Analysis of Heterogeneity of Atypia Within Melanocytic Nevi

Ronald J. Barr, MD; Kenneth G. Linden, PhD, MD; Gennady Rubinstein, MD; Kenneth A. Cantos, MD

Background: Incisional biopsy of clinically atypical nevi continues to be a common practice. Questions can arise as to the adequacy of these partial biopsies.

Objective: To determine whether incisional (partial) biopsy specimens may be considered representative of the entire lesion, atypical nevi submitted to our dermatopathology laboratory were examined for the presence or absence of heterogeneity of atypia within the individual nevi.

Design: The study included 250 histologically atypical nevi that were selected consecutively from pigmented lesions that were submitted to our dermatopathology laboratory by community and academic dermatologists for histopathologic analysis. Also, 23 moderately to severely atypical and 25 severely atypical nevi from consecutive submissions were added for statistical reasons. Lesions with both clear and involved margins were used. Lesions were considered homogeneous if the atypia involved the entire lesion or heterogeneous if either the atypia was focal or if different degrees of atypia occurred within the same lesion. Atypia was defined by the usual parameters of architectural and cytologic atypia and host response. Also, the degree of atypia in relationship to heterogeneity and to patient age was determined.

Setting: The Dermatopathology Laboratory, University of California, Irvine.

Main Outcome Measures: Outcome measures included the percentage of nevi exhibiting heterogeneity of atypia, heterogeneity of atypia in relation to patient age, degree of atypia in relation to patient age, and degree of atypia in relation to the presence of heterogeneity of atypia.

Results: Of the 298 nevi examined, 107 (35.9%) were heterogeneous in atypia and 191 (64.1%) were homogeneous in atypia. There was no significant difference in age between patients with heterogeneous lesions and those with homogeneous lesions. There was a statistically significant correlation between the degree of atypia and patient age. The average age of patients with a lesser degree of atypia was 36.9 years, while the average age of patients with a greater degree of atypia was 44.8 years (P<.005). There was no significant correlation between degree of atypia and heterogeneity of atypia (correlation coefficient, 0.1).

Conclusions: A clinically significant proportion of atypical nevi exhibited heterogeneity of atypia. Also, there was a significant relationship between the degree of atypia and increasing age (P<.005). Therefore, if a clinically atypical nevus warrants a biopsy, these results give additional support for complete excisional biopsy (which can include shave or punch) to assure adequate histopathologic sampling of the lesion.

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logic and architectural atypia. This grading appears to be a continuous spectrum, ranging from completely benign-appearing nevi to obvious melanoma, both clinically and histopathologically. When biopsy specimens are obtained from suspicious pigmented lesions for histopathologic analysis, there can be conflicts between the adequacy of the sampling for histopathology and the cosmetic consequences of the sampling. Over the past few years, we have received increasing numbers of specimens from partial biopsies of nevi. Questions can arise as to what constitutes an adequate biopsy specimen of a suspicious pigmented lesion. Therefore, evaluating the variability of histopathologic atypia within nevi is important. The purpose of this study was to analyze histopathologically atypical nevi in regard to the homogeneity or heterogeneity of the atypia within the individual nevi.

A total of 298 histopathologically atypical nevi were selected for analysis. Two hundred fifty nevi were obtained in sequential order from specimens of histopathologically proven atypical nevi submitted to the Dermatopathology Laboratory of the University of California, Irvine. The reported diagnosis for all specimens was nevus with atypia, with the type (compound, junctional, etc) and level of atypia specified.

In addition, after the initial 250 nevi were selected, 48 more moderately to severely atypical or severely atypical nevi were obtained. As in the case of the bulk of the specimens examined, these 48 nevi were selected consecutively from those submitted to our dermatopathology laboratory. The additional lesions with moderate to severe atypia and severe atypia were added because there were too few of these more atypical lesions in the 250 consecutive specimens to make statistical analysis meaningful. Both incisional and excisional specimens were analyzed. Nevii with known histopathologic atypia were retrospectively examined for the presence or absence of heterogeneity of atypia. The study did not include Spitz or other types of atypical nevus other than dysplastic (Clark’s) nevi.

