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Metastatic Melanoma of Unknown Primary in a 56-Year-Old Filipina: A Case Report

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This is a case of a 56-year-old Filipina female who presented with a four-month history of a palpable right infraclavicular lymph node that was diagnosed as metastatic melanoma on histopathology and immunohistochemical staining with no apparent primary tumor on physical examination, nasopharyngoscopy, colonoscopy and imaging studies. Patient then underwent modified radical neck dissection, right, with an unremarkable intra-operative and post-operative course. This report aimed to document the clinical profile, laboratory and imaging parameters and treatment of melanoma of unknown primary on a 65-year-old female.

Key words: melanoma; neoplasm, unknown primary; neck dissection; Philippines

Melanoma of unknown primary (MUP) or occult primary melanoma accounts for approximately 3% of all melanomas and is defined as the presence of histologically confirmed melanoma metastasis to either lymph nodes, subcutaneous tissue, or visceral sites without a history or evidence of a cutaneous, mucosal, or ocular primary lesion. Nodal metastasis as the most common site of occurrence in about 60% of cases[1-4], with cervical lymph node involvement reported at 32.7%.[2]

While this condition was first described by Pack et al in 1952, Das Gupta in 1963 proposed the four exclusion criteria aid in the characterization of MUP: 1. Evidence of previous orbital exenteration or enucleation; 2. Evidence of previous skin excision, electrodessication, cauterization, or other surgical manipulation of a mole, freckle, birthmark, paronychia, or skin blemish; 3. Evidence of metastatic melanoma in a draining lymph node with a scar in the area of skin supplying that lymph node basin; 4. Lack of a non-thorough physical examination, including the absence of an ophthalmologic, anal, and genital exam. If any of the following is present, the diagnosis is excluded.[1-3]

This report aimed to document the clinical profile, laboratory and imaging parameters and treatment of melanoma of the cervical lymph nodes of unknown primary on a 65-year-old Filipina female. This report intends to add to the local epidemiologic data on the incidence of melanoma of unknown primary. This study was approved by the Research Ethics Review Board.

The Case

The patient is a case of a 56-year-old Filipina female of Caucasian descent who presented with a four-month history of a palpable right infraclavicular nodule measuring about 2 cm in diameter, characterized as firm, movable and non-tender, associated with malaise. No other associated symptoms were noted.

Persistence of the nodule prompted patient to seek consult with an otorhinolaryngologist. Fine needle aspiration biopsy done on the nodule revealed only atypical round cell proliferation. Patient then underwent excision biopsy of the nodule, which was then read as suggestive for non-small cell carcinoma, poorly differentiated, metastatic to lymph node. The said specimen was subjected to immunohistochemical staining and was positive to HMB45 and S-100, and negative for pancytokeratin, CK20, CK7, p40 and CD 45, which was diagnostic of Metastatic Melanoma.

The patient then sought consult with a dermatologist, where a full skin evaluation revealed no dermal lesions. She had also undergone nasopharyngoscopy by an otorhinolaryngologist, and colonoscopy, with no visible

lesions noted. By this time, the patient sought consult with a medical oncologist, where an 18FDG PET CT scan revealed prominent to enlarged right supraclavicular/ level V cervical lymph nodes with increased metabolic activity and few nonspecific sub-centimeter solid and ground-glass nodules scattered in both lungs. She was then advised chemotherapy but decided to seek consult with a surgical oncologist for second opinion.

A repeat 18FDG PET CT scan performed 2 months later revealed a slight increase in sizes of the prominent to enlarged malignant right supraclavicular/level V cervical lymph nodes with interval increase in metabolic activity of the of the right supraclavicular lymph nodes and interval note of focal hypermetabolic activity in the right level V cervical lymph nodes (Figure 1). The patient was then advised surgical excision and was subsequently admitted to this institution.

The patient had a history of gastroesophageal reflux disease (GERD) and was maintained on proton pump inhibitors. She had previously undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy for endometriosis and adenomyosis nine years prior at another institution. The patient declared the absence of alcohol intake, smoking, or illicit drug use. She disclosed a heredofamilial history of lung and brain cancer on the paternal side, and breast cancer on both paternal and maternal sides.

