The Recurrent Nevus Phenomenon
A History of Challenge, Controversy, and Discovery

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Context.—The diagnosis of recurrent nevus poses a potential challenge to practicing pathologists. Although most recurrent nevi show uniform microscopic findings and pose no great diagnostic difficulty, a few cases exhibit some histopathologic features similar to, and in some cases indistinguishable from, melanoma. Historically, the term pseudomelanoma has been used in the literature to describe such recurrent nevi, although this label has the potential for confusion and is no longer the favored term for recurrent pigmented melanocytic nevi.

Objective.—To describe historical, histopathologic, and immunohistochemical features of recurrent pigmented melanocytic nevi.

EARLY STUDIES

Some dermatologists in the 1950s held the disturbing opinion that partial removal of melanocytic nevi, particularly when performed by electrodesiccation, might induce the nevic remnant to change into a melanoma; however, no published studies proved that such malignant transformation occurred. To address this topic, Walton et al1 examined 112 biopsy specimens of pigment ed nevi from 75 patients that were removed by shave technique, followed by light electrodesiccation, and subsequently completely excised at intervals of from 3 to 12 months. This seminal report marked the beginning of what would henceforth become the challenging, often controversial, and ultimately edifying study of the recurrent nevus phenomenon.

In their study, Walton et al1 found no evidence of malignant change in either the original nevus (ON) or the recurrent nevus. The authors concluded that partially removed nevi, which later gave rise to melanoma, were more likely already to have been undergoing malignant change at the time of initial biopsy than to have been transformed by the biopsy process itself. Clinical recurrence of pigmentation at the biopsy site was reported to occur in more than half of subjects and, although of concern clinically, it was reported to represent the presence of pigmented nevus cells, with no signs of increased mitotic index.1 A subsequent study of 19 recurrent nevi (RN) similarly reported no evidence of malignant change, as evidenced by absence of mitotic figures, cellular enlargement, or reactive inflammatory infiltrate. A prototypic histologic pattern of RN was described as consisting of a junctional melanocytic component with varying degrees of pigmentation overlying fibrous scar tissue and deep, residual, monomorphous nevus cells lacking mitotic figures; this pattern would later be termed trizonal.2 Several of the earlier studies involving RN disagree with regard to junctional melanocytic activity, a term used to describe excessive pigmentation of epidermal cells and increased prominence of melanocytes in the basal layer, without implying increased mitotic figures (which were not observed). Initial studies described such so-called junctional melanocytic activity as being restricted to specimens in which it was present in the ON; the activity in the RN was said to be morphologically similar but quantitatively diminished.3,4 Later studies, in contrast, reported cases of intradermal nevus removed by shave biopsy, resulting in RN with pronounced junctional changes not present in the initial specimen. Increased prominence of intraepidermal melanocytes in some RN as compared with the ON was also reported, and this change was found to be inversely related to the time elapsed from removal of the ON, with the most dramatic increase being shown in the first 6 months. Independent of any other factor, increased prominence of junctional melanocytes and the clinical presence of increased epidermal pigment in RN were found only when residual dermal nevus cells existed.4,5

PSEUDOMELANOMA

In 1975, Kornberg and Ackerman6 reported that pigmented RN could closely resemble superficial spreading melanoma. However, subsequent studies have shown that such nevi are similar histologically and have no clinical features that distinguish them from melanoma. The diagnostic dilemma of recurrent nevus has not been clarified.
malignant melanoma (SSMM), both clinically and histologically, and proposed the term pseudomelanoma to describe this benign phenomenon. Their series involved 8 cases of a pigmented lesion appearing up to 6 weeks after shave removal of a benign nevus, at the biopsy site. In addition to intradermal nests of nevus cells present in 7 specimens, an additional 9 microscopic features were described: (1) sharp circumscription of the melanocytic lesion within the epidermis, with no tendency to spread laterally among keratinocytes peripheral to the lesion; (2) atypical melanocytes confined to the epidermis; (3) increased numbers of melanocytes singly and in nests, within and above the basal layer; (4) variation in size and shape of melanocytic nests; (5) confluent melanocytic nests as well as discrete nests; (6) a few atypical melanocytes with large, hyperchromatic, and pleomorphic nuclei; (7) few, if any, melanocytes in mitosis; (8) fibrosis in the papillary and in some cases the reticular dermis; and (9) a sparse, superficial, perivascular lymphohistiocytic infiltrate.

