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A Rare Case Of Nodular Melanoma With Extensive Reactive Squamous Epithelial Proliferation: Diagnostic Challenges And Pathological Insights

N. Naganandhini[1] , Dr. J. Thanka[2] , Dr. Mary Anelia Correya[3] , Dr. Shobana. B[4]

[1]Post Graduate, Sree Balaji Medical College and Hospital Email: nagamedico87@gmail.com ORCID: 0009-0001-2253-2062
[2]MD, DNB (Pathology), Director and Professor of Pathology, Sree Balaji Medical College and Hospital
Email: thanka7paul@gmail.com ORCID: 0000-0002-7499-5552
[3]MD pathology, Assistant professor, Department of pathology, Sree Balaji medical college and hospital
Email: maryaneliacorreya@gmail.com ORCID: 0009-0008-2265-1900
[4]MD pathology, Associate Professor, Department of pathology, Sree Balaji medical college and hospital
Email: shobdr@gmail.com ORCID:0000-0003-4880-7279

ABSTRACT

Background:
Among the various subtypes of cutaneous melanoma, nodular melanoma is considered the most aggressive, characterized by a high metastatic potential, rapid vertical growth, and deep tissue invasion. Acral melanoma, although relatively rare, poses diagnostic challenges due to its subtle clinical presentation and resemblance to benign ulcers.
In this case report, we describe a case of nodular melanoma presenting as a non-healing ulcer on the foot, with histological findings notable for extensive adjacent reactive squamous epithelial proliferation.

Case Presentation:
An 82-year-old male presented with a non-healing ulcer on the plantar aspect of the right heel, persisting for one year. The patient underwent wide local excision of the lesion along with an inguinal block dissection. Gross examination revealed an ulceroproliferative lesion measuring 7 × 6 cm, with prominent brownish-black discoloration. Microscopic examination demonstrated a nodular malignant melanoma with a Breslow thickness of 8 mm, Clark level V invasion, and ulceration exceeding 2 cm in diameter.Notably, extensive adjacent reactive squamous epithelial proliferation was observed, characterized by dyskeratotic cells, keratin pearl formation, and melanin pigment deposition. Despite these features mimicking squamous cell carcinoma, immunohistochemistry confirmed the diagnosis of malignant melanoma.

Conclusion:
This case underscores the diagnostic challenges associated with melanoma, particularly when it presents with features mimicking squamous cell carcinoma. It highlights the crucial role of immunohistochemistry in distinguishing between these entities. Accurate histopathological evaluation is essential for appropriate treatment planning and prognostication, especially in lesions exhibiting biphasic or misleading morphological features.

Keywords: *Nodular melanoma, squamomelanocytic tumor, pseudoepitheliomatous hyperplasia, acral melanoma.*

INTRODUCTION:

Malignant melanoma is an aggressive cutaneous malignancy arising from melanocytes. It exhibits diverse histological presentations and has the potential to mimic or coexist with other cutaneous malignancies. The major histological subtypes include superficial spreading melanoma, nodular melanoma, acral lentiginous melanoma, and lentigo maligna melanoma[1]. Diagnostic challenges arise particularly when melanoma occurs in conjunction with other neoplastic processes, such as in chronic ulcers or longstanding skin lesions with epithelial proliferation [2].

The coexistence of epithelial and mesenchymal tumors in the skin has been described using various terms, including biphasic, biphenotypic, composite, collision, and contiguous colonization tumors. Microscopically,

these tumors may appear as a single lesion composed of two distinct cell types, either closely adjacent or as separate entities.

To standardize the terminology, pool et al. proposed the term "combined tumors" for neoplasms showing dual or biphasic differentiation. These are further subclassified into Collision tumors, where the two components remain distinct and separate and Intermingled tumors, where the components are intimately admixed[2].