On physical examination, the patient was seen alert and cooperative with normal vital signs. Pertinent findings included palpable firm movable, nontender nodules on the right supraclavicular area (approximately 2cm x 2cm). The rest of the physical examination findings were unremarkable.

The patient underwent modified radical neck dissection, right, type III. Intra-operatively, multiple enlarged lymph nodes on cervical levels IV and V were found. The largest node was approximately 1.5cm in widest diameter (Figure 2). The patient had an unremarkable intra-operative and post-operative course. She was discharged on the fourth post-operative day. Histopathology (Figure 3) reported round cell malignancy suggestive of Malignant Melanoma in two of the sixteen lymph nodes (stage III, pT0N2M0). No further immunohistochemical staining done since the prior specimen was already diagnostic. The patient was then advised to undergo adjuvant immunotherapy.

Discussion

Melanoma of unknown primary (MUP) is reported to comprise 3.2% of all new melanoma diagnoses and occurs more commonly in men than in women, with a peak incidence in the fourth and fifth decades of life, which is comparable to that of cutaneous melanoma.[1,2,4] It commonly presents in axillary and cervical lymph nodes in men, and in inguinal lymph nodes in women. It also generally occurs in subcutaneous sites and in various visceral organs.[2,4] While cutaneous melanoma has known risk factors, including increased age, fair skin and/or hair, exposure to ultraviolet radiation, and

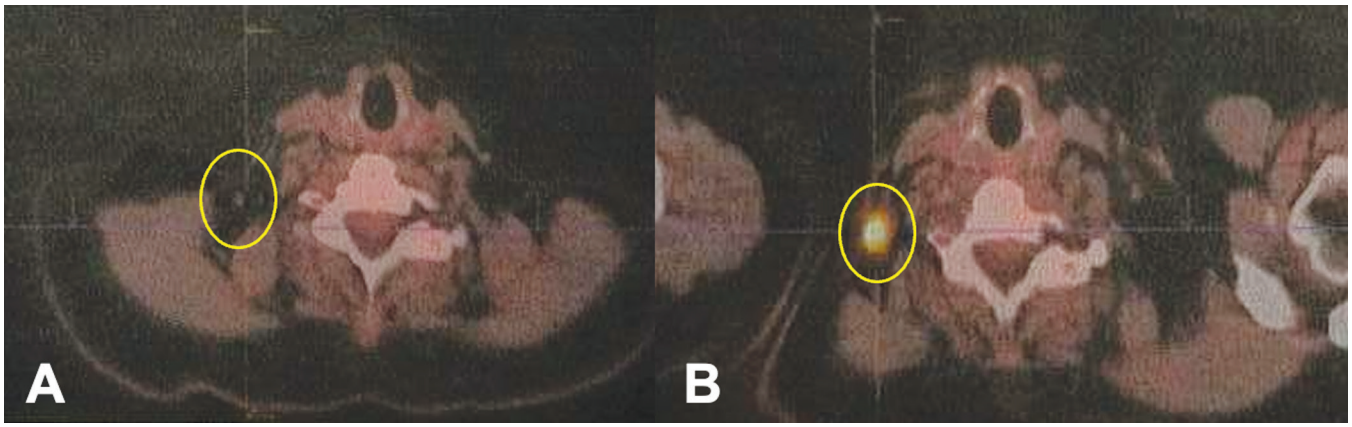

Figure 1. 18FDG PET CT comparative representative images of the enlarged cervical lymph nodes (encircled in yellow). A. Initial scan. B. Scan taken 67 days later.

