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Case Report

Subepithelial conjunctival nevus with atypia: Expanding our understanding of a challenging diagnosis

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ABSTRACT

Equivocal cases of conjunctival subepithelial melanocytic nevus with atypia may on occasion be difficult to distinguish histopathologically and immunohistochemically from melanoma. We describe the clinical presentation and histopathological features of an atypical amelanotic conjunctival nevus, along with its differential diagnosis and pertinent literature review.

A 55-year-old Caucasian male presented with an amelanotic epibulbar conjunctival lesion extending onto the cornea, mimicking a pterygium. The histopathological examination of the excision revealed a well-circumscribed subepithelial amelanotic spindle cell melanocytic proliferation with fascicular growth, focal nuclear and cellular enlargement, reverse maturation, less than 1% of cells in cycle, and no mitotic figures. The spindle cells were diffusely immunoreactive to Mart-1, S100, SOX-10, and superficially to MITF and HMB-45. Given the histopathological atypia and ambiguity of stains, the 5-probe fluorescence in situ hybridization *NeoSITE* (NeoGenomics, Irvine, CA) was performed and found to be normal.

The presence of atypia, a sign of pre-malignancy, in amelanotic subepithelial nevi should be suspected, even in cases of presumed pterygia, to ensure that appropriate histopathological evaluation and subsequent management are pursued. Immunohistochemical stains and molecular studies can be crucial in differentiating benign from potentially malignant conjunctival nevi with atypia.

1. Background

Conjunctival nevi represent about 52% of conjunctival melanocytic lesions [1,2]. They present as fleshy, well-defined, flat or raised nodules usually located in the interpalpebral bulbar conjunctiva, the plica semilunaris, the caruncle, or the eyelid margin. Conjunctival nevi are most commonly darkly pigmented (in 65% of the cases), lightly pigmented (19%), and less frequently, nonpigmented (16%) [3]. Compound melanocytic nevi, usually developing in children and young adults, are the most common type, followed in frequency by subepithelial, junctional, and blue nevi. 13% of benign nevi have been found to change in color and 8%, in size [3]. This is commonly due to cystic growth, progressive pigmentation of previously amelanotic areas, or increased inflammation.

Despite their largely benign behavior, there is a small potential for malignant transformation. In a case series of 410 conjunctival nevi, 3 patients developed melanoma over a mean of 7 years [3]. Conjunctival melanoma may arise from primary acquired melanosis (PAM) with atypia (53–74%), de novo (37–39%), or less frequently, in a nevus (4%) [1,4]. Cellular atypia, a predecessor of malignancy, has been reported in various types of nevi, such as inflamed cystic compound nevi [5,6], primary acquired melanosis with atypia superimposed on pre-existing nevi [7], dysplastic nevi, and blue nevi [8].

Subepithelial nevi represent approximately 24% of all excised conjunctival nevi [3], and show oval, cuboidal, or spindle-like melanocytes in the substantia propria without an intraepithelial component. Atypia in subepithelial conjunctival nevi is very uncommon [9,10]. We discuss the histopathological, immunohistochemical, and molecular features of a masquerade case of subepithelial nevus with atypia presenting as a pterygium.

2. Case presentation

A 55-year-old Caucasian man presented with an amelanotic,

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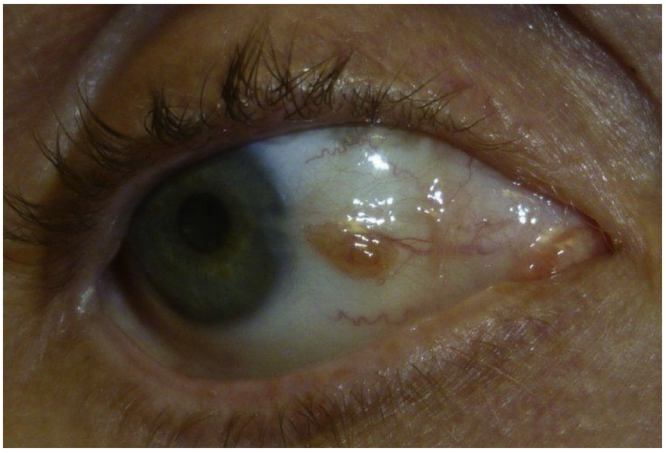

Fig. 1. Photograph of the right eye showing an amelanotic mildly vascularized and elevated conjunctival lesion with a fleshy center, extending onto the cornea.

primarily epibulbar conjunctival lesion extending onto the cornea, that had enlarged over several years. The patient more recently complained of redness, irritation, and foreign body sensation. The vision was unaffected. On exam, the lesion was located on the nasal bulbar conjunctiva, extending 1.5 mm onto the medial cornea and measuring approximately 8 × 4 mm in total, with a fleshy mildly elevated noncystic center (Fig. 1). The patient, a roofing contractor, reported significant sun exposure, often without protective eyewear, and no personal or family history of malignancies. He denied any previous chemical, thermal, or mechanical injuries to the eye. Clinically, the lesion was diagnosed as a pterygium. Differential diagnosis included conjunctival nevi, ocular surface squamous neoplasia, and lymphoproliferative and vascular tumors. Due to worsening symptoms of redness and foreign body sensation, the lesion was excised. The tissue sample was paraffin-embedded, formalin-fixed, and stained with hematoxylin and eosin (H&E) and immunohistochemical stains for Mart-1, HMB-45, S100, MITF, SOX-10, Ki-67, EMA, SMA, CD34, and neurofilament. The melanoma 5-probe fluorescence in situ hybridization (FISH) test, *NeoSITE* (NeoGenomics Laboratories, Irvine, CA), was also performed.

