Computed Tomography with Histopathologic Correlation in Children with Leukokoria

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Introduction

During the past decade, computed tomography (CT) has become a valuable diagnostic modality in the management of many patients, including those with primarily eye disease. CT has been used to a considerable extent in evaluating children with leukokoria, with the hope that it could make the distinction between children with retinoblastoma and those with pseudoglioma (a term used collectively to include those eye conditions that simulate retinoblastoma).

Retinoblastoma is the most common intraocular malignancy in childhood as well as the major cause of leukokoria that is life-threatening. The clinical distinction of retinoblastoma from the pseudogliomas can often be exceedingly difficult, especially when media opacities preclude adequate visualization of the posterior segment, or when detached retina obscures potential malignancy in the subretinal space. Some studies reveal that approximately 25% of those eyes enucleated because of a diagnosis of retinoblastoma contain simulating lesions. The most common conditions that mimic retinoblastoma are persistent hyperplastic primary vitreous (PHPV), Coats' disease, sclerosing endophthalmitis, and chronic retinal detachment. Intraocular biopsy is not considered an acceptable diagnostic procedure at this time because of the possible risk of seeding the orbit with tumor. Therefore, noninvasive tests assume a major role in the evaluation of children with leukokoria. Indirect ophthalmoscopy, fluorescein angiography, and diagnostic ultrasonography may all potentially increase the accuracy of diagnosis. Since calcium is common in retinoblastoma and absent in most pseudogliomas, CT has been of particular value because of its greater sensitivity in detecting calcium compared to conventional radiography.

It is the purpose of this report to discuss the CT findings in patients with retinoblastoma and various pseudogliomas. In most cases of pseudoglioma the diagnosis was verified and the CT findings correlated with histopathology. The role of CT in the evaluation of children with leukokoria will be discussed in the context of these cases.

Case Reports

CASE 1

An 18-month-old boy was evaluated at the Walter Reed Army Medical Center (WRAMC) Ophthalmology Service, because of a history of an abnormal pupillary reflex and "wandering" of the left eye for several months. Examination revealed that vision was central, steady, and maintained in the right eye, and without any evidence of light perception in the left. Twenty prism diopters of exotropia was present. The right eye was normal to examination. The left retina was totally detached and a yellowish, subretinal mass was present. CT revealed calcification in the vitreous cavity of...
the left eye (Figure 1). The left eye was enucleated and a moderately well-differentiated retinoblastoma with an exophytic pattern of growth was present histopathologically.

CASE 2

A 14-month-old boy presented with a history of abnormal pupillary reflex of the right eye for three months. There was no evidence of light perception in the right eye. Central, steady and maintained fixation was present in the left eye. The retina of the right eye was totally detached. A yellowish exudate appeared to occupy the subretinal space. The left eye was normal to examination. CT revealed homogenous opacification without calcification of the posterior two-thirds of the vitreous cavity of the right eye (Figure 2). The right eye was enucleated and a poorly differentiated exophytic retinoblastoma was present. No calcium was demonstrated in this tumor histologically.

CASE 3

An eight-week-old boy was referred to the WRAMC Ophthalmology Service for evaluation of leukokoria of the right eye. No demonstrable light perception was present in the right eye and fixation appeared normal for his age in the left. The eyes appeared equal in size. Examination of the right eye revealed a shallow anterior chamber and a clear lens. No ciliary processes were seen behind the lens, but since the right pupil could be only dilated to 2 mm with mydriatics it was conceivable that central dragging of ciliary processes was obscured by the iris. The vitreous cavity was occupied by a yellowish white mass. The left eye was normal to examination. B-scan ultrasonography showed a pattern consistent with total retinal detachment. CT revealed a conical mass occupying the vitreous cavity which was best seen with enhancement of the CT density setting (Figure 3). A high-density layered mass occupied the region of the posterior pole. Since retinoblastoma could not be excluded, the right eye was enucleated. Histopathologic examination revealed a detached and dysplastic retina in the area corresponding to the conical density observed on CT (Figure 4). Anteriorly, the ciliary processes were dragged centrally into a mass of mesenchymal tissue present behind the lens. Subretinal blood was present and corresponded to the high-density layered mass on CT. A diagnosis of PHPV with elements of retinal dysplasia was made.

CASE 4

An 18-month-old boy was evaluated at the WRAMC Ophthalmology Service for strabismus of six months' duration. Vision was central, steady, and maintained in the right eye, and no light perception was present in the left. Twenty-five diopters of exotropia was present by the Kincksky test. The right eye was completely normal. The left eye was normal in
FIGURE 4: Histopathologic appearance of Case 3 revealing a detached and dysplastic retina in the area corresponding to the conical density on CT. The retrolental mass consists of loose fibrous connective tissue representing the primary vitreous. Subretinal blood corresponding to the high-density layered mass on CT is noted. Inset shows dragged ciliary processes. (H&E × 2.5; inset H&E × 25)

FIGURE 5: (Case 4) Totally detached retina noted with telangiectatic vasculature and subretinal exudate.

