ISSN 2664-8075 (Print) & ISSN 2706-5774 (Online)
South Asian Research Journal of Applied Medical Sciences
Abbreviated Key Title: South Asian Res J App Med Sci

| Volume-7 | Issue-4 | Jul-Aug- 2025 | **DOI: https://doi.org/10.36346/sarjams.2025.v07i04.003**

Case Report

Fast-Track Melanoma Metastatic: A Case Report of Accelerated Progression

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Article History
Received: 23.05.2025
Accepted: 30.06.2025
Published: 07.07.2025

Abstract: Metastatic malignant melanoma is the most lethal cutaneous neoplasm, originating from melanocytes and characterized by aggressive behavior and distant dissemination via lymphatic and hematogenous routes. Risk factors include phenotypic traits, genetic mutations, and environmental exposures. Histologically, it presents with atypical melanocytes invading the dermis, often showing nuclear pleomorphism, mitoses, and ulceration. Breslow thickness is the key prognostic indicator. Management is multidisciplinary, with surgical resection as first-line when feasible. In unresectable cases, treatment is guided by molecular profiling. We present the case of a 81-year-old female with rapid progression of the disease and ganglionar metastases.

Keywords: Dermatology, Melanoma, Lethality, Aggressive Skin Tumor, Metastatic Melanoma.

INTRODUCTION

Malignant metastatic melanoma is a potentially fatal neoplastic disease that originates in epidermal melanocytes [1]. It may initially be asymptomatic, but it behaves aggressively and is frequently accompanied by lymph node and distant metastases [2], predominantly affects the female gender, age of presentation varies, and it characteristically has a high capacity for spread, which favors its high possibility of metastasizing and resisting conventional treatments [1-3]. Histopathologically, invasive melanoma demonstrates atypical melanocytic proliferation with dermal infiltration, nuclear pleomorphism, mitotic activity, and, frequently, ulceration. Breslow depth remains the most reliable prognostic parameter. Staging investigations are guided by clinical presentation, with advanced imaging reserved for high-risk or symptomatic patients. Therapeutic strategies require a multidisciplinary approach. While surgical resection is preferred in localized disease, advanced cases benefit from molecular profiling to guide targeted therapies and immunotherapy. These recent advances have significantly improved outcomes, with selected patients achieving long-term survival [1-4].

CASE PRESENTATION

An 81-year-old female with previous medical history of type 2 diabetes mellitus and hypertension presented with a progressive dermatosis on the right lower extremity, the lesions consisted of multiple well-demarcated, ulcerative plaques measuring 2–5 cm, with necrotic bases and active bleeding, accompanied by several non-tender subcutaneous nodules (3–8 cm). Surrounding the primary lesions were satellite pigmented macules (0.5–2 cm), black to violaceous in color, with indurated, irregular surfaces, extending along the anterior aspect of the middle and distal third of the leg (Figures 1 to 3). The lesions were associated with severe burning pain and functional impairment due to claudication. Histopathological evaluation revealed intraepidermal melanocytic proliferation with cytologic atypia, invasion into the reticular dermis, and lymphovascular involvement (Figure 4)—findings consistent with malignant melanoma. Staging with contrast-enhanced chest-abdominopelvic CT identified a right inguinal lymphadenopathy, suggestive of metastasis. A month later she

presented to his medical oncology appointment with progression of the disease and increase in lesions. Surgical treatment with limb amputation and lymphadenectomy was recommended, however the patient refused surgical intervention. She was initiated on immunotherapy with nivolumab and ipilimumab as palliative treatment aimed at prolonging survival and controlling disease progression.

