Pathology Review of Cases Presenting to a Multidisciplinary Pigmented Lesion Clinic

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Objectives: To determine if pathology review, within the context of a multidisciplinary pigmented lesion clinic, results in changes in diagnosis of melanocytic lesions and to ascertain if the change in diagnosis altered clinical management and outcome.

Methods: Retrospective review of pathology reports, progress notes, and diagnoses entered in the University of Pennsylvania (Philadelphia) Pigmented Lesion Clinic database.

Results: A total of 5136 primary melanocytic lesions from patients referred to the pigmented lesion clinic between 1991 and 1999 were reviewed by a single pathologist. Of these, 559 (11%) had diagnoses that were changed significantly from the submitting diagnosis, with 120 (2.3%) undergoing a “critical” revision, 63 (1.2%) defined as a change from malignant to benign, and 57 (1.1%) from benign to malignant; 171 (3.3%) remained within the same category (benign or malignant) but had a downgrade in diagnosis (less severe) that would have a significant impact on treatment, prognosis, and research. Likewise, 268 (5.2%) remained within the same category but had an upgrade in diagnosis (more severe) that would have a significant impact on the same parameters. In addition, 257 reexcisions of melanocytic lesions were reviewed, of which 15 (5.8%) were changed from clear to involved margins, while another 16 (6.2%) were changed from involved to clear margins, for a total of 12%. Of the lesions with a critical revision, follow-up was obtained in 98 (83%). The patients in the malignant-to-benign category were followed up for an average of 2.6 years while those in the benign-to-malignant category were followed up for an average of 4.2 years. The change of diagnosis from malignant to benign resulted in 9 patients (17%) being spared a reexcision while 12 patients (23%) were downgraded from a radical to moderate reexcision. The change in diagnosis from benign to malignant resulted in 45 patients (98%) requiring a reexcision after review. Twenty-five of these patients were found to have residual disease in their reexcision specimens or had already had recurrence at the excision site. Furthermore, 7 patients (15%) underwent lymph node dissection or sentinel lymph node biopsy after review. However, none of the nodes were positive for metastatic disease. During this time, 8 patients (17%) in the benign-to-malignant category, and 1 patient (1.9%) in the malignant-to-benign category (who had previously had 4 primary melanomas) developed metastatic disease.

Conclusions: Pathology review of primary melanocytic lesions, within the context of a multidisciplinary pigmented lesion clinic, results in changes in diagnosis in a significant proportion of cases. These changes have important implications for clinical decision making, patient outcome, and research data collection.

Arch Dermatol. 2002;138:617-621

Several studies have shown that despite the existence of well-established criteria for the diagnosis and microscopic staging of melanocytic lesions, there is still considerable disagreement among pathologists when faced with actual histologic specimens. Misdiagnosis and/or incorrect microscopic staging of melanocytic lesions can result in unnecessary psychological distress to the patient, undertreatment or overtreatment, inaccurate prognosis and improper follow-up, and family member surveillance. Research efforts to further elucidate the biologic and clinical behavior of melanoma are also hindered.

Pathology review of all melanocytic lesions that are sent to us from outside facilities is an established practice in our multidisciplinary pigmented lesion clinic (PLC). We sought to determine the frequency and characterize the types of changes in histopathologic diagnosis that resulted from our PLC pathology review process, hypothesizing that pathology re-
METHODS

A total of 539 melanocytic lesions of discrepant pathologic diagnosis were identified out of 5136 melanocytic lesions that were referred to our PLC for management. In all cases, there was an established outside diagnosis. No cases were referred for medicolegal reasons. Each lesion was reviewed by a single dermatopathologist (D.E.E.) in our PLC between 1991 and 1999. In difficult cases, the lesions were reviewed and discussed with other intrastitutional dermatopathologists, and diagnosis was achieved by consensus.

