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Case report

A CHALLENGING "SILENT DEPTH" CLINICAL SCENARIO IN NORTH MACEDONIA: UNMASKING A RARE CASE OF AMELANOTIC MELANOMA WITH TRAPEZIUS MUSCLE INVASION AND METASTATIC DISEASE

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Abstract: **Introduction:** Amelanotic melanoma is a subtype of melanoma that exhibits little or no pigment on visual or histological examination. Approximately 1–8% of all melanomas are amelanotic. It can mimic various benign or malignant melanocytic and non-melanocytic skin tumors, thereby presenting a significant diagnostic challenge. Primary amelanotic melanoma with muscle involvement is an extremely rare entity. A review of the literature revealed no series or case reports.

Case Report: We present the case of a 62-year-old female patient with primary amelanotic melanoma infiltrating the trapezius muscle. The tumor was excised together with a clinically positive lymph node on the right side of the neck. Computed tomography (CT) angiography of the lungs, abdomen, and pelvis demonstrated bilateral diffuse nodular changes, a mediastinal pretracheal lymph node, and multiple diffuse liver lesions, consistent with secondary deposits. Molecular pathology revealed positivity for the BRAF V600E2/K/R/D mutation, and the patient began first-line targeted therapy with BRAF/MEK inhibition in accordance with protocols for BRAF-positive metastatic melanoma. Three months later, a follow-up CT scan demonstrated complete remission of the previously observed metastatic changes.

Conclusion: Primary amelanotic melanoma with muscle involvement is exceptionally rare, with no published series or case reports identified. This case highlights the importance of early detection and treatment in suspected melanoma and underscores the need to consider melanoma in all clinically unclear cases.

Keywords: amelanotic melanoma, muscle invasion, trapezius muscle, metastatic disease.

INTRODUCTION

Melanoma is a malignant tumor arising from melanocytes in the skin, mucosa, and various internal organs. Amelanotic melanoma (AM) is a subtype that shows little or no pigment on visual or histological examination (1, 2). It is classified into three groups according to the presence and amount of melanin: amelanotic, partially pigmented, and lightly colored melanoma (3). Although completely amelanotic melanomas are rare, hypomelanotic melanomas with slight pigmentation are more common. Approximately 1–8% of all melanomas are amelanotic; however, the true incidence is difficult to determine due to frequent misdiagnosis (4, 5).

Amelanotic melanoma typically appears as a pink, red, or flesh-colored lesion and may mimic both benign and malignant melanocytic and non-melanocytic skin tumors, as well as inflammatory skin diseases, thereby posing a diagnostic challenge. Therefore, any erosive tumor should raise suspicion for amelanotic melanoma, particularly when located on the palms or soles (6, 7).

Dermoscopy is an essential diagnostic tool for pigment evaluation and for identifying characteristic

vascular structures that are not visible to the naked eye. A polymorphous vascular pattern, especially with irregular dot vessels or a combination of dotted and linear irregular vessels, is the most frequent dermoscopic finding (8, 9). In some cases, a full-thickness biopsy is required for definitive diagnosis.

Surgical excision remains the gold standard for primary melanoma treatment. The National Comprehensive Cancer Network (NCCN) recommends surgical margins based on Breslow depth. For tumors thicker than 2 mm, wide local excision with a 2-cm negative margin is advised, with the deep margin extending to, but not including, the fascia—the first lymphovascular barrier (10, 11).

Targeted therapy with BRAF/MEK inhibitors has emerged as a critical treatment strategy for patients with metastatic BRAF-positive melanoma. This approach specifically targets aberrant signaling pathways driven by BRAF mutations, leading to enhanced therapeutic efficacy and improved clinical outcomes (12–15).

Primary amelanotic melanoma with muscle involvement is exceedingly rare. A review of the literature revealed no series or case reports. Here, we present a case of amelanotic melanoma with invasion of the trapezius muscle.

