Vitreoretinal Lymphoma

A 20-Year Review of Incidence, Clinical and Cytologic Features, Treatment, and Outcomes

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Objectives: To determine the incidence and clinical and cytologic diagnostic accuracy of vitreoretinal lymphoma (VRL) and to evaluate its clinical features, management, and outcomes in a cohort of patients who underwent diagnostic vitrectomy.

Methods: Retrospective medical record review of 463 diagnostic vitrectomy specimens from 430 patients collected from October 1, 1990, through December 31, 2010, from Vancouver General Hospital and the British Columbia Cancer Agency.

Results: A total of 22 patients were diagnosed as having VRL with a preoperative clinical diagnostic sensitivity of 77%, specificity of 73%, positive predictive value of 13%, and negative predictive value of 98%. The cytologic diagnostic sensitivity was 87% (27 of 31 specimens). The incidence of VRL in British Columbia doubled from 1990 to 2010, with a final incidence of 0.047 cases per 100,000 people per year. The mean age at diagnosis was 66 years. Seventeen patients (77%) were women. The initial diagnosis of lymphoma was VRL in 19 patients (86%), of whom 7 (37%) had concurrent central nervous system lymphoma. Recurrent disease was found in 11 patients. Large B-cell lymphoma was diagnosed in 20 patients (91%). The median progression-free survival was 11 months, and the median survival was 33 months from the initial diagnosis.

Conclusions: Vitreoretinal lymphoma remains a clinical diagnostic challenge. Early clinical suspicion with subsequent diagnostic vitrectomy for cytologic analysis and collaboration with the oncology department is critical to appropriate and prompt staging and treatment. More interdisciplinary studies are required to further characterize VRL and maximize the therapeutic options, thus improving the morbidity and mortality associated with the disease.


Vitreoretinal lymphoma (VRL), formerly known as primary intraocular lymphoma (PIOL), is a rare subtype of primary central nervous system lymphoma (PCNSL). The disease is usually a high-grade, malignant, large B-cell, non-Hodgkin lymphoma. The prognosis of VRL remains poor and is associated with an overall survival time of 3 years after diagnosis. Often masquerading as idiopathic uveitis, VRL may be misdiagnosed as intraocular inflammation and treated with corticosteroids. Given the aggressive nature and poor prognosis associated with this malignant neoplasm, prompt diagnosis of VRL is critical to ensure appropriate referral and treatment.

Given the lack of clinical pathognomonic findings, the diagnosis of VRL is difficult and requires malignant cells or tissue, often collected by means of diagnostic vitrectomy. Owing to the paucity of malignant cells in the vitreous, the difficulty of distinguishing malignant cells from inflammatory lymphoid infiltrates, and the fragility of lymphoma cells, a definitive diagnosis of VRL can be challenging and depends heavily on the local pathologist’s experience and expertise. Additional diagnostic tests include flow cytometry, immunohistochemistry, and molecular and cytokine analysis. These tests are available as an adjunct to cytopathology to further support the diagnosis of VRL, thus increasing the diagnostic sensitivity and specificity.

We reviewed all cases of VRL diagnosed by means of vitreous cytology in British Columbia during the past 20 years. We sought to determine the accuracy of clinical and cytologic diagnosis of VRL and the incidence of VRL and to evaluate the...
clinical features in a cohort of patients who underwent a diagnostic vitrectomy.

**METHODS**

After institutional review board approval was obtained from the University of British Columbia Clinical Research Ethics Board, a retrospective search of the Anatomical Pathology Database Sunset (a proprietary hospital archive system of Vancouver Coastal Health Authority) was completed at Vancouver General Hospital for all patients who underwent collection of vitreous cytology specimens by standard 3-port pars plana vitrectomy from October 1, 1990, through December 31, 2010. All patients with a diagnostic pars plana vitrectomy from 1990 through 2005 were included in a previous study assessing the contribution of vitreous cytologic evaluation to the diagnosis of vitritis of unknown etiology. The incidence was calculated with the denominator as the mean of British Columbia population estimates at 5-year intervals from the Statistics Canada 2011 annual report. The data were analyzed using commercially available software (SAS, version 9.3; SAS Institute Inc) to calculate the Kaplan-Meier survival curve and the 95% confidence interval for the incidence. Undiluted vitreous was aspirated manually into a syringe attached to the vitrectomy cutter, and a complete vitrectomy was performed. The undiluted vitreous sample and diluted vitreous washings were sent immediately to the laboratory with a requisition that included a presumptive diagnostic and type of specimen (aspirate, washings, or both). From 1990 to 2005, 1 or 2 cytospin preparations were processed in a commercially available cytocentrifuge (Shandon cytospin; Thermo Electron Corporation) from undiluted vitreous specimens. We first concentrated vitreous washings in a tabletop centrifuge (Silencer model H-103NA; Western Scientific), resuspended the pellet, and used it to make 2 to 8 cytospins. Beginning in 2005, we used a liquid-based preparation method (ThinPrep; Hologic) in which neat vitreous and cell pellets from washings were added to the cytology solution (CytoLyt; Hologic) with a fixative (PreservCyt; Hologic) for 15 minutes before slide preparation (ThinPrep 2000 processor; Hologic). All slides were examined after staining with hematoxylin-eosin. Specimens suggestive of VRL were sent to the British Columbia Cancer Agency for molecular genetic studies to confirm monoclonality, as previously described. In our institution, the cytology specimen is the criterion standard and of diagnoses. We attempted to perform molecular studies for clonal origin. All patients in the present study had at least 1 specimen that showed definitive large-cell lymphoma cytologically. We attempted to perform molecular studies for clonal origin. However, that was not always possible owing to insufficient material or degraded DNA. Cytokine studies are not performed in our institution. Most of the cytologic specimens were examined by a single ophthalmic pathologist (V.A.W.).

