Prevalence of Melanoma Clinically Resembling Seborrheic Keratosis

Analysis of 9204 Cases

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Objective: To estimate the prevalence of melanoma clinically mimicking seborrheic keratosis.

Design: Retrospective review of cases submitted for histological examination with a clinical diagnosis of seborrheic keratosis or with a differential diagnosis that included seborrheic keratosis.

Setting: A tertiary medical care center-based dermatopathology laboratory serving academic dermatology clinics that have a busy pigmented lesion clinic.

Materials and Methods: A total of 9204 consecutive pathology reports containing a diagnosis of seborrheic keratosis in the clinical information field were identified between the years 1992 and 2001 through a computer database search. Reports with a final histological diagnosis of melanoma were selected for further review and clinicopathological analysis.

Main Outcome Measures: Histological diagnosis, which was correlated with the preoperative clinical diagnosis.

Results: Melanoma was identified in 61 cases (0.66%) submitted for histological examination with a clinical diagnosis that included seborrheic keratosis. Melanoma was in the clinical differential diagnosis of 31 cases (51%). The remaining lesions had a differential diagnosis of seborrheic keratosis vs melanocytic nevus (17 cases, 28%), basal cell carcinoma (7 cases, 12%), or a squamous proliferation (3 cases, 5%). In 3 cases (5%), seborrheic keratosis was the only clinical diagnosis. All histological types of melanoma were represented.

Conclusions: Our results confirm that melanoma can mimic seborrheic keratosis. These data strongly support the current policy of submitting for histological examination all specimens that have been removed from patients.

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SEBORRHEIC KERATOSIS is one of the most common benign neoplasms in adults. Seborrheic keratoses begin to appear after the age of 30 years in genetically susceptible individuals and continue to develop throughout their life span. These lesions account for a large number of physician visits and have an associated significant health care cost. Most clinically diagnosed seborrheic keratoses are untreated or removed by cryotherapy without histological confirmation of the diagnosis despite limited accuracy of the clinical diagnosis of seborrheic keratosis.1-5

Seborrheic keratoses are most often confused clinically with actinic keratoses or benign conditions such as solar lentigo or viral warts, with relatively little consequence for prognosis or therapy. In contrast, misdiagnosis of skin cancer, especially melanoma, as seborrheic keratosis might have untoward implications for the patient, as both diagnostic procedures and treatments may be suboptimal. For these reasons, clinicians must balance a high index of suspicion for malignancy in clinically diagnosed seborrheic keratoses against the impracticality and costs of histological evaluation of all lesions. Thus, appropriate clinical management of seborrheic keratosis requires an understanding of the frequency with which melanoma clinically mimics this benign lesion.

We have encountered several cases of melanoma clinically resembling seborrheic keratosis in our dermatopathology practice at the Massachusetts General Hospital Dermatopathology Unit and in our clinical practice at the Massachusetts General Hospital Pigmented Lesions Clinic, Boston. Two small retrospective series addressing this issue identified 2 cases of melanoma among 577 specimens6 and 1 case among 328 specimens7 submitted for histological examination with a clinical diagnosis that included seborrheic kerato-
sis. Seborrheic keratosis was one of the most common nonmelanoma diagnoses in retrospective studies that examined the accuracy of clinical diagnosis of histologically confirmed melanomas.\textsuperscript{7-16}

In the present article, we assess the prevalence of melanoma resembling seborrheic keratosis in our tertiary medical care center–based dermatopathology practice serving a large academic dermatology practice and a busy pigmented lesion clinic and provide a clinicopathological analysis of identified cases.

**METHODS**

Pathology reports generated at the Massachusetts General Hospital Dermatopathology Unit from 1992 to 2001 were searched to identify those cases in which the clinical diagnosis of seborrheic keratosis was entered as the primary diagnosis or was included in the differential diagnosis for the submitted specimen. This search yielded 9204 reports, from which 61 cases with the histopathological diagnosis of melanoma were identified for further analysis. The vast majority of our laboratory’s material is submitted by dermatologists from Massachusetts General Hospital dermatology clinics, including the Massachusetts General Hospital Pigmented Lesion Clinic, which are staffed by full- and part-time clinical staff supervising residents and fellows. Community dermatologists and Massachusetts General Hospital surgical and medical services submit a small percentage of cases. In our practice, residents and fellows do not make decisions regarding biopsy specimens without the input of staff members.

