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What's New in . . .

Blue Nevus: Classical Types and New Related Entities

A Differential Diagnostic Review

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SUMMARY

Blue nevus is an uncommon pigmented lesion of dermal melanocytes. By convention, two well defined histologic variants, designated as "common" and "cellular", have been recognised. In the last few years, these lesions have attracted much attention due to the recognition of news entities and to its confusion with malignant melanoma. In the present review, we point out the more striking features of new related entities (combined nevus, deep penetrating nevus, compound blue nevus) and establish the differential diagnosis with conflictive lesions such as atypical blue nevus, locally aggressive blue nevus, congenital giant melanocytic nevus with nodular growth and melanocytic dermal tumor of unpredictable outcome. We also review the concept of malignant blue nevus and the significance of lymph node metastases.

The blue nevus is an uncommon pigmented lesion consisting of dermal melanocytes that can appear in diverse forms: dendritic, spindle-shaped, oval-shaped, or polyhedral. Although it usually occurs in skin, it has been reported in other locations, such as oral mucosa, sclera, uterine cervix, vagina, prostate, spermatic cord, pulmonary hilus, orbit, conjunctiva, maxillary sinus, breast, and lymph nodes[3,8,42,49]. Generally, it occurs in adults as a single, acquired, intensely pigmented lesion, although familial and multiple nevi have been reported[7,39]. By convention, there are two well-defined histologic variants, designated as "common" and "cellular", but lesions often manifest intermediate features.

In the last few years, blue nevus has attracted much attention due to the recognition of new (clinical and histologic) entities and to its confusion with malignant melanoma. Our aim is to review the most striking features of the new related entities and to establish the differential diagnosis with conflictive lesions. We also review the concept of malignant blue nevus and the significance of lymph nodes metastasis.

Common Blue Nevus

Common blue nevus is a flat or discretely raised lesion of dark blue color, usually less than 1 cm in diameter, with no preferred location. It contains only long, dendritic melanocytes with abundant melanin, situated predominantly in the reticular dermis in alignment with the bundles of collagen fibers (Fig. 1). Usually asymptomatic, it shows no propensity to ulceration or malignization[18,28].

Dermal melanocytoses (nevus of Ota, nevus of Ito, and mongolian spot) are pigmented lesions similar to blue nevus, but congenital in origin, larger in size, and defined by their anatomic location. The nevus of

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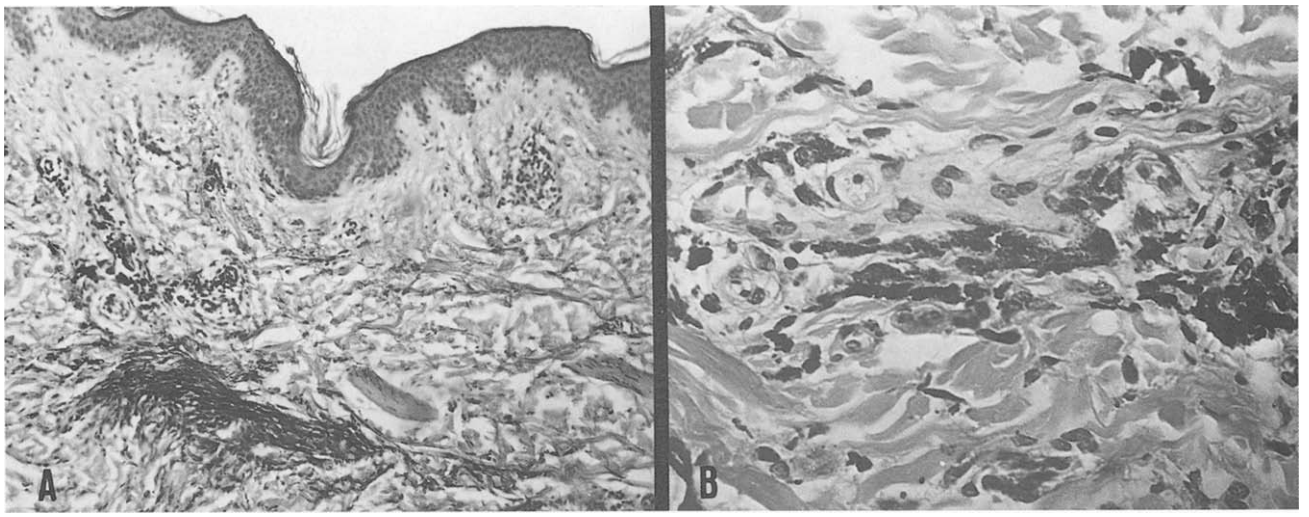

Fig. 1. Common blue nevus. A. Low power view showing an ill defined melanocytic lesion predominantly located in the reticular dermis. HE 25 ×. B. Elongated dendritic melanocytes rich in pigment arrayed between bundles of collagen fibers. HE 380 ×.

