

Case Report

Persistent Melanoma with a Striking Well Differentiated Neural Component

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Although neurotropism and focal neural differentiation are fairly common in the setting of desmoplastic and spindle cell melanoma, in situ melanoma exhibiting a significant well differentiated neural component is very rare. We report the case of a 70 year old man with persistence of melanoma at the site of excision of a melanoma in situ of lentigo maligna type. The patient presented three years later noting thickening of the skin at the site of his previous surgery. Scar revision led to the unexpected identification of underlying melanoma with a marked and striking neural component. Obvious melanoma was noted in the epidermis and dermis, along with a deeper spindle cell component that exhibited routine histologic and immunopathologic features of a well differentiated neural tumor. If not for the gradual transitions and continuity of these components, a second bystander tumor would have been considered. Without the ample specimen received, misdiagnosis would have been likely. We review phenomenon of neural differentiation with our unusual illustrative case.

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Key Words: melanoma, neural tumor, neurotropism, melanoma recurrence

INTRODUCTION

The incidence of melanoma continues to rise and melanomas with unusual presentations are becoming increasingly common as a result. Not only can melanoma mimic nevi, but there are many unusual forms of melanoma that include angiomatoid, angiotropic, balloon cell, bullous, blue nevus like, chondroid, cystic, desmoplastic, equine, follicular, ganglioneuroblastic, malignant peripheral nerve sheath tumor like, melanocarcinoma, myxoid, neuroendocrine, neurotropic, osteogenic, plasmacytoid, pseudoglandular, pseudolipoblastic, rhabdoid, schwannoid, signet ring type, small cell, spindle cell type, spitzoid, verrucous, vitiligo like, and other variants. Often identifying the specific type is critical to initiating proper therapy. Recent studies have identified important paracrine relationships between melanoma and vascular as well as neural elements.¹ Desmoplastic melanomas have long been known to exhibit neural differentiation and perineural invasion, but superficial melanoma exhibiting advanced neural differentiation is very rare.²⁻⁵

CASE HISTORY

A 70 year old man presented for evaluation of an unusual scar in the right post auricular sulcus. He had undergone surgery three years earlier for melanoma in situ of lentigo

maligna type. After clear margins had been ascertained, the wound was closed with a local flap. The patient became aware that the skin at that site had become increasingly thick and tender. Clinical exam was consistent with a nonpigmented hypertrophic scar (**Figure 1**). The patient underwent scar revision surgery and histology now revealed melanoma in situ in the overlying epidermis (**Figure 2A**). Spindle cell tumor-like lesions were noted in the dermis with embedded nests of epithelioid melanoma cells and areas of obvious melanoma were noted beneath the spindle cell proliferation (**Figure 2B**). Spindle cells were noted in the dermis with embedded nests of epithelioid melanoma cells and areas of obvious melanoma were noted beneath the spindle cell proliferation (**Figures 3A, 3B**). Neurofilament protein stain decorated axons within some nerve bundles (**Figure 4**). A CD34 stain decorated some of the spindle cells in the myxoid areas and an epithelial membrane antigen stain decorated the perineurium around some nerve bundles. The histologic findings represented a malignant melanoma with neural differentiation.

DISCUSSION

It has been long recognized that melanoma has had a close association with neural tumors because of its ectodermal origin.⁶ Metastatic melanoma has been noted to resemble malignant peripheral nerve sheath tumor.² Our case is interesting and unusual because areas of neural differentiation are noted between junctional components typical of melanoma in situ as well as deep dermal

