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CASE REPORT

Primary Sinonasal Mucosal Melanoma with Aberrant Diffuse and Strong Desmin Reactivity: A Potential Diagnostic Pitfall!

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Abstract The broad morphologic spectrum, inherent immunophenotypic heterogeneity of malignant melanoma and its rarity in the sinonasal tract are major challenges in eliciting the correct diagnosis, which may lead to misclassification and inadequate medical management. Herein, we describe a single case of a 70 year-old male with sinonasal mucosal melanoma, exhibiting varying histologic phenotypes including small round blue cell morphology, epithelioid and focal rhabdoid morphology and strong, diffuse desmin immunoreactivity. These constellation of features initially prompted the diagnosis of rhabdomyosarcoma. The differential diagnosis in this anatomic area includes other malignant small round blue cell tumors of the sinonasal mucosa such as rhabdomyosarcoma, olfactory neuroblastoma, sinonasal undifferentiated carcinoma, and lymphoma. We reviewed precedent literature and further discuss the potential pitfalls to which pathologists may be prone.

Keywords Melanoma · Sinonasal mucosa · Desmin · Rhabdoid · Pitfalls

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Introduction

Sinonasal melanomas (SNM) represent less than 1 % of all melanomas and less than 5 % of all sinonasal tract neoplasms. They usually present in the 5th–8th decade with nasal obstruction, epistaxis or nasal discharge, polyp, and rarely pain. SNM have a wide-variety of symptoms which may be confused for benign diagnoses; for this reason they usually present at more advanced stages. The prognosis is overall poor, with common recurrences and low 5-year survival reported to be less than 50 % [1, 2]. SNM are immunohistochemically identical to cutaneous melanomas. They are usually positive for one or a combination of melanocytic markers including S100, HMB-45, Melan-A, tyrosinase, and vimentin, and often negative for cytokeratins, epithelial membrane antigen (EMA), and myogenic markers [3–5].

Useful morphologic clues for the diagnosis of primary melanoma include: junctional activity, cytomorphologic atypia with prominent nucleoli, brisk mitotic rate, melanin pigment; however, in a significant proportion of cases these findings are either absent or difficult to evaluate. Therefore, the accurate diagnosis often relies on maintaining a high index of suspicion and ordering a complete immunohistochemical panel. Not infrequently, in step with its divergent phenotypic mimicry, melanomas have been known to express a variety of markers including cytokeratins, EMA, myogenic markers that can lead to erroneous diagnosis [4, 5].

There is precedent literature on aberrant desmin expression in malignant melanomas but documentation of strong and diffuse desmin reactivity in a primary mucosal melanoma with rhabdoid morphology has not been previously reported to the best of our knowledge. We report a case of a primary melanoma of the sphenoid sinus in which a strong and diffuse expression of desmin on an initial

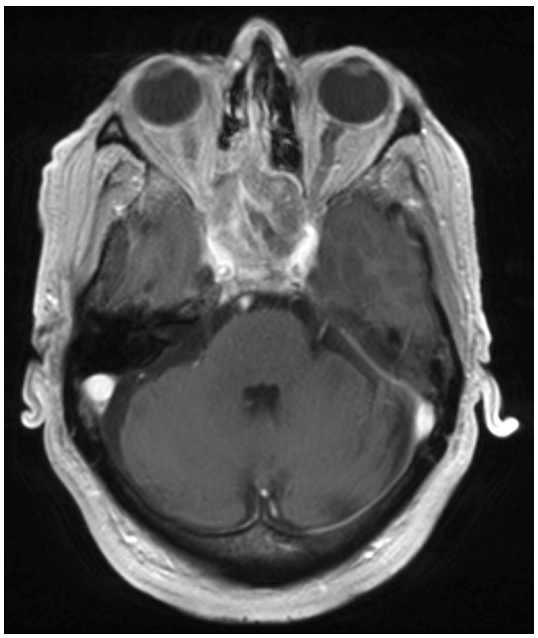

Fig. 1 Axial magnetic resonance imaging (MRI) showing a large irregular mass filing the right sphenoidal sinus and laterally displacing the right sphenoid lamina papyracea

biopsy led to an initial consideration of a rhabdomyosarcoma. However, subsequent evaluation of the melanocytic markers facilitated prompt and accurate diagnosis.

