

Pigmented Lesion Pathology: What You Should Expect From Your Pathologist, and What Your Pathologist Should Expect From You

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The diagnosis and treatment of melanoma and related neoplasms is difficult and dangerous for all concerned. In the typical scenario, a lesion is identified by a dermatologist or other clinician as sufficiently atypical to warrant biopsy; a dermatopathologist or general pathologist renders the “gold standard” (i.e., histologic) diagnosis, and stages the lesion; and the patient is referred to a surgeon (and oncologist if necessary) for treatment appropriate to the stage of his disease.

In this sequence, several things can go wrong. The patient may not seek care while the lesion is curable; the practitioner to whom he initially presents may fail to recognize it; the pathologist may misdiagnose it; and the surgeon may misinterpret and therefore fail to act appropriately on the pathologist’s report. These errors would usually lead to undertreatment, but overtreatment of, for example, a mildly atypical dysplastic or spitzoid lesion, can also lead to unnecessary morbidity and cost.

That these problems are real, and bear especially on pathology, is attested by the experience of a large pathology insurer, that melanoma is responsible for more malpractice claims than any other diagnostic entity [1], a frequency disproportionate to the prevalence of this disease (13% of claims [1] but only 4-5% of cancers [2]). Errors can and should be minimized at each stage of the pipeline. Patients can benefit from public education programs that emphasize melanoma prevention and detection, while the accuracy of screening personnel can be improved by novel diagnostic modalities such as dermoscopy. Pathologists can benefit from technical controls and consultation, within their own labs [3,4]. These measures do not, however, address problems that may arise at the *interface* between clinical and pathologic practice. What clinicians do — how they obtain and submit specimens — influences the accuracy of the pathology report they will in turn receive. The quality of that report (the accuracy and completeness of staging information, for example) then feeds back to the treating clinician. And some reports may contain terms, such as dysplastic nevus, nevus with architectural disorder and cytologic atypia, atypical Spitz tumor, atypical blue nevus, and melanocytoma, that are frankly mystifying to the clinician, who may not even understand whether they refer to a benign or malignant diagnosis.

In what follows we will tread the interface between clinical and pathologic practice, which

holds the promise of the most fruitful diagnostic and therapeutic collaborations, but also carries the risk of serious error. We will review data on the reliability of pathologic diagnosis, in melanoma and other pigmented lesions; discuss measures that may be taken by the clinician to help maximize that reliability; and review some of the more confusing diagnoses in pigmented lesion pathology, such as those mentioned above.

1 Reliability of histologic diagnosis of melanocytic neoplasms

1.1 Interobserver concordance

There are several studies of interobserver concordance in the histologic diagnosis of melanocytic neoplasms. For the most part they are not encouraging. One of the first and most cited was part of the Consensus Development Conference on the Diagnosis and Treatment of Early Melanoma, convened by the National Institutes of Health [5]. 37 cases, submitted as “classic” examples of melanoma and nevi, were reviewed by seven panelists selected for their publications and recognized expertise in pigmented lesion pathology. There was complete concordance in only 13 of the cases, with almost complete concordance (none or one dissenter) in 23 (64%). When the diagnoses were grouped into benign, intermediate, and malignant categories, the κ value was 0.50, indicating only moderate agreement [5]. (One of the panelists subsequently commented that the cases were in fact not “classic” [6].)

A somewhat similar experiment was performed in 2000 at the 21st Symposium of the International Society of Dermatopathology [7]. Here, 71 “difficult” melanocytic neoplasms were reviewed by a panel of six experts. Complete agreement was achieved in 49% of cases, with almost complete agreement (only one dissenter) in another 31% [7]. While one of the participants described the experience as producing “the impression of watching a slow-motion multivehicle accident” [8], these results are probably not that bad, considering the “difficult” nature of the cases. Further, there was excellent concordance in several areas traditionally regarded as problematic, including desmoplastic melanomas and nevi, recurrent melanomas and nevi, and nevoid melanoma [7]. Spitz nevi and other childhood lesions were responsible for much of the

discordance [7].

These studies are somewhat difficult to interpret because of questions involving case selection (just how “classic” were the cases in the first study [5] and how “difficult” were they in the second [7]?). Two studies from Italy are of interest because they employed unselected, sequential accessions [9, 10]. In the first, 100 melanomas and 20 nevi were evaluated by four dermatopathologists [9]. There was complete agreement in 76% of cases, with a κ value for the diagnosis of melanoma of 0.61. κ values for melanoma features were fairly low; for example, 0.76 for Breslow depth. The second Italian study measured concordance for 13 histologic features in 64 melanomas evaluated by nine dermatopathologists [10]. κ values were quite high, greater than 0.75 for 10 out of the 13.

Concordance has been assessed for specific subsets of melanocytic neoplasms. As mentioned, childhood lesions are especially problematic. 85 childhood melanomas were examined by a panel of eight expert dermatopathologists, divided into four pairs [11]. There was complete agreement within each pair for only 39% of cases. When, as a control, 20 adult melanomas and 15 nevi were evaluated by the same mechanism, there was complete agreement for all cases.

Thirty spitzoid lesions were collected by a panel of 10 dermatopathologists, and then categorized by the members of the panel as Spitz nevus, atypical Spitz nevus, melanoma, or indeterminate [12]. Seventeen of the 30 lesions were regarded by at least some members of the panel as displaying features of Spitz nevus, but in only one case was there agreement by a majority of panelists on that diagnosis. That case eventuated in metastasis and death.

Atypical cellular blue nevus is another problematic entity. A collection of these lesions was examined, in a set that included typical cellular blue nevi, common blue nevi, and melanomas, by a panel of ten experienced dermatopathologists [13]. A majority selected the correct diagnosis in only 38% of cases; average sensitivity for the diagnosis of atypical cellular blue nevus was 35%; and overall κ was 0.25 [13].

149 nevi were classified as dysplastic, banal, or intermediate by a panel of six dermatopathologists, divided into pairs [14]. There was 56% concordance, with a κ of 0.34. When intermediate and dysplastic categories were pooled, the κ rose to 0.49. Interestingly, intraobserver

concordance was also measured. It was 85% for the same slide and 78% for recuts [14].

Concordance is only moderate for margin assessment in lentigo maligna and lentigo maligna melanoma. These tumors occur on sun-exposed skin, which may have a baseline of increased melanocyte density and atypia. When five pathologists evaluated excision margins from these lesions, there was only 72% agreement with the original pathologic diagnosis (as involved or not), and κ was 0.4-0.5 for agreement within the panel [15].

All of these studies investigated concordance among experienced dermatopathologists, generally academic dermatopathologists with a record of publication in the area. Concordance among general pathologists in melanoma diagnosis is much worse [16].

1.2 Be kind to your pathologist

Faced with these dismal statistics, what should be done? First, cheer up: they probably overstate the problem. In reviewing some of this work, Glusac expressed his opinion “that experts would disagree significantly (benign vs. malignant) on less than 1% of randomly selected melanocytic neoplasms”. While concrete evidence for this view is lacking, it probably is substantively correct.

Second, recognize that the clinician is not a passive bystander in the process of histologic diagnosis, but rather an active participant with a great deal of influence over its outcome. The clinician can contribute through expert clinical assessment, clear communication of clinical observations to the lab, optimal biopsy technique, and judicious interpretation of the final pathology report.

