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Sentinel lymph node biopsy as an adjunct to management of histologically difficult to diagnose melanocytic lesions: A proposal

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There is a significant subset of primary cutaneous melanocytic neoplasms that are difficult to diagnose with the use of routine light microscopy. The currently recommended approach in assessing such lesions is to make a histopathologic diagnosis that reflects some uncertainty and then to recommend complete surgical excision. While adequate in many cases, the excision that might be recommended for such a lesion if malignant would be mutilating in many others. To increase the sensitivity of diagnosis and to provide potentially useful prognostic information, we propose that sentinel lymphadenectomy be considered in patients with melanocytic neoplasms of uncertain behavior that are 1.0 mm or more in thickness. (J Am Acad Dermatol 2000;42:527-30.)

The histologic diagnosis of malignant melanoma, while often straightforward, may be quite difficult to make with certainty in several instances. In fact, by some persons melanocytic neoplasia is considered to be the most difficult subject in all of surgical pathology. Several reasons explain this. First, there are benign processes that histologically appear virtually identical to melanoma, such as Spitz nevi, some blue nevi, halo nevi, persistent (recurrent) nevi, congenital nevi biopsied in infants, and nevi near genitalia and in the axilla. Some "dysplastic" nevi may have foci that appear very similar to evolving melanoma in situ and other processes such as intraepidermal melanocytic proliferations on sun-damaged skin, and melanocytic hyperplasia within solar lentigines may rather closely simulate evolving melanoma. Processes that cause vacuolar degeneration of the dermoepidermal junction such as discoid lupus erythematosus and benign lichenoid keratoses may also be confused with melanoma in situ. Finally, conditions in which there is abundant pigment in the dermis may simulate melanoma, such as some dermatofibromas, postoperative scars containing iron from Monsel's solution, and processes with numerous melanophages such as regressed nevi.

Conversely, melanoma may simulate several less serious benign processes including compound, junctional, and intradermal nevi. They may also simulate blue nevi, "dysplastic" nevi, and, as noted above, Spitz nevi. They may be poorly differentiated with minimal melanin and can therefore simulate less aggressive nonmelanocytic neoplasms such as squamous cell carcinoma, basal cell carcinoma, and atypical fibroxanthoma. They may assume unusual morphologic features such as in desmoplastic melanoma, wherein a scar or benign fibrosing or neural process may be simulated. Completely regressed melanoma may demonstrate only a band of melanophages in the dermis with no residual melanocytes. Pagetoid intraepidermal melanocytic proliferation in melanoma may be confused with other processes that give rise to similar histologic features including Merkel cell carcinoma, pagetoid reticulosis, sebaceous carcinoma, mammary and extramammary Paget's disease, and Langerhans cell histiocytosis. Furthermore, metastases of melanoma may be confused with nevi as they may be small and symmetrical.

In addition to the aforementioned, melanomas are prone to sampling error by clinicians who are only about 67% accurate in making the clinical diagnosis of melanoma.[1] Punch and shave biopsies, especially when small, may fail to sample diagnostic areas, and curettage specimens may destroy architecture so that an accurate histologic evaluation cannot be made at all.[2] Finally, there are no special stains that are specific for melanocytic differentiation, much less for the diagnosis of melanoma.

For all of these reasons, it may be impossible to make a histologic diagnosis of melanoma with certainty. This problem has been documented on more

than one occasion in the literature. A recently published article described the results when slides of a selected group of melanocytic neoplasms were sent to several leading experts in dermatopathology for histologic interpretation. Disagreement in diagnosis was found approximately 65% of the time.[3] Thus if experts in dermatopathology experience significant difficulty in rendering definitive diagnoses of melanocytic neoplasms, it is likely that the average practitioner would have even greater problems.

