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Malignant Melanoma With Neural Differentiation: An Exceptional Case Report and Brief Review of the Pertinent Literature

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Abstract

The term neurotropic melanoma has been used to refer to malignant melanoma with associated infiltration of nerve or “neural differentiation”—that is, melanoma cells exhibiting cytological characteristics of nerve cells. Historically, neurotropic melanoma has generally been discussed within the context of desmoplastic melanoma. We report an exceptional case of melanoma notable for a very well-differentiated neural component that was contiguous with obvious overlying melanoma. After careful consideration of all pertinent histological features, the overall diagnostic impression was that of melanoma with associated “malignant neurotization.” We have not encountered a previously reported case with such a well-differentiated neural component. The following article details our exceptional case of melanoma with “malignant neurotization” and presents a discussion of the differential diagnosis and brief review of the pertinent literature.

Keywords

neurotropic melanoma; malignant neurotization; neural differentiation; desmoplastic melanoma; neural crest

INTRODUCTION

In 1979, Reed and Leonard[1] described a new variant of desmoplastic melanoma notable for a neuroma-like growth pattern and characterized by striking neuroid features indicative of Schwann cell differentiation. Due to the propensity for infiltration of cutaneous nerves, Reed and Leonard referred to these melanomas as “neurotropic.” Indeed, subsequent series of melanomas displaying neural differentiation and/or infiltration of nerves have generally been reported in the context of desmoplastic melanoma and illustrate a measure of ambiguity in their classification.[2] Herein, we report an exceptional case of melanoma notable for a very well-differentiated neural component and discuss our findings in relation to the current and historical classification of these malignant tumors.

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CASE REPORT

A 56-year-old white man presented for treatment of a 2-cm, slightly raised, pruritic, red-pink lesion with scalloped borders on his left infraclavicular chest wall. The lesion had arisen de novo, and the patient had noticed it for over a year. The patient also observed that the lesion had begun to enlarge and display more irregularity, and he reported increasing irritation and sensitivity with time. There was no ulceration, bleeding, or darkened hyperpigmentation. The patient had a long history of sun exposure, but there was no significant sun exposure on the area of the chest lesion. His dermatologic history also included sunburns, actinic keratoses, benign nevi, and a previous superficial spreading type melanoma that had been removed from his left forearm approximately 2 years prior. There was no history of café au lait spots, excess congenital nevi, or neurofibromatosis. In addition, there was no family history of skin cancers. Physical examination confirmed the presence of the chest lesion and revealed Fitzpatrick type I skin with evidence of sun exposure. There were no stigmata of neurofibromatosis or congenital neural melanocytosis on examination. An excisional biopsy of the chest lesion was performed, and the specimen was submitted for pathological examination.

The specimen was examined grossly, serially sectioned, and submitted for routine processing with hematoxylin and eosin staining. Routine immunohistochemistry with antibodies to the following markers was performed: S-100, Melan-A, human melanoma black (HMB)-45, SOX10, vimentin, neuron-specific enolase (NSE), microphthalmia transcription factor (MITF), epithelial membrane antigen (EMA), and neurofilament.

Histopathologic Findings

Histologically, a biphasic tumor was observed consisting of malignant melanoma overlying and in close approximation with a very mature-appearing neural component (Fig. 1). The melanoma displayed typical features with confluent and layered melanocytes along the dermoepidermal junction with focal extension of melanocytes into overlying epidermis (pagetoid spread). Associated enlarged and confluent melanocytic nests of varying sizes and shapes were seen along the dermoepidermal junction with some surrounding cleft-like spaces. These junctional melanocytes were observed in continuity with similar-appearing atypical melanocytes within the superficial dermis.

Interestingly, an associated proliferation of very mature neuroid cells arranged in small packets, nests, and sheets was identified below the obvious invasive malignant melanoma component. Rare nests of melanoma cells were observed within this rather mature neural component and were contiguous with the overlying dermal melanoma cells (Fig. 2). Despite the overall mature appearance of the neural component, focal areas showed atypical cells and numerous mitoses in neural-appearing cells (Fig. 3). Therefore, this neural component was considered most consistent with “malignant neurotization” of melanoma cells. In addition, no definite infiltration of cutaneous nerves was observed. No features of desmoplastic melanoma were seen. Pigmented cells were not observed in the neural component. There was no paradoxical maturation (pseudomaturation) of the dermal component.

