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Generalized lymphadenopathy as the first manifestation of metastatic malignant melanoma: a diagnostic paradox

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Summary. *Background:* Although more than 90% of melanomas have cutaneous origin, there are a few cases who present with lymph nodal disease or metastatic viscera lesions, with no identifiable primary, described as melanomas of unknown primary site. *Case Report:* We report a case of a morbidly obese 63-year-old male, with multiple comorbidities, who presented with neurological symptoms, while extensive lymphadenopathy was revealed on clinical examination and imaging. Excisional biopsy and histopathological examination of a supraclavicular nodal mass, with the aid of immunohistochemistry, led to the diagnosis of metastatic malignant melanoma. Despite investigations the primary tumor site remained unrevealed and the patient received palliative chemotherapy. *Discussion:* Generally, melanomas evolve from any site of the body containing melanocytes or cells that are capable of differentiating into melanocytes, although cases without an identifiable cutaneous, ocular, or mucosal primary, claimed as melanomas of unknown primary, comprise only 1-4% of melanoma cases per year. Extensive work-up sometimes seem meaningless. It is also stated that such patients with lymph nodal disease, despite the unfavorable sign of nodal involvement fare better survival rates than common melanoma patients with known primary and metastasis to lymph nodes.

Key words: malignant melanoma; melanoma of unknown primary; lymph node metastasis; immunohistochemistry

Background

Malignant melanoma incidence is worryingly increasing worldwide. National Cancer Institute's (NCI) data imply that the increase in malignant melanoma patients has a higher rate than the current increase in all other types of cancer (1). Although more than 90% of melanomas have cutaneous origin, there are a few cases who present with lymph nodal involvement or metastatic viscera lesions, with no identifiable primary, described as melanomas of unknown primary site (MUPs) (2). MUP generally have a very low incidence in the range of 2-6% of all malignant melanoma patients, and the natural history of metastatic melanoma involving lymph nodes, with unidentified primary site is not studied enough to develop definite treatment protocols and guidelines. We present a case of a 63-year-old man with complex initial presenting symptoms and signs who finally was diagnosed with MUP, aiming to emphasize the challenging diagnosis of this rare entity.

Case report

We report a case of a morbidly obese 63-year-old male (BMI 49), with multiple comorbidities: hypertension, diabetes mellitus type II, heavy smoker,

presenting with dysarthria and right limb formicary. After his admission the patient developed new onset aphasia, right hemiplegia and loss of consciousness. An urgent head computed tomography (CT) scan revealed a hemorrhagic stroke of the left temporal lobe, implying also the presence of a space occupying lesion. On initial physical examination a left supraclavicular prominent mass measuring about 10x6 cm was found, as well as generalized lymphadenopathy, including cervical, axillary and inguinal palpable lymph nodes. Detailed history revealed that all these nodes appeared over the last few weeks. The lymph nodes ranged in size from 1 cm to 3.5 cm, and similarly to the supraclavicular mass, they were firm, hard, immobile and completely painless. Moreover, there was no personal history of lymphoma like symptoms as fever, chills, and loss of energy or weight. Blood tests were unremarkable and virology was negative as well. CT scan of the chest, abdomen and pelvis with oral and IV contrast was performed (Figure 1a, b) and showed an enlarged (2.5 cm) lymph node at the prevascular space, as well as an enlarged (5.5 cm) right anterior diaphragmatic lymph node. Axillary lympadenopathy was also noted, most pronounced on the left. Also, multiple enlarged retrocrural, paraaortic and left common/external iliac lymph nodes were found. Soft-tissue masses were detected at the site of the adrenals bilaterally, the largest on the left, measuring 10X5.3 cm.

