;117:591–599.
12. Pan D, Hirose T. Vogt-Koyanagi-Harada syndrome: review of clinical features. *Semin Ophthalmol* 2011;26:312–315.
13. Bordaberry MF. Vogt-Koyanagi-Harada disease: diagnosis and treatments update. *Curr Opin Ophthalmol* 2010;21:430–435.
14. Rao N a. Pathology of Vogt-Koyanagi-Harada disease. *Int Ophthalmol* 2007;27:81–85.
15. Ishihara K, Hangai M, Kita M, Yoshimura N. Acute Vogt-Koyanagi-Harada disease in enhanced spectral-domain optical coherence tomography. *Ophthalmology* 2009;116:1799–1807.
16. Lee J, Park S, Lee J. Edema of the photoreceptor layer in Vogt-Koyanagi-Harada disease observed using high-resolution optical coherence tomography. *Korean J Ophthalmol* 2009;23:74–79.
17. Chaithanyaa N, Devireddy SK, Kishore Kumar RV, Gali RS, Aneja V. Sympathetic ophthalmia: a review of literature. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012;113:172–176.
18. Chang GC, Young LH. Sympathetic ophthalmia. *Semin Ophthalmol* 2011;26:316–320.
19. Croxatto J, Rao N, McLean I, Marak G. Atypical histopathologic features in sympathetic ophthalmia. A study of a hundred cases. *Int Ophthalmol* 1982;4:129–135.
20. Lubin J, Albert D, Weinstein M. Sixty-five years of sympathetic ophthalmia. A clinicopathologic review of 105 cases (1913-1978). *Ophthalmology* 1980;87:109–121.
21. Shukla D, Agrawal D, Dhawan A, Ramchandani B. Posterior scleritis presenting with simultaneous branch retinal artery occlusion and exudative retinal detachment. *Eye (Lond)* 2009;23:1475–1477.
22. McCluskey P, Watson P, Lightman S, et al. Posterior scleritis: clinical features, systemic associations, and outcome in a large series of patients. *Ophthalmology* 1999;106:2380–2386.
23. Benson E. Posterior scleritis. *Surv Ophthalmol* 1988;32:297–316.
24. Errera M-H, Fardeau C, Cohen D, et al. Effect of the duration of immunomodulatory therapy on the clinical features of recurrent episodes in Vogt-Koyanagi-Harada disease. *Acta Ophthalmol* 2011;89:e357–e366.
25. Kim R, Lowenstein J. Systemic diseases manifesting as exudative retinal detachment. *Int Ophthalmol Clin* 1998;38:177–195.