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# CLINICAL PATHOLOGIC REVIEWS

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# Plexiform Pigmented Schwannoma of the Uvea

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**Abstract.** Schwannoma is a slow growing solitary tumor that preferentially involves spinal nerve roots, and sympathetic, cervical, and vagus nerves. There are several clinico-pathologic variants of schwannoma, including schwannoma with a degenerative change (ancient schwannoma), cellular schwannoma, plexiform schwannoma, epithelioid schwannoma, and melanotic schwannoma. About 10% of cases of schwannomas are associated with multi-system disorders such as neurofibromatosis, schwannomatosis, multiple meningiomas, and Carney complex. Schwannoma rarely present as an intraocular tumor and is often misdiagnosed as malignant melanoma. Immunohistochemical positivity with S-100 stain and demonstration of long-spaced collagen (Luse bodies) are helpful in establishing the diagnosis. In this article, we review the clinical and histopathological findings of a sporadic plexiform pigmented schwannoma involving the iris, ciliary body, and the choroid. (**Surv Ophthalmol 51**:162–168, 2006. © 2006 Elsevier Inc. All rights reserved.)

**Key words.** pigmented • plexiform • schwannoma • tumor • uveal

Schwannoma is a slow growing solitary tumor that occurs sporadically. The tumors have a tendency to preferentially involve head, neck, and the extremities.[18] The spinal nerve roots, and sympathetic, cervical, and vagus nerves are most commonly affected. Smaller tumors do not cause pain or other neurologic symptoms. The clinico-pathologic variants of schwannoma include schwannoma with a degenerative change (ancient schwannoma), cellular schwannoma, plexiform schwannoma, epithelioid schwannoma, and melanotic schwannoma.[10] In addition, about 10% of cases of schwannomas are associated with multi-system disorders such as neurofibromatosis,[14] schwannomatosis,[12] multiple meningiomas,[1] and Carney complex[2] (Table 1).[1]

Benign peripheral nerve sheath tumors rarely present as intraocular tumors, and are often misdiagnosed as malignant melanoma.[5] In this report, we review the clinical and histopathological findings of a sporadic plexiform pigmented schwannoma involving the iris, ciliary body, and the choroid.

## Case Study

A 9-year-old white girl was referred to the Cole Eye Institute by her ophthalmologist for evaluation of iris and choroidal masses in her left eye. At the age of 7 years she was diagnosed with anisometropic amblyopia in her left eye, which was treated with corrective lenses and patching. Her vision improved to 20/25. Iris nodules at the pupillary margin were initially observed at that time. The patient stopped using her glasses and despite the reinstitution of





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TABLE 1

*The Clinical–Pathologic Variants and Multi-system Associations of Schwannoma*

| Types | Salient Feature |
|---|---|
| Variants | |
| Degenerative change (ancient schwannoma) | Retroperitoneal marked nuclear atypia |
| Cellular schwannoma | Predominant Antoni A type |
| Plexiform schwannoma | Multinodular |
| Epithelioid schwannoma | Epthelioid Schwann cells |
| Melanotic schwannoma | Melanogenesis within Schwann cells, sympathetic nervous system |
| Associations | |
| Neurofibromatosis type 2 | Bilateral vestibular schwannoma |
| Neurofibromatosis type 1 | Multiple neurofibromas |
| Schwannomatosis | Multiple schwannomas (extra vestibular), segmental distribution |
| Multiple meningiomas | Multiple meningiomas |
| Carney complex | Melanotic schwannoma, myxoma, spotty skin pigmentation, endocrine tumors |

Based on data from Weiss and Goldblum.[18]

corrective lenses and full-time patching for 3 months, the vision in her left eye did not improve beyond 20/200. There was no personal or family history suggestive of neurofibromatosis.