**RESULTS**

A total of 463 diagnostic vitrectomy specimens from 430 patients were collected from October 1, 1990, through December 31, 2010. Preoperative findings in 128 cases were clinically suggestive of VRL. Of these, 17 cases had cytology-proven VRL. Findings in the other 302 patients were not clinically suggestive of VRL. Of these, we identified 5 cases of cytology-proven lymphoma. These findings resulted in a clinical sensitivity of 77%, specificity of 73%, positive predictive value of 13%, and negative predictive value of 98%.

<table>
<thead>
<tr>
<th>Feature</th>
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<tbody>
<tr>
<td>No. of patients</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Mean</td>
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<tr>
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<td>Primary organ affected</td>
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<tr>
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<td>Lymphoma type</td>
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<tr>
<td>T cell</td>
<td>2 (9)</td>
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<td>Metamorphopsia</td>
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<td>Initial neurological symptoms</td>
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<td>Seizures</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Diplopia</td>
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</table>

aUnless otherwise indicated, data are expressed as number (percentage) of patients.

Of the 22 patients with confirmed VRL, a total of 31 vitrectomies were performed. One patient required 3 vitrectomies before receiving a cytologic diagnosis of VRL. The first specimen was hypocellular, whereas the second had granulomatous inflammation. Recurrence of vitritis in patients with a previous cytologic diagnosis of VRL led to a second diagnostic vitrectomy in 7. Five of these repeated vitrectomies yielded findings positive for VRL. The repeated vitrectomies in the other 2 patients had negative cytologic results, including granulomatous inflammation in one and occasional atypical cells that were not diagnostic for lymphoma in the other. Both patients developed PCNSL 13 and 21 months after the negative vitrectomy results. Assuming the diagnostic vitrectomy findings were false-negative, we determined that the cytologic diagnostic sensitivity in our series was 87% (27 of 31 specimens). Twenty vitrectomy specimens had adequate DNA for analysis of at least 1 of 3 molecular signatures. Of these, 8 were clonal for the IgH gene, 2 for the minor cluster region of the t(14;18) translocation seen in follicular lymphoma, and 2 for the T-cell receptor gene.

The incidence of VRL in British Columbia in 5-year intervals per 100,000 people was 0.023 (95% CI, 0.003 to 0.049), 0.017 (0.004 to 0.039), 0.033 (0.003 to 0.063), and 0.048 (0.012 to 0.083) in chronological order from 1990 through 2010. The patient demographics and clinical features are shown in Table 1. The mean and median ages at the time of diagnosis were 66 and 69 years, respectively (range, 33-84 years). Seventeen patients were women (77%) and 5 (23%) were men. All patients were immunocompetent. The initial diagnosis of
lymphoma from all 22 cases of intraocular lymphoma was VRL in 19 (86%) and PCNSL in 3 (14%). Of the patients with VRL, 7 (37%) had concurrent central nervous system lymphoma (CNSL) at the time of diagnosis discovered via head imaging (computed tomography and/or magnetic resonance imaging). Two patients with isolated VRL were lost to follow-up. The 3 patients with isolated PCNSL later developed VRL a median of 11 (range, 2-26) months after the initial diagnosis. After successful treatment, VRL recurred in 8 of the 20 patients available for follow-up (40%), with a median of 16 (range, 1-60) months after initial diagnosis. Recurrence of lymphoma affecting the central nervous system (CNS) occurred in 2 patients (10%) a median of 26 (range, 9-37) months after the initial diagnosis. One patient (5%) had recurrence of disease affecting the lungs after treatment for VRL with concurrent CNSL.

