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Spontaneous Regression of Cutaneous Melanoma With Subsequent Metastasis

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There has been a 4-fold increase in the incidence of cutaneous malignant melanoma during the past 25 years.[1] However, the ratio of expected deaths from melanoma to new melanoma cases has actually decreased steadily during this time period, largely as a result of increased public awareness leading to earlier diagnosis and treatment.[2] Standardized staging systems by both Breslow and Clark have facilitated the procurement of a vast array of prognostic data for this patient population.[3,4]

The relationship between malignant melanoma and melanocytic nevi is well recognized; more than 80% of patients with melanoma reported a change in a preexisting nevus as the initial sign of their disease.[5] The clinical diagnosis of cutaneous melanoma generally is not difficult. Occasionally, however, metastatic malignant melanoma presents without clear evidence of a primary cutaneous or mucosal source. This presents a challenging clinical situation with respect to diagnosis, treatment, and prognosis.

We present the case of a patient with an apparent spontaneous regression of a presumed malignant melanoma that arose from a long-standing cutaneous melanocytic nevus followed by the development of a regional lymph node metastasis.

Report of a Case

A 57-year-old Caucasian woman in otherwise good overall health with no known medical problems presented with a 3-month history of a progressively enlarging subcutaneous nonpigmented, erythematous, nonpainful nodule superficial to the left angle of the mandible (Fig 1). On questioning, the patient denied a previous history of cutaneous or any

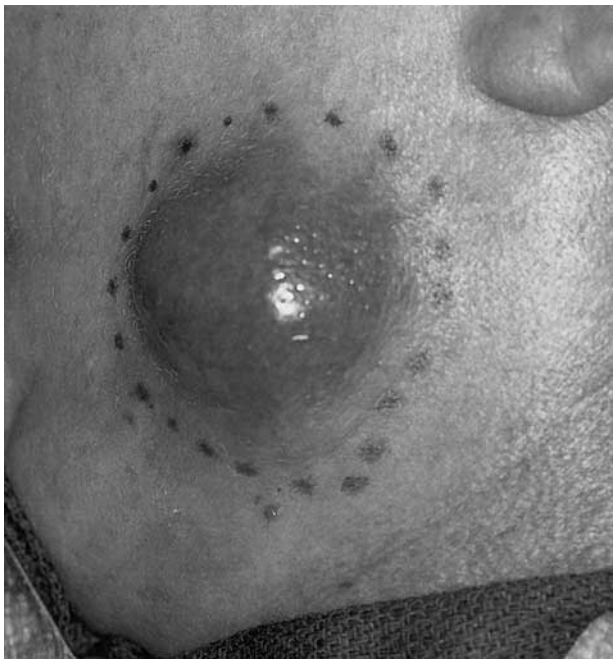

FIGURE 1. Erythematous subcutaneous nodule, preoperative clinical presentation. Mass represented metastatic melanoma within a left facial lymph node.

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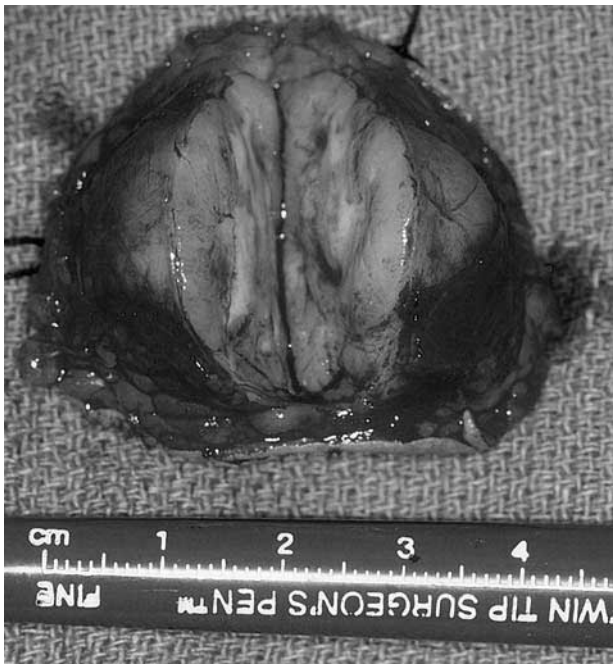