Immunohistochemical stains showed the neurotized component diffusely/strongly positive for S-100, vimentin, and NSE and focally positive for SOX10 (approximately 50% of lesional spindled cells) and MITF but negative for Melan-A (Figs. 4, 5). In contrast, the typical melanoma component was strongly positive for Melan-A, SOX10, and MITF and showed similar positive staining for S-100, vimentin, and NSE (Fig. 4). HMB-45 was weakly positive only in melanocytes. Stains for EMA and neurofilament were negative within the neurotized component (Fig. 5) (see also Table 1).

The overall histological and immunologic impression was that of invasive malignant melanoma with marked “malignant neurotization.” Complete excision of the lesion with appropriate lesion-free margins, and possible sentinel lymph node sampling was recommended. The patient underwent wide reexcision and biopsy of 2 sentinel lymph nodes, all of which were negative for melanoma. Nine months after the initial excisional biopsy, the patient is reported to be doing well with no signs of recurrence.

DISCUSSION

Neurotization is a recognized phenomenon in melanocytic nevi and characterized by the maturation of typical rounded or more “epithelioid” nevus cells into more elongate or spindled forms with a conspicuous neural appearance. Furthermore, it is known that several benign melanocytic nevi, including congenital and blue nevi, may exhibit prominent neurotropism (ie, nevus cells aggregated around associated nerve).

The features of neural cytomorphology and neural infiltration also have been described in the context of malignant melanoma. In 1979, Reed and Leonard[1] reported a group of 22 melanomas whose histological appearance was dominated by neuroid features and Schwann cell differentiation. This new melanoma variant was termed as “a variant of desmoplastic melanoma.” These tumors either arose de novo or in association with overlying lentigo maligna type or “minimal deviation melanoma.” Of note, desmoplasia was a feature of many of the reported cases. In addition to neural differentiation, these melanomas also showed a propensity for infiltration of cutaneous nerves and the term “neurotropic melanoma” was introduced as well. It has been estimated that neural invasion or neural differentiation occurs in at least 30% of desmoplastic melanomas.[3] Since the initial report of neurotropic melanoma, melanomas with combinations of the features of desmoplasia, infiltration of nerves, and/or neural differentiation have been considered variations on this theme and, therefore, generally have been referred to as desmoplastic neurotropic melanoma or, simply, neurotropic melanoma.[4–23] Hundreds of cases have been reported in the literature.[9,24]

Desmoplastic neurotropic melanoma comprises a subgroup of melanoma with unique clinical features from conventional melanoma. These melanomas tend to occur in elderly patients with a male preponderance.[4,5,9,10,13,25] The lesions are often amelanotic,[4,9,10,13] and there is a predilection for the head and neck area.[4,5,9,10,12,13,25] This fact, combined with the propensity for neural infiltration, has resulted in many reported cases of desmoplastic neurotropic melanoma associated with cranial neuropathies and neuralgias.[4,8,10,20,21,23,26] Other sites of involvement such as the foot[14] and vulva[18,22] have been reported. There is a high rate of local recurrence, and in some cases, recurrence may be

attributed to prior misdiagnosis.[4,10,12,13] Neurotropism is often a mechanism for tumor spread beyond the clinical margins.[24] Clear surgical margins help minimize the rate of local recurrence and, when margins are compromised, radiotherapy may help reduce local recurrence.[5] The rate of regional lymph node involvement has been estimated to be approximately 15%.[9,16] Sentinel lymph node biopsy may be helpful for detecting subclinical metastases.[25] It has been suggested that, overall, desmoplastic neurotropic melanoma may be associated with a better survival rate compared with conventional melanoma with a similar depth of invasion.[9]

The differential diagnostic considerations associated with neurotropic melanoma may include a variety of other spindle cell lesions, including benign and malignant peripheral nerve sheath tumor. Our case of melanoma is remarkable for a very mature-appearing neural component without prominent desmoplasia or definite infiltration of associated nerve. Additionally, this component lacked the Melan-A positivity seen in the associated typical melanoma component. The MITF staining in the neurotized component was markedly reduced compared with the typical melanoma component. Rare examples of malignant melanoma with a prominent “neuroid” component have been reported.[11,15] The prominent well-differentiated neuroid histological features and immunohistochemical staining in our case led us to also entertain the possibility of a collision tumor between malignant melanoma and a peripheral nerve sheath tumor. However, the focal nuclear atypia with focally numerous mitoses, rare nests of melanoma cells within the neural component, and contiguity of these melanocytic nests with overlying atypical dermal melanocytes led us to an interpretation of melanoma with neural differentiation. The finding of only partial expression (estimated approximately 50% of dermal spindled tumor cells) by SOX10—a recently established immunohistochemical marker—is of unknown significance, but suggests some loss of normal melanocytic gene expression within the spindled neurotized tumor component.[27]