Of these features, (3), (4), (5), and (6) were held in common with SSMM, whereas (1), (2), (7), and dermal fibrosis were found to distinguish pseudomelanoma. Furthermore, the fibrosis found in “pseudomelanoma” was a result of the trauma of the previous biopsy, in contrast to the fibrosis found in SSMM, which was associated with a relative paucity of melanocytes and melanin in the overlying epidermis, and which signified regression. The clinical appearance of pseudomelanoma was described as variegated pigmentation, with jet-black foci resembling SSMM; the authors suggested that this change resulted from scattering of melanocytes through the stratum corneum. As in previous reports, the authors stressed the importance of reviewing the original biopsy specimen, although they proposed that the diagnosis of pseudomelanoma might be suspected if the above histologic criteria were met.

In 1986, Trau et al reported a case of pseudomelanoma after CO2 laser ablation therapy for a congenital nevus. Pseudomelanomatous changes have subsequently been described after use of erbium:yttrium aluminium garnet, alexandrite, and Q-switched ruby lasers as well. Because of the incomplete destruction of the dermal portion of nevi, the potential for recurrence, and the lack of histopathologic confirmation of the initial lesion, most authors argue against the use of lasers for the cosmetic removal of clinically benign nevi. Recurrent nevi described as “pseudomelanoma” have also been reported in the literature after treatment with Solcoderm, dermabrasion, acid, electrocautery alone, radiotherapy, and non biopsy trauma such as chronic irritation from clothing.

The term pseudomelanoma is controversial. Some authors consider the label misleading and inappropriate because of its use in the past to describe hemosiderotic histiocyteoma, while others recommend that the term be dropped for fear of medicolegal inferences. For our part we do not recommend this designation, because we consider it potentially confusing; moreover, we prefer not to designate pathologic entities by reference to what they are not. Regardless of the term chosen, the observation that the intraepidermal portion of a recurrent nevus could resemble SSMM would be confirmed and the proposed histopathologic criteria would serve as useful guidelines for pathologists evaluating questionable specimens.

**EPIDEMIOLOGY AND HISTOPATHOLOGY OF RECURRENT NEVI**

Recurrent nevi characteristically occur in women from 20 to 30 years of age, most often on the trunk (specifically, the back), followed by face and extremities. Recurrence usually appears within 6 months of the original biopsy and is clinically manifested by a macular area of scar with variegated hyperpigmentation and hypopigmentation, linear streaking, and halo, stippled, and/or diffuse pigmentation patterns. Most RN originate as “ordinary” or common acquired nevi; less often, recurrences arise from congenital, atypical/dysplastic, and Spitz nevi (see below), and other specialized nevi such as blue and spindle cell nevi. Of the common acquired nevi giving rise to recurrences, most are compound (50%–60%) and most of the remainder are intradermal. The trizonal histologic pattern of RN has been confirmed in many studies (Figures 1 and 2). The dominant melanocyte in RN has been described as having epithelioid cytologic features, with a round nucleus and an even chromatin pattern; however, in 1 study, 26% of RN showed melanocytic atypia including nuclear hyperchromasia and enlargement. Suprabasal (pagetoid) spread of melanocytes, extension down adnexal structures, confluent growth pattern, and prominent dermal inflammation have each been present in a small minority of RN. “Dropping off” of junctional nevus cells into the dermal scar has also been deduced in 36% to 42% of RN, as evidenced by rounded nesting patterns without differentiation into type B or type C nevus cells. These nests are thought to represent a form of maturational arrest in the evolution of RN.

Challenges in the histopathologic diagnosis of RN have been described in 1 series of 175 RN, specifically in cases demonstrating prominent pagetoid scattering of melanocytes (3%), rare mitotic figures (8%), moderate nuclear atypia (12%), and marked lentigious hyperplasia (35%). Park et al concluded that RN with atypical features rarely resembled SSMM, thereby posing “significant diagnostic difficulties,” but added that most RN did not mimic melanoma histologically; therefore, they did not recommend the term pseudomelanoma. Recently, it has been observed that some cases of RN have histopathologic overlap with regression in melanoma. This was particularly the case when there was retention of the retiform epidermis, as observed in 15% of RN, and confluent proliferation of atypical melanocytes. Thirteen percent of RN with epidermal effacement demonstrated pagetoid spread and inflammatory response and had considerable overlapping histopathologic changes with melanoma in intermediate/late stages of regression. The authors of this study noted that, without knowledge of a previous biopsy, a diagnosis of melanoma from these challenging specimens could not have been ruled out.