Two basic categories of altered diagnosis were identified: (1) a “critical” revision and (2) an upgrade or downgrade in diagnosis. A critical revision was defined as a change from a benign to malignant lesion or vice versa. The subcategories included:

1. malignant melanoma (MM) ↔ banal nevus
2. MM ↔ dysplastic nevus
3. MM ↔ other

An upgraded or downgraded diagnosis was defined as a lesion that remained within the same category (either benign or malignant), but whose revised diagnosis would alter the management and/or outcome of that patient. The subcategories included:

1. dysplastic nevus ↔ banal nevus
2. MM ↔ equivocal (deep)
3. MM ↔ Melanoma in situ
4. MM AJCC stage II ↔ MM AJCC stage I

To accommodate all of the changes identified, an additional subcategory “MM to equivocal (superficial)” was included under downgraded diagnoses. Under upgraded diagnoses, the subcategories “banal nevus to equivocal (superficial)” and “dysplastic nevus to equivocal (superficial)” were added.

RESULTS

Of the 5136 lesions reviewed, 539 (11%) had diagnoses that were changed significantly from the submitting diagnosis, with 120 (2.3%) undergoing a “critical” revision (Table 1). Of these, 63 (1.2%) diagnoses were changed from malignant to benign, of which 13 (0.25%) were changed from MM to banal nevus, 49 (0.95%) were changed from MM to dysplastic nevus, and 1 (0.02%) was changed from MM to an actinic lentigo.

Fifty-seven diagnoses (1.1%) were changed from benign to malignant, with 20 (0.39%) changing from banal nevus to MM, 25 (0.49%) changing from dysplastic nevus to MM and 12 (0.23%) changing from “other” to MM. The “other” category included 5 Spitz nevi, 1 cellular blue nevus, 1 traumatic neuroma, 1 seborrhoeic keratosis, 1 basal cell carcinoma, 1 subacute dermatitis, 1 stasis dermatitis, and 1 actinic change with fibrosis.

As noted above, equivocal lesions were divided into 2 major categories: “superficial” and “deep” equivocal melanocytic lesions (EML). “Superficial” EML were intraepidermal or predominantly intraepidermal lesions believed to have possible locally recurrent but not metastatic potential. Examples of an “intraepidermal” EML descriptive diagnosis include “atypical intrapethelial melanocytic proliferation suggestive but not diagnostic of evolving melanoma in situ” and “severe melanocytic dysplasia with focal pagetoid melanocytic proliferation cannot rule out evolving melanoma in situ.”

“Deep” EML were lesions with a dermal component, believed to have possible metastatic potential, for example, “melanocytic tumor of uncertain malignant potential” and “atypical dermal-epidermal melanocytic proliferation.” Typically, such descriptive diagnoses were accompanied by a comment or note indicating that a benign diagnosis was favored, but that an unusual form of melanoma could not be ruled out. Thus, a “superficial” EML diagnosis may favor a melanoma in situ, but the biopsy specimen does not meet all the pathologic criteria required to definitively make the diagnosis, while a “deep” EML diagnosis is a descriptive diagnosis in which the differential diagnosis lies between a benign lesion involving the papillary and/or the reticular dermis (such as a Spitz, pigmented spindle cell, or cellular blue nevus), and a level III or IV malignant melanoma. In the initial period of the study, the term “atypical melanocytic lesion” was commonly used. Currently, we favor the terminology “melanocytic tumor of uncertain potential,” with an explanatory note presenting the differential diagnostic possibilities.

For the critical revision category, patient charts were obtained and reviewed for change in management and outcome. For the upgraded/downgraded diagnoses, the changes were simply tabulated.

A third category, changes in reexcision specimens, was also identified. These changes, either involving margins to clear reexcision or vice versa, were also recorded.
Table 1. Changes in Primary Melanocytic Lesion Diagnosis*

