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Primary and metastatic melanoma with NTRK-Fusions

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Abstract

A number of oncogenic driver mutations have been identified in melanocytic nevi and melanoma, but translocations also play a role in tumorigenesis and provide potential therapeutic targets for malignant lesions. Various translocations, such as those involving the anaplastic lymphoma kinase (*ALK*), *NTRK1*, and *NTRK3* have been reported in spitzoid melanocytic neoplasms leading to kinase-fusion proteins that result in immunohistochemically detectable ALK or NTRK expression. We have previously reported that ALK expression can be found in non-spitzoid primary and metastatic cutaneous melanomas. In this study we report that non-spitzoid metastasizing melanomas of adults may also harbor *NTRK* fusions and that NTRK expression can be immunohistochemically detected in these tumors. Out of 751 melanomas analyzed by next generation sequencing, 4 metastatic melanomas were identified with *NTRK* fusions, three involving *NTRK1*, one involving *NTRK2*. They occurred in three women and one man. Two of the corresponding primary tumors were from the trunk, one from an extremity and one tumor arose in anal skin. One primary tumor displayed features of superficial spreading melanoma and three were nodular melanomas. All tumors were cytologically characterized by the presence of large epithelioid melanocytes. All tumors were immunoreactive with anti-Trk antibody. Next generation sequencing documented that the *NTRK1* fusion partners included *TRIM63*, *DDR2* and *GON4L*. One tumor harbored an *NTRK2-TRAF2* fusion. Thus, our findings document that *NTRK* kinase fusions can occur in non-spitzoid metastasizing melanomas of adults. The presence of an *NTRK* family fusion in these tumors may provide a therapeutic opportunity in a small subset of patients with metastatic melanoma.

Keywords

NTRK; immunohistochemistry; melanoma; pathology

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INTRODUCTION

Several driver mutations have been identified in melanoma. Four major mutation categories have been proposed for cutaneous melanoma: mutant *BRAF*, *RAS*, *NF1*, and Triple-wild-type (WT) tumors(1). The latter group encompasses melanomas with molecular aberrations that are infrequent, such as mutations of *KIT*(2, 3), GNA11(4), and *GNAQ*(4), or genomic rearrangements of *BRAF*(5, 6) and *RAF1*(7). Aside from mutations, the pathogenesis of melanoma is also influenced by other events, including, but not limited to DNA copy number changes(8–11), translocations(12–15), DNA methylation(16), and alternative transcriptional initiation(17).

With regard to genomic rearrangements in melanocytic tumors, much has been learned from the study of spitzoid neoplasms(10, 18). The most common type of aberrations in this subclass of melanocytic tumors involve various receptor tyrosine kinases, including *ALK*, *ROS1*, *NTRK1, NTRK3*, *RET*, or *MET*, and the serine-threonine kinases *BRAF*(12, 19, 20). The rearrangements link the kinase domain of these signaling proteins to a wide range of fusion partners, leading to highly expressed and kinase-active proteins. The resulting chimeric proteins stimulate multiple oncogenic signaling pathways and promote tumor initiation and progression(12).

Recent searches for possible similar genomic rearrangements in melanomas led to the discovery of a novel *ALK* isoform(17). This transcript is expressed from a *de novo* alternative transcription initiation (ATI) site in *ALK* intron 19, and was accordingly named ALK^{ATI}. Melanomas with ALK^{ATI} expression show positive staining by ALK immunohistochemistry(17). In a large set of primary and metastatic melanomas ALK immunoreactivity was found only rarely, and if present, was not associated with *ALK* translocations, but with the truncated ALK^{ATI} isoform(21). Nonetheless, for the few patients whose tumors express ALK, it may provide a unique therapeutic opportunity.

In this study we sought to determine the *frequency of neurotrophic tropomyosin receptor kinase* (*NTRK)* gene rearrangements in metastasizing melanomas as this would also provide an option for targeted therapy, if the tumor did not respond to immunotherapy or other available treatments.