Clinical analysis involved a review of patients’ charts for any clinical and historical information relevant to the diagnosis of melanoma, including site, clinical appearance, clinical differential diagnosis, and personal or family history of melanoma. Data were collected in accordance with the institutional and National Institutes of Health guidelines for clinical studies, and the experimental protocols were approved by the institutional review board.

Pathological analysis included a review of available diagnostic material from biopsy or excision specimens, which consisted of formalin-fixed, paraffin-embedded sections stained with hematoxylin-eosin. Histological information included maximal tumor thickness, Clark anatomical level of invasion, presence of ulceration, evidence of regression, presence of microsatellites, evidence of precursor lesion, and lymphovascular invasion.

**RESULTS**

In our series, of the 9204 consecutive lesions clinically diagnosed as seborrheic keratosis or with seborrheic keratosis in the differential diagnosis, 61 (0.66%) revealed melanoma on histological examination. Of note, melanoma was included in the clinical differential diagnosis in only 50% of these cases. Based on the clinical description and clinical differential diagnosis, the remaining cases can be divided into 4 broad diagnostic categories: (1) cases in which seborrheic keratosis was the only diagnostic consideration; (2) cases in which the differential diagnosis was between seborrheic keratosis and a squamous lesion, malignant or benign; (3) cases in which the differential diagnosis was between seborrheic keratosis and basal cell carcinoma; and (4) cases in which the differential diagnosis was between seborrheic keratosis and a melanocytic nevus.

Table 1. Demographic and Clinical Characteristics of Patients With Melanoma Clinically Resembling Seborrheic Keratosis

<table>
<thead>
<tr>
<th>Clinical Diagnostic Group (n)</th>
<th>Mean Age, y</th>
<th>M/F Ratio</th>
<th>Distribution*</th>
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<tbody>
<tr>
<td>All cases (61)</td>
<td>60.5</td>
<td>37/24 (1.54)</td>
<td>20 H/N, 23 T, 18 E</td>
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<tr>
<td>Seborrheic keratosis (3)</td>
<td>61.3</td>
<td>0/3</td>
<td>1 H/N, 2 E</td>
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<tr>
<td>Seborrheic keratosis vs squamous proliferation (3)</td>
<td>75.3</td>
<td>1/2 (0.5)</td>
<td>1 H/N, 2 E</td>
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<tr>
<td>Seborrheic keratosis vs basal cell carcinoma (7)</td>
<td>61.8</td>
<td>3/4 (0.75)</td>
<td>1 H/N, 4 T, 2 E</td>
</tr>
<tr>
<td>Seborrheic keratosis vs melanocytic nevus (17)</td>
<td>55.8</td>
<td>9/8 (1.12)</td>
<td>4 H/N, 7 T, 6 E</td>
</tr>
<tr>
<td>Seborrheic keratosis vs melanoma (31)</td>
<td>61.3</td>
<td>24/7 (3.4)</td>
<td>13 H/N, 12 T, 6 E</td>
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*H/N indicates head/neck; T, trunk; and E, extremities.

Demographic and clinical information about the identified cases is summarized in Table 1. We found a slight male predominance among the patients, and 54 patients (80%) were 50 years of age or older. The lesions were distributed almost equally on the head and neck region, extremities, and trunk. As expected, the trunk was the most common site in men (16 of the 37 cases); the extremities were the most common site in women (11 of the 24 cases).

Of note, but without obvious explanation, all 3 cases in which seborrheic keratosis was the only clinical consideration occurred in women. The choice of diagnostic procedure depended on the clinical differential diagnosis. Eight lesions (85%) with the clinical differential diagnosis of squamous proliferation or basal cell carcinoma were sampled as shave biopsy specimens. Shave biopsy specimens were obtained in 18 cases (37%) in which a melanocytic lesion was included in the clinical differential diagnosis. The rest of the cases were submitted as punch biopsy (n=19 [39%]) or excision (n=9 [19%]) specimens. One case clinically diagnosed as seborrheic keratosis was submitted as a curettage specimen. The remaining 2 cases were shave biopsy specimens.

A clinicopathological analysis of the cases is summarized in Table 2. The diagnosis of melanoma was considered in the clinical differential diagnosis of 31 specimens (51%). Seborrheic keratosis was the only clinical diagnosis in 3 cases (5%). One lesion was described as an inflamed stucco keratosis. All 3 lesions were invasive melanomas, with a mean thickness of invasion of 0.84 mm. One case was a superficial spreading melanoma, one was lentigo maligna melanoma, and the third was an invasive melanoma not further classified.

