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CASE REPORT

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Malignant melanoma with metaplastic cartilaginous transdifferentiation: A case report

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Abstract

Malignant melanoma is notorious for its remarkable morphological variation and aberrant histopathological patterns. However, melanoma with prominent cartilaginous transdifferentiation simulating chondrosarcoma is extremely rare. A 75-year-old male developed a swelling in his left inguinal region and was diagnosed with a metastatic melanoma, which was found to harbor a *BRAF* V600E mutation. Later on, the left inguinal lymph node was excised and immunohistochemistry done on the specimen revealed an undifferentiated component negative for S-100 protein, HMB-45 and Melan-A and a cartilaginous component positive for S-100 protein and diffusely positive for *BRAF* V600E mutation. To our knowledge, there are around 14 cases reported in the literature of malignant melanoma with pure cartilaginous transdifferentiation. In all cases, immunohistochemistry of the cartilaginous component was positive for S-100, which is not an indicator of melanoma because cartilage expresses S-100. *BRAF* mutational studies support that the tumor arose from a common melanoma cell that harbored the mutation and subsequently transdifferentiated. This case illustrates the importance of an accurate and thorough clinical assessment when it comes to the diagnosis of melanomas as they are notable for their impressive degree of morphologic variability. Moreover, this report helps shed light on the use of immunohistochemical analysis to reach a definitive diagnosis.

KEYWORDS

BRAF, cartilaginous transdifferentiation, melanoma, S-100

1 | INTRODUCTION

Malignant melanoma has a wide variety of histopathological patterns that can mimic other malignant tumors. Several variants have been identified such as polypoid, verrucous, desmoplastic, myxoid, chondroid, among many others.[1]

Malignant melanoma cells have some degree of plasticity and are capable of losing certain melanocytes markers and undergoing extensive metaplastic transdifferentiation[2,3] which is a rare phenomenon. This term is used to describe the development of morphologically, immunohistochemically and or ultrastructurally recognizable non-melanocytic cell or tissue components.[4] Osteocartilaginous differentiation can occur sometimes, and it involves the formation of osteoid, woven bone, and cartilage. Taking into account osteocartilaginous differentiation in melanomas is important, as melanomas may be misdiagnosed as osteosarcomas or chondrosarcomas. The mechanisms underlying these heterologous differentiations are not very well understood.[2]

In this report, we describe an unusual case of a melanoma that exhibits a transdifferentiated cartilaginous phenotype with loss of all melanocytic markers in the undifferentiated component.

Juliett Berro and Nour Abdul Halim contributed equally to this manuscript.

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1.1 | Case presentation

A 75-year-old male presented to our institution in July 2016 complaining of an enlarged left inguinal lymph node. A core biopsy of the inguinal lymph node performed at an outside hospital had shown metastatic melanoma positive for HMB-45 and Melan-A. He had been non-responsive to an unclear regimen of non-surgical treatment prior to presentation to our institution.

On physical examination there were no significant findings except for some inguinal lymphadenopathy, measuring 4.5 cm. The patient underwent full-body skin examination for detecting a primary lesion, however, the exam was unremarkable. Repetition of positron emission tomography-computerized tomography (PET-CT) imaging and pathology was requested. PET-CT showed an enlarged metastatic left inguinal lymph node, in addition to multiple metastatic lung nodules. Core biopsy of the inguinal lymph node showed metastatic melanoma positive for S-100 and Melan-A, while the pulmonary nodules (Figure 1A) were positive for HMB-45 and Melan-A (Figure 1B). SOX10 test was not performed.

