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The oral blue nevus: Histogenetic implications of its ultrastructural features

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Three cases of oral blue nevus are presented. A comparison of the ultrastructural features of blue nevus cells with those of schwannoma cells indicates that, among other similarities, both exhibit a surrounding external lamina (basement membrane). The significant difference is that blue nevus cells are capable of synthesizing melanin as evidenced by the presence of the entire melanosome maturation sequence within their cytoplasm, a feature not seen in the cells of schwannomas. This fundamental difference suggests that blue nevus cells are more closely related to melanocytes, although they possess some of the characteristics of Schwann cells.

The blue nevus is a benign tumor of pigmented, dendritic melanocytes located in the middle to lower dermis or lamina propria. Two types, the common blue nevus and the cellular blue nevus, occur on skin, but only the common type has been reported to occur on oral mucous membranes.[1] The spindle-shaped melanocytes of the blue nevus are usually oriented with their long axes parallel to the surface epithelium. Their cytoplasm usually contains numerous melanosomes which occasionally obscure the nucleus.

Intraoral blue nevi most commonly occur on the hard palate in the third and fourth decades of life. Women exhibit these lesions somewhat more commonly than men.[1] Clinically, the blue nevus appears as an asymptomatic, small, slightly elevated or flat, blue to brown discoloration of the mucosa.[2]

At the time of Scofield's[3] first report, the intraoral blue nevus was considered to be a rare lesion. However, the recent study by Buchner and Hansen[1] indicated that blue nevi comprise 25 to 36.4 percent of all intraoral nevi which, although uncommon, are not rare. There are numerous case reports of intraoral blue nevi in the literature,[4] but a search of the English-language literature suggests that only one ultrastructural study has been published.[5]

The purpose of this article is to report three additional cases of oral blue nevus and to describe the ultrastructural features in two of these three lesions.

CASE REPORTS

CASE 1

A slightly elevated, smooth-surfaced, bluish brown lesion measuring 5 mm. in diameter, located near the midline of the right hard palate, was noted during a routine dental examination of a 26-year-old man. The lesion was asymptomatic and of unknown duration. The fact that the patient had suffered a broken nose 2 years previously led the clinician to suspect that the discoloration was the result of an implanted foreign body. The lesion was excised, fixed in 10 percent buffered formalin, and submitted for histopathologic examination. A diagnosis of blue nevus was rendered. A portion of the paraffin-embedded tissue was deparaffinized and processed for electron microscopic examination.

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Fig. 1. Blue nevus excised from the hard palate of the patient described in Case 1. The lesion consists of a fibrous proliferation which blends into the adjacent normal connective tissue. Moderate amounts of melanin pigment are evident within the lesion. (Hematoxylin and eosin stain. Magnification, ×35.)