On presentation, right eye uncorrected vision was 20/20 and left eye best corrected ($-6.00$ $+2.00 \times 115$) visual acuity 20/200. The right eye was entirely normal. Examination of the left eye revealed darkening and a peculiar thickening of the iris from 7 o'clock to 1 o'clock, with loss of iris architecture (Fig. 1, left). The pigmented area superiorly demonstrated partially collapsed pupillary margin cysts (iris flocculi) with irregularity of the pupillary margin. Ophthalmoscopic examination revealed multiple raised amelanotic choroidal nodules in the supero-nasal and supero-temporal quadrants ranging in size 2.5–6.0 mm in basal dimension and 0.5–3.0 mm in thickness (Fig. 2, top left). Areas of sub-retinal fluid were noted adjacent to the larger nodule in the supero-temporal quadrant. B-scan ultrasonography showed a multi-focal thickening of the choroids (Fig. 2, top right) in the corresponding areas with low internal reflectivity (Fig. 2, bottom). Ultrasound biomicroscopy revealed thickening of the iris and ciliary body with greatest thickness of 1.3 mm at 9 o'clock (Fig. 1, right). Although the differential diagnosis included ocular melanocytosis, uveal metastasis, and uveal neurofibromatosis, the possibility of a diffuse uveal melanoma could not be completely excluded. Systemic evaluation was negative for primary systemic malignancy and neurofibromatosis. Following detailed discussions with the parents close observation was elected.

Subsequent clinical examination and ultrasound findings suggested enlargement of all lesions. An iris

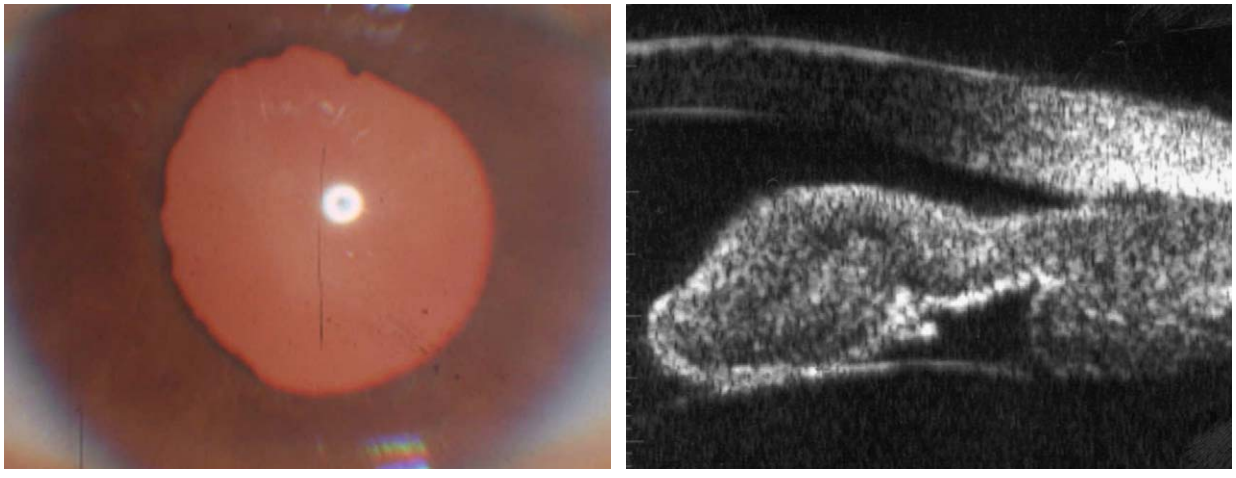

*Fig. 1.* *Left:* External appearance of the left eye. Note hyperpigmentation of the nasal iris and irregularity of the pupillary margin with nasal pupillary margin cysts (iris flocculi). *Right:* Ultrasound biomicroscopy demonstrating thickened iris and ciliary body.