To further evaluate the tumor on the molecular level BRAF V600 mutation genotyping via polymerase chain reaction (PCR) testing for the inguinal lymph node showed positivity for *BRAF* V600E mutation. Accordingly, the patient was treated with BRAF/MEK inhibitor therapy with cobimetinib (20 mg for 1 week) in combination with vemurafenib (240 mg for 3 weeks), starting November 2016. The patient showed good tolerance while being mostly asymptomatic, except for muscle weakness and joint pain. A month later, the patient developed peripheral neuropathy as a consequence of vemurafenib, resulting in cessation of targeted therapy and was switched to immunotherapy with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab monotherapy of 240 mg every 2 weeks. PDL-1 expression level was not tested as it was uncommon until recently in Lebanon.

The patient was regularly followed up with repeated PET-CT imaging and clinical examination. In addition, magnetic resonance imaging (MRI) of the brain was performed every 3 months. MRI showed no evidence of brain metastasis. PET-CT showed resolution of the pulmonary nodules and interval increase in the size of the inguinal lymph node. This suggested responsive disease, except focally in the inguinal lymph node. Subsequently, in December 2017, the patient underwent inguinal lymphadenectomy after a discussion within the multidisciplinary team. The excisional biopsy however revealed two different neoplastic phenotypes (Figure 2). The first one consisted of an undifferentiated component with round cells and spindle cell morphology and high nuclear/cytoplasmic ratio negative for S-100, Melan-A and HMB45, while the other one consisted of a cartilaginous component (Figure 3) positive for S-100 and diffusely positive for BRAF (Figure 4), which was detected via BRAF VE1 immunohistochemistry. Also, the pathology reports showed that the surgical margins were clear.

Post-operation the disease progressed further during the course of immunotherapy treatment. MRI revealed multiple secondary lesions in the brain, however, no biopsy was performed. In April 2018, the patient was admitted for inguinal bleeding. Aggressive local recurrence was observed and subsequently the patient passed away due to pneumonia. The patient had a severe hypotension followed by a cardiac arrest and a pulmonary arrest.

2 | DISCUSSION

Undifferentiated phenotypes of melanoma are occasionally associated with divergent or metaplastic transdifferentiation.[2] It is conceivable that in tumor cells, transdifferentiation may in part be the result of somatic activation of lineage-foreign transcription factors. Mechanisms driving such transdifferentiation involve epigenetic alterations caused by malfunction of genes involved in maintaining chromatin