Ota lies in the territory of the first and second branches of the trigeminus and usually affects the eye; in contrast, the nevus of Ito is situated in the territory of the posterior subclavian and brachial cutaneous nerves. Mongolian spot is smaller and is located in the sacral region. It differs from other melanocytoses in that it tends to disappear in the first years of life. Histologically, the dendritic melanocytes of mongolian spot are arranged more loosely than in common blue nevus. In the Ito and Ota nevi the melanocytes are distributed mainly in the upper dermis, while in mongolian spot they are found in the lower dermis. Uehara et al.[52] have found that extracutaneous blue nevus shows macroscopic and histologic features similar to those of dermal melanocytosis rather than those of cutaneous blue nevus and have proposed the term stroma melanocytosis as more appropriate. Malignant transformation of dermal melanocytoses is exceptional and has been reported only in Ota and Ito nevi[9, 16, 35, 45, 53]. In the same way, the association of nevus of Ota and malignant cerebromeningial melanoma is also exceptional[2, 6, 22].

Cellular Blue Nevus

Cellular blue nevus is an unusual variant of pigmented nevus which has special diagnostic interest because of the potential for clinical and morphologic confusion with malignant melanoma. In most patients, it is diagnosed before the age of 40. Nonetheless, the age range for occurrence is much wider, from birth to senility[28, 41, 49]. Clinically, the lesions are papulous, dome-shaped or flat, smooth-surfaced, hairless, of blue-black color, and measure 0.2 – 2 cm in diameter[49] (Fig. 2). They usually are located on the buttocks and coccygeal region, but they can occur on the head, face, hands, and feet[28, 41, 49]. Dermal nevus, resembling cellular blue nevus, has been reported in ovarian dermoid cysts[51].

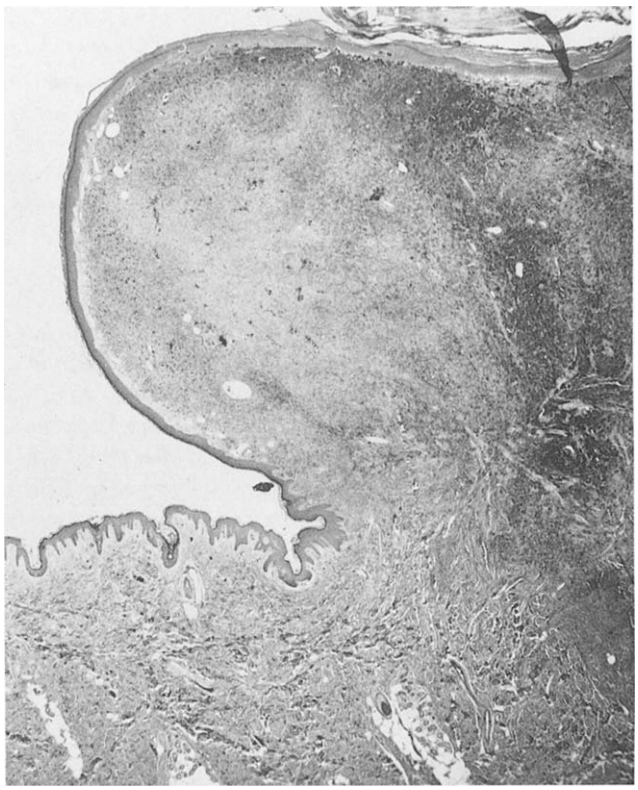

Fig. 2. Cellular blue nevus. Partial view of a large pedunculated pigmented lesion with irregular distribution of the pigment. HE 16 ×.