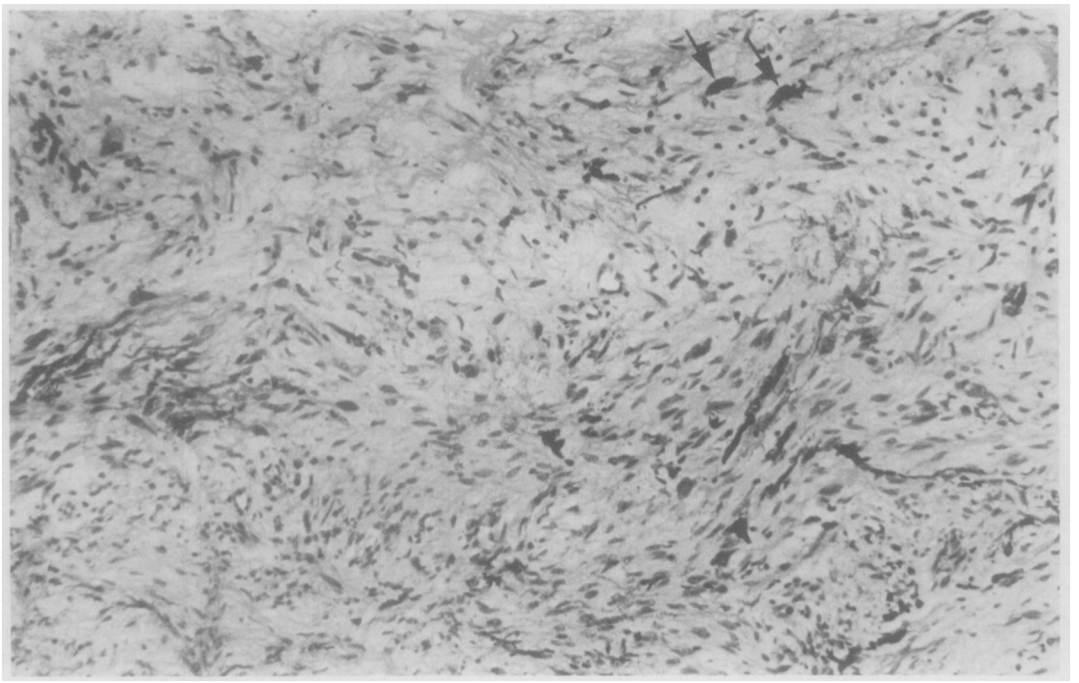

Fig. 2. Blue nevus excised from the hard palate of the patient described in Case 2. The lesion consists of a fibrocellular proliferation exhibiting cells with spindle-shaped, vesicular nuclei. The dendritic shape of some of the blue nevus cells is outlined by their melanin pigment. Occasional rounded, intensely pigmented cells, interpreted to represent melanophages, are also evident *(arrows)*. (Hematoxylin and eosin stain. Magnification, ×140.)

CASE 2

Routine dental examination of a 54-year-old man disclosed a bluish gray papule located on the right hard palate adjacent to the second molar. The lesion was asymptomatic and of unknown duration. The clinical diagnosis was mucous retention cyst. The lesion was excised, fixed in 10 percent buffered formalin, and submitted for histopathologic evaluation. Half of the tissue specimen was embedded for routine light microscopy, while the remaining tissue was processed and embedded for electron microscopic examination. The histopathologic diagnosis was blue nevus.

CASE 3

A 20-year-old Caucasian woman was found to have a small, asymptomatic papule on the vermilion border of the upper lip, just to the left of the midline. With the exception of two brown areas on its surface, the lesion was the color of a normal lip. The lesion had been present for approximately 3 years. After surgical excision, the tissue was fixed in 10 percent buffered formalin and submitted for histopathologic examination. The diagnosis was blue nevus.

MORPHOLOGIC FINDINGS

Light microscopic features

Each of the three tissue specimens consisted of a strip of mucosa exhibiting a relatively well-defined area of pigmented, fibroblast-like cells in the connective tissue (Figs. 1 and 2). The lesional tissue was composed primarily of cells with ovoid, vesicular nuclei exhibiting a moderate variation in size and a cytoplasm containing variable amounts of finely granular, brown pigment. The intracytoplasmic pigment outlined the long, dendritic cell processes and at times almost obscured the nucleus. The cells were largely oriented parallel to the epithelial surface (Fig. 2). The pigmented cells were interpreted to be blue nevus cells. Occasional cells, interpreted to be melanophages, containing abundant, coarsely granular, brown melanin pigment which usually obscured the nucleus were also present. As indicated in Fig. 3, these cells did not exhibit apparent cytoplasmic processes.