The differential diagnosis in this situation could include melanoma arising along with or from an atypical neurofibroma. Within the setting of neurofibromatosis type 1, atypical neurofibromas are considered premalignant lesions.[28,29] Additionally, dysplastic nevi associated with solitary neurofibromas have also been reported,[30] and acquired and congenital nevi associated with neurofibroma are seen especially within the setting of neurofibromatosis type 1.[31,32] The increased cellularity of lesional cells with enlarged hyperchromatic nuclei within the neuroid component of our reported case resembled those of an atypical/dysplastic neurofibroma; however, the focally high mitotic rate was not compatible with atypical neurofibroma. In one series of atypical neurofibroma, many lesions displayed at least focal EMA positivity; most also showed conspicuous axons and/or small nerve twigs that were then highlighted by the neurofilament stain.[33] The lack of staining with EMA and neurofilament within the neuroid component of our case further argued against a diagnosis of atypical neurofibroma.

The tendency to discuss melanomas with a combination of the features of desmoplasia, neural differentiation, and infiltration of cutaneous nerves within the same context is likely related to theories of their histogenesis and the common embryologic origin of melanocytes and Schwann cells from the neural crest.[1,9,12,34] In 1983, Reed discussed the

neuromesenchyme and the concept of a neurocristic effector cell.[35] He postulated that melanocytes are derived from a parent neurocristic effector cell and have the ability to acquire fibrogenic, melanogenic, or neurosustentacular properties. Desmoplastic melanoma and melanomas with neural differentiation would therefore be examples of the fibrogenic and neurosustentacular properties, respectively, of dysplastic neurocristic cells. Some authors cite the propensity of some melanomas to infiltrate cutaneous nerves as also consistent with this concept,[4] although many carcinomas (eg, those of the pancreas, colon and rectum, prostate, and head and neck) frequently show invasion of nerves as well,[36] suggesting that this feature is not solely a property of a neurocristic effector cell. Ultrastructural studies have supported the presence of Schwannian differentiation in melanoma cells and support the idea that neural crest-derived cells retain the ability to express different phenotypes.[7,37] Barnhill et al[38] suggested that desmoplastic melanoma and desmoplastic neurotropic melanoma are part of a continuum of malignant neuroectodermal tumors with a close relationship to malignant peripheral nerve sheath tumor, as supported by neural differentiation and neurotropism histologically, a common immunohistochemical profile (ie, positivity for vimentin and S-100 and negativity for most other melanocytic makers), and clinical behavior resembling malignant peripheral nerve sheath tumor. Interestingly, although it is thought that melanocytes are derived from the neural crest, which then migrate and populate the skin, recent evidence also suggests that at least some cutaneous melanocytes may be derived from Schwann cell precursors contained within growing nerve tissue.[39]

Although our case could arguably be classified as a variant of desmoplastic neurotropic melanoma—in keeping with the historical classification—our group generally reserves the term “neurotropic melanoma” for cases with obvious infiltration of cutaneous nerves by melanoma cells. This is consistent with the dictionary definitions of “neurotropic” (having an affinity for the nervous system) and “neurotization” (the acquisition of nervous substance).[40] We believe that there is merit in distinguishing between neural infiltration and neural differentiation, and therefore, we offer the term “malignant neurotization” to describe the well-differentiated neural component noted in our reported case.

We believe that the peculiar histological features of our case have only rarely, if ever, been described and raise questions about the general category of hybrid melanocytic/neural tumors. As previously mentioned, neurotized melanocytic nevi contain areas with a neural appearance. In addition, nerve sheath tumors such as pigmented neurofibroma and melanotic schwannoma may show areas with melanin production and immunohistochemical positivity for melanocytic markers. Recently, novel entities exhibiting both melanocytic and neural features have been described, including cutaneous melanocytoneuroma[41] and plexiform melanocytic schwannoma.[42] Thus, it is becoming increasingly apparent that tumors of neural crest origin are associated with a wide range of appearances.