In 3 cases (5%), a differential diagnosis of seborrheic keratosis vs a squamous lesion was considered. Suspected squamous lesions included squamous cell carcinoma (2 cases) and clear cell acanthoma vs large cell acanthoma (1 case). Both cases with the differential diagnosis including squamous cell carcinoma turned out to be superficial spreading melanomas invasive to 2.3 and 2.8 mm, respectively.

In 7 cases (12%), biopsy specimens were obtained to differentiate between seborrheic keratosis and basal
cell carcinoma. In 5 cases, the clinical impression was pigmented basal cell carcinoma. Histologically, 3 lesions were melanomas in situ. Four lesions were invasive melanomas, with a mean thickness of 1.2 mm. Histological types of invasive melanoma included lentigo maligna (1 case) and nodular (1 case) and 2 cases in which subtyping could not be made.

Finally, a differential diagnosis of seborrheic keratosi
vs benign melanocytic nevus was considered in 17 cases (28%). Clinical diagnoses included dysplastic/atypical nevus (10 cases), lentigo (4 cases), and benign nevus (5 cases). In this group, histological examination revealed that 7 melanomas were in situ. Ten melanomas were invasive, with a mean maximal depth of invasion of 0.98 mm. Histological types of melanoma in this group included superficial spreading (2 cases), lentigo maligna (3 cases), nevoid (1 case), desmoplastic (1 case), and acral lentiginous (1 case). Two melanomas were not further classified. None of the cases represented melanoma arising in a seborrheic keratosis or collision between melanoma and a seborrheic keratosis.

Reflecting the pattern of referrals in our laboratory’s practice, in 54 cases the diagnosis was made by a dermatologist. A plastic surgeon and internist submitted 1 case each. In 5 cases submitted from outside institutions as second-opinion consultations, the subspeciality of the physician performing the biopsy was not established. Two of the cases submitted as seborrheic keratosis without the differential diagnosis were diagnosed by dermatologists, and 1 case was diagnosed by a plastic surgeon.

In our series of 9204 consecutive cases submitted for histological examination in which a clinical diagnosis of seborrheic keratosis, or in which a differential diagnosis that included seborrheic keratosis, was made, the prevalence of melanoma was 0.66%. Only half of the cases represented true diagnostic mistakes, as in 51% cases the clinical differential diagnosis included melanoma. This prevalence is similar to that reported in previously published smaller retrospective series,\textsuperscript{5,6} which established a prevalence of 0.3% for melanoma in lesions submitted for histological examination in which a clinical diagnosis of seborrheic keratosis had been made.

Our results are in agreement with those of a number of previous studies that retrospectively investigated the clinical diagnoses of histologically confirmed melanomas.\textsuperscript{7-17} Those studies clearly illustrated that the clinical diagnostic accuracy of melanoma ranges from 48% to 67%. They also confirmed that seborrheic keratosis is one of the lesions for which melanoma is commonly misdiagnosed. This error occurred in 7.7% to 31.0% of cases, depending on the study.

Seborrheic keratoses come to clinical attention for cosmetic reasons; for symptoms associated with the lesions, such as itching or inflammation; or for an atypical clinical appearance that necessitates the exclusion of a malignant lesion. Most seborrheic keratoses in the first category and many in the second are correctly diagnosed clinically and followed up or are treated using cryotherapy, without histological confirmation of the diagnosis. Lesions removed for histological examination are more likely to be atypical. Consequently, our results reflect the prevalence of melanoma in lesions resembling seborrheic keratoses submitted for histopathological examination rather than in all seborrheic keratoses. Consistent with this assumption, only 3 (5%) of the 61 melanomas had seborrheic keratosis as the only clinical diagnosis. Detailed review of the charts revealed that 2 of these 3 lesions closely resembled seborrheic keratosis, and 1 was believed to be an inflamed seborrheic keratosis. This is an important observation, as it illustrates that melanoma can appear clinically identical to seborrheic keratosis. Because we studied only seborrheic keratosis–like lesions submitted for histological examination, the true prevalence of melanoma in all clinically diagnosed and normal-appearing seborrheic keratoses cannot be determined. However, common sense would suggest that it is much lower than 0.66%.

