Malignant Melanoma Arising From Unusual Conjunctival Blue Nevus

Hakan Demirci, MD; Carol L. Shields, MD; Jerry A. Shields, MD; Ralph C. Eagle, Jr, MD

Cellular blue nevus is an uncommon pigmented tumor in the conjunctiva, where it generally appears as a deep, circumscribed, pigmented conjunctival mass. We report a case of conjunctival blue nevus that clinically resembled primary acquired melanosis and gave rise to conjunctival melanoma. A 41-year-old man developed a diffuse pigmented mass in the inferior fornix of his left eye. Over a 20-year period, he noted slight progression of the pigment. Foci of epibulbar pigmentation were also present. The lesion resembled primary acquired melanosis. Excisional biopsy and adjuvant cryotherapy were performed. Histopathologic examination disclosed an intense infiltrate of heavily pigmented dendritic melanocytes with aggregates of less pigmented plump cells in the substantia propria. The conjunctival epithelium was normal. Malignant cellular features consistent with melanoma were observed in some foci. Cellular blue nevus of the conjunctiva can simulate primary acquired melanosis and can give rise to malignant melanoma.

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Blue nevus is a relatively uncommon benign pigmented lesion of the dermal melanocytes. Although blue nevus is classically considered to be a skin lesion, it has also been observed in the oral mucosa, vagina, uterine cervix, axillary lymph nodes, and prostate. Blue nevus has the potential for malignant transformation into melanoma.

Blue nevus has rarely occurred in the conjunctiva, eyelids, orbit, episclera, and sclera. In a series of 2455 conjunctival lesions in adults, only 3 (1.5%) of 317 pigmented lesions were found to be blue nevus. Additionally, only 1 (1.6%) of 71 conjunctival melanocytic lesions in children were blue nevi. Likewise, malignant transformation of cutaneous blue nevus into melanoma is very uncommon. To our knowledge, transformation of conjunctival blue nevus into melanoma has not been reported. Crawford et al recently reported that none of 30 cases with combined blue nevi had a malignant component. In a series of 150 consecutive patients with conjunctival melanoma, we are not aware of any that arose from blue nevus (personal observations). We report the clinical and histopathologic findings of a patient with an unusual cellular blue nevus of the conjunctiva that simulated primary acquired melanosis (PAM) clinically and underwent focal malignant transformation into malignant melanoma.

Report of a Case

A 41-year-old white man was referred to the Oncology Service at Wills Eye Hospital, Philadelphia, Pa, for evaluation of a patchy pigmented conjunctival lesion on his left eye. The lesion was first detected when the patient was 21-years-old. During the subsequent 2 decades, the lesion progressed slightly and became more confluent.

Examination revealed a movable, diffuse, blue-black lesion that lined the entire inferior fornix and inferior bulbar conjunctiva. It appeared to be located deep
within the conjunctiva and had no apparent nodularity, vascularity, or cysts (Figure 1). The caruncle, plica semilunaris, inferonasal bulbar conjunctiva, and inferior and infero-temporal limbal conjunctiva were all speckled with apparent intraepithelial and superficial and deep subepithelial brown pigmentation. There was corneal epithelial pigmentation near the limbus inferiorly. Findings from the remainder of the ocular examination were unremarkable.

There was no preauricular or cervical lymphadenopathy and no cutaneous blue nevi or dysplastic nevi. Because of suspicion for PAM with conjunctival melanoma, we performed excisional biopsy with no-touch technique and double-freeze thaw cryotherapy to the surrounding conjunctiva.15 Multiple map biopsies of the presumed normal conjunctival epithelium were performed. The conjunctiva was closed with bilimbal transpositional conjunctiva flaps. A symblepharon ring was used to prevent conjunctival adhesions with excellent results.

Histopathologic examination of the fornical lesion revealed melanocytic proliferation in the substantia propria with no junctional or epithelial component (Figure 2). The cells showed a biphasic pattern with ovoid aggregates of less pigmented plump cells and intense infiltrate of heavily pigmented dendritic cells with bland nuclei (Figure 2 and Figure 3). The dendritic cells innocuously infiltrated the deep tissue surrounding the blood vessels and within the orbital fat. In one area, nuclear atypia indicative of malignant transformation into melanoma was present (Figure 4). Histopathologic examination of several limbal and bulbar conjunctival biopsies disclosed other smaller foci of pigmented cells consistent with cellular blue nevus in the substantia propria. The conjunctival epithelium contained no pigmentation or atypical hyperplasia. The patient has done well on 13 months of follow-up with no recurrence of melanoma or blue nevus.