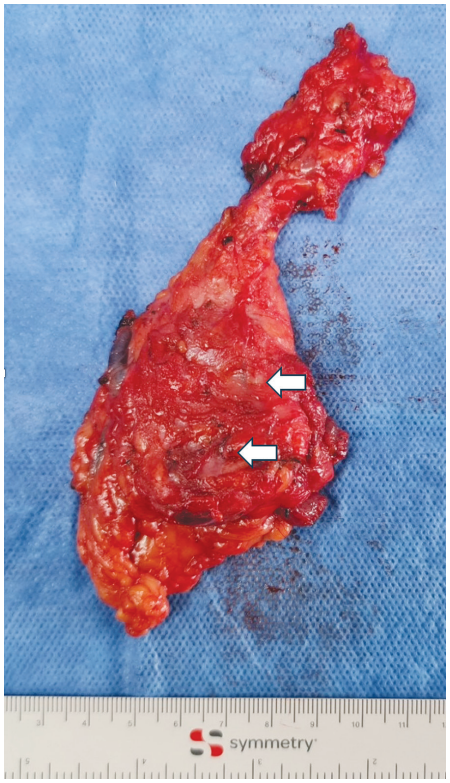

Figure 2. Specimen photo of the lymph nodal harvest, with enlarged multiple, fleshy to firm, gray-brown nodules (arrows).

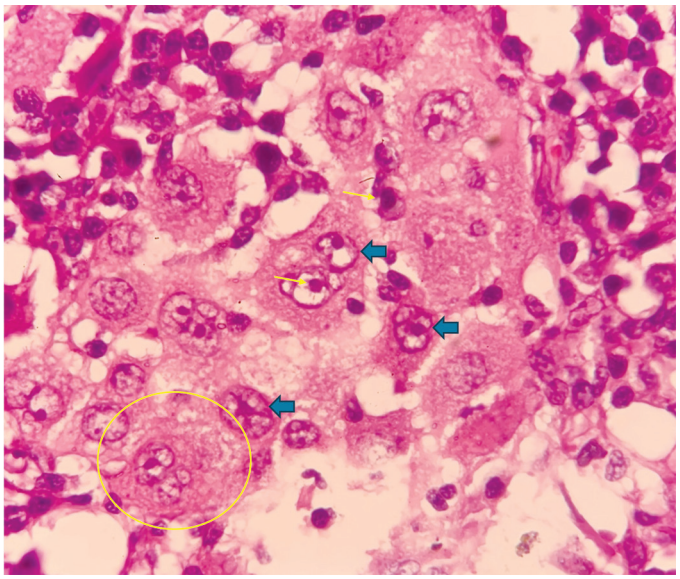

Figure 3. Specimen slide photo showing round cell malignancy, composed of large hyperchromatic nuclei (thick arrows) with prominently enlarged macronucleoli (thin arrows) and abundant foamy to eosinophilic cytoplasm (encircled) (H&E stain, 100x magnification)

a family history of melanoma, no specific risk factors have been linked to the development of MUP.[2,3]

The pathophysiology of MUPs was first proposed by Smith and Stehlinin to involve spontaneous regression of melanoma from a known primary site. The process is likely immune-related. Melanomas are estimated to account up to 11% of all cases of spontaneous tumor regression.[1,2,4] Other suggested explanations for MUPs include a concurrent, unrecognized melanoma; a previously excised melanoma that was misdiagnosed either clinically or pathologically; or de novo malignant transformation of an aberrant melanocyte within a lymph node.[4,5] MUP shares many of the genetic and molecular signatures of melanoma arising from intermittently sun-exposed sites on the skin, with BRAF and NRAS mutations occurring in 53% and 14% of MUP specimens, respectively.[1,2]

Kamposioras et al., in their systematic review, noted that patients with MUP presented with lymphadenopathy when the lymph nodes were the only sites involved. Inguinal node disease is more prevalent in females, while cervical and axillary nodes are more frequently seen in males. In cases of disseminated disease, the initial symptoms could be site-specific (e.g., hepatomegaly, jaundice, or abdominal mass for hepatic melanoma; pulmonary lesion or pleural effusion in lung involvement). Symptoms of fever, weight loss, and anemia could be related to cytokine production.[4]

The American Joint Committee on Cancer (AJCC) melanoma staging system classifies MUP as stage III disease if there is only lymph node or subcutaneous involvement at initial presentation, while it is classified as stage IV disease if there is spread to the viscera.[2,13]

A thorough evaluation, including ophthalmologic and anogenital exams, is required when melanoma is diagnosed within the subcutaneous fat, lymph nodes, or visceral organs without an obvious primary source.[1,5,6] Figure 4 shows a diagnostic algorithm proposed by Scott and Gerstenblith for patients newly diagnosed with MUP. Conversely, the exact type of work-up that is recommended for MUP patients after a complete physical examination is controversial.[2] With regard to extensive screening for primary tumor, Tos et al have found that special screenings (ophthalmoscopy, sigmoido/rectoscopy, gynecological, and ENT examinations) can

be considered as redundant and recommend obtaining a detailed history and performing a standard physical examination, in addition to a histopathological review and CT/PET for the diagnosis and staging of MUP.[6]