FIGURE 2. Resection of gross surgical specimen including overlying skin. No evidence of cutaneous origin or extension was noted on histopathologic evaluation despite gross and microscopic evidence of melanoma in the 4-cm lymph node.

other cancer. There was no history of a previous skin biopsy or of past treatment of any skin lesions. However, she did report having had a long-standing pigmented nevus on the left cheek, measuring approximately 1 cm in dimension, that had been present since childhood. During the 1 year before presentation, this lesion progressively darkened in color, tripled in size, and developed an irregular border, according to the patient. However, the patient did not seek medical attention. Eventually, both she and her family noted complete regression of the enlarging cheek lesion over the course of 2 to 3 months. Within 1 month of disappearance of the cheek lesion, the patient noted a growing subcutaneous nodule centered over the left angle of the mandible.

Examination revealed a 4- × 3-cm firm erythematous, subcutaneous mass. There was paralysis of the marginal branch of the seventh cranial nerve on the ipsilateral side. No other regional lymphadenopathy was noted, and no other suspicious lesions were noted on the skin surface of the head and neck, including the scalp. Specifically, there was no evidence of any cutaneous abnormality or scarring on the left cheek in the area of the previously evolving nevus that had disappeared.

Analysis of a fine-needle aspiration biopsy suggested a highly cellular tumor. In the operating room, a wide excisional biopsy of the lesion was performed (Fig 2). Microscopic sections revealed a moderately circumscribed cellular proliferation within a facial lymph node. There were streaming cords and nests of undifferentiated cells with moderate amounts of amphophilic cytoplasm and single nuclei with prominent nucleoli (Fig 3). No pigment was identified. There was brisk mitotic activity with 10 to 15 figures per high-power field. There was no apparent involvement of the overlying epidermis. Immunoperoxidase staining demonstrated positive reactivity for S-100, HMB 45, and vimentin and was negative for cytokeratin and leukocyte common antigen (Fig 4). These findings were consistent with a diagnosis of malignant melanoma metastatic to a left facial lymph node.

The patient subsequently returned to the operating theater, where she underwent wide reexcision (2-cm margin) of the previous site and had a reconstructive procedure performed with a rotational chest/neck flap (Figs 5, 6). She underwent concurrent panendoscopy (rigid and flexible esophagoscopy, flexible bronchoscopy, direct laryngoscopy, and nasal endoscopy). A subsequent, complete dermatologic examination of the entire body revealed no remarkable findings. Gastroduodenoscopy, colonoscopy, and

