DERMATOLOGY PRACTICAL & CONCEPTUAL
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Atypical or typical pagetoid cell: a subtle clue to differentiate a melanoma from a melanocytic nevus

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Key words: melanoma, melanocytic nevus, pagetoid cell

Citation: Hurwitz R. Atypical or typical pagetoid cell: a subtle clue to differentiate a melanoma from a melanocytic nevus. Dermatol Pract Conc. 2013;3(2):3. http://dx.doi.org/10.5826/dpc.0302a03.

Received: December 28, 2012; **Accepted:** March 1, 2013; **Published:** April 30, 2013

Funding: None.

Competing interests: The author has no conflicts of interest to disclose.

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Introduction

Differentiation of a melanocytic nevus and melanoma is often a dilemma clinically as well as histologically. This dilemma involves inexperienced as well as knowledgeable pathologists. The provoking question turns out to be: why is this differential diagnosis often a quandary? The answer lies in the fact that there are overlapping cytological and architectural criteria used interchangeably for a melanoma and melanocytic nevus. The criteria emphasized often vary from institution to institution and pathologist to pathologist. Regrettably, similar criteria attributed to both benign and malignant melanocytic proliferations, melanocytic nevus and melanoma, are used interchangeably: thus the quandary.

Discussion

Melanocytes in the skin situated at the dermoepidermal junction are relatively monomorphic, with clefting of their small dark nuclei from their paltry cytoplasms [1]. Melanocytic nevi are hamartomas composed of melanocytes with relatively monomorphic basophilic nuclei with paltry, clefted cytoplasm in nests, fascicles, columns, cords, and aggregates, as well as solitary units that may involve the epidermis, dermis, and structures of adnexal.

Cytologically, the monomorphous melanocytes of melanocytic nevi are in an erratic, unpredictable assortment of small and minimally larger sizes and shapes, e.g., round, oval, spindle-shaped, polygonal, plasmacytoid, ballooned, fusiform, dendritic, pagetoid and multinucleate. Not uncommonly, they are associated with pseudoacantholysis. Melanocytes of melanocytic nevi in the skin are usually small, monomorphous and routinely are located at the dermoepidermal junction and not above it, as solitary units as well as in nests at the dermoepidermal junction and dermis. Nuclei may be diverse, as well, ranging from typical small and uniform small round/oval with small nucleoli, to atypical large, pleomorphic, hyperchromatic, heterochromatic, with prominent nucleoli, necrosis, mitosis, and above the dermoepidermal junction as seen in a genital melanocytic nevus, melanocytic nevus of the palm/sole, and in the so-called Spitz's nevus [2]. The amount of cytoplasm within an individual melanocyte of a melanocytic nevus is routinely paltry and insignificant, but may be variable, inconsistent and unpredictable. Architecturally, criteria for melanocytic nevi usually include symmetry, sharp circumscription, wedge-shaped, maturation with progressive decent into the dermis, and lack of scatter of melanocytes above the dermoepidermal junction (pagetoid pattern) across a broad front.

To the contrary, criteria for melanoma cytologically and architecturally are usually the reverse to those of melanocytic nevus, but not always. Shapes of melanocytes of a melanoma are similar to a melanocytic nevus, e.g., round/oval, spindle-shaped, fusiform, polygonal, with pseudoac-

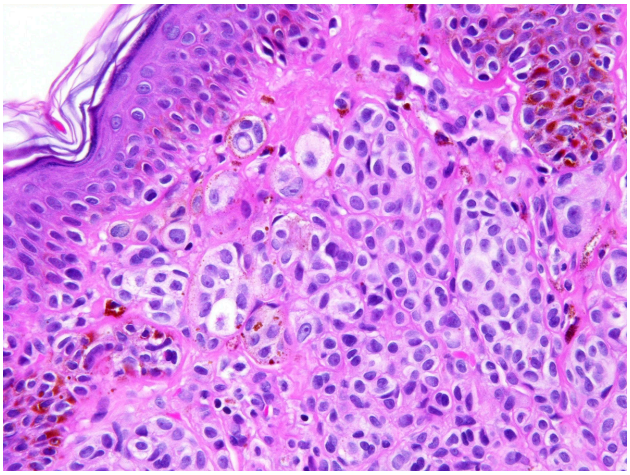

Figure 1. Melanocytic nevus with typical pagetoid melanocytes. Typical pagetoid melanocytes are round with abundant pale cytoplasm with uniform staining small, and slightly large round/oval basophilic nuclei. Numerous routine appearing small round/oval melanocytic nevus cells are present in number with their usual paltry, clefted cytoplasm with periodic patchy melanin, in association with variable size and shaped aggregates of routine appearing basophilic small and large round/oval nucleated melanocytic nevus cells.

