Analysis of Clinical Misdiagnoses in Children Treated With Enucleation

Susan Huang, MD; Tina Rutar, MD; Michele Bloomer, MD; J. Brooks Crawford, MD

Objective: To evaluate discordant clinical and pathological diagnoses leading to pediatric enucleations over time.

Methods: All pathology reports of pediatric enucleation specimens (subjects aged 0 to 18 years) from 1960 to 2008 were reviewed. Specimens with discordant clinical and pathological diagnoses were further analyzed. Formalin-fixed, paraffin-embedded sections of enucleated eyes of any misdiagnosed cases were reevaluated.

Results: Of 729 pediatric patients (746 eyes) who had enucleation from 1960 to 2008, 29 patients (4.0%) and 30 eyes (4.0%) had discordant clinical and pathological diagnoses. The misdiagnosis enucleation rate decreased with each respective decade studied, with the highest rate of 6.5% (18 of 276 eyes) in the 1960s and no misdiagnoses from 1990 to 2008. Of the 369 eyes enucleated for the clinical indication of malignancy, 22 eyes (6.0%) were misdiagnosed in that no evidence of malignancy was found on histopathological examination. Of the 377 eyes enucleated for benign clinical indications, 7 cases (1.9%) were found to be malignant by histopathology.

Conclusions: Misdiagnoses leading to pediatric enucleation have decreased during the past 5 decades, likely owing to improved diagnostic techniques. Benign and malignant intraocular conditions can simulate each other, especially retinoblastoma, Coats disease, nematode and bacterial endophthalmitis, panuveitis, and persistent hyperplastic primary vitreous.


E Nucleation is an accepted treatment for some end-stage conditions such as blind, painful eyes and advanced ocular malignancies. At times, it may be difficult to make an accurate clinical diagnosis, especially with pediatric ocular conditions that may simulate each other. For example, retinoblastoma may simulate benign conditions such as Coats disease, panuveitis, retinal detachment, and persistent hyperplastic primary vitreous (PHPV). Moreover, there are special challenges in working with the pediatric population such as obtaining an accurate history of ocular symptoms and performing a thorough examination. Even when clinically indicated, the loss of an eye causes significant psychological and social morbidity in both adult and pediatric patients. The loss of an eye owing to a potentially avoidable cause is especially devastating, even more so in a pediatric patient, who will live with the visual and functional deficit for many years.

Studies published several decades ago reviewed misdiagnosed leading to enucleations, with the longest study looking at 3 decades. We reviewed pediatric enucleations during a span of nearly 5 decades (1960-2008) to evaluate which clinical misdiagnoses, if any, have resulted in potentially avoidable enucleations in children. We hypothesized that misdiagnoses of pediatric enucleation specimens decreased over time. Improved diagnostic techniques such as indirect ophthalmoscopy, fluorescein angiography, ultrasonography, computed tomography, magnetic resonance imaging, and laboratory studies would be expected to reduce the frequency of misdiagnoses over time.

METHODS

All records of pathologic specimens (27,422 total) from our institution, the eye pathology laboratory of the University of California, San Francisco, between January 1960 and December 2008 were reviewed to identify pediatric enucleation specimens. Between 1960 and 1989, the laboratory kept paper records, which were manually reviewed. Between 1990 and 2008, the laboratory kept an electronic database of all pathological specimens, and pediatric enucleation specimens were identified.
Since the inception of the eye pathology laboratory, each specimen was evaluated by 2 independent pathologists. Cases were rereviewed by a pathologist (J.B.C. or M.B.) who confirmed pathologically, and suspected benign conditions found to be malignancy or tumor, 22 (6.0%) were misdiagnosed in that no evidence of malignancy was found on histopathological examination (Table 2).

Possible tumor was considered the same as possible malignancy in this setting because general practice does not include the aggressive treatment of enucleation as first-line treatment for possible benign tumor. These 22 misdiagnosis cases were submitted with the clinical diagnoses of retinoblastoma (13), possible retinoblastoma (6), possible tumor (2), or possible malignant melanoma (1) by the submitting ophthalmologists. Histopathology revealed 5 cases of retinal detachment, 4 of Coats disease, 4 of congenital anomalies, 4 of nematode endophthalmitis, 3 of infectious (nematode) endophthalmitis, 1 of benign granulomatous iris tumor, and 1 of cavernous hemangioma of the optic nerve.

