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Solar elastosis correlates with high tumor mutation burden and better 5-year disease-specific survival in patients with stage II/III melanoma

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Abstract

Objective: To evaluate the relation between solar elastosis and tumor mutation burden (TMB) in a large clinically annotated cohort of stage II and III melanoma patients.

Methods: Primary cutaneous melanomas from 469 AJCC (8^{th} edition) stage II and III patients with clinical annotation including outcome at 5 years of diagnosis were histopathologically evaluated for solar elastosis. Next-generation sequencing assay MSK-IMPACT™ was employed to determine TMB. Analysis by Fisher's exact test, chi-square, and Kruskal-Wallis were performed, as well as uni- and multivariate logistic regression.

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CRediT authorship contribution statement

Marianne Berwick: Formal analysis, Funding acquisition, Methodology, Writing – review & editing. **Klaus J Busam:** Conceptualization, Writing – review & editing. **Nancy E Thomas:** Funding acquisition, Writing – review & editing. **Irene Orlow:** Formal analysis, Writing – review & editing. **Ronglai Shen:** Formal analysis, Writing – review & editing. **Li Luo:** Formal analysis, Writing – review & editing. **Cecilia Lezcano:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

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Results: Tumors stratified by low and high TMB showed marked and statistically significant differences in presence and extent of associated solar elastosis. Lower risk patient stage (II versus III by AJCC 8th edition) as well as better 5-year melanomaspecific survival (as binary variable of controls-survivors versus cases-dead of disease at 5 years of diagnosis) were associated with severe solar elastosis. On univariate and multivariate logistic regression models, severe solar elastosis predicted significantly decreased odds of dying of melanoma within 5 years of diagnosis (OR 0.60, 95 % CI 0.39–0.89; and OR 0.42, 95 % CI 0.20–0.83, respectively; both $p<0.05$)

Conclusion: The association of solar elastosis to TMB and 5-year melanoma specific survival points to its potential as a biomarker of clinical relevance that can be assessed by routine histopathology.

Keywords

Melanoma; Solar elastosis; Tumor mutation burden

1. Introduction

InterMEL, an international biorepository and clinical database case-control study, was developed to explore the prognostic value of demographic, pathological, and molecular characteristics in AJCC 8th Edition stage II and III cutaneous melanoma[1].

Solar elastosis, a change in dermal matrix secondary to ultraviolet radiation (UV)-induced damage of collagen that is replaced by altered elastin fibers, has been previously studied as it relates to its association with melanoma anatomic site, age at diagnosis, histologic subtype, pathobiology, molecular tumor drivers, and patient outcome[2-9].

Tumor mutation burden (TMB) defined as the number of non-synonymous mutations per megabase of genome analyzed, has been proposed as a biomarker for immunotherapy response[10,11]. There is a continued need to improve prognostic models and to best identify patients with the highest likelihood of benefit from systemic therapy, with cost-efficiency and availability of these tools being key determinants of their impact in real-world patient care.

In this study we evaluated 469 patients with stage II/III cutaneous melanoma with detailed clinical annotation, extensive assessment of pathologic parameters, and molecular data obtained by next-generation sequencing with particular interest in analyzing the association of solar elastosis to TMB.

2. Methods

Primary cutaneous melanomas from 469 AJCC (8th edition) stage II and III patients were studied under an IRB-approved protocol involving a collaborative international consortium of institutions from Australia, Spain, and the United States. Extensive demographic and clinical annotation allowed for definition of “cases” (n= 209) as those patients that died of disease within 5 years of diagnosis and “controls” (n=260) as those that lived more than 5 years after diagnosis without evidence of disease progression.

Histopathology review of specimens was centrally performed by two dermatopathologists (CL, KB). Solar elastosis was classified as absent, mild/moderate or severe.

Molecular analysis was performed for all specimens by the FDA-approved hybridization capture-based next-generation sequencing assay MSK-IMPACT™ which allows for detection of all protein-coding mutations of targeted genes, copy number alterations, select promoter mutations and gene rearrangements, and calculation of tumor mutation burden (TMB).

Descriptive statistical analysis by Fisher's exact test, chi-square, and Kruskal-Wallis were performed. Univariate logistic regression for solar elastosis as well as a multivariate model incorporating various clinical, pathologic, and molecular data of patients and tumors to predict odds of death of disease within 5 years of melanoma diagnosis were carried out.

3. Results

We found statistically significant associations between amount of solar elastosis and older age at diagnosis, presence and extent of solar elastosis with male gender, head and neck tumor site, lentigo maligna melanoma histologic tumor subtype, and ulceration status. Differences in the frequency and extent of solar elastosis encountered in tumors harboring the different main melanoma driver mutations were also statistically significant.

Tumors stratified by low and high TMB showed marked and statistically significant differences in presence and extent of associated solar elastosis. Lower risk patient stage (II versus III by AJCC 8th edition) as well as better 5-year melanoma-specific survival (as binary variable of controls-survivors versus cases-dead of disease at 5 years of diagnosis) were significantly associated with presence of severe solar elastosis. These and additional parameters as they relate to solar elastosis are detailed in Table 1.

On univariate and multivariate logistic regression models, the context of severe solar elastosis predicted decreased odds of dying of melanoma within 5 years of diagnosis (OR 0.60, 95 % CI 0.39–0.89; and OR 0.42, 95 % CI 0.20–0.83, respectively; both $p<0.05$) (Table 2).

4. Discussion

Solar elastosis is due to chronic sun-damage (CSD) and accordingly studies looking at solar elastosis in the context of malignant melanoma have documented correlations with factors influencing CSD such as anatomic site -sun-exposed skin of the head and neck region-, more advanced patient age at diagnosis, as well as melanoma histologic subtypes related to high CSD such as lentigo maligna melanoma and desmoplastic melanoma and their corresponding underlying genomic pathways[2,3,5]. Our findings are in line with these prior results.

We reasoned that solar elastosis may also be associated with TMB. Our study results confirm a strong association between presence and extent of solar elastosis with TMB. While this could be inferred from the known correlation between high-CSD with increased

UV-mutagenesis leading to high-TMB, the results presented here provide supportive evidence for the use of solar elastosis as a probability biomarker of high-TMB. This is an important finding given that solar elastosis is a feature readily assessed by light microscopy routine examination of H&E-stained tissue sections whereas molecular assays required to establish TMB status are not always feasible due to limitations in available tissue, laboratory infrastructure, and cost [12]. Furthermore, this is clinically relevant as high-TMB has been proposed as a marker of improved response to immunotherapy, probably related to an increase in tumor neoantigens which may influence recognition of the tumor by the host immune system[10,11]. Additional patient cohorts and prospective studies are needed to more precisely delineate the uses and limitations of solar elastosis as a potential surrogate of TMB status for clinical decision making.

Here, in a 5-year melanoma specific survival case-control cohort, we found that the context of severe solar elastosis is associated with better survival. While there have been reports with conflicting results[2,3,6,7,13], a