Leading Simulators of Retinoblastoma

Many pediatric disorders can simulate retinoblastoma; a detailed history and clinical examination are crucial for timely diagnosis.

BY APARNA RAMASUBRAMANIAN, MD; AND CAROL L. SHIELDS, MD

Retinoblastoma is the most common pediatric intraocular malignant tumor.[1] A study from London showed that 5-year survival rate for children with unilateral retinoblastoma increased from 85% for those diagnosed from 1963 to 1967 to 97% for those diagnosed from 1998 to 2002.[2] Although chemotherapy has played an important role in improved survival, others speculate that early diagnosis could also contribute. Timely diagnosis and appropriate treatment are crucial in the management of retinoblastoma.

The most common presenting signs of retinoblastoma are leukocoria (56%), strabismus (4%) and poor vision (8%).[3] These presenting symptoms can be common to numerous pediatric eye conditions including hereditary, developmental and inflammatory disorders.[4] Shields and co-workers[5] studied 500 patients referred with the diagnosis of possible retinoblastoma and, following evaluation, found that 212 had simulating lesions and not retinoblastoma. The three conditions that most closely simulated retinoblastoma were persistent hyperplastic primary vitreous (PHPV) (28%), Coats disease (16%) and ocular toxocariasis (16%).[5] (Table 1) In this review we discuss the differential diagnoses of retinoblastoma and elaborate the key features to distinguish them.

COATS DISEASE

Coats disease is an idiopathic condition characterized by telangiectatic and aneurysmal retinal vessels with intraretinal and subretinal exudates.[6] The median age of diagnosis is approximately 5 years (range, 1 month to 63 years).[7]

The stages of Coats disease[8] are:

- Stage 1: Retinal telangiectasia only
- Stage 2: Telangiectasia and exudation
  - A: Extrafoveal exudation
  - B: Foveal exudation
- Stage 3: Exudative retinal detachment
  - A: Subtotal detachment
    - 1: Extrafoveal detachment

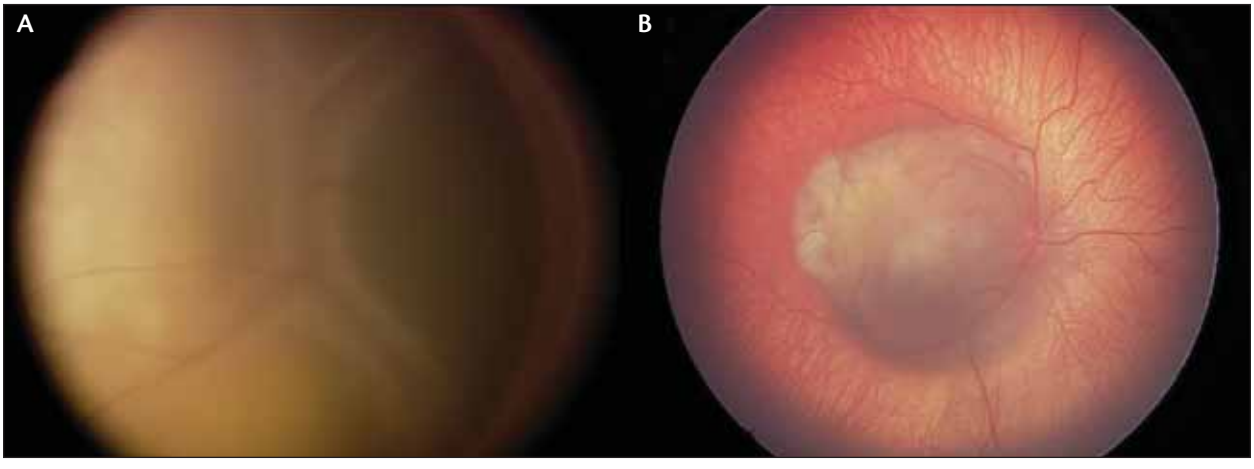

Figure 1. Clinical features of retinoblastoma. Retinoblastoma with total retinal detachment (A). Macular retinoblastoma with feeder vessels (B).

2: Foveal detachment
B: Total detachment

• Stage 4: Total retinal detachment and glaucoma

• Stage 5: Advanced end stage disease

The early stages of Coats disease can simulate retinoblastoma due to the presence of macular exudation (Figure 2B). The differentiating features[9] include:

• Coats disease shows irregular lightbulb telangiectasia in the peripheral fundus;

• Coats disease shows yellow subretinal and intraretinal exudation; and

• the retinal vessels in Coats disease tend to course over the detachment (Figure 2B) and do not dip into it as in retinoblastoma (Figure 1B).

The advanced stages of Coats disease (total retinal detachment, xanthocoria, painful glaucoma secondary to angle closure glaucoma) are difficult to differentiate from retinoblastoma. In more advanced cases of Coats disease (Figure 2A) the differentiating features from retinoblastoma[9] (Figure 1A) include:

• yellow pupillary reflex (xanthocoria) in Coats disease compared with white reflex (leukocoria) in retinoblastoma;

• presence of yellow subretinal material (exudates) and peripheral telangiectasia in Coats disease; and

• fundus fluorescein angiography documentation of retinal telangiectasia in Coats disease.