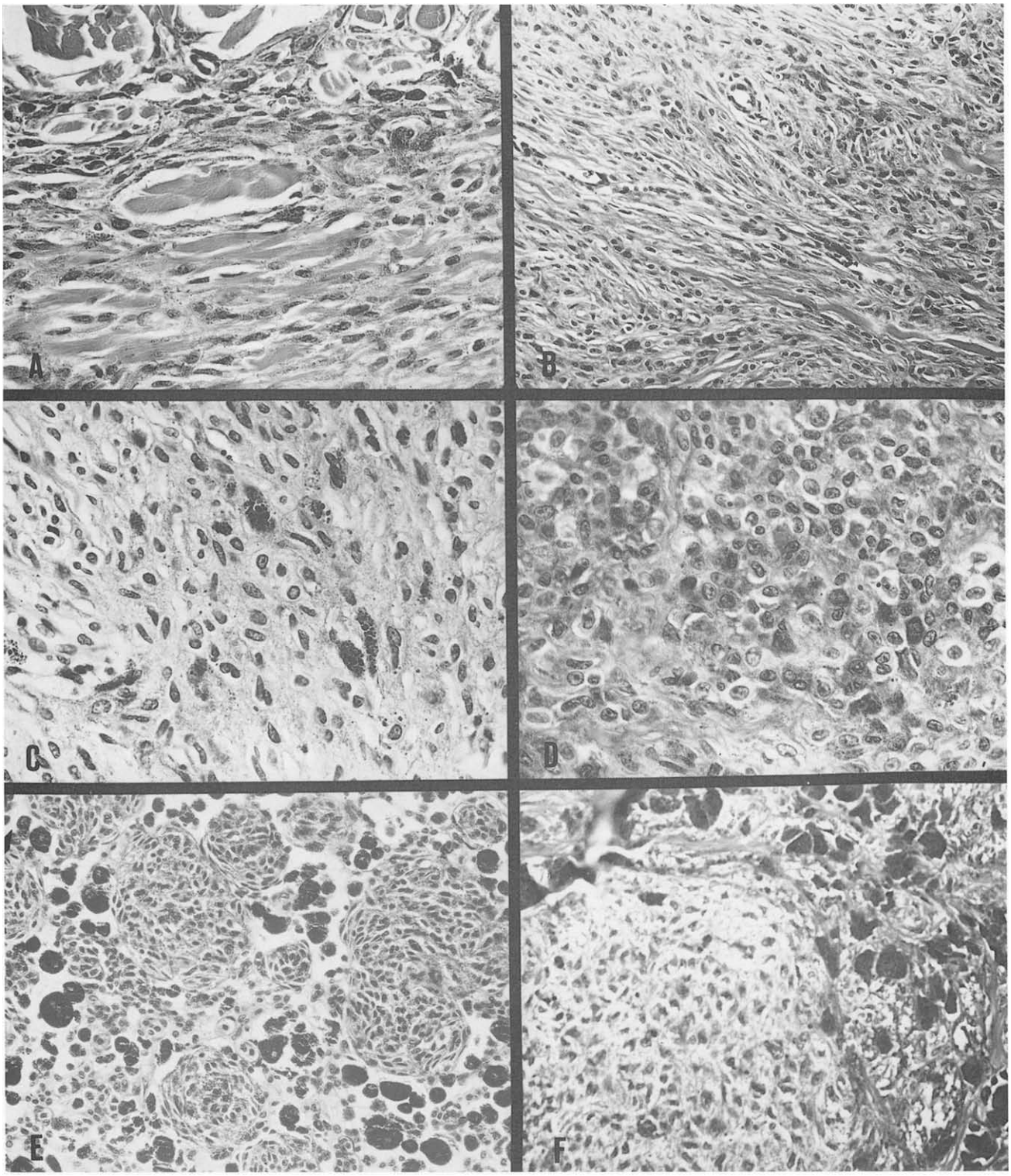

Fig. 3. Cells and growth patterns in cellular blue nevus. A. Biphasic pattern with spindle and dendritic melanocytes. HE 243×. B: Fascicular pattern with clear spindle-shaped cells. HE 97×. C. Clear cells with fine scanty cytoplasmic pigment. HE 390×. D. Polygonal cells intensively pigmented. HE 390×. E. Alveolar pattern with intersparse pigment containing phagocytes. HE 243×. F. Large mass of clear cells containing very little pigment, surrounded by collagenous stroma in which spindle-shaped melanocytes and phagocytes were present. HE 97×.

Histologically, cellular blue nevus is a compact lesion located in dermis and hypodermis, that often takes an hourglass shape. It is constituted by clumps of spindle-shaped, oval-shaped, or polyhedral melanocytes arranged in a biphasic, alveolar, neuroid or fascicular pattern (Fig. 3). Among the most salient cytological features are the absence of nuclear pleomorphism and alternation of clear cells with intensely pigmented spindle cells. Mitoses and necrotic foci are exceptional[41, 49]. Individual nevus cells may contain intracytoplasmic eosinophilic inclusions that are PAS (+) and diastase resistent, corresponding to macromelanosomes with centrifugal melanization[50].

The term *atypical blue nevus* has been used to label lesions that exhibit the features of blue nevus, as well as cellular atypia, prominent nucleoli, and a mitotic index of less than 2 figures/mm^2 [5, 20]. The term *locally aggressive blue nevus* is used for lesions with marked local invasion[17, 27, 46]. There have been few case reports of atypical and locally aggressive blue nevi and the follow-up has been short, so it is advisable to use these terms carefully, particularly in view of the fact that one case of locally invasive blue nevus reported by Silverberg[46] presented metastases and that at least four cases of melanoma on blue nevus reported in literature[9, 13], corresponded to blue nevus with focal atypia that later developed massive lymphatic metastases. Immunohistochemical demonstration of antigen HMB 45 is of little use in the differential diagnosis with malignant melanoma because the antigen is often expressed by the cells of common and cellular blue nevus[47, 48, 55].