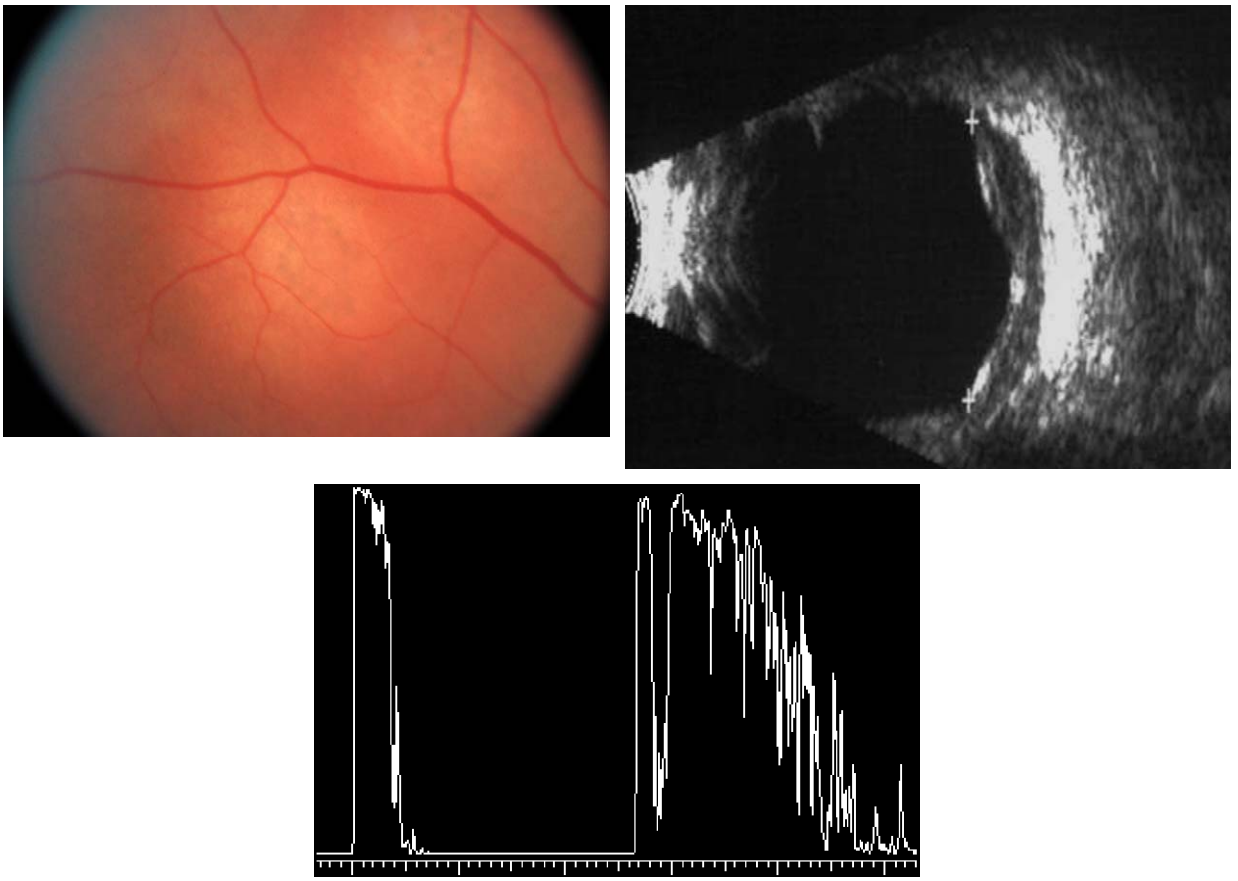

*Fig. 2.* *Top left*: Fundus photograph showing two raised amelanotic choroidal nodules in the supero-nasal quadrant of the left eye. *Top right:* B-scan ultrasonograph. Multi-focal thickening of the choroid in the corresponding areas. *Bottom:* A-scan ultrasonograph showing low internal reflectivity of the lesions.

biopsy was performed through a clear corneal incision without disturbing the conjunctiva. Preplaced 5-0 nylon sutures parallel to the incision were used to gape the wound and prolapse iris to minimize dispersion of tumor cells. A DeWecker's scissors and Castroviejo 0.12 forceps were used to make a single full-thickness iridectomy at 11 o'clock position.