MATERIALS AND METHODS

Case Selection

The institutional data set (MSK BioPortal) was searched for cases of melanoma, which had been analyzed by MSK-IMPACT for treatment purposes(22). 751 cases were identified, including melanomas of cutaneous (449 total, 395 non-acral, 54 acral), mucosal/paramucosal (113), uveal (70) and primary CNS (2) origin, as well as metastases with unknown primary site (117). Of the 751 lesions, three metastatic melanomas of cutaneous origin and one metastasis from an anal primary melanoma were found with *NTRK* fusions.

The corresponding histopathologic material was retrieved and reviewed, including the metastatic lesions, which were subjected to sequence analysis, and the respective primary melanomas.

Immunohistochemical Analysis

Five micron thick tissue sections were cut from tissue blocks. All four metastatic lesions were examined and two primary tumors, from which tissue was available.

A commercially available anti-TRK rabbit monoclonal antibody (clone EP1058Y; Abcam, Cambridge, MA) was used for immunohistochemical expression analysis of NTRK. The immunohistochemical assays were performed on a Leica-Bond-3 (Leica, Buffalo Grove, IL) automated stainer platform. The staining extent and pattern was recorded for each tumor.

Next-Generation Sequencing

Next-Generation Sequencing (NGS) analysis was carried out within the context of an Institutional Review Board–approved protocol using MSK-IMPACT (NCT01775072), a deep-coverage hybridization capture-based assay encompassing 410 cancer-associated genes. MSK-IMPACT can detect missense mutations, indels, copy number alterations, and select gene fusions(22). Analysis of tumor and normal (typically from blood) DNA was carried out to allow for accurate somatic mutation calling.

RESULTS

Clinical Findings

Four patients with metastatic melanomas harboring *NTRK* rearrangements were identified out of 751 melanoma lesions for which NGS analysis (MSK-IMPACT) was available. They included three women and one man, in a range of 36 – 63 years of age (Table 1).

Pathologic Findings

All four metastatic tumors with documented *NTRK* gene fusions (Table 1) were amelanotic and displayed epithelioid cell features (Figs. 1, 2). The metastatic sites included lymph nodes, skin, colon, and duodenum. All metastatic tumors were immunoreactive for NTRK. No immunoreactivity for NTRK was found in a separate analysis of 20 lesions of metastatic melanoma lacking *NTRK* rearrangement.

Of the primary melanomas, two tumors were from the trunk, one from the lower extremity, and one arose in perianal skin. The latter showed features of superficial spreading melanoma, with an in situ component displaying intraepithelial pagetoid spread (Fig. 3). The three other tumors were primary nodular melanomas (Table 1, Fig 4). Tumor thickness ranged from 2.3 to 6.2 mm (mean = 4 mm; median = 3.7 mm). The tumor mitotic rates ranged from 4 to 27 mitoses per mm^2 (Table 1). Three melanomas were amelanotic. One tumor was focally pigmented. One tumor was ulcerated. The tumors were predominantly composed of epithelioid melanocytes (Figs. 3, 4). Tissue material for immunohistochemistry was available for two of the primary tumors. They were immunoreactive for NTRK. Positive staining was seen in both the in situ and invasive component (Fig. 4).

Sequence Analysis

MSK-IMPACT identified the presence of *NTRK* fusion and partners. For *NTRK1*, the partners included *TRIM63*, *DDR2* and *GON4L*. *NTRK2* was fused to *TRAF2* (Table 1). In two cases, the kinase fusions were found co-existing with known melanoma driver mutations, including an *NF1* mutation (case 3) and *NRAS Q61L* mutation (case 4). Two tumors (cases 1 and 2) lacked a known driver mutation.

