Melanoma Arising in a Pre-Existent Nevus

44.1 Introduction

Melanoma develops in a preexisting conventional nevus in two major patterns.

By far the most frequent form is melanoma arising in the junctional portion of a nevus. This type of melanoma can most likely emerge in all forms of acquired or congenital nevus, although documentation of a distinct, unequivocal area of melanoma arising at the junction in an indisputable Spitz nevus has never been shown, to our knowledge.

The second, much more rare form of melanoma develops in the dermal portion of a nevus. The most convincing examples have involved a large or giant congenital nevus. The two entities are described separately.

44.2 Melanoma Arising at the Junction of a Nevus

44.2.1 Clinical Features

This form of melanoma usually develops in small congenital nevi or in acquired nevi (Bevona et al. 2003; Weatherhead et al. 2007). It is by far the most frequent form of melanoma arising in a nevus encountered in everyday practice. In our experience, the most frequent form of nevus with subsequent melanoma is the “early onset” nevus, that is, a nevus that was, by history, an acquired one with some of the histological features of congenital nevus (see Chap. 6). In the literature, remnants of a nevus are found in sections from a melanoma in a very broad range, from 4.7 to 50% (García-Cruz et al. 2009). We will discuss the difficulties involved in evaluating this in the section on histopathology.

Clinically, melanoma first appears as an enlarging macule or papule or plaque on a preexisting, long-lasting, and hitherto, clinically stable nevus. The color of the area of new growth is usually different from that of the nevus. If the change is macular, it has the indistinct borders and variable colors seen in melanoma in situ (see Chap. 28), and if papular or a plaque, similar irregularities obtain.

As mentioned above, this evolution usually affects small- or medium-sized nevi, but occasionally, also giant nevi can give rise to a conventional melanoma that develops at the dermoeidermal junction (Togawa et al. 2010).

Melanoma developing within a nevus spilus has been reported in about 20 cases, usually in the large segmental forms of the latter (Haenssle et al. 2009). Whether this is more likely in so-called dysplastic nevus spilus (in which small foci of dysplastic nevus are present) or not is a determination that cannot be made, due to the rarity of the condition.

44.2.2 Dermoscopic Features

According to Stante et al. (2003), features characterizing nevus-associated melanoma are an atypical pigment network and regression pattern. Irregular blotches and an atypical vascular pattern, typical of de novo melanoma, are less frequent. At least in its early stage, melanoma ex nevus resembles the architectural pattern of the nevus in which it is evolving. This finding was confirmed with confocal microscopy (Longo et al. 2011).

44.2.3 Histological Features

Melanoma in situ above a nevus (Fig. 41.1) usually arises at the edge of a preexisting lesion, rather than above its center. The preexistent nevus usually has small, round melanocytes, arranged as discrete nests, cords, and strands, often involving the superficial reticular dermis and having a periappendageal distribution (a “congenital pattern”). Less commonly, one sees a clear-cut residuum of a “Clark” or “dysplastic” nevus.

The earliest changes are those of an increased number of single melanocytes along the junction, and these may not be strikingly atypical. In this early stage, the distinction between evolving melanoma in situ above a nevus and benign simulants of it may be impossible, especially in teenagers, and in nevi that have been irritated or recently been challenged by intense ultraviolet light exposure.

Moreover, the change is less convincing of melanoma in situ if there are melanocytes above the junction only above zones in which a dermal component is present or in which the junctional component is mostly nested. We do not generally make a diagnosis of a melanoma in situ arising in a nevus lightly. The diagnosis is best made if there is a cytological difference between the intraepidermal melanocytes
and those of the preexisting nevus, with no transition between the two cell types, and if the single cells extend to only one side beyond the confines of the dermal part of the nevus.

In the differential diagnosis, involvement of the papillary dermis by a contrasting population of cells outlined by lymphocytes also helps (Fig. 44.1). In its infiltrative stage, a melanoma arising in a nevus shows no special features that distinguish it from primary melanomas arising de novo (Fig. 44.2, 44.3, 44.4, 44.5, and 44.6). The cells of the nevus often look like they had been displaced. They are usually cytologically distinct from the atypical melanocytes above them. Very rarely, immunohistochemistry can identify the two different neoplastic components, staining only the malignant one, but in our experience this maneuver is most often mysteriously disappointing. On occasion, melanoma cells seem to insinuate themselves in nests of the preexistent nevus.