<table>
<thead>
<tr>
<th>Change</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant to benign</td>
<td></td>
</tr>
<tr>
<td>MM to banal nevus</td>
<td>13</td>
</tr>
<tr>
<td>MM to dysplastic nevus</td>
<td>49</td>
</tr>
<tr>
<td>MM to other</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>63 (1.2)</td>
</tr>
<tr>
<td>Benign to malignant</td>
<td></td>
</tr>
<tr>
<td>Banal nevus to MM</td>
<td>20</td>
</tr>
<tr>
<td>Dysplastic nevus to MM</td>
<td>25</td>
</tr>
<tr>
<td>Other to MM</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>57 (1.1)</td>
</tr>
<tr>
<td>Downgraded diagnosis</td>
<td></td>
</tr>
<tr>
<td>Dysplastic nevus to banal nevus</td>
<td>80</td>
</tr>
<tr>
<td>MM to equivocal (superficial)</td>
<td>27</td>
</tr>
<tr>
<td>MM to equivocal (deep)</td>
<td>17</td>
</tr>
<tr>
<td>MM AJCC stage II to I</td>
<td>36</td>
</tr>
<tr>
<td>MM to MIS</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>171 (3.3)</td>
</tr>
<tr>
<td>Upgraded diagnosis</td>
<td></td>
</tr>
<tr>
<td>Banal nevus to dysplastic nevus</td>
<td>147</td>
</tr>
<tr>
<td>Banal nevus to equivocal (superficial)</td>
<td>24</td>
</tr>
<tr>
<td>Dysplastic nevus to equivocal (superficial)</td>
<td>8</td>
</tr>
<tr>
<td>Equivocal (deep) to MM</td>
<td>3</td>
</tr>
<tr>
<td>MM AJCC stage I to II</td>
<td>21</td>
</tr>
<tr>
<td>MIS to MM</td>
<td>65</td>
</tr>
<tr>
<td>Total</td>
<td>268 (5.2)</td>
</tr>
<tr>
<td>Total No. of Changes</td>
<td>559 (10.9)</td>
</tr>
<tr>
<td>Total No. of Lesions Reviewed</td>
<td>5136</td>
</tr>
</tbody>
</table>

*MM indicates malignant melanoma; AJCC, American Joint Committee on Cancer; and MIS, melanoma in situ.

Moreover, these changes may lead to important modifications in management, such as a wide reexcision and/or lymph node dissection when a benign lesion is upgraded to malignant lesion, or may spare a patient from the same when their lesion is downgraded from malignant to benign. It is important to note that the biologic behavior of the lesions supports the change in histologic diagnosis. In other words, in the benign-to-malignant category, there was a rate of metastatic disease of 17%, compared with a rate of 2% in the malignant-to-benign category. The 1 death in the malignant-to-benign category was most likely due to the presence of 4 additional primary melanomas, at least 1 of them high risk.

Potential difficulties in interpreting these data include the following: (1) the majority of patients in the malignant-to-benign category were originally treated as though they had a malignant lesion; (2) there was often a delay in the treatment in cases of a change from benign to malignant (though because this is a prospective clinical referral series, these delays were typically measured in weeks, a time frame that has not been associated with increased risk in the literature); and (3) the benign-to-malignant group was followed up for an average of 4.2 years compared with only 2.6 years in the malignant-to-benign category. Indeed, in neither case is the follow-up long enough to rule out late metastasis.
To our knowledge, there are only 2 other studies that have evaluated this type of review process for melanocytic lesions. The first study was performed by Porkka et al at the Massachusetts General Hospital PLC (Boston). This study evaluated a total of 139 lesions and found that the outside diagnosis was changed in 59.7% of cases. However, discrepancies between the 2 studies may well be accounted for by different criteria for judging pathologic discrepancy, the much smaller number of lesions examined in their study and possibly different referral base (eg, a greater proportion of general pathologists vs dermatopathologists in one or the other study).

The second study was performed by Kronz et al at the Johns Hopkins Medical Center (Baltimore, Md) as part of a larger study examining the role of mandatory second opinion of surgical pathology. In this study, a rate of diagnostic change of 2.9% was found for skin lesions, where a change in diagnosis was defined as “a discordant diagnosis resulting in a major modification in therapy or prognosis.” However, the total number of specimens was relatively small and the changes involving a modification of tumor grade or stage were not included. Thus, when compared with our study, the numbers are comparable only when the benign-to-malignant and malignant-to-benign categories are considered.

