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Metastatic Melanoma of Unknown Primary Revealed by Granulomatous Cervical Lymphadenitis

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Abstract **Case Report**

Metastatic melanoma of unknown primary (MUP) is very uncommon and represents 3% of all melanomas. It is discovered first as a secondary deposit within lymph nodes essentially, subcutaneous tissues, or other organs without a clearly evident site of origin. The main hypothesis is that the primary melanoma undergoes immune-induced reaction after metastatic spread of tumor cells had taken place which involves a spontaneous regression but other theories are possible as well. It occurs mostly in men in their forties or fifties. Lymph nodes are the most common site since it represents 40 to 60%, for women it is the inguinal lymph nodes that are usually involved. Early aggressive surgical excision seems to be the best treatment but adjuvant therapy may also be proposed. Furthermore, in these lymph nodes it is exceptional to witness a granulomatous reaction coexisting with metastatic cells in case of melanoma. We report the case of a metastatic MUP in a 27 young women revealed by a granulomatous lymphadenitis treated with lymphadenectomy and 30 sessions of radiotherapy with no signs of relapse or active disease for three years now.

Keywords: Metastatic, hypothesis, radiotherapy.

INTRODUCTION

Melanomas are malignant tumors derived from melanocytes that accounts for 1–3% of all malignancies. The most common site of involvement is usually the skin, although occasionally primary melanoma develops in other organs such as the eyes or mucous membranes. Melanoma incidence has increased worldwide over the last three decades with an important death rate. In fact, over 90 000 new cases approximately were diagnosed in the year 2018 in the United States [1]. Although, more than 97% of all melanomas are diagnosed with a known primary site; rarely, it is diagnosed without an obvious primary site, and is referred to as melanoma of unknown primary (MUP). In this situation, it is discovered first as a secondary deposit within lymph nodes essentially, subcutaneous tissues, or other organs without a clearly evident site of origin [2]. Furthermore, in case of metastatic MUP, a granulomatous response occurring within regional lymph nodes is very uncommon unlike metastatic carcinomas. In fact, to the best of our knowledge, this latter phenomenon has only been reported a few times in the literature. To this day, MUP is still biologically ill defined, and clinically understudied [3].

We report the case of a metastatic MUP in a 27 young women revealed by a granulomatous lymphadenitis.

CASE REPORT

A 27-year-old female patient with no particular pathological history presented for almost a year a firm, fixed, painless and non-inflammatory cervical swelling with no fever or other general symptoms. A lymph nodes biopsy was realized by an otorhinolaryngologist. The histological examination concluded to a metastatic melanoma. The patient was then referred to Dermatology department for further investigations and specialized care. To discover the primary lesion, a total body skin examination was realized using dermoscopy when necessary. Two suspicious lesions were biopsied that turned out to be just histiocytofibromas. In addition to that, a rhinocavoscopy and a detailed ophtalmological examination were performed. It all came back negative. PET scanning revealed several right superior jugular hypermetabolic lymphadenopathies without suspected hypermetabolism of primary neoplasia on the entire integument explored. The brain MRI was normal. We performed then a

lymph nodes dissection. Microscopic examination showed nodular cell infiltration and pseudogranulomatous appearance with epithelioid cells of histiocytic appearance. The cells were strongly expressing PS100 and Melan A, the CD68 was totally negative. Histolopathological findings suggested the diagnosis of metastatic melanoma with granulomatous reaction. Tuberculosis and sarcoidosis were excluded. The patient was treated with 30 sessions of radiotherapy in the cervical area with close follow ups. Every six months a PET scanning, a brain CT and a total body exam are realized showing no signs of relapse or active disease. It's been three years now and the patient is closely followed.

DISCUSSION

The first case of MUP dates back to 1917 [4]. Pack et al reported a series of 1,190 patients treated at Memorial Hospital between 1917 and 1950, of which 29 (2.4%) patients were classified as having an occult primary [4]. Then, it was Das Gupta in 1963 who defined MUP as one discovered in lymph nodes mostly (LNs), subcutaneous tissue, or visceral organs without a cutaneous, ocular, or mucosal primary site despite detailed examination [5]. Diagnostic criteria used by Das Gupta for MUP excluded from this category patients who did not receive complete physical examination, patients with evidence of previous orbital enucleation and patients who underwent surgical or nonsurgical procedures, without histological documentation [6]. However, only 16% of published peer-reviewed studies used these full criteria as proven by Kamposioras and al systematic review [7]. In fact, the majority of studies make the diagnosis based only on history, physical examination, pathology, and imaging.