Of the 7 suspected malignancies that were found to be (nematode or nonnematode) endophthalmitis on histopathology, 3 patients had no light perception visual acuity and 2 had progressively decreasing vision. Two patients’ medical records did not report visual acuity but the pathological specimens showed total retinal detachment.

In 1962, a 2-month-old boy was clinically diagnosed with bilateral retinoblastoma, and both eyes were enucleated on the same day. Histopathology showed bilateral retinal detachment of unknown etiology. No evidence of retinoblastoma tumor cells was seen in any of the sections. There were 11 patients who had bilateral enucleations for suspected retinoblastoma (22 eyes) in our series, and this patient was the only misdiagnosis (9.1%). Of 339 unilateral suspected retinoblastoma cases, 4.7% (16 of 335) were misdiagnoses.

Of 729 pediatric patients (746 eyes) who had enucleation from 1960 to 2008, there were 29 patients (4.0%) and 30 eyes (4.0%) with discordant clinical and pathological diagnoses (Table 1). All 30 eyes rereviewed by the pathologists were reconfirmed to be misdiagnoses. Figure 1 shows representative histopathological sections of some of the misdiagnosed cases. The misdiagnoses occurred in 13 girls (45%) and 16 boys (55%). The mean (SD) age of misdiagnosed patients was 2.6 (2.3) years, with a range of 3 weeks to 9 years and a median of 2 years. The mean (SD) age of correctly diagnosed patients was 6.6 (3.9) years, with a range of 2 weeks to 18 years and a median of 4 years. There was a statistically significant difference in the mean younger age of misdiagnosed cases compared with the mean older age of correctly diagnosed cases (P < .001, t test). The misdiagnosis enucleation rate decreased with each respective decade studied, with the highest rate of 6.5% (18 of 276 eyes) in the 1960s and no misdiagnoses occurring from 1990 to 2008 (Figure 2). Of the 369 eyes enucleated for the clinical indication of malignancy or tumor, 22 (6.0%) were misdiagnosed in that no evidence of malignancy was found on histopathological examination (Table 2).

We defined a case as misdiagnosis when the histopathological diagnosis did not show any correlating evidence with the clinical condition and/or showed a completely different etiological process. The histopathological findings of end-stage diseased eyes can be nonspecific, however. For example, chronic nonhegmatogenous retinal detachment may be due to underlying Coats disease, retinopathy of prematurity, endophthalmitis, uveitis, or other entities. Thus, we did not classify a histopathological diagnosis of chronic nonhegmatogenous retinal detachment and a clinical diagnosis of Coats disease as a misdiagnosis in our study because the characteristic vascular malformations of Coats disease could have been obliterated by secondary processes in longstanding disease. Phthisis bulbi is another example of an end-stage histopathological diagnosis. Thus, we did not classify a histopathological diagnosis of phthisis bulbi with a clinical diagnosis of trauma, postoperative complication, or endophthalmitis as a misdiagnosis, even if histopathological evidence of the original clinical condition could no longer be identified.

Clinical and histopathological diagnoses were categorized as malignant or benign conditions. Malignancies were further subcategorized as retinoblastoma or nonretinoblastoma. Misdiagnoses owing to suspected malignancies found to be benign by histopathology, and suspected benign conditions found to be malignant by histopathology were analyzed separately.

To confirm the histopathological diagnoses, misdiagnosed cases were rereviewed by a pathologist (J.B.C. or M.B.) who was unaware of the initial histopathological diagnosis. Thus, each specimen was evaluated by 2 independent pathologists. Since the inception of the eye pathology laboratory, the glass slides used for microscopic evaluation of all the submitted cases and the paraffin-embedded tissue blocks from which these slides were prepared have been stored and cataloged. The original slides were available for rereview of all misdiagnosis specimens. If the original slides were not adequate for evaluation because of degradation over time, new slides were prepared from the paraffin blocks.

