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Cytologic Features in Vitreous Preparations of Patients With Suspicion of Intraocular Lymphoma

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Abstract

Intraocular lymphoma may occur, primarily with or without overt parenchymal CNS lymphoma or secondarily from a variety of other lymphomas. The diagnosis is frequently based on cytologic features and/or a limited panel of ancillary techniques.

Twenty-seven cytology samples from the vitreous preparations of 20 patients with clinical suspicion or histopathologic diagnoses of lymphoma were retrospectively reviewed (2007–2011).

Floater and decreased visual acuity were the most common ocular symptoms. Sixteen (of 20) patients had at least one cytology that was “positive” or “suspicious” for lymphoma (F = 10; M = 6, median age = 71 years, range = 52–82). Involvement was limited to the eye in half of the cases (n = 8). Seven patients had CNS involvement, and three had systemic lymphoma. Cytologic specimens were classified as large B cell lymphoma (LBCL) (n = 13), *suspicious for LBCL* (n = 5), *atypical/negative* (n = 5), and *consistent with NK-T cell lymphoma* (n = 1). Three cytologic samples were acellular. Cytologic findings included increased cellularity (high n = 7, *moderate* n = 7), *large to medium* (n = 19) cell size, *marked nuclear irregularities* (n = 12), *frequent apoptosis* (n = 7), *lymphoglandular bodies* (n = 12), and *necrosis* (n = 12). Easily identifiable mitotic figures were present in two cases. CD20 immunocytochemistry performed in 15 cases with available cell blocks/destained cytopins preparations, was confirmatory in 8 cases.

Cytologic evaluation of intraocular lymphoma is possible in vitreous specimens. Extraocular involvement was not present in half of the cases. The most useful cytologic features include increased cellularity, necrosis, and nuclear enlargement. Ancillary immunocytochemical studies are useful and support the morphologic impression in a subset of cases.

Keywords

vitreous cytology; intraocular lymphoma; lymphoma; CNS lymphoma; optical coherence tomography; vitritis; floaters

Intraocular lymphoma encompasses a heterogeneous group of lymphoproliferative disorders that may involve different compartments of the eye. It comprises less than 1% of non-Hodgkin lymphoma. It can be primary or secondary to a systemic lymphoma. Primary intraocular lymphoma (PIOL) is a subset of primary central nervous system lymphoma (PCNSL) which initially presents in the eye with or without overt CNS parenchymal involvement.¹ PIOL is the most common lymphoma of the eye, and the majority represents large B-cell lymphoma (LBCL).² Also, a variety of lymphomas may involve the eye secondarily.^{3,4}

Intraocular lymphoma is the most common malignancy masqueraded in the differential diagnosis of specific clinical presentations, such as uveitis and chronic vitritis.⁵ It is often misdiagnosed as intraocular inflammation which delays treatment and can impact patient survival.^{3,6}

Cytologic assessment of the vitreous often obtained by vitrectomy is the main diagnostic tool for vitreous opacities, including lymphoma.⁷ The diagnosis can be challenging, as it is frequently based on morphologic features only or a panel of ancillary techniques, limited by the scarcity of the materials available from the vitreous. Herein, we report our findings in a four-year period with the cytologic evaluation of intraocular lymphoma in vitreous specimens.

Materials and Methods

The Johns Hopkins pathology database was searched for intraocular cytologies examined in a four-year period (2007–2011). In order to maximize the possibility and opportunity in detecting atypical or malignant cells in the vitreous of patients suspicious of having intraocular lymphoma, the vitreous was submitted in pure, undiluted form. During the vitrectomy (surgery), the vitrectomy system was not primed prior to the collection of the pure vitreous to avoid any fluid being present in the collecting line. Prior to the full vitrectomy and the initiation of any infusion, pure vitreous was obtained and collected directly into a syringe. The syringe containing the pure vitreous, with proper capping, was then sent directly to the laboratory. After the pure vitreous was sent, the infusion was turned on, and the complete vitrectomy was then completed.