A case from my practice briefly illustrates these principles. A tiny (1 mm) specimen was submitted by a generalist without any clinical information. It was entirely ulcerated, so that the epidermal component of the lesion, if any, could not be evaluated. At the base of the ulcer a small number of melanocytes were observed. They were somewhat atypical, but this could be explained by proximity to the ulcer, and the findings were regarded as most consistent with traumatized nevus. A second experienced dermatopathologist concurred with this interpretation. Two weeks after the case was completed, a call was received from ancillary staff at the

referring practice. The staff member said that the referring physician was entirely satisfied with my diagnosis, but would I be interested to learn that the specimen had been obtained from a 2 cm black plaque?

With respect to clinical assessment, it is obvious that lesions susceptible to unequivocal clinical diagnosis will not be biopsied at all. Nevertheless, skilled clinical evaluation, even when it is not conclusive, reduces the opportunity for histologic error. There are differences in the ability of clinicians to evaluate pigmented lesions [17–19], and most of us have room for improvement. (Dermatologists, for example, do as well or better than other practitioners [18, 19], but are only about 64-80% accurate in the clinical diagnosis of melanoma [20, 21].) For most practitioners the introduction of dermoscopy would be the quickest route to improved screening accuracy. This technique employs a simple hand-held instrument (the dermatoscope), that provides a low (approximately 10X) magnification view of the skin, with cross-polarization or immersion oil to eliminate specular reflectances from the skin surface. Structures from the epidermis to the deep papillary dermis can be visualized. The dermoscopy literature is immense and encompasses several different approaches to the interpretation of dermoscopic imagery. Nevertheless, practitioners can realize substantial improvements in clinical screening accuracy after a day or less of dermoscopic training [22–24]. In expert hands, dermoscopy improves the mean log odds ratio for the diagnosis of melanoma from 2.7 to 4.0, in effect increasing screening accuracy by 49%, according to a meta-analysis of 27 studies [25].

To be most useful, clinical information must be generously shared with the pathologist. The pathology submission slip has been called “one of the most underutilized documents in medicine” [3, 26]. As a minimum, age, sex, site, and relevant clinical history should be included. Site is important because nevi from the “special sites” frequently display architectural irregularities that may create some resemblance to melanoma. These sites include acral locations, genitals, breast, scalp, ear, flexural regions, and the conjunctiva [27]. History should include recent change, trauma, sun-exposure, phototherapy, and personal or family history of melanoma and dysplastic nevus syndrome. Trauma [28] and ultraviolet light exposure [29, 30] (either natural or from phototherapy) can produce pagetoid spread and other changes that can

be misinterpreted as evidence for melanoma. (For this reason it has been suggested that biopsy of traumatized or UV-irradiated lesions be deferred for four weeks, unless there is strong clinical evidence for melanoma [31].) If the lesion was previously biopsied this should also be recorded, as surgery and subsequent reparative change can also distort nevus architecture [32], and because sampling errors can occur in a lesion that was removed in stages. For example, a previous specimen might contain melanoma, while the current specimen reveals only precursor nevus. For previously biopsied lesions the pathologist will in many instances want to review the original specimen, and the clinician should facilitate this by providing the necessary information.

A description of the lesion's clinical appearance should also accompany the specimen. The "ABCDE" screening criteria [33] might provide a framework for this description, as they are easily learned and applied. If the lesion is clinically heterogeneous (for example if it contains a "black dot" [34]), this should be communicated, as it would stimulate the pathologist to section through the block if initial sections are negative for melanoma. Results of dermoscopic examination, if performed, should be recorded. If the pathologist, but not the clinician, has dermoscopic expertise (entirely possible if the former is a dermatologist/dermatopathologist), dermoscopic photographs might be transmitted to the lab. They would be especially valuable for heterogeneous lesions, e.g. melanoma originating in nevus. Dermoscopy and histopathology are complementary in such cases, because the former visualizes the entire lesion in the horizontal plane (parallel to the skin surface), while the latter visualizes only a limited number of vertical planes through it. Dermoscopy can guide sectioning towards the most suspicious area, or at least ensure that multiple sections are obtained. Four cases of melanoma originating in nevus, which would have been misdiagnosed without dermoscopy, have been reported [35, 36]. More generally, in a series of 301 nevi and melanomas, the submission of dermoscopic images caused the pathologic diagnosis to be revised in 11 equivocal cases, 8 from melanoma to nevus and 3 from nevus to melanoma [37]. When this series was evaluated by pathologists at two centers, the addition of dermoscopic images improved concordance between the centers from a κ of 0.81 to 0.88 [37]. Lesions that are histologically equivocal also tend to be dermoscopically

equivocal [38], so correlation between the two modalities is important [39].

Biopsy technique is critical for accurate histologic evaluation. The guidelines of the American Academy of Dermatology (AAD) [40] and the National Comprehensive Cancer Center (NCCN) [41] both call for removal of the entire lesion with narrow (1-3 mm) margins, at the initial encounter. The AAD guidelines specify that “an incisional biopsy technique is appropriate when the suspicion for melanoma is low, when the lesion is large, or when it is impractical to perform an excision” [40], while the NCCN states that “full thickness incisional or punch biopsy of the clinically thickest portion of the lesion is acceptable, in certain anatomic areas (eg, palm/sole, digit, face, ear) or for very large lesions” [41]. Partial biopsy should be avoided, when at all possible, because it can lead to errors in diagnosis and staging, and possibly a worse clinical outcome.

One study evaluated the accuracy of partial biopsy by comparing the initial and final histologic diagnoses in a series of 63 lesions obtained from patients with dysplastic nevus syndrome [42]. Punch biopsies were obtained from 41 of these lesions, and shave biopsies from the remainder; all were then reexcised, and the excision and biopsy specimens compared. In 12 of the punch biopsied lesions, but only 1 of the shaved lesions, there was diagnostic discordance between the biopsy and excision specimens. In 2 cases the punch biopsy specimen was interpreted as nevus but excision revealed melanoma; in one case a melanoma interpreted as in situ in the punch biopsy specimen was found to be invasive in the excision specimen; and in one case shave biopsy revealed in situ melanoma but invasive disease (Breslow depth 2.85 mm) was found in the excision specimen [42].

In a series of 1784 histologically diagnosed melanomas, melanoma had not been clinically suspected in 503. Of these, diagnosis was compromised in 31 and histologic staging was impossible in 62 because of inadequate biopsy technique [43]. For 10 specimens (5 punch biopsy specimens, 5 shaves) the diagnosis of melanoma was completely missed, and established only at a later date by rebiopsy [43].

Diagnostic certainty was subjectively evaluated in a retrospective study of 525 specimens with a pathologic diagnosis of certain or probable melanoma [44]. Of these specimens, 37%

had been obtained by excision, 36% by punch biopsy, 9% by shave biopsy, 4% by deep shave biopsy, and 14% by unknown technique. The pathologic diagnosis was regarded as certain in 65% of cases, and at least somewhat doubtful in the remainder (35%). In 25% uncertainty was the unavoidable result of equivocal pathologic findings, but in 9% inadequate specimen width was partially or entirely responsible for the uncertainty. In no case was uncertainty caused by inadequate depth. Comparing specimen types, 23% of punches, 21% of shaves, 11% of deep shaves, and 9% of excisions were assigned the lowest category of diagnostic certainty [44].