## Histopathological Features

Light microscopic examination of the specimen showed a section of iris including the anterior border layer, stroma, and pigmented epithelium (Fig. 3, top left). There was a heavily pigmented melanocytic proliferation on the posterior aspect of the iris (Fig. 3, top right). The stroma contained proliferation of spindle shaped cells with bland nuclei and abundant eosinophilic cytoplasm. Certain areas of tissue demonstrated groups of nuclei tending to palisade, in an Antoni A pattern (Fig. 3, bottom). Verocay bodies were not evident. The light microscopic findings were most suggestive of a benign neoplasm of neural origin, either a neurofibroma or a schwannoma.

Immunohistochemistry would not have differentiated a neurofibroma from a schwannoma as both tumors would have stained positively with the S-100 stain. Therefore, electron microscopy was performed on refixed tissue. It revealed spindle cells with interdigitating long, tapering processes consistent with Schwann cell origin (Fig. 4, top left). Mixed in with the non-pigmented cells were cells containing numerous melanin granules (Fig. 4, top right). Long-spaced collagen (Luse bodies)[11] were also noted in the sample (Fig. 4, bottom). There was no evidence of a complex network of branching rough endoplasmic reticulum, which typically characterize fibroblastic proliferation. Given these findings, a diagnosis of pigmented schwannoma was made.

## Follow-up

Over the next 2 years the visual acuity continue to be reduced due to progressive accumulation of the subretinal fluid and, faced with a possibility of an

