Published in final edited form as:

Am J Surg Pathol. 2018 March ; 42(3): 372–375. doi:10.1097/PAS.0000000000000978.

Distinguishing neurofibroma from desmoplastic melanoma: the value of p53

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Abstract

Background—Distinguishing desmoplastic melanomas (DMs) from neurofibromas (NFs) can be histologically challenging in some cases. To date, a reliable marker to differentiate the two entities has remained elusive. S100 subtyping and CD34 fingerprinting have been proposed, but controversy remains as to their reliability. Missense mutations in TP53 are often found in DMs, resulting in a dominant negative effect and paradoxical accumulation of the tumor suppressor protein p53.

Hypothesis—We hypothesized that p53 may be expressed differentially in DMs, making it a valuable tool in differentiating DMs from NFs. Using immunohistochemistry, we compared p53 protein expression in 20 DMs and 20 NFs retrieved from our tissue archives and stained with p53 antibody (Monoclonal, DO-7).

Results—Patients with DM included 18 men and 2 women (age 36–95 years (mean=70.5 years, median = 70 years). Fifteen (15/20) tumors occurred in head and neck area; 2 (2/20) on the trunk; and 3 (3/ 20) on the extremities. Patients with NF included 12 men and 8 women (age 47–85 years (mean=65.2 years, median=69.5 years). Eleven (11/20) tumors occurred on the trunk, 6 (6/20) on the extremities, and 3 (3/20) on the head and neck area. A total of 19/20 (95%) desmoplastic melanomas were positive for p53. Desmoplastic melanoma H-scores ranged from 0-300 (mean=203, median=260). Nuclear accumulation of p53 was seen in all 19 positive DMs. None of the 20 neurofibromas were positive for p53 (two-tailed t-test p-value<0.0001).

Conclusion—Detection of p53 by immunohistochemistry can help to distinguish desmoplastic melanomas from neurofibromas.

Keywords

p53; desmoplastic melanoma; neurofibroma

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Conflicts of Interest: None

Introduction

First described in 1971 by Conway *et al.,* desmoplastic melanoma (DM) is a rare variant of melanoma that is characterized by an infiltrative malignant spindle cell tumor with marked interstitial fibrosis and collagenization[1,2]. Clinically, DM can simulate amelanotic lesions resembling scars, making the diagnosis difficult. Histologically, DM also presents a diagnostic challenge as it is often confused with neurofibroma (NF)[3-5]. These two entities share similar immune-phenotyping profiles: S100 and SOX-10 positive but Melan-A and HMB-45 negative, making the differentiation between DM and NF difficult in some cases, even with immunohistochemistry[6]. Previous studies have suggested that various S100 family protein members may be differentially expressed in DMs compared to NFs, and that the subtype S100A1 is often found in DM and not NF[4]. However, the commonly used polyclonal S100 antibody does not differentiate the subtypes and also stains immature fibroblasts, epithelioid granulomas and histiocytic proliferations in scars and may be inferior to SOX-10[7]. CD34 fingerprint immune-reactivity has been shown to be more prominent in NFs compared to DM[5] but this has been controversial as a similar pattern was observed in an early desmoplastic melanoma by a different group[3]. Thus, a reliable marker to differentiate between DM and NF remains elusive.

From a genetic standpoint, DM is unique from conventional melanomas. It lacks classic mutations such as BRAF, NRAS and KIT, instead harboring a higher frequency of loss of function NF1 mutations [8-11]. Exome sequencing showed that DM carries a significantly higher mutation burden compared to other melanomas with ultraviolet radiation as the dominant mutagen[12]. It was also shown that missense mutations in TP53 are often found in DMs, resulting in a dominant negative effect and paradoxical accumulation of the tumor suppressor protein p53. Given these findings, we hypothesized that p53 staining may be expressed differentially in DMs, making it a valuable tool in differentiating DMs from NFs. To test our hypothesis, we compared p53 protein expression in 20 DMs and 20 NFs using immunohistochemistry.