Based on our results, melanomas mimicking seborrheic keratoses can be divided into 3 principal clinical categories, each associated with a different set of clini-

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<th>Table 2. Clinicopathological Analysis of Melanomas Clinically Resembling Seborrheic Keratosis</th>
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<td><strong>Clinical Diagnostic Group</strong></td>
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* LMM indicates lentigo maligna melanoma; SSM, superficial spreading melanoma; NM, nodular melanoma; and NOS, not otherwise specified.
Histological sections of a curettage specimen from a lesion clinically diagnosed as seborrheic keratosis. A, At scanning magnification, it has a verrucous architecture, hyperkeratosis, and acanthosis reminiscent of seborrheic keratosis (hematoxylin-eosin, original magnification ×40). B, Examination at higher magnification reveals diagnostic features of an underlying melanoma (hematoxylin-eosin, original magnification ×200).

Most problematic is the group of lesions in which the diagnosis of melanoma or other malignancy is not suspected clinically, since the presumed seborrheic keras- toses were removed for cosmetic reasons or because of inflammation. Such lesions may not be treated at all or may be treated by locally destructive methods, without histological confirmation. As in this series, even when submitted for histological examination, lesions in this category are most likely to be sampled by superficial shave biopsies or submitted as curettage specimens. Because of scant tissue, the dermatopathological interpretation of such specimens can be very difficult. This point is well illustrated in the Figure, which shows histological features of a curetted lesion with the presumptive clinical diagnosis of seborrheic keratosis. The verrucous architecture, hyperkeratosis, acanthosis, and inflammatory infiltrate of this lesion are all very reminiscent of seborrheic keratosis. Moreover, superficial shave biopsy or curettage specimens do not provide optimal prognostic indicators in melanoma, eg, maximal tumor thickness, which are critical for clinical management. It is important to emphasize that this group of lesions with a sole diagnosis of seborrheic keratosis contained 2 (66%) deeply invasive melanomas with a significant risk of metastasis and mortality.

The third group comprises lesions in which seborrheic keratosis was clinically considered along with an atypical squamous lesion, such as invasive or in situ squamous cell carcinoma. Clinical management of these lesions is likely to be appropriate, as suspected squamous lesions are usually adequately sampled.

Melanomas with a clinical differential diagnosis of seborrheic keratosis and basal cell carcinoma are not a surprising occurrence, as some basal cell carcinomas, as do most melanomas, present as pigmented lesions. Misdiagnosis of melanoma as seborrheic keratosis or pig- mented basal cell carcinoma may have adverse management implications, as both lesions are likely to be sampled by superficial shave biopsies, which may compromise definitive pathological diagnosis and prognostic information needed for further management.

Finally, lesions resembling benign pigmented lesions, such as lentigo and common or dysplastic/atypical nevi, may represent melanoma. Clinical management of these lesions will most likely include sampling of representative tissue via punch biopsy, deep shave biopsy, or excision.

Clinicopathological analysis of melanomas in the present study revealed that all histological types of melanoma can mimic a seborrheic keratosis. Because the number of invasive melanomas in each diagnostic group was small, it is difficult to make definitive statements regarding the association between a particular histological type of melanoma and a particular clinical appearance of the lesion. It is likely that melanomas clinically resembling seborrheic keratosis may share certain histological features of seborrheic keratosis, such as acanthosis, hyperkeratosis, horn pseudocysts, epidermal hyperpigmentation, and verrucoid or papillo- matous architecture. The case illustrated in the Figure supports this notion. However, comprehensive study of this issue would require rigorous comparison of histo- logical features of melanomas clinically mimicking seborrheic keratosis with those of clinically typical melanomas, a topic beyond the scope of the present study. Of interest is the presence of 2 cases of nevoid melanoma, a verrucous hyperkeratotic variant of which is especially likely to resemble seborrheic keratosis clinically. Finally, although several cases of melanoma arising within seborrheic keratosis have been reported, none of the lesions in our study had the features of a collision between melanoma and seborrheic keratosis or evidence of melanoma arising in an existing seborrheic keratosis.

In conclusion, our results estimate the prevalence of melanoma in lesions clinically resembling seborrheic keratosis and submitted for histological examination at 0.66%. This observation supports the current policy of submitting all specimens removed from patients for histological examination.

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REFERENCES


