

# Primary Solitary Melanoma of the Lymphatic Nodes Or a Single Metastasis of Unknown Melanoma: Do We Need a New Staging System?

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## Abstract

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**BACKGROUND:** Malignant melanoma is a disease which has a cutaneous origin in 90% of the patients, but in rare cases, it could be discovered as secondary deposits with unknown primary site. Metastatic Malignant Melanoma occurs without a primary site in about 3% of all melanoma patients, and it could be divided into two main groups: metastatic lymph nodes' involvement or non-lymph nodes disease. The lack of unified classification and staging system, provided by AJCC (2009), as well as the lack for certain diagnostic and therapeutic protocol, prompt us to raise the question what is the right way to precede in cases of metastasis of the lymph nodes, without evidence of a primary tumour?

**CASE REPORT:** We report a case of 67-years- old woman who presented in the dermatology clinic after a surgical removal of an enlarged lymph node in her left femoral area, verified histologically as a metastasis of melanoma. After a diagnostic refinement in the clinic, the diagnosis of metastasis of malignant melanoma was confirmed by histology revision. We use the presented case to create for the first time in the world literature a novel stereotype of thinking, which is also followed by a stereotype of clinical behaviour – gentle to the patient, but providing a certain amount of security and satisfaction for the medical staff.

**CONCLUSION:** The affection of a single lymph node in the absence of a primary tumour should not automatically lead to the conclusion that it is a single metastasis, but rather a primary melanoma of the lymph nodes, in cases of a negative PET scan, for example. In these cases, the measuring of the tumour thickness should guide the further therapeutic behaviour and determine the approach.

## Introduction

Metastatic melanoma with unknown primary site (MUP) is defined as the progressive stage of disease, with no evidence of a primary tumour [1]. Although with rare incidence, metastatic melanoma with unknown primary site could occur in the lymph nodes, the skin or the inner organs, like lung, brain or liver metastasis, occupying 2-6% of all melanoma cases [1, 2]. According to results from a retrospective review for a period of ten years, made by Massachusetts General Hospital (MGH) and the Dana-Farber Cancer Institute (DFCI) the epidemiology of MUP shows higher prevalence of the cases, affecting the lymph nodes (35 patients), compared to

those, affecting the skin (12 patients) or viscera (23 patients) [2]. Although the aetiology of MUP is not fully understood, an unrecognised or misdiagnosed primary melanoma seems to be the most logical explanation for its occurrence [1, 3]. Regarding the fact that such primary lesion is usually not found, the strong immunological potential of melanoma itself, which could lead to incomplete or complete remission of the primary lesion by the host's immune response has been implicated as a possible explanation of this phenomenon [3]. Another explanation for the possible reason for MUP is based on the theory that a prior lesion had been removed without a straight-laced histology or it is linked to nevus cell aggregates (NCA) in the lymph nodules [4, 5] It has been also hypothesized that ectopic melanocytes, located in

lymph nodes or inner organs could undergo malignant transformation in the same way as the cutaneous cells, in response to oncogenic stimuli or genetic predisposition [1, 6]. Hence, it has been established that relatives of patients with all kinds of cancers with unknown origin are at increased risk of developing the same, or other malignancies, including lung, pancreatic and colon cancers [6]. This in turn confirms the pleomorphic nature and oncogenesis of these types of cancers, which remain in top 5 reasons for death among cancer patients around the world [1]. Most of the cases have been diagnosed at stage III, followed by stage IV disease, while the most common primary site of metastatic affection is the lymph nodes, followed by lungs and skin [1]. Staging classification resembles this in cutaneous melanoma, where limited cutaneous or nodal metastasis are classified in stage III, in contrast to those, disseminated in various body sites – in stage IV [1, 2].

Although, there is no significant differentiation in staging between MUP and melanoma with known origin, according to American Joint Committee of Cancers' recommendations from 2009, there are some differences in the biological behaviour, as well as in the prognostic rate and genetic signature of these two sides of the same coin [1]. MUP patients have a better prognosis than those with metastatic melanoma with a known primary and better survival rate compared to non-lymph nodes MUP in general [1, 3]. Herein, we present a case of metastatic melanoma in the lymph node, without evidence of primary site tumour, as we focus the attention on some critical points in the diagnostic and therapeutic behaviour, which are often challenging.

## Case report

We present a 67-years-old Caucasian female patient who came to the dermatology clinic for a diagnostic clarification and follow up. A surgical removal of an atypical and enlarged lymph node in the left femoral area was done a month ago, according to her medical history (Fig. 1a). Detailed medical history was obtained, but the patient did not report any precipitating event for the swelling. Postoperatively, the histological evaluation confirmed: metastases in the lymph node from Melanoma (Fig. 1b, c, d). Comorbidities include colon irritable, stomach polyps, arterial hypertension, endometrial hyperplasia, uterine fibroids. No surgical history was reported before the lymph node removal. The patient was recommended for a diagnostic refinement which was done in a month after the surgical treatment in an internal disease clinic. All necessary examinations for confirmation of the diagnosis of MUP according to the oncology protocols [7] were done. The patient

underwent thorough examinations, including detailed medical history, physical examinations and consultations with different medical specialists, as well as positron emission tomography (PET scan), biochemical and haematological tests and histology revision. Physical examination with otorhinolaryngology specialist showed up two enlarged lymph nodes in her neck: one at each side: measuring 2/1 cm, painless, firm on palpation and non-fluctuant. The overlying skin was described as intact with no redness.