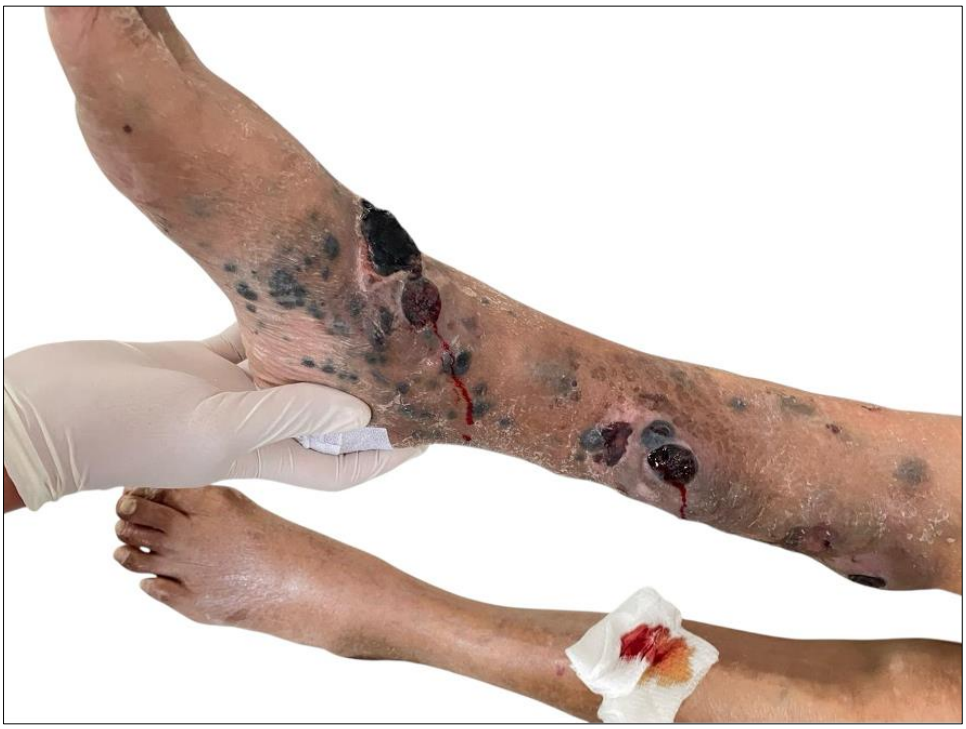

Figure 1: Clinical image, multiple flat, black/ purplish macules distributed on the leg and foot, some of them ulcerated