Since its original definition, the incidence of MUP varied between different studies, ranging from 1.2% to 18% [8]. To help explain this biological phenomenon, numerous theories have been developed. The predominant hypothesis is that the primary melanoma undergoes immune-induced reaction after metastatic spread of tumor cells had taken place which involves a spontaneous regression. This theory was first proposed by Smith and Stehlin in 1965. Since then, the partial or complete spontaneous regression of melanoma from a known primary site has been well documented in the literature; it accounts for 11% of all cases of spontaneous tumor regression [9]. Alternatively, MUP could also be explained by the fact that melanoma metastases are induced by a previously excised melanoma that was originally misdiagnosed as a benign nevus or mole or that the primary tumor arises from the beginning in lymph nodes or visceral organs [10]. The median age of presentation of MUP is typically in the forties to fifties same as cutaneous melanoma [11]. Another peak of incidence is also observed in younger patient that may be attributed to their robust immune responses, resulting in a higher rate of primary site regression. In fact, MUP has also been reported in children, it may present and behave differently from typical adult melanoma [12]. Moreover, studies showed that MUP occurs twice as often in men as in women; in a meta-analysis of 18 studies of MUP, the median male to female ratio was 2.2[11]. The reason for male predominance is not well identified. This may be attributed to the fact that men may be more likely to ignore a primary cutaneous melanoma until after it completely regresses and they are more prone to developing melanoma in the back or scalp where regression may be more likely to occur [7].

Lymph nodes are the most common metastatic site since it represents 40 to 60% of all cases. It seems to be the axillary and cervical area in men, whereas in women it is most likely to present in inguinal LNs [11]. Patients can also present with subcutaneous nodules or bony metastases or visceral including the brain, parotid gland, heart, mediastinum, lung, breast, liver, common bile duct, small and large intestine, kidney, adrenal gland, prostate and muscle. In some rare cases though, we witness a paraneoplastic syndrome or a vitiligo-like reaction [13]. Depending on which site was first involved, the patient can be classified. The American Joint Committee on Cancer 2009 melanoma staging system stated to classify MUP with nodal or subcutaneous involvement as stage III and cases with visceral metastasis as stage IV [6].

In our case, the patient was a 27 years old female with no prior history presenting with cervical metastatic lymph nodes with no occult primary melanoma (stage III).

What was more interesting in our case was the histological presentation of the metastatic melanoma since there was a granulomatous reaction within the lymph nodes.

A granulomatous response occurring within regional lymph nodes draining carcinomas or within the stroma of tumors is a well-recognized entity and has been reported in various neoplasms [14]. However, the presence of coexisting metastatic tumor and a non-caseating granulomatous reaction in lymph nodes has been reported only in nasopharyngeal carcinoma, seminoma and extremely few cases of melanoma [15]. The pathological mechanism of this rare phenomenon remains uncertain and it may be the intervention of a cell mediated immune response to soluble tumor related antigens released from the tumor site [16]. On the other hand, before retaining this diagnosis, it is important to exclude other causes of granulomatous inflammation, especially tuberculosis and sarcoidosis [17] and to be aware that granulomatous lesions mimicking melanoma metastases may occur and should lead to careful histological examination. In our patient, there were no signs of tuberculosis or sarcoidosis and we used Melan

A, PS100 and CD68 to confirm the metastatic melanoma.

When it comes to management, numerous studies have supported the consensus that MUP patients should be treated with early aggressive surgical excision [18]. Patients with nodal MUP typically undergo lymph node dissection as the standard of care and in case of subcutaneous lesion; wide local excision is recommended [19]. In some cases, adjuvant therapy may also be proposed for stage III and IV patients. In fact, among patients who underwent lymphadenectomy for nodal MUP at the John Wayne Cancer Institute, for example, 66% received adjuvant immunotherapy, 37% received chemotherapy, and 26% received radiation therapy [8]. In our case, our patient underwent lymphadenectomy and 30 sessions of cervical radiotherapy.

Moreover, regional lymphadenectomy for palpable LN metastases was associated with significantly improved 5-year overall survival for stage III MUP patients compared to melanoma with known primary (MKP) patients [8]. Relapses are common though at a rate of 42% to 62% after initial treatment, diagnosed within two years of initial presentation [7]. Some prognosis factors have been identified such as patient age, gender, and the number of lymph nodes or distant metastatic sites involved [20]. Comparing younger and older age groups, several studies found a survival advantage in the younger cohort [21]. In addition to that, Lee *et al*. [8] found improved survival outcomes in female compared with male patients presenting with nodal extension. In this case report, our patient was a 27 years old female with cervical lymph nodes and no subcutaneous or visceral lesions with three years follow up and no relapses.

CONCLUSION

MUP refers to metastatic melanoma in lymph nodes, subcutaneous tissue, or visceral sites in the absence of a detectable primary tumour despite detailed examination. It comprises 3% of all melanomas and occurs more commonly in men with a peak incidence in the fourth and fifth decades of life. For nodal MUP, patients who undergo surgery are less likely to have a recurrence of the malignancy and have improved survival. Furthermore, the presence of coexisting metastatic tumor deposits and a non-caseating granulomatous reaction in lymph nodes is a very rare phenomenon. However, before labeling this reaction as an immunological response to tumor antigens, it is important to exclude other causes of granulomatous inflammation, especially tuberculosis and sarcoidosis.

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