The authors of this study suggested that subtotal biopsy can contribute to diagnostic uncertainty in a number of ways. Some pathologic features—such as size, symmetry, and margination (abrupt vs. indistinct lateral boundaries)—cannot be evaluated unless the full breadth of the lesion is visible [44]. Some features are assessed at smaller scale but may vary within the tumor, so that an accurate summary judgement requires the entire lesion. These include spacing between epidermal melanocytes, size and shape of nests, pagetoid spread, and cytology [44]. Maturation (diminishing melanocyte size with depth) and deep mitotic activity, which are especially important for spitzoid and other nodular tumors, cannot be evaluated in superficial specimens. Heterogeneous lesions, consisting of both melanoma and precursor nevus, are of course especially problematic in partial specimens. The authors illustrate one such case, in which punch biopsy through the thickest part of the lesion would have sampled only nevus and missed the surrounding melanoma [44]. Sampling only the regressed area in a partially regressed melanoma can create similar difficulties [4].

Several studies have compared Breslow depth in initial partial biopsy and subsequent reexcision specimens of invasive melanoma. Ng et al. found concordance in 88% of 145 such cases [45]. For 28 of 30 superficial shave biopsy specimens, 34 of 37 deep shave biopsy specimens, and 33 of 41 punch biopsy specimens, Breslow depth in the biopsy specimen was equal to or greater than depth in the reexcision specimen [45]. Concordance was thus lower (80%) for punch biopsy than for shave, and was only 53% for the subset of punch biopsy specimens with involved margins. However, punch biopsied tumors were thicker than shaved lesions [45]. In similar work, Stell et al. compared 224 melanomas, evaluated initially by excisional, shave, or

punch biopsy [46]. Shave biopsy specimens had a significantly higher proportion of involved deep margins than punch or excision specimens (22, 7, and 2%, respectively). However, reexcision increased the Breslow depth in a much higher proportion of punch biopsied than shaved cases (26 vs. 4%), and this resulted in significant upstaging (higher T score) in many more punched than shaved cases (12% vs. 2%) [46].

These studies suggest that shave biopsy might be preferable to punch biopsy if partial biopsy cannot be avoided, although differences between the tumors sampled by the two procedures (punched lesions were generally deeper than those shaved) casts some doubt on this conclusion. They also support the recommendations of the NCCN and AAD for complete initial excision. In addition to the diagnostic and staging errors found in these studies to result from partial biopsy, a further concern has been that cutting through the tumor might facilitate metastasis by providing vascular access or displacing tumor into deeper tissue layers. Some studies have shown initial partial biopsy to adversely affect survival [47, reviewed in], but many have not [48, reviewed in]. In any case, it is likely to be unhealthy for the practitioner, if not the patient. Of all medical malpractice claims involving melanoma submitted between 1995 and 2001, the tumor had been biopsied by shave, punch, or incisional technique in 83% of cases [49], while complete excisional biopsy was performed in only 17% [49].

Despite their ample justification, the guidelines are not being followed—at least not in England, where compliance was recently investigated [50]. Of 100 melanoma patients referred to a plastic surgery practice, 50 were referred without biopsy and in the rest there were 17 excisional, 20 punch, 3 shave, and 1 incisional biopsies and 1 curettage. Punch biopsies were more common than excisions for patients referred by both dermatologists and generalists. Almost all of the punch biopsied lesions were small and/or from sites (trunk and extremities) where excision with primary closure would have been feasible, and in almost all these cases melanoma had been suspected clinically. Breslow depth could be determined in only 45% of the punch biopsy specimens. The authors speculate that the punch biopsies were performed because they were “more accessible to the outpatient setting” [50].

Shave biopsy remains a reasonable approach for pigmented lesions with a convincingly

benign clinical appearance, because it has been demonstrated in several studies to produce the best cosmetic outcome [48, reviewed in]. NCCN guidelines regard it as “acceptable when the index of suspicion is low” [41].

The clinician’s responsibility does not, of course, end with the submission of the specimen. Discordance between clinical and pathologic diagnoses should always be pursued [4]. Although pathologic examination is traditionally regarded as the diagnostic “gold standard” for pigmented lesions, it is subject to error for all the reasons described above, and its conclusions cannot be uncritically accepted. Even if an optimal (complete excisional) specimen was submitted, the initial sections may not be representative of the entire lesion, revealing, for example, only nevus in a specimen that also contains melanoma [4, 35, 36, 44]. Most pathologists will step-section specimens clinically suspected of melanoma, when the initial sections do not show it; but in some cases this may be done only at the clinician’s request [4, 49]. When the initial specimen was suboptimal (partial), the appropriate response to clinicopathologic discordance is to remove the remainder of the lesion.

The clinician should note elements in the pathology report that express diagnostic uncertainty, such as “consistent with”, “suggestive of”, “atypical melanocytic neoplasm”, etc. According to Crowson, “the more frequent scenario in litigation . . . is that a lesion with a metastatic potential has been considered . . . benign *without any equivocation or caveats applied in the pathology report* [italics mine]” [4]. In some cases, even if the specimen was optimal and exhaustively sectioned, the pathology itself will be equivocal. Treatment of such cases must be individualized and may test the experience and judgement of both pathologist and clinician.

Finally, diagnostic terminology varies among pathologists and the clinician should become familiar with that used by his or her pathologist(s). Some of the more confusing and controversial diagnostic terms and entities are addressed in what follows.

2 Problem diagnoses

2.1 Dysplastic nevus

The dysplastic nevus is perhaps *primum inter pares* among controversial entities in pigmented lesion pathology. Disputed issues include the diagnostic terminology that should be applied to this entity, the reproducibility and significance of histologic grading, and the biologic status of the lesion as fully benign or in some way intermediate between benign and malignant. Related questions address the primacy of clinical or histologic features for diagnosis, prevalence, and clinical management (should a dysplastic nevus diagnosed in a partial biopsy be reexcised, and if so, does this apply to all such nevi or only to particular histologic grades?).

The dysplastic nevus was described in 1978 by Clark, as the “B-K mole”, a nevus with distinctive clinical and histologic features occurring at high density in individuals with the “B-K mole syndrome”. These were members of 6 families afflicted by multiple melanomas [51]. Subsequently Clark’s group proposed the term “dysplastic nevus”, because they regarded the entity as a stage in the evolution of melanoma, analogous to lesions recognized as carcinoma precursors [52]. In the next decade, it became apparent that nevi with similar clinical and histologic characteristics occur sporadically, as single lesions or in small numbers, in patients with no relevant family history. It also became apparent that these lesions are common [53,54], with about 20% of nevi meeting histologic criteria for dysplasia [53,55]. Clearly, most of these will not evolve to melanoma. Writing in the late 1980’s, the influential dermatopathologist A.B. Ackerman asserted that the dysplastic nevus is in fact “the most common nevus”, and, when sporadic, poses no risk of progression (“wholly benign”) [56]. He further complained that the clinical and histologic criteria proposed for the recognition of dysplastic nevus and dysplastic nevus syndrome could not be reproducibly applied [56]. He proposed renaming the entity “Clark nevus”, to avoid the unjustifiably negative implications of its original designation [57].

An NIH Consensus Conference held in 1992 had a slightly more muted response [58]. It recognized a “10-fold difference in estimates of . . . frequency”, but attributed this to variation in the application of histologic criteria for diagnosis. These criteria had included certain archi-

tectural features and mild (“random” [51]) cytologic atypia. The 1992 Consensus Conference uncoupled architecture and cytology, regarding architecture as constant but cytologic atypia as variable and in some cases absent [58]. In their view the histologic architecture of a lesion places it within the spectrum of dysplastic nevus, while its cytology defines the position it occupies within that spectrum. Consistent with this understanding, and to avoid the “controversy” that then attended the term “dysplastic nevus”, the NIH recommended that the lesion be renamed “nevus with architectural disorder”. This (subsequently amended to “nevus with architectural disorder and cytologic atypia”) should be the preferred histologic diagnosis, and accompanied by a comment specifying the degree of cytologic atypia [58].