Case Report

The patient is a 70 year old male with past medical history significant for type II diabetes mellitus who presented with a two-week history of diffuse throbbing headache, lightheadedness and lassitude, bilateral blurry vision and diplopia. Brain magnetic resonance imaging (MRI) scans revealed a large contrast-enhancing and expansile mass in the right sphenoid sinus with internal fluid levels (Fig. 1). Physical examination revealed cranial nerve III palsy. Upon admission he experienced one episode of generalized tonic seizure. Subsequent computerized tomography (CT) and MRI scans revealed a lesion abutting (but distinct from) the pituitary gland, right orbital apex, and bilateral carotid arteries at the skull base. There was erosion of the posterior nasal septum and anterior margin of the sella turcica. Positron emission tomography-CT (PET-CT) confirmed a sphenoid mass with central photopenia, concerning for malignancy. Angiography of the mass was negative for carotid aneurysm. Biopsy of the mass was found to be a malignant small round blue cell tumor, with subsequent immunohistochemical staining best classifying the tumor as "malignant melanoma." The patient had no documented history of any pigmented skin lesion and an extensive skin examination failed to identify a lesion.

Table 1 Panel of immunohistochemical stains used in the study

Antibody	Clone	Titer	Source[a]
Cytokeratins AE1/AE3	AE1& AE3	1:300	Dako
S 100 protein	R polyclonal	1:3000	Dako
HMB-45	HMB45	1:100	Dako
Melan-A	A103	1:600	Dako
CD45	2B11+PD7/26	1:700	Dako
CD31	JC 70A	1:400	Dako
CD34	QBEnd/10	1:400	Cell Marque
CD117 (c-kit)	R polyclonal	1:400	Dako
DOG1	K9	1: 100	Novocastra
Smooth muscle actin	1A4	1:600	Dako
Smooth muscle myosin	SMMS-1	1:350	Dako
Des min	D33	1:200	Dako
H-Caldesmon	h-CD	1:50	Dako

[a] Dako North America Inc., Carpinteria, CA, USA; Cell Marque Corporation, Rocklin, CA, USA; Novocastra by Leica Biosystems, Newcastle upon Tyne, UK

An endoscopic endonasal tumor resection was performed followed by radiation therapy. A follow-up PET-CT scan 4 months post-resection showed multiple hypermetabolic bilateral cervical and left axillary lymph nodes, with hypermetabolic nodules in the retroperitoneum, spleen, right ureter and mesentery, all concerning for multifocal metastases. He received four cycles of ipilimumab before expiring seven months post-surgical resection.

Methods

All surgical specimens were fixed in 10 % formaldehyde, embedded in paraffin, sectioned (4 μm) and stained with hematoxylin and eosin. A panel of immunohistochemical stains was performed on the formalin fixed paraffin-embedded sections from both the biopsy and resection specimens, using commercially available antibodies. The antibodies, their clones, dilutions, sources that were used inthis study are summarized in Table 1. Translocation involving the *FOXO1* gene (13q14) was evaluated with interphase fluorescent in situ hybridization (FISH) on formalin-fixed paraffin-embedded tissue using a commercially available LSI breakapart probe set (Vysis, Abbott Laboratories. Abbott Park, IL, USA).

Results

Grossly, the resection specimens consisted of two aggregates of red, pale white rubbery tissue and bony fragments measuring $4.0 \times 3.0 \times 2.5$ cm and $4.0 \times 3.0 \times 2.0$ cm.