CASE REPORT

A 62-year-old female patient with a large lump in the right scapular region extending to the supraclavicular fossa was referred to the University Clinic for Plastic and Reconstructive Surgery in Skopje, North Macedonia, from a smaller hospital in the country (Figure 1). The patient's history revealed progressive tumor growth over several years. Two years prior, at the hospital from which she was referred, the lesion had been

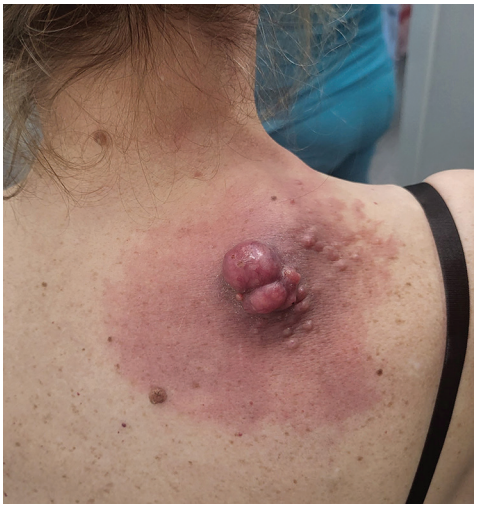

***Figure 1**. A large, pink-grey, multinodular dermal tumor measuring 7 × 8 cm, with the largest nodule protruding 2 cm above the surrounding skin*
(The image is from the authors' personal archive)

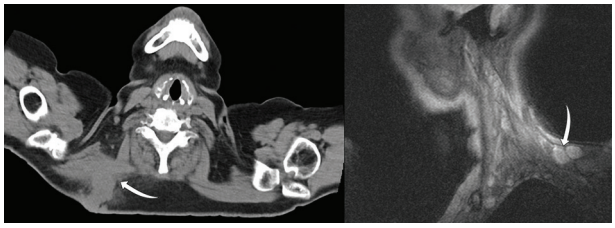

***Figure 2**. (Left Image) The arrow shows the tumor infiltrating the trapezius muscle (CT scan)*
(Right image) The arrow points the 2 subcutaneous nodules at the posterolateral site of the neck on the MRI
(The image is from the authors' personal archive)

followed with a differential diagnosis of a lipoma. The patient was advised to have it removed for pathological examination but declined the recommendation.

At presentation, clinical examination revealed a large, pink-grey, multinodular dermal tumor in the right scapular region extending toward the right supraclavicular fossa. The tumor measured 7 × 8 cm, with the largest nodule protruding 2 cm above the surrounding skin. On physical examination, the tumor was firm and relatively immobile to the underlying tissues. Additionally, two subcutaneous palpable masses were noted at the back of the neck, along with an enlarged lymph node on the right side of the neck. Clinically, it was an unclear case, which prompted further examinations.

Therefore, the patient underwent computed tomography (CT) angiography, magnetic resonance imaging (MRI), and fine-needle aspiration (FNA) biopsy. The CT and MRI revealed a tumor infiltrating the trapezius muscle (Figure 2), and the FNA biopsy categorized the tumor in the V classification group for malignancy, strongly suggesting melanoma. Owing to the tumor's aggressiveness and muscle involvement, sarcoma was also considered in the differential diagnosis.

Surgical removal of the tumor and the positive cervical lymph node was planned. Under general anesthesia, with the patient positioned in lateral decubitus, the tumor was excised with a 2-cm free lateral margin, and the deep

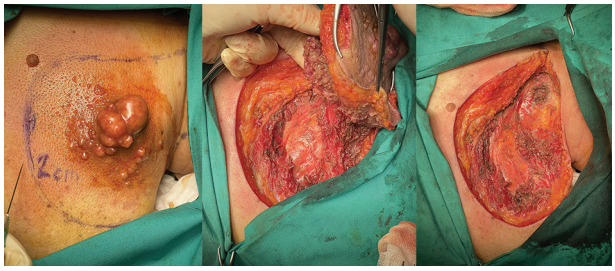

***Figure 3**. Intraoperative view: the tumor was excised with a 2-cm healthy lateral margin, and the deep margin included part of the trapezius muscle*
(The image is from the authors' personal archive)

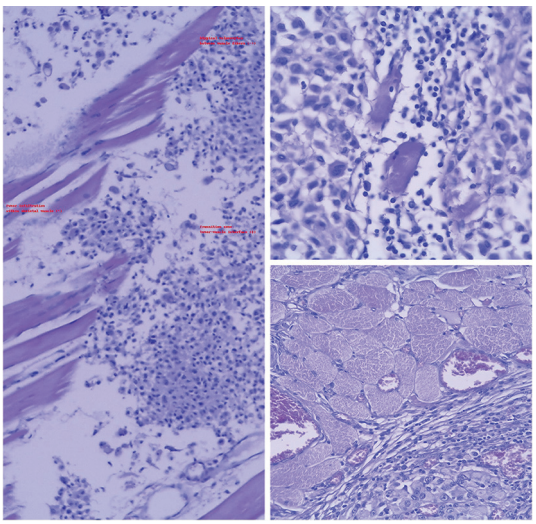

***Figure 4**. Histopathological Features of Amelanotic Melanoma with Muscle Invasion (H&E)*

(*) Tumor infiltration within skeletal muscle: The left panel demonstrates extensive infiltration of atypical amelanotic melanocytes between and around skeletal muscle fibers.