Materials and Methods

The study was approved by the University of California Irvine's Institutional Review Board (IRB). Twenty desmoplastic melanomas and 20 neurofibromas were analyzed. DMs were retrieved from the Dermatopathology and Pathology Databases at the University of California Irvine Medical Center and the Laguna Pathology Medical Group in Laguna Hills, California. The search term “Desmoplastic melanoma” was used, and years “2010-2017”. Cutaneous NFs were retrieved from the Dermatopathology and Pathology Database at the University of California Irvine Medical Center. The search term “Neurofibroma” was used, and years “2015-2017” were searched. Sections for all specimens were taken from formalin-fixed, paraffin-embedded tissue, and stained with p53 antibody (Monoclonal, DO-7) at the University of California Irvine Department of Pathology Laboratories. A number of specimens were also stained with CD34 (Monoclonal: My10) and Sox-10 (Monoclonal: N-20) antibody.

Appropriate positive and negative controls were included with study sections. p53 staining intensity was qualitatively graded by a dermatopathologist where: 0, no tumor cells staining; 1+, weak tumor cell staining; 2+, moderate tumor cells staining; 3+, strong tumor cells staining. The percentage of tumor cells staining positive in each staining intensity category (0, 1+, 2+, and 3+) was qualitatively determined by dermatopathologist review. Using the staining intensities observed for each DM, the Histo (H)-Score was then calculated using the following formula: [1 × (% cells staining 1+) + 2 × (% cells staining 2+) + 3 × (% cells staining 3+)], resulting in a final score ranging from 0-300[13,14]. A two-tailed t-test was performed to determined statistical significance in p53 staining between the two groups (DMs and NFs).

Results

Twenty DMs were analyzed. Patient age ranged from 36 – 95 years (mean = 70.5 years, median = 70 years). They included 18 men and 2 women. Fifteen (15/20) tumors occurred in head and neck area; 2 (2/20) on the trunk; and 3 (3/ 20) on the extremities (Table 1). Twenty NFs were analyzed. Patient age ranged from 47 – 85 years (mean = 65.2 years, median = 69.5 years). They included 12 men and 8 women. Eleven (11/20) tumors occurred on the trunk, 6 (6/20) on the extremities, and 3 (3/20) on the head and neck area (Table 2). A total of 19/20 (95%) desmoplastic melanomas were positive for p53. Desmoplastic melanoma H-scores ranged from 0-300 (mean=203, median=260). Nuclear accumulation of p53 was seen in all p53 positive DMs (19/19); one (1/19) of which showed both nuclear and cytoplasmic staining. A total of 0/20 neurofibromas were positive for p53 (two-tailed t-test p-value < 0.0001) (Figures 1,2). Clinical and immunohistochemical features are summarized in Table 3.

Discussion

Distinguishing neurofibromas (NF) from desmoplastic melanomas (DM) can be challenging in some cases. Differentiating DMs from NFs proves particularly challenging in the following scenarios: 1.) An early DM that may not show significant cytological atypia to be readily differentiated from NF; 2.) When a superficial or limited biopsy of a DM is taken; 3.) When a NF-like proliferation arises within severely sun-damaged skin, a location where DMs typically develop, and 4.) When an intraepidermal group of melanocytes is located above a dermal population of spindled S100-positive cells. In these particular scenarios, a marker of differentiation would be desirable. To date, a reliable histologic marker to differentiate the two entities has remained elusive. S100 subtyping and CD34 fingerprinting have been proposed as potential avenues, but controversy remains about the practicality and reliability of these methods.

Based upon our immunohistochemical analysis— which showed p53 to be positive in 95% of DMs and negative in 100% of NFs— we conclude that p53 can help to distinguish desmoplastic melanomas from neurofibromas. In addition, we observed nuclear accumulation of p53 in all p53 positive DMs, except in one case that showed both nuclear and cytoplasmic accumulation. This finding differs from previous reports of melanoma showing predominately cytoplasmic overexpression of p53[15]. We hypothesize that this

stress-induced nuclear accumulation of p53 may be due to mutations resulting in decreased nuclear export and or enhanced nuclear import of p53 in this melanoma subtype[16].