To the best of our knowledge, the prognostic significance of neural differentiation alone has not been clearly established. In a large series of desmoplastic melanoma and desmoplastic neurotropic melanoma presented by Quinn et al,[13] neurotropism (defined as tumor in a perineural or intraneural distribution or with neural differentiation) was significantly associated with a shorter time to recurrence; however, the separate subgroups (tumor within

nerves vs neural differentiation) were not studied. Baer et al[19] studied the prognostic significance of desmoplasia and neurotropism (defined as perineural and/or endoneural involvement by tumor) in patients with stage I melanomas and concluded that neurotropism was associated with a statistically significant decrease in survival in patients with melanomas with desmoplasia. In that study, the 8-year survival for desmoplastic neurotropic melanoma was 60% versus 90% for desmoplastic melanoma. However, the series of Baer et al[19] did not include any melanomas with neural differentiation. Similarly, in a recent study of head and neck desmoplastic melanoma, neurotropism (defined as perineural or intraneural involvement) was significantly associated with worse disease-specific survival and recurrence-free survival.[43]

In summary, we report an exceptional case of malignant melanoma notable for a very mature well-differentiated neural component that was strikingly different from the obvious melanoma component. Although rare examples of malignant melanoma with a prominent "neuroid" component have been reported,[11,15] we believe that our present case highlights a unique, exceptionally well-differentiated neural component, heretofore not described in the literature. The particular histological features of our case of malignant melanoma may represent an example of another peculiar entity within the spectrum of hybrid melanocytic/neural tumors. Although rare, such cases deserve further study so that we may increase our understanding of the complex relationship between melanocytic and neural lineages and may one day offer additional useful information for the prognosis and treatment of affected patients.

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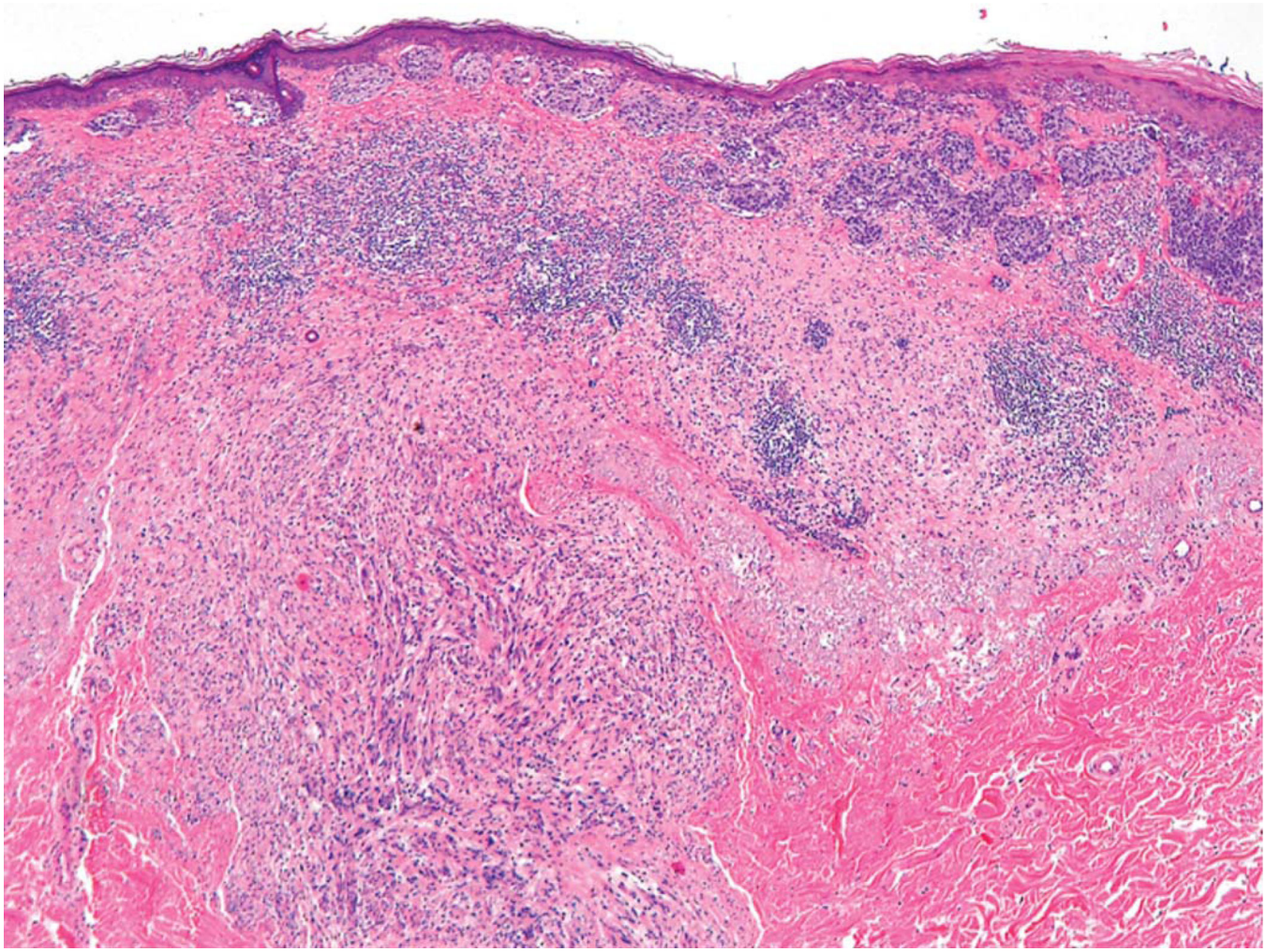

FIGURE 1.