**IMMUNOHISTOCHEMICAL STUDIES**

Immunohistochemical analysis has been shown to be useful in differentiating severely atypical RN from melanoma. Labeling for gp100 (with HMB-45) has been found to be strong in the junctional but not the intradermal components of RN, in contrast with melanoma, in which there is strong immunolabeling in both the junctional and deep dermal components. Labeling of ON and RN for both tyrosinase and Ki-67...
demonstrates a maturation pattern, that is, a greater degree of labeling at the junctional component and progressive reduction in expression with increasing dermal depth. The junctional proliferation index in such specimens has been shown to be less than 5%, as evidenced by Ki-67 expression. These findings are in contrast with the patterns of immunolabeling in melanoma, in which tyrosinase is expressed throughout the lesion and the proliferative fraction of the junctional component may be much higher. The patterns of immunolabeling for Melan-A and S100 protein have not been shown useful for distinguishing melanoma from RN.

RECURRENT DYSPLASTIC NEVUS

The concept of the dysplastic nevus (DN) and its association with melanoma entered the literature around 1978 with the description by Clark et al of the familial B-K mole syndrome, a concept subsequently clarified and expanded to include nonfamilial, sporadic cases. The first reported case of recurrent DN after inadequate shave excision further extended the RN spectrum. Nests of atypical melanocytes were present in the junctional component of the recurrent lesion, in association with a strikingly pigmented and densely cellular dermal infiltrate. The authors stressed that such cases were benign, while acknowledging that, in addition to the degree of junctional atypia expected in RN, additional atypia attributable to the original DN might further compound diagnostic difficulties. An additional challenge in the case of some recurrent DN was the dermal reaction to Monsel solution, already reported in the literature as a confounder. Recurrent nevi have been shown to originate from DN in 20% to 28% of cases. Recurrent Spitz nevi (RSN) are rare. In a recent study and review of the literature surrounding RSN, Spitz nevi (SN) were found to recur with an overall incidence of 0.9%, after an average interval of 16.7 months from the initial biopsy, and most commonly recurred on the extremities. In contrast to RN, RSN are less common, occur later, and do not favor the trunk. Four histopathologic patterns of RSN were identified in this study: (1) a prominent intraepidermal pattern resembling "pseudomelanoma"; (2) a compound, mostly nested pattern above or within scar that was nearly identical to the originally biopsied SN; (3) a nodular growth pattern closely simulating invasive melanoma; and (4) a desmoplastic pattern resembling an intradermal desmoplastic SN. Immunostaining revealed identical expression of S100 protein and gp100/HMB-45 in SN and RSN, with strong label present in the junctional component and diminishing or absent staining in the dermal component. The proliferation rate, assessed by Ki-67 expression, was uniformly low, between 1% to 2%, in both SN and RSN. This study highlights the fact that, although most RSN are readily identified by their resemblance to conventional SN, a small subset presents a serious diagnostic challenge. Features distinguishing RSN from melanoma are the absence of ulceration, high mitotic rate, or atypical mitotic features. Immunohistochemical study for HMB-45 and Ki-67 may also be helpful in select cases. Complete but conservative reexcision of RSN with periodic follow-up has been proposed.

SCLEROSING NEVUS WITH PSEUDOMELANOMATOUS FEATURES

Fabrizi et al have proposed the term sclerosing nevus with pseudomelanomatous features (SNPF) for a group of melanocytic nevi that closely resemble melanoma with regression. The term nevi with regression-like fibrosis (NRLF) has been used by others to describe this entity. Irrespective of nomenclature, these lesions are histopathologically characterized by a trizonal pattern consisting of (1) atypical junctional proliferation of melanocytes with pagetoid spread above the basal layer; (2) prominent dermal fibrous scarlike tissue containing large, irregular, and confluent melanocytic nests; and (3) residual nevus cells adjacent to or below the scar. In contrast to melanoma with regression, cytologic atypia and pleomorphism are
not reported in SNPF, and mitotic figures are typically absent or few and restricted to the junctional melanocytic proliferation. Sclerosing nevi with pseudomelanomatous features closely resemble RN; however, aspects that distinguish SNPF from RN include the presence of atypical nests of melanocytes occupying the entire scar, rather than the upper most portion of the dermis, and the absence of prior biopsy or nonsurgical trauma. Immunohistochemical analysis of SNPF for expression of HMB-45 and Ki-67 is similar to that of RN. It has been proposed that SNPF, or NRLF, occur as the result of unnoticed trauma or chronic friction, as may occur on the back, involving preexisting nevi, and may represent chronically recurrent nevi.  