Excisional biopsy of the supraclavicular mass followed and histopathological examination revealed a malignant neoplasm, consisting of variable sized nests of neoplastic cells, separated by thin fibrous septa. Neoplastic cells were mainly small, round with dark stained nuclei and conspicuous nucleoli. Mitosis were numerous. A neoplastic embolus was also observed in the lumen of a surrounding vessel (Figure 2). Reticulin stain displayed a carcinomatous growth pattern. Immunohistochemical analysis showed positive staining for vimentin, melan-A (Figure 3a), S100p (figure 3b), HMB45, CD56, CyclinD1, Bcl-2, CD99 and CD117. Markers of lymphoid (LCA, CD20, CD3, CD5, CD10, PAX5, Bcl-6), neuroendocrine (chromogranin, synaptophysin) and myoid (actin, desmin) differentiation were negative. Neoplastic cells showed no reactivity for high and low molecular weight keratins, CK20, CK7, CD30, CD34, PLAP, PSA, PSAP, calretinin, GCDFP-15, inhibin and TTF1. Final histopathological diagnosis was set as malignant melanoma. In addition, special genetic testing was performed and BRAF gene exon 15 was positive for the mutation V600E.

Careful personal history and thorough physical examination were obtained once more, with special

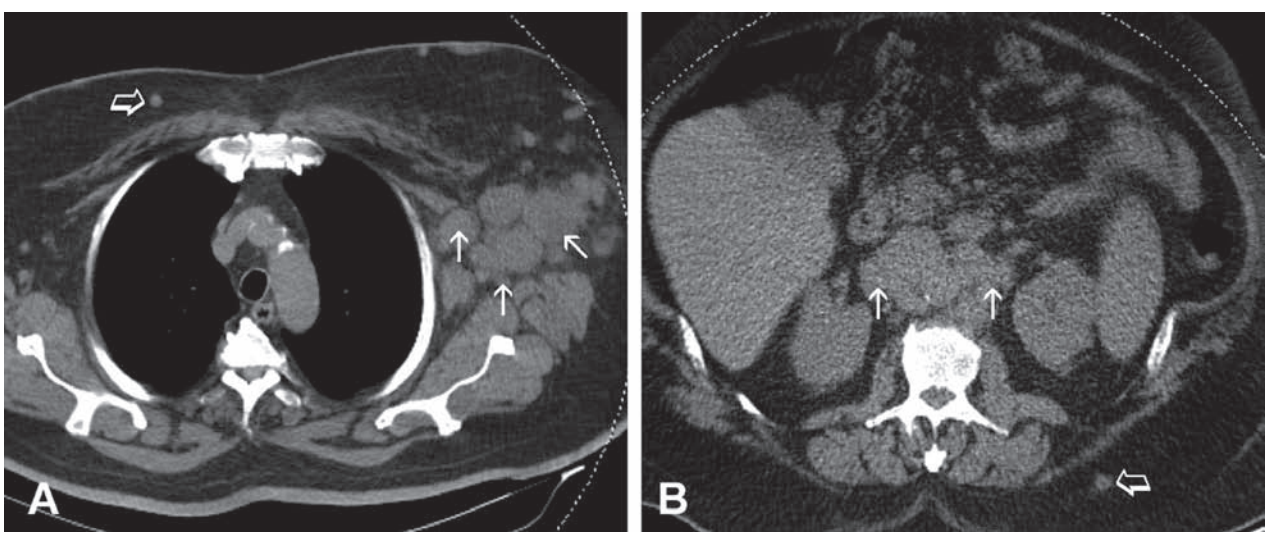

Figure 1. Chest CT image (A), shows pronounced enlargement of left axillary lymphnodes (arrows). Abdominal CT image (B), shows multiple enlarged paraaortic lymphnodes (arrows). Subcutaneous nodules (open arrows) are also noted on both chest and abdominal CT images.