Congenital giant melanocytic nevus often develops nodular growths, generally in the form of nodes smaller than 5 mm in diameter, that usually protrude on the surface and are accompanied by a focal increase in color. These nodular growths may simulate a cellular blue nevus because they are composed of larger and more pigmented cells than the surrounding nevus cells. In contrast with these benign nodules, malignant melanoma developing on congenital nevus presents nodular formations over 5 mm in diameter and exhibits numerous mitoses (typical and atypical), marked nuclear atypia, macronucleoli, an infiltrative and destructive growth pattern, and spontaneous geographic necrosis[24]. The diagnosis of melanoma developed on a congenital melanocytic nevus in the neonatal period should be made with extreme caution because lesions with all the attributes of malignancy cited may have a favorable course[4, 24].

New Entities Related to Blue Nevus

The classic form of cellular blue nevus should be differentiated from the recently described combined, compound and deep penetrating nevi.

Combined nevus is a benign, mixed, pigmented lesion consisting of dermal nevus cells with the usual attributes, spindle cells (blue nevus type), and, occasionally, epithelioid and spindle cells (Spitz nevus type). These nevi are generally small and stable in size and color. The blue nevus component may be arrayed in pigmented nests within a common melanocytic nevus or on its periphery. It affects mainly vascular walls and dependent structures[37] (Fig. 4). Malignant transformation has been reported in the junctional component of the melanocytic nevus[15, 38]. Kamino and Tam[25] have introduced the term *compound blue nevus* for those melanocytic lesions with features of blue nevus in the dermis that additionally shows junctional dendritic component (Fig. 5).

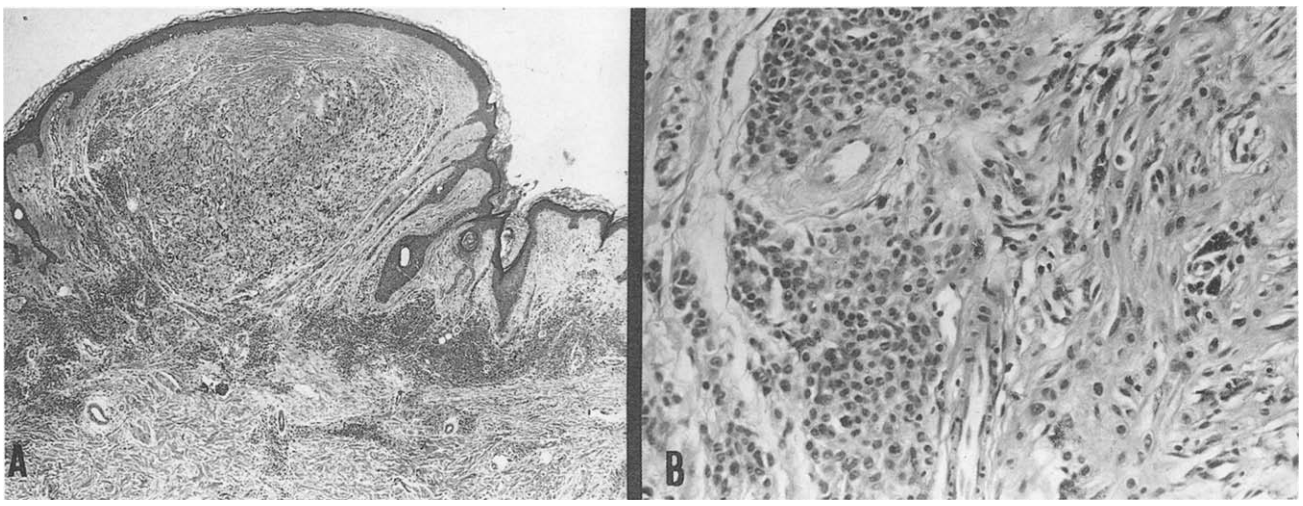

Fig. 4. Combined nevus. A. Intradermal melanocytic nevus with a well defined nodule of cellular blue nevus. HE 9,6×. B. Detail showing the interface between melanocytic nevus (right) and cellular blue nevus (left). The intradermal nevus is composed of clamps of small polygonal cells. The cellular blue nevus component is arranged in a fascicular pattern with scattered pigmented phagocytes. HE 240×.