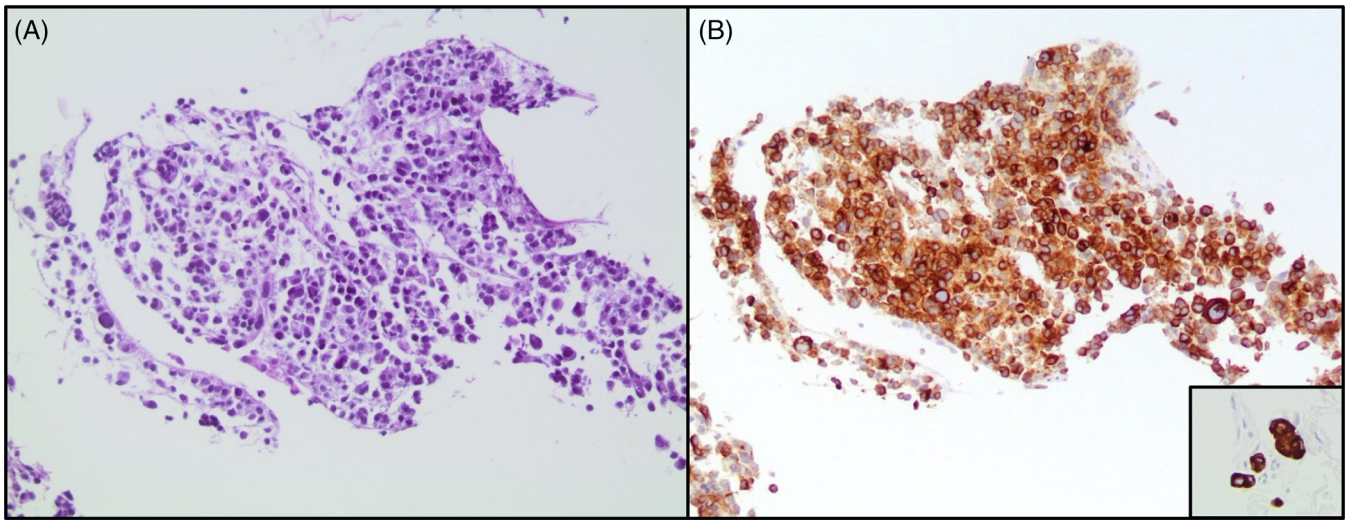

FIGURE 1 A, Malignant melanoma, metastatic to the lung (hematoxylin–eosin, original magnification ×20). B, Melan-A immunohistochemical stain, positive in metastatic melanoma (original magnification ×10). Inset: Melan-A positive control

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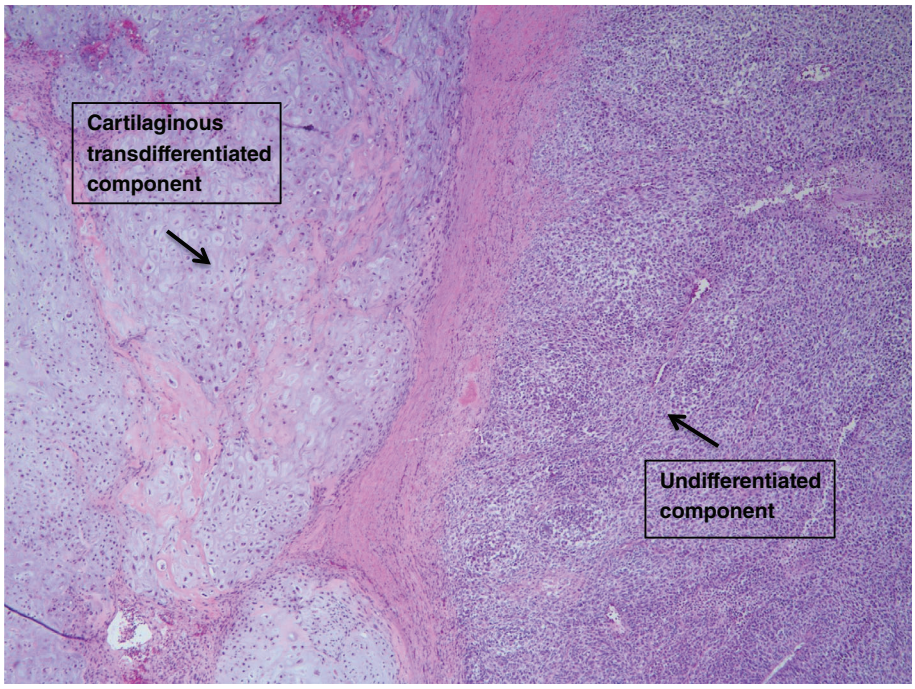

FIGURE 2 Inguinal mass involved by metastatic malignant melanoma with chondrosarcomatous metaplasia (hematoxylin-eosin, original magnification ×4)