A total of 1–2 cc of fluid collected at the time of surgery for in-house specimens was sent fresh to the laboratory. Cytospins were prepared, fixation performed in 95% ETOH, and stained with a standard Papanicolaou procedure which usually yields 1–2 slides for evaluation in these samples. We chose this procedure because it provides excellent cytologic detail, and is very useful in the evaluation of a spectrum of neoplastic, inflammatory, and infectious processes that may involve the vitreous. Cell block preparations were performed when sufficient material was available, and cells were available for evaluation in seven

cases. All available cytology slides were retrospectively reviewed by two of the authors (EFR, FJR). Among 68 cytologic specimens, 27 were obtained from 20 patients with clinical suspicion or histopathologic diagnosis of lymphoma at intra and/or extraocular sites. Features evaluated and scored included cellularity (low, moderate, high), average cell size (large/medium, small), nuclear irregularities (mild/moderate, marked), pleomorphism (mild/moderate, marked), mitotic activity (brisk, non-brisk), presence of lymphoglandular bodies (present, absent), apoptosis (absent, mild, marked), and necrosis (present or absent). In a subset of cases, immunohistochemical stains for CD3 (PS1 clone, Lecia Microsystems, prediluted), CD20 (L26, Ventana, Prediluted), and CD68 (KP1 clone, DAKO, 1:4,000) were performed on cell blocks or destained smears depending on material availability.

All studies were performed under Institutional Review Board (IRB) approval, and following established ethical guidelines.

Results

Demographics

Demographic and clinical findings are summarized in Table I. We identified 16 (of 20) patients with a cytologic diagnosis of “positive,” “consistent with,” or “suspicious” for lymphoma (F = 10; M = 6, median age = 71 years, range = 52–82). Seven patients had sequential cytologies.

Clinical Presentation

Among the patients, five were seen at the Wilmer Eye Institute by one of the authors (QDN) for management of their visual complaints. Floaters and decreased visual acuity were the most common symptoms. On examination, patients initially presented with keratic precipitates, hypopyon, anterior chamber cells and flare, vitreous cells, and/or macular edema. Three patients had the diagnosis of extraocular lymphoma prior to ocular symptoms, thereby contributing to the suspicion of intraocular lymphoma. The other two patients were initially misdiagnosed with uveitis. Vitrectomies of all five patients were diagnostic of LBCL. The patients were treated with systemic methotrexate and rituximab, as well as intravitreal methotrexate when indicated.

One patient suffered rapid deterioration of visual acuity in the eye previously diagnosed with PIOL. The suspicion of superimposed infection was raised, considering the rapidity of vision loss and his status of immunosuppression with rituximab. However, PCR of ocular fluid was negative for infectious agents while cytology of the vitreous revealed that it was a recurrence of PIOL.

Optical Coherence Tomography

Spectral-domain optical coherence tomography (SD-OCT) of these eyes with intraocular lymphoma followed longitudinally showed the presence of different features including macular edema, pigmented epithelium following detachment, and subretinal fluid. Abnormal hyper-reflective signals ($n = 5$) appeared as dots, nodules, and bands. An increase in the hyper-reflective signal was also observed with disease progression.

Cytology

Cytologic findings are summarized in Table II and Figures 1–3. Seven patients had associated CNS involvement, and three systemic lymphoma (natural-killer T cell lymphoma ($n = 1$), LBCL ($n = 2$)). Cytologic specimens were categorized as positive for lymphoma ($n = 14$) (Fig. 1), suspicious for lymphoma ($n = 5$) (Fig. 2), or atypical/negative ($n = 5$) (Fig. 3). Three cases were acellular. Findings included increased cellularity (high $n = 7$, moderate $n = 7$), large to medium ($n = 19$) cell size, marked nuclear irregularities ($n = 12$), frequent apoptosis ($n = 7$), lymphoglandular bodies ($n = 12$), and necrosis ($n = 12$).