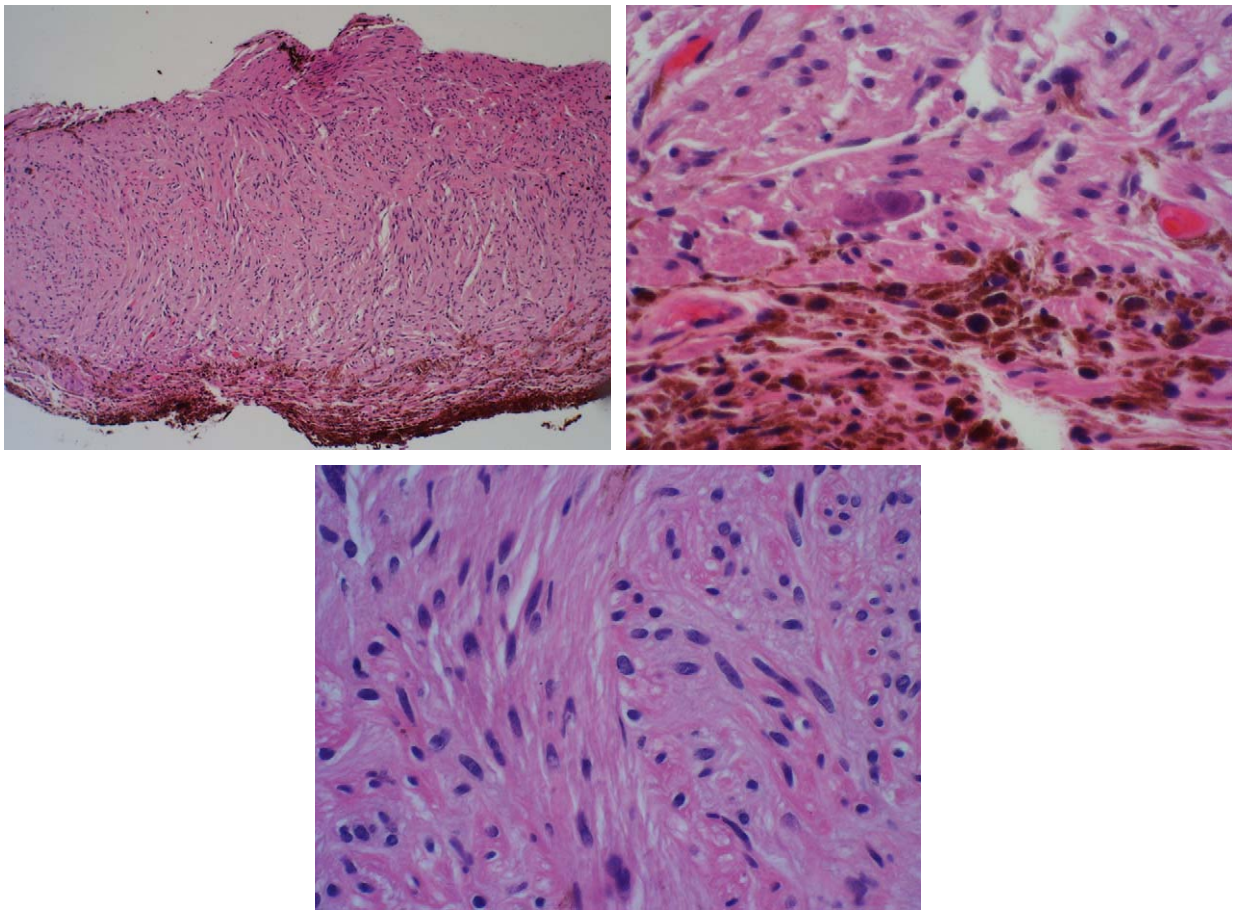

*Fig. 3.* *Top left*: Photomicrograph showing iridectomy specimen (hematoxylin and eosin, ×10). *Top right:* Note heavily pigmented melanocytic proliferation on the posterior aspect of the iris (hematoxylin and eosin, ×200). *Bottom*: The spindle shaped cells have bland nuclei and abundant eosinophilic cytoplasm with nuclei tending to palisade (hematoxylin and eosin, ×250).

unusual uveal tumor, enucleation was performed. The histopathologic findings of the enucleated globe suggested pigmented schwannoma and were similar to the features of an incisional biopsy described above. However, the tumor revealed a multinodular configuration with full thickness involvement of the choroid (Fig. 5) suggestive of a plexiform variant of schwannoma. In the posterior choroid tumor had areas with numerous ganglion cells. The tumor also had extended around the blood vessels through the emissarial canals and around the optic nerve. Although cytologic and histologic appearance of the neoplasm were benign, the growth pattern indicated locally aggressive behavior. Therefore, the neoplasm was classified as having uncertain malignant potential.

## Discussion

The clinical findings of a uveal schwannoma have been well documented in the literature.[5] The tumor appears as a solitary, amelanotic lesion usually of the ciliary body or choroid. The ophthalmoscopic, angiographic, and ultrasonographic findings are not helpful in differentiating it from uveal melanoma.[5] Diffuse hyperpigmentation and irregular thickening of the iris in association with uveal melanoma should always raise the suspicion of ocular melanocytosis,[16] even in absence of cutaneous, episcleral, or choroidal hyperpigmentation.[7] Considering the fact that uveal melanoma is rare in children,[17] and that the multi-focal tumor in absence of a systemic primary malignancy seemed to grow slowly, we considered the possibility of other unusual tumors such as neurofibroma or schwannoma. Involvement of iris provided an opportunity to obtain tissue biopsy. A clear corneal approach was used to avoid access of tumor cells to conjunctival vasculature.

Light microscopy revealed that the tumor was pigmented and was composed of spindle cells with bland nuclei that were palisading in an Antoni A

