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Primary Intraocular Lymphoma

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Primary intraocular lymphoma (PIOL) is an uncommon neoplasm that often poses a diagnostic challenge by masquerading as uveitis or vitritis, particularly in its most common form, primary vitreoretinal lymphoma (PVRL). PIOL mainly arise from the central nervous system (CNS); however, ocular symptoms precede central nervous system symptoms in a majority of patients. Among PIOL patients, the percentage of cases that involve CNS is 60%-80%. While 15%-25% of primary central nervous system lymphoma (PCNSL) patients develop ophthalmic manifestations of lymphoma, 56%-90% of PIOL patients have or will develop CNS manifestations of lymphoma. Numerous case reports and case series in the ophthalmic literature have documented ocular lymphoma initially misdiagnosed as idiopathic uveitis or vitritis.

PIOL presenting as vitritis may show an initial response to corticosteroid therapy, because some of the vitreous cells (20%) are reactive T lymphocytes rather than malignant cells and thus respond to corticosteroids. Additional factors contributing to diagnostic difficulty include challenges in obtaining adequate vitreous samples or biopsy specimens to confirm malignant lymphocytes. Moreover, because central nervous system involvement often lags ocular manifestations, cerebrospinal fluid cytology, neurologic examination, and imaging studies (including magnetic resonance imaging) are frequently normal. In initially unilateral cases, PIOL frequently spreads to the fellow eye and later progresses to central nervous system involvement. The mortality rate from the latter is extraordinarily high.

We conducted a study to determine whether the cytologic features of vitreous biopsy specimens from patients ultimately diagnosed with PIOL contain markers or characteristics predictive of subsequent development of central nervous system lymphoma. For this purpose, we retrospectively reviewed 35 vitreous samples by two ocular pathologists in a masked manner. All vitreous specimens were obtained using a standard three-port pars plana vitrectomy technique. Before initiating infusion, 1 mL of undiluted vitreous was aspirated into a 3 mL syringe attached to a 20-gauge needle. If this aspiration was not feasible, the syringe was connected via a stopcock to the vitrectomy cutter handpiece, and a “dry” vitrectomy was

performed to obtain 1 mL of specimen. Infusion was then initiated, and a complete vitrectomy was performed. Both the 1 mL undiluted specimen and the diluted vitreous from the vitrectomy cassette were immediately submitted to the cytopathology laboratory. The specimens were processed in 10% neutral buffered formalin in a dilution of one part 10% formalin to one part specimen, with fixation proceeding for approximately twelve hours. A 0.5 cc fixed specimen was then pipetted into the cytospin chamber and spun at 1000 rpm for five minutes, concentrating the cells in the specimen onto a glass slide. Air drying, staining with hemotoxin and eosin, and microscopy for pathology analysis were then conducted. Spinal tap cerebrospinal fluid cytology and MRI scanning of the brain were also performed in these patients. The samples were classified as negative (no malignant cells), suspicious (atypical features not sufficient for a definitive diagnosis), or positive (frank malignant cells present).

The cytopathic results of twenty-one vitreous specimens from 16 patients were identified as negative, and 11 specimens from 9 patients were either frankly positive or suspicious of malignancy. The vitreous specimen of one patient was negative initially, but a later second specimen. There was 100% concordance between cytologic interpretations independently rendered by two ocular pathologists over a five-year period of specimen accession. Negative specimens contained lymphocytes and some plasma cells and an occasional histiocyte, without evidence of mitotic figures, prominent nucleoli or irregular nuclear outline, features which were routinely present with the exception of mitotic figures in those specimens read as definitely positive.

Specimens that were highly suspicious but not diagnostic were further evaluated with a second pars plana vitrectomy, using both conventional histopathologic techniques and measurement of intravitreal IL-10 and IL-12 levels.

Despite being tedious and challenging, the following components are critical to optimizing the detection of malignancy in patients with large cell lymphoma masquerading as uveitis:
1) A properly-collected vitreous specimen, undiluted, preferably without the need for cutting action from the vitrector, with specimen transported immediately for preparation and analysis by an expert cytopathologist. *2)* Evaluation of the cytospin preparation by an expert cytopathologist who has access to monoclonal antibody staining strategies. *3)* Availability of ELISA assays for both IL-10 and IL-12. *4)* PCR studies for IgH gene rearrangements (especially IGHV4-34).

Based on this study, we conclude that, given the historically high mortality rate of large cell lymphoma masquerading as uveitis, improved recognition of cytologic features in vitreous biopsy specimens and increased availability of IL-10 and IL-12 ELISA assays may enable earlier diagnosis, potentially improving outcomes compared with the typically late presentation of most cases.

In general, multidisciplinary approach is required for the diagnosis of PIOL, incorporating morphologic assessment alongside immunocytochemistry and molecular analyses, such as flow cytometry and PCR. However, histologic identification remains a key diagnostic component. Additionally, Molecular analysis demonstrating immunoglobulin gene rearrangements in lymphoma cells, along with ocular cytokine analysis of vitreous fluid showing elevated IL-10 and an IL-10:IL-6 ratio >1.0, is helpful for diagnosis. A recent systematic review shows that an IL10/IL-6 ratio >1 provides the highest sensitivity for diagnosing PVRL at 89.39%, with comparable sensitivity between vitreous and aqueous sample.

Recent studies have shown that identification of recurrent mutations significantly improves the diagnostic yield of vitreous specimens, with detection of the MYD88 mutation serving as a valuable adjunct in the diagnosis of PIOL. MYD88 and CD79B mutations detected in CSF samples, in conjunction with elevated CSF IL-10 levels, may serve as promising adjunct tools to aid in diagnosing PIOL.

References

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