Immunocytochemistry

CD20 Immunocytochemistry, performed in 15 cases with available cell blocks ($n = 7$) or destained cytopsins ($n = 8$), demonstrated large CD20 positive cells in eight (of eight cases) in the positive LBCL group, and three (of three) in the suspicious group, with numerous associated CD68 macrophages in two (of three). CD20 was negative in two (of three) cases in the atypical/negative group, and in one case non-contributory due to tissue exhaustion. The single case of NK lymphoma demonstrated CD3/CD56 positive neoplastic cells.

Flow Cytometry

Flow cytometry results supported the diagnosis of LBCL in two (of three) cases in the positive group (one case was not successful secondary to low cellularity).

Discussion

The vitreous humor is a lucent extracellular gel, with a complex composition of collagen, proteins, hyaluronic acid, and water, filling the posterior segment of the eye, between the lens and the retina.⁷ Very few cells are normally present and they are predominantly in the cortex and consist of hyalocytes of Ballazs, and glial cells.⁸

Several terms are used to describe vitreous abnormalities; vitreous opacities refer to visible structures in the vitreous gel. Vitreous opacity was traditionally divided in two main etiologic categories: congenital and acquired. With diagnostic advancements and improvement of understanding of the etiology, acquired vitreous opacities have been reclassified as genetic, inflammatory non-infectious, inflammatory infectious, inflammatory iatrogenic, degenerative (vitreous detachment), traumatic, neoplastic, and idiopathic.⁷

PIOL is a unique lymphoproliferative disorder that affects immune privileged sites such as the retina, vitreous, and optic nerve. In many instances, it masquerades as uveitis⁵ and may be initially mistreated as one of the inflammatory conditions with corticosteroids or antiviral medications. However, a prompt diagnosis of lymphoma and proper treatment is imperative since most patients with PIOL have or eventually will have involvement of the central nervous system, which may yield a poor prognosis.^{3,9} From 65 to 90% of patients presenting with PIOL will develop intracranial lymphoma usually within 29 months.^{3,10} The incidence of PCNCL has increased over the last three decades, on both immunodeficient and immunocompetent patients, and 15–25% of the patients have intraocular involvement.^{3,4}

Evaluation of patients with intraocular lymphoma may include several imaging studies such as ultrasonography, fluorescein angiography, optical coherence tomography, and magnetic resonance imaging. Slit-lamp examination may be normal, and anterior segment findings are often not observed or may show mild anterior inflammation with flare cells and keratoprecipitates. In the posterior segment, vitreous cells and haze are the most characteristic findings and are present in the majority of the cases.^{10,11} Nevertheless, cytological examination of the vitreous is the main diagnostic tool. The specimen can be obtained by different techniques. Fine-needle aspiration (FNA) and pars plana vitrectomy are two common methods. During FNA, the vitreous fluid is aspirated into a syringe via a 21- to 25-gauge needle. Artifacts caused by mechanical disruption of cell structures are not usually present. The main disadvantage is a limited sample amount. Pars plana vitrectomy is now the preferred method for vitreous biopsy.^{9,11} Although it is a surgical procedure, in symptomatic patients it can be both diagnostic and therapeutic, as it leads to improvement in vision by clearing the hazy vitreous. It also maximizes the amount of sample obtained, facilitating cytologic analysis and ancillary techniques. Important steps to avoid artifacts include gentle manipulation of the sample and processing the material as soon as possible. A high false negative rate is expected if these recommendations are not followed.⁹⁻¹¹

The main diagnostic problems that the pathologist may face with these specimens is to confirm or exclude the possibility of intraocular malignancy or rule out an infectious process,¹² as well as to confirm or exclude the possibility of a vitreous hemorrhage caused by intraocular neoplasia. From the pathologist point of view, the vitreous sample can be divided in two main categories: acellular and cellular specimens. In cellular vitreous samples, two important considerations include inflammation and lymphoma involvement. Inflammatory non-infectious vitreous fluids are predominantly composed of lymphocytic infiltrates, usually CD4 positive T cells. Condensed vitreous strands admixed with hyalocytes, macrophages, monocytes, plasma cells, and neutrophils may be present in varying proportions.