A rare subtype under this classification is the squamomelanotic tumor**,** which consists of malignant melanocytes and keratinocytes closely interwoven. It was first described by Rosen et al**.**, and only a limited number of cases have been documented in the literature. These lesions must be carefully differentiated from Collision tumors**,** where melanoma and squamous cell carcinoma coexist as separate entities and Tumor colonization, where melanoma secondarily overgrows or infiltrates a preexisting epithelial malignancy[3].

The origin and biological behavior of squamomelanotic tumors remain poorly understood. Some studies suggest they may have a less aggressive clinical course compared to conventional melanoma, but due to their rarity, long-term prognostic data are lacking.

In the present case, we report a diagnostically challenging ulcerated nodular melanoma on the foot of an 82-year-old male. The lesion exhibited extensive reactive squamous epithelial proliferation, histologically mimicking squamous cell carcinoma.

This case highlights the critical role of **immunohistochemistry** alongside **routine histopathological examination** (HPE) in differentiating true biphasic neoplasms from reactive squamous changes associated with melanoma. Accurate diagnosis is essential for guiding appropriate treatment and assessing prognosis.

CASE REPORT:
An 82-year-old male presented with a non-healing ulcer over the right heel, persisting for one year. The patient underwent wide local excision along with inguinal block dissection, and the specimen was submitted for histopathological evaluation.

Gross examination revealed a specimen measuring 16.8 × 11 × 4.5 cm with an ulceroproliferative lesion measuring 7 × 6 × 1.6 cm, exhibiting blackish-brown discoloration. All resection margins were free of tumor.

Microscopic examination demonstrated a nodular malignant melanoma with a Breslow thickness of 8 mm and invasion into the subcutaneous tissue, corresponding to Clark level IV. The lesion also showed ulceration extending more than 2 cm. Histologically, the tumor exhibited a lobular growth pattern composed of polygonal and spindle-shaped cells with vesicular nuclei, prominent nucleoli, and abundant melanin pigmentation in some areas .

Extensive pagetoid spread was noted, along with a compound nevus displaying junctional activity. There was moderate tumor-infiltrating lymphocytic response, with no evidence of regression, lymphovascular invasion, or perineural invasion.Adjacent to the melanoma, areas of squamous epithelial proliferation were noted, characterized by dyskeratotic cells and keratin pearl formation (Figs. 2 & 3). These findings raised the suspicion of either a combined squamomelanotic tumor or melanoma arising in association with squamous cell carcinoma.

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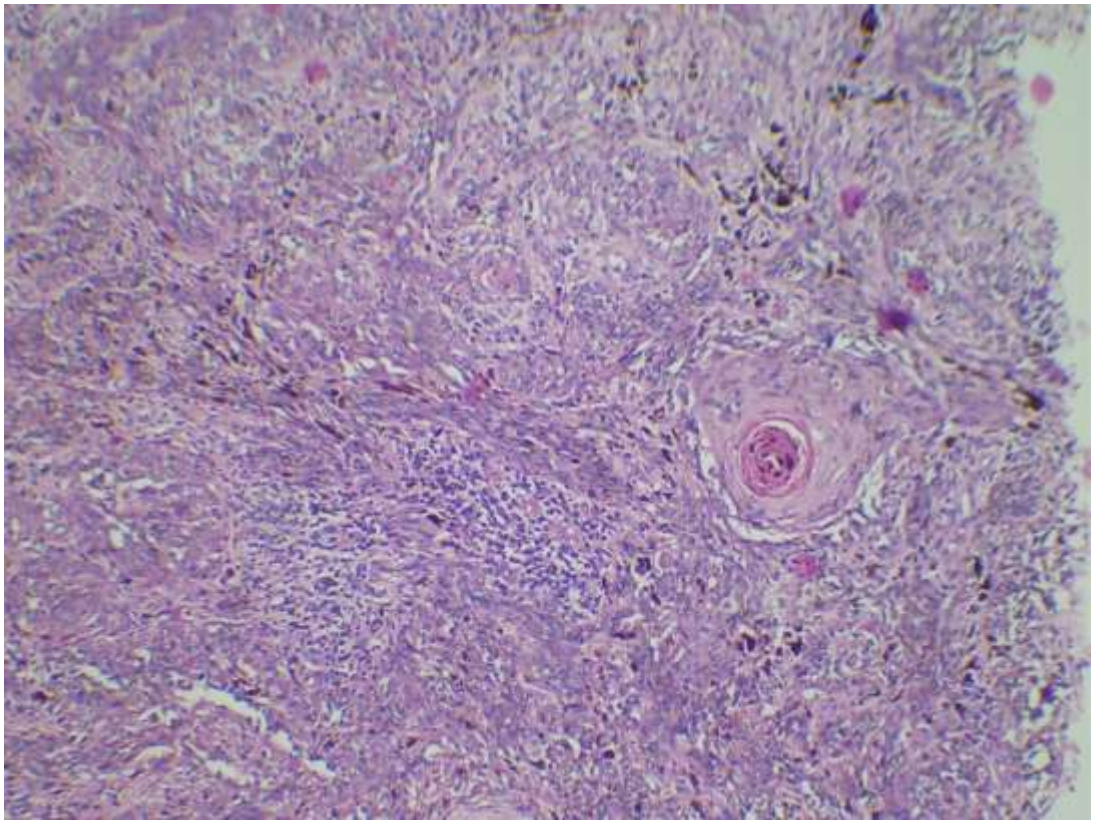