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component with more conventional features of melanoma. The complete excision allowed for identification of all these unusual features, and clearly demonstrated areas of seamless transition from melanoma in situ to a neural component with an additional deep component of conventional invasive melanoma. Immunohistochemistry confirmed the presence of axons and neural filaments by immunohistochemical staining (**Table 1**). Byanu Iyengar has demonstrated patterns of neural differentiation in tumor vascular complexes Richard Reed presaged some of these findings with his hypothesis of a neurocristic effector cell and studies by Luggasy et al^{1,7,8} demonstrate that melanoma skin cells may develop migratory capabilities through contact with the abluminal surface of vessels.⁴ We suspect that other factors in the microenvironment can lead to neural differentiation. We share Su et al.'s belief that tumors exhibiting advanced neural differentiation should not simply be classified as a type of neurotropic melanoma.⁵ Our patient's tumor did not invade a pre-existing nerve but rather exhibited neural differentiation. Masson's neuronevus, cutaneous melanocytoneuroma, plexiform melanocytic schwannoma, giant congenital nevi associated with neurinoma and malignant peripheral nerve sheath tumor, all demonstrate a close association between

melanocytic and neural differentiation. Melan-A staining is thought to be helpful in differentiating neurofibroma from a neurotized nevus and was useful in our case.⁹



Figure 1. Initial clinical image of biopsy site.

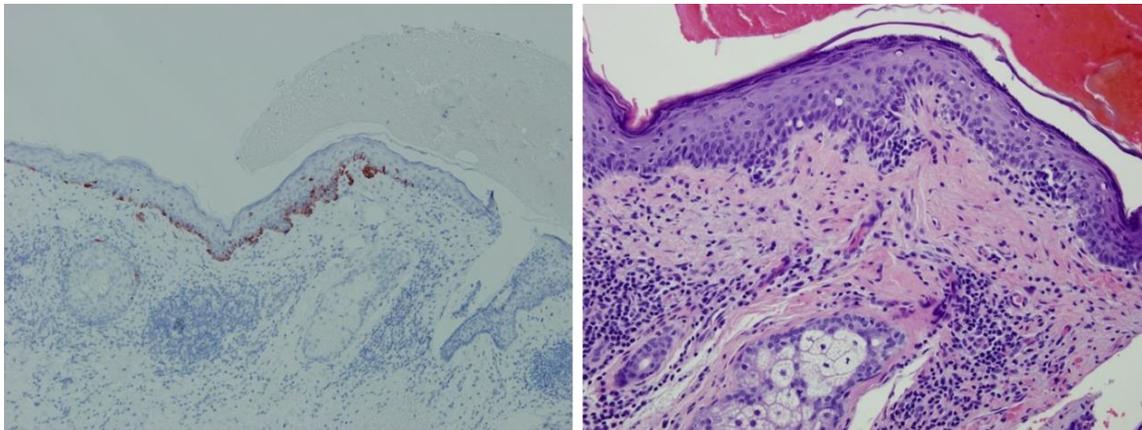


Figure 2. Biopsy reveals melanoma in situ with spindle cell tumor. **2A.** Melanoma in situ was noted in the overlying epidermis. **2B.** The initial biopsy specimen reveals a spindle cell tumor surrounded by abundant mucin, with atypical melanocytes noted along the dermal epidermal junction and are highlighted by Melan-A staining (magnification 100x).