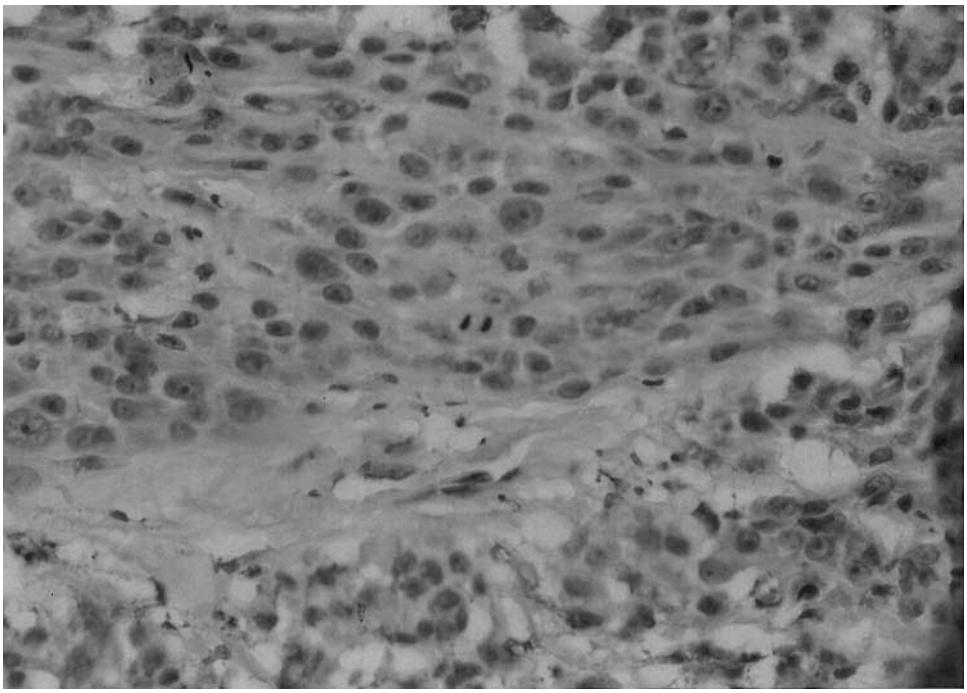

FIGURE 3. Photomicrograph of lymph node architecture replaced by proliferation of highly cellular infiltrate of cells with large nuclei, prominent nucleoli, and moderate to abundant amounts of cytoplasm. There are numerous mitotic figures (hematoxylin-eosin stain, original magnification ×250).

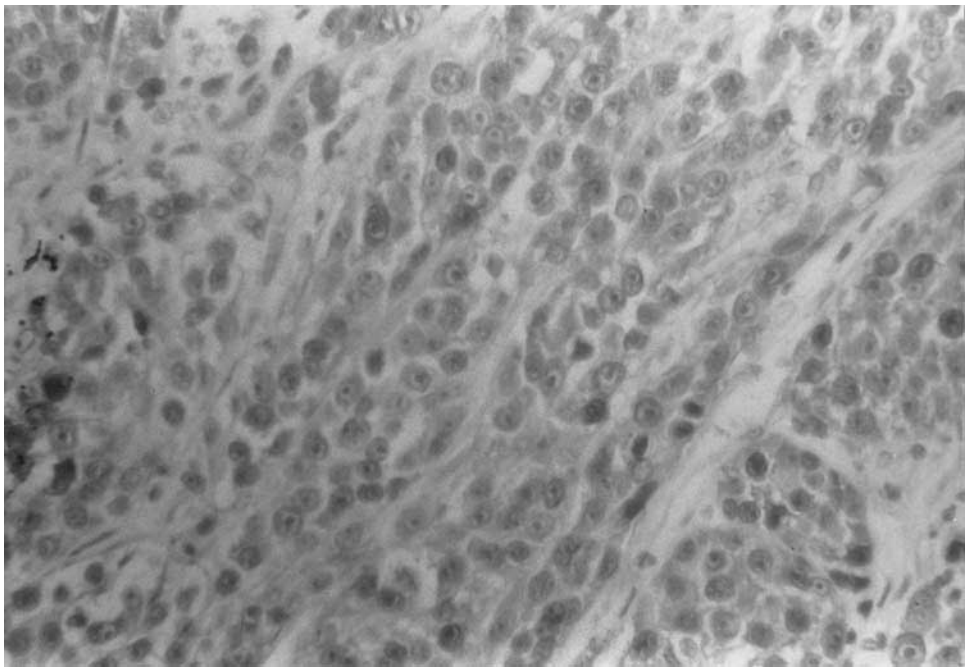

FIGURE 4. Nests of tumor show reactivity for S-100 protein (immunoperoxidase technique PAP, original magnification ×250).