Clues to the presence of two populations, i.e., melanoma and nevus, also include a lymphocytic infiltrate, fibrosis, and neovascularization that are present only beneath the larger cells. The small, round cells of many small congenital or congenital-like acquired nevi are often present in much more discrete aggregations with delicate stroma, often around the adnexa, a pattern that is as a rule not seen in melanomas.

A melanoma that arises in a nevus can undergo regression and a dense inflammatory infiltrate only replacing most of the malignant component can be seen, whereas the nevus remnants are untouched. This event may be very difficult to distinguish from a nevus with partial regression.

Part of the bizarrely broad range of answers to the question “how many melanomas arise in nevi?” is that small melanoma cells are often labeled as those of a nevus. Moreover, nested patterns of melanoma in situ at the edges of invasive melanomas are labeled as “melanocytic dysplasia” and included with formerly stable, preexistent nevi as signifying origin in a nevus.

**44.2.4 Differential Diagnosis**

Melanoma evolving in the junctional component of a compound congenital or acquired nevus can be confused with many forms of nevus, namely, “dysplastic” nevus, “Clark” nevus, nevi on genital and acral skin, and nevi in adolescents or in the milk line. All these forms of nevi have in common a disorderly arrangement of melanocytes and nests along the junction or sometimes above it.

The differential diagnosis of the different entities is discussed separately:

- In the case of “dysplastic” or “Clark” nevus, we consider the presence of many melanocytes or a cytologically distinct population of more atypical melanocytes singly at or above the junction as a prerequisite for the diagnosis of an evolving melanoma in situ. A few melanocytes at or above the junction are, in fact, an expected occurrence in the center of a “dysplastic” nevus, especially if these cells are discovered by immunostaining. The change is most convincing if it is at the edge of the lesion, with no underlying dermal component, and accompanied by a change in the pattern of rete ridges vis-a-vis in the rest of the lesion. A denser lymphocytic infiltrate in the asymmetrically affected area also helps.
  - In genital nevi, large, laterally confluent nests of pale cells are an expected finding; the plump melanocytes should mature gradually with descent. Few genital melanomas arise in nevi.
  - Acral nevi have upward migration of single cells in about half of cases; rules for evaluating them are outlined in Chap. 19.
  - Nevi on the milk line in other special sites or in teenagers frequently have striking large irregular junctional nests, but florid pagetoid spread is not at all characteristic.
  - Combined nevi can simulate a melanoma evolving from a nevus, especially if the junctional component is strikingly different from the intradermal one. In these cases, the two parts of the lesion should be considered separately and the nature of each part should then be assessed.

A particular challenge in many examples of melanoma arising in a nevus is the establishing the thickness of the malignant portion. This problem arises in particular when some or all of the melanoma cells are small, round ones (nevoid melanoma) similar to the cells in the deeper portion of the lesion. In this case, remember that the pattern of the two populations usually contrasts, as does the inflammatory and stromal reaction to their presence (see the section above on histopathology).

We have been disappointed by the unreliability of immunostaining in separating melanoma cells from the subjacent cells of a nevus. The gradient pattern of staining with HMB45, in which the junctional component labels strongly, while the dermal component progressively looses positivity, is the most commonly found one in melanoma. This blunts its use in this situation. Only if there is a clear contrast between the two putative populations can one assume that one is melanoma and one nevus. Many melanomas have relatively low Ki-67 labeling rates, and in such cases no distinction is possible using this stain. Somewhat more credence can be given to a p16 stain in which large superficial cells lack positivity, while deeper ones retain it.

The pattern of elastic tissue staining can also be of use. The elastic fibers in between melanoma cells are often lysed, while those between the cells of a nevus are preserved (Kamino et al. 2010). The elastic fibers in between the cells of a congenital nevus can have an exaggerated pattern, which is particularly helpful when contrasting them with the absence of fibers in between the cells of small cell melanomas.

One can possibly use fluorescence in situ hybridization to distinguish these two populations. The presumption is