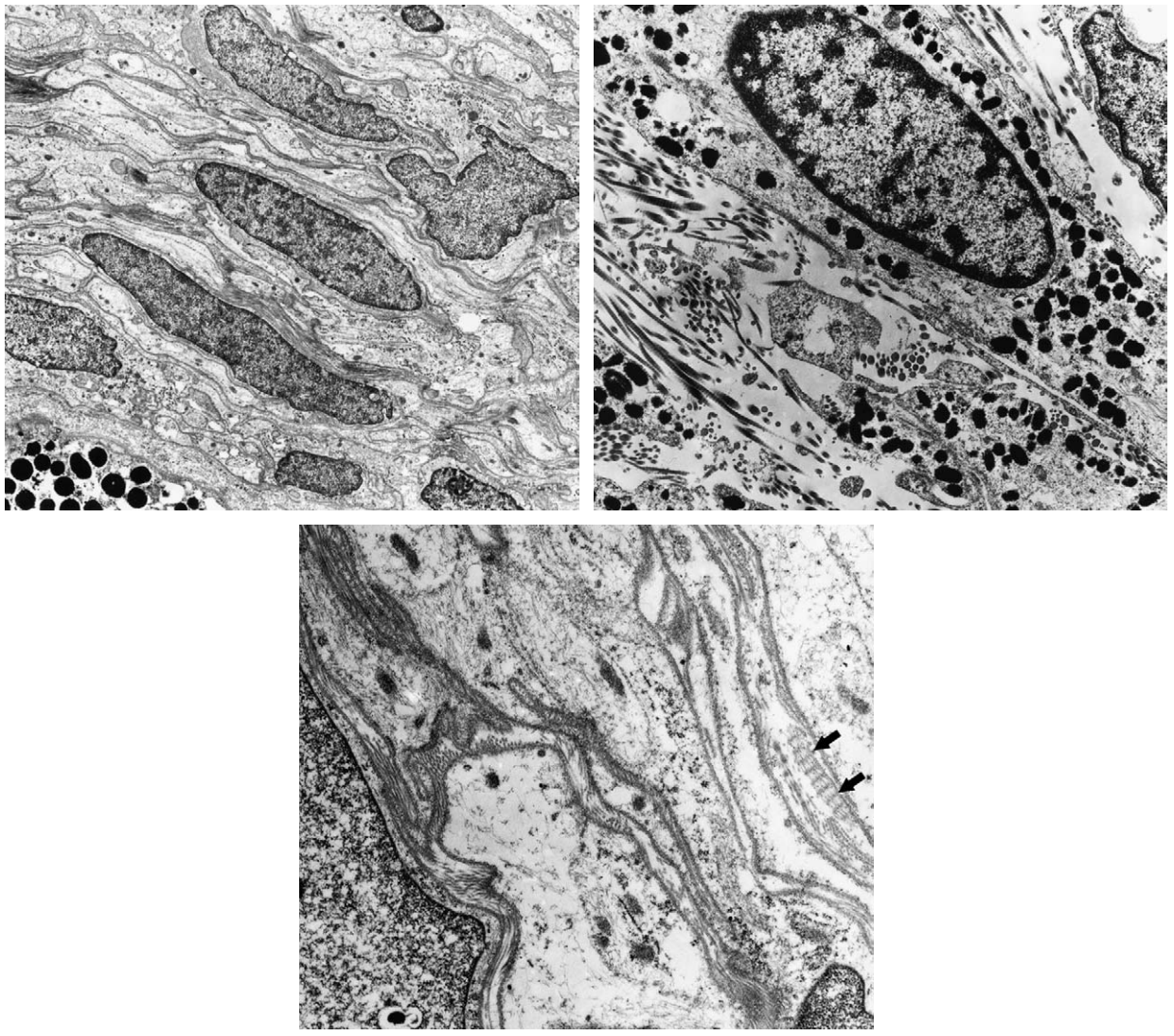

*Fig. 4. Top left:* Electron photomicrograph microscopy shows spindle cells with interdigitating tapering processes consistent with Schwann cell origin. *Top right:* Cells containing numerous melanin granules. *Bottom:* Long-spaced collagen (Luse bodies, arrows).

pattern, findings which were highly suggestive of a schwannoma. In contrast, neurofibromas are composed of a heterogeneous cell population of axons, fibroblasts, and Schwann cells.[18] Although multifocal uveal melanoma can arise in the setting of oculo(dermal) melanocytosis,[8] the light microscopic finding of bland cytology was against the diagnosis of a malignant tumor such a melanoma. The electron microscopy showed features of Schwann cells and long-spaced collagen (Luse bodies) confirming the diagnosis of a schwannoma. Numerous cells containing melanin granules were also observed but there was no convincing evidence of melanogenesis indicative of in situ melanin synthesis. These findings led to the final diagnosis of pigmented schwannoma rather than a melanotic schwannoma.[13]

To our knowledge, there is one previously published case of a melanotic schwannoma of the choroid.[15] A 21-year-old woman underwent enucleation of the right eye for a slowly enlarging pigmented choroidal mass that was suspected to be a choroidal melanoma. Although, the histopathologic findings of our case are similar to the findings of the published case, there are marked differences in clinical presentation of the two cases.[15] Our case presented as a diffuse multi-nodular involvement of the iris, ciliary body, and the choroid reminiscent of a plexiform schwannoma. In addition, there was absence of melanogenesis, an important feature of melanotic schwannoma.

