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Case 2-2007: A 49-Year-Old Woman with a Pigmented Lesion on the Arm

John F. Thompson, M.D., F. Stephen Hodi, M.D., and Artur Zembowicz, M.D.

PRESENTATION OF CASE

A 49-year-old woman was seen in the outpatient surgical clinic of this hospital because of a diagnosis of melanoma.

The patient had noted a flat, pigmented lesion on her left upper arm approximately 1 year earlier. Three months later, it began to itch and became slightly raised. Approximately 3 months before the current evaluation, the lesion began to bleed when she scratched it. She saw a dermatologist at another facility, who performed a punch biopsy. Pathological examination was reported to show an atypical Spitz tumor; reexcision was recommended. The lesion was reexcised; pathological examination disclosed a superficial, spreading malignant melanoma, 0.91 mm in thickness, with a vertical growth phase and dermal mitoses, extending to within 1.5 mm of the nearest margin. Her dermatologist referred her to this hospital for further care.

The patient had no history of skin cancers, and she felt well. An ovarian cystectomy had been performed at the age of 25 years. She had smoked for 10 years but quit at the age of 29 years, and she drank alcohol occasionally. She had siblings with nonmelanoma skin cancers. Her maternal grandmother had breast cancer at 76 years of age, her aunt at 65 years of age, and a cousin at 45 years of age. Her maternal grandfather had throat cancer in his 70s. Her four children were well.

On physical examination, the patient appeared healthy, and the vital signs were normal. There was a 3-mm linear scar on the left upper posterior arm, with no residual pigmented lesion and no satellite nodules. No other suspicious pigmented lesions were identified. There was no palpable lymphadenopathy. The remainder of the examination was normal.

Three weeks later, wide excision of the surgical site to 1 cm and sampling of the sentinel lymph node after injection of technetium-99–labeled sulfur colloid were performed. Metastatic melanoma was identified on immunohistochemical staining of one of two sampled sentinel nodes. Two weeks later, the patient returned to the clinic for discussion of further care.

PATHOLOGICAL DISCUSSION

Dr. Artur Zembowicz: The excisional biopsy of the lesion (Fig. 1) showed a compound melanocytic proliferation (involving both the epidermis and the dermis) composed

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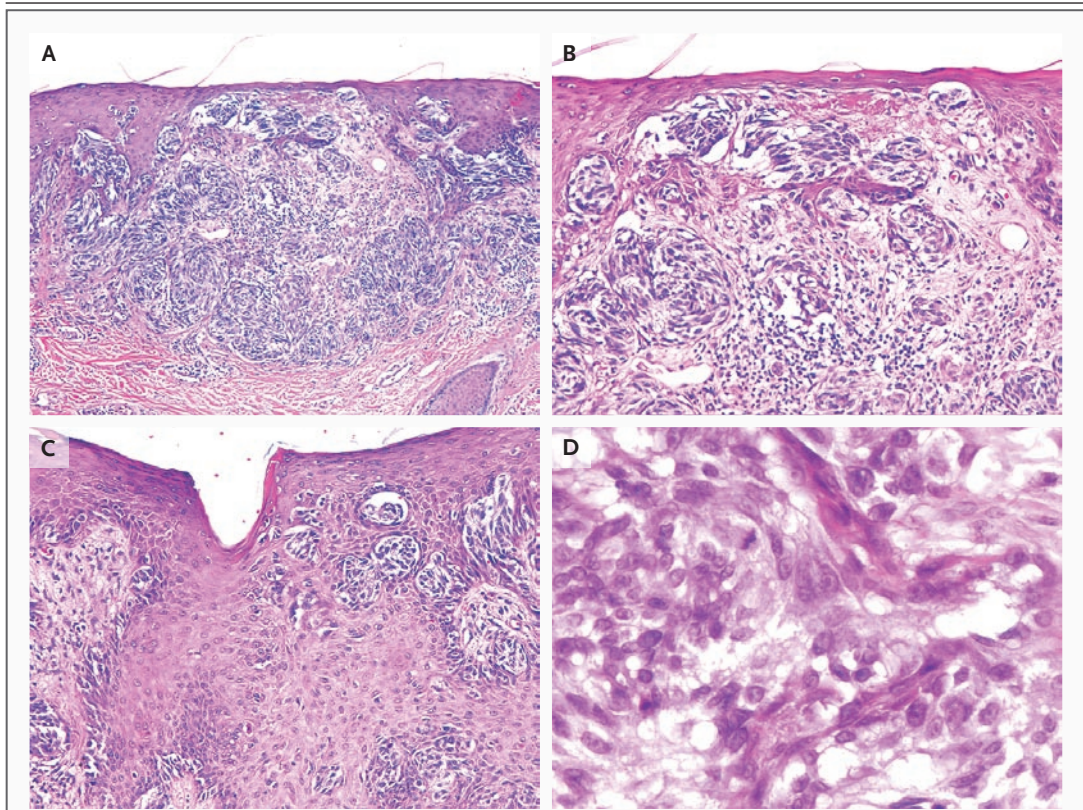


Figure 1. Specimen from the Excisional Biopsy of the Skin Lesion (Hematoxylin and Eosin).

