ABSTRACT

The authors report two cases of retinoblastoma with extension along the optic nerve sheath with negative surgical margins, a pattern not considered in current classifications but suggesting a high risk of metastasis. Both patients were treated with adjuvant chemotherapy alone and remain free of extraocular disease 15 and 22 months later. [J Pediatr Ophthalmol Strabismus. 2016;53:e51-e53.]

INTRODUCTION

Isolated post-laminar optic nerve invasion in retinoblastoma is generally considered an independent high-risk feature sufficient to recommend post-enucleation chemophrophylaxis, although the number of cases in studies comparing adjuvant treatment with enucleation alone is limited.1 The exact mechanism of metastasis in cases of post-laminar optic nerve invasion is unclear but may be explained by privileged access to cerebrospinal fluid beyond the lamina cribrosa. Invasion through the optic nerve sheath rather than through the optic nerve axis alone is a rarer event. It is mentioned in the historic literature but its prognostic value is unclear and histologic images have not been published. We report two cases of retinoblastoma with direct extension through the edge of the optic disc into the optic nerve sheath and provide detailed histologic images with treatment and survival data.

CASE REPORTS

Case 1

A 3-year-old child presenting with leukocoria underwent enucleation for a unilateral stage D retinoblastoma. Pathology showed a tumor without choroidal involvement but with intra-axial optic nerve invasion up to 1.55 mm beyond the lamina cribrosa and an unusual second front of tumor exiting through the temporal edge of the optic disc and forming a mass expanding the optic nerve subarachnoid space (Figure 1A). On all serial sections examined, this mass was covered by a capsule continuous with the optic nerve pia (Figures 1A-1F). Immunohistochemistry for synaptophysin (1:500 dilution, Dako) highlighted tumor cells within the mass but did not reveal tumor explants further down the subarachnoid space or within the arachnoid itself (Figure 1G). Genetic analysis revealed a non-germline Rb mutation.

Given the presence of tumor in the optic nerve sheath, we deemed the patient at high risk of cerebrospinal fluid seeding and considered enrollment in the extraocular retinoblastoma COG protocol (ARET0321), which includes adjuvant chemotherapy, orbital radiotherapy, and intensification with high-dose chemotherapy and stem cell rescue. However, in the absence of documented extraocular extension, the patient was ineligible for this protocol and was treated off-study with an etoposide/cyclophosphamide/cisplatin/vincristine combination, without radiation therapy.
or high-dose chemotherapy. Due to significant ototoxicity after the first cycle of chemotherapy (> grade 2), the second cycle was given without cisplatin. The patient received two additional cycles of chemotherapy with a carboplatin/etoposide/vincristine combination. Lumbar puncture and bilateral bone marrow biopsy following treatment were negative and the patient was followed up with central nervous system/orbital magnetic resonance imaging every 3 months during the first year and every 6 months thereafter. The patient wears hearing aids due to platinum-induced ototoxicity but is currently recurrence-free 22 months after chemotherapy.

Case 2

A 2-month-old infant presenting with stage E retinoblastoma with unilateral chemosis was treated with intravenous antibiotics and decadron. After an initial delay in obtaining consent for surgery, corneal perforation prompted emergent enucleation at an outside institution. Pathology initially did not report high-risk features. Genetic analysis revealed a germline Rb mutation. Contralateral eye examination under anesthesia revealed a stage A tumor, which was treated with laser photocoagulation. Re-examination of the pathology specimen with immunohistochemistry for synaptophysin and epithelial membrane antigen (1:300 dilution, Dako) revealed tumor explants along the optic nerve sheath with only pre-laminar intra-axial optic nerve invasion (Figures 2A-2F). As in case 1, the tumor had seemingly exited the intraocular space through the edge of the optic disc.

Given the presence of tumor in the optic nerve sheath, we deemed the patient at high risk of cerebrospinal fluid seeding but, as in case 1, the patient was not eligible for the ARET0321 protocol. Due to the patient's young age and body weight of less than 7 kg, we could not consider stem cell collection or radiation therapy. We decided to treat the patient with four cycles of a carboplatin/etoposide/vincristine combination, followed by two additional cycles of a carboplatin/etoposide/cyclophosphamide/vincristine combination as a form of intensification. The patient did not present ototoxicity or any other significant toxicity. Follow-up was performed as in case 1. The patient is currently recurrence-free 15 months following chemotherapy.

**DISCUSSION**

Isolated optic nerve sheath invasion has not been addressed as an individual risk factor in recent retinoblastoma literature. Historically, it was associated with higher mortality compared with pre-laminar intra-axial invasion, and with similar or higher mortality compared with post-laminar intra-axial inva-
In these cases, combined post-laminar invasion of the nerve axis and sheath was associated with an even higher mortality rate, similar to that seen in nerve invasion to the resection line. In a more recent study, invasion of the subarachnoid space was deemed equivalent to invasion to the resection line and was not addressed separately.4

This report provides two recent examples of patients with optic nerve sheath invasion and negative surgical margins who did not recur after enucleation and adjuvant chemotherapy without radiation therapy and/or intensification chemotherapy. We provide histologic evidence that invasion of optic nerve sheath may occur directly through the edge of the optic disc, possibly bypassing the lamina cribrosa via an optic pit or another point of least resistance. Optic nerve sheath involvement is not routinely looked for in current specimen examination protocols5 and is not specified in the American Joint Committee on Cancer classification of retinoblastoma.6 We suggest that immunohistochemistry for synaptophysin be included in future specimen examination protocols as a tool to help identify inconspicuous tumor explants along the optic nerve sheath. We also recommend that optic nerve sheath invasion be added to the pathology classification to help identify, study, and treat patients with this type of extension.

REFERENCES