A study by Zhai et al. correlating cytologic findings and the final clinical diagnosis reported that in patients whose cytologic specimens were predominantly composed of macrophages or lymphocytes, the most common final diagnosis was intraocular inflammatory process of uncertain etiology. Other diagnoses included viral endophthalmitis, toxoplasmosis, non-malignant intraocular hemorrhage, retinal detachment/epiretinal membrane, and lymphoma.¹³

The diagnosis of IOL can be challenging. The samples have scarce cellularity, and the neoplastic cells are often mixed with non-neoplastic inflammatory cells such as macrophages, small mature lymphocytes, and cellular debris. The non-neoplastic cells can outnumber the malignant cells, increasing the diagnostic difficulties. The neoplastic cells are very fragile, and disruption results in artifacts. Pre-procedure steroids may induce tumor necrosis. These features may affect diagnostic assessment of cases.^{12,14,15}

The main cytologic features of malignant lymphoid infiltration in our study were increased overall cellularity and necrosis. The abnormal lymphocytes form a poorly cohesive population with enlarged nucleoli and irregular nuclear contours. Our findings compare

favorably with those of Farkas et al. who identified hypercellularity (11 of 13 cases) and necrosis (9 of 13 cases) in their samples.¹⁵ Ancillary techniques, particularly immunocytochemical studies can help in the differential diagnosis and optimal classification of the neoplasm.^{2,12,14–17} In our study, CD20 immunocytochemistry was helpful in confirming the morphologic impression, either in destained cytologic smears or in embedded cell blocks.

In summary, our study highlights the utility of cytologic evaluation of vitreous specimens in the diagnosis of intraocular lymphoma. Clinicians should have an appropriate threshold in having the vitreous biopsied and carefully evaluated in patients where intraocular lymphoma is in the differential diagnosis. Pathologists who encounter these unique specimens should also be aware of the cytologic features of intraocular lymphoma, since the main challenge is the scant amount of material often obtained from this site limiting the extent of ancillary testing possible.

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Fig. 1.

Cytologic features of intraocular lymphoma. Clusters of large neoplastic lymphoid cells were a feature of a subset of positive cases (Papanicolaou stain 600 $\times$) (A), while in others the neoplastic cells were distributed singly. Mitotic figures were found in some cases (arrow) (Papanicolaou stain 600 $\times$) (B). Areas of necrosis were a feature mostly of positive cases, particularly when extensive (Papanicolaou stain 200 $\times$) (C). Cell blocks were obtained in a subset of cases, particularly those with high cellularity (H&E 200 $\times$) (D), and facilitated confirmatory immunocytochemistry (CD20 400 $\times$) (E). Brain involvement was present in a subset of cases before or after intraocular diagnosis (H&E 400 $\times$) (F).

Fig. 2.

Cytologic features of cytologies suspicious for intraocular lymphoma. A case suspicious for intraocular lymphoma, characterized by large, abnormal lymphoid cells (arrows) in a reactive, histiocytic background (Papanicolaou stain 600 $\times$) (**A**). In another case cellularity was very low, but large lymphoid cells with macronucleoli were suggestive of lymphoma (arrowhead points to a normal sized lymphocyte for comparison) (Papanicolaou stain 600 $\times$) (**B**).

Fig. 3.