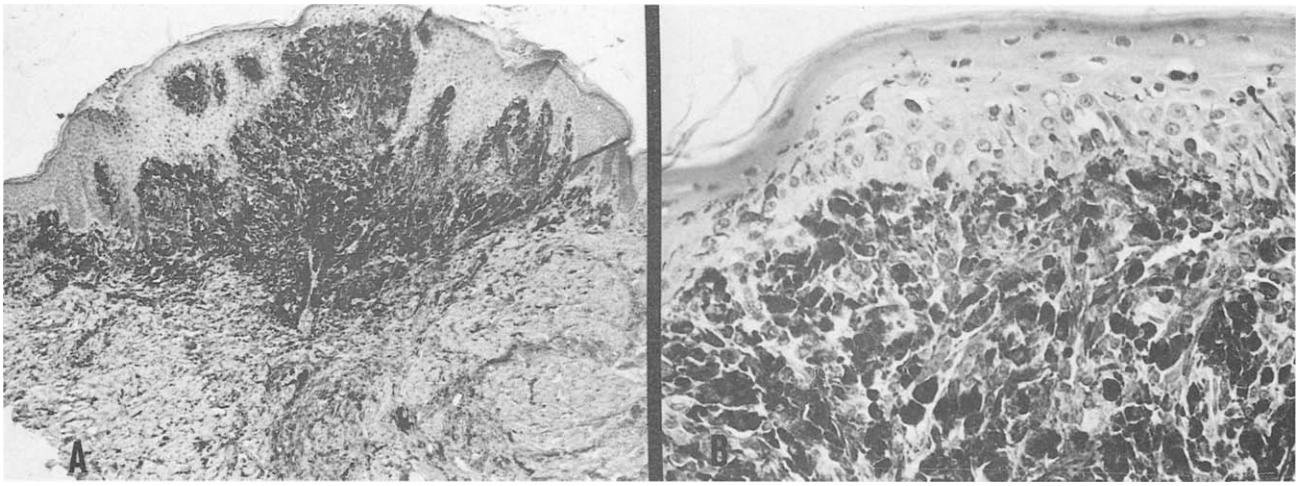

Fig. 5. Compound blue nevus. A. Dome-shaped and symmetrical proliferation of heavely pigmented melanocytes at the dermoepidermal junction and upper dermis. HE 23×. B. Detail showing dendritic melanocytes in the epidermis. HE 374×.

Deep penetrating nevus, also known as plexiform spindle cell nevus, is a peculiar lesion presenting some of the features of combined melanocytic nevus, blue nevus, and Spitz nevus. It's clinical manifestation may be similar to blue nevus, but very often shows some variegation in color that create clinical concern regarding malignant melanoma[14]. It occurs mainly in the second and third decades of life, is somewhat more common in females, and is located preferentially on the head, neck, proximal extremities and back. A noteworthy negative finding is its absence from hands and feet[44]. Histologically, deep penetrating nevus is a wedge-shaped lesion with the vertex located in the reticular dermis or hypodermis, and a laterally infiltrating pattern (Fig. 6). A discrete thecal component is often found in the dermoepidermal junction. The dermal component consists of intensely pigmented spindle cells arranged in loose thecae or bundles and numerous melanophages dispersed throughout the lesion (Fig. 7). Characteristically, deep penetrating nevus shows no signs of melanocytic maturation in depth and the cells often present nuclear pleomorphism, hyperchromatism, pseudoinclusions, and even prominent nucleoli (Fig. 8). Occasionally, isolated mitoses are seen in the more superficial dermal component. Notable negative findings, which are important for differentiating deep penetrating nevus from melanoma, are the absence of atypical mitoses, of foci of geographic necrosis, and of a destructive infiltrative pattern, findings which are typical of malignant melanomas[14, 18, 33, 44].

Further, a new term *melanocytic dermal tumor of unpredictable outcome* has been applied to certain lesions of highly heterogeneous morphology that cannot be classified clearly as one of the classic entities, and present one or more histologic criteria of malignancy, but insufficient in number or intensity to justify classification as a melanoma. This denomination includes the former atypical blue nevus, blue nevus with

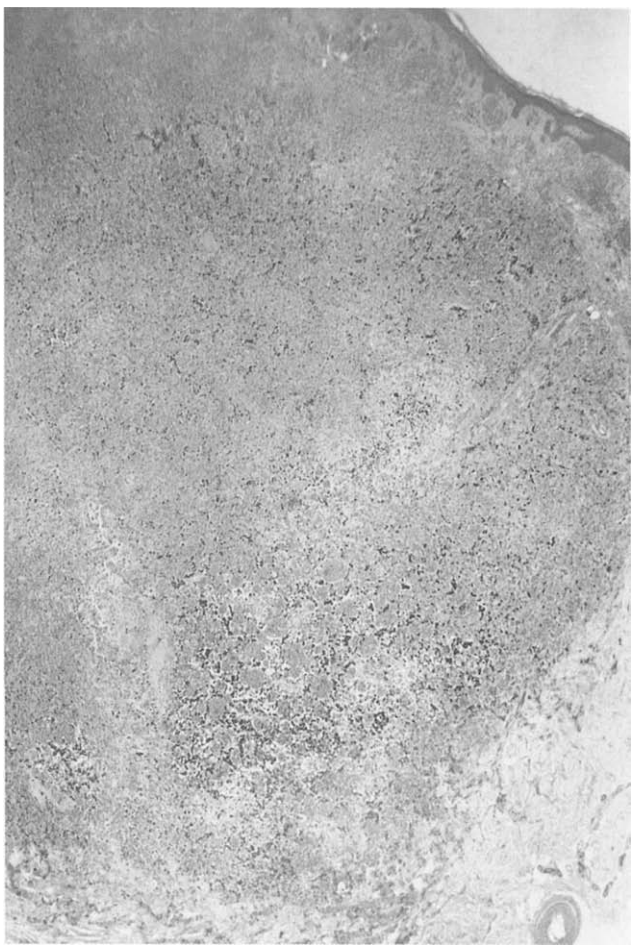

Fig. 6. Deep penetrating nevus involving reticular dermis and hypodermis. HE 11×.