DISCUSSION

While early-stage primary cutaneous melanoma is surgically curable, the prognosis is less favorable for patients with regional metastasis, and survival has historically been poor for patients with distant metastatic disease(23). However, recent advances in immunotherapy and the development of selective kinase inhibitors(24–29) have provided new opportunities for treatment of patients with advanced metastatic melanoma. Patients whose tumors harbor activating *BRAFV600* mutations achieve improved overall survival and durable responses(30, 31). Tumors with *NRAS* (32)and *KIT* (2, 33–35) alterations have been targeted with more modest success.

While mutations of *BRAF, NRAS* and *NF1* are the most common alterations in melanoma(1), a number of less common genomic aberrations have been identified, which might also provide new therapeutic opportunities(19, 36). The identification of new targets continues to increase therapeutic options for cancer patients(37). We have recently found a new isoform of the *ALK* receptor-tyrosine kinase in melanoma and other cancer types, and reported on a patient harboring this isoform who had transient clinical benefit to crizotinib(17).

In this study, we sought to determine the frequency of *NTRK* family rearrangement and expression in melanoma. Reviewing NGS data for melanomas of 751 patients, we found four metastatic lesions that harbored NTRK fusions. Three were derived from cutaneous primary tumors, one from a mucosal/paramucosal primary tumor.

Based on our cohort, the frequency of *NTRK* rearrangement in metastatic non-acral cutaneous melanoma is approximately 0.8% (3/395) and 0.9% (1/113) in mucosal/paramucosal melanomas. This is lower than the previously found expression rate for ALK (2.3%) in a series of 603 melanomas(21). However, in contrast to ALK expression in melanoma, which was related to the presence of an ALK isoform, NTRK expression was associated with the presence of a kinase fusion. Notably, two *NTRK* fusions co-occurred with other putative drivers (*NF1* and *NRAS*). While this observation makes one consider that some melanomas may harbor multiple drivers, it is also possible that in context with a known driver mutation, the genetic alteration involving *NTRK* may not be critical for tumor growth and merely reflect a “passenger” aberration. Nonetheless, co-existing genetic abnormalities, whether at the intratumoral or intracellular level, may have implications for therapeutic efficacy of targeting a single driver alteration as previously observed in other tumors and implicated genes(38–40).

The presence of a fusion with placement of *NTRK1* or *NTRK2* downstream to a constitutively expressed promoter explains the homogenous expression of NTRK in melanomas, as detected by immunohistochemistry. This lies in contrast to ALK, which tends to show heterogeneous ALK immunoreactivity from focal and weak to strong and diffuse, likely related to epigenetic regulation of ALK^{ATI} expression.

While a prior IHC study used the pan-TRK antibody clone EPR17432 to document NTRK expression(41), in this study we used the clone EP1058Y, because it produces more consistent and reliable results in our clinical laboratory.

NTRK comprises a family of tropomyosin receptor kinases (42). Members include three transmembrane proteins referred to as Trk A, B and C receptors. The corresponding genes are *NTRK1*, *NTRK2* and *NTRK3*, respectively. These receptors play an important role in the development and function of neuronal tissue(42). The *NTRK1* gene is located on chromosome 1q21-q22(43). The *NTRK2* gene is located on 9q21.33. Gene fusions represent the main molecular aberration involving *NTRK* in tumorigenesis, and have been found in various malignancies across different histologic phenotypes, including many different epithelial malignancies as well as glioblastomas, sarcomas, and so-called spitzoid melanomas(12, 44–46). The type of *NTRK* fusions previously reported to be associated with spitzoid melanocytic neoplasms included *LMNA-NTRK1* and *TP53-NTRK1*(12), and *ETV6-NTRK3*, *MYO5A-NTRK3* and *MYH9-NTRK3*[13].

