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Images in Dermatology

Where Did It Start? Subcutaneous Metastatic Melanoma

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PRESENTATION

The warning signs of melanoma have been well characterized, but in some cases, those harbingers are absent. A 43-year-old Caucasian woman was admitted to our clinical department with a 2-month history of painful subcutaneous nodules. These had a hard, elastic, wooden texture and appeared on her neck, chest, abdomen, and axillary regions. With time, they became ecchymotic.

During the previous month, the patient also developed progressive asthenia with dyspepsia and episodes of vomiting. The gastrointestinal symptoms were associated with an unintentional weight loss of approximately 8.8 lbs (4 kg), and they improved slightly with the use of a proton pump inhibitor. She also reported a productive cough with occasional hemoptysis. Her medical history included hepatitis C virus infection and bipolar disorder, which was diagnosed at the age of 20 years. She was being treated with valproic acid, clonazepam, and behavioral therapy.

ASSESSMENT

Several subcutaneous nodules were disseminated on the patient's thorax, chest, jugular region, neck, abdomen, and axilla. These had the texture of hard wood, and ecchymosis was present in some cases (Figures 1 and 2A). A dysplastic nevus, measuring 5 mm in diameter, was evident in the patient's left submammary region (Figure 2B). Auscultation confirmed a 2/6 systolic cardiac murmur at the aortic valve.

Laboratory test results included a low hemoglobin level (10 g/dL), a high erythrocyte sedimentation rate (105 mm/hr), and a normal lactate dehydrogenase level of 232 U/L. Levels of the tumor markers CEA, Ca 19-9, Ca 125, and Ca 15-3) were within normal ranges. Total body computed tomography (CT) showed multiple solid lesions, some with necrotic foci, involving subcutaneous adipose tissue in the thoracic and abdominopelvic regions. Voluminous lesions were mostly localized on the right side of the anterior chest wall (diameter, 30 mm), on the right periumbilical region (diameter, 27 mm), and on the left side dorsal region (diameter, 22 mm) (Figure 3A).

CT also displayed deep visceral lesions, which appeared as solid hypodense tissue with necrotic areas, in the hilar region of the upper lobe of the left lung and in the lingula. These encompassed the bronchovascular structures, compressing the lower bronchial branches and causing atelectasis. Some mediastinal lymph nodes were necrotic as well. The largest nodes were detected in the subcarinal region (diameter, 26 mm) and at the right cardiophrenic space (diameter, 20 mm). Solid noncalcific nodules were found, bilaterally, in the lung parenchyma. The biggest was located in the left lower lobe (12.5 mm). We suspected these nodules were metastases.

In addition, several abdominopelvic solid round nodules, some with necrotic foci, were noted in the intra- and retroperitoneal spaces. The largest lesions were localized in the mesenteric root (diameter, 20 mm), in the left perirenal space (diameter, 18 mm), in the back pararenal band (15 mm), and in the mesogastric region (18 mm). Contrast-enhanced magnetic resonance imaging showed multiple secondary cortical and subcortical nodular lesions. The largest, marked by signs of perilesional edema, was at the right temporoparietal junction; others were noted in the right thalamic region and bilaterally in the frontal area (Figure 3B).

Excisional biopsy was performed on a left subclavicular dermal nodule. Cutaneous and subcutaneous tissue, including a deep-seated black nodular lesion (0.7 cm), were removed, fixed in neutral formalin, and submitted for histological analysis. Microscopic examination revealed a subcutaneous melanoma (Figure 4A). Neoplastic cells were heavily pigmented, and they showed an infiltrative pattern of growth within connective and subcutaneous fat tissue. Neoplastic spreading was associated with the presence of inflammatory cells (Figure 4B).

Immunohistochemistry showed that the neoplastic cells were positive for the melanoma markers S100 protein, HMB-45, and MART-1. The epidermis and papillary dermis had no pathological features. Molecular analysis demonstrated the presence of the activating mutation V600K, also known as p.Val600Lys, in the BRAF oncogene; the coding DNA sequence mutation was c.1798_1799delGTins> AA. The mutation rate was 33.7%. All of this information suggested increased sensitivity to BRAF inhibitors.

