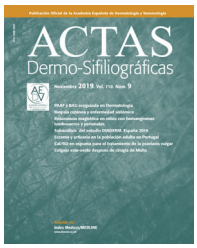
ACTAS Dermo-Sifiliográficas 116 (2025) 118–121

ACADEMIA ESPAÑOLA DE DERMATOLOGÍA Y VENEREOLOGÍA

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org



CASE AND RESEARCH LETTER

Mutational Study Through Massive Sequencing of 12 Desmoplastic Melanomas and Clinical and Histopathological Features

Estudio mutacional por secuenciación masiva de 12 melanomas desmoplásicos y características clínicas e histopatológicas

To the Editor,

Desmoplastic melanoma (DM) is a rare subtype of melanoma that affects patients older than 70 years with intense sun damage. DM shows a good response to immunotherapy and is characterized by a high mutation rate.[1–3]

We studied a total of 12 cases of DM and analyzed the clinical and histopathological variables. Mutational studies were performed through massive sequencing of all tumours. DNA and RNA were amplified with the Oncomine Precision Panel – GX5 – Solid Tumour w2.6.0 DNA and Fusion Panel (Thermo Fisher Scientific), generating a library and including amplicons for the study of mutations and INDELs in the hotspot regions of 45 genes, copy number variations in 14 genes, and fusions in 18 genes. Sequencing was analyzed on the Genexus System platform.

A total of 12 patients (8♂:4♀) with a median age 70 years and diagnosed with DM were studied. The most common presentation was nodules on the scalp (5 cases, 41.6%), with other common presentations being nodules on the cheek, arms, nose and ear (Fig. 1). Histopathologically, eight pure and four mixed cases were found, being the median Breslow thickness, 7.3 mm, with no significant differences being reported between pure and mixed cases. Only 25% of the cases (3 cases) were pigmented, 50% (6 cases) presented neurotropism, and all cases lymphoid aggregates. Patient staging (computed tomography) turned out negative in all patients at diagnosis except for one patient, 16% (2 cases) showed positive sentinel lymph nodes, all of which were of the mixed subtype, and 25% (3 cases) had local recurrences. A total of 75% (6 cases) of all pure DMs were stage IIB, and 25% (2 cases), stage IV. A total of 50% (2 cases) of all mixed DMs were stage IIB, and the remaining 50% (2 cases), stages III and IV. Systemic therapy with anti-PD-L1 and/or anti-CTLA4 was started in 41% of the patients (5 patients), with excellent responses in all them (Table 1). No patient has died due to melanoma to this date. Twenty-five mutations were found in 13 different genes – 21 were somatic mutations – and four copy number variations with amplifications. The most widely mutated gene was the TP53, found in 50% (6 cases) of all DMs. Mutations in the EGFR, IDH1 and RET genes were the next most widely found in 16% (2 cases) of all DMs reported. Other mutations found were in the ALK, MET, CTNNB1, CD274/PD-L1, FGFR 1 and 3 genes. Only one case of DM exhibited the mutated BRAF gene, while no mutated gene was ever found in three DMs (Table 2). Not differences were found in Breslow thickness or in pure or mixed DM cases with mutations in TP53 vs the remaining cases of DMs.

The diagnosis of DM can be complicated as they are usually nonspecific lesions. Frequent locations are photoexposed regions with sun damage, which happen to be strongly associated with UV radiation. Lymphoid aggregates and perineural invasion are common histopathological findings in DM,[4,5] which is a subtype of melanoma with a high mutation rate. In our study, the most widely mutated gene was the TP53 without correlation with Breslow thickness or the DM subtype. The TP53 mutation is associated with cumulative sun damage. Similar results have been obtained in other studies, where the most common mutation found in DM was TP53. However, in other studies, the most widely identified mutation was in the NF1 gene.[6] In our panel of studied genes, the NF1 gene was not included, which accounts for a limitation of our results. In contrast, the BRAF mutation is rare in this subtype of melanoma.[7,8] DMs have a good response to immunotherapy (anti PD-L1/anti-CTLA4) and prognosis looks good.[9,10]