Schwannoma is known to occur in the setting of various multi-system disorders. Vestibular schwannoma is the hall mark of neurofibromatosis type 2[4] and

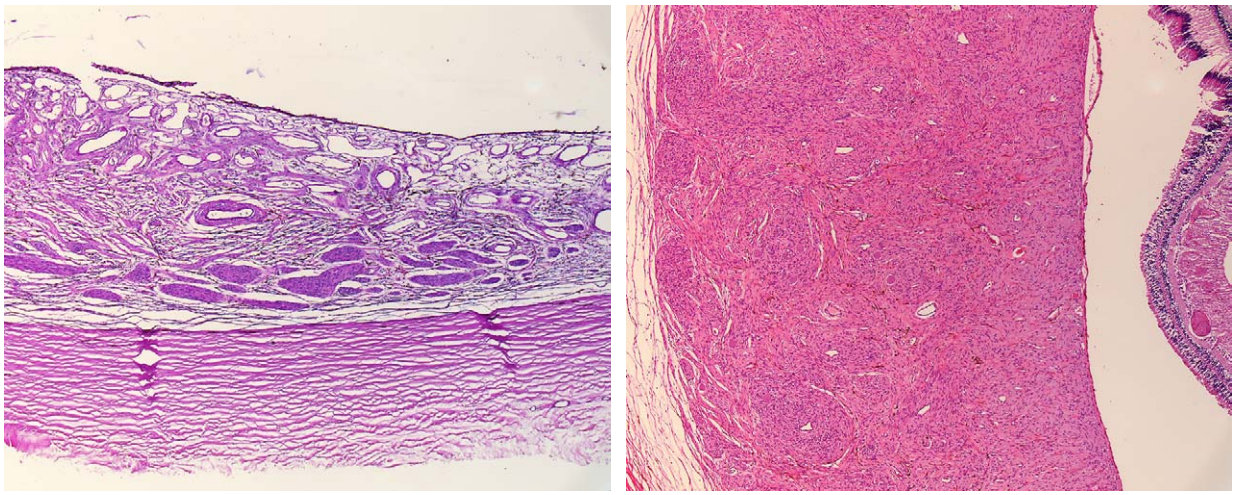

*Fig. 5. Left:* Histopathologic evaluation of the enucleated globe showing involvement of anterior choroid. (hematoxylin and eosin, ×150). *Right:* In the posterior choroid, tumor is multinodular and has areas with numerous ganglion cells (hematoxylin and eosin, ×100).

extravestibular schwannoma is only rarely associated with neurofibromatosis type 1.[6,14] Schwannomatosis is now considered to be a genetically distinct entity manifesting as multiple extra-vestibular schwannomas.[9,12] The Carney complex is an association of melanotic schwannoma with myxomas, spotty skin pigmentation, and endocrine tumors, which is transmitted as an autosomal dominant trait.[2] About half of the cases with melanotic schwannoma have findings of Carney complex and about 20% of melanotic schwannoma may be multiple with greater probability of associated Carney complex.[3] Our case did not have clinical findings suggestive of Carney complex.

Our case represents a rare variant of uveal schwannoma diagnosed by an iris biopsy. Benign peripheral nerve sheath tumor should be considered in the differential diagnosis of an atypical uveal mass.

## Method of Literature Search

The Ovid Medline database from 1966 to March 2005 was searched using key words *pigmented schwannoma*, which were mapped to the subject headings. The search was limited to humans but no other limits were imposed. Combining these results with search results of *uveal neoplasms* did not identify any publication. However, when less restrictive key word *schannoma* was used, 12 articles were identified. A review article previously published in *Survey of Ophthalmology* was identified and used as a reference.

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The authors reported no proprietary or commercial interest in any products mentioned or concepts discussed in this article.

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