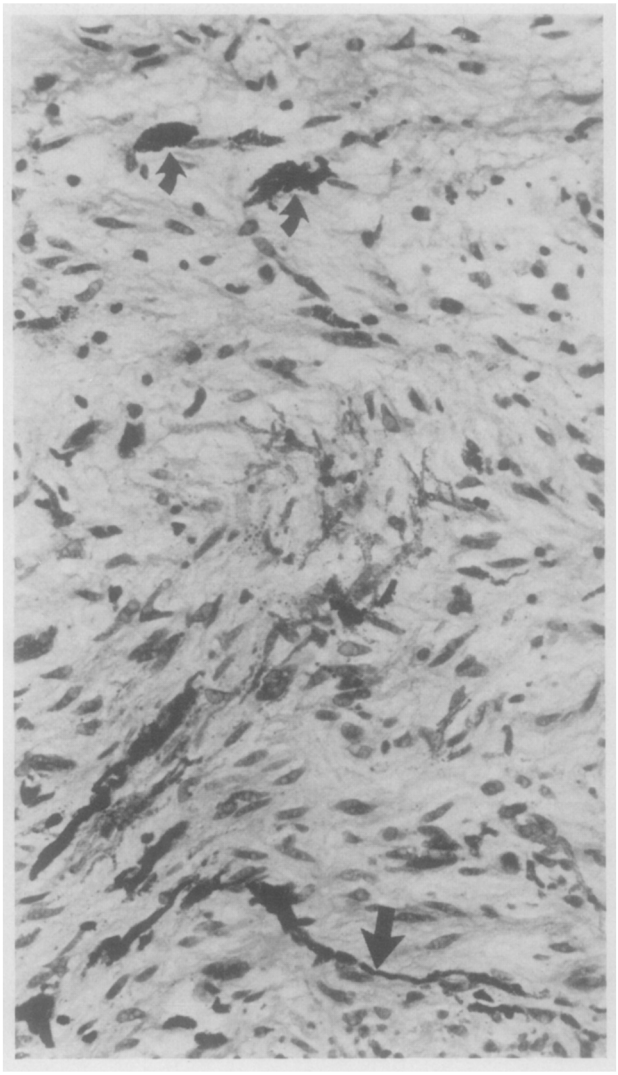

Fig. 3. A higher magnification of the blue nevus shown in Fig. 2. The spindle-shaped, vesicular nuclei of the nevus cells and their dendritic shape, as outlined by their melanin granules, are evident *(arrow)*. Occasional rounded, intensely pigmented cells, interpreted to represent melanophages, are also evident *(curved arrows)*. (Hematoxylin and eosin stain. Magnification, ×280.)

Ultrastructural features

The blue nevus cells exhibited relatively smooth, elliptical nuclei. Indentations in the prominent nuclear envelope, occasionally presenting as pseudoinclusions, were present (Fig. 4). The nucleoli were inconspicuous. The cytoplasm extended in a bipolar direction as long dendritic processes. An indistinct and incomplete external lamina (basement membrane) surrounded the cells. Numerous pinocytotic vesicles studded the cell surface. Occasional microfilaments were evident throughout the cytoplasm. Numerous individual melanosomes at various stages of development, including premelanosomes, were present. With increased melanin pigmentation, these structures exhibited increased electron density and decreased lamellar definition (Fig. 5). Moderate numbers of other organelles, including mitochondia, endoplasmic reticulum, Golgi complexes, and ribosomes, were also present.

DISCUSSION

There appears to be little doubt that blue nevi are of neural crest origin.[6-8] The present controversy