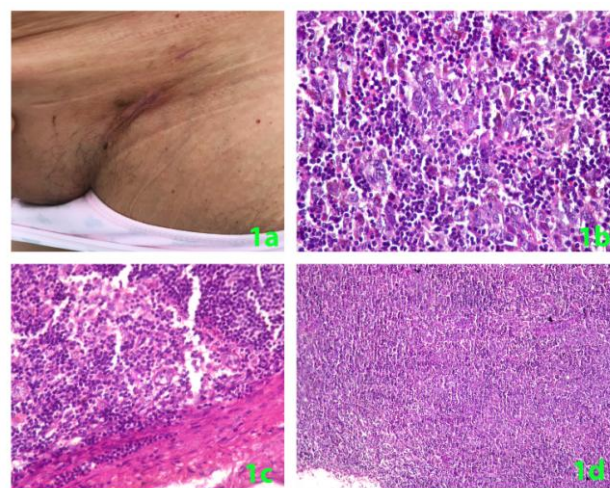


Figure 1: a) Patient with melanoma of the lymph node, treated surgically; b, c, d) Tumour cells infiltrating the lymphatic node

PET scan performed with oral and i.v. contrast did not show any abnormalities. No primary site tumour evidence or metastatic lesion was seen. Physical examination with gastroenterologist, gynecologist and ophthalmologists were done. The genital examination did not detect any primary site lesion. Both gastroscopies of gullet, stomach and duodenum and colonoscopy did not reveal any abnormalities which could be related to a primary site tumour. Blood tests established high levels of S-protein and LDH, considered as markers for melanoma. Second histology revision confirmed metastases of malignant melanoma as the previous one. The patient was referred for immunohistochemical tests, which revealed a positive staining for Melan A and HMB 45.

## Discussion

Metastatic melanoma of unknown origin is a diagnosis of exclusion. A wide range of diagnostic procedures should be performed to exclude primary cutaneous, lymph node or visceral organ affection [1, 2]. Except for the ordinary diagnostic procedure with clinical examination, blood tests, biochemistry and

imaging diagnosis in order to exclude metastatic spread in melanoma with cutaneous or mucosal origin, a multidisciplinary approach is required to exclude any primary involvement in cases of metastatic disease, including otorhinolaryngological examination; ophthalmological examination, gynecological examination for women and urological for men [8]. Although imaging diagnostic procedures are also considered helpful, some studies show that although better than CT scan in lymph node staging, the false-positive rate is high in PET-positive lymph nodes measuring less than 1 cm in diameter [9]. Although F-18 FDG PET/CT is found as a useful method in staging cutaneous and non-cutaneous melanoma, an extremely low detection rate is reported in locating the primary carcinoma of metastatic melanoma and axillary metastasis in patients with cancer of unknown primary site [10]. Differentiation in genetic signature of primary and metastatic melanoma with unknown origin has also been provided, with a higher rate of mutations in BRAF and NRAS genes in MUP patients, as well as more common mutations in TERT-promoter [1]. Although promising, these discoveries could not be implicated as routine diagnostic procedures, because of the high price of the method and its limitations.

The lack of unified classification and staging system, provided by AJCC (2009), as well as the lack for certain diagnostic and therapeutic protocol, prompt us to raise the question what is the right way to proceed in cases of metastasis of the lymph nodes, without evidence of a primary tumour? Furthermore, the lack of unified including criteria and staging in all of the studies on that issue often leads to contradictory results regarding the best diagnostic approach and prognosis rate, which additionally confuse the clinicians and patients themselves.

We use the presented case to create for the first time in the world literature a stereotype of thinking, which is also followed by a stereotype of clinical behaviour – gentle to the patient but providing a certain amount of security and satisfaction for the medical staff. The important point is to pay accurate attention to these data in future guidelines, which are not insignificant.

The affection of a single lymph node in the absence of a primary tumour should not automatically lead to the conclusion that it is a single metastasis, but rather a primary melanoma of the lymph nodes, in cases of a negative PET scan, for example. In these cases, the measuring of the tumour thickness should guide the further therapeutic behaviour and determine the approach. Herein, we suggest the staging of MUP to be similar to stage I and II of cutaneous melanoma but strictly referred to the primary melanoma of the lymph nodes.

In this way, a lymphadenectomy should be recommended for tumours with thickness over 1 mm,

or less than 1 mm, but with additional risk factors such as increased number of mitosis, age under 40 years, vessels invasion, and so on. This group should also include cases of melanomas that have been regressed and subsequent they could not be detected after the metastatic spread. But we should not forget that the mucosal melanomas can be amelanotic and composed by up to a hundred malignant cells, which would be undetectable on PET scan also.

Despite all the mentioned variants, the presence of several affected lymph nodes should be interpreted as a sure marker for metastatic disease, weather, the affection of a single lymph node is more indicative for a primary lymph node melanoma, which would require more soft approach in cases with smaller tumour thickness, or at least in some acceptable limits with which clinicians should comply with. Therefore, the former statement that MUP of single lymph nodes has similarities to Stage III disease and should be treated with aggressive surgical management [11] is no longer needed.

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