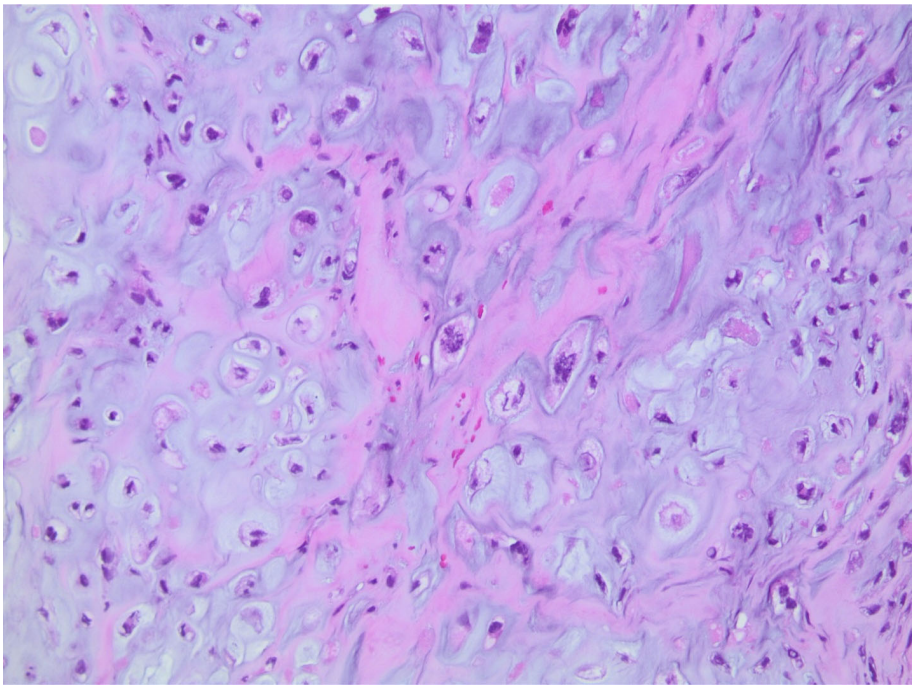

FIGURE 3 Metastatic malignant melanoma with chondrosarcomatous metaplasia (hematoxylin–eosin, original magnification ×20)

markers and/or DNA methylation, as shown in several tumors including melanoma.[5] Banerjee and Eyden[6] have defined this phenomenon in melanomas as the development of immunohistochemically and morphologically recognizable non-melanocytic components within an existing melanoma. Transdifferentiation has also been seen in some cancers such as urothelial carcinomas, neuroendocrine tumors, and melanomas.[7] The common types of transdifferentiation reported in melanomas include schwannian, myofibroblastic, smooth muscle, neuroendocrine, ganglionic, and osteocartilaginous differentiation among others.[2]

Pure cartilaginous devoid of osseous differentiation in melanomas is among the least frequently occurring histological patterns, described in only few case studies.[8] The exact mechanism is not very well understood but has been postulated to be a metaplastic process secondary to Melanoma-Inhibiting Activity (MIA) factor known to be present in most metastatic melanomas.[4] Overexpression of MIA might contribute to cartilaginous differentiation, supporting the cartilaginous phenotype while inhibiting osteogenic differentiation.[9] Furthermore, a study done by Bosserhoff and Buettner[10] showed evidence that MIA plays a significant role in melanoma metastasis and invasion, thus

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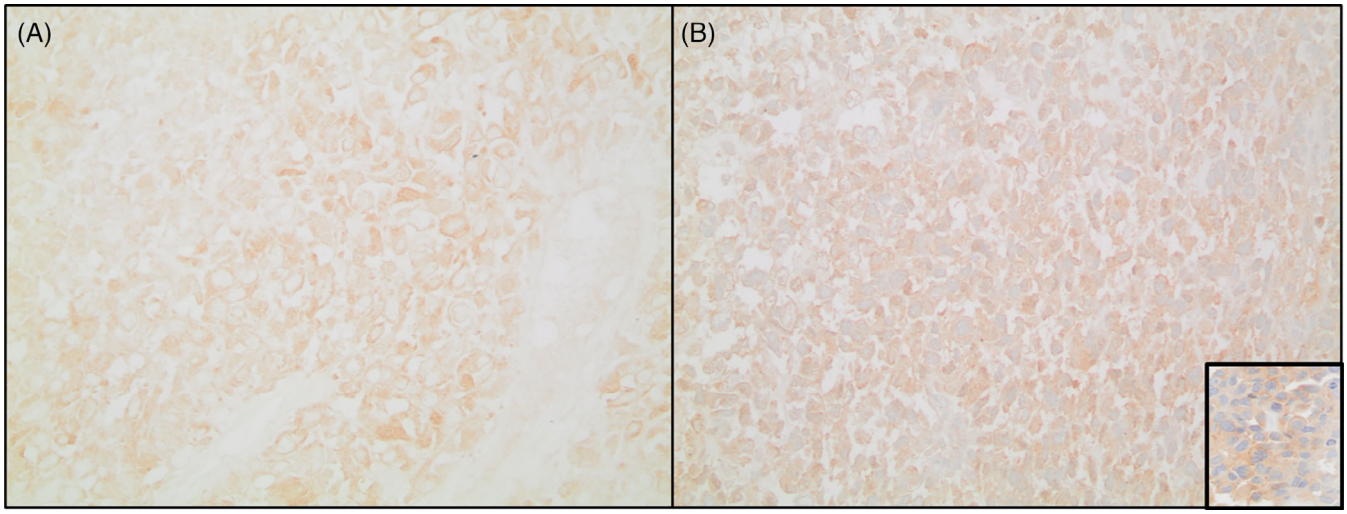