The fusions found in this series included *TRIM63-NTRK1*, *TRAF2-NTRK2*, *DDR2-NTRK1* and *GON4L-NTRK1*; all intrachromosomal rearrangements. The *Tripartite Motif Containing (TRIM) 63* gene encodes for an E3 ubiquitin protein ligase(47, 48) that that mediates ubiquitination and proteasomal degradation of muscle proteins and that has been implicated in melanoma cell invasion(49). The *TNF receptor-associated factor 2 (TRAF2)* is involved in signal transduction from TNF receptors acting as a mediator of anti-apoptotic signals and activation of MAPK and NFkB(50–52). The *discoidin domain tyrosine kinase 2 (DDR2)* encodes a collagen-induced receptor that activates pathways relevant to wound repair, tumor growth and invasiveness(53). The GON-4 like gene *GON4L* encodes a transcription factor associated with expression of CD24, a driver of progression and metastases in certain tumors(54, 55). Although the role of the specific kinase fusions in the pathogenesis of melanoma and their impact on the phenotype is speculative and needs to be addressed by future studies; the promising responses seen to tyrosine kinase inhibitors in a wide variety of *NTRK*-rearranged tumors irrespective of histology and fusion partner, and the development of tyrosine kinase inhibitor-resistance through additional mutations on the kinase domain of the chimeric protein give testimony of NTRK's relevance in tumorigenesis and tumor survival.(56, 57)

With regard to the histopathologic characteristics of the primary melanomas of this series, none of them displayed Spitz nevus-like features or was associated with a pre-existing nevus that had changed. Thus, our observations document that *NTRK* fusions in melanocytic neoplasms are not unique to Spitz tumors, and can also be found in association with adult-type non-spitzoid melanomas.

Most importantly, however, the fact that *NTRK* rearrangements and NTRK protein expression can be found in a small subset of cutaneous melanomas using NGS and immunohistochemistry, has relevance for clinical care. Targeting NTRK and NTRK fusions represents a promising new opportunity for cancer treatment(58, 59). Recently, the NTRK inhibitor larotrectinib demonstrated a 78% objective response rate in tumors with NTRK family fusions, regardless of histology(58–61). Given this efficacy, it would be worth testing the tumors of patients diagnosed with metastatic melanomas arising from cutaneous and paramucosal primary sites for NTRK fusions. IHC is an efficient way for screening for such NTRK kinase fusions. Thus, this provides another opportunity for pathologists to assist their clinical colleagues and patients in the search for personalized cancer treatment options.