Acknowledgments

Funding: None

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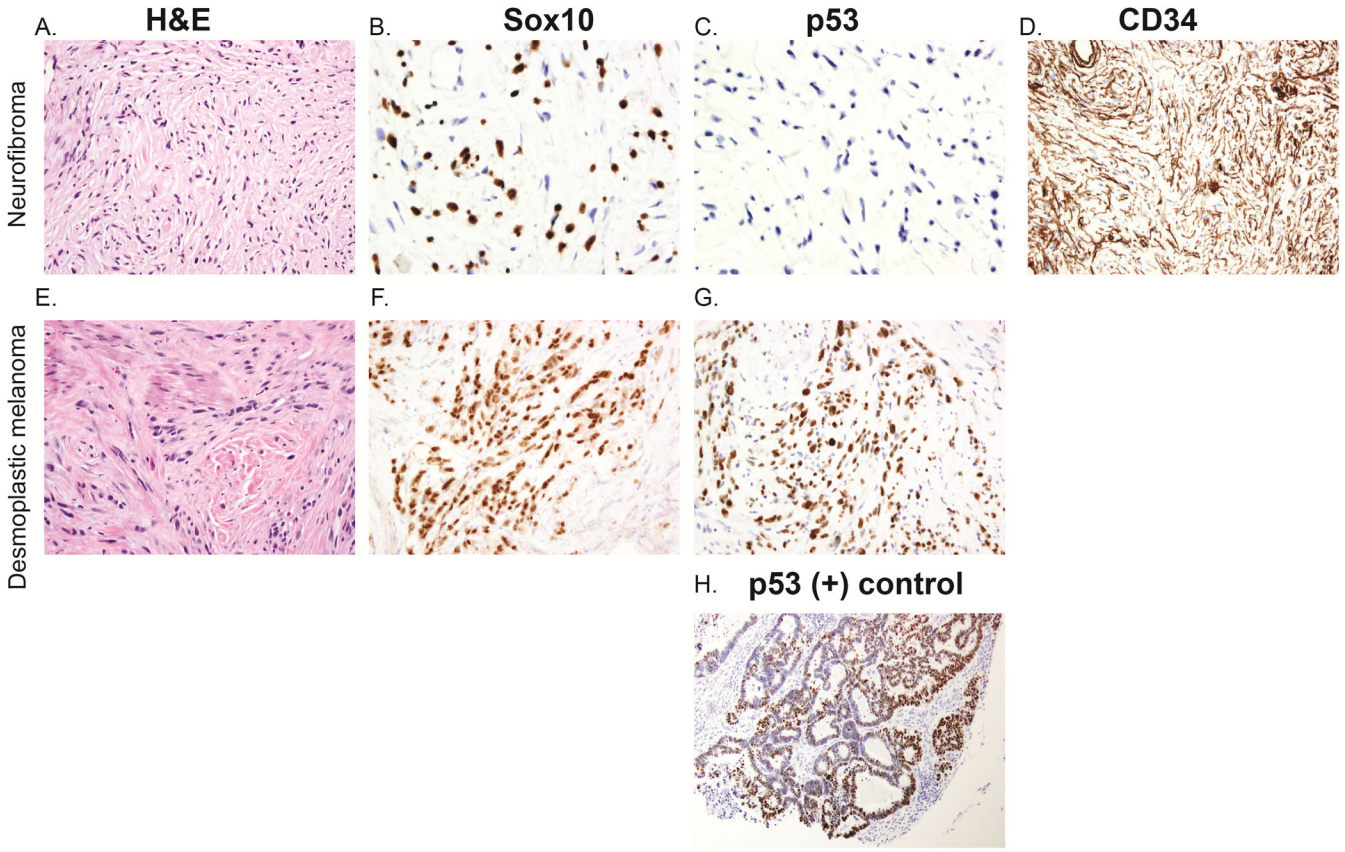

Figure 1.

H&E of desmoplastic melanoma (A) and neurofibroma (E) at 200x magnification. p53 and SOX-10 staining of desmoplastic melanomas x 200x magnification (F,G) and neurofibromas at 400x magnification (B,C). Desmoplastic melanomas demonstrate strong positive p53 staining (G) while neurofibromas remain negative (C). In contrast, SOX-10 staining is comparable in desmoplastic melanoma (F) and neurofibroma (B). Neurofibromas also demonstrate CD34 fingerprinting pattern, 200x magnification (D). Positive control of p53 staining (H).