Cytologic features in atypical/negative cases. Atypical/negative cases were characterized by inflammatory infiltrates containing histiocytes and small lymphocytes (Papanicolaou smear 600×) (**A**), or by the presence of scattered small to medium sized mononuclear cells lacking significant atypia (Papanicolaou smear 200×) (**B**). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Demographics and Clinical Findings of Study Patients

Table 1

Patient	Age	Sex	Symptoms	Slit-lamp and Fundusoscopic Examination	Immunosuppression/other illnesses	History of lymphoma	Original and subsequent cytologies	Ancillary Techniques
1	80	F	Scotomata, light head, mild left side weakness, floaters	OD: 3+ vitreous cells and haze	No	CNS LBCL 2 years prior	LBCL	ND
2	56	F	Blurred vision	OD: 3+ vitreous cells, clumps of opacities OS: 2+ vitreous cells, clumps of opacities, solitary hypopigmented lesions	No	CNS LBCL diagnosed after eye cytology	Specimen 1: LBCL Specimen 2: Negative	1-Flow cytometry: light chain restriction 2-IHC in cell block: CD20–, CD68–
3	75	M	Floaters and vision loss, unilateral, foreign body sensation	OS: Fine keratic precipitates, 1+ anterior chamber cells, 1+ flare; 3+ vitreous cells with vitreous debris, disc edema, hemorrhages at the border of the disc, several foci of retinal edema	No	No	Specimen 1: LBCL Specimen 2: Suspicious for LBCL	1-IHC: CD 20+, CD3–, KI-67=50% 2-IHC in cell block: CD20+, CD68+histiocytes
4	63	F	Pain, “redness”. Blurred vision	OS: Hypopyon	No	NK-T cell lymphoma of nasal cavity, palate, lymph nodes	Consistent with NK-T cell lymphoma	IHC: CD3+/CD56+
5	75	F	Blurred vision, floaters, photosensitivity	OU: 2+ vitreous cells and debris, RPE changes in the foveal center	Rheumatoid arthritis and diabetes melitus	No	Specimen 1: Suspicious for lymphoma Specimen 2: Atypical	ND
6	56	M	Decreased visual acuity	OS: subtle yellowish chorioretinal lesions, old vitreous hemorrhage	No	No	Suspicious for neoplasm/lymphoma	Flow cytometry not contributory

Patient	Age	Sex	Symptoms	Slit-lamp and Funduscopic Examination	Immunosuppression/other illnesses	History of lymphoma	Original and subsequent cytologies	Ancillary Techniques
7	57	F	Decreased visual acuity, blurred vision, floaters	OS: 3+ vitritis with cells deposited on the posterior lens capsule	No	CNS LBCL	Acellular	ND
8	76	F	Floaters, inferior blackening of vision	OD: 0.5+ anterior chamber cells; 2+ vitreous cells and, 1+ vitreous haze OS: 1+ pigmented vitreous cells, 1+ red blood cells	No	No	Consistent with LBCL	IHC: CD20+
9	66	F	Worsening bilateral vision	OU: keratic precipitates; OS: 0.5+ anterior chamber cells, 2+ vitreous cells and haze	No	LBCL involving neck region	Consistent with LBCL	IHC: CD20+
10	61	F	Floaters, dizziness	OD: 1+ vitreous cells and haze OS: 2+ vitreous cells and haze, optic disk swelling, vascular sheathing along arteries and veins	Renal transplant	No	Negative	ND
11	82	M	Decreased VA	NA	No	No	Atypical/chronic inflammation	IHC: CD20 not contributory
12	56	F	Blurred vision, decreased visual field, bilateral weakness	OU: 1+ vitreous debris, mild pigmentary changes in the fovea; few drusen (<6) in the macula	Crohn disease	No	Specimen 1: Acellular Specimen 2: Acellular	ND
13	78	F	Decreased VA and floaters	OD: Stellate keratic precipitates	No	No	Specimen 1: Suspicious for LBCL Specimen 2: LBCL	1-IHC CD20+ 2-IHC in cell block CD20+