This history has left a legacy of confusion. In a 2004 survey of the membership of the American Society of Dermatopathology and the American Academy of Dermatology, Shapiro et al found that no single diagnostic term was preferred by a majority of dermatopathologists [59]. “Dysplastic nevus” was the most common term, used by 39% of dermatopathologists, while some variant of “nevus with architectural disorder” was used by 28%, and “Clark’s nevus” by 10%. These terms are essentially synonymous, but 4% of dermatopathologists use the term “atypical nevus”, 2.7% “compound nevus”, 1.5% “compound nevus with extension of the junctional component”, and 1% “atypical melanocytic hyperplasia” [59]. For these dermatopathologists, presumably, the dysplastic nevus is not a histopathologic entity.

33 of the 39% of dermatopathologists calling these lesions “dysplastic nevus” scored them for the degree of dysplasia (as mild, moderate, or severe). Of those preferring “nevus with architectural disorganization” what proportion rated them for cytologic atypia (in accordance with NIH recommendations) was apparently not investigated [59]. The dermatologists were slightly more consistent: 62% used “dysplastic nevus”.

Shapiro et al questioned whether those using older language were unaware of the NIH terminology or actively opposed to it. It can be criticized for lack of specificity; that is, dysplastic nevi are not just disorganized and cytologically atypical but have specific architectural and cytologic features; alternatively, some nevi with “architectural disorganization and cytologic atypia” are not dysplastic (traumatized, sun-exposed, and halo nevi, for example). Also, it appears that all

dysplastic nevi are cytologically atypical [54], and that cytologic atypia should not be the sole basis for grading dysplasia [60]. There is evidence that the severity of architectural abnormality and the degree of cytologic atypia are highly correlated [60–63].

Nevertheless, recent work suggests that the Consensus Conference was justified in trying to define a spectrum of histologic dysplasia. DNA content [64] and microsatellite instability [65] were found to increase with the degree of dysplasia. It also correlates with melanoma risk. Arum-Uria et al examined all of the dysplastic nevi accessioned to single lab between 1989 and 1996 [60]. There were 6275 nevi belonging to 4481 patients. For each nevus the degree of dysplasia was rated as mild, moderate, or severe according to combined architectural and cytologic criteria. Patients were classified according to their most dysplastic nevus. Of the 4481 patients, the worst nevus was mildly dysplastic in 2504, moderately dysplastic in 1657, and severely dysplastic in 320 patients. Pathology submission slips were examined to determine whether the specimen had been obtained from a patient with a history of melanoma. Such a history was reported for 5.7%, 8.1%, and 19.7% of patients with mildly, moderately, and severely dysplastic nevi, respectively [60].

Approaching this question from the opposite direction, Shors et al. examined the most clinically atypical nevus in 80 melanoma patients and 80 spousal controls [66]. The nevi were graded as mildly, moderately, or severely dysplastic by a panel of 13 dermatopathologists, who had not previously met to agree on rating criteria. Most (82%) of nevi were rated mildly dysplastic. The presence of a severely dysplastic nevus was significantly associated with melanoma, with an odds ratio of 2.6. This correlation remained significant after adjustment for number of nevi and many other known melanoma risk factors [66].

These studies point to differences *within* the group of histologically recognizable dysplastic nevi, a concept that may help to reconcile the conflict, noted earlier, between the clear epidemiologic association of dysplastic nevus and melanoma, in some settings, and the frequency of the diagnosis.

One difficulty with Shors' study was that, while the consensus dysplasia score predicted the presence or absence of melanoma, the scores of individual pathologists generally did not

[66]. Of the 13 dermatopathologists, only one pathologist's scores correlated significantly with melanoma risk [66]. There was no statistical analysis or other evaluation to determine whether this was a chance association, or reflected greater experience or the application of unique diagnostic criteria by this dermatopathologist. If the latter, then accurate grading of histologic dysplasia might be a teachable skill.

In Shors' study, κ for agreement among the 13 pathologists was only 0.28 [66]. Other work showed somewhat better concordance in rating dysplasia. In one study, 30 dysplastic nevi were graded as mild, moderate or severe by three experienced dermatopathologists and two dermatopathology fellows, divided into pairs [62]. Concordance among the pairs of experienced dermatopathologists was 35-58%, for κ values of 0.38-0.47. Concordance among the trainees was lower (16-65%). 20 common nevi and 10 melanomas were also included in the study, and concordance for the diagnosis of dysplastic nevus was 69-80% (κ 0.53-0.71) for the experienced dermatopathologists and 61-88% (κ 0.55-0.84) for the trainees. Apparently, less experience is required to recognize dysplastic nevi than to grade them. Concordance was 90% for the distinction between dysplastic nevus and melanoma and was better for the distinction between severely dysplastic nevus and melanoma than among the lesser grades of dysplasia [62].

The frequency of various diagnoses rendered by two dermatopathologists in evaluating 2631 melanocytic neoplasms was compared [67]. Although concordance between the two was not investigated, they assigned a remarkably similar proportion of cases to mildly, moderately, and severely dysplastic categories. One regarded 8.8%, 7.0%, and 2.7% of melanocytic lesions as mildly dysplastic, moderately dysplastic, and severely dysplastic nevi, respectively, and the comparable percentages for the other dermatopathologist were 12.0%, 6.8%, and 1.6%. Interestingly, the two dermatopathologists articulated different formal criteria for the diagnosis of dysplastic nevus, with only one requiring cytologic atypia. Note that in this study, as in those of Arum-Uria et al [60] and Shors et al [66], only a small minority of nevi were judged to be severely dysplastic.

There are other studies of concordance in the histologic diagnosis of dysplastic nevus. Clemente reported 92% concordance among a panel of 6 dermatopathologists, in distinguishing

among 114 examples of banal nevus, dysplastic nevus, and melanoma [68]. Most discordance involved the distinction between severely dysplastic nevus and melanoma. The panel had agreed in advance on diagnostic criteria for dysplastic nevus. In a similar but smaller study there was 87% agreement among 10 dermatopathologists in distinguishing dysplastic nevus from banal nevus and melanoma [69].

Other recent research confirms that Clark was correct in placing dysplastic nevus on the spectrum from banal nevus to melanoma. Unlike ordinary nevi, dysplastic nevi share genetic lesions (such as loss of heterozygosity at 1p36 [70, 71], 9p22-21 [70–72], and 17p13 [72]) with melanoma. They are intermediate between banal nevus and melanoma in DNA content [64, 73–75], immunohistochemical labeling fraction for proliferation markers [76–78], and telomerase activity [78]. Microsatellite instability is present in dysplastic nevi, at a frequency only slightly lower than in melanoma, but absent in other nevi [65, 79]. Severely dysplastic nevi show more microsatellite instability than lower grades [65]. Mismatch repair proteins are reduced in dysplastic nevi, to a level intermediate between that in banal nevus and melanoma [80]. These findings suggest that dysplastic nevi manifest the same kind of genetic instability as has been observed in premalignant and early malignant lesions in other cell lineages [65]. Dysplastic nevi serve as an epidemiologic marker of melanoma risk in familial melanoma kindreds [81] and in patients without a family history but large numbers of nevi [82, reviewed in]. Dysplastic nevus remnants have been found in 7-60% of unselected melanomas [83, 84] and up to 80% of familial melanomas [81], suggesting that Clark was also correct that the lesion itself constitutes part of at least one important pathway to melanoma formation.