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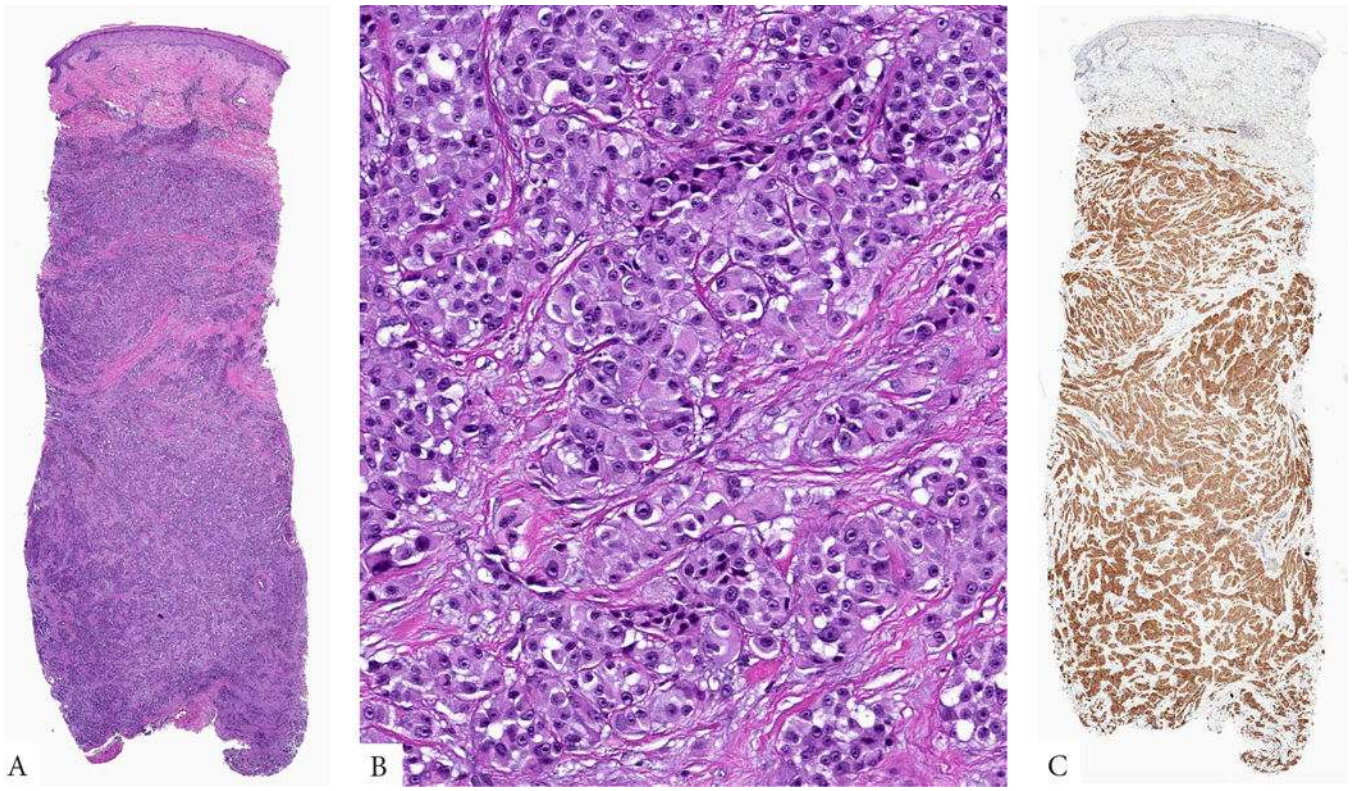

Figure 1.

Metastatic melanoma in dermis (case 1). A: Amelanotic tumor is present in the dermis. B: The tumor is composed of epithelioid melanocytes. C: The tumor cells are immunoreactive for NTRK.

