

Ocular Lymphoma

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Primary ocular lymphoma, an infrequent neoplasm, typically represents a diagnostic challenge masquerading as uveitis or vitritis. Ocular symptoms precede central nervous system involvement and symptoms in approximately 80% of patients. More than 150 cases of ocular lymphoma have been reported in the ophthalmic literature, and most of these cases were initially misdiagnosed as idiopathic uveitis or vitritis. Ocular lymphoma "vitritis" can even respond to steroid therapy, since the majority of cells present in the vitreous of patients with this malignancy are in fact not malignant cells but rather are "reactive" lymphocytes, sensitive to steroid therapy. Additional features contributing to the diagnostic difficulties of this disorder include the fact that, since so few of the cells present in the vitreous are frankly neoplastic, cytologic examination of vitreous biopsy specimens in the earlier stages of the disease often discloses little to no atypicality in the lymphocytes present in the specimen. Additionally, since CNS involvement lags ocular manifestations, cytologic analysis of cerebral spinal fluid, neurologic examinations, and imaging studies (including magnetic resonance imaging) are frequently normal.

Undiagnosed and untreated, the disorder typically progresses from unilateral to bilateral "vitritis", and then to central nervous system involvement. The mortality rate from the latter is extraordinarily high.

We wondered if the cytologic features of vitreous biopsy specimens from patients who were ultimately proven to have ocular lymphoma might be predictive of subsequent development of central nervous system lymphoma. The purpose of this report is to describe our review of 35 such specimens reviewed independently, in a masked manner, by two ocular pathologists.

We reviewed 35 cytology specimens harvested from the vitreous of 27 patients evaluated in the Cogan Eye Pathology Laboratory over a five-year period. The cytologic features of the specimens were reviewed by two ocular pathologists (Frederick A. Jakobiec and Thaddeus P. Dryja) in a masked manner. A negative specimen for lymphoma cells was indicated by the absence of any cells with malignant features in the specimen. A "suspect" diagnosis included those specimens for which sufficient atypicality existed that the pathologists were significantly concerned that early features of malignancy were present. A positive specimen met the cytologic criteria for frank malignant changes in the cells.

All of the vitreous specimens were obtained through standard preparation of a three port pars plana vitrectomy procedure. Before instituting infusion, however one cc of "neat," undiluted vitreous was aspirated into a three cc syringe with an attached 20 gauge needle. If such aspiration were impossible, the syringe was attached, via stopcock, to the vitrectomy cutter hand piece, and a "dry" vitrectomy was performed so that one cc of specimen could be obtained into the syringe. The infusion was then begun, total vitrectomy performed, and both the one cc "neat" specimen and the diluted specimen in the vitrector cassette were immediately delivered 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 cytopspin chamber and spun at 1000 rpm for five minutes, concentrating the cells in the specimen onto a glass slide. Air drying, staining with hematoxylin 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 cytopathic results disclosed 16 cases which were unequivocally negative, four instances where the specimen was unequivocally positive, and three specimens which were highly suspicious but not diagnostic of malignancy, and specimens from an additional three patients resulting in an indeterminate reading, necessitating repeat vitreal biopsy. There was a 100% concordance between cytology results read independently by the two ocular pathologists over a five-year period of accession of the patient specimens. 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 which were highly suspicious but not diagnostic could eventually be analyzed, through repeat vitrectomy, not only with classic histiopathologic techniques, but also through assay of intravitreal IL-10 and IL-12 levels. (See article this month in the "Laboratory" section.)

We believe that, while tedious and challenging, the following components are essential if one is to maximize the likelihood that malignancy will be detected in a patient with large cell lymphoma masquerading as uveitis:

1. A properly-collected vitreal 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.

Because the mortality rate is so extraordinarily high, historically, in patients with large cell lymphoma masquerading as uveitis, it is to be hoped that increasing awareness of the aforementioned features to analysis of vitreous biopsy specimens, and the increasing availability of ELISA studies for IL-10 and 12 will result in earlier diagnosis of patients with this disease, hopefully at a time, when the "cure rate" will be considerably higher than it currently is, with the relatively late diagnosis of most cases.