Low-magnification photomicrograph showing superficial malignant melanoma in confluence with an underlying spindle cell proliferation exhibiting “neuroid” features (hematoxylin and eosin, ×20).

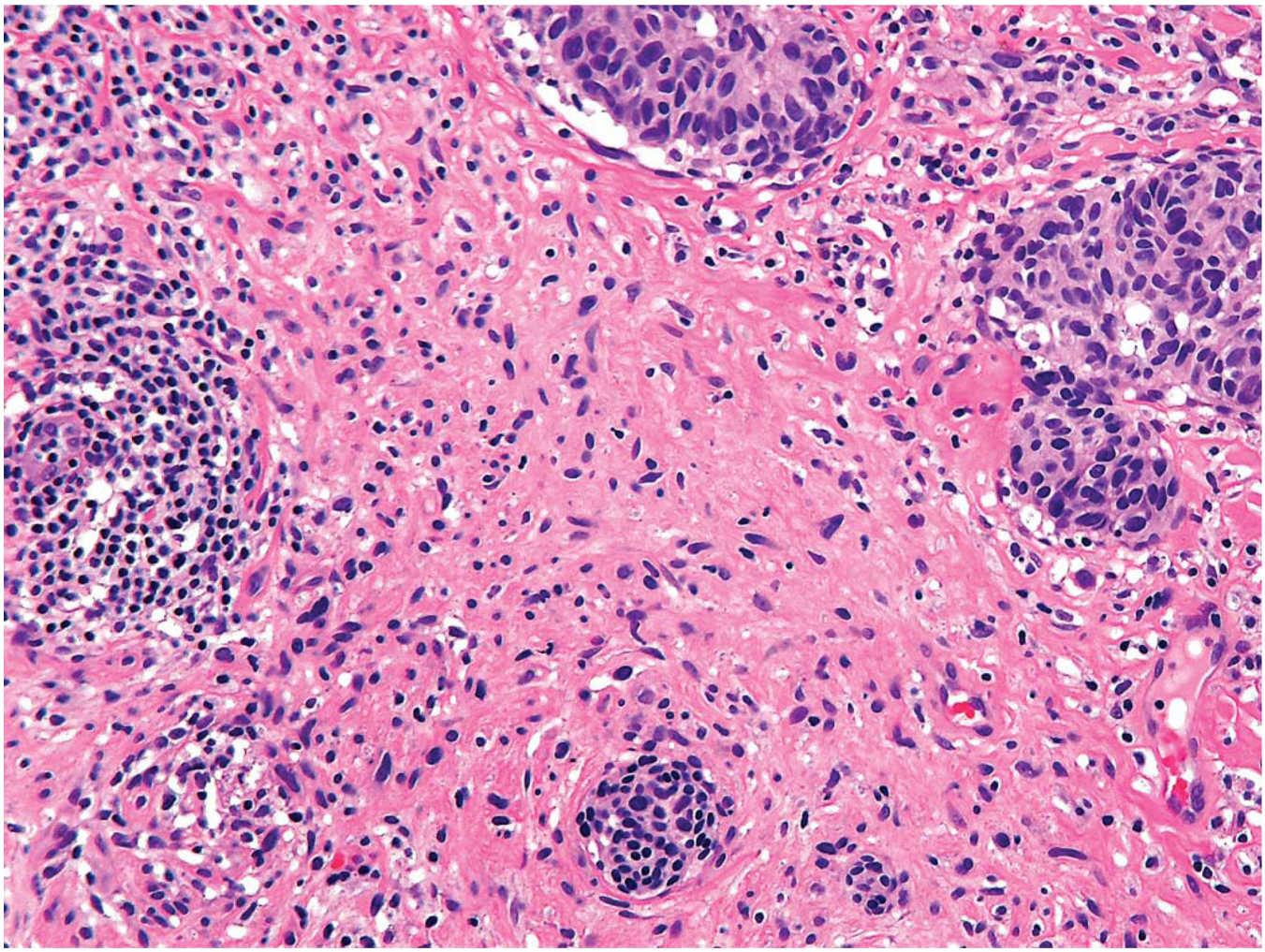

FIGURE 2.