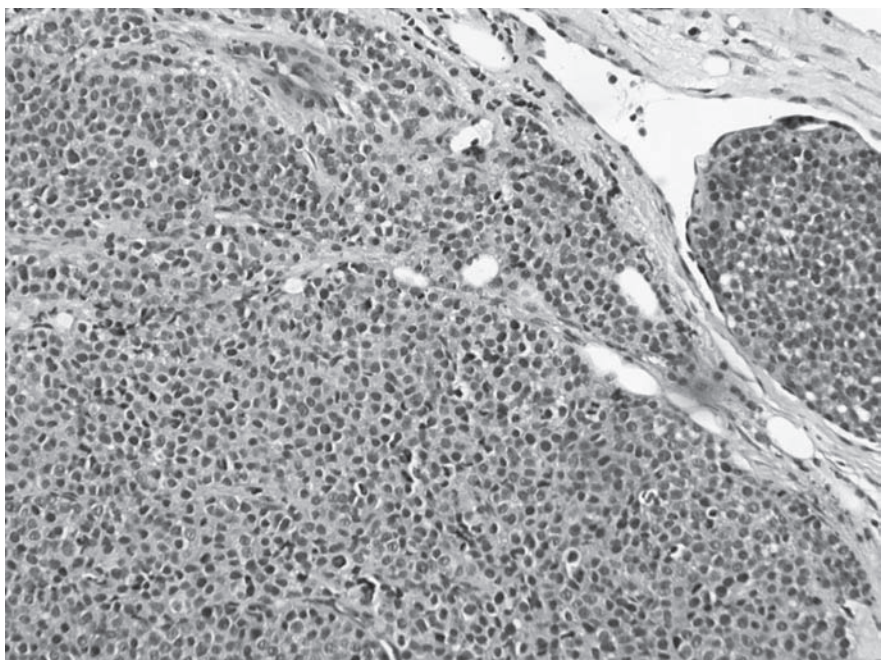

Figure 2. Neoplastic cells with dark stained nuclei, arranged in variable sized nests. Note the presence of a cacinomatous emboli in the lumen of a surrounding vessel (H-Ex100)

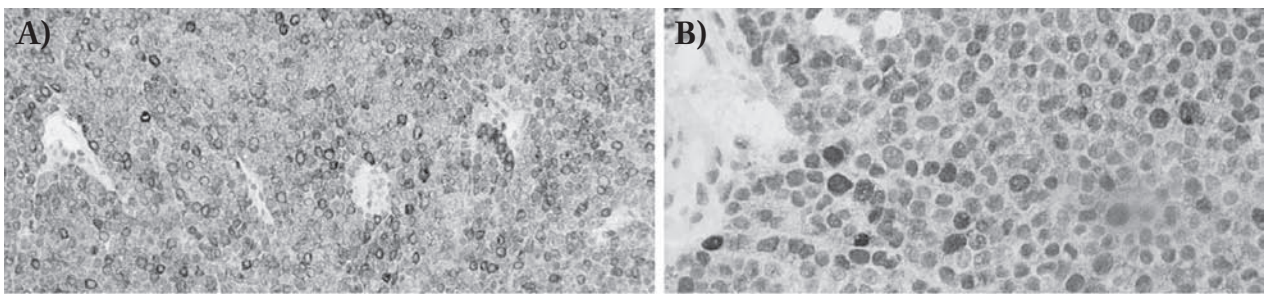

Figure 3. (A) Neoplastic cells showed positive staining for Melan-A (Melan-Ax400); (B) Neoplastic cells were positive for S100p (nuclear stain) (S100px400).

emphasis of skin examination. Interestingly the patient's wife mentioned that 3 years before hand he had underwent excision of a skin lesion from his forehead, which according to the histopathology report was a basal cell carcinoma (BCC) of adenoid subtype, excised in tumour free margins. A review of the histopathology slides was obtained and additional immunohistochemical examination was performed as well. Both confirmed the initial diagnosis of BCC. Genital examination and digital rectal examination with additional proctoscopy did not show any evidence of a primary lesion as well as opthalmology examination. Positron Emission Tomography PET/CT scan was performed which once again confirmed the presence of extensive lymphadenopathy without further delineation of a primary melanoma site. Patient was referred to a dermatologist for specialist's evaluation and in a desperate effort to identify the primary site, one lesion from his upper back was excised, which turned out being seborrheic keratosis. Hospital's multidisciplinary meeting (MDM) declared the case as a metastatic MUP, and further investigations were deemed unnecessary. Patient received palliative head radiotherapy and then was started on ipilimumab, which is a monoclonal antibody used in metastatic melanoma. He remains on chemotherapy three months later.