The most common initial clinical presentation of intraocular lymphoma was vitritis in 12 patients (60%), vitritis with chorioretinal infiltrates in 5 (25%), and panuveitis in 3 (15%). Floaters were noted in 12 patients (60%) followed by decreased vision in 10 (50%) and metamorphopsia in 2 (10%). No clinical information was available for 2 patients. Bilateral disease was documented in 8 patients (40%). Among the 12 patients with CNS involvement, the most common symptom was cognitive deterioration in 4 (33%) and behavioral changes in 3 (25%). Ataxia, headaches, and seizures were noted separately in 2 patients each (17%). Diplopia was also noted in 1 patient owing to CNS involvement (8%) (Table 1).

A medical history of malignant disease was found in 3 patients. One patient had a history of breast cancer; 1, a history of prostate cancer and pheochromocytoma; and 1, breast and colorectal cancer.

All patients had a cytologic diagnosis of lymphoma. Twenty cases (91%) were of the large B-cell type, whereas the remaining 2 (9%) were diagnosed as T-cell lymphoma (Table 1). The source of tissue for the initial diagnosis was the vitrectomy in 19 cases (86%) and brain biopsy in 3 (14%). At the time of diagnosis, lumbar puncture yielded negative findings in 14 patients despite CNS lesions on imaging in 6 of these patients.

The treatment of all patients with isolated VRL, which included the initial diagnosis and recurrences, if applicable, is outlined in Table 2. Of those with an initial diagnosis of isolated VRL, recurrence of lymphoma oc-
Intraocular lymphoma was first described in 1951 and is a rare malignant lymphoma constituting less than 1% of non-Hodgkin lymphoma.13 When combined with CNSL, intraocular lymphoma has a 5-year survival rate of less than 25%.14

During the past 3 decades, the incidence of PCNSL has increased 3-fold in the United States.1,14,15 This increase has mostly been attributed to the increasing number of immunocompromised and immunosuppressed patients; however, an inexplicable increase of PCNSL has mostly been attributed to the increasing number of cases in the immunocompetent population.16 According to the most recent Central Brain Tumor Registry of the US Statistical Report, the incidence of PCNSL in the immunocompetent population was 0.46 per 100,000 from 2004 to 2007.17 To date, no epidemiologic studies have looked specifically at the incidence of VRL. In our patient cohort, we also noted an increase in the incidence of VRL from 1990 through 2010 by a factor of 2.1 per 100,000.18,19 This apparent increased incidence of VRL may therefore be the result of better recognition and diagnosis of the disease in addition to an actual increase in the number of cases in the immunocompetent population.

Vitreoretinal lymphoma typically masquerades as chronic intermediate and/or posterior uveitis in older patients with no history of uveitis, and it is unresponsive to corticosteroid therapy. In keeping with our results, this disease typically occurs in patients in the middle of the sixth decade of life18,19,20 but can also affect much younger individuals.21 Vitreoretinal lymphoma is frequently bilateral, however, only 8 of 20 patients in our study (40%) had documented bilateral disease at the initial examination. This finding may be an underestimation of the true value because VRL is often asymmetric and initially may appear to be unilateral.22 At the time of diagnosis, Whitchurch et al23 reported that 50% of patients with PIOL had concurrent CNS involvement. Fardeau et al24 found a lower rate, with 33% of patients with PIOL having CNS lesions. Our results were comparable, with 7 of 19 patients (37%) demonstrating concurrent CNS involvement at the time of PIOL diagnosis. During follow-up, 2 additional patients developed CNSL, one of these 144 months after the initial diagnosis. This finding demonstrates the importance of regular oncology follow-up, including appropriate neuroimaging, for these patients after the initial diagnosis and treatment, since they maintain a persistent risk for recurrence for several years after the disease has been dormant.

With advances in vitreoretinal surgery during the past 3 decades, diagnostic vitrectomies have become widely accepted and the preferred procedure for diagnosing VRL, thus replacing the historic need for brain biopsy.17 The fragility and paucity of lymphoma cells in the vitreous, however, make adequate tissue challenging to harvest and preserve for cytologic analysis.9 To increase the cytologic diagnostic yield, we must use a low cut rate and gentle aspiration during the vitrectomy. The specimen should be transported promptly to the prenotified pathologist for rapid processing and cytologic analysis.8,24,26 Lymphoma cells within the vitreous are usually much larger than normal lymphocytes and have scanty cytoplasm. The nucleus is pleomorphic and has prominent nucleoli. When these characteristic lymphoma cells are visualized cytologically from the vitreous samples, the sensitivity and specificity have been shown to be high.