A compound melanocytic proliferation (Panel A) involves both the epidermis and dermis, with effacement of the normal dermoepidermal architecture by a nested melanocytic proliferation (Panel B). Tumor is present within the epidermis in both single-cell and nested patterns, involving the upper portion of the epidermis ("pagetoid spread") (Panel C). At higher magnification (Panel D), the tumor is densely cellular and has a moderate degree of nuclear pleomorphism and hyperchromasia.

of oval and spindled melanocytes. The junctional component (at the dermoepidermal junction) showed a confluent growth pattern, extension into superficial follicular infundibular epithelium, and prominent pagetoid spread. The dermal component showed a cellular melanocytic proliferation formed by expansile, closely apposed nests of cells invading focally into the reticular dermis. Focally, the dermoepidermal junction was effaced by the tumor, with loss of the normal pattern of rete ridges. The tumor cells were uniform in appearance, with moderate hyperchromasia and easily identifiable nucleoli. Dermal mitotic activity, mentioned in the report from the other facility, was not identified in the sections available for review. These features are typical of superficial spreading melanoma.

PATHOLOGICAL PROGNOSTIC FACTORS IN MELANOMA

In addition to establishing the diagnosis of melanoma, the pathological evaluation of biopsy specimens obtained from a patient such as this one includes a report on histologic features that guide the management of the disease. These features are usually listed in a standardized pathology report of melanoma, which differs slightly from institution to institution. The report must include the status of the surgical margins and histologic variables used in the staging system of the American Joint Committee on Cancer (AJCC), which include the presence or absence of ulceration, lymph-node status, and the presence or absence of microscopic satellites (Table 1).¹

Tumor thickness is measured as described by

Table 1. American Joint Commission on Cancer Tumor–Node–Metastasis (TNM) Classification for Clinical Staging of Malignant Melanoma.*

Tumor	Thickness of Lesion	Other Characteristics
T1a	≤1.0 mm	Without ulceration
T1b		With ulceration or Clark level IV or V
T2a	1.01–2.0 mm	Without ulceration
T2b		With ulceration
T3a	2.01–4.0 mm	Without ulceration
T3b		With ulceration
T4a	>4.0 mm	Without ulceration
T4b		With ulceration
Node	No. of Nodes	Other Characteristics
N1a	1	Micrometastasis†
N1b		Macrometastasis‡
N2a	2 or 3	Micrometastasis†
N2b		Macrometastasis†
N2c		In-transit metastases or satellites without metastatic lymph node
N3	≥4 Metastatic or matted lymph nodes or combinations of in-transit metastases or satellites or ulcerated melanoma and metastatic lymph nodes	
Metastasis	Types of Metastases	Other Characteristics
M1	Distant skin, subcutaneous, or lymph-node metastases	Normal lactate dehydrogenase level
M2	Lung metastases	Normal lactate dehydrogenase level
M3	All other visceral or any distant metastases	Normal lactate dehydrogenase level; elevated lactate dehydrogenase level with any metastasis

* Data are adapted from Balch et al.¹

† Micrometastases are diagnosed on lymph-node biopsy.

‡ Macrometastases are clinically detectable and confirmed on biopsy or when any lymph-node metastasis exhibits extra-capsular extension.

Breslow,² from the top of the granular-cell layer of the epidermis or the surface of the ulcer to the point of the deepest invasion of the melanoma. The presence and size of the surface ulceration recently emerged as the most important features modifying the predictive prognostic value of tumor thickness.^{3,4} Microscopical satellites (nests of melanoma cells >0.05 mm in diameter that are separated from the main body of the tumor by normal tissue) correlate with the presence of lymph-node metastases and with the risk of local recurrence or death.^{5–8}

At this hospital, the pathology report also includes a number of histologic features that have emerged as independent prognostic indicators in clinical studies but that remain to be validated in large multiinstitutional series. In intermediate or thick melanoma (>1 mm), we report the number of mitoses per square millimeter of tumor, the presence or absence of tumor regression, and the amount of lymphocytic infiltrate around the tumor (host reaction).^{9–11}