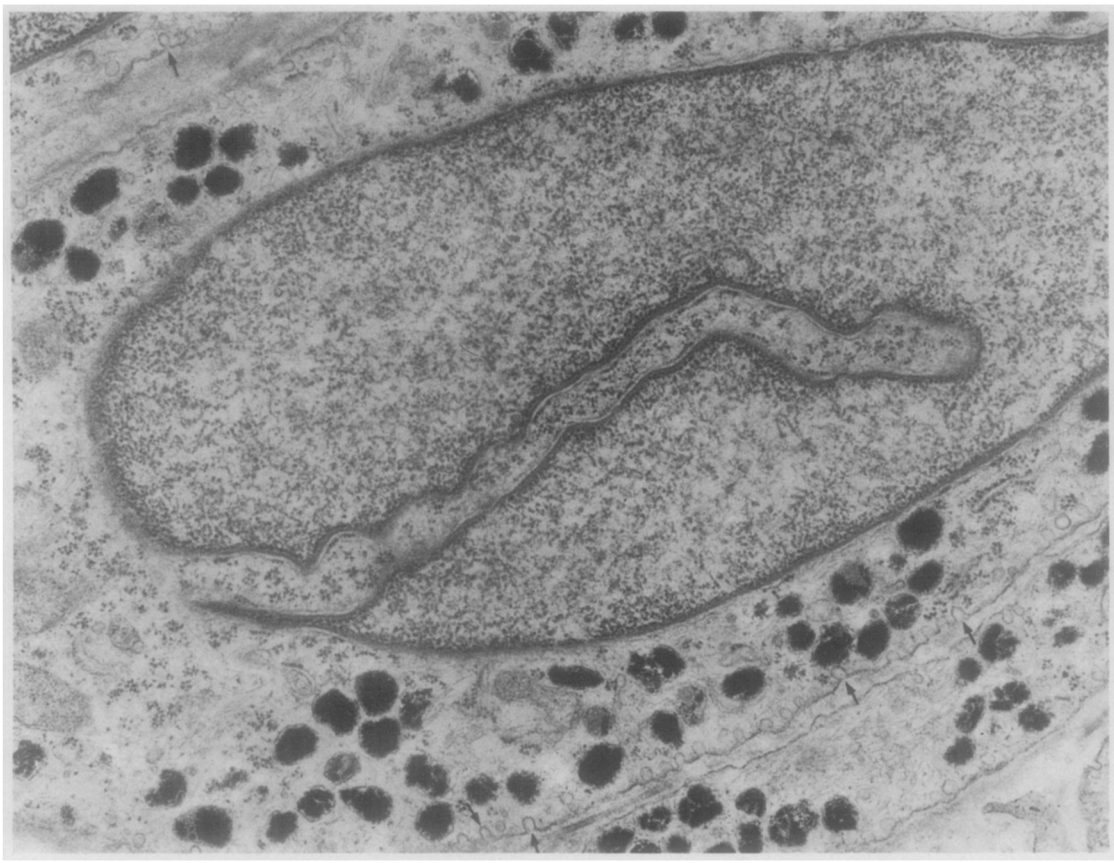

Fig. 4. Electron micrograph of a blue nevus cell exhibiting numerous melanosomes and pinocytotic vesicles *(arrows)*. The nucleus exhibits a relatively thick nuclear envelope and a pronounced nuclear infolding which, in other planes of section, appear as intranuclear pseudoinclusions. (Uranyl acetate and lead citrate stain. Magnification, ×25,000.)

centers around the immediate precursor of the lesional cells. Are they Schwann cells, perineurial cells, or melanocytes?[8] The elaborate schematic presented by Pinkus[7] indicates that the evidence for differentiation of neural crest cells to Schwann cells, nevoblasts, and melanoblasts, which further differentiate before giving rise to the various melanin-producing tumors, is based mainly on morphologic and partly on histochemical evidence.[9] Acknowledging the limits of comparative ultrastructural evidence as a method of ascertaining histogenetic derivations, the nature of the immediate precursor of the blue nevus cell remains somewhat obscure.

The Schwann cell origin of blue nevus cells cannot be dismissed solely on the basis that the latter do not form mesaxonal configurations as suggested by Diaz de Molnar and colleagues.[8] These configurations are not a constant feature of the cells of schwannomas either, and yet little doubt exists as to their histogenesis. A comparison of the ultrastructural features of blue nevi and schwannomas (Table I) reveals a surprising degree of similarity. Although pinocytotic vesicles are uncommon in Schwann cells[8, 11] and in the cells of schwannomas,[10, 12] they do occur as part of a repair mechanism following injury and in the early stages of maturation.[8] We have recently observed an intraoral schwannoma which, on ultrastructural examination, revealed numerous pinocytotic vesicles in its tumor cells (Fig. 6). Since this feature was observed in both the original biopsy material and the subsequent surgical specimen, the biopsy procedure cannot be implicated as a cause of the injury which may have resulted in the formation of the pinocytotic vesicles. It is recognized, however, that many intraoral lesions may be traumatized during mastication; thus, the possibility that the pinocytotic vesicles were reactive in nature cannot be excluded entirely.

From the available evidence, it appears that melanocytes are the only cells capable of synthesizing melanosomes which occur as solitary membrane-bound organelles in various stages of melanization.[12] Mature melanosomes occurring in groups within a