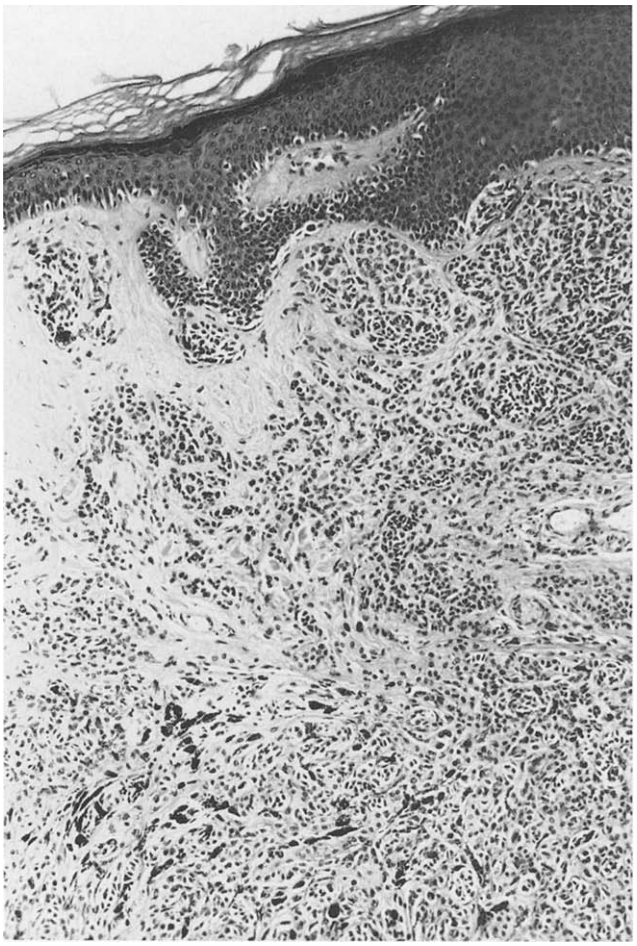

Fig. 7. Deep penetrating nevus. Detail showing intraepidermal component, lack of maduration, and features of combined nevus. HE 105×.

local infiltration, Spitz nevus with deep component mitoses, and other less defined lesions[18]. Generally, they are large, exophytic tumors consisting of spindle cells with abundant melanic pigment, large nuclei and prominent nucleoli, as well as numerous melanophages and a variable lymphocytic infiltrate. Useful negative findings for differentiating it from melanoma are the scarcity of mitoses and the absence of anomalous mitoses, geographic necrosis, or ulceration[12, 18]. This category also includes lesions similar to spontaneous or induced melanoma in animals. These tumors consist of nodular clumps of intensely pigmented cells that at first sight look like melanophages; when studied more closely, tumoral cells can be differentiated from melanophages. Although most of the tumors of this morphology reported in humans have had a biologically benign behavior, there have been reports of massive metastases in regional lymph nodes[12].

Two clinical subtypes of blue nevus characterised by their irregular distribution of the pigmentation have been recognised: the plaque-type[23, 36] and the target-

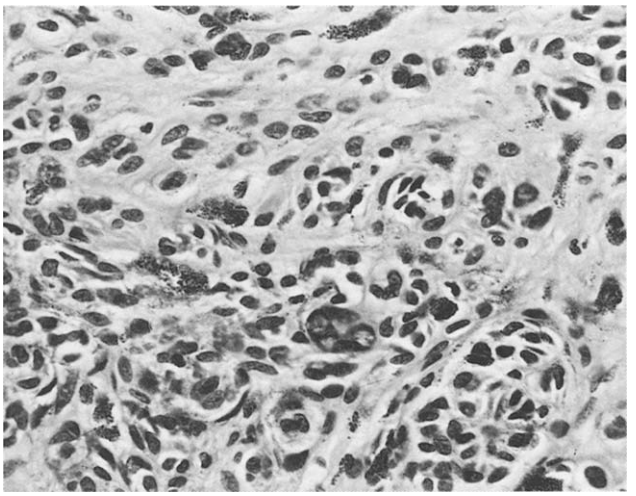

Fig. 8. Deep penetrating nevus. Slight nuclear pleomorphism and occasional nuclear inclusions. HE 377×.