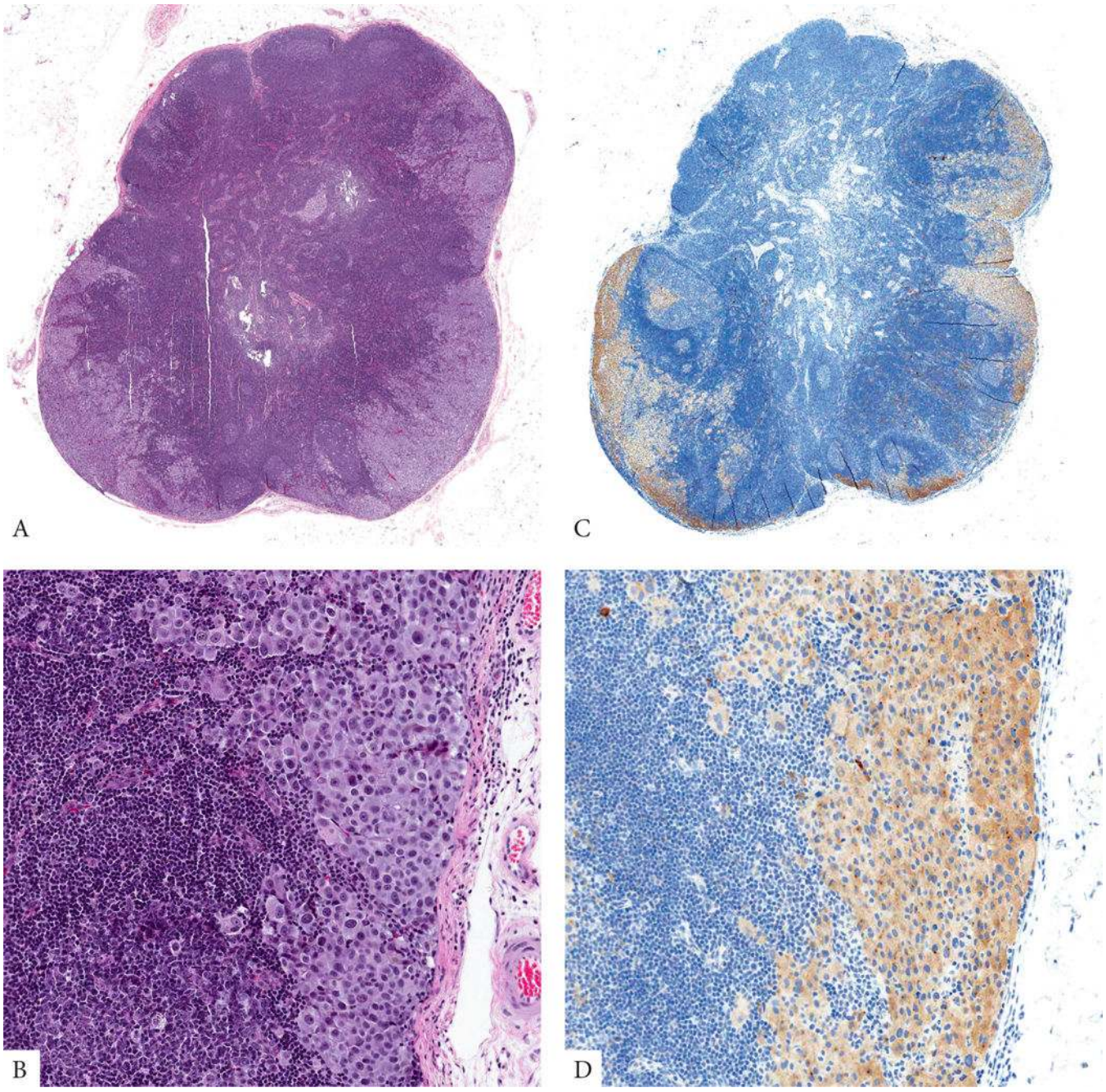

Figure 2.

Metastatic melanoma in lymph node (case 2). A: Amelanotic melanoma is located predominantly at the periphery of the node. B: The tumor cells display epithelioid cell features. C: The tumor cells are immunoreactive for NTRK.