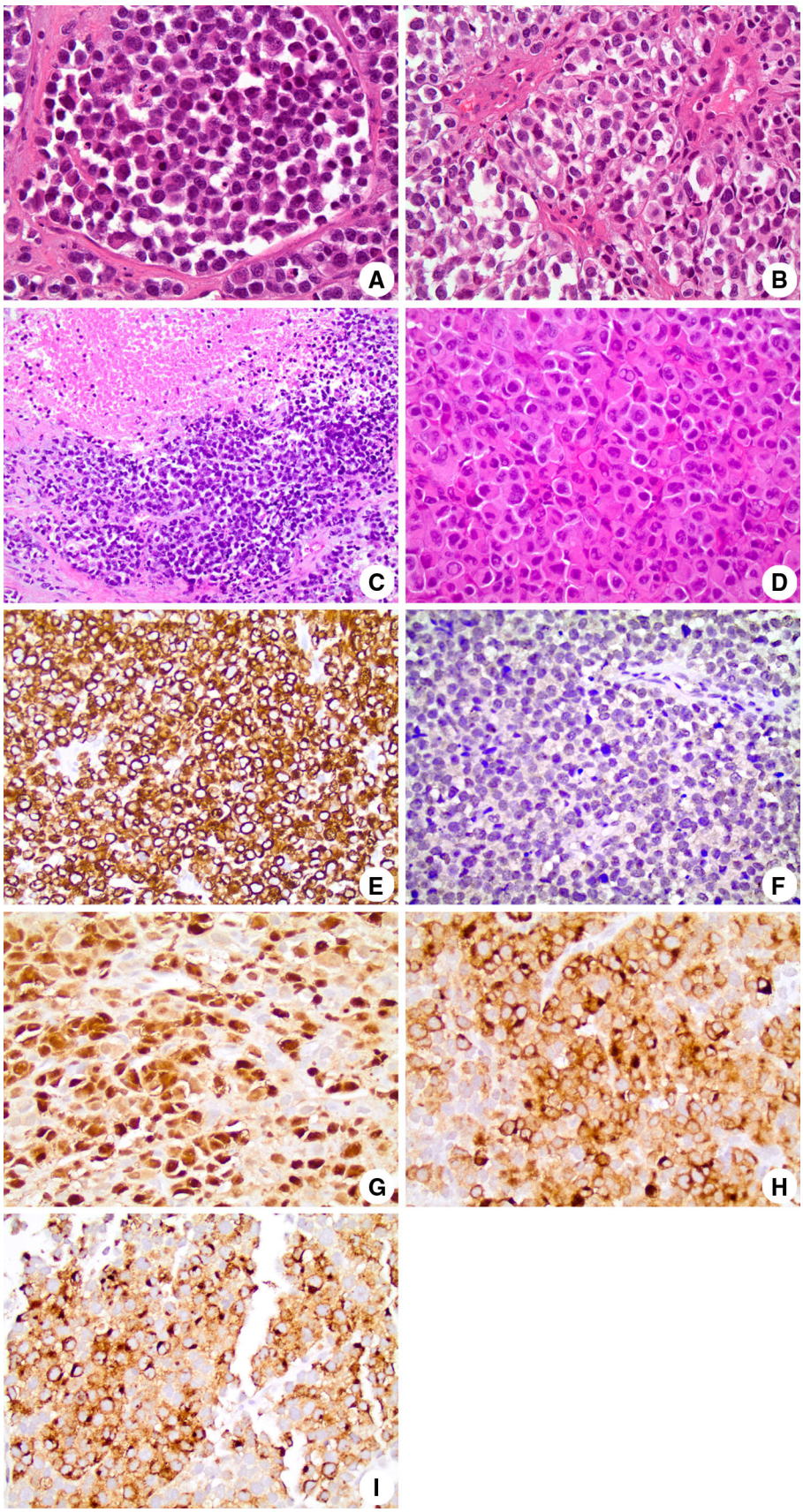

Fig. 2 Histomorphology and Immunophenotype of the Sinonasal Mucosal Melanoma. **a** Hematoxylin and Eosin (Mag. ×200) showing areas of tumor exhibiting "a small round blue cell" morphology. **b** Hematoxylin and Eosin (Mag. ×200) showing more eosinophilic cytoplasm. **c** Hematoxylin and Eosin (Mag. ×200) showing coagulative tumor necrosis. **d**: Hematoxylin and Eosin (Mag. ×400). Areas of tumor with rhabdoid appearing phenotype. **e** (Mag. ×200): Strong and diffuse immunoreactivity for desmin. **f** (Mag. ×200): Negative reactivity for myogenin. **g** (Mag. ×200): Diffuse reactivity for S-100. **h** (Mag ×200): Positivity staining for Tyrosinase. **i** (Mag. ×200): Positive staining for HMB-45