**MECHANISM OF RECURRENTNESS**

The mechanism of recurrence in nevi remains unproven, though many theories have been proposed. The observation of nevi recurring in the scar of previously destroyed nevi led Gougerot to propose seeding during removal as the mechanism for their recurrence, a concept that led some European physicians to use high doses of irradiation before removal of pigmented lesions to prevent growth of theoretically seeded cells. Schoenfeld and Pinkus suggested that junctional stimulation, following partial removal, might represent reversion to an earlier stage of the natural history of the nevus. They referenced the observed patterns of perifollicular and peripheral repigmentation during wound healing of pigmented skin to support their theory that the junctional component of RN originated from remaining hair roots and the periphery of the lesion. Other proposals have included a growth stimulation signal mediated by residual nevus cells, repopulation by adnexal structures, and regrowth from the residual dermal nevus, as evidenced by perivascular S100 protein/factor VIII–/factor XIIIa–fibroblast-like nevus cells within the scar of RN. Sexton and Sexton suggested that the identical immunoperoxidase profiles of ON and RN indicate that the intraepithelial melanocyte population in RN is derived from residual melanocytes located in the epithelium for, if a dermal origin were supposed, some of the residual dermal population should show increased immunolabeling with HMB-45. Repopulation of junctional melanocytes from remaining adnexal structures is supported by studies in the murine model of Nishimura et al, in which melanocyte stem cells found in the lower portion of hair follicles had the ability to migrate to “niches” lacking melanocytes and repopulate them.

**CONCLUSIONS**

Despite more than 50 years of comments, observations, and studies on the RN phenomenon, elements of both controversy and consensus remain. Common acquired nevi may be removed by shave biopsy with cosmetically pleasing results without fear of contributing to malignancy; however, all nevus specimens should be submitted for histopathologic examination, and patients and clinicians need to be aware that incompletely removed nevi may recur. Clearly, not all nevi require special treatment; nevi that are clinically benign, for which the patient seeks removal for cosmetic reasons, may safely be treated with partial biopsy (eg, shave technique) and pathologic diagnosis. It is prudent to inform patients that incompletely excised nevi may recur, and that in such cases, a conservative, complete excision is usually indicated. Moreover, we believe that lesions clinically diagnosed as Spitz nevi or atypical/dysplastic nevi should either be completely excised rather than sampled, or else be closely monitored clinically.

Despite some potentially disturbing clinical and histopathologic features, most RN show uniform microscopic findings and pose no great diagnostic difficulty. Nevertheless, it is clear that a small percentage of RN have some histopathologic features similar to and in some cases indistinguishable from melanoma. The appropriate diagnosis in such cases may be obscured further by features consistent with intermediate/late stage regression of melanoma, dermal scar extending to the margin of the biopsy specimen, and sometimes the lack of a history of previous biopsy. Clinical-pathologic correlation is of particular importance in these instances, but may prove difficult to achieve in our increasingly fractured medical system. Immunohistochemical analysis with gp100/HMB-45, tyrosinase, and Ki-67 may offer considerable diagnostic benefit in equivocal cases, especially if history of a previous biopsy and/or previous biopsy results cannot be obtained. Given the rarity of RN cases that seem indistinguishable from melanoma, the term pseudomelanoma, although established in the literature, seems applicable to at best a small minority of RN, and in our view is best eschewed. The term persistent (recurrent) melanocytic nevus, although an acceptable synonym, fails to address the clinical phenomenon of repigmentation and for this reason, the term recurrent pigmented melanocytic nevus is the most specific and addresses both the clinical and histopathologic features of the lesion. The origin of RN has yet to be completely explained, although recent discoveries in melanocyte stem cell populations and immunohistochemical profiles of RN have introduced strong evidence in support of the theory of repopulation of melanocytes from remaining adnexal structures, even as proposed by Schoenfeld and Pinkus in 1958. As the scientific community continues to learn more about melanocytic biology and signaling, it is hoped and expected that our understanding of the recurrent nevus phenomenon will continue to deepen in coming years.

**References**