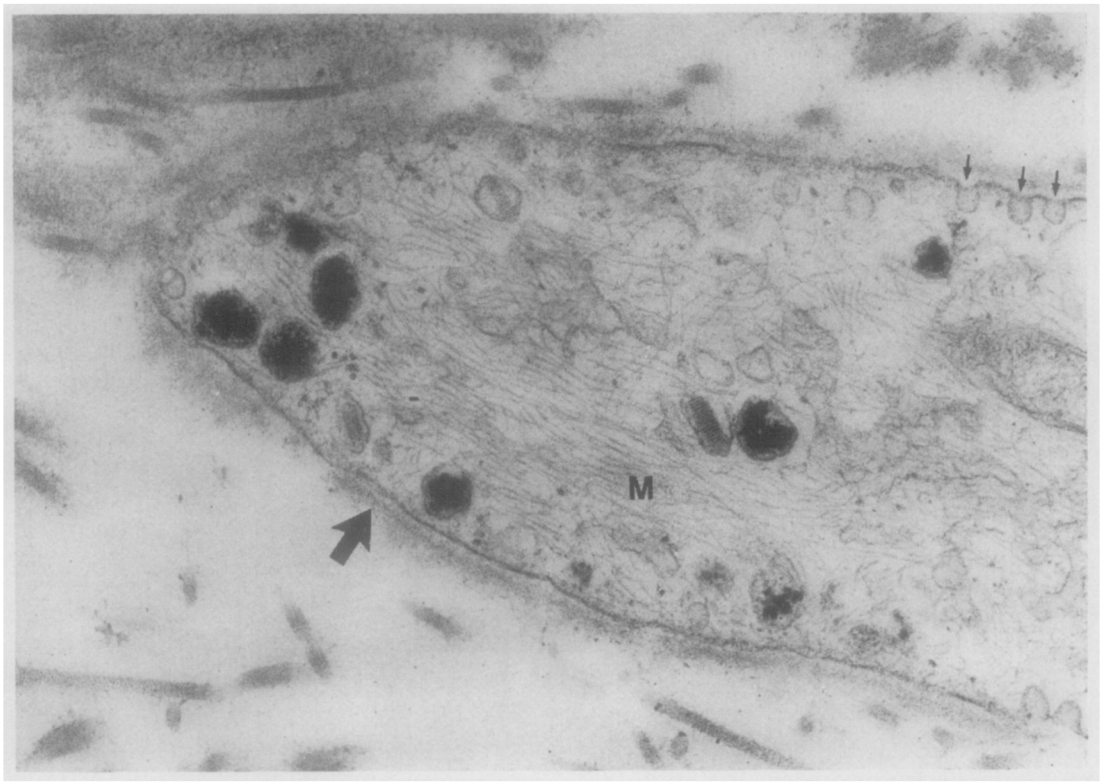

Fig. 5. Electron micrograph of a portion of a blue nevus cell exhibiting melanosomes at various stages of development, multiple pinocytotic vesicles *(small arrows)*, external lamina *(large arrow)*, and moderate numbers of microfilaments *(M)*. (Uranyl acetate and lead citrate stain. Magnification, ×47,000.)

Table I

Ultrastructural feature	*Blue nevus cells*		*Schwannoma cells*
	Kjaerheim et al.[5]	*This paper*	
Overall smooth nuclear outline	+	+	Crenated
Nuclear pseudoinclusions	+	+	+
Thickened nuclear membrane	+	+	+
Prominent nucleolus	Occasionally	−	+
Individual premelanosomes	+	+	−
Individual melanosomes	+	+	−*
Compound melanosomes	+	+	+
Pinocytotic vesicles (many)	+	+	+
External lamina (basement membrane)	+	+	+
Dendritic cytoplasmic processes	+	+	+
Well-developed Golgi	+	−	?
Microfilaments (8 nm.)	+	+	+
Microtubules	+	−	−
Cilia	+	−	−
Mesaxonial configurations	−	−	Occasionally (12)
Myelin figures	−	−	Occasionally (12)
Desmosome-like structures	−	−	Infrequent (10, 12)
Luse bodies (long spacing collagen)	−	−	+ (10, 12)

*This is theoretically possible, if not probable, secondary to phagocytosis.[12]

Fig. 6. Electron micrograph of a portion of a cell from a schwannoma. Numerous pinocytotic vesicles *(small arrows)* and a prominent external lamina *(large arrows)* are evident. (Uranyl acetate and lead citrate stain. Magnification, ×34,000.)

single membrane-bound space are called compound melanosomes or melanosome complexes which are usually found in melanophages or in keratinocytes of Caucasians and Mongoloids.[12] They may also occur as autophagic vacuoles within melanocytes and blue nevus cells.[4, 8, 12]

Although Schwann cells are capable of synthesizing a wide variety of products,[13] Ghadially[12] has suggested that the occasionally observed compound melanosomes of Schwann cells are probably manifestations of phagocytic rather than synthetic capabilities. The observation that during phagocytosis histiocytes acquire numerous pinocytotic vesicles,[14] as do regenerating Schwann cells, supports the concept of a phagocytic mechanism of compound melanosome acquisition by Schwann cells. The melanosome maturation sequence has not, to our knowledge, been observed in Schwann cells, as it has in melanocytes. This observation casts considerable doubt on the melanin-synthesizing capability of Schwann cells and thus on their role as precursors of blue nevus cells.

Perineurial cells, although sharing many of the ultrastructural features of blue nevus cells,[3] also fall short because of their inability to synthesize melanin.

By demonstrating the presence of melanosomes at various stages of development within the cytoplasm of blue nevus cells, and by excluding Schwann cells and perineurial cells as its cell of origin, one is left with the likelihood that the blue nevus is a hamartoma or a benign neoplasm of melanocytes.

SUMMARY

The evidence obtained from this study indicates that blue nevus cells are similar to the cells of schwannomas in that an external lamina (basement membrane) surrounds both of them. The significant difference is that blue nevus cells are capable of melanin synthesis, a feature shared only by melanocytic cells. Blue nevus cells are therefore considered to be melanocytic in origin.

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