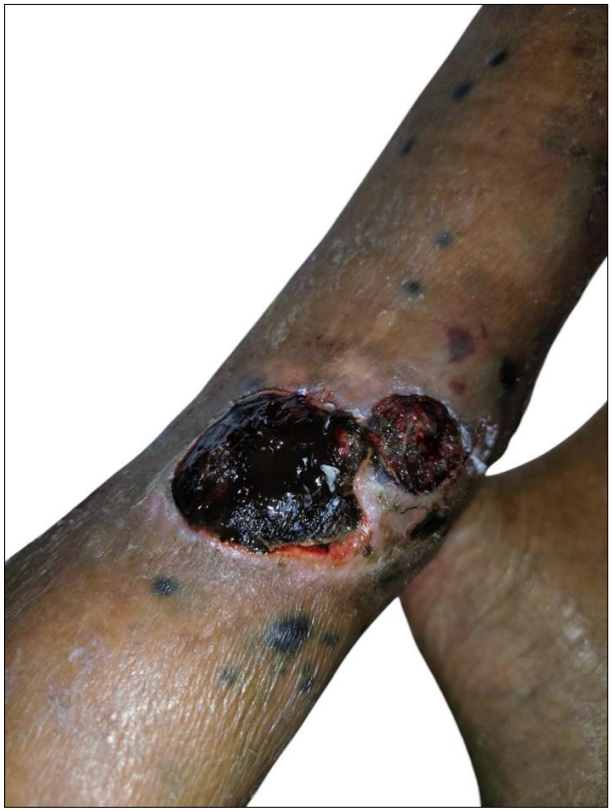

Figure 2: Clinical image, ulcerated lesion surrounded by multiple black macules

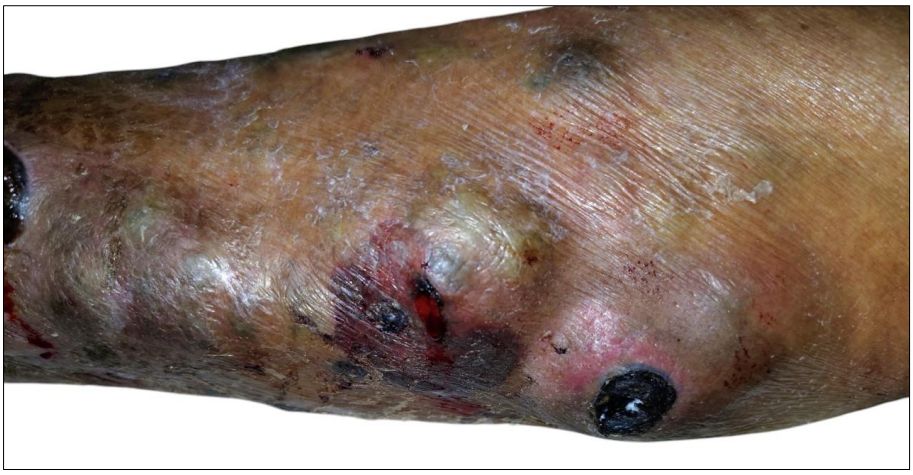

Figure 3: Clinical image, close up of the multiple non-tender nodule, one of them ulcerated with hemorrhagic fundus

Figure 4: Clinical image, multiple disseminated non-tender nodules, some ulcerated, surrounded by black macules, some of them ulcerated

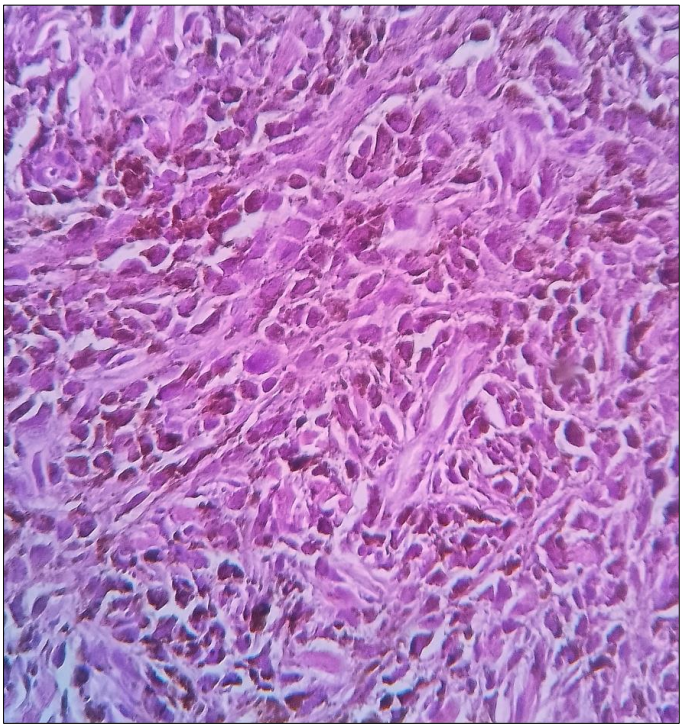

Figure 5: Epithelioid malignant neoplasm with abundant melanin production (Hematoxylin and eosin (40x))

DISCUSSION

Melanocytes are neural crest-derived cells in the basal layer of the epidermis and located in the skin, hair, uvea, mucosal epithelia, and meninges. The primary function of melanocytes is to synthesize melanin within melanosomes and transfer melanin via dendritic processes to neighboring keratinocytes [1], the main function of melanin is photoprotection as it absorbs ultraviolet (UV) radiation; it also acts as an antioxidant and free radical scavenger, protecting the skin from oxidative stress induced by radiation, in addition to participating in thermoregulation and pigmentation. The loss of control over the growth and homeostasis between melanocytes and keratinocytes, caused by various factors including exposure to radiation and mutations in melanocytes that promote malignant transformation, is referred to as melanomagenesis [2], several risk factors have been described: 1. Phenotypic (light phototypes, high total number of nevi, specifically melanocytic nevi) and presence of dysplastic or atypical nevi. 2. Genetic, family or personal history of melanoma, mutations in high-penetrance genes such as CDKN2A and, to a lesser extent, CDK4, POT1, TERT, and pigmentation-related genes. In primary and metastatic melanomas, BRAF is the most frequently mutated oncogene found in nearly 50% of cases. 3. Environmental: sun exposure or exposure to other sources of artificial UV, immunosuppression, and prior radiotherapy [2].

Melanoma is the solid tumor with the highest number of mutations and capacity to evade the immune system. [3], by upregulating immune checkpoint molecules that also physiologically prevent the body from escalating immune responses [4]. The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) interferon signaling pathway is an important regulator of the immune checkpoint molecule PD-1. Upon recognition of tumor antigens by T cells, the tumor secretes interferons, which trigger JAK-STAT-mediated expression of PD-1 ligands (PD-L1 and PD-L2) on the surface of melanoma cells. Binding of PD-L1 and PD-L2 to the surface receptor PD-1 leads to suppression of T cell effector activity and an antitumor immune response (adaptive immune resistance) [4].