https://doi.org/10.1016/j.ad.2023.11.022

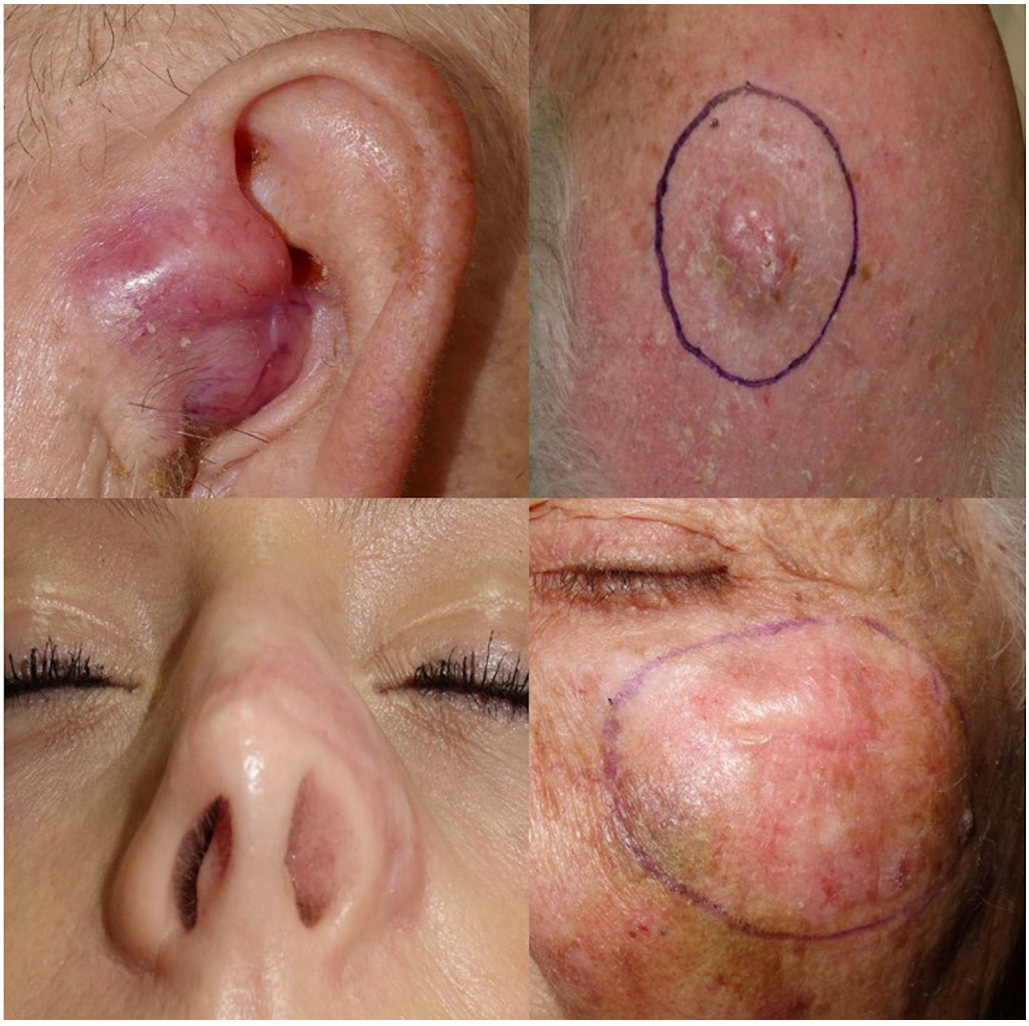


Figure 1 Images of different forms of desmoplastic melanomas from our series showing clinical differences vs non-desmoplastic melanomas.

Table 1 Clinical and histopathological characteristics of patients diagnosed with DM.

Case	Age/sex	Clinic	Pigmented	Neurotropism	Lymphoid aggregates	Extension study (CT)	Sentinel lymph node	Local recurrence	Inmunotherapy
1	66 Male	Scalp nodule	No	No	Yes	Negative	Negative	Yes	Ipilimumab → Nivolumab
2	64 Male	Scalp nodule	No	No	Yes	Negative	Negative	No	No
3	89 Female	Cheek plaque	Yes	Yes	Yes	Negative	Negative	No	No
4	27 Female	Nose nodule	No	Yes	Yes	Negative	Negative	Yes	Nivolumab + Ipilimumab
5	95 Female	Cheek nodule	No	Yes	Yes	Negative	Negative	No	No
6	70 Male	Arm nodule	Yes	No	Yes	Negative	Positive	No	Nivolumab
7	79 Female	Scalp nodule	No	No	Yes	Negative	Positive	Yes	Nivolumab
8	92 Male	Scalp nodule	No	Yes	Yes	Negative	Negative	No	No
9	87 Male	Scalp nodule	No	No	Yes	Negative	Negative	No	No

Table 1 (*Continued*)

Case	Age/sex	Clinic	Pigmented	Neurotropism	Lymphoid aggregates	Extension study (CT)	Sentinel lymph node	Local recurrence	Inmunotherapy
10	80 Male	Cheek nodule	No	No	Yes	Negative	Negative	No	No
11	42 Male	Back nodule	Yes	Yes	Yes	Positive	Unrealized	No	Nivolumab
12	68 Male	Ear nodule	No	Yes	Yes	Negative	Negative	No	No

Table 2 Subtype, Breslow thickness and mutations of DM tumors.