Yeh et al27 diagnosed PIOL on the basis of cytologic findings in only 3 of 8 patients (38%) who underwent diagnostic vitrectomy. The remaining 5 required additional gene rearrangement studies, cytokine studies, or flow cytometry to establish the diagnosis. On the other hand, Akpek et al28 reported only 1 of 13 cases (8%) with an initial negative cytologic finding that was later diagnosed as PIOL. Zaldivar et al22 also reported a sensitivity of 91% (10 of 11 cases) for diagnosing PIOL with cy-
tocologic findings. Our cytologic diagnostic sensitivity for VRL was 87% (27 of 31 specimens), which compares favorably well with the current literature and emphasizes the importance of a dedicated and experienced ophthalmic pathologist. To the best of our knowledge, only 2 patients had negative diagnostic vitrectomy findings and subsequently developed CNSL.

Given the aggressive and lethal nature of VRL, many clinicians will consider these studies as part of the differential diagnosis that must be ruled out by the pathologist when receiving the specimen for cytologic analysis. The clinicians from our database had a preoperative clinical diagnostic sensitivity and specificity for identifying VRL of 77% and 73%, respectively. The positive predictive value was low, with only 13% of those with possible VRL preoperatively confirmed as having the malignant neoplasm after cytologic and molecular genetic analysis. Other publications have reported comparable results. Akpek et al reviewed all diagnostic vitrectomies to rule out PIOL during a 5-year period. They found a total of 26 patients, 10 of whom had confirmed PIOL, giving a positive predictive value of 38%. Similarly, Lobo and Lightman performed a retrospective analysis among all patients from their center who had undergone diagnostic vitrectomy during a 5-year period. They reported a preoperative clinical diagnostic sensitivity of 88%, a specificity of 56%, a positive predictive value of 26%, and a negative predictive value of 96%. With the severity of disease associated with VRL, most clinicians consider it part of the differential diagnosis when submitting vitreous specimens for cytologic analysis in patients with undiagnosed uveitis, although the likelihood of disease is low. This study suggests that better clinical prescreening should be possible.

Until now, treatment guidelines have not been established. The ultimate goal of treatment is to eradicate the intraocular lymphoma cells, eliminating the potential reservoir of untreated disease that could cause recurrence or CNS extension. Radiotherapy, administration of high-dose systemic methotrexate, myeloablative chemotherapy, and immunotherapy have been reported to achieve adequate rates of remission, although many patients have recurrent disease. To overcome the poor intraocular penetration of systemically delivered chemotherapeutic agents and their inherent systemic toxic effects, intrathecal therapy has become increasingly popular during the past decade. Grimm et al recently found that specific ocular therapy, defined as ocular radiotherapy or intraocular chemotherapy, for patients with PCNSL with intraocular involvement resulted in prolonged disease control but did not affect survival or the risk for recurrent disease. In our series, 8 of 21 patients (38%) with isolated PIOL and no concurrent CNS involvement received isolated radiotherapy to the orbits followed by combined systemic administration of high-dose methotrexate and radiotherapy in 5 (24%). All 21 cases of isolated VRL received specific ocular therapy with or without systemic therapy. Intravitreal injections of methotrexate and/or rituximab or cytarabine were used for 5 patients (24%). For those demonstrating concurrent CNS and intraocular involvement of lymphoma, 5 of 7 (71%) received systemic high-dose methotrexate combined with radiotherapy to the brain and orbits. In the future, treatment of VRL will likely rely more on local biological methods, such as rituximab, to overcome the adverse effects and the frequency of intravitreal injections of methotrexate.

With an overall 5-year survival rate of less than 25%, the prognosis of VRL remains poor despite advancements in treatment. Grimm et al reported a median progression-free survival and overall survival of 18 and 31 months, respectively, with a total mortality of 67.9% (150 of 221). That study was the largest series, involving 16 centers from 7 countries from 1977 through 2005. We reported a median progression-free survival of 11 months and a median survival time of 33 months. Fourteen of 20 patients (70%) had died by the end of the study. Similar to the study by Grimm et al, the primary cause of death was PCNSL.

Vitreoretinal lymphoma remains a clinical diagnostic challenge with an increased incidence among immunocompetent patients. This potentially lethal malignant neoplasm should be considered early in any patient with corticosteroid-resistant posterior uveitis on initial examination. We believe that performing a diagnostic vitrectomy for cytologic analysis with prompt handling is critical for the diagnosis of VRL and should be repeated when necessary if the clinical suspicion remains high. Cytologic sensitivity is high when vitrectomy specimens are treated promptly and appropriately. When VRL is diagnosed, all patients should undergo screening in collaboration with an oncologist for subtle neurological symptoms and signs and neuroimaging for any evidence of CNS involvement. These patients require long-term follow-up to rule out recurrence of disease or adverse effects of radiotherapy or chemotherapy. Although several advancements have been made in treating VRL, the prognosis remains poor and requires more interdisciplinary collaboration.

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Conflict of Interest Disclosures: None reported.

CONCLUSIONS

REFERENCES