Calcification is uncommon in Coats disease and if present appears as linear shadows along the retinal pigment epithelium (RPE) or minimally scattered in chronically detached retina on ultrasonography. The calcification seen in Coats disease is usually due to osseous metaplasia of the RPE.[10]

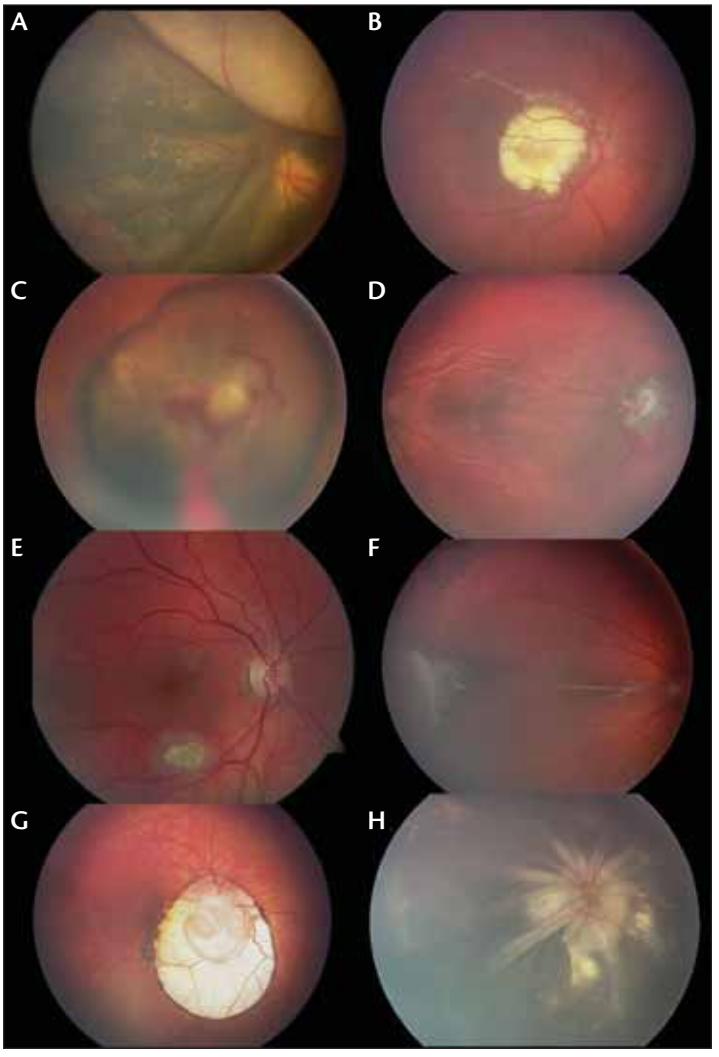

Figure 2. Clinical features of lesions that simulate retinoblastoma. Advanced Coats disease with total retinal detachment, subretinal exudation and peripheral telangiectasia (A). Macular exudation in Coats disease with shallow retinal detachment mimicking retinoblastoma (B). Fibrovascular stalk and vitreous hemorrhage in a patient with persistent hyperplastic primary vitreous (C). Ocular toxocariasis with peripheral granuloma and vitreoretinal traction causing straightening of retinal vessels (D). Retinal astrocytic hamartoma; note the mild traction on the artery underlying the mass (E). Retinal fold and peripheral fibrovascular proliferation in a patient with familial exudative vitreoretinopathy (F). Inferior optic disc and chorioretinal coloboma (G). Total exudative retinal detachment in a patient with morning glory disc anomaly (H).

PERSISTENT HYPERPLASTIC PRIMARY VITREOUS (PHPV)

Persistent hyperplastic primary vitreous (PHPV) or persistent fetal vasculature (PFV) is a disease of uncertain etiology that manifests in healthy full-term infants.[11] PHPV is the result of anomalous development of the primary vitreous as it persists into the period of formation of the secondary vitreous.[12] The severity of PHPV can range from pupillary strands across the iris or an isolated Mittendorf dot on the back of the lens to more severe forms with retrolenticular membranes, retinal dysplasia, or detachment.[11]

The features that help distinguish retinoblastoma from PHPV include:

• PHPV is usually a unilateral condition with no family history;

• PHPV displays microphthalmia, microcornea, shallow anterior chamber, persistent tunica vasculosa lentis, and

TABLE 1. LEADING SIMULATORS OF RETINOBLASTOMA IN AN ANALYSIS OF 500 CHILDREN[5]

Pseudoretinoblastoma	%
Persistent hyperplastic primary vitreous	28
Coats disease	16
Ocular toxocariasis	16
Retinopathy of prematurity	5
Combined hamartoma	4
Coloboma	4
Vitreous hemorrhage	4
Astrocytic hamartoma	3
Familial exudative vitreoretinopathy	3
Rhegmatogenous retinal detachment	2
X-linked retinoschisis	2
Medulloepithelioma	2
Congenital cataract	2

cataract, features that are uncommon in eyes with retinoblastoma; and

• PHPV shows a central fibrovascular stalk emanating from the disc often with retinal detachment (Figure 2C).