Case	DM type	Breslow (mm)	Mutated gene	Type	Chr	Exon	Mutation: amino acid change	Ratio
1	Pure	25	RET	Somatic	10		c.2428G>A; p.(Gly810Ser)	
2	Pure	5	FGFR1	Somatic	8		c.1774G>A; p.(Val592Met)	
			RET	Somatic	10		c.1894G>A; p.(Glu632Lys)	
			TP53	Somatic	17	5	c.637C>T; p.(Arg213Ter)	
			ALK	Copy number variation	2			Amplification: 1.29
			ERBB2	Copy number variation	17			Amplification: 1.23
3	Mixed	3.7	TP53	Somatic	17	8	c.842A>G; p.(Asp281Gly)	
			MET	Somatic	17		c.2962C>T; p.(Arg988Cys)	
			EGFR	Copy number variation	7			Amplification: 4.46
4	Pure	1.5	None					
5	Pure	10	None					
6	Mixed	7	BRAF	Somatic	7		c.1798_1799 delGTinsAA; p.(V600K)	
			IDH1	Somatic	2		c.394C>T; p.(R132C)	
			CTNNB1	Somatic	3		c.109T>C; p.(S37P)	
7	Mixed	8.6	none					
8	Mixed	7.3	FGFR3	Somatic		15	c.1922A>C; p.(Asp641Ala)	
			ROS1	Somatic	6	36	c.5845C>T; p.(Leu1949Phe)	
			TP53	Somatic	17	7	c.722C>T; p.(Ser241Phe)	
9	Pure	17	TP53	Somatic	17	7	c.733G>A; p.(Gly245Ser)	

Table 2 (*Continued*)

Case	DM type	Breslow (mm)	Mutated gene	Type	Chr	Exon	Mutation: amino acid change	Ratio
10	Pure	15	TP53	Somatic	17		c.809T>G; p.(Phe270Cys)	
			TP53	Somatic	17	8	c.817C>T; p.(Arg273Cys)	
			EGFR	Somatic	7	8	c.2305G>A; p.(Val769Met)	
11	Pure	13	IDH1	Somatic	2		c.394C>T; p.(Arg132Cys)	
12	Mixed	5.2	TP53	Somatic	17	4	c.395A>T; p.(Lys132Met)	
			CD274/PD-L1	Copy number variation	9			Amplification: 1.61

RET: ret proto-oncogene; FGFR: fibroblast growth factor receptor; TP53: tumor protein p53; ALK: anaplastic lymphoma kinase; ERBB2: erythroblastic oncogene B2; MET: MET proto-oncogene, receptor tyrosine kinase; EGFR: epidermal growth factor receptor; BRAF: B-Raf proto-oncogene, serine/threonine kinase; IDH1: isocitrate dehydrogenase (NADP (+)) 1; CTNNB1: β-catenin 1; ROS1: ROS proto-oncogene 1, receptor tyrosine kinase; CD274/PD-L1: programmed cell death 1 ligand.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Shi P, Xu Z, Lei X, Yibulayin F, Wushou A. Desmoplastic melanoma: demographic and clinicopathological features and disease-specific prognostic factors. Oncol Lett. 2019;17:5619–27.
2. Yang K, Mahalingam M. Differing biologic behaviors of desmoplastic melanoma subtypes: insights based on histopathologic, inmunohistochemical and genetic analyses. J Am Acad Dermatol. 2020;83:523–31.
3. Huayllani MT, Sisti A, Restrepo DJ, Boczar D, Cochuyt JJ, Spaulding AC, et al. Desmoplastic melanoma: clinical characteristics and survival in the US population. Cureus. 2019;11:e4931, http://dx.doi.org/10.7759/cureus.4931.
4. Varey AHR, Goumas C, Hong AM, Mann GJ, Fogarty GB, Stretch JR, et al. Neurotropic melanoma: an analysis of the clinicopathological features, management strategies and survival outcomes for 671 patients treated at a tertiary referral center. Mod Pathol. 2017;30:1538–50.
5. Stowman AM, Hickman AW, Mauldin IS, Mahmutovic A, Gru AA, Slingluff CL. Lymphoid aggregates in desmoplastic melanoma have features of tertiary lymphoid structures. Melanoma Res. 2018;28:237–45.
6. Wiesner T, Kiuru M, Scott SN, Arcila M, Halpern AC, Hollmann T, et al. NF1 mutations are common in desmoplastic melanoma. Am J Surg Pathol. 2015;39:1357–62.
7. Hadfield MJ, Helsing R, Grant-Kels JM. Desmoplastic melanoma: an updated clinical review and the emerging role of genetic markers and immunotherapies. Melanoma Res. 2020;30:429–32.
8. Alos L, Fuster C, Castillo P, Jares P, Garcia-Herrera A, Marginet M, et al. TP53 mutation and tumoral PD-L1 expression are associated with depth of invasion in desmoplastic melanomas. Ann Transl Med. 2020;8:1281.
9. Eroglu Z, Zaretsky JD, Hu-Lieskovan S, Kim DW, Algazi A, Johnson DB, et al. High response rate to PD-1 blockade in desmoplastic melanomas. Nature. 2018;553:347–50.
10. Hughes TM, Williams GJ, Gyorki DE, Kelly JW, Stretch JR, Varey AHR, et al. Desmoplastic melanoma: a review of its pathology and clinical behaviour, and of management recommendations in published guidelines. J Eur Acad Dermatol Venereol. 2021;35:1290–8.

A. Casanova-Esquembre[a,*], J. Lorca-Spröhnle[a], J.Á. García-García[b], G. Pérez-Pastor[a]

[a] *Dermatology Department, Hospital General Universitario de Valencia, Spain*
[b] *Pathological Anatomy Department, Hospital General Universitario de Valencia, Spain*

[*] Corresponding author.
E-mail address: avonasac.94@hotmail.com
(A. Casanova-Esquembre).