Atypia was defined by the usual parameters of cytologic and architectural atypia and the host response. Our criteria essentially correspond to those recently elucidated by Crowson, Magro, and Mihm. Architectural or pattern atypia manifests as one or more of the following: asymmetry; bridging of the epidermis between the rete ridges; nevus cells at the shoulders of the rete ridges; lentiginous distribution of nevus cells at the dermoepidermal junctions; and nevus cells present above the basal layer. Cytologic atypia manifests as one or more of the following: increase in the nuclear-cytoplasmic ratio; prominent nucleoli; irregular chromatin pattern; variations in thickness of the nuclear membrane; and finely distributed melanin pigment within the cytoplasm (smoky cytoplasm). A host response consisted of one or more of the following: a lymphocytic infiltrate; fibroplasia (concentric or lamellar); capillary-endothelial hyperplasia; and incontinence of pigment.

These criteria for atypia were used to determine the overall degree of atypia: minimal, minimal to moderate, moderate to severe, and severe. For those lesions with minimal atypia, the nevus cells were usually cytologically similar to conventional acquired nevus cells, although small, inconspicuous nucleoli were often present, and the nuclei varied slightly in size from one cell to the next. These cells often extended beyond the intradermal component (shoulder) and were concentrated primarily in the theques at the tips of the rete ridges, with some cells migrating to the sides of the ridges and involving the interridge junction. The host response included a mild perivascular lymphocytic infiltrate, and the fibroplasia was concentric around the rete ridges. For the lesions with moderate atypia, the nevus cells often had nucleoli; there was an increase in the nuclear-cytoplasmic ratio; and the chromatin pattern was irregular. The overall size of the nuclei was larger than that of the keratinocyte nuclei. The nevus cells were predominantly nested, with more extensive involvement of the sides of the rete ridges and the interridge space. There was no upward spread. The fibroplasia was more prominent and both concentric and lamellar, and the inflammatory infiltrate was more prominent but still perivascular. For the lesions with severe atypia, the nuclei were larger than the keratinocyte nuclei; the nucleoli were prominent; and there was considerable variation in nuclear size and shape. The chromatin pattern was irregular. Often, these cells were epithelioid or spindled. Very rare mitotic figures could be present. Nests were still predominant, but many cells were irregularly dispersed at the dermoepidermal junction, and there was some upward migration involving the lower half of the epidermis. The host response exhibited an inflammatory infiltrate that was focally bandlike, not just perivascular, and the fibroplasia was concentric, lamellar, and at times linear.

Very small lesions, in which it would not be reasonably expected that a partial biopsy could be performed, were not included (lesions approximately 2 mm in diameter or smaller). Homogeneous lesions that were present at the margins (not completely sampled) were excluded because heterogeneity at nonsampled areas could not be ruled out. Lesions were considered heterogeneous in regard to atypia if an incisional biopsy such as a shave or a punch biopsy, in the opinion of the evaluator, could have been performed on the specimen, and this partial sampling of the biopsy specimen would not have been representative of the specimen as a whole and would have led to a different level in the grading of atypia (Figures 1, 2, and 3). Every specimen was evaluated by a single observer (R.J.B.) who is a board-certified dermatopathologist with many years of experience in evaluating nevomelanocytic neoplasms microscopically, giving consistency to the application of these criteria.

The total percentage of specimens showing heterogeneity of atypia was determined, and the degree of overall atypia of the specimens in relation to the presence or absence of heterogeneity, the relationship of patient age to the overall degree of atypia, and the age distribution and age range of patients in regard to the presence or absence of heterogeneity of atypia were analyzed.

Figure 1. A typical example of a heterogeneous nevus. If a partial biopsy specimen were obtained, the left half of the lesion would be interpreted as a compound primarily intradermal nevus without atypia. In contrast, the right half of the lesion would be interpreted as a junctional nevus with moderate atypia (hematoxylin-eosin, original magnification ×100).
RESULTS

Of the 298 nevi examined, 107 (35.9%) were heterogeneous in atypia and 191 (64.1%) were homogeneous in atypia. There were no significant differences in age between patients with heterogeneous atypia and those with homogeneous atypia or among the group as a whole (based on $t$ test analysis) (Table). The average age in the homogeneous group was 40.2 years, while the average age in the heterogeneous group was 37.2 years.

The overall degree of atypia was analyzed in regard to age (Figure 4), revealing a correlation coefficient of 0.19. Also, a lower-atypia group, consisting of minimal and minimal to focally moderate atypia, and a higher-atypia group, consisting of moderate to focally severe and severe atypia, were created. The ages of patients in the 2 groups were compared. The average age of the patients with less atypia was 36.9 years, while that of the patients with more atypia was 44.8 years ($P<.005$). The heterogeneity of atypia was analyzed in relation to the overall degree of atypia (Figure 5) and showed no significant trends (correlation coefficient, 0.1).