type[11]. The plaque-type, also denominated eruptive blue nevus[23], is a large (usually larger than 5 cm), congenital or acquired lesion that is preferentially located in the trunk. The plaque is composed of multiple blue papules with intervening bluish discoloration of the skin. Clinically it may recapitulate a vascular lesion, a malignant melanoma or a nevus spillus[23, 36]. The target-type blue nevus represents an acquired change in the pigmentation in a previous blue nevus. It is usually located in the dorsal aspect of the foot and its occurrence is probably in relation with some local factors, such as friction from foot wear. Clinically, it is a small dome-shaped nodule with a central-grey area surrounded by a flesh-colored slightly hyperpigmentated raised area which, in turn, merges with an outer rim of macular blue-black pigmentation[11]. Most of these clinical subtypes display the histologic features of common blue nevus, but cases with the findings of cellular blue nevus have also been reported[11, 23, 36].

Malignant Blue Nevus

Malignant blue nevus is defined by the presence of cytologically malignant dermal melanocytes, usually forming nodules, developing on a pre-existing blue nevus, or by the occurrence of melanoma at the site of an excised blue nevus[13, 32]. Its biological behavior has originated much controversy in the literature because there are few case reports and no uniform histologic criteria, and cutaneous lesions classified as "benign" have developed eventually lymphatic metastases. Using strict diagnostic criteria as mentioned above there are no more than 50 cases. The biological behavior of malignant blue nevus is extremely aggressive: 80% of patients have metastasis at the time of diagnosis and the 5-year mortality is high[13, 41]. In contrast with cellular blue nevus, melanoma arising in blue

nevus is located mainly on the head and has a predilection for males[10].

Among the histologic findings suggesting malignancy (size larger than 3 cm, nuclear pleomorphism, atypical mitotic figures, spontaneous necrosis, expansive destructive growth and lack of biphasic pattern), the single criterion that best helps to differentiate malignant blue nevus from cellular blue nevus is the existence of atypical mitoses. Other criteria, although frequent in melanomas, are not absolute criteria for malignancy[10, 12, 31, 41]. The time lapse between the occurrence of a blue nevus and development of malignant melanoma varies greatly.

The pigmented lesion from which malignant blue nevus arises may be congenital (Ito or Ota type dermal melanocytosis) or acquired (cellular blue nevus)[9, 16, 24, 31, 35]. Exceptionally, association with common blue nevus has been reported[34]. In patients with nevus of Ota, malignant transformation can occur in choroid, central nervous system, orbit, or skin[45]. Clinically, there are no premonitory signs of malignant transformation of blue nevus; malignant transformation is recognized by progressive development of a nodule or plaque on a previous lesion.

Malignant blue nevus should be differentiated from melanomas consisting of spindle cells rich in pigment melanin. These lesions bear extraordinary similarity with cellular blue nevus, but a thorough study reveals the features of spindle-cell melanoma, such as presence of an epidermal component or nevocytic type cellular component.

Exceptionally, skin lesions with all the cytological features of a benign of cellular blue nevus are associated with the massive regional lymphatic metastases of malignant melanoma[9]. These lesions should be interpreted as malignant melanoma simulating blue nevus.

Lymph Node Metastases

As for the diagnosis of lymph node metastases, it should kept in mind that benign nevus cells have been reported in lymph nodes under three different circumstances:

1) *Benign metastasizing blue nevus* (pseudomelanoma, pseudometastasizing blue nevus). In 1953, Allen and Spitz[1] described four cases of apparently benign cellular blue nevi associated with small clumps of nevus cells having characteristics similar to those of skin cells in the peripheral sinuses of regional lymph nodes. Later, Rodríguez and Ackerman[41] stated that this finding is relatively frequent, with an approximate incidence of 5%. The main problem of this lymphatic dissemination, presumably resulting from lymphatic invasion by cells of the pigmented skin lesion[21, 26], is differentiating it from malignant melanoma metastases. It has been reported that the cytological features and location of the cells inside the lymph node are the most significant differential aspects. Whereas "malig-

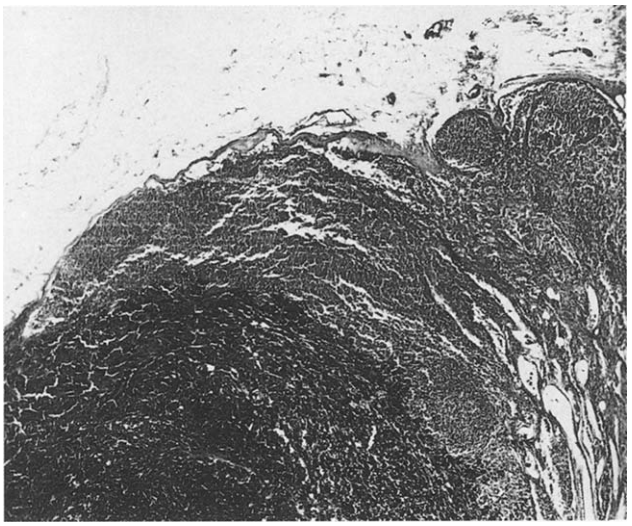

Fig. 9. Lymph node with melanoma metastasis. Massive invasion of tumoral pigmented cells throughout the pulp of the lymph node. HE 26×.