### RESULTS

**Table 1. Analysis of Pediatric Enucleations Submitted to UCSF Eye Pathology (1960-2008)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Eyes, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>746</td>
</tr>
<tr>
<td>Total misdiagnoses</td>
<td>30 (4.0)</td>
</tr>
<tr>
<td>Clinical diagnosis of malignancy, including</td>
<td></td>
</tr>
<tr>
<td>retinoblastoma</td>
<td>369</td>
</tr>
<tr>
<td>Confirmed pathologically</td>
<td>347</td>
</tr>
<tr>
<td>Benign condition found on pathology</td>
<td>22 (6.0)</td>
</tr>
<tr>
<td>Clinical diagnosis of retinoblastoma</td>
<td>355</td>
</tr>
<tr>
<td>Confirmed pathologically</td>
<td>336</td>
</tr>
<tr>
<td>Retinoblastoma not found on pathology</td>
<td>19 (5.4)</td>
</tr>
<tr>
<td>Clinical diagnosis of benign condition</td>
<td>377</td>
</tr>
<tr>
<td>Confirmed pathologically</td>
<td>369</td>
</tr>
<tr>
<td>Malignancy found on pathology</td>
<td>7 (1.9)</td>
</tr>
<tr>
<td>Other benign condition found on pathology</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

Abbreviation: UCSF, University of California, San Francisco.
Of the 377 eyes enucleated for benign clinical indications, 7 cases (1.9%) were found to be malignancies by histopathology. The clinical diagnoses included nematode endophthalmitis (2), nonnematode endophthalmitis (1), Coats disease (1), uveitis (1), and painful eye (1), and all 6 of these proved to be retinoblastoma by histopathology. Another clinical diagnosis of phacolytic glaucoma (1) proved to be medulloepithelioma by histopathology.

One specimen clinically diagnosed as possible retinoblastoma was read as necrotizing metastatic endophthalmitis of unknown etiology by the original pathologist. Two pathologists (J.B.C. and M.B.) rereviewed the specimen slides and diagnosed granulomatous iris tumor of unknown etiology. This case could be a forme fruste of juvenile xanthogranuloma but it did not contain the classic finding of touton giant cells. The case was included as a misdiagnosis owing to the discordance between the initial clinical diagnosis and either histopathological diagnosis.

A miscellaneous misdiagnosis was 1 case identified clinically as PHPV that histopathologically showed retinal detachment of unknown etiology. The absence of hyaloid system remnants or elongated ciliary processes and the intact nature of the lens capsule mitigated against a diagnosis of PHPV.

**COMMENT**

**BENIGN CONDITIONS THAT SIMULATE MALIGNANCY**

We found that between 1960 and 2008, 6.0% of eyes were initially clinically misdiagnosed with malignancy when histopathological examination did not show any evidence for malignancy. Studies from earlier decades reported a higher prevalence of misdiagnosis. Between 1928 and 1949, Sanders' found that 20% of eyes enucleated from children...
The 2 most common simulating conditions were Coats disease and retinal detachment of uncertain etiology.

Our findings are similar to previous studies of eyes that received enucleation for suspected retinoblastoma, with the most common simulating conditions being retinal detachment, Coats disease, and nematode and non-nematode endophthalmitis. Congenital anomalies were also found in our study, which previous studies did not discuss. The results of our study and the older studies remind clinicians of the broad differential diagnosis for suspected retinoblastoma.

We observed a decrease in simulated malignancy misdiagnoses with each decade, with no misdiagnoses beginning in 1990 (Figure 1). Our lower retinoblastoma misdiagnosis rate compared with older studies may reflect diagnostic improvements in differentiating malignant tumors from benign lesions. Ophthalmultrasnography was developed in the 1960s and improved to its current form in the 1990s.9 Likewise, computed tomography and magnetic resonance imaging were developed in the 1970s and have technically improved since then to play a significant role in diagnosis.10,11

**MALIGNANCY THAT SIMULATES BENIGN CONDITIONS**

In our study, 1.9% of enucleated eyes with a clinical diagnosis of a benign condition were found to have a malignancy on histopathology. Six cases (1.7%) showed retinoblastoma on histopathology and 1 case showed medulloepithelioma. Margo and Zimmerman8 found that 2 of 268 (0.7%) enucleated eyes harbored unsuspected retinoblastoma. Kogan and Boniuk found 10 unsuspected retinoblastomas in 750 eyes (1.3%) enucleated for suspected benign conditions.2 Our overall rate is similar to earlier studies, though we also found a trend toward fewer misdiagnoses of malignancies simulating benign conditions over time.