A significant proportion of nevi (35%) exhibited heterogeneity in their distribution of atypia. This heterogeneity was not significantly correlated to the age of the patients. Exclusion of homogeneous lesions that were present at the margin may have slightly affected the percentage of heterogeneous lesions that were found, but the number of lesions that were excluded was small and would not have significantly affected the overall results. There were significant differences in the ages of patients in the lower- and higher-atypia groups ($P<.005$). Previous work\textsuperscript{9} has indicated that increasing the overall degree of histopathologic atypia may be correlated with increasing age. There do not appear to be any signifi-

**Table**

| Age of Patients in Relation to Heterogeneity of Atypia |
|---------------------------------|------|-----|
| Age, y                          | Mean ± SD | Range |
| Total study population          | 39.1 ± 2.0 | 7-82 |
| Patients with heterogeneous specimens | 37.2 ± 3.6 | 7-82 |
| Patients with homogeneous specimens | 40.2 ± 2.4 | 8-80 |

**Figure 2.** Higher magnification of the left half of the nevus seen in Figure 1, exhibiting a few nevus cells at the dermoepidermal junction and uniform small, round nevus cells within the subjacent dermis (hematoxylin-eosin, original magnification $\times200$).

**Figure 3.** Higher magnification of the right half of the nevus seen in Figure 1, exhibiting nevus cells within the epidermis and at the dermoepidermal junction both individually and in nests, both at the tips and at the sides of the rete ridges. The nevus cells do exhibit cytological atypia characterized by an increase in their overall size and in the nuclear-cytoplasmic ratio. The lesion is also associated with concentric fibroplasia and a perivascular lymphocytic infiltrate (hematoxylin-eosin, original magnification $\times200$).

**Figure 4.** Overall degree of atypia vs age of patients.

**Figure 5.** Heterogeneity of atypia in relation to degree of atypia.
cant trends in heterogeneity vs severity (Figure 5). Therefore, it does not seem to follow that more severely atypical lesions have a greater likelihood of being heterogeneous.

As with all studies on atypical nevi, it must be recognized that grading the level of atypia is somewhat subjective, and in this study, categorizing a nevus as heterogeneous or homogeneous in regard to atypia is also somewhat subjective. However, studies have shown that with proper definition of variables and training, there can be good agreement among different evaluators.2,4

The finding that a significant proportion of nevi show heterogeneity of atypia means that a partial biopsy might inadequately sample the lesion and give a false impression as to the overall severity of atypia manifested. This could result in the lesion not being treated in the same manner that it would be if the lesion had been completely sampled. We recognize that there are those who believe that it is not appropriate to grade atypia or to recommend therapy based on the level of atypia.3

Also, it is well documented that melanomas may be contiguous with an atypical nevus component.10,11 It would be hoped that partial biopsies would sample the most clinically atypical portion of the suspicious pigmented lesion, but the most clinically suspicious portion does not necessarily coincide with the histopathologically most atypical portion.12 Therefore, it is not surprising that partial biopsies yielding an atypical nevus upon histopathologic analysis have revealed melanoma on complete excision.12,13 Therefore, it appears wise, when possible, to perform complete clinical removal of suspicious pigmented lesions so that adequate histopathologic analysis may be performed. Complete removal of some pigmented lesions can be cosmetically problematic, and the performance of an appropriate biopsy must be tempered with clinical judgment of the benefits and risks involved. In highly suspicious lesions, a biopsy or excision that includes the total thickness of the lesion is important because of the risk of not reaching the base of a melanoma and therefore preventing accurate staging with appropriate follow-up and therapy.

In summary, a significant proportion (35%) of atypical nevi in this study displayed heterogeneity of atypia, supporting the concept that if a nevus is clinically atypical, a total biopsy rather than a partial biopsy is preferred. We also found a statistically significant relationship between increasing age and severity of atypia in melanocytic lesions.

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Corresponding author and reprints: Kenneth G. Linden, PhD, MD, Department of Dermatology, University of California, Irvine, 101 The City Drive, Orange, CA 92868 (e-mail: kglinden@uci.edu).

REFERENCES