(→) Atypical melanocytes between muscle fibers: High magnification shows pleomorphic, non-pigmented tumor cells infiltrating the muscle tissue.

(#) Transition zone: tumor-muscle interface: The bottom right highlights the border between invaded tumor areas and relatively preserved skeletal muscle bundles.

(The image is from the authors' personal archive)

margin included part of the trapezius muscle (Figure 3). The clinically positive lymph node on the right side of the neck was also removed. After achieving hemostasis, the wound was left open to heal by secondary intention pending the pathohistological results. One week later, the pathology report confirmed primary amelanotic nodular melanoma involving the skin, subcutaneous tissue, and infiltrating the trapezius muscle, along with satellitosis and amelanotic metastases to the cervical lymph node (pT4a, pN3, pMX, R0, stage IIIC according to the AJCC staging system) (Figure 4). Both the lateral and deep margins were tumor-free. Additional molecular pathology findings confirmed positivity for the BRAF V600E2/K/R/D mutation. At that time, the wound was closed using a split-thickness skin graft (STSG), and a second subcutaneous metastatic deposit was removed.

Laboratory findings supported the diagnosis, with an increased S-100 protein level of 0.432 µg/L (reference < 0.12 µg/L). The postoperative course was uneventful, and one week after the second operation, the patient was discharged and referred to the University Clinic for Oncology and Radiotherapy for further evaluation and treatment.

CT angiography of the lungs, abdomen, and pelvis showed bilateral diffuse nodular changes predominantly in the basal lung regions, with the largest lesion in the right basal lung measuring up to 11 mm, consistent with secondary deposits. A mediastinal pretracheal lymph node measured up to 1.25 cm. Additionally, the liver exhibited multiple (approximately seven) diffuse hypodense lesions that were poorly demarcated in the venous phase; the largest lesion in segment 6 measured up to 1.2 cm, suggestive of secondary deposits.

The patient began first-line targeted therapy with BRAF/MEK inhibitors following National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) protocols for BRAF-positive metastatic melanoma (Vemurafenib 1920 mg daily and Cobimetinib 60 mg daily) (12–15).

Three months later, a follow-up CT angiography of the lungs, abdomen, and pelvis demonstrated complete remission of the previously observed metastatic changes in the lungs, mediastinum, and liver. The patient continues targeted therapy with BRAF/MEK inhibitors, with no reported adverse effects.

The patient was last evaluated at the University Clinic for Oncology and Radiotherapy on April 22, 2025, after 8 months of therapy. At that time, it was decided to transition melanoma treatment from targeted therapy (Vemurafenib/Cobimetinib) to immunotherapy (Pembrolizumab). This change in therapeutic approach was prompted by the diagnosis of a second, independent malignancy—stage IIB squamous cell carcinoma of the cervix—for which concurrent radiochemotherapy was indicated and will also be administered at the Clinic for Oncology and Radiotherapy. The second tumor was diagnosed eight months after the initial diagnosis of amelanotic melanoma.

DISCUSSION

Amelanotic melanoma is a variant characterized by the absence of melanin production, which complicates early detection, identification, and pathological diagnosis. The absence of ulceration may mislead clinicians, although it can be associated with a better prognosis; however, it does not mitigate the risks of deep infiltration and metastasis.

In this case, the clinical examination showed no tumor ulceration, while MRI confirmed muscle involvement—a rarity in melanoma cases. Although the fine-needle biopsy suggested melanoma, its limited sensitivity contributed to the initial exclusion of dermoscopy from the diagnostic workup. As supported by the literature, the absence of melanin combined with the lack of ulceration and the presence of muscle involvement initially obscured the diagnosis of melanoma.