FIGURE 4 BRAF immunohistochemical stain, diffusely positive in metastatic melanoma: A, BRAF positive in the cartilaginous component (original magnification ×40), B, BRAF positive in the undifferentiated component (original magnification ×40). Inset: BRAF positive control

explaining the aggressiveness of the tumor. In addition, various studies indicated that MIA is a highly specific and sensitive marker for the progression of malignant melanoma; this is useful for follow-up and therapy-monitoring.

B-type Raf kinase oncogene *BRAF* is a key mitogen-activated protein kinase (MAPK) pathway, essential for the transduction of signals from Ras, an oncogene. When mutated, *BRAF* results in continuous proliferation and neoplastic growth responsible for several cancers.[12] *BRAF* mutation is present in 7% of all cancers and more than 60% in melanomas.[13,14] Few studies reported *BRAF* mutations or rearrangements in sarcomas; however, none were reported in chondrosarcomas. Chondrosarcomas have different pathways than melanomas including Hedgehog, Src and PI3K-Akt-mTOR pathways.[15] Furthermore, in our case the cartilaginous component was nested within an undifferentiated component negative for all melanocytic markers, giving the impression of chondrosarcoma. It is important to exclude such a possibility before rendering a diagnosis of a collision tumor; two histologically distinct tumor types occurring at the same anatomic site.

Various cases (Table 1) have thus far been reported in the literature. The tumors in almost all cases including our case had a differentiated component positive for S-100 except for few cases, which were also positive for HMB-45 and/or Melan-A. Chondrosarcoma and melanoma IHC biomarkers and distinct molecular genetic markers are listed in Table 2. However, the several candidates for chondrosarcoma biomarkers listed in Table 2 are not yet accurate as limited data is available regarding their frequency of expression. Hence, it is not clear how useful they are for detection and diagnosis of chondrosarcoma. BRAF VE1 IHC is a useful tool for melanoma diagnosis. Approximately 50% of melanomas harbor this mutation. The application of BRAF VE1 IHC or the detection of V600E mutation in an undifferentiated or transdifferentiated component is a reasonably specific result to support the diagnosis. However, in melanomas with cartilaginous transdifferentiation it is limited due to overlapping IHC patterns, because cartilage normally expresses S-100 protein, so positivity for S-100 serves little purpose in recognizing melanocytic differentiation in a melanoma with cartilaginous metaplasia.[11]

A study done by Cipriani et al showed that none of the patients diagnosed with sarcoma (constituted of different sarcoma subtypes including a group of patients with cartilaginous sarcomas) harbored a BRAF mutation, while in the patients of the differentiated melanoma group (including a group of cases of melanoma with cartilaginous transdifferentiation), three sarcomas harbored a *BRAF* mutation, which was correlated to melanoma dedifferentiation because the control group (sarcoma only) did not harbor the mutation.[16] In another study done by Movva et al 2539 sarcomas were profiled by IHC, FISH/CISH, NGS and Sanger sequencing and none harbored a BRAF mutation.[17] Notably, *BRAF* fusions have been detected in few sarcomas (non-chondrosarcomatous), as reported by Kao et al.[18,19] On the other hand, *BRAF* mutation has not yet been reported in chondrosarcoma. Therefore, with regards to our patient, *BRAF* mutation in the cartilaginous component supports the interpretation of melanocytic differentiation.