In conclusion, the dysplastic nevus remains a problem, but it can and must be recognized. It is simply unacceptable for pathologists to apply nonspecific diagnostic terms such as “compound nevus” (as did almost 10% of dermatopathologists in Shapiro’s survey). The lesions should be graded (basically as mild, moderate, or severe). The reliability of this grading will not be perfect, but it should be attempted, as histologic grade correlates with melanoma risk and biologic markers of malignancy. While dysplastic nevi are moderately common, only a small proportion will be rated as severely dysplastic [60, 66, 67].

Should the diagnosis of dysplastic nevus stimulate reexcision, for a partially biopsied nevus? Although some authorities have recommended reexcision in all such cases [4], in my opinion it is a question that each practitioner must answer for himself, because it involves trade-offs between risk, inconvenience, and cost in which the risk cannot be precisely quantified and the risk tolerance of the practitioner and the patient must be accommodated. For the reasons described above, in my practice dysplastic nevi are graded, and an explicit recommendation to reexcise accompanies reports of incompletely removed, severely dysplastic examples. Margin information is provided for mildly dysplastic nevi, but it seems reasonable not to reexcise such lesions, and few experienced clinicians do so.

It may be that in the future we will have markers to help establish the significance of an individual lesion, in the same way that immunohistochemical staining for mismatch repair proteins can be performed to determine whether an individual sebaceous adenoma is a manifestation of Muir-Torre syndrome or is sporadic [85,86]. Meanwhile, the clinician must, of course, consider clinical as well as histologic findings in his assessment of the patient and in therapeutic planning for individual lesions [53,54,87,88].

2.2 Spitzoid lesions

Like dysplastic nevi, spitzoid neoplasms can be arranged along a spectrum, extending in this case from a fully benign lesion (Spitz nevus) to a fully malignant one (spitzoid melanoma). Intermediate positions within the specimen are occupied by the “atypical Spitz nevus” and “atypical Spitz tumor” (or “spitzoid tumor of uncertain malignant potential”, “STUMP”) [89]. These intermediate entities are regarded as posing some risk of malignant behavior, but less than that of histologically unequivocal melanomas. The term “atypical Spitz nevus” has been applied to lesions regarded as probably, but not certainly, benign, while “atypical Spitz tumor” or “STUMP” reflects greater diagnostic uncertainty [89]. Many authors have not distinguished between atypical Spitz nevus and tumor, but recognize only a single intermediate category [90–92].

But what explains the unpredictable behavior of the intermediate lesions? Are they discrete biologic entities, whose behavior is indeterminate because they have traversed only the

initial stages of progression towards full-fledged malignancy, and may or may not complete the remainder? Or do the intermediate terms describe not discrete entities, but a heterogeneous mixture of completely benign and completely malignant tumors, which are confounded because they cannot be distinguished histologically? In the first interpretation the “atypical Spitz nevus” would be a less advanced entity than the “atypical Spitz tumor”; in the second interpretation, a sample of “atypical Spitz nevi” simply contains a higher proportion of benign tumors than a sample of “atypical Spitz tumors”.

As Lee has written, “What is not clear in all of these [equivocal] designations is whether the issue is the inability of the histopathologist to discriminate between benign and malignant, in which case they represent euphemisms for ‘I don’t know’, or whether the issue is that these difficult lesions actually lie somewhere between the spectrum of benign and malignant in accordance with the multistep theory of carcinogenesis” [93]. If the latter is correct, and true biologic intermediates exist, how many are there? Two (“atypical Spitz nevus” and “atypical Spitz tumor”), more than two, or only one? How can the intermediates be recognized?

And there are more questions. Do we even really know what to from expect the polar entities (typical Spitz nevus and spitzoid melanoma), based on analogies to common nevi and melanomas? There is some molecular evidence that the spitzoid lesions constitute a distinct lineage separate from that of ordinary nevi and melanomas [90]. H-ras activation occurs in about a quarter of Spitz nevi [89, 94–97], but they very infrequently reveal B-raf or N-ras mutations [89]. The opposite profile is observed in other melanocytic neoplasms. In most common nevi, dysplastic nevi, and melanomas, B-raf and N-ras mutations are very common, while H-ras abnormalities are extremely rare [89, reviewed in]. H-ras mutations have been identified in atypical Spitz nevi and in a single spitzoid lesion suspicious for melanoma [98]. The presence of B-raf or N-ras mutations in a minority of Spitz nevi, atypical Spitz tumors, and spitzoid melanoma [89, reviewed in], and in a majority of spitzoid melanomas in one study [98], does cast some doubt on a separate progression pathway for spitzoid lesions, however.

There are case reports of histologically typical Spitz nevi that metastasized. [12]. It may be that the pathologic diagnosis was simply wrong, but maybe it was correct; maybe even

typical Spitz nevi are not always (only almost always) as harmless as, for example, intradermal nevi. At the other end of the spectrum, it seems increasingly clear that there is a group of spitzoid neoplasms that would classically be regarded as malignant but do not behave as typical melanomas, because they are capable of nodal but not distant metastases (see below). Can these be distinguished from the smaller group of spitzoid malignancies that do metastasize widely?

As the plethora of questions suggests, histopathologists have not been successful in predicting the behavior of spitzoid lesions. Cerroni speaks of the “frustration of a seemingly never-ending search for . . . morphologic criteria that would allow dermatopathologists to reliably and repeatably differentiated spitzoid tumors that behave in a benign fashion from those that will eventually metastasize . . . these criteria simply do not exist” [99]. As mentioned earlier, melanoma is the single largest cause of malpractice claims against pathologists [1], and 29% of such claims involve melanoma misdiagnosed as Spitz nevus [1]. In a concordance study mentioned above, 31 spitzoid lesions were diagnosed by a panel of 10 dermatopathologists as Spitz nevus, atypical Spitz nevus, melanoma, or uncertain [12]. 17 of the 31 were diagnosed as melanoma by 6 or more of the 10 panelists, and of these, 13 eventuated in local recurrence, metastasis, or death. The remaining 14 cases received other diagnoses from a majority of the panelists, but 10 of these cases also resulted in local recurrence, metastasis, or death [12]. The one case which received a majority diagnosis of typical Spitz nevus was fatal [12].

As mentioned, there is molecular evidence for a lineage of spitzoid tumors. In practical terms, a tumor, whether nevus or melanoma, is regarded as spitzoid because of its cytologic characteristics. All spitzoid tumors are composed of large epithelioid and/or spindle-shaped melanocytes with large, open, variable nuclei and abundant, lightly pigmented cytoplasm [100]. There are, of course, architectural and cytologic differences within the spectrum of spitzoid tumors, which provide the criteria for histologic diagnosis. These have been reviewed in detail elsewhere [91, 92, 100, 101]. As discussed, their reliability is far from perfect, especially for the intermediate lesions. It is generally accepted that the polar entities (Spitz nevus and melanoma) can be recognized with good if not perfect reliability [102], while intermediate lesions have been more problematic. Several modalities have been explored as a

diagnostic adjunct in the histologic diagnosis of spitzoid neoplasms.