The suspicious pigmented lesion in the left submammary region was excised in order to define the primary melanoma, but the specimen proved negative for malignancy (Figure 2B). A cytological examination of the patient's sputum did not disclose any neoplastic cells. Aside from a detailed physical evaluation, she underwent esophagogastroduodenoscopy, colonoscopy, transvaginal ultrasound, and an examination of the nose and throat mucous membranes. Her eyes, specifically, her choroids, were inspected with an ophthalmic microscope, and a Wood's lamp was used to scrutinize her skin. Nonetheless, a primary tumor site could not be found.

DIAGNOSIS

The patient's diagnosis was metastatic melanoma of unknown origin with extensive visceral and subcutaneous spread. In about 3% of patients, metastatic melanoma can be subcutaneous, visceral, or in the lymph nodes, without evidence of a primary tumor, despite a thorough physical examination.[1] Most commonly, metastatic melanoma of unknown primary origin is first discovered in the lymph nodes, whereas 12-39% of patients without an identifiable primary tumor have

subcutaneous tissue involvement. Possibly, the primary melanocytic neoplasm cannot be found because the immune system induced its regression.[3]

Our patient's clinical presentation, along with the histological features of her biopsy sample, led us to consider that her metastatic disease stemmed from a regressed cutaneous melanoma. This hypothesis was supported by the absence of visceral or mucocutaneous primary lesions and by the evidence of a mutated BRAF gene. The BRAF V600E hotspot mutation is believed to be a driver mutation for cutaneous melanoma. However, in mucosal melanoma, mutations of the BRAF and KIT genes are rare, with frequencies below 10%.[4] In mucosal melanoma, as well as in acral melanoma, where disease is not the result of events spurred by ultraviolet light, tumor proliferation is attributed to a combination of early chromosomal instability, characterized by copy number gains in TERT, CCND1, and KIT genes, and non-UV-related activating mutations in KIT and PDGFRA genes.[5]

Recent extensive molecular analysis performed to elucidate the genomic landscape of melanoma, subclassified tumors into 4 molecular groups.[6] These subgroups encompass tumors associated with mutant BRAF, with mutant RAS, with mutant NF1, and triple wild type melanoma, and each category correlates with clinical and prognostic features and with therapeutic options. For example, patients who have metastatic melanoma with activating mutations of BRAF are more likely to respond to BRAF inhibitors.[7] Although our patient's primary melanoma was not discovered, molecular analysis allowed us to classify her case as melanoma delineated by mutations in the BRAF gene, based on the pattern of the most prevalent mutated gene. Moreover, the presence of lymphocytic infiltration, regardless of molecular subtype, is linked with improved survival and offers an additional management option, namely, immunotherapy with immune checkpoint inhibitors.[8]

MANAGEMENT

The patient's treatment plan began with administration of corticosteroids and whole brain radiotherapy delivered via linear accelerator for a total dose of 30 Gy (fractionation, 300 cGy/day). This was followed by combined chemotherapy with cobimetinib and vemurafenib. Her subcutaneous nodules were greatly reduced in size or disappeared, and her clinical symptoms improved remarkably. Therapy is still ongoing. It has been suggested that patients with metastatic melanoma of unknown origin in the lymph nodes or subcutaneous tissue might have a better prognosis when compared to patients with melanoma that has spread from a known primary site.[4]

In conclusion, we present the case of a young woman with an unusual subcutaneous metastatic melanoma without evidence of a cutaneous or visceral primary melanoma. The extensive

metastatic distribution first seen on clinical and radiological examination improved with the use of BRAF inhibitors. Aside from allowing us to plan the patient's therapy, the molecular profile, when combined with her clinical status, suggested that the disease originated from a regressed primary skin melanoma.

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Figure 1. Subcutaneous nodules were disseminated on the patient's thorax, chest, jugular region, neck, abdomen, and axilla. The black arrows point to ecchymosis that developed later. An excisional biopsy was performed on a dermal nodule in the left subclavicular region (red arrow).