According to the American Joint Committee on Cancer (AJCC), amelanotic melanoma carries a poor-

er prognosis than other melanoma types due to deeper infiltration from delayed diagnosis and its inherently aggressive nature.

The aggressive tumor behavior in this case is exemplified by the muscle involvement. It remains a subject of discussion whether muscle involvement was solely a function of tumor aggressiveness in the absence of ulceration. Skeletal muscle is generally resistant to primary and metastatic cancer; however, primary malignant tumors—including melanomas—can involve skeletal muscle more commonly than metastases. This muscle resistance to cancer may be related to the inherent resistance of muscle tissue to tumor growth, its variable blood flow, and metabolism (15). The rich vasculature of skeletal muscle, regulated by beta-adrenergic receptors, results in highly variable blood flow (16). Some studies suggest that lactic acid production by muscles may inhibit tumor cell growth (17), and that cancer cell survival is enhanced in denervated muscle compared to electrically stimulated muscle (18).

The pathology report confirmed the presence of satellitosis and amelanotic metastases to the cervical lymph node in this case of primary amelanotic nodular melanoma.

A meta-analysis on nodular melanoma indicated that lymph node involvement is associated with a reduced 5-year survival rate—estimated at around 40–60%, depending on tumor characteristics and treatment options. Furthermore, amelanotic metastases in amelanotic melanoma are linked to a poorer prognosis, as documented in the literature (5).

The anatomical distribution of amelanotic melanoma varies by gender. In males, these lesions are typically located on the trunk, whereas in females they are more commonly found on the limbs. In contrast to these trends, the present case involves a female patient with an amelanotic melanoma located on the trunk (19).

Systemic therapy is recommended for stage III cutaneous melanoma following wide local excision, with or without sentinel lymph node biopsy and lymph node dissection (12–15). Evaluation for potential hereditary syndromes and appropriate genetic referral should also be considered.

CONCLUSION

Primary amelanotic melanoma with muscle involvement is exceptionally rare. A review of the literature revealed no series or case reports.

This case underscores the importance of early detection and treatment in suspected melanoma and highlights the need to consider melanoma in all clinically unclear cases. Due to the aggressive nature of the disease, timely surgical management and careful monitoring are essential to address potential metastases and ensure comprehensive care.

Conflict of Interest Statement

The authors declare that there is no conflict of interest related to this study.

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Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

IZAZOVAN KLINIČKI SLUČAJ U SEVERNOJ MAKEDONIJI: REDAK SLUČAJ AMELANOTIČNOG MELANOMA SA INVAZIJOM TRAPEZASTOG MIŠIĆA I METASTATSKOM BOLEŠĆU

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Uvod: Amelanotični melanom je podtip melanoma koji pri vizuelnom ili histološkom pregledu pokazuje malo ili nimalo pigmenta. Čini 1–8% svih melanoma. Može imitirati različite benigne i maligne tumore kože, kako melanocitne tako i nemelanocitne, što često predstavlja dijagnostički izazov. Primarni

amelanotični melanom sa zahvatanjem mišića je izuzetno redak, a u literaturi nisu opisane serije slučajeva ili pojedinačni izveštaji.

Prikaz slučaja: Predstavljamo slučaj 62-godišnje pacijentkinje sa primarnim amelanotičnim melanomom koji infiltriše trapezasti mišić. Tumor je hirurški odstranjen zajedno sa klinički pozitivnim limfnim čvorom sa desne strane vrata. CT pluća, abdomena i karlice pokazao je bilateralne difuzne nodularne promene, pretrahealni mediastinalni limfni čvor i više difuznih lezija u jetri, u skladu sa sekundarnim promenama. Molekularna analiza otkrila je BRAF V600E2/K/R/D mutaciju, te je pacijentkinja započela ciljanu terapiju BRAF/MEK inhibitorima po protokolu za BRAF-pozitivni metastatski melanom. Tri meseca kasnije kontrolni CT je pokazao potpunu remisiju prethodno registrovanih metastatskih promena.

Zaključak: Primarni amelanotični melanom sa zahvatanjem mišića je izuzetno redak, bez ranije objavljenih slučajeva. Ovaj slučaj ističe značaj ranog otkrivanja i pravovremenog lečenja sumnjivih melanoma i podseća da melanom treba razmatrati u svim klinički nejasnim slučajevima.

Ključne reči: amelanotični melanom, infiltracija mišića, trapezasti mišić, metastatska bolest.

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