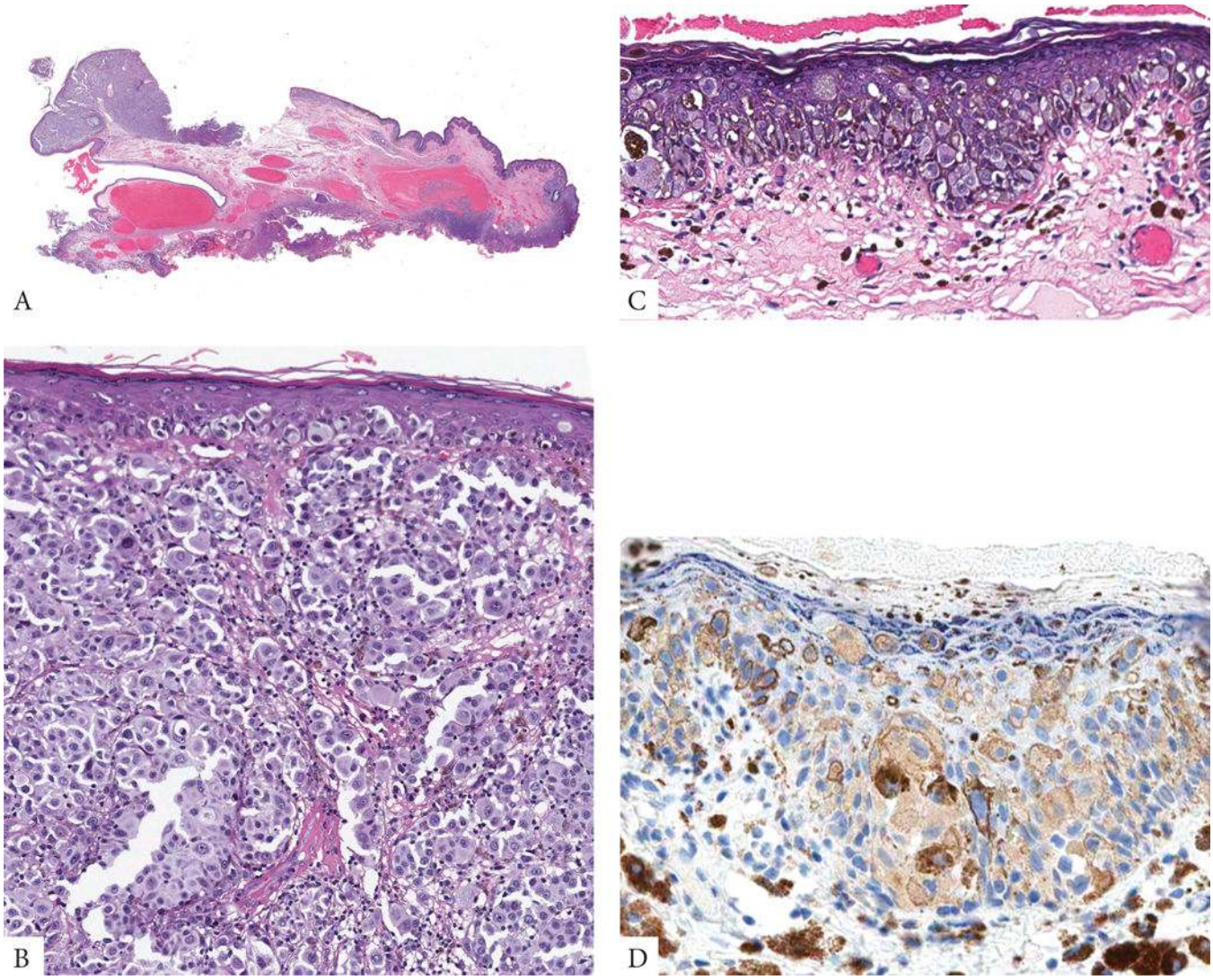

Figure 3.

Primary perianal melanoma (case 2). A: Silhouette of the tumor. B: There is intraepithelial melanoma characterized by pagetoid spread overlying invasive melanoma composed of sheets of large epithelioid cells. C: The melanoma in situ peripheral to the invasive tumor displays prominent pagetoid spread and is pigmented. D: The melanoma in situ is immunoreactive for NTRK.