Figure 2. **A,** A subcutaneous metastatic nodule was identified in the patient's jugular region. B, This lesion, suspicious for melanoma, was excised from the left submammary area.
Figure 3. **A,** Total body computed tomography demonstrated multiple metastatic solid lesions of the subcutaneous adipose tissue at the thorax. **B,** Contrast-enhanced magnetic resonance imaging of the brain showed multiple metastatic cortical and subcortical nodular lesions.

Figure 4. The histology of the cutaneous lesion pointed to the diagnosis. **A,** A deep-seated dermal nodule marked by prominent melanin pigmentation was evident when viewed in a low-power microscopic field (hematoxylin and eosin stain). **B,** When the biopsy sample was examined in a high-power field, melanin pigment was visible within the cytoplasm in the neoplastic cells. Intra- and peritumoral lymphocytes were also evident (hematoxylin and eosin stain).

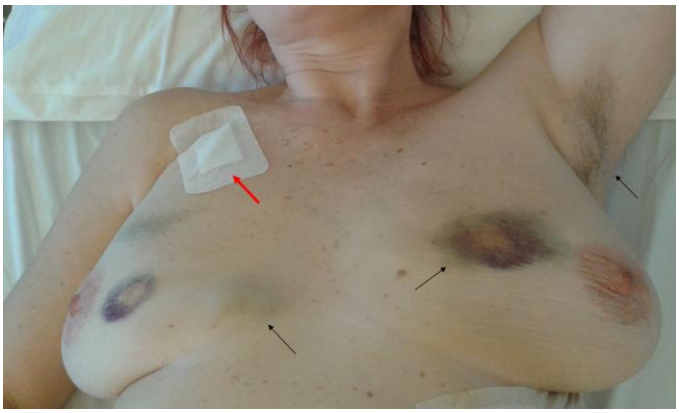
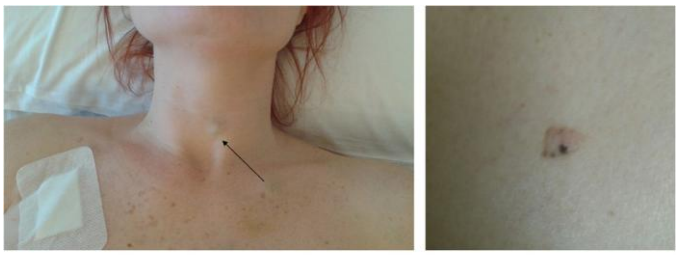


Figure 1.jpg



A B

Figure 2.jpg

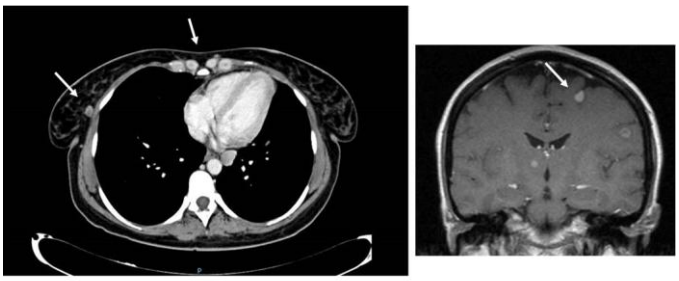


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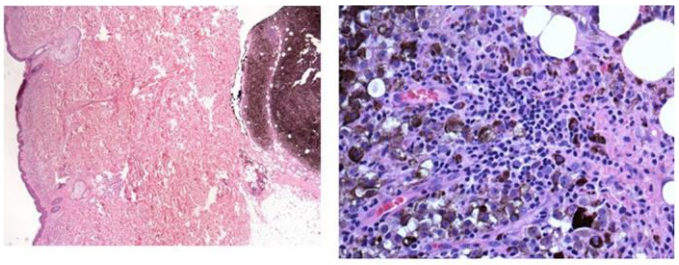
Figure 3.jpg



A B

Figure 4.jpg