The use of pathology review for other cancers, including gynecologic cancers, testicular cancer, prostate cancer, bladder cancer, lymphoma, and sarcoma, in contrast, has been repeatedly examined and reclassified as benign, resulting in cancellation of 6 surgical procedures. The benefits of review are likewise demonstrated in gynecologic and prostate cancer literature. In a review by Santoso et al of 720 gynecologic cancers, 2% were found to have major discrepancies, which resulted in the cancellation of 6 surgical procedures, the modification of 2 others, the addition of radiation therapy to 1, the addition of chemotherapy to 1, and the cancellation of 5 other chemotherapy treatments. Similarly, Epstein et al examined 535 cases of needle biopsies of the prostate that were referred to the Johns Hopkins University Medical Center with the diagnosis of adenocarcinoma, and found that 1.3% were reclassified as benign, resulting in cancellation of 6 surgical procedures. The benefits of review are likewise realized when it results in proper risk assessment and surveillance of family members.

Additionally, the elimination of unnecessary procedures as well as the theoretical decrease in metastatic disease may have significant financial benefits both to the patient with melanoma and the health care system overall. Again, these benefits have already been demonstrated in other cancers. Wurzer et al at Fox Chase Cancer Center, looked at 538 pathology reports of prostate biopsies and found that while the pathology review added approximately $104 per case, the changes in treatment decisions that resulted from the review had a savings in health dollars of over $12000 for the 538 cases reviewed. Similarly, in the Epstein et al study, a net savings of approximately $40000 was found.

With respect to research benefits, review by an experienced pathologist offers not only the advantage of diagnoses that are internally consistent, but also a valuable second opinion. These 2 factors are crucial in developing an accurate and reliable database that can be used to study the biologic and clinical behavior of melanoma and other cancers. For example, Sharkey and Sarosdy evaluated the review of transitional cell carcinoma in situ for clinical studies and concluded that the “lack of a well-accepted standard for the histopathologic diagnosis of transitional cell carcinoma in situ poses a major problem for multi-institutional studies of this disease” and that “central review of pathological specimens is essential to maintain data integrity.” Likewise, Kempson, upon analysis of many pathology review studies, concluded that “pathology quality control is an essential part of clinical cancer research.”

In summary, our study corroborates other studies demonstrating that review of melanocytic lesions by an experienced pathologist results in a change in diagnosis in a significant number of cases. Furthermore, these histologic changes are supported by the biologic behavior as demonstrated by the greater incidence of metastatic disease in the benign-to-malignant group. More important, these changes play a vital role in clinical management decisions as shown by the number of patients who were spared reexcisions as well as those who benefited from the more aggressive therapy that their revised diagnosis implied.

These findings provide not only further testimony to the difficulty of melanocytic lesion histopathologic diagnosis, but also present a strong argument in support of the practice of pathology review on both clinical and research grounds. While review of all melanocytic lesions is an unreasonable expectation, pathology review appears to be warranted, at least in unusual lesions or when clinical-pathological disparity exists.

Accepted for publication November 29, 2001.

This study was supported by grants P30 CA 16520, PO1 CA 75343, and K24 AR 02102 from the National Institutes of Health, Bethesda, Md.

This work was presented as a poster at the American Society of Clinical Oncology Meeting, New Orleans, La, May 20–23, 2000.

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REFERENCES


The Regional Conference on Dermatological Laser and Facial Cosmetic Surgery 2002 will be held from September 13-15, 2002, at the new wing of the Hong Kong Convention and Exhibition Center. The conference is jointly organized by the University of Hong Kong, the Hong Kong Society of Dermatology and Venereology, and the Hong Kong Society of Plastic & Reconstructive Surgeons.

Renowned authorities to speak at the conference include Dr Yung-Lung Lai (Chang Gung Memorial Hospital, Taiwan), Dr Dieter Manstein (Harvard Medical School, United States), Prof Rolf Nordstrom (Nordstrom Hospital for Plastic and Reconstructive Surgery, Finland), Dr Niwat Polnikorn (Ramathibodi Hospital, Thailand), and Dr Wolffs Wu (Woflles Wu Aesthetic Surgery and Laser Center, Singapore).

For more information on the conference, please contact the secretariat at phone (852) 23278898; fax: (852) 28667330, or e-mail: cosfmshk@netvigator.com.