nant" cases usually have pleomorphic cells with frequent mitoses forming large foci that affect lymph node sinuses, capsule, and parenchyma, as well as geographic necrosis (Fig. 9), benign cases contain homogeneous, nonmitotic cells forming small clumps usually lining the peripheral sinuses[41].

2) *Clumps of nevus cells.* These cells are similar in every respect to those seen in cellular blue nevus. They present generally an epithelioid appearance and are arranged into syncytia within the fibrous connective tissue of the lymph node (capsule and trabeculae), or the perilymphatic fat of superficial lymph nodes (axilla and groin)[43] (Fig. 10). The frequency of this finding ranges from McCarthy's report[30] of an average of 5% overall in lymph nodes to the much smaller figures given by Ridolfi and others[40]: 0.03% in the axillary lymph nodes of patients operated on for breast cancer and 3% in lymph nodes excised for malignant melanoma. Currently, it is thought that these clumps proceed from aberrant emigration of progenitors derived from the neural crest that later undergo nevocytic differentiation[43]. Recently, Vittal Shenoy and colleagues[54] reported an extraordinarily singular case in which clumps of cells of nevus, common blue nevus, and primary malignant melanoma were found coexisting independently in an axillary lymph node, presumably having developed from the precursors of clumps of nevus cells.

3) *Ectopic blue nevus in lymph node.* These nevi consist mainly of dendritic cells with fine prolongations filled with melanic pigment as in a common blue nevus. At present, only a few cases have been reported in the literature[19, 29, 43], all found incidentally while examining enlarged lymph nodes for other disorders (especially breast cancer)[19]. Like the clumps of nevus cells mentioned above, dendritic cells are found in

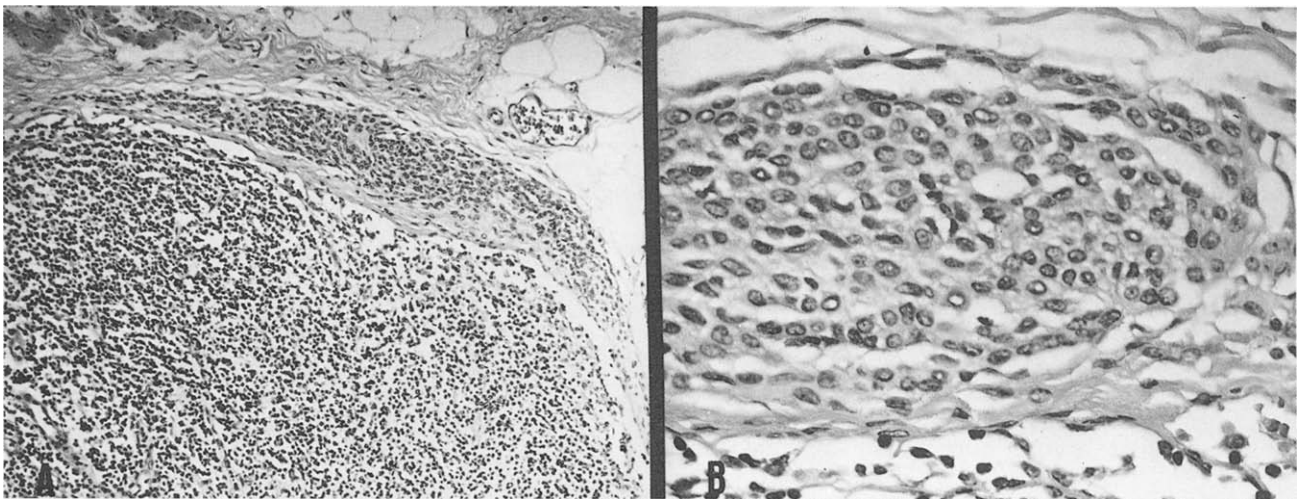

Fig. 10. Nevus cells inclusion in lymph nodes. A. Clumps of polygonal nevus cells arranged in syncytia within the capsular fibrous connective tissue of the lymph node. HE 250×. B. Detail showing bland nuclear features. HE 386×.

the trabecular and capsular connective tissue of the lymph node, and in perilymphatic fat. Just as for the nevus cell clumps, it is assumed that the dendritic cell clumps are the result of anomalous emigration of melanocytic progenitors from the neural crest[19].

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