Histologic sections demonstrated a high grade malignant small round blue cell neoplasm (Fig. 2a) with other areas showing more epithelioid phenotype in approximately 30 % of the tumor cells, abundant dense eosinophilic cytoplasm with large vesicular nuclei was identified, reminiscent of rhabdoid cells (Fig. 2b–d). An in situ component was present. By immunohistochemistry, the tumor cells are strongly and diffusely positive for desmin (Fig. 2e) initially prompting a diagnosis of rhabdomyosarcoma; however, the myogenic markers (myogenin and myo-D1) were negative (Fig. 2f). Additional immunohistochemical studies revealed the tumor cells to be positive for S-100, tyrosinase, HMB-45 and Melan-A (Fig. 2h, i) and negative for AE 1/3, synaptophysin, chromogranin, EMA, CD99, CD45, CD3 and CD20. Flow cytometry failed to provide evidence of clonal B cell or T-cell populations. FISH analysis of the *FOXO1* gene (13q14) for alveolar rhabdomyosarcoma was negative for translocation.

Discussion

We report an unusual occurrence of melanoma with rhabdoid features within the sinonasal tract which, to our knowledge, is the first documented case in this location to show strong, diffuse desmin reactivity. The poor outcome and rarity of SNM has lead to efforts to distinguish these lesions from their cutaneous counterparts [2]. Despite these efforts, however, the risk factors, staging and prognostic indicators for mucosal melanomas remain poorly-delineated [6, 7]. Characterization of the morphologic spectrum of SNM has lead to the description of numerous morphologic variants, in terms of cell shape, cell size, nuclear features, stromal reaction, architecture, pattern and inclusions [3, 8]. Well-documented in the literature as protean entities, both mucosal and cutaneous melanomas frequently appear in the differential diagnosis for a variety of neoplasms.

Bittesini et al. [9] are credited with the first publication of a primary malignant melanoma with rhabdoid features. “Rhabdoid” tumor cells, as originally described by Haas et al. [10] in childhood renal tumors, resemble rhabdomyoblasts on light microscopy: dense eosinophilic cytoplasm, eccentric nuclei, large prominent single nucleoli, and frequently contain globular hyalin cytoplasmic inclusions. However, the extent of the rhabdoid morphologic change and the immunoprofile of rhabdoid melanomas may vary considerably. The ultrastructural findings may be highly variable, however, and convincing evidence of rhabdomyoblastic differentiation is frequently absent with rare documented exception [11–13]. Melanomas with rhabdoid immunophenotype can express α-smooth muscle actin, HHF-35 and desmin [8, 14, 15]. Subsequent studies have shown that these entities are variably positive for HMB-45 and S100; alternatively, they can be HMB-45 negative and S100 negative making a diagnosis of melanoma arduous and suggesting that the development of rhabdoid morphology may occur with subsequent loss of pertinent melanocyte-specific membrane antigens [12, 16–18].

Occasionally, melanomas can demonstrate aberrant immunophenotypic expression of a variety of markers, which may include cytokeratins, smooth muscle actin, CD68, CEA, EMA, CD99, WT1, glial fibrillary acidic protein, and neuroendocrine markers; however, aberrant strong and diffuse desmin expression is only rarely observed [8, 13, 19, 20]. Desmin is an intermediate filament protein typically positive in normal muscle cells, muscle derived neoplasms, submesothelial fibroblasts, lymph node dendritic cells, endometrial stromal cells, and rarely myofibroblasts [20, 21]. Non-specific antibody cross-reactivity for desmin with other intermediate filaments is well documented; however, strong and diffuse staining in melanomas is not commonly observed [20, 21]. Desmin expression may also be occasionally noted in desmoplastic melanomas and melanomas with rhabdomyoblastic differentiation [13, 15, 22].