FIGURE 6: CT appearance of Case 4 revealing homogenous opacification of the left vitreous cavity.

FIGURE 7: Histopathologic appearance in Case 4 reveals total retinal detachment with eosinophilic subretinal exudate containing cholesterol clefts. Some retinal vascular anomalies (arrows) are noted in the inset. (H&E × 2.5; inset H&E × 25)

size with a clear lens. The retina was totally detached and focal telangiectatic vessels were present (Figure 5). There was a yellowish subretinal exudate. CT revealed homogeneous opacification of the left vitreous cavity (Figure 6). The left eye was enucleated. Histopathologic examination revealed findings consistent with a diagnosis of Coats’ disease (Figure 7).

CASE 5

A three-year-old girl was referred to the Ophthalmology
Service, WRAMC, for evaluation of strabismus, presumably secondary to total retinal detachment of the right eye. There was no history of trauma. No light perception was present in the right eye and her vision was 20/20 in the left eye. Thirty prism diopters of esotropia was present by the Krimsky test. The left eye was entirely normal to examination under anesthesia. Examination of the right eye revealed a totally detached retina with many fixed folds (Figure 8). Giant intraretinal cysts were noted in the inferior quadrant. In the superior temporal quadrant a retinal dialysis with rolled edges was noted. CT revealed minimal opacification of the right vitreous cavity (Figure 9). A diagnosis of inoperable rhegmatogenous retinal detachment was made and it was decided to follow the patient closely. The ocular condition has remained stable over a period of two years.

Discussion

Computed tomography has significantly altered the diagnostic approach to many diseases, including the workup of leukokoria in children where it has improved the accuracy of diagnosis of retinoblastoma. The CT features of retinoblastoma have been well documented. An abnormal intraocular calcific density is the hallmark of CT diagnosis of retinoblastoma. A variety of other ocular lesions containing calcium, e.g., ptosis, choroidal osteoma, drusen of the optic disc, and glial hamartoma are usually distinguishable from retinoblastoma by history and clinical examination. Calcium can be demonstrated in the majority of retinoblastomas although it is usually absent in the orbital portions of tumors with extraocular extension (Figure 10). Though CT is more sensitive than conventional radiography in detecting intraocular calcium, its relative sensitivity as compared to diagnostic ocular ultrasonography has not been determined. Retinoblastomas show variable degrees of CT enhancement with intravenous injection of contrast material, but this feature has not proven to be particularly useful in establishing the diagnosis. Additionally, CT may demonstrate extraocular spread and extension along the optic nerve, findings which may be impossible to document prior to surgery using other tests. The presence of orbital spread and optic nerve invasion can have a significant bearing on the selection of therapy.

Since the initial description of the entity known as trilateral retinoblastoma, a condition where children with bilateral retinoblastomas develop a primary intracranial retinoblastoma, CT has played a major role in establishing the diagnosis and distinguishing the entity from direct intracranial spread. The tumor is typically located in the pineal or parasellar region. When located in the pineal region, the tumor usually manifests itself years after the diagnosis of bilateral retinoblastoma. On the other hand, tumors in the parasellar region typically occur before or at the same time as the ocular tumors. The intracranial tumors histologically may reveal features of well-differentiated retinoblastoma or may show only non-specific features of primitive, neuro-ectodermal tumors (PNET). This entity should be considered in the differential diagnosis of
FIGURE 10: CT view of the orbits in a boy with a calcified retinoblastoma. Calcium cannot be seen in the portion of tumor that has invaded the orbit.

FIGURE 11: Follow-up CT scan in a child with trilateral retinoblastoma shows ectopic retinoblastoma in the region of the pineal gland and secondary hydrocephalus. Views of the orbits (inset) demonstrate the ocular prosthesis implanted during previous surgery. Retinoblastoma in the other eye was not present at this time.

FIGURE 12: Histopathologic appearance in sclerosing endophthalmitis revealing chronic inflammation manifested by round cell infiltration and collagen formation. Arrow indicates site of intravitreal larval granuloma. (H&E × 2.5)

children with bilateral, familial retinoblastoma who present with symptoms suggestive of an intracranial space-occupying lesion. Computed tomography, besides showing an abnormal midline intracranial density which enhances with contrast, may reveal bone destruction and hydrocephalus (Figure 11).\(^\text{10}\) It remains to be determined whether children at risk for developing such ectopic intracranial retinoblastomas should have periodic CT evaluations. Guidelines for the intervals between such studies and the period of time during which the children remain at risk also need to be established.