One of these is immunohistochemistry. Proliferative activity can be assessed by immunohistochemical staining with antibodies such as MIB-1, that stain cells in or past the late G1 phase of the cell cycle. The proliferation fraction is the proportion of cells staining with such antibodies, and it is greater for melanoma than Spitz nevus [89, reviewed in]. Unfortunately, all studies have shown some degree of overlap (at a proliferation fraction of approximately 2-6%) [103]. Worse, it is the histologically equivocal lesions that tend to have an intermediate proliferation fraction [104], so the technique is least useful where it is most needed.

Spitz nevi resemble common nevi in displaying a zonal pattern of reaction with HMB-45 antibody, staining in the epidermis and upper dermis, but not the deep dermis. Melanomas stain throughout [105, 106]. Similar differences in zonal staining are observed with bcl-2 [106] and cyclin D1 antibodies [107]. Unfortunately there is some overlap, and atypical spitzoid lesions have not been studied. An antibody to p53 (which probably labels only the mutant form of this suppressor gene product) stains a higher proportion of melanomas than Spitz nevi [105, 108]. There are differences in staining for fatty acid synthase among Spitz nevus, atypical Spitz nevus, and melanoma, with little overlap among the three groups [104]. Differences in staining for a number of cell cycle regulators, including p-16, p-27, Rb, cyclin A, and cyclin B1, have been reported [108–111].

As mentioned, about a quarter of Spitz nevi reveal characteristic abnormalities in H-ras, consisting of gene duplication and, in some cases, mutation [94–97]. Duplication of H-ras can be detected by a variety of molecular techniques, including comparative genomic hybridization (CGH) [94–96], array-based comparative genomic hybridization [97], fluorescence in situ hybridization (FISH) [94, 95], and multiplex ligation-dependent probe amplification (MLPA) [112, 113]. These techniques fail to demonstrate any cytogenetic abnormalities in the three quarters of Spitz nevi with normal H-ras copy number. By contrast, they show multiple chromosomal abnormalities in the vast majority of melanomas [96, 97, 112, 114]. In one series of 132 melanomas, for example, 96% displayed chromosomal gain or loss by CGH [96].

There is preliminary evidence that these molecular techniques may be of practical value

as a diagnostic adjunct for histologically indeterminate spitzoid tumors. Bauer and Bastian described two such equivocal lesions evaluated by CGH [115]. One revealed no cytogenetic abnormalities, and was judged benign, while the other displayed the multiple chromosomal gains and losses typical of melanoma. Harvell et al. examined 16 recurrent Spitz nevi by CGH and/or FISH [116]. Twelve were normal, in two there was 11p (H-ras) amplification, in one multiple chromosomal gains and losses, and in one gain of 1q and loss of 9p [116]. After an average 4.8 years of follow-up, there was no further evidence of disease in all but the last case, which eventuated in nodal metastasis [116]. Takata et al. applied MLPA to 16 atypical spitzoid lesions. Of these, 13 revealed no abnormalities, but in 3 there was a reduced copy number of the cyclin-dependent kinase inhibitor 2A gene (CDKN2A) [113]. This was detected in 0 of 12 typical Spitz nevi but 12 of 22 melanomas [113].

These modalities are new and have not yet been thoroughly evaluated. They must be applied to many more lesions, and their results correlated to both histopathology and clinical outcome. Nevertheless, preliminary results are encouraging.

In 2000, Kelley and Cockerell advised sentinel node biopsy for histologically equivocal melanocytic neoplasms, including equivocal spitzoid tumors, more than 1 mm in thickness [117]. Thinner tumors could be treated by simple excision [117]. They argued that, since the tumors were equivocal, their treatment should accommodate the worst possibility (melanoma), and this meant sentinel lymphadenectomy followed by completion lymphadenectomy if the sentinel node was positive. They argued further that the procedure could play a diagnostic, as well as therapeutic, role because sentinel node involvement would push the diagnostic compass towards melanoma while its absence would favor benignity [117].

There have subsequently been a number of case reports and small series describing atypical spitzoid lesions managed in exactly this manner [118–124]. Recently, however, several of the world's most prominent dermatopathologists, including Philip LeBoit [125], Mark Wick [126], and Klaus Busam [127], have strongly criticized the approach. They question the fundamental assumption that nodal involvement by an equivocal melanocytic neoplasm implies melanoma: “So what do the melanocytes in the lymph node . . . prove? To some, everything—a sure diag-

nosis of melanoma. To me, nothing.”(LeBoit [125]).

Normal tissue elements, including breast epithelium and mesothelium, can sometimes be found in nodes, apparently as a result of passive lymphatic transport [127]. The same mechanism apparently also explains nodal nevi [128], which are common. Nodal nevi have been observed, for example, in 3-22% of melanoma patients and 0.33% of breast cancer patients undergoing sentinel lymphadenectomy [128, reviewed in]. The critical issue is their frequency in association with benign Spitz nevi, and this is unknown. As LeBoit suggested, only a series of sentinel lymphadenectomies in patients with unequivocally benign Spitz nevi would establish the necessary baseline frequency, and this experiment will never be performed [125].

There are, of course, histologic differences between nodal nevi and nodal deposits of melanoma. The former tend to involve the nodal capsule and trabeculae, the latter the parenchyma. However, melanoma can involve the capsule [127] and nevi the parenchyma [127, 129]. Nodal nevi are smaller and less cytologically atypical than metastases. However, the cytology of nodal deposits tends to resemble that of the primary, and the latter is at least somewhat atypical in the case of an atypical spitzoid neoplasm. Conversely, bland cytologic features do not entirely exclude melanoma [127]. Diagnosis might be facilitated by various immunohistochemical markers, including Melan-A to label melanocytes, HMB-45 to identify malignant melanocytes, and MIB-1 to assess proliferation rate, which is higher in melanoma than nevus. All of these procedures have limitations which can lead to both over- and underdiagnosis of melanoma [127].

Busam and Pulitzer have emphasized the remarkable fact that no patient with an atypical spitzoid neoplasm and positive sentinel node has subsequently developed distant metastasis [118–124, 127], even when completion lymphadenectomy revealed additional nodal involvement. The significance of this observation is limited by short follow-up times [127], and it might even be marshalled as support for the procedure. More fundamentally, it invites comparison with conventional melanoma, in which half of patients with positive sentinel nodes would experience distant metastasis. It suggests that these atypical spitzoid lesions are either benign or malignant but incapable of distant metastasis. The latter possibility was suggested by Smith et al. who reported as “malignant Spitz nevus” a series of 32 tumors with distinctive

(atypical) histologic characteristics and an apparent capacity for nodal, but not distant, metastasis [130]. Six of their cases had nodal involvement (manifest not just histologically but as clinical adenopathy), but no further extension occurred after an average of six years of follow-up [130]. A meta-analysis demonstrating 88% 5-year survival for spitzoid melanoma diagnosed in the first ten years of life, despite a mean thickness of 4.67 mm, is consistent with the concept of limited malignancy [131]. Other organ systems provide examples of similarly limited malignancies, such as papillary carcinoma of the thyroid, and an explanation for this behavior has been proposed [101].

In summary, histopathologists can recognize typical Spitz nevi with good reliability, although lesions regarded as such by competent dermatopathologists have occasionally metastasized. For this reason, it is reasonable to completely excise every Spitz nevus, even histologically typical examples [127]. At the other extreme, an unequivocal histologic diagnosis of spitzoid melanoma can also be accepted. Such a lesion should be treated like any other melanoma, although there is evidence suggesting much more favorable outcomes.