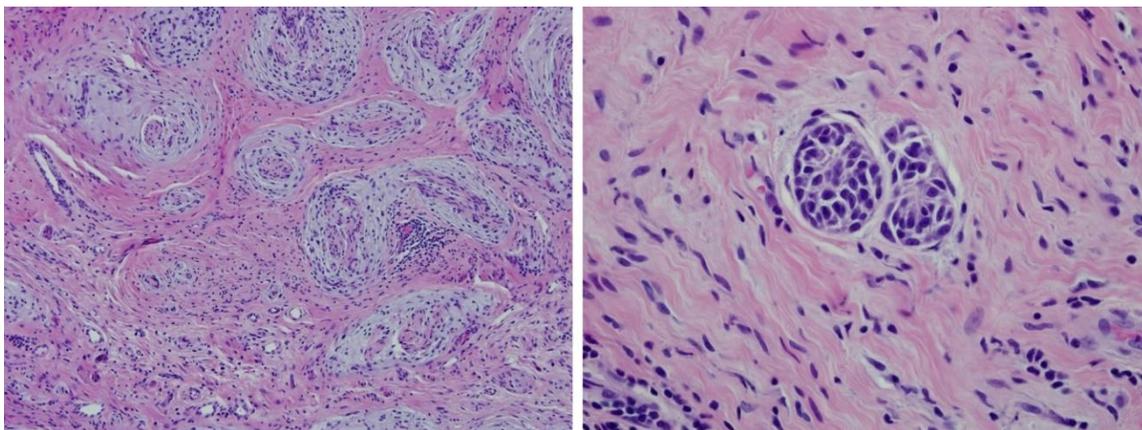
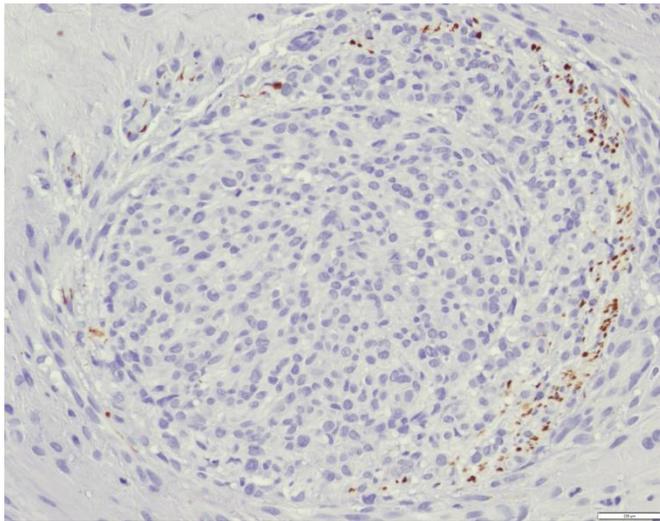


Figure 3. Areas of obvious melanoma noted beneath the spindle cell proliferation with embedded nests of epithelioid melanoma cells. **3A:** Atypical spindle cells with mucinous stroma are noted beneath areas of melanoma in situ of lentigo maligna type. **3B:** Nests typical of conventional melanoma are embedded within an eosinophilic stroma.

Table 1. Immunohistochemical markers of differentiation.

Melanocytic and Neural	Melanocytic	Neural
S-100	Melan-A	GFAP (glial fibrillary acidic protein)
SOX-10	HMB-45	SYN (synaptophysin)
	MITF	NFP (neural fibrillary protein)

**Figure 4.** Neurofilament stain highlights the presence of axons in some bundles.

This case illustrates that dermatologists and dermatologic surgeons should maintain a high index of suspicion whenever changes are noted at the site of a previous melanoma surgery. In addition, the pathology of the initial melanoma in situ demonstrated that the inked tissue edges were negative in the histologic planes of section, which does not imply a complete excision. Locoregional recurrences may occur despite no visible malignant cells seen at the margin. Some scenarios that illustrate when margins fail include the presence of a scar between the neoplastic cells and the margin; part of the tissue at the margin being out of the plane of section; area of the margin is obscured by electrocautery; perineural invasion is present close to a margin.¹⁰ In this case the recurrence was non pigmented occurring in the post auricular sulcus and it is quite conceivable that hypertrophic scarring could have developed from rubbing of eyeglasses or other local trauma. Our patient required a complete auriclectomy but

fortunately had no intracranial involvement. Rather than excision had his dermatologist elected to perform periodic intralesional steroid injections in attempt to shrink the mass the diagnosis may have been significantly delayed and the tumor more advanced. Dermatologists and dermatologic surgeons need to be aware of these unusual presentations so that a timely diagnosis can be made. A full thickness punch or excisional biopsy needs to be strongly considered since a partial biopsy may miss deeper invasion leading the physician to consider inadequate topical treatments such as imiquimod.¹¹

Although cases are rare, we expect that the biologic behavior of these tumors will likely be analogous to spindle cell melanoma, that is somewhat better than for a melanoma of the same Breslow thickness but limited to an epithelioid pattern of neoplastic cells. We advise complete excision with careful margin control in a manner analogous to other melanomas with a prominent spindle cell component.

CONFLICT OF INTEREST

None.

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