Melanomas with aberrant desmin expression can be immunophenotypically and ultrastructurally diverse, as they may show rhabdoid or smooth muscle differentiation [14, 15]. However, melanomas with rhabdoid morphology are notoriously heterogenous as they may or may not have a rhabdoid immunophenotype [12, 23]. Thus, in the sinonasal tract this can be a significant source of diagnostic error, since in this site the differential diagnosis of melanoma includes other malignant small round blue cell tumors that may show diffuse and strong desmin positivity, such as rhabodmyosarcoma. The present case shows minimal histologic and immunophenotypic forms of a rhabdoid melanoma. Only focal rhabdoid features were noted in less than 30 % of tumor cells; however, 100 % of tumor cells demonstrated diffuse and strong desmin staining with negative myogenic markers (myo-D1, and myogenin).

It is perhaps the unusual location of this desmin-positive rhabdoid phenotype that is most intriguing. The precedent reported cases of desmin positive melanomas vis-a-vis anatomic sites and pattern of reactivity are summarized in Table 2. Interestingly, Reiman et al. [22] documented desmin positivity in seven of nine desmoplastic melanomas and 10 of 10 not-otherwise-specified melanomas, all located within the head and neck. These findings seem to suggest that positive desmin staining in melanomas could have a site predilection for the head and neck. However, a more recent study of head and neck desmoplastic melanomas revealed a 0 % desmin positivity in a total of 28

Table 2 Rhabdoid melanoma by location and immunophenotype

Study [reference]	N	Location	Rhabdoid morphology (% of cells expressing)	Rhabdoid immunophenotype	Melanoma immunophenotype
Gharpuray-Pandit et al. [13][a]	2	Pinna, submandibular soft tissue	Yes (unspecified)	(+): Desmin (diffuse), myoglobin (cytoplasmic), myogenin (nuclear), MyoD1 (nuclear)	(+): S100, HMB-45 (focal) (−): MelanA, tyrosinase [2/2]
Schindler et al. [41]	1	Urinary bladder	Yes (unspecified)	Not assessed[c]	(+): S100, CD56 (−):MelanA, HMB-45
Chung et al. [23]	1	Forearm	Yes (100)	(−) SMA desmin	(+): S100, HMB-45
Nakamura et al. (2009) [25]	1	Subcutaneous[e]	Yes (unspecified)	(+): INI1 (−): desmin	(+): S100, MelanA (−): HMB-45
Tallon et al. [38]	1	Subcutaneous[e]	Yes (100)	(−): Desmin	(+): S100, (−): HMB-45, Mart-1
Gattenlöhner et al. [39][b]	1	Scalp	Yes (unspecified)[b]	(+): Myogenin, desmin	(+): S100, Mart-1
Gattenhoher et al. [39][b]	1	Lymph node, cervical[e]	Yes (100)	(+): Desmin (strong), myoglobin	(+): S100, Mart-1
Gavino et al. [17]	1	Thigh[e]	Yes (unspecified)	(−): SMA, MSA, desmin	(+): S100, HMB-45 (focal)
Abbott et al. [11]	1	Lung[e]	Yes (100)	(−): Desmin, SMA	(+): S100 (−): HMB-45, MelanA, tyrosinase
Borek et al. [12]	3	Scalp, thigh, back	Yes (unspecified)	(−): SMA (2/3), desmin (3/3)	(+): S100 [3/3] (−): HMB-45 [3/3]
Laskin et al. [18]	1	Subcutaneous[e]	Yes (100)	(−): Myoglobin, HHF35	(−): S100, HMB-45
Chang et al. [16]	31	Various[ef]	Yes[d]	(−): MSA (31/31)	(+): S100 [26/31], HMB-45 [25/31]
Parham et al. [40]	1	Skin over deltoid	Yes (unspecified)	Not assessed[c]	(+): S100
Bittesini et al. [9]	1	Left axilla[e]	Yes (unspecified)	(+): Desmin	(−): S100, HMB-45

N number of cases, *SMA* smooth muscle actin, *MSA* muscle specific actin, *HHF35* muscle-actin-specific monoclonal antibody

[a] Gharpuray-Pandi et al. have defined their finding as "melanoma with rhabdomyoblastic differentiation", given the positivity in myogenin and MyoD1