With regards to the pathologic evaluation of regional lymph node metastasis, immunohistochemistry is an important adjunct to routine histology and can minimize both overdiagnosis and underdiagnosis of metastatic disease in regional lymph nodes. These markers include S-100, a calcium-binding protein that is a sensitive marker of melanocyte differentiation (sensitivity 97-100%); melanoma antigen recognized by T cells 1 (MART-1) and melan-A antibodies that target the product of the MART-1/Melan-A complex, a small protein that is expressed in melanomas as well as normal adult melanocytes (sensitivity 75-92%); and HMB45, an antibody that reacts with a 10-kDa cytoplasmic glycoprotein 100 (gp100) premelanosome complex and provides strong evidence of melanocytic histogenesis (sensitivity 69-93%).[7,8]

MUP patients should be treated with early aggressive surgical management in a similar fashion as those with Melanoma of Known Primary (MKP).[2] Patients presenting with stage III lymphadenopathy should undergo either radical or modified lymph node dissection. In spite of recurrence rates, wide excision with 1-2 cm margins is the best treatment recommendation for subcutaneous disease. The addition of a one-year adjuvant regimen of nivolumab or pembrolizumab is generally recommended.[2,12] Stage IV MUP warrants aggressive therapy and should be treated similarly to stage IV MKP with a combination of surgery, chemotherapy, immunotherapy, and radiotherapy. Immunotherapeutic or chemotherapeutic regimens such as interferon-a, interleukin, dacarbazine, procarbazine, cisplatin, cyclophosphamide, etc. are utilized.[2,4,12]

MUP patients presenting with nodal disease have a median overall survival ranging between 24 and 127 months, a 5-year survival rate between 28.6% and 75.6%, and a 10-year survival rate between 18.8% and 62.9%.[4] Retrospective studies have demonstrated that patients with MUP who had undergone therapeutic lymph node dissection showed a statistically better overall survival compared to MKP treated similarly. Extracapsular extension and an increased number of positive lymph nodes were negative prognostic factors for overall survival.[9,10]

The majority of recurrences of MUP occur within 2 years of initial presentation; mean times to recurrence for men and women are 7.4 and 8.3 months, respectively. Those with nodal MUP relapse at a rate of 42–62%, following the completion of the initial treatment.[4]

Verver et al., using the prospective nationwide Dutch Melanoma Treatment Registry, found that in advanced and metastatic cutaneous disease, the overall survival of MUP patients was superior to patients with MKP. MUP patients had superior survival in adjusted analysis despite presenting with poorer prognostic characteristics. They concluded that MUP patients would benefit at least equally from treatment with novel therapies such as immune checkpoint inhibition and targeted therapy.[11]

Surveillance of MUP patients is similar to patients with MKP. The National Comprehensive Cancer Network (NCCN) recommends history and physical examination every 3-6 months for 2 years, then every 3-12 months for 3 years, then annually as clinically indicated. Imaging such as nodal basin ultrasound and cross-sectional imaging (CT with IV contrast or whole-body FDG PET/CT) would be indicated to investigate specific signs and symptoms. In patients with no clinical evidence of disease, surveillance imaging is recommended every 3–12 months for 2 years, then every 6–12 months for another 3 years to screen for recurrence.[13]

An occult primary can become clinically apparent over 5 years after the original diagnosis of MUP. Long-term follow-up is recommended, as evidenced by case reports of a primary mucosal or cutaneous melanoma becoming clinically evident 6 to 15 years after original visceral MUP was diagnosed. It has been suggested that this could be related to alterations in the patients' immune responses over time.[2]

Conclusion

MUP are an uncommon subset of melanomas that present as a diagnostic challenge and are histologically and immunochemically similar with its classic counterparts with known primaries. This disease entity is managed similarly with classically occurring melanomas with nodal/metastatic disease and tend to have a more favorable outcome.

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