**COMMENT**

Blue nevus cells are derived from melanocytes of neural crest origin that become arrested during the course of embryonic migration to the surface epithelium.13 When these pigmented dendritic melanocytes aggregate together as a distinct mass in the dermis, the lesion is called a blue nevus. The blue color of this cutaneous lesion is due to the Tyndall phenomenon, which is caused by absorption of longer, less energetic wavelengths of visible light as they pass through the dermis.3

By convention, 2 well-defined histopathologic variants of blue
nevus are recognized, designated as “common” and “cellular” blue nevus.\textsuperscript{13} However, other new and related entities, including combined nevus, deep penetrating nevus, compound blue nevus, atypical blue nevus, and malignant blue nevus, have been reported recently.\textsuperscript{2,3,14} Differentiation of the blue nevus from these related but rare entities is usually based on histopathologic features.\textsuperscript{2,3} Crawford and associates\textsuperscript{14} recently reported that combined blue nevus can occur in the conjunctiva, but the other variants of blue nevus are extremely rare in the conjunctiva. Among these variants of blue nevus, the cellular blue nevus rarely undergoes malignant transformation into melanoma.\textsuperscript{12}

Several forms of blue nevi can affect the epibulbar and adnexal tissues, including ocular melanocytosis, common blue nevus, and cellular blue nevus.\textsuperscript{13} These conditions are usually diagnosed at birth or shortly thereafter. Congenital ocular melanocytosis is characterized by flat, slate-gray pigmentation of the sclera, generally without conjunctival involvement. Although uveal melanoma, primary orbital melanoma, and leptomeningeal melanoma have been reported in patients with ocular melanocytosis affecting these tissues, conjunctival melanoma has not been identified.\textsuperscript{13} Conjunctival blue nevus appears as a noncystic brown or black-blue mass in the stroma.\textsuperscript{13,16} Common blue nevus is composed of a uniform population of pigmented dendritic cells. Cellular blue nevus shows a biphasic cellular pattern with lightly pigmented nodules consisting generally of uniform spindle cells surrounded by heavily pigmented dendritic melanocytes. As observed in our case, malignant changes tend to occur in the central oval or spindle cells, which are considered to be immature and have greater malignant potential.\textsuperscript{12}

Common blue nevus and cellular blue nevus are extremely uncommon in the conjunctiva.\textsuperscript{13} Grossniklaus et al\textsuperscript{19} reported 5 cases of blue nevus (1.5%) in 317 pigmented conjunctival lesions in adults. McDonnell et al\textsuperscript{11} observed only 1 case of blue nevus (1.6%) in 71 conjunctival melanocytic lesions in children. Other studies have confirmed the rarity of conjunctival blue nevi.\textsuperscript{17,18}

The differential diagnosis of conjunctival blue nevus includes common congenital and acquired nevus, congenital ocular melanocytosis, PAM, and malignant melanoma. Clinically, unlike the common nevus, the blue nevus lacks cystic inclusions of conjunctival epithelium.\textsuperscript{13} In contrast to the flat, slate-gray episcleral pigmentation of ocular melanocytosis and the diffuse, brown epithelial pigmentation of PAM, cellular blue nevus generally is well-circumscribed and located deep within the conjunctival stroma.\textsuperscript{13} In our case, the blue nevus was atypical because it was diffuse and resembled PAM clinically.

Conjunctival melanoma can originate from PAM, a preexisting conjunctival nevus, or de novo.\textsuperscript{19,20} Our group recently reviewed 150 cases of conjunctival melanoma and found histopathologic evidence of possible origin from preexisting nevus in 4%, PAM in 57%, and de novo in 39%. There were no cases of conjunctival melanoma arising from cellular blue nevus.\textsuperscript{21} Folberg et al\textsuperscript{19} found the distribution of nevus in 20%, PAM in 75%, and de novo in 5%. In the case presented here, a focus of conjunctival melanoma originated in the cellular blue nevus.

Patients with orbital cellular blue nevus have been found to be at risk for malignant transformation of the nevus into melanoma.\textsuperscript{5,22} Primary orbital melanoma likely develops from congenital rests of cellular blue nevus in the orbit.\textsuperscript{23} Tellado et al\textsuperscript{22} found that 19 (90%) of 21 patients with orbital melanoma had blue nevus of the orbit.

The prognosis of melanoma arising from cutaneous blue nevus is poor, with a high incidence of recurrence and metastasis.\textsuperscript{4,12} Connolly and Smith\textsuperscript{1} reported that 10 (83%) of 12 patients with melanoma arising from blue nevus in the skin developed metastases over a mean period of 40 months. Our group described 2 patients with extensive periorcular cutaneous and orbital cellular blue nevus who developed orbital melanoma and eventually died of intracranial melanoma in both cases.\textsuperscript{5} The overall survival for conjunctival melanoma is 69% to 87% at 10 years.\textsuperscript{23} Since the focus of melanoma in our patient is relatively small, we are uncertain about the risk for metastatic disease.

In summary, the unusual case reported here documents a cellular blue nevus, which simulated PAM clinically, and eventually developed into malignant melanoma. We believe that patients with suspicious, pigmented conjunctival lesions should have wide exci-
sional biopsy and adjuvant cryotherapy.

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Corresponding author: Carol L. Shields, MD, Oncology Service, Wills Eye Hospital, 900 Walnut St, Philadelphia, PA 19107.

REFERENCES


From the Archives of the Archives

Muller reports from the Giessen clinic 80 cases of perforating injury of the ball treated with sutures. In 61 patients the ball was preserved; in 17 it was enucleated later, six times for suppuration in the vitreous, and in the other cases for foreign bodies, rupture of the posterior pole, etc. Sutures prevent loss of vitreous and secondary infection, and secure a smooth union of the edges of the wound, thus shortening the healing process.