Fig 1. (10X) Lobular arrangement of tumor cells (spindle shaped) with melanin pigmentation.

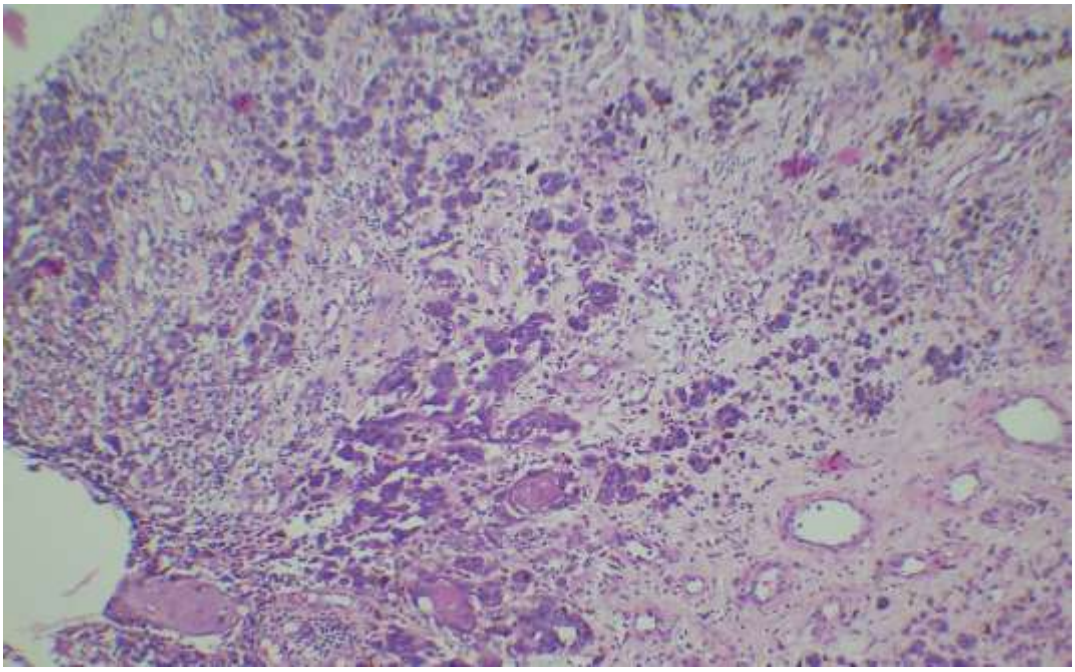

Fig 2. (10X) Reactive squamous pearls adjacent to tumor cells

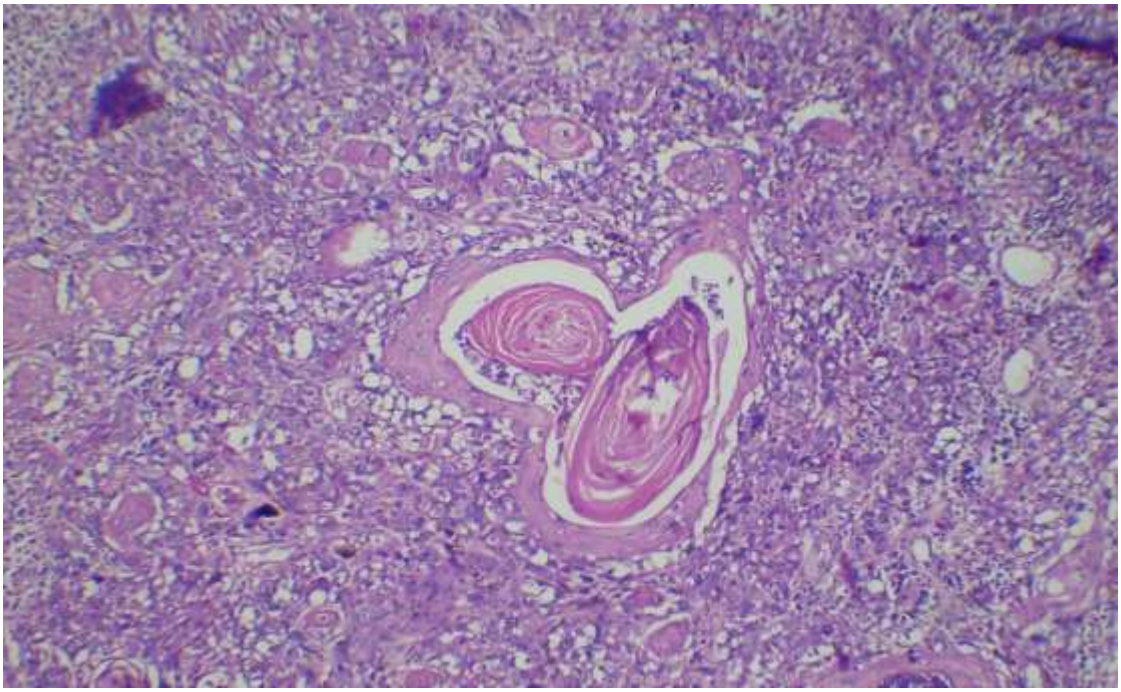

Fig 3. (10X) Reactive squamous epithelium showing keratin pearls.

To clarify the diagnosis, immunohistochemistry was performed. The tumor cells were positive for SOX10 and negative for p63, confirming melanocytic origin and excluding squamous cell carcinoma.A total of 16 regional lymph nodes were examined and found to be free of tumor.Final diagnosis was made as Nodular malignant melanoma of the right foot with extensive adjacent reactive squamous epithelial proliferation, pT4bN0.