CURRENT STATUS

Because the treatment of melanoma differs significantly from virtually all of the other processes with which it may be confused histopathologically and because failure to diagnose melanoma has serious clinical as well as medicolegal implications, clinicians need a management strategy so that lesions that are not readily diagnosable with routine methods can be dealt with reasonably. Currently, the practice that is considered standard by dermatologists and dermatopathologists when confronted with a melanocytic neoplasm in which the diagnosis of melanoma cannot be excluded with certainty is that it be completely excised. While this seems reasonable, the surgical margins recommended to be taken around a melanoma are based on the thickness (Breslow depth) of the lesion. The recommendations for surgical margins used most commonly by surgeons in cases of melanoma were issued by the National Institutes of Health (NIH) at a consensus conference in January 1992.[4] These recommendations state that the most conservative margin for melanoma involving the dermis is 1 cm of normal skin taken around the lesion extended to the level of the fascia. For thicker lesions, even wider margins, sometimes as much as 3 cm, are recommended. These margins are excessive for benign lesions because they can be mutilating, especially in cosmetically sensitive areas. Thus the NIH recommendations might be excessive for lesions in which the diagnosis is uncertain but likely to be benign. Nevertheless, the NIH recommendations remain standard in most centers in the United States and would therefore be followed by many surgeons faced with a possible but uncertain diagnosis of melanoma. This would result in overtreatment in some cases.

In contrast, dermatologic surgeons often use a more conservative approach, especially when the dermatopathologist has a strong suspicion that the lesion is truly benign but has unusual features that prevent melanoma from being excluded with certainty. Recent studies have suggested that the NIH recommendations are excessive, even for melanomas in which the diagnosis is certain. For this reason, many dermatologic surgeons do not adhere to them and, in fact, Mohs micrographic surgery is performed on many melanomas in several centers and has been shown to be as successful as conventional surgery.[5,6] As such, when confronted with a melanocytic neoplasm of uncertain biologic behavior, many dermatologists either perform the surgery themselves or refer the patient for Mohs surgery. Although most such lesions excised with "narrow" margins are usually removed in toto and never recur, occasionally a recurrence develops at the site or a regional metastasis develops. In such cases, the pathologist is often held medicolegally liable for not having made a definitive diagnosis of melanoma initially, even though complete removal might have been recommended. Furthermore, experts in surgery can be found who will testify that had a wider excision been performed initially, the patient would have been cured of the disease, whether or not the lesion involved the dermis and whether or not the patient was at risk for metastatic disease at presentation.

Although the NIH recommendations can usually be followed in lesions that are less than 1 mm in thickness irrespective of whether or not there is a question about the diagnosis, the most important decision concerns treatment of lesions deeper than 1 mm. Although controversial, recent studies have suggested that some patients with melanomas measuring between 1 and 4 mm in thickness have a survival benefit if they undergo elective lymph node dissection (ELND) at the time of diagnosis as opposed to waiting for clinically apparent metastases.[7] Unfortunately, ELND is an aggressive procedure that can result in serious sequelae, such as chronic lymphedema, and as such, it would be potentially harmful to patients with a melanocytic lesion of uncertain behavior who in reality had a benign nevus. Furthermore, in many centers, because of sequelae and dubious benefit, ELND is not performed at all. An approach that we propose is that in lieu of performing ELND in patients with intermediate-thickness melanocytic lesions of uncertain behavior, local excision with concurrent sentinel lymph node (SLN) removal be considered.

SENTINEL LYMPHADENECTOMY

The lymphatic drainage of a given portion of the body generally occurs in a predictable pattern. The lymph channels drain to a chain or group of lymph nodes usually situated proximally. For example, lymph in the hand passes in lymphatic vessels proximally and collects in lymph nodes in the tissues of the forearm, the epitrochlear area, the upper arm, and eventually the axilla. The SLN is defined as the

first lymph node that drains a certain region. While usually one specific node can be identified as the SLN, on some areas of the body such as the face or the back, more than one lymph node, sometimes even in anatomically distinct areas, are identified as SLNs. When multiple, all such nodes are considered to be important and are treated as if they all represent SLNs. The technique for identification of SLNs consists of injection of blue dye and technetium-labeled sulfur colloid into the site of the primary cutaneous melanoma. These materials pass from the site of injection into lymphatics and to lymph nodes. A lymphoscintigram is performed and the pattern of lymphatic drainage is determined. At the time of surgery, the blue dye can be visualized directly within the draining lymph node. In addition, a Geiger counter is used to detect radioactivity from the technetium-labeled sulfur colloid that collects in lymph nodes, allowing even greater accuracy of detection. It has been determined that by using this technique, it is possible to detect SLNs in 82% to 99% of cases.[8,9]

Although the SLN can be identified in the vast majority of patients, the most important point is its predictive value about prognosis if it is found to contain neoplastic cells. It has been demonstrated that that if the SLN is normal on routine light microscopic study, histologic evaluation of the rest of the lymph nodes in a given lymph node basin will be found to be normal in approximately 99% of patients.[8] Conversely, if the SLN is found to contain neoplasm, additional lymph nodes in the draining basin will be similarly affected in 17% to 33% of cases.[9,10] Although light microscopy remains the most important method for assessment of neoplasm within lymph nodes, special techniques are available that increase sensitivity, such as immunoperoxidase stains directed to markers of melanocytic differentiation and the polymerase chain reaction to amplify tyrosinase messenger RNA. These techniques have been shown to increase detection of neoplastic cells within the SLN by an additional 9% to 44%.[11,12] Although the significance of detection of subclinical involvement using these highly sensitive techniques remains controversial, they are being used routinely in some centers.