There are several studies that describe the CT findings of the more common causes of pseudoglioma. Mafee and Goldberg\(^\text{11,12}\) have described computed tomography of eyes with PHPV. Their description includes microphthalmos, shifting, layered (subhyaloid) blood, axial intravitreal opacities which enhance with intravenous contrast, and absence of calcification. The axial mass was attributed to retrolental vascularized soft tissue along Cloquet's canal. Histopathologic correlation of their findings was not made. In our patient with PHPV (Case 3), the axial conical opacity, though not clearly seen on routine CT, was quite obvious after manipulating the density settings of the computer. Contrast material was not injected. We have noted this phenomenon on other occasions in PHPV.\(^\text{13}\) The high den-
sity shifting layer thought to be subhyaloid blood by Mahee and associates was present in the CT studies of our patient also, but on histopathological examination proved to be subretinal rather than subhyaloid blood. In our patient, the axial conical opacity corresponded to detached and dysplastic retina. Our patient had a normal-sized globe. Microphthalmia in itself is not diagnostic of PHPV, though it is often present. Secondary glaucoma which sometimes accompanies PHPV may enlarge a previously small globe. Microphthalmia is probably better assessed clinically and by A-mode ultrasonography than CT. Mafee and associates found CT more reliable than ultrasound in diagnosing PHPV. Our experience parallels theirs. Finally, it may be noted that on rare occasions retinoblastoma may coexist with PHPV in the same or opposite eye thus adding further complexity to the situation.14

Sherman, McLean and Brallier15 described a homogeneous intravitreal density in two patients with unilateral Coats' disease diagnosed histopathologically. The total retinal detachment and subretinal exudate corresponded to the homogeneous intravitreal density on CT which they felt was indistinguishable from that of a noncalcifying retinoblastoma.

Endophthalmitis, secondary to the larval stage of Toxocara canis is now a well-recognized cause of leukokoria in children.16 In such patients, the death of the larva has resulted in severe intraocular inflammation. Even if the larva cannot be found in histologic sections, the pathologic changes are highly characteristic and referred to as sclerosing endophthalmitis (Figure 12). We have previously described CT findings in three cases of histologically proven sclerosing endophthalmitis.17 These findings consist of a homogeneous intravitreal density that corresponds to detached retina, organized vitreous and inflammatory subretinal exudate. These CT findings are similar to those seen in Coats' disease (Case 4), and noncalcifying retinoblastoma (Case 2).

Similarly, CT studies in longstanding, retinal detachments may reveal intravitreal opacification, corresponding to thickened, degenerated retina and subretinal exudate. When such a diagnosis is made and it is felt that the detachment is of a rhegmatogenous type, the patient should continue to be followed closely so that any change in the appearance of the eye heralding a subretinal malignancy can be discovered early (Case 5).

Retinopathy of prematurity (retrolental fibroplasia) may on occasion present as unilateral or bilateral leukokoria. The history and clinical findings are usually diagnostic in this bilateral but often markedly asymmetric disease. In the most advanced situation, both eyes are microphthalmic with very shallow anterior chambers and totally detached and organized retinas which are usually visible through a translucent retrolental cyclic membrane.

In conclusion, the major drawback of CT in the differential diagnosis of leukokoria is the inability to distinguish between noncalcifying retinoblastoma and several types of pseudogliomas which present with a similar appearance on CT, i.e., a homogeneous intravitreal density without evidence of calcium. This homogeneous density appears to be a common feature of degenerative retina with thick subretinal fluid in longstanding rhegmatogenous retinal detachments, exudate rich in protein and lipid in Coats' disease, thick inflammatory subretinal exudate and membranes in sclerosing endophthalmitis, or noncalcifying retinoblastoma.

Summary

Computed tomography (CT) constitutes a major advance in noninvasive diagnostic investigation of children with leukokoria, especially where media opacities preclude adequate visualization of the posterior segment, and, performed in conjunction with other studies such as diagnostic ultrasonography, has significantly improved diagnostic accuracy.

Although retinoblastoma, the most common life-threatening cause of leukokoria, usually presents with characteristic CT findings of intraocular calcification, during extraocular extension, the orbital portions of the tumor are non-calcific and contrast dramatically with the intraocular portion.

Currently CT is also the best available technique for diagnosis of trilateral retinoblastoma.

Computed tomographic features of several types of pseudogliomas (a collective term for lesions commonly mistaken for retinoblastomas) are also discussed with histopathologic correlation. In persistent hyperplastic primary vitreous, a conical density in CT corresponded to detached and dysplastic retina. A high density layered opacity corresponded to subretinal blood. In Coats' disease and sclerosing endophthalmitis homogenous intraocular CT density corresponds to vitreous and subretinal exudates radiologically indistinguishable from non-calcific retinoblastoma. Long-standing retinal detachments in children occasionally presenting with leukokoria showed subtle homogenous intraocular densities on CT.

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References

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