Lymphovascular invasion has correlated with the risk of metastases in retrospective studies,¹²

Table 2. Clark Levels of Melanoma Invasion.*

Level	Characteristics
I	Confined to epidermis (in situ); never metastasizes; 100% cure rate
II	Invasion of papillary dermis; invasion past basement membrane (localized)
III	Papillary dermis (localized) filled by tumor and reticular dermis compressed
IV	Invasion of reticular dermis (localized)
V	Invasion of subcutaneous tissue (regionalized by direct extension)

* The information is from Clark et al.⁹

although it is rare and has not had a significant influence on survival in multivariate analysis of data from large series. We also report perineural involvement, which is rare, but when present, it indicates an increased risk of local recurrence.

In thin melanoma (<1 mm), ulceration and the anatomical level of invasion (Clark level) are the only prognostic indicators required for AJCC staging (Table 2). Tumors invading or filling the papillary dermis (Clark level II or III) without ulceration are designated as stage T1a. Tumors with ulceration or invasion of the reticular dermis (Clark level IV) are associated with a worse prognosis and are designated as stage T1b. In a superficial spreading melanoma, which this patient has, we also evaluate the growth phase according to the Clark model of melanoma progression,^{9,13} which may be more accurate than the current AJCC criteria for predicting the outcome. According to this model, centrifugally growing in situ melanoma (the radial growth phase) can be associated with early invasion of the papillary dermis without an increase in the risk of metastases. To progress and metastasize, tumor cells must acquire the ability to invade the reticular dermis (the vertical-growth phase). The identification of histologic features of the vertical-growth phase is subjective, requires training and experience, and has not been widely adopted among pathologists. Finally, we report the presence or absence of tumor regression, since a number of studies point to regression as an important predictor of progression in thin melanoma.¹⁴⁻¹⁶

This patient has a thin melanoma. The staging and prognostic factors are listed in the pathology report shown in Table 3.

EVALUATION OF SENTINEL LYMPH NODE

On sampling of the sentinel lymph nodes, two nodes were harvested and submitted for pathologi-

cal analysis. Current protocols call for the evaluation of multiple sections from sentinel lymph nodes with the use of at least two immunohistochemical stains to help detect micrometastasis. At this hospital, we evaluate three sets of consecutive sections stained with hematoxylin and eosin and the melanocytic immunohistochemical markers S-100 and MART-1, with the sections separated from one another by 250 μ m of tissue.

The relationship between the volume of tumor metastases in the sentinel lymph nodes and the likelihood of the involvement of nonsentinel lymph nodes is an area of active research. Several approaches, including the anatomical distribution of metastases and the surface area of sections occupied by the tumor, are being evaluated. In this case, a single cluster of metastatic melanoma cells was identified on routine pathological examination of the sections of one of two lymph nodes, as confirmed on immunohistochemical staining (Fig. 2). The specimen of skin obtained on reexcision contained no residual melanoma.

DISCUSSION OF MANAGEMENT

SURGICAL MANAGEMENT OF MELANOMA

Dr. John F. Thompson: This patient had a thin melanoma with clear surgical margins of excision. Did she receive adequate surgical treatment?

Excision Margins

There is still some uncertainty about the definitive surgical excision margins that are appropriate for patients with primary melanomas that are more than 2 mm thick.¹⁷⁻²⁰ There is also an ongoing debate about whether margins of 1 cm or 2 cm are required for melanomas that are 1 to 2 mm thick.²¹ However, the general consensus, supported by the results of clinical trials, is that 1-cm margins are adequate and appropriate for invasive primary melanomas less than or equal to 1 mm thick, as in this case, and that margins 0.5 cm in width are adequate for in situ melanoma.²²

Sentinel Lymph-Node Biopsy

Was a sentinel lymph-node biopsy indicated in this case? During the past decade, the introduction, validation, and widespread application of the technique of sentinel-node biopsy have resulted in a completely new paradigm of the initial treatment of patients with primary cutaneous melanoma. Elective radical dissection of the regional lymph-node field has been abandoned, and only patients

found to have metastatic disease in a sentinel lymph node now undergo this procedure. The concept of the sentinel node is simple.²³ Lymphatic mapping is performed usually with both blue dye and a radiolabeled colloid tracer, and afferent lymphatic vessels are traced from the site of the primary melanoma until they reach the regional-node field and enter one or more nodes. Any node receiving direct lymphatic drainage from the primary melanoma site is designated a sentinel node.²⁴ This node is the one most likely to contain metastatic disease, and if the sentinel node is tumor-free, it can be safely assumed that all other nodes in the node field will also be free of tumor.²⁵⁻²⁷ Thus, if there is no evidence of metastatic disease in a sentinel node, complete lymph-node dissection is unnecessary. It is now well established that the sentinel-node biopsy provides the most reliable information for staging and prognosis that is currently available.²⁸⁻³¹