For lesions that fall into the intermediate categories of “atypical Spitz nevus”, “atypical Spitzoid tumor”, “STUMP”, etc, the limitations of histologic analysis *must* be kept in mind. Immunohistochemical labeling for proliferation markers, HMB-45, bcl-2, and other moieties have revealed differences between Spitz nevus and melanoma, but overlaps and lack of experience with intermediate spitzoid lesions limit their usefulness. Molecular techniques such as comparative genomic hybridization may, in some cases, be highly informative: H-ras (11p) duplication without other chromosomal abnormalities strongly implies benignity; no chromosomal abnormality also implies nevus but can occur in melanoma; and multiple chromosomal gains and losses constitute strong evidence for melanoma. In uncertain cases a sentinel node biopsy can be performed, but a number of authorities have argued against it and the approach is unsupported by outcomes research. If a nodal deposit is observed it should be assessed for size, location, cytology, and perhaps staining for HMB-45 and other markers. The mere fact of nodal involvement should not be accepted as conclusive evidence for malignancy and complete justification for therapeutic interventions such as completion adenectomy and adjuvant

chemotherapy.

2.3 Cellular blue nevi

As with Spitz nevi, there is a spectrum of cellular blue nevi, extending from a fully benign nevus, through an intermediate category (“atypical cellular blue nevus”, ACBN), to the fully malignant pole (“malignant cellular blue nevus”, MCBN). All of these are uncommon; the great majority of blue nevi encountered in ordinary clinical practice are common blue nevi, which are relatively small (< 1 cm/d); distributed on the dorsal hands and feet, buttocks, scalp, and face; and histologically straightforward [132]. Cellular blue nevi (CBN) are somewhat larger, and often located on the sacrococcygeal area, buttocks, or distal extremities [133]. They are more complex histologically, manifesting three distinct histologic patterns [133].

This term “malignant cellular blue nevus” is generally applied to melanoma originating within a cellular blue nevus, i.e., a melanoma with a histologically identifiable blue nevus remnant [134, 135]. However, it has also been used for melanomas originating within common blue nevi (thought to be very rare) [136, reviewed in]; for melanomas originating within other dermal melanocytoses, such as nevus of Ota [134, reviewed in]; and for melanomas resembling cellular blue nevi but not associated with a nevus remnant [136, reviewed in]. In older work it was suggested that MCBN is a discrete entity, separate from melanoma [135, 137]. This concept was supported by molecular analysis of a single case, which failed to reveal loss of heterozygosity at any of 8 genes frequently abnormal in melanoma, such as 9p21, while all of 28 melanomas evaluated by the same procedure were genetically abnormal [138]. Subsequently, however, all of 7 MCBN evaluated by CGH revealed cytogenetic abnormalities typical of melanoma, especially losses of chromosome 9 and gains of chromosome 20 [139]. An additional case revealed mutation at 3p26, which is fairly common in conventional melanoma [140]. Clinically, MCBN is large (> 2 cm) and almost always located on the scalp.

Compared to other melanomas, MCBN exhibits unusually aggressive clinical behavior. In the largest series, 10 of 12 cases metastasized and 8 were fatal [141]. In a series of 10 cases, of the 7 for which follow-up information was available there was distant metastasis in 4 and

local recurrence in the rest [136]. Of 6 cases, 2 were fatal and 2 spread regionally and to nodes [142]. Other small series and case reports describe a metastatic rate of approximately 80% [143, reviewed in].

The atypical cellular blue nevus is an entity with clinical features of ordinary cellular blue nevus (size < 2 cm, location on the extremities, trunk, buttocks, and scalp [144]), but histologic features overlapping with malignant cellular blue nevus [13, 133, 144–146]. These features may include larger size, asymmetry, infiltrative architecture, hypercellularity, mitotic activity, and cytologic atypia [13, 133, 144–146]. Most authors have indicated that the severity of these features is what distinguishes ACBN from MCBN, but some have suggested that atypical mitotic figures are unique to MCBN [144], or that cytologic atypia is focal in ACBN but diffuse in MCBN [134, 147].

Early work showed that ACBN could be recognized despite its histologic overlap with MCBN. Tran et al. reviewed 16 cases that had been diagnosed by a single expert as atypical cellular blue nevus [144]. On review, 7 of these were reclassified as deep penetrating nevus (see below). The other 9 displayed fairly uniform histologic characteristics and, most importantly, had not recurred after an average 42 months of follow-up [144].

A recent study was far less encouraging. 26 lesions in the spectrum of CBN, including 8 CBN, 11 ACBN, 6 MCBN, and 1 ordinary blue nevus, were evaluated by a panel of 14 expert pathologists [13]. At least 4 years of follow-up was available for all cases, and for each outcome was consistent with pathologic diagnosis (no progression for the CBN and ACBN, metastasis or death for half of the MCBN). The correct diagnosis was rendered by a majority of panelists in only 38% of cases. A majority recognized only 2 (18%) of ACBN, 3 (37%) of CBN, and 4 (67%) of MCBN [13]. κ values were extremely low: 0.02, 0.20, and 0.52, for ACBN, CBN, and MCBN, respectively [13]. In a much earlier study of CBN, 16% had been originally misdiagnosed as melanoma [148].

The role of genomic analysis in diagnosing equivocal blue nevi remains to be determined. As mentioned, chromosomal abnormalities resembling those of ordinary melanoma were identified by CGH in 7 of 7 MCBN [139]. The same study found chromosomal abnormalities in 3

of 11 ACBN, and in 2 of these the abnormality (loss of 3q) was not typical of melanoma [139].

Sentinel lymphadenectomy would be a particularly unrewarding diagnostic adjunct for this group of lesions. Nodal extension occurs in about 5% of ordinary cellular blue nevi [148, 149], and frequently involves the subcapsular sinuses and parenchyma, rather than the capsule [133, 137, 149]. Nodal disease may be even more common in ACBN. Of 11 cases, 3 involved sentinel or regional nodes but did not recur after a mean 4.4 years of follow-up [13]. Interestingly, blue nevi can occur primarily in nodes [149, 150], and have been found in various other tissues, including mouth, lung, prostate, cervix, and muscle [137, reviewed in].

In summary, the cellular blue nevi define a problematic histologic spectrum analogous to the spitzoid tumors. As with the latter, polar diagnoses (ordinary cellular blue nevus and MCBN) are probably reliable, but intermediate examples should be treated with respect. Tran et al. advised that all ACBN be excised with 1 cm margins, followed by careful clinical surveillance [144], and it is difficult to argue with this recommendation.

2.4 Animal-type melanoma

Animal- or equine-type melanoma is a rare and equivocal entity that overlaps histologically with several types of blue nevi. It was named for its clinical and histologic resemblance to a dermal malignancy that affects elderly, darkly colored (especially gray) horses, called equine melanotic disease. These are dark nodules whose appearance is accompanied by spontaneous depigmentation of the horse, from gray to white. They are often indolent, and even after widespread metastasis are rarely fatal [151].

The putative human analog presents as a heavily pigmented nodule or, less commonly, plaque, about 1 cm in diameter. It occurs much earlier than other melanomas, at a median age of 28 [152], 39 [151], and 24 [153], in the three reported series. It seems to be much less aggressive than other melanomas. Of the 84 cases reported by 2007, sentinel lymphadenectomy was performed in 63%, and 41% of the sentinel nodes were positive [154]. Nevertheless, only 2% of patients died of their disease, after 0.5 to 17 years of follow-up [154]. Because of the low frequency of distant metastasis and death, several authors have suggested that this is a

uniquely low-grade or indolent form of melanoma [134, 151, 152], and have compared it to the spitzoid neoplasms (described above) that are apparently capable of lymphatic but not distant metastasis [135, 152, 155].