[b] Gattenholler et al.showed focal rhabdomyoblastic differentiation in the primary resection specimen, but nearly 100 % rhabdoid morphology in the metastic lesions

[c] Schindler et al. and Parham et al. have documented a rhabdoid melanoma by morphology alone without immunophenotypical confirmation

[d] 15 cases showed 100 % rhabdoid staining and 16 cases showed <25 % 16 cases

[e] metastatic site

[f] Chang et al. documented metastases most commonly to the lymph nodes, followed by soft tissue, liver, lung, small intestine and skin

cases studied [24]. A similar study limited to rhabdoid melanomas has yet to be performed, given the rarity of this tumor subtype. Most cases of rhabdoid melanomas described in the literature consisted of metastatic lesions, whose prognosis did not appear to differ significantly from conventional melanomas; however, the rhabdoid phenotype in primary melanomas has been so infrequently reported that the precise prognostic significance of this finding in primary lesions remains elusive [11, 17].

The location and histologic appearance of the presenting mass warrants the consideration of several key differential diagnoses, including both small round blue cell tumors and rhabdoid-appearing tumors.

Rhabdomyosarcoma is perhaps the closest morphologic entity arising in the sinonasal tract which may be confused for rhabdoid melanoma. In addition to the presence of rhabdoid cells, several forms of rhabdomyosarcoma classically fall into the "small round blue cell tumor" category. By definition, however, a "rhabdoid" tumor must not contain elements of true rhabdomyoblastic differentiation [10], and thusly would stain negative for most myogenic markers [12, 23, 25]. Moreover, positive staining of rhabdoid tumor cells for melanoma markers precludes a diagnosis of rhabdomyosarcoma. Thus, positive desmin staining in the present case is designated as truly aberrant in light of unequivocal HMB-45 and S-100 staining.

The recently described epithelioid variant of rhabdomyosarcoma must now be considered in this differential diagnosis, given its "epithelioid morphology, reminiscent of poorly-differentiated carcinoma or melanoma" [26–28]. Unlike the more common variants of rhabdomyosarcoma,

these tumor cells have abundant amphophilic or eosinophilic cytoplasm with large vesicular nuclei, prominent nucleoli, variably distinct cell membranes and little pleomorphism—features strikingly similar to those seen in the present case. Consistent immunoreactivity for Myo-D1 and or Myogenin and absent expression of melanocytic markers will help clinch the diagnosis. The spectrum of Ewing's sarcoma and primitive neuroectodermal tumors (ES/PNET) enter the differential of any small blue round cell tumor. ES/PNET has been previously described as arising from the sinonasal tract, albeit rarely [29]. ES/PNET can undertake a variety of patterns, but commonly forms sheets of small round blue cells, similar to that seen in the present case. Of note, in a study of 66 cases of ES/PET tumors by Folpe et al., desmin reactivity was only found in a single case [30]. Frequent membranous pattern of expression for CD99 is present in 95 % of Ewing's family of tumors [31, 32] and *EWSR1* (22q12) gene rearrangement is confirmatory [29].

Epithelioid sarcoma also presents a diagnostic challenge given its morphologic appearance of uniform polygonal cells, solid-sheet growth pattern and rhabdoid-type cells has lead to the creation of a "proximal type" or rhabdomyosarcoma-type variant [33, 34]. Loss of INI1 with frequent expression of epithelial markers (AE1/3 and EMA) and CD34 would facilitate the diagnosis.

Esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma, can present as a small round blue cell tumor that, like melanoma, appears to be of neuronal or neural crest origin [35, 36]. However, ENB consistently expresses neuroendocrine markers (synaptophysin and chromogranin) and lacks expression of the melanocytic markers (HMB-45 or Melan-A) [37].

Conclusion

This case illustrates the tremendous histologic and immunophenotypic mimicry of malignant melanomas and the diagnostic challenges that they pose. We highlight the importance of considering melanoma with aberrant desmin expression in the differential diagnosis of a poorly-differentiated small round blue cell tumor with co-expression of melanoma markers. Accordingly, we strongly caution against a limited immunohistochemical panel in these cases.

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