The Role of Sentinel-Node Biopsy in Thin Melanomas

Rates of sentinel-node positivity are well documented for thick melanomas: 10.5% for tumors that are 0.75 to 1.50 mm thick, 23.4% for those that are 1.51 to 4.00 mm thick, and 28.3% for those that are more than 4.00 mm thick.²⁷ Among patients with tumors that are less than or equal to 1 mm thick, the reported positivity rate ranges from 0 to 9.8%, but in most series, the rate is less than 5%.³² The probability of finding a positive sentinel node in patients with thin melanomas depends on whether adverse prognostic factors are present. These factors include ulceration, invasion to Clark level IV or V, an age of less than 45 years, a mitotic rate greater than 0 per square millimeter of tumor tissue, the presence of the vertical-growth phase, and possibly tumor regression and male sex. It therefore seems inappropriate to recommend sentinel-node biopsy for patients with primary melanomas that are less than 1 mm thick unless one or more of these risk factors are present. This patient had a tumor that was only 0.91 mm thick; however, there was invasion to Clark level IV, and a positive sentinel node was found.

Complete Lymphadenectomy after Detection of a Positive Sentinel Node

What should the next step be when the patient is found to have a positive sentinel node? An important but unresolved question is whether all patients with metastatic disease in a sentinel node require

Table 3. Pathology Report for This Patient's Melanoma.

Malignant Melanoma	Finding
Histologic type	Superficial spreading
Tumor thickness	0.9 mm
Clark level	IV
Precursor lesion	Absent
Margins	Not involved
Ulceration	Absent
Microscopical satellites	Absent
Vertical-growth phase	Present
Mitotic activity	Absent
Regression	Absent
Tumor-infiltrating lymphocytes	Absent
Vascular or perineural invasion	Absent

complete lymph-node dissection. Although the interim results of a large multicenter trial³³ have shown no statistically significant overall survival benefit among patients with a positive sentinel node who were treated with immediate complete lymph-node dissection, as compared with patients who did not undergo sentinel-node biopsy the rate of relapse-free survival improved among the patients who underwent complete dissection. Moreover, the survival rates were better for these patients than for those who did not undergo sentinel-node biopsy and in whom clinically detectable disease subsequently developed in regional lymph nodes.

Only about 20% of patients with positive sentinel nodes have metastatic disease in nonsentinel nodes if complete lymph-node dissection is performed, and the percentage is considerably lower among patients with thin melanomas. The volume of tumor in the node and its location within the node (whether subcapsular or more deeply placed) are the likely determinants for identifying patients at high risk for the involvement of nonsentinel lymph nodes. The patient under discussion had low-volume, subcapsular disease in only one of two sentinel nodes sampled, making her risk of having a positive nonsentinel node very low. At present, however, complete lymph-node dissection must be regarded as the standard therapy for any patient found to have a positive sentinel node, because there is no reliable method of predicting nonsentinel-node disease in a patient. A second Multicenter Selective Lymphadenectomy Trial has recently commenced, in which patients who are found to have positive sentinel nodes are randomly assigned either to immediate, complete lymph-

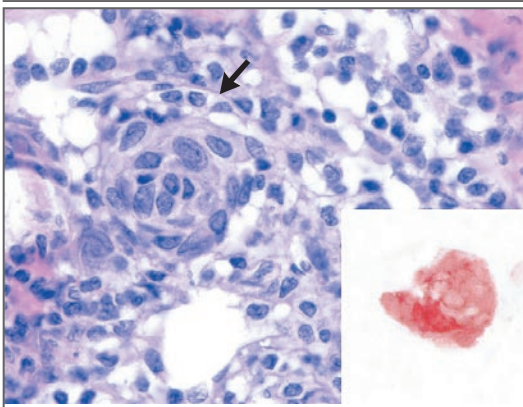


Figure 2. Specimen from the Sentinel Lymph-Node Biopsy (Hematoxylin and Eosin).

A cluster of metastatic melanoma cells (arrow) is present in one of the two sentinel lymph nodes sampled. Immunohistochemical staining of a consecutive section with S-100 (inset) confirmed the melanocytic nature of the cells.

node dissection or to observation with subsequent dissection if metastatic disease in the regional-node field becomes clinically apparent.