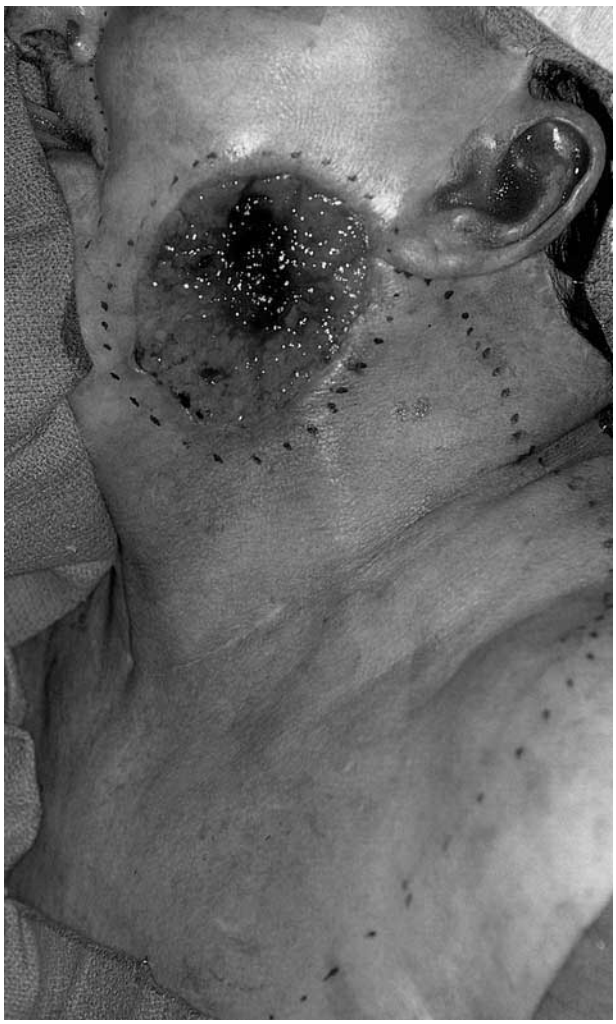

FIGURE 5. Surgical defect with preparation for chest-neck rotation flap.

upper gastrointestinal series with small bowel examination revealed completely normal findings. Computed tomography scans of the head, neck, chest, abdomen, and pelvis, as well as bone scans, likewise revealed unremarkable findings.

The patient was thus staged as TX N1 (stage III melanoma). She was subsequently referred for hypofractionated external beam radiotherapy to a total dose of 50 Gy and remains disease free at 18 months after radiation treatment. To date, there is no evidence of locoregional or distant metastatic recurrence.

FIGURE 6. Patient's postoperative appearance at approximately 1 year after surgical excision.

Discussion

It is well recognized that melanocytic nevi may undergo regression and that the regression may be partial or complete. Partial regression of a choroidal melanoma has been reported.[6] To our knowledge, our patient represents the first documented case of spontaneous complete regression of a melanoma with subsequent development of fixed regional adenopathy in the absence of a primary lesion. Admittedly, no biopsy-documented confirmation of the patient's suspicious left cheek lesion was obtained. However, the history of a progressively enlarging pigmented lesion that arose from a longstanding previously nonchanging melanocytic nevus is highly suggestive of malignant melanoma. The postulated mechanism of subsequent regression involves alteration in immunologic factors associated with the biology of the neoplastic process. The regression of malignant melanomas appears to have a strong immunologic basis. This has fostered the burgeoning development of immunotherapy for treatment of this disease.[7-9]

Conley and Hamaker[10] reported a 10-year survival rate of 8.2% for patients presenting with some evidence of spontaneous partial regression of a head and neck melanoma. This represents a dismal overall survival rate. Surgery remains the mainstay of treatment for malignant melanoma. Locoregional control may be significantly improved with the adjunctive use of external beam hypofractionated radiotherapy.[11] The treatment of disseminated melanoma with cytotoxic drugs has been discouraging. No single agent has been found that is capable of inducing positive objective tumor responses in more than 25% of patients. The most active agents appear to be the nitrosureas and DTIC (dimethyltriazenoimidazole carboxamide).[12] There have been improved responses with combination chemotherapy.[13] The poor prognosis and lack of effective treatment for patients with stage III and IV disease have led to the investigation of a number of immunologic response modifiers with activity against this tumor. Interferon-α and interleukin 2 have shown the most promising results to date.[14] Monoclonal antibodies and the use of melanoma vaccines may prove promising in the future for the treatment of stage IV melanoma.[15]

The ideal management of "occult" primary malignant melanoma with metastasis remains unresolved due to the rarity of this lesion. The most important aspect of the treatment plan is centered in the search to detect the primary melanoma. A biopsy should be performed on any suspicious pigmented lesion or any lesion that has increased or decreased in size. A complete systemic workup as well as meticulous examination of the mucosal surfaces in the head and neck and the entire body surface should be carried out. Positron emission tomography scanning appears to be efficacious in the search for occult primary or occult metastatic disease.[16] Unfortunately, positron emission tomography scanning was not available at our institution. Because the natural history and response to treatment of metastatic melanoma have not been fully elucidated, multimodality therapy with wide surgical excision of the gross lesion appears to offer the most favorable opportunity for locoregional control and, therefore, prolonged disease-free survival.

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