PROPOSAL
The use of sentinel node lymphadenectomy in the management of melanocytic neoplasms of uncertain behavior

As noted above, sentinel lymphadenectomy has several potential benefits in the treatment of melanoma. It allows for identification of aberrant lymphatic drainage patterns that may be found in up to 59% of patients and has far fewer side effects than regional lymphadenectomy.[13] Furthermore, it has a predictive value that correlates with the presence of disease in lymph nodes in the regional lymphatic basin. Hence it is a procedure that could be used in a setting in which there was no definitive diagnosis of malignancy, such as when a patient presents with a melanocytic lesion of uncertain behavior. Although virtually any melanoma involving the dermis has the potential to metastasize, current protocols for sentinel lymphadenectomy only include those in which the thickness is greater than 1 mm. Conversely, because the likelihood of regional lymph node involvement is so great in lesions 4 mm thick or more, sentinel lymphadenectomy is not routinely performed. Although these criteria are reasonable when dealing with a known melanoma, in the setting in which a patient has a melanocytic neoplasm of uncertain behavior, they would of necessity be distinct because the information gained would be used both for diagnosis as well as for staging. Patients with equivocal lesions less than 1.0 mm in thickness with minimal involvement of the papillary dermis (Clark level 2) would not be candidates for sentinel lymphadenectomy because the likelihood of regional nodal metastasis is extremely remote and simple excision with 1-cm margins would be the treatment in all such cases. In patients with equivocal lesions 1.0 mm or more, especially those in which the papillary dermis is filled or the reticular dermis is involved (Clark level 3 or 4), sentinel lymphadenectomy could be offered. In cases in which evaluation of the SLN reveals obvious malignant metastatic disease, the lesion in which the diagnosis was originally questionable would then be known to be malignant. The patient could then be accurately staged by completing the lymphadenectomy of the affected lymph node basin. On the other hand, if evaluation of the SLN revealed no evidence of metastatic disease, especially if the primary lesion was thicker than 4 mm, this would favor the diagnosis of the primary melanocytic lesion as being benign. Because absence of metastatic disease in the SLN is not proof positive that the primary lesion is benign, however, such patients should still be followed up vigilantly but could be given more reassurance about prognosis. Sentinel lymphadenectomy, if agreed to by the patient, should be performed shortly after the initial biopsy so that there could be no consideration that the diagnosis had been delayed because of failure to render an unequivocal diagnosis by the pathologist.

It is important that the findings in the sentinel node be correlated with clinical and histologic features of the primary lesion because there are cases in which benign melanocytic processes may spread to local lymph nodes. Some of these include blue nevi,

compound nevi, and some Spitz nevi. Thus it remains important to ensure that one of these benign simulators of metastatic melanoma not be confused with metastatic disease. When the morphology of cells in lymph nodes is compared with that of the primary lesion, however, they are usually similar. Furthermore, nevus cells involving lymph nodes are usually present in the subcapsular area only and not in the nodal parenchyma. Thus, although there is a possibility that cells of nevi and melanoma in lymph nodes may be confused, this is relatively uncommon. In lesions in which the diagnosis remains in doubt, other studies such as fluorescence in situ hybridization in search of genetic abnormalities could also be used.

CONCLUSIONS

The accurate diagnosis of melanoma remains one of the most important and most challenging aspects of dermatology and dermatopathology. Furthermore, as more effective adjuvant therapy is developed, the correct staging of patients with melanoma will become even more important. Sentinel lymphadenectomy is a promising technique that provides accurate staging with minimal morbidity. Because of its low morbidity, we propose that its use be expanded to selected cases in which patients have melanocytic lesions that cannot histopathologically be diagnosed with certainty. By so doing, the accuracy of diagnosis of this subset of melanocytic neoplasms may be increased with obvious benefits to both patients and their physicians.

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