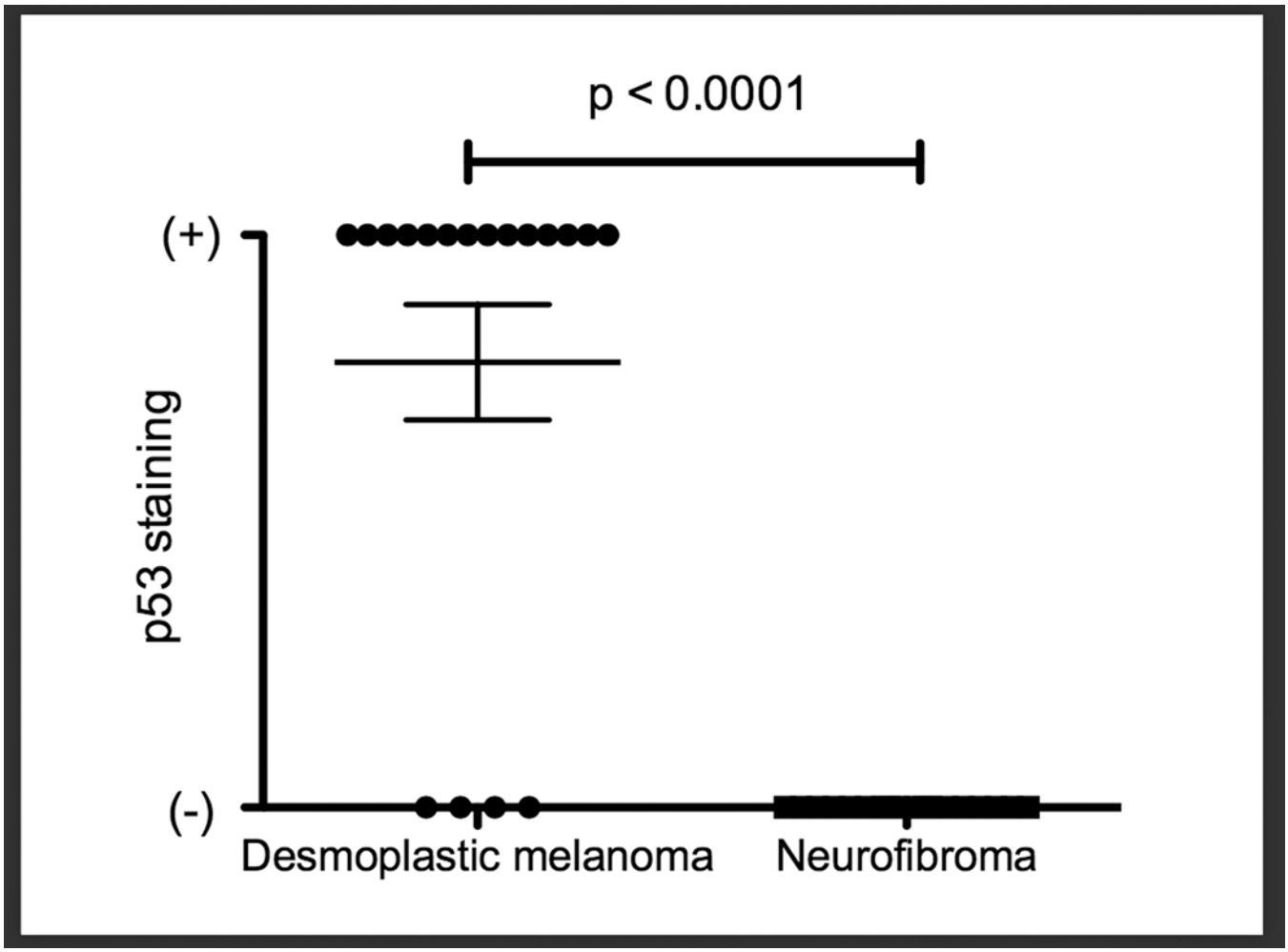

Figure 2.
Two-tailed t-test of p53 positivity in desmoplastic melanomas versus neurofibromas, p-value <0.0001.