Discussion

Theoretically, melanomas evolve from any site of the body containing melanocytes or cells that are capable of differentiating into melanocytes, and these sites are either cutaneous or noncutaneous in origin (3). Melanomas without an identifiable cutaneous, ocular, or mucosal primary, claimed as MUP, comprise only 1-4% of melanoma cases per year (3, 4). There are case series proposing that lymph nodes are the most common site of metastasis for MUP (5, 6). Although the true etiology of the disease is non proven, various theories have been proposed and include a. a concurrent, unrecognized melanoma; b. a previously excised melanoma that was misdiagnosed either clinically or pathologically; c. an antecedent, unrecognized, spontaneously regressed primary melanoma; and finally d. the de novo malignant transformation of an aberrant melanocyte within a lymph node (7). In favor of the latter, benign nevus cells are commonly found in lymph nodes, and melanomas arising from nevus cells in lymph nodes have been already described for other tissues (8, 9), many years ago. Overall, the model c, and theory of spontaneous regression is the most widely accepted scenario as that sequelae has been found to be applicable to melanoma. The reason for this regression could be due to alterations in immunologic status, like after exposure to human body stress including infection and pregnancy which are known factors triggering immunologic response (3).

MUP patients may present in multiple ways. Similar to patients with known primary, but already metastatic melanoma, and MUP patients can present with subcutaneous, nodal metastasis, and/or metastasis to the viscera, bones or brain. From the usual nodal disease sites, the axilla is more common for MUP patients, as inguinal and cervical nodal metastases are the least common (7).

Recommended work up for MUP should include: meticulous skin evaluation, brain imaging (CT or MRI), and CT imaging of the chest/abdomen and pelvis to rule out distant metastatic disease (10). Otorhinolaryngological examinations when metastases are mostly located to the head and neck region and proctoscopy and gynecologic examinations for patients with inguinal lymph node metastases are also suggested. Opthalmologic examinations should be reserved for patients who have MUP with visceral metastases, primarily of the liver (11).

As in our case, a previously excised skin lesion in patient's surgical history should be reexamined to exclude the possibility of them being a melanoma that was misdiagnosed.

American Joint Committee on Cancer (AJCC) has suggested to divide the metastatic malignant melanoma cases in three subgroups. Malignant melanoma with skin, subcutaneous tissues, or distant lymph node metastasis are classified as M1a; cases with lung metastases are called M1b and metastasis to any other solid organ is classified as M1c (12). Overall survival of patients in stage M1a ranges from 10 to 18 months and it has been proposed that radical surgical resections can be applicable to these patients, extending the survival up to 50 months in specific circumstances (13). Based on the above prevalent etiology theory of primary site regression due to immunologic reasons, it is argued that lymph nodal disease only should be treated aggressively with surgical means when localized and amenable to surgical clearance, since the primary tumor has already regressed (14, 15). Adjuvant chemotherapy is commonly applied with multiple agents in use and has favorable results (16). It is also stated that MUP with lymph nodal disease, despite the unfavorable sign of nodal involvement fare better survival rates than common patients with known primary and lymph nodal metastatic disease (17).

In summary, our case underlines the value of thorough physical examination, in which despite patient's comorbidities and main neurological symptoms, extensive lymphadenopathy was revealed and his MUP diagnosis was not overlooked. Moreover, immunohistochemistry is of paramount importance in histopathological work up of such a case. Finally, it needs to be highlighted that MUP is an exclusion diagnosis, and based on theories of primary's regression and better prognosis of MUP with lymph nodal involvement only patients, a meticulous staging and assessment is necessary to safely declare the condition as such. However, MDM discussion and rationale investigations, while individualizing diagnostic and treatment options is equally important, often avoiding exhausting, interventional and high cost exams, which do not benefit the patient.

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