Clinically, melanoma usually presents as an asymmetric pigmented lesion with irregular borders, variation in color, and changes in size or shape [5], an excisional biopsy should be taken with a margin of 3 mm around the pigment, but if we are dealing with a very extensive lesion or one in a difficult-to-access site like the nail bed, interdigital areas, palms, or soles, an incisional or punch biopsy should be performed. The invasive melanoma is histologically characterized by the presence of atypical melanocytic cells that have penetrated beyond the dermal-epidermal junction, invading the dermis. These cells are often of variable morphology, including epithelioid, spindle-shaped, or nevoid forms, and exhibit abundant cytoplasm, enlarged nuclei, prominent nucleoli, and nuclear pleomorphism. Invasion is evidenced by the presence of tumor cells in the papillary or reticular dermis, often in nests or as individual cells, and may be accompanied by mitosis, ulceration, and, in some cases, inflammatory response or stromal fibrosis [6]. Tumor thickness (Breslow index) is the main prognostic parameter and is measured from the upper part of the granular layer of the epidermis (or from the base of an ulcer, if present) to the deepest tumor cell in the dermis [6, 7], other relevant findings include ulceration, mitotic rate, and the presence of perineural or vascular invasion, although mitosis is no longer used as a criterion for staging in tumor [7]. Metastatic melanoma manifests following a sequence of steps: from primary melanoma to regional metastasis and distant metastasis; the latter can occur bypassing regional lymph nodes, indicating hematogenous dissemination [5-8], regional lymphatic metastases are common in melanoma and can be found near the original tumor or along the pathway between the tumor and the regional lymph nodes [2-6], distant metastases generally occur to lymph nodes, skin, and subcutaneous tissue (42 to 57%), lungs (18 to 36%), liver (14 to 29%), brain (12 to 20%), bone (11 to 17%), and intestines (1 to 7%) [8]. Extension studies should be used based on the initial clinical staging. In localized stages, the likelihood of suffering from lymphatic or systemic disease is low, so it is not necessary to conduct any studies. Computed tomography, positron emission tomography (PET), and magnetic resonance imaging will only be indicated for investigating symptoms, not routinely in asymptomatic patients, not even in stage III [5].

The treatment is generally surgical with the aim of preventing recurrence at the site of origin; however, in cases that are beyond this therapeutic possibility, immunotherapy with immune checkpoint inhibitors is the mainstay of systemic treatment. Recommended options include the combination of nivolumab plus ipilimumab, followed by nivolumab monotherapy, or nivolumab monotherapy, pembrolizumab monotherapy, or the combination of nivolumab with relatlimab. These combinations have demonstrated objective response rates and overall survival superior to traditional chemotherapy, with durable responses in a significant proportion of patients [9]. In patients with a BRAF V600 mutation, it is recommended to consider targeted therapies with BRAF inhibitors in combination with MEK inhibitors. Approved combinations include dabrafenib plus trametinib, encorafenib plus binimetinib, and vemurafenib plus cobimetinib [9, 10], however combination immunotherapy is associated with significantly greater toxicity [4].

CONCLUSIONS

The uncontrolled proliferation of melanocytes can initially lead to the development of melanoma. Metastatic malignant melanoma is a clinically and biologically complex entity, characterized by its high capacity for dissemination and therapeutic resistance. It requires a multidisciplinary and personalized diagnostic and therapeutic approach, based on

the location of metastases and the molecular profile of the tumor; diagnosis of melanoma is based on a combination of clinical evaluation, dermatoscopy, and histopathological confirmation. Most patients with metastatic melanoma treated with modern targeted therapies and/or immune checkpoint blockade will progress, owing to profound tumor cell plasticity fueled by genetic and nongenetic mechanisms and dichotomous host microenvironmental influences. The current standard of care for metastatic melanoma is immunotherapy with immune checkpoint inhibitors and, in patients with BRAF mutations, targeted therapy with BRAF and MEK inhibitors.

Conflict of Interest: The authors declare that there are no conflicts of interest at the time of publication of this article.

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