High-magnification photomicrograph showing nests of malignant melanoma cells that seem to float on a fairly well-differentiated background of more eosinophilic spindled cells with a “neuroid” appearance and associated lymphocytepredominant inflammation (hematoxylin and eosin, ×200).

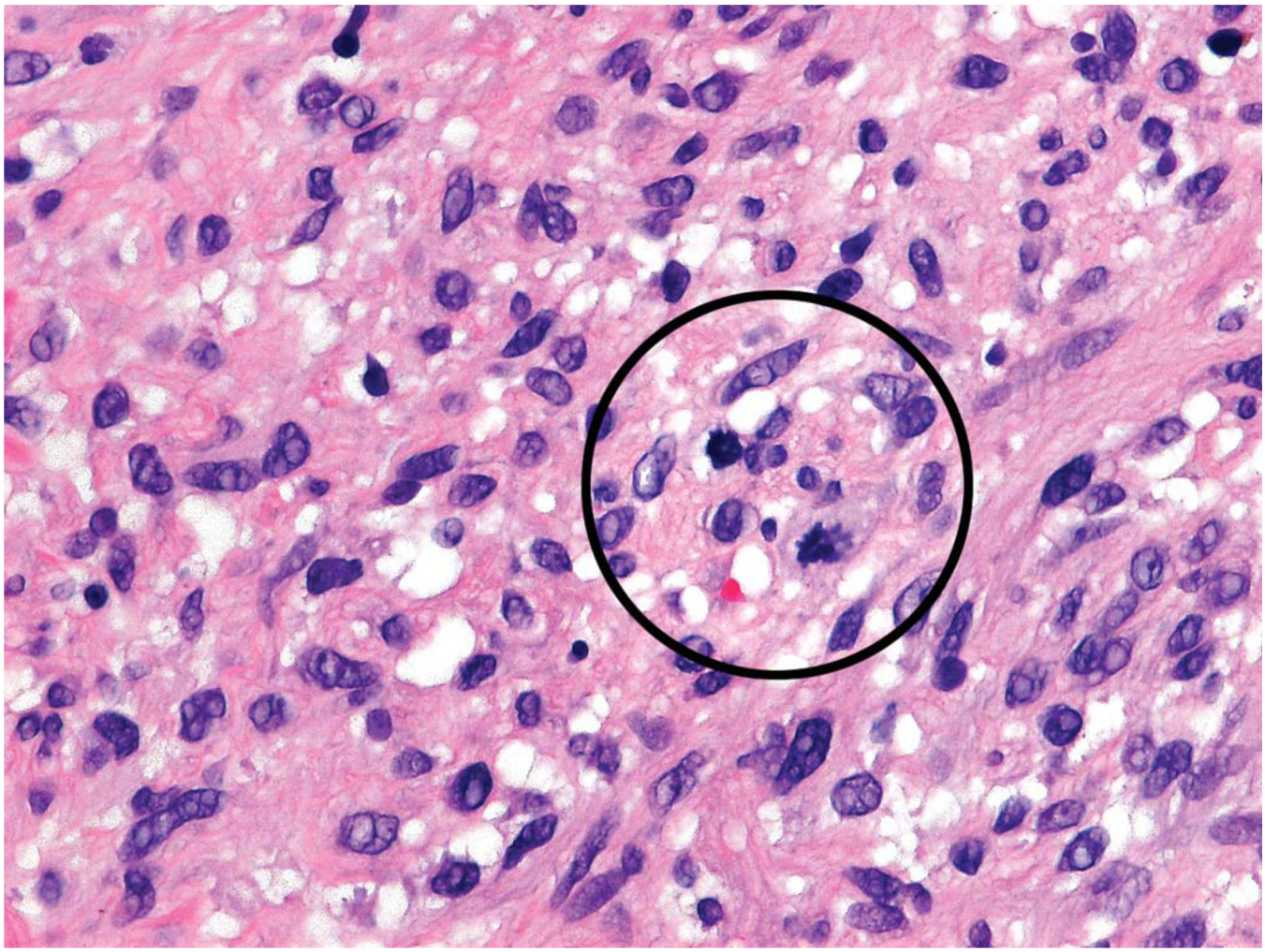

FIGURE 3.
High-magnification photomicrograph revealed an increase in atypical mitoses and more marked cytological atypia within the neurotized component (hematoxylin and eosin, ×600).