Retinoblastoma has been known to simulate nonmalignant conditions.4,11 Four of the 6 misdiagnosed retinoblastoma cases in our study presented as intraocular inflammation. Stafford et al13 found that 6.6% of all retinoblastoma cases were misdiagnosed as inflammation. Panophthalmitis, endophthalmitis, and uveitis were the most common terms used for the clinical diagnoses, similar to our findings. This supports the fact that retinoblastoma must be considered in the differential diagnosis of ocular inflammations of childhood.

**CHALLENGING DIFFERENTIATION BETWEEN RETINOBLASTOMA AND COATS DISEASE**

Coats disease and retinoblastoma can also be confused with one another, with previous case reports and series describing histopathologically confirmed retinoblastoma simulating Coats disease clinically.14-18 We found 4 cases of Coats disease simulating retinoblastoma and 1 case of retinoblastoma simulating Coats disease. The time period for these diagnostic errors was 1967 to 1980. However, Steidl et al16 described 2 cases in which Coats disease was misdiagnosed as retinoblastoma and retinoblastoma was misdiagnosed as Coats disease in the 1990s. Even with advances in diagnostic ocular imaging, clini-
cians may still encounter difficulty differentiating between the 2 diseases.

The average age at diagnosis for Coats disease is 11 years and for retinoblastoma is 18 months.2,10 However, in our study, the average age of misdiagnosed Coats disease (simulating retinoblastoma) was 10 months (range, 9 months to 1 year). Perhaps confusion between these 2 diagnoses occurs more often if the patient’s age at presentation is atypical. The 4 patients with misdiagnosed Coats disease were already blind, so enucleation did not alter their visual potential.

**MISDIAGNOSIS OF ENDOPHTHALMITIS**

We found 7 cases of endophthalmitis, nematode (4) and nonnematode (3), misdiagnosed as malignancy. The cases of nematode (presumed Toxocara infection) endophthalmitis all presented with retinal detachments as well. Irvine and Irvine described a case in which Toxocara endophthalmitis was misdiagnosed as retinoblastoma preoperatively. Enucleation owing to undiagnosed endophthalmitis can present a serious consequence because both nematode and nonnematode endophthalmitis are potentially medically and surgically treatable. Pars plana vitrectomy was introduced in 1970, and intravitreal antibiotics were popularized in 197412,13; the 7 cases of misdiagnosed endophthalmitis occurred from 1960 through 1989.

Three of the 7 patients had no light perception visual acuity. Two did not have visual acuity reported but showed total retinal detachment, suggesting light perception visual acuity at best. For 2 patients, visual acuity was described as “progressively decreasing.” Thus, the 2 of 7 eyes enucleated for suspected malignancy but found to have endophthalmitis may have had salvageable, reasonable vision. With better diagnostic means to identify endophthalmitis prior to enucleation, these eyes may have had vision- or eye-sparing treatment.

**CONCLUSIONS**

Misdiagnoses leading to pediatric enucleation have steadily decreased during the past 5 decades, likely owing to improved diagnostic techniques. However, even with advanced technologies, some cases may still be difficult to differentiate. This study reminds ophthalmologists that, in children, benign and malignant intraocular conditions can simulate each other, especially retinoblastoma. Coats disease, Toxocara infection, other types of endophthalmitis, panuveitis, and PHPV. When a diagnosis cannot be established without histopathology, clinicians need to weigh the diagnostic and therapeutic benefits of enucleation against the risk of potential morbidity and mortality without enucleation. In uncertain cases, we recommend discussing the remote possibility of clinical misdiagnosis with caregivers during the pediatric enucleation consent process.

Submitted for Publication: October 3, 2009; final revision received January 4, 2010; accepted January 7, 2010.

Correspondence: Tina Rutar, MD, Department of Ophthalmology, Pediatric Ophthalmology and Strabismus, University of California San Francisco, 10 Koret Way, Room K301, San Francisco, CA 94143 (rutart@vision.ucsf.edu).

**REFERENCES**