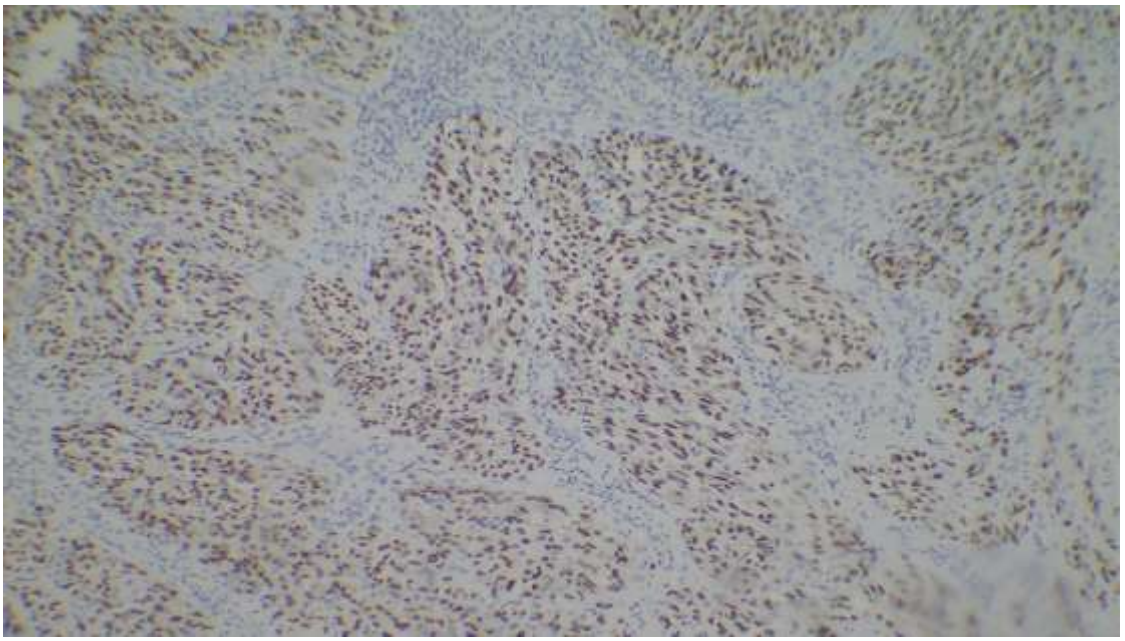

Fig 4. (10X) SOX 10 showing nuclear positivity in tumor cells.

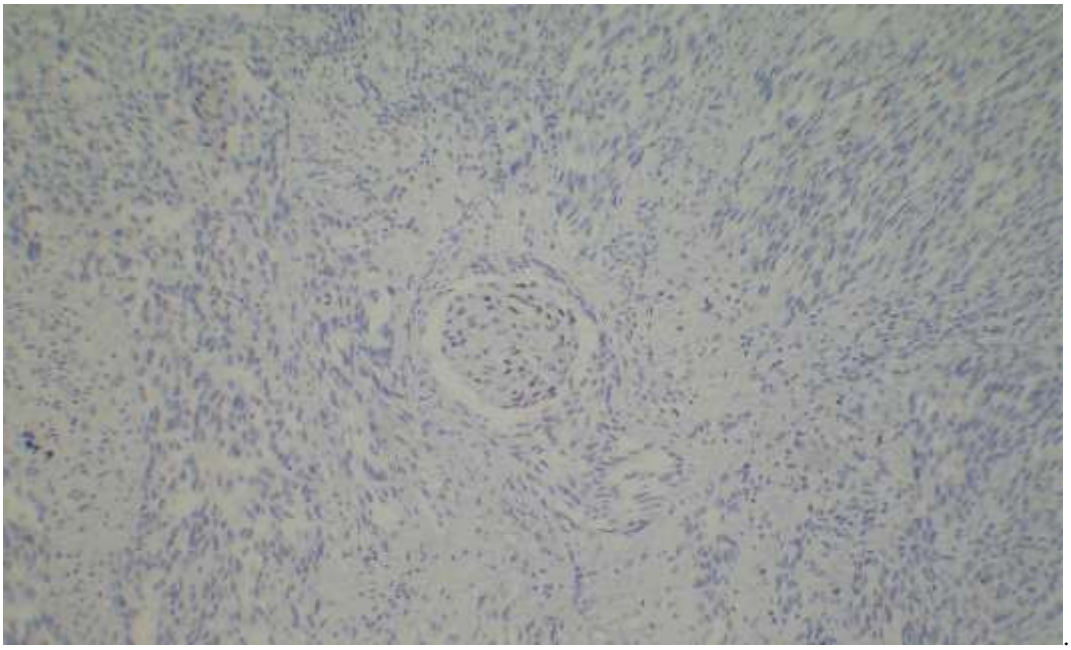

Fig 5. (10X) P63 showing negative for melanoma cells and positive in the squamous pearl.