Histologically, the entity is characterized by very heavy pigmentation and a distinctive architecture. These are large and deep tumors, with dense, sheetlike dermal deposits towards the center, and infiltration of the dermis, subcutis, and sometimes adnexae at the periphery. Many display little or no necrosis, mitotic activity, or cytologic atypia [134, 151–153], and thus may lack conventional criteria for malignancy [153]. The degree of mitotic activity and cytologic atypia appears not to correlate with the likelihood of lymphatic metastasis [152].

Because of the deceptively bland cytology and low mitotic rate, this lesion can be confused with several types of nevi, including cellular blue nevus, other blue nevi, darkly pigmented Spitz nevus, pigmented spindle cell nevus, and deep penetrating nevus [134, 147, 153]. It can also be confused with several other forms of melanoma, including malignant blue nevus, melanoma regressing with melanophage deposition [134, 153], and perhaps primary dermal melanoma. Zembowicz et al. who reported the largest series of 41 cases, found it to be indistinguishable from epithelioid blue nevus, an unusual type of nevus that is associated with Carney syndrome but can also occur spontaneously [152]. They proposed a new term, pigmented epithelioid melanocytoma, as a “provisional histologic entity encompassing . . . both animal-type melanoma and epithelioid blue nevus” [152]. Cases have subsequently been reported as pigmented epithelioid melanocytoma [154–156], but not all have welcomed this nomenclature [147, 157], and some continue to insist that animal-type melanoma and epithelioid blue nevus can and must be distinguished [147]. Other terminology has been proposed, including pigmented synthesizing melanoma [151, 158], and, in older literature, pilar neurocristic hamartoma (because of the tumor’s tendency to infiltrate around follicles and other adnexae [153, 159, 160]).

It has been uniformly recommended that animal-type melanoma be managed like other melanomas, with wide local excision and sentinel lymphadenectomy [134, 152, 153, 155, 156, 158]. The depth of these tumors and their uncertain biologic potential probably underlies the recommendation for sentinel lymphadenectomy, which was in fact performed in most reported

cases. However, given the high frequency of sentinel node involvement (41% [154]), but rarity of distant metastasis and death, a positive sentinel node clearly does not have the same prognostic implications for animal-type as for other forms of melanoma, and the value of sentinel lymphadenectomy in the management of this condition has recently been questioned [154,157].

2.5 Deep penetrating nevus

Deep penetrating nevus (DPN) overlaps somewhat with animal-type melanoma, because it is deep, may be moderately pigmented, contains both epithelioid and spindle-shaped melanocytes, and characteristically infiltrates adnexae. Further, there is usually inflammation, a degree of cytologic atypia, and, in some cases, mitotic activity [161–165]. For these reasons, misdiagnosis as melanoma is not uncommon [165, reviewed in]. The lesion may also be confused with a variety of benign entities, including blue nevus, cellular blue nevus, pigmented Spitz nevus, and combined nevus [161, 162]

Fortunately, DPN (also known as plexiform spindle cell nevus [162]) has a characteristic clinical presentation, as a heavily pigmented, smooth-surfaced, dome-shaped nodule, < 1cm/d, located on the upper body of an adolescent or young adult [161–165]. It also has a distinctive histologic architecture [161–163], with a wedge-shaped, symmetric configuration, deeper than it is wide. Also, cytologic atypia and mitotic activity, while present in many cases, are much milder than in most melanomas [161, 163–165].

Mehregan et al. reported a much lower proliferation fraction, measured by immunohistochemistry, in a small series of DPN, compared to melanoma [166]. Roesch et al. confirmed the difference in mean labeling fractions, but found it to be an unreliable basis for diagnosis because of overlap between the two groups [167]. They also investigated Rb, metalloproteinases, and integrin β 3, and demonstrated that immunohistochemical staining for dipeptidyl peptidase IV reliably distinguishes melanoma and DPN. This peptidase is a cell surface marker found in normal melanocytes and nevus cells, but not melanoma [167]. Subsequently they used a microarray containing 47,000 genes to screen transcripts from DPN and nodular melanoma [168]. A difference in ataxia-telangiectasia mutated gene transcripts motivated immunohistochemical staining

for the product of this gene, which was found to reliably distinguish DPN and melanoma [168]. While commercially sourced antibodies were used in both studies, unfortunately they are not available in routine clinical practice.

DPN exhibits reliably benign clinical behavior, as no recurrences were observed in several large series, which included atypical and incompletely excised examples [161,165]. (However, a single case of “malignant deep penetrating nevus”, with axillary but not distant metastasis, has been briefly described [169].) The main problem seems to be the possibility of histologic misdiagnosis. How frequently this occurs, and the direction of the error (DPN misdiagnosed as melanoma or melanoma misdiagnosed as DPN) is unknown, since diagnostic concordance and other reliability metrics have not been estimated for DPN and its simulants, as they have for spitzoid lesions and cellular blue nevi (see above). Because of the possibility of histologic underdiagnosis, most dermatopathologists recommend that an incompletely removed DPN be reexcised.

2.6 Atypical melanocytic hyperplasia

This is merely a descriptive term referring to epidermal features that might occur in early or nondiagnostic examples of melanoma, but could also be observed in lentiginos, nevi, or even normal skin as a result of physical trauma or UV exposure. They include increased melanocyte density and architectural disorganization, with melanocytes arranged not in nests but as single cells within, or in some cases above, the epidermal basal layer. Melanocytic atypia is generally absent or slight, because severe cytologic atypia in combination with these architectural features would generally result in an unequivocal diagnosis of melanoma (except perhaps for a tiny specimen whose size alone might preclude diagnostic certainty).

3 Conclusion

In summary, nevi and melanomas continue to present formidable challenges to the histopathologist. In most practices the great majority of such lesions will be unequivocal examples of

common entities, and can be reliably diagnosed by an experienced dermatopathologist. Formal studies of diagnostic concordance have not, however, been entirely reassuring, especially with regard to some diagnostic categories, such as the spitzoid tumors. No doubt some of the variance simply results from the subjective nature of histopathologic analysis, but it is also clear that histology is not a perfect guide to clinical behavior. Better tools are needed, and they seem to be arriving, in the form of molecular diagnostics such as CGH. Meanwhile, the clinician can contribute by cultivating his own diagnostic skills (perhaps incorporating new modalities such as dermoscopy), submitting adequate specimens, communicating clearly with the lab, and intelligently interpreting pathology reports. In my opinion it is critical that practitioners avoid two over-simplifications: that all pigmented lesions may be divided into two homogeneous categories, benign (nevus) and malignant (melanoma); and that a positive sentinel node justifies assignment to the latter group. Some of the problematic entities described above, such as spitzoid and animal-type melanomas, appear to be low-grade malignancies capable in most cases of lymphatic but not distant metastasis; while others, such as malignant cellular blue nevus, seem to be more high-grade than other melanomas. Some benign lesions, in particular dysplastic nevi, also must be graded, as their clinical associations and appropriate management vary with the degree of dysplasia. The status of these complex entities will become more certain as clinical experience accumulates and their molecular mechanisms are worked out.

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