In summary, I believe that sentinel-node biopsy was indicated in this case, and although its value is unproved, I would recommend complete axillary lymph-node dissection.

MEDICAL MANAGEMENT OF STAGE IIIa MELANOMA

Dr. F. Stephen Hodi: This patient had AJCC stage IIIa melanoma with microscopic involvement of one lymph node and no evidence of distant metastases. The updated AJCC 2001 staging system¹ represents the most recent prognostic stratification on the basis of the features currently identified in analyses of extensive databases. Of the prognostic features highlighted, this patient's positive sentinel lymph-node status is the most important for recommending further treatment: in patients with stage I or II cutaneous melanoma and clinically negative lymph nodes, the status of the sentinel lymph node is the most significant prognostic factor for recurrence.³⁴ For a patient such as this one with a T1a lesion (<1 mm thick, with no ulceration), the 5-year rate of survival with a negative sentinel-node biopsy is 94%, whereas the rate is only 64% with a positive biopsy.¹

The goal of adjuvant therapies for this patient, who is at marked risk for recurrence, is to improve the overall length of her survival. Decades of clinical

investigation that have included many randomized, controlled trials have tested adjuvant therapies for such patients, including bacille Calmette–Guerin, *Corynebacterium parvum*, levamisole, radiation therapy, isolated regional perfusion of an extremity, chemotherapy and immunotherapy, vaccines, and interferon. Most of these investigations have included relatively small numbers of patients or heterogeneous groups of patients, making the results inconclusive.

INTERFERON THERAPY FOR MELANOMA

An understanding of the importance of the immune system in controlling melanoma led to the investigation of interferon therapy for this disease. Initial studies of interferon alfa-2a (at a dose of 3 million IU given subcutaneously three times per week for 3 years) in patients with positive lymph nodes did not show a survival benefit.³⁵ Treatment with interferon alfa-2b at the maximal tolerated dose for 1 year³⁶ (20 million IU per square meter of body-surface area given intravenously 5 days per week for 4 weeks, followed by 10 million IU per square meter given subcutaneously 3 days per week for 48 weeks) improved relapse-free survival ($P=0.003$) and overall survival ($P=0.0273$) among patients with stage III disease. A study comparing high-dose interferon with low-dose interferon and observation³⁷ showed improved relapse-free survival but not improved overall survival in the group receiving high-dose interferon. Finally, a prospective trial comparing high-dose interferon with vaccination with GM2 ganglioside, a melanoma antigen conjugated to keyhole limpet hemocyanin,³⁸ showed a benefit in relapse-free survival ($P=0.015$) and overall survival ($P=0.046$) in the group receiving high-dose interferon.

Most of the randomized trials of interferon therapy were conducted before the widespread use of sentinel lymph-node biopsy. As a result, there are few prospective, randomized data on the efficacy of adjuvant high-dose interferon for a patient such as this one, with only microscopical evidence of sentinel lymph-node disease, detected by either histologic examination alone or immunohistochemical staining alone. A decision to proceed with a year of adjuvant interferon therapy in this patient should also reflect consideration of potential side effects and toxic effects. The most commonly reported side effects of high-dose interferon therapy include constitutional symptoms

(fever, chills, arthralgias, myalgias, fatigue, malaise, and diaphoresis), myelosuppression, hepatotoxicity, and neurologic compromise. Approximately 20 to 40% of patients report marked constitutional symptoms, evidence of transient hepatotoxicity develops in 20%, and 40% have marked granulocytopenia. In addition, neuropsychiatric changes that include severe depression, altered mental status, and seizures develop in approximately 5 to 10% of patients receiving this therapy.

Although it would be reasonable to consider the use of high-dose interferon for this patient, one must individualize such a discussion. The risks and potential benefits of the treatment as well as the patient's quality of life should be considered in making a decision to proceed.

Dr. Nancy Lee Harris (Pathology): Dr. Tanabe, will you tell us what the decision was in this case?

Dr. Kenneth K. Tanabe (Surgical Oncology): We performed a complete axillary lymph-node dissection in this case, and no tumor was identified in the resected lymph nodes. The patient received interferon therapy for 11 months, discontinuing it 1 month before completion of the intended 12-month course because of adverse effects, and she remains free of disease 5 years after her initial treatment.

PATHOLOGICAL DIAGNOSIS

Malignant melanoma, invasive to 0.9 mm, with metastasis to one of two sentinel lymph nodes.

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