In our case the patient was initially treated as being diagnosed with melanoma, without knowledge that he harbored a transdifferentiated component. Therefore, targeted therapy (BRAF inhibition) showed resolution of the lung nodules, while interval increase in the size of the inguinal lymph node was observed on imaging examinations. The resistance to therapy and the persistence of the disease correlates histologically to the transdifferentiation of the tumor, which may explain the limited clinical response of the tumor. It is unclear if systemic therapy played a role in the further progression of transdifferentiation of melanoma. Besides, *BRAF* also correlates with poor prognosis, resistance to targeted therapy within 6-7 months or no response and is associated with recurrence and progression.[20] Furthermore, the mimicry of other tumor phenotypes could also provide an evasion mechanism from immune surveillance, based on gene expression associated with normal cell phenotypes. Nevertheless, this is a daunting speculation which requires further investigation. Even with the knowledge that the patient had a

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TABLE 1 Reported cases of melanoma exhibiting cartilaginous differentiation

Reference	Year	Age, gender	Primary/metastatic	Location	Follow up	Size	Cell shape	IHC positive
Ali et al[23]	2017	68, F	Primary/metastatic	Macule on left cheek	Metastasis to L3-para-spinal soft tissue mass, brain and lungs	0.57 mm	Epithelioid	S-100 in both primary and para-spinal soft tissue
Parente et al[9]	2013	47, F	Primary	Subungual nodule	Distal phalanx amputation of the big right toe, no recurrence and metastasis	9.9 mm	Epithelioid	S-100
Murali[24]	2010	59, M	Primary	Polypoid tumor on lip	After 9 months recurrence occurred without chondroid differentiation	N/A	Epithelioid and spindle	S-100
Murali[24]	2010	88, M	Primary	Shoulder		N/A	Spindle	S-100
Murali[24]	2010	57, F	Primary	Subungual nodule	Amputated; after 1 year no recurrence	N/A	Epithelioid	S-100, HMB-45
Mete et al[25]	2010	30, F	Metastatic	Left axillary lymph node		N/A	Epithelioid and spindle	S-100
Piana et al[22]	2009	66, F	Metastatic	Six recurrent lesions in the breast	Previously underwent mastectomy, SLN negative	Thickness per nodule 12 mm	Epithelioid and spindle	S-100
Hanley et al[26]	2008	46, F	Metastatic	Left inguinal lymph node	Widespread; death in 7 months	3.5 × 2.5 cm	Epithelioid	S-100, HMB-45, Melan-A
Rinaggio et al[27]	2008	76, M	Primary	Nasal cavity	Had radiotherapy	35 mm	Epithelioid and spindle	S-100, HMB-45
Slavik et al[28]	2007	61, F	Primary	Nose		1.1 mm	Epithelioid	S-100
Ackley et al[8]	2001	73, F	Primary	Subungual		16 mm	Epithelioid and spindle	S-100
Ackley et al[8]	2001	61, F	Primary	Ankle		11 mm	Focally epithelioid and spindle	Not reported
Banerjee et al[29]	1998	79, F	Primary	Polypoid lesion in vagina	Local recurrence after 1 month, no metastases	27 mm 40 mm (recurrent lesion)	Epithelioid	S-100-HMB-45
Banerjee et al[29]	1998	67, M	Primary, metastatic	Mucosal	Multiple local recurrence		Epithelioid and spindle	S-100
Grunwald et al[21]	1985	50, F	Metastatic	Calf	Further metastasis in leg, 2 months	1.5 × 1 × 1 cm	Single large pleomorphic hyperchromatic nuclei	N/A

Abbreviations: F, female; IHC, immunohistochemistry; M, male; SLN, sentinel lymph node.

heterogenous cancer after surgery, the tumor was still treated based on the diagnosis of melanoma.