DISCUSSION:

Among the various subtypes of cutaneous melanoma, nodular melanoma is considered the most aggressive. It is characterized by a high metastatic potential, rapid vertical growth, and deep tissue invasion[1]. Unlike superficial spreading melanoma, nodular melanoma often presents at an advanced stage due to its subtle clinical features. It tends to invade the deeper dermal and subcutaneous tissues before being clinically detected, leading to complications and limited intervention options[4].

In our case, the patient presented with a one-year history of a non-healing ulcer, eventually diagnosed as nodular malignant melanoma with a Breslow thickness of 8 mm and Clark level IV invasion. According to the AJCC 8th edition staging system, this case was staged as pT4bN0, indicating an advanced tumor with poor prognostic implications.

Acral melanoma, a subtype that affects the palms, soles, and nail beds, is relatively rare in the Western population but more commonly observed in individuals with darker skin[6]. These tumors are frequently misdiagnosed as benign conditions such as traumatic ulcers, diabetic foot ulcers, or chronic pressure sores. This diagnostic ambiguity often leads to delayed recognition and, consequently, presentation at a more advanced stage, as was evident in our patient[7].

One of the most diagnostically challenging and academically interesting aspects of this case was the presence of extensive reactive squamous epithelial proliferation adjacent to the melanoma. Histological features such as dyskeratosis, keratin pearl formation, and melanin pigment deposition raised a suspicion of either a collision tumor—representing the coexistence of squamous cell carcinoma and melanoma—or a true biphasic neoplasm like squamomelanotic tumor[8]. However, true biphasic tumors containing both malignant melanocytes and keratinocytes are exceedingly rare[9].

To differentiate between these possibilities, immunohistochemistry (IHC) played a critical role. The tumor cells showed diffuse positivity for SOX10, a highly sensitive marker of melanocytic differentiation, confirming melanoma[10]. The lack of p63 expression, a marker for squamous differentiation, ruled out squamous cell carcinoma. These findings established the diagnosis of melanoma with extensive pseudoepitheliomatous

hyperplasia—a benign reactive process that can mimic squamous cell carcinoma histologically, especially in the context of chronic ulcers or inflammation[11].

The presence of such reactive squamous epithelial changes may be attributed to the release of local cytokines and growth factors as part of the tissue injury response induced by melanoma and its associated inflammation. These reactive changes are more commonly seen in melanomas arising within chronic ulcers or longstanding nevi, further contributing to diagnostic delays[12].

Another notable finding in this case was the presence of tumor-infiltrating lymphocytes (TILs), which is a favorable prognostic marker in melanoma. Studies have demonstrated that a brisk TIL response indicates effective immune surveillance and is associated with improved patient outcomes[13]. Additionally, the absence of lymphovascular and perineural invasion supports a relatively favorable prognosis. However, the tumor depth (Breslow thickness) and presence of ulceration are strong adverse prognostic indicators[14].

CONCLUSION:

This case report highlights the diagnostic and clinical complexity associated with **nodular malignant melanoma** accompanied by extensive reactive squamous epithelial proliferation**.** Pseudoepitheliomatous hyperplasia can closely mimic squamous cell carcinoma**,** posing a potential diagnostic pitfall. Therefore, **a** thorough histopathological evaluation supported by immunohistochemistry is essential to distinguish true biphasic neoplasms from reactive changes.

Accurate interpretation is critical to avoid misdiagnosis and to ensure appropriate therapeutic decisions. Despite high-risk histologic features such as ulceration and deep invasion**, the** absence of lymph node metastasis and the presence of brisk tumor-infiltrating lymphocytes may indicate a relatively favorable prognosis.

This case underscores the importance of early detection**,** meticulous pathological assessment**, a**nd multidisciplinary coordination in managing complex melanoma cases with unusual histological presentations.

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