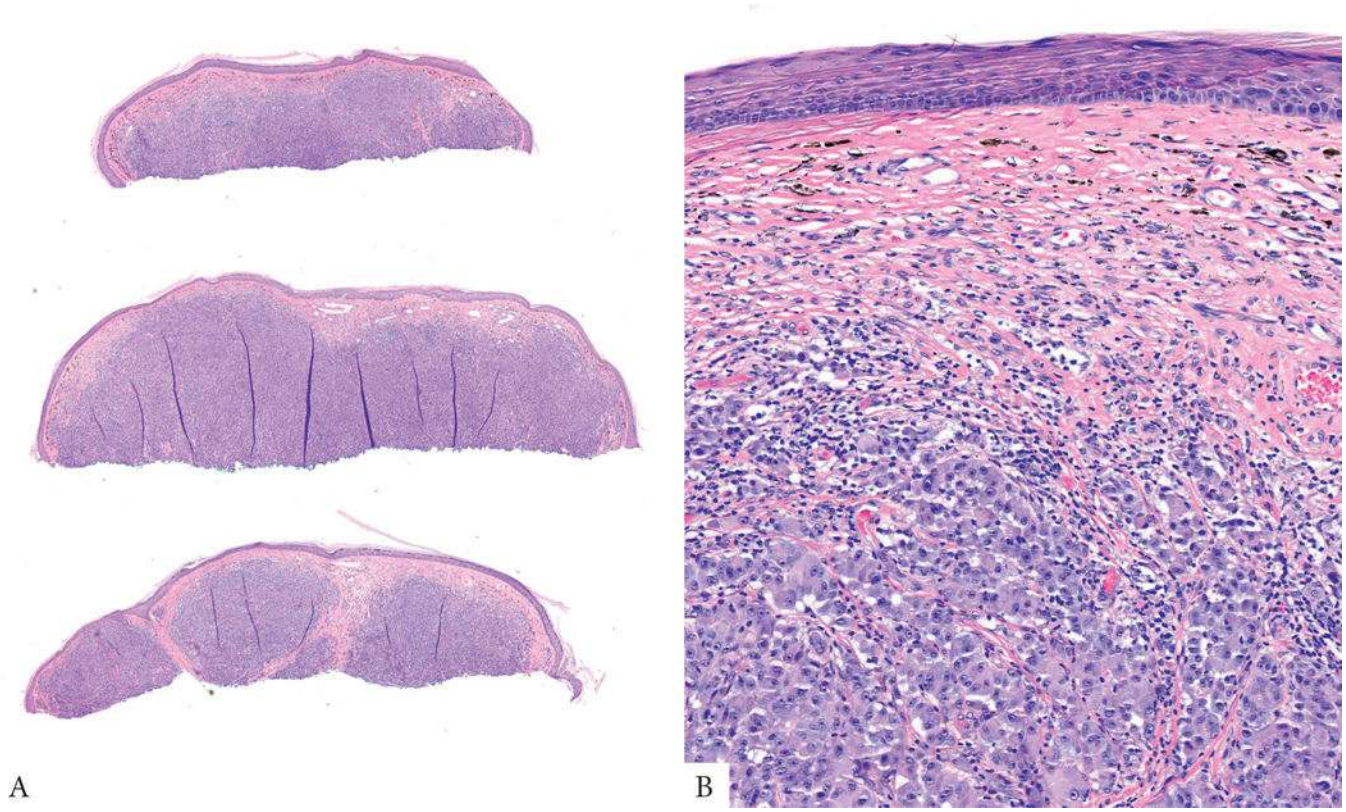

Figure 4.

A: Silhouette of the primary nodular melanoma (case 3). B: The tumor is composed of large amelanotic epithelioid melanocytes.

Table 1

Clinical, pathologic and molecular findings of melanomas with NTRK fusions

	Case 1	**Case 2**	**Case 3**	**Case 4**
Age (years)	63	47	55	36
Gender	Male	Female	Female	Female
Site of primary	Shin	Perianal	Umbilical	Back
Breslow	2.3 mm	2.8 mm	4.5 mm	6.2 mm
Ulceration	No	No	No	Present
Tumor mitotic rate	11/mm^2	8/mm^2	4/mm^2	27/mm^2
Type	Nodular	Superficial spreading pattern	Nodular	Nodular
Cytology	Large epithelioid	Large epithelioid	Large epithelioid	Large epithelioid
Melanin	Absent	Present	Absent	Absent
Age (years) at metastasis	65	47	58	39
Site of metastasis	Skin, lymph node	Lymph node	Colon	Duodenum
NTRK1-Fusion	NTRK1-TRIM63	NTRK2-TRAF2	NTRK1-DDR2	NTRK1-GON4L
Other driver mutations	None	None	NF1 truncation; RAC1 p295	NRAS Q61L