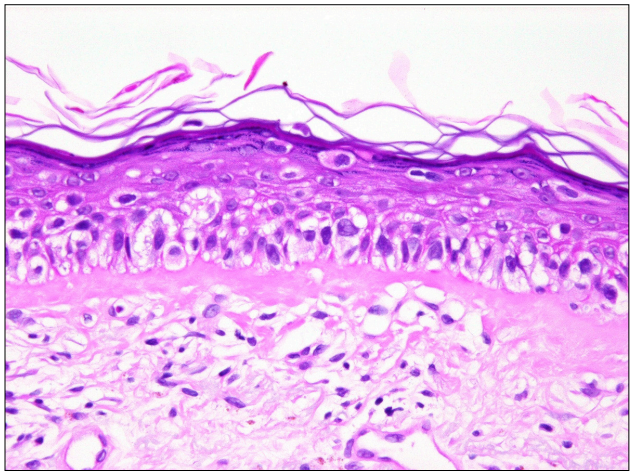

Figure 2. Melanoma in situ with numerous atypical pagetoid melanocytes in pagetoid pattern. The atypical pagetoid melanocytes are large round and polygonal-shaped with abundant pale staining cytoplasm with large round, pleomorphic, hyperchromatic, heterochromatic basophilic nuclei. The scatter of notorious, atypical pagetoid melanocytes involving the basal, spinous and granular layers of the epidermis, i.e., pagetoid pattern.

antholysis, etc., but time and again with large round pleomorphic nuclei, often with some frequency large vesicular nuclei with prominent large red centrally located nucleoli. On the other hand, for example, some melanomas may have an increased number of solitary small melanocytes at the dermoepidermal junction, with solitary melanocytes outnumbering those in aggregations and nests, especially early in its evolution. In addition, periodically, a melanoma early in its evolution may exhibit a number of melanocytes with riveting, elongated, pigmented dendrites that extend into the upper spinous layer. Interestingly, as well as fascinatingly, and to the contrary, some melanocytic nevi may also have a number of similar criteria of melanoma, e.g., small melanocytes and small nests of melanocytes. In addition, an early or evolving melanoma may have increased elongated dendritic melanocytes, while to the contrary a Spitz's nevus with elongated dendritic melanocytes commonly are seen in Asians and African Americans [3]. Congenital melanocytic nevus shortly after birth, and nevi involving "special sites" such as the genitalia, perianal, breast/nipple/areola, palms/soles, scalp, ear and umbilicus, as well as in the often perplexing persistent (recurrent) nevus, regularly have criteria common to melanoma, e.g., scatter of melanocytes above the dermoepidermal junction. Noticeably, if not outright stunning, some melanocytic nevi with criteria of a melanoma have been added to a bewildering and confusing register of melanocytic nevi which supposedly have a propensity to evolve into a melanoma, i.e., the so-called pre-melanoma. Some monikers include an atypical mole, dysplastic nevus, nevus with architectural disorder and cytologic atypia, atypical Spitz nevus/tumor, as well as neoplasms of indeterminate malignant potential with evasive monikers (NIMP, SAMPUS, MELTUMP) [4,5,6,7].

Noteworthy, the so-called pagetoid cell [7] is the quintessential example of uncertainty and misunderstanding as to whether the melanocyte with abundant pale cytoplasm is truly an atypical pagetoid cell of melanoma, or a typical pagetoid cell of a melanocytic nevus. The typical pagetoid cell is located commonly at the dermoepidermal junction or dermis in customary, routine traditional junctional or compound melanocytic nevi, Spitz's nevus, or genital melanocytic nevus (Figure 1). On the other hand, the atypical Pagetoid cell of melanoma is considered a cell that simulates those cells seen in extramammary Paget's disease, which have large nuclei with abundant pale staining cytoplasm. In a melanoma, there may be many melanocytes with large, basophilic round/oval, fusiform or polygonal shaped melanocytes with riveting large pleomorphic nuclei, large nucleoli, abundant pale staining cytoplasm, and frequently in pagetoid pattern (Figure 2). In addition to melanoma and some Spitz's nevi, atypical pagetoid cells are common to squamous cell carcinomas, e.g., Bowen's disease, Paget's disease of the breast, and apocrine carcinomas. Therefore, when a melanocyte has abundant pale cytoplasm and is associated with a large round/oval pleomorphic nucleus, it is acknowledged and known as an atypical pagetoid cell. This is contrasted to a typical pagetoid cell, which has a small or slightly large round/oval nucleus with abundant pale cytoplasm but without significant nuclear atypia and pleomorphism. To boot, a mitotic figure, typical or atypical may be observed on occasion in either a typical or atypical pagetoid melanocyte.

Conclusion

In summary, the dilemma of whether a pigmented melanocytic proliferation is a melanoma or melanocytic nevus perhaps rests on the recognition of overlapping criteria, and the detection of the typical or atypical pagetoid melanocyte.

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