Ultrasonography confirms the retinal detachment or stalk of PHPV, whereas retinoblastoma often displays a calcified mass.

OCULAR TOXOCARIASIS

Toxocariasis constitutes 1% to 2% of all uveitis in children, and the average age at diagnosis is 8 years (ranging from 2 to 31 years).[13] There are three manifestations of ocular involvement, including chronic endophthalmitis, posterior granuloma, and peripheral granuloma.[13] Chronic endophthalmitis due to toxocariasis presents as severe granulomatous vitreitis with cyclitic membrane, retinal detachment, leukocoria, and hypopyon. The granulomas present as white pseudogliomatous mass with vitreous traction membranes and retinal folds (Figure 2D). The features that aid in establishing the clinical diagnosis of toxocariasis include:

• history of exposure to puppies;

• lack of calcification on ultrasonography;

• marked vitreous inflammation with yellow grey vitreous strands extending from the chorioretinal lesion;

• retinal dragging with fixed folds in the retina; and

• solitary granulomas with a translucent center (in some cases this can resemble retinoblastoma, but the granuloma does not grow over time).

A positive serologic test, such as enzyme immunoassay, is supportive but not diagnostic, as exposure to the *toxocara* organism is common.

RETINAL ASTROCYTIC HAMARTOMA

Retinal astrocytic hamartoma is the best-known ocular manifestation of tuberous sclerosis complex and is generally a sessile or slightly elevated lesion in the nerve fiber layer of the retina (Figure 2E).[14]

The clinical features of astrocytoma that differentiate it from retinoblastoma include:

• systemic and ocular manifestations of tuberous sclerosis complex such as ash leaf macules, adenoma sebaceum, intracranial astrocytoma, cardiac rhabdomyoma, and renal angiomyolipoma;[15]

• lack of retinal detachment;

• the retinal blood vessels course under or around the astrocytic tumor showing subtle traction component; and

• in rare cases, astrocytic hamartoma shows retinal exudation, unlike retinoblastoma.

In case of suspicion, the lesion can be monitored monthly to confirm stability, unlike retinoblastoma, which would typically show growth within 1 to 2 months. Fine needle aspiration biopsy can rarely be performed to establish diagnosis.

FAMILIAL EXUDATIVE VITREORETINOPATHY

FEVR is characterized by failure of peripheral retinal vascularization, and the complications result from subsequent retinal ischemia.[16] The diagnosis of FEVR (Figure

Timely diagnosis and treatment are of paramount importance for preservation of the eye and for life prognosis.

2F) is based on:

• family history compatible with autosomal dominant inheritance; and

• bilateral peripheral retinal avascularity, which is more apparent on fundus fluorescein angiography.

Other retinal findings include retinal neovascularization, fibrovascular mass, falciform retinal folds and retinal traction causing straightening of vessels.

COLOBOMA

Optic nerve and retinochoroidal coloboma are caused by incomplete closure of the embryonic fissure during fetal development.[17] A chorioretinal coloboma appears as a sharply demarcated, glistening white, bowl-shaped excavation in the fundus (Figure 2G), and the white color is caused by the sclera being visible in the absence of the choroid, retina, and RPE. If the coloboma is large enough, it can present as leukocoria.[17]

RETINAL DETACHMENT

Retinal detachment caused by any condition can lead to diagnostic dilemma due to suspicion of retinoblastoma. Figure 2H demonstrates retinal detachment due to morning glory disc anomaly. This can be differentiated from retinoblastoma by the excavated anomalous disc and presence of yellow subretinal exudation. Careful ophthalmoscopic evaluation to detect tumor and seeds has paramount importance to differentiate retinal detachment from retinoblastoma and other disorders.

RETINOPATHY OF PREMATURITY

Retinopathy of prematurity results from the failure of development of the normal retina in premature neonates exposed to high levels of oxygen during the postnatal period. It is associated with abnormal vascularization, fibrosis, and retinal detachment, which can produce a white reflex.[18]

MISCELLANEOUS CONDITIONS

The other conditions that can simulate retinoblastoma include Norrie disease, incontinentia pigmenti, congenital retinoschisis, endogenous endophthalmitis, medulloepithelioma, and vitreous hemorrhage.[4]

SUMMARY

Many pediatric eye disorders can simulate retinoblastoma. Timely diagnosis and treatment are of paramount importance for preservation of the eye and for life prognosis. Detailed history including family history and meticulous ophthalmoscopic examination is crucial for differential diagnosis. Ancillary testing like ultrasonography, fluorescein angiography, computed tomography, and magnetic resonance imaging, such as aid in the diagnosis. ■

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