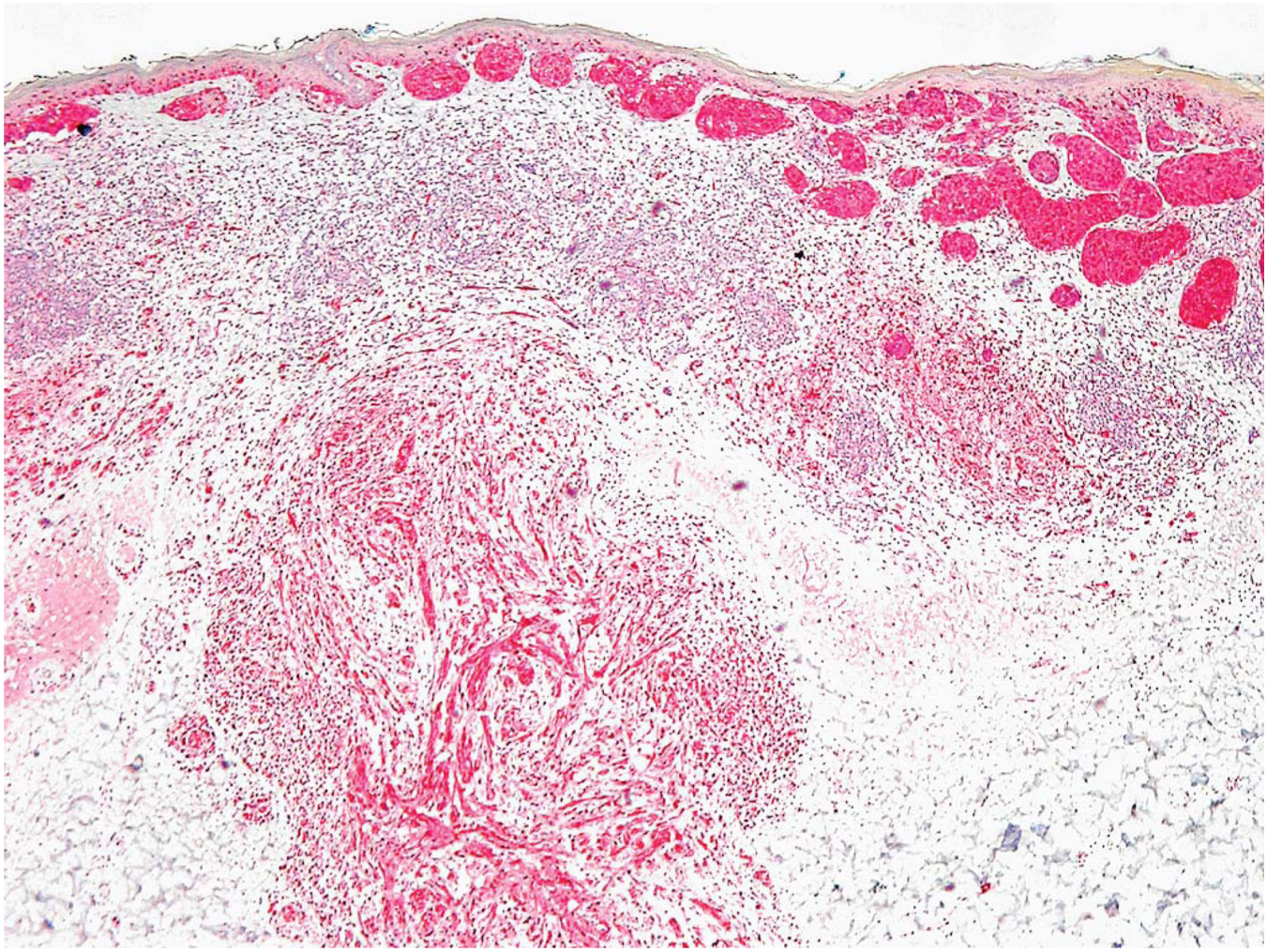

FIGURE 4.

S-100 strongly highlights both the superficial conventional melanoma and the underlying associated neurotized component (immunohistochemistry, ×40).