Patient	Age	Sex	Symptoms	Slit-lamp and Funduscopy Examination	Immunosuppression/other illnesses	History of lymphoma	Original and subsequent cytologies	Ancillary Techniques
14	79	F	NA	OU: 2+ vitreous cells OU: 2+ vitreous cells NA	No	No	LBCL	IHC: CD20+, CD3-; flow cytometry: light chain restriction
15	64	M	Blurred vision	OD: 1+ vitreous cells and 2+ vitreous haze OU: Yellowish chorioretinal lesions in the inferotemporal quadrant	No	Systemic LBCL	LBCL	IHC: rare CD20+ cells
16	72	M	Decreased VA, watery eye, blurred vision, bilateral	OD: 2+ vitreous cells yellowish chorioretinal lesions OS: 0.5+ vitreous cells	No	CNS LBCL prior	Specimen 1: LBCL Specimen 2: LBCL	1-IHC in cell block CD20+, CD3+ (rare)
17	63	F	Decreased VA, floaters, redness, flashes	OD: 2+ vitreous cells; hypopigmented retina lesions OS: 2+ vitreous cells	No	No	Specimen 1: Suspicious for LBCL Specimen 2: Negative	1-IHC CD20+ (rare), CD68-2-IHC in cell block: CD20-, CD68+ (rare)
18	70	M	Blurred vision and floaters	OU: Large sheets of vitreous cells	No	CNS LBCL 3 years prior	LBCL	ND
19	74	F	Blurred vision	OD: 3+ vitreous cells OS: 1+ anterior chamber cells; 4+ vitreous cells	No	CNS LBCL by imaging	LBCL	ND
20	52	F	Blurred vision, floaters, unilateral	OD: 4+ vitreous cells, sheets of vitreous cells, peripapillary atrophy, significant macular edema, deep yellow creamy	No	CNS LBCL 1.5 years prior	Consistent with LBCL	1-IHC in cell block: CD20+, CD3-; CD68+ histiocytes

Patient	Age	Sex	Symptoms	Slit-lamp and Funduscopy Examination	Immunosuppression/other illnesses	History of lymphoma	Original and subsequent cytologies	Ancillary Techniques
				chorioretinal lesions; chorioretinal lesions; OS: peripheral chorioretinal lesions				

F: Female, M: Male, OD: Right Eye, OS: Left Eye, OU: Both Eyes, VA: Visual Acuity, LBCL: large B-cell lymphoma, CNS: central nervous system, ND = not done.

Table II**Cytologic Findings by Category**

N (%)	Positive 14 (52)	Suspicious 5 (19)	Atypical/Negative 5 (19)	Acellular 3 (11)
Cellularity				NA
High	6 (43)	1 (20)	0	
Mod	4 (29)	1 (20)	2 (40)	
Low	4 (29)	3 (60)	3 (60)	
Cell size				NA
Medium/Large	14 (100)	4 (80)	1 (medium)(20)	
Small	3 (21) ^a	1 (20)	4 (80)	
Cell distribution				NA
Single	11 (79)	5 (100)	5 (100)	
Single and cluster	3 (21)	0	0	
Nuclear irregularity				NA
Marked	10 (71)	2 (40)	0	
Mild-Mod	4 (29)	3 (60)	3 (60)	
None			2 (40)	
Pleomorphism				NA
Marked	7 (50)	0	0	
Mild-Mod	7 (50)	4 (80)	3 (60)	
Absent		1 (20)	2 (40)	
Mitotic Activity				NA
Brisk	1 (10)	1 (20)	0	
Non-brisk	9 (90)	4 (80)	5 (100)	
Lymphoglandular bodies				NA
Present	8 (57)	4 (100)	0	
Absent	6 (43)		5 (100)	
Macrophages/Histiocytes				NA
Present	10 (77)	3 (60)	4 (80)	
Absent	3 (23)	2 (40)	1 (20)	
Apoptosis				
Marked	6 (43)	1 (20)	0	
Mild	4 (29)	2 (40)	1 (20)	0
Absent	4 (29)	2 (40)	4 (80)	
Necrosis				
Present	8 (67)	1 (25)	0	
Present on cell block only	2 (17)	1 (25)	0	0
Absent	2 (17)	2 (50)	5 (100)	

^a A component of small lymphoid cells was present in addition to a large cell component.