Usually chondrosarcoma is treated best by surgery, which has been done before knowing that it was heterogenous. However interestingly, the disease recurred and progressed rapidly post-lymphadenectomy, followed by brain metastasis and local recurrence at the inguinal region 4 months later. So far in literature such heterogenous tumors are aggressive and have worse prognosis than melanoma alone, although

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TABLE 2 Diagnostic IHC biomarkers and genetic mutations of melanoma and chondrosarcoma

Melanoma IHC markers (sensitivity/specificity)[30,31]	Cartilaginous sarcoma IHC markers[15,37-39] (expression)
S100 (97%-100%/75%-87%)	S100 (20%)
HMB-45 (69%-93%/77%-100% primary; 56%-83% metastatic)	SOX4 (30.4%)
Melan-A/MART-1 (75%-92%/95%-100%)	SOX9 (NR)
SOX10 (100%/93%)	CD117 (30%)
Tyrosinase (84%-94%/97%-100%)	Leptin and adiponectin (NR)
MiTF (81%-100%/88%-100%)	Periostin (NR)
NKI/C3 (86%-100%/poor)	Amphiregulin (NR)
	BDNF (NR)
Melanoma genetic mutations[32-36] (expression)	Cartilaginous sarcoma genetic mutations[15,37,40,41] (expression)
BRAF (>60%); BRAF V600E (80%)[a]	HOTAIR (NR)
NRAS (15%)	AMACR (21.1%)
IDH-1 (10%)	IDH-1 (56%); IDH-1 R132C (40%)
IDH-2 (10%)	IDH-2 (56%)
TP53 (~60%)	BMPs (NR)
CDKN2A (8-15%)	HEY1-NCOA2 (NR)
PTEN (7.3% primary; 15.2% metastatic)	Sphk1 (NR)
	2-HG (NR)
	Not EXT (NR)
	EWSR translocation (NR)
	VEGF-A (NR)
	VEGF-C (NR)
	TGF-β (NR)
	RUNX2 (NR)
	S1P (NR)

Abbreviations: IHC, immunohistochemistry; NR: not reported.
[a]In melanomas harboring *BRAF* mutations, approximately 80% of these are *BRAF* V600E.

that the cartilaginous tumors are treated best with surgery in melanomas with cartilaginous transdifferentiation surgery worsened the disease. Many of the melanomas with cartilaginous/osseous transdifferentiation are associated with a history of previous trauma which includes surgery and radiotherapy,[21,22] which is what happened to our patient. It might be a form of the host response to injury which leads to alteration of benign stromal fibroblastic cells to differentiate along cartilaginous lines.[9]

Owing to the rarity of the phenomenon, management guidelines for melanomas exhibiting transdifferentiation are lacking. Based on the survey of literature and our own published data, we believe that there is a need for critical evaluation of differentiation and transdifferentiation markers as prognostic and/or predictive markers. This underscores the critical need to continue to clinical experience with melanomas showing cartilaginous differentiation in order to add to the cumulative understanding of this process and how best to manage it.

In conclusion, melanoma is notable for an impressive degree of morphologic variability which accounts for it being a diagnostic challenge. There are still several limitations in distinguishing between two morphologically distinct tumor populations and transdifferentiation. Our case, among several others, highlights the importance of an accurate and thorough clinical history followed by molecular genetic analysis for the classification and clinical management of melanoma. This provides significant information to resolve complex neoplasms and phenotypic plasticity.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

J.B. and N.A.B. drafted the manuscript. C.K. drafted the pathological part of the manuscript. H.A. conceived the idea for the paper, followed-up the patient and proofread the manuscript. All authors have read and approved the final manuscript.

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