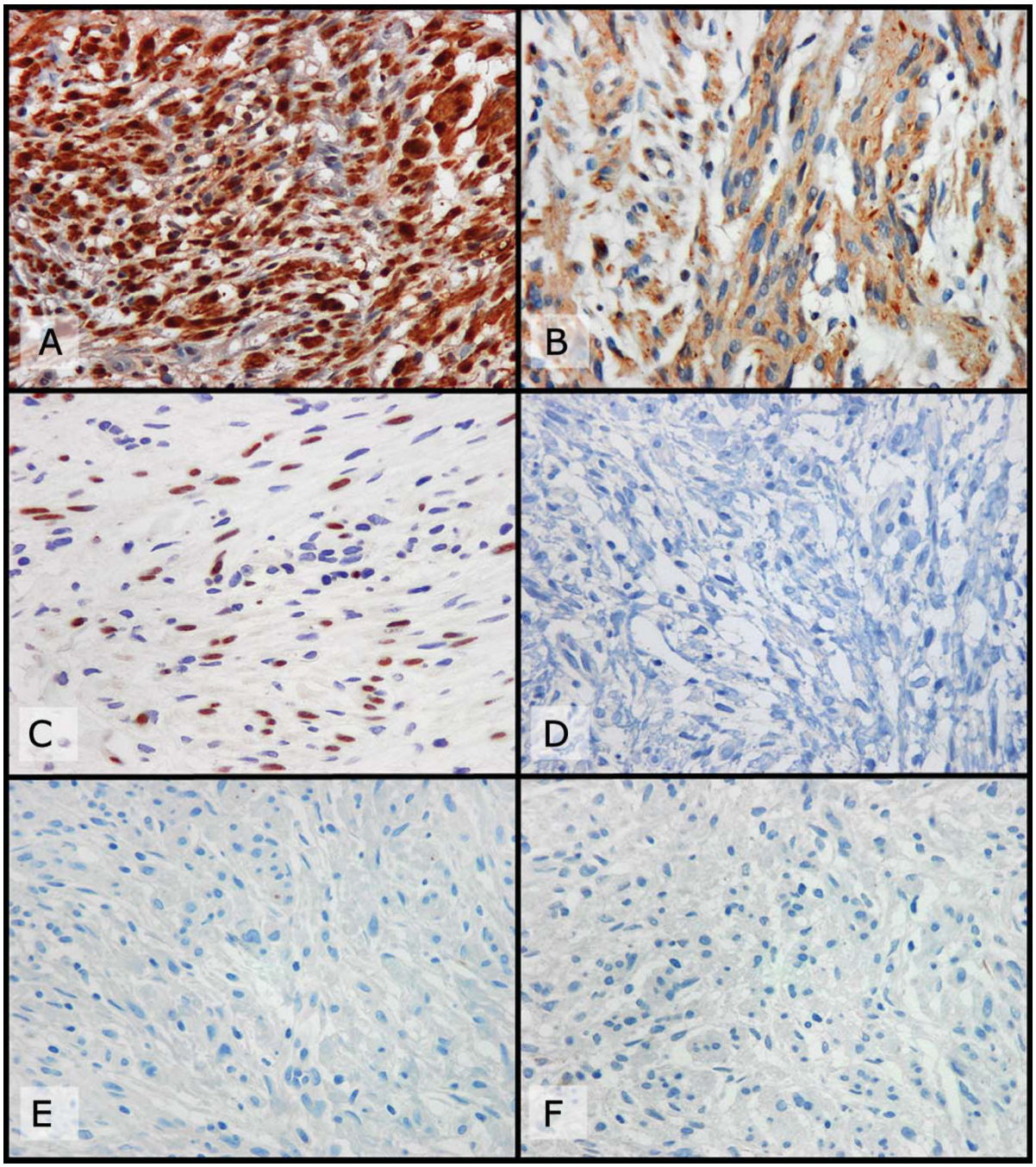

FIGURE 5.

Immunohistochemical characteristics of the neurotized tumor component. A, S-100 strongly highlights the neurotized component (immunohistochemistry, ×400). B, NSE is positive in the neurotized component (immunohistochemistry, ×400). C, SOX10 is focally positive (approximately 50% of lesional cells staining) within the neurotized component (immunohistochemistry, ×400). D, HMB-45 is negative within the neurotized component (immunohistochemistry, ×400). E, Neurofilament is negative within the neurotized

component (immunohistochemistry, ×400). F, EMA is negative within the neurotized component (immunohistochemistry, ×400).

TABLE 1

Results of Immunohistochemical Staining

Marker	Superficial Conventional Melanoma	Underlying Neural Component
S-100	Diffusely positive	Diffusely positive
Melan-A	Diffusely positive	Negative
HMB-45	Weakly positive in superficial melanocytes	Negative
SOX10	Diffusely positive	Focally positive (approximately 50%)
Vimentin	Diffusely positive	Diffusely positive
NSE	Diffusely positive	Diffusely positive
MITF	Diffusely positive	Focally positive
EMA	Negative	Negative
Neurofilament	Negative	Negative