Histopathological evaluation showed a well-circumscribed subepithelial, amelanotic, spindle cell melanocytic proliferation with a fascicular growth pattern, focal hyperchromatic nuclei and cytoplasmic enlargement, and absence of normal maturation (Fig. 2A–C). No subclinical microscopic epithelial inclusion cysts or mitotic figures were identified. Ki-67 showed less than 1% of melanocytic cells in cycle. The spindle cells were immunoreactive to Mart-1, S100, Sox-10, and focally to MITF and HMB-45 (Fig. 2D–F; S100 not shown). EMA, SMA, CD34, and neurofilament stains were negative (not shown). The atypical features of nuclear hyperchromasia, cytoplasmic enlargement, lack of normal maturation, and hypercellularity raised the possibility of a subepithelial amelanotic nevus with atypia, a hypopigmented cellular blue nevus, or a spindle cell desmoplastic melanoma. The 5-probe *NeoSITE* FISH test was within normal range. The diagnosis of atypical subepithelial amelanotic nevus was rendered. The lesion had been narrowly excised, so re-excision followed by clinical monitoring were recommended. The lesion has not recurred after 2 years of follow-up.

3. Discussion

Conjunctival nevi are more commonly seen in white individuals (89% of nevi) with a mean of 32 years of age at presentation [3]. Males and females are equally affected. Acquired conjunctival nevi include compound, junctional, subepithelial, combined, Spitz, inflamed, dysplastic, and pigmented spindle cell nevus of Reed [11]. Congenital nevi include common and cellular blue cell nevus, and melanocytoma [12].

The natural history of acquired conjunctival nevi begins as a melanocytic proliferation in the epithelium, progressively developing junctional theques, and subsequently evolving into a compound or completely subepithelial lesion as the patient ages. Therefore, compound and junctional nevi are more common in younger age groups, while subepithelial and blue nevi are seen in slightly older age groups [3,8].

Compound nevi are the most common type, accounting for approximately 70% of all nevi [3]. Histopathologic examination shows intraepithelial or junctional melanocytes with oval shape (type A melanocytes), followed in depth by sheets of oval to cuboidal cells (type B melanocytes), and spindle-like cells in the subepithelium (type C melanocytes). A cystic component is present in up to 50% of cases [9]. In children and young adults, atypical features may be more commonly present, such as intraepithelial melanocytes with paradoxical reverse maturation, where the melanocytes in the substantia propria show larger nuclei and cytoplasms than those in the epithelium [2,5]. Subepithelial nevi show melanocytes in the substantia propria commonly arranged in nests with usual maturation toward the deeper portion of the lesion. Conjunctival melanoma infrequently, if ever, demonstrates intralesional cysts, while they are seen in nearly 60% of subepithelial conjunctival nevi [3].

Conjunctival blue nevi can be brown, as opposed to the skin, where the Tyndall effect predominantly causes reflection of the blue wavelengths [10]. Additionally, their cells are usually more superficial in location (substantia propria) than those of the skin (dermis) [13]. There are two histologic groups of blue nevi: common blue nevi and cellular blue nevi. The common blue nevus shows an inverted wedge-shape configuration, composed of a uniform population of loosely aggregated pigmented dendritic cells or benign type C spindle melanocytes without atypia. On the other hand, cellular blue nevi show a biphasic cellular pattern consisting in a highly cellular center with spindled to oval melanocytes with clear or finely pigmented cytoplasms and little mitotic activity surrounded by sclerotic regions and heavily pigmented dendritic melanocytes resembling common blue nevi. Most lesions appear well-circumscribed, although the cellular areas may emerge from the far deep portion extending vertically deeper into the substantia propria with a dumbbell-shaped outline [2,8,9].

Conjunctival nevi may rarely progress to malignant melanoma in less than 1% of the cases [14]. Conversely, conjunctival melanoma has been found to be associated with nevus in 4% of the cases [14]. The clinical features suggestive of malignancy include extension to the cornea, scleral attachment, and presence of feeder vessels (although feeder vessels are also noted in a third of conjunctival nevi) [2,3]. Histopathologically, the diagnosis of conjunctival melanoma is usually not challenging since these lesions tend to show highly atypical epithelioid and spindle cell proliferations with increased mitotic figures and invasion into the stroma.

The presence of atypia in subepithelial conjunctival nevi may pose a diagnostic challenge, but it should always be studied given its menacing biologic potential. In this case, although the lesion was circumscribed, atypical features of nuclear hyperchromasia, cytoplasmic enlargement, lack of normal maturation, and hypercellularity were concerning. The presence of abnormal amelanotic spindle melanocytes with the above findings raised the possibility of a spindle cell desmoplastic melanoma. Cellular blue nevus was also considered in the differential diagnosis since amelanotic blue nevi have been reported [15].

Although the presence of symptoms can point toward other diagnoses, such as pterygium, the physician should keep in mind that patients with nevi are not always asymptomatic since 3% have been found to experience symptoms related to inflammation and 1%, pain [3]. Also, any pigmented lesion in the cornea, tarsus, or fornix can suggest malignancy, as these locations are more commonly involved in conjunctival melanoma [14]. Invasion through Bowman's membrane or into the conjunctival stroma is virtually diagnostic of melanoma [2].

To aid in the diagnosis, are there any key diagnostic clues the