Table 1

Clinicopathologic characteristics associated with desmoplastic melanomas

Case	Age	Gender	Site	Morphology	Presence of MIS	Weak (1+)	Moderate (2+)	Strong (3+)	H-score	P53 staining positive
1	90	Male	Arm	Spindle, pleomorphic	Yes	0%	0%	100%	300	Yes
2	95	Male	Scalp	Spindle, pleomorphic	No	10%	0%	1%	13	Yes
3	70	Male	Neck	Mixed epithelioid spindle pleomorphic	No	0%	10%	0%	20	Yes
4	89	Male	Scalp	Mixed epithelioid spindle	No	0%	0%	100%	300	Yes
5	54	Female	Chest	Spindle	No	10%	0%	0%	10	Yes
6	70	Male	Scalp	Epithelioid/focal spindle	Yes	69%	30%	1%	132	Yes
7	69	Male	Ear	Mixed epithelioid spindle pleomorphic	Yes	0%	0%	100%	300	Yes
8	60	Male	Face	Mixed epithelioid spindle pleomorphic	No	0%	50%	50%	250	Yes
9	69	Male	Face	Mixed epithelioid spindle pleomorphic	No	0%	0%	100%	300	Yes
10	66	Male	Back	Spindle	No	0%	50%	20%	160	Yes
11	80	Male	Scalp	Pleomorphic spindle	Yes	0%	0%	100%	300	Yes
12	36	Male	Neck	Mixed epithelioid spindle	Yes	0%	10%	90%	290	Yes
13	58	Male	Scalp	Mixed epithelioid spindle pleomorphic	No	0%	0%	100%	300	Yes
14	77	Male	Scalp	Mixed epithelioid spindle	Yes	0%	0%	25%	75	Yes
15	78	Male	Scalp	Mixed epithelioid spindle	No	0%	0%	80%	240	Yes
16	83	Male	Scalp	Spindle, pleomorphic	No	0%	25%	75%	275	Yes
17	74	Male	Scalp	Mixed epithelioid spindle pleomorphic	No	0%	0%	100%	300	Yes
18	81	Male	Arm	Spindle, pleomorphic	No	0%	30%	70%	270	Yes
19	57	Male	Arm	Spindle	No	0%	80%	20%	220	Yes
20	54	Female	Face	Spindle	No	0%	0%	0%	0	No

Table 2

Clinicopathologic characteristics associated with neurofibromas

Case	Age	Gender	Site	Intensity of p53 staining	% of p53+ tumor cells	P53 staining positive
1	61	Female	Leg	0	0%	No
2	57	Male	Back	0	0%	No
3	71	Male	Chest	0	0%	No
4	72	Male	Abdomen	0	0%	No
5	58	Female	Face	0	0%	No
6	50	Male	Neck	0	0%	No
7	71	Female	Arm	0	0%	No
8	84	Female	Arm	0	0%	No
9	85	Male	Back	0	0%	No
10	73	Male	Back	0	0%	No
11	28	Male	Leg	0	0%	No
12	69	Female	Arm	0	0%	No
13	81	Male	Back	0	0%	No
14	47	Female	Back	0	0%	No
15	61	Female	Abdomen	0	0%	No
16	63	Male	Arm	0	0%	No
17	70	Male	Back	0	0%	No
18	70	Male	Back	0	0%	No
19	73	Male	Scalp	0	0%	No
20	60	Female	Back	0	0%	No

Table 3

Summary of clinicopathologic characteristics of desmoplastic melanoma and neurofibroma cases

	Desmoplastic Melanoma	Neurofibroma
Age (median)	70 years	69.5 years
Site	Head and neck - 15	Head and neck - 3
	Trunk - 2	Trunk - 11
	Extremities - 3	Extremities - 6
Gender	Male - 18	Male - 12
	Female - 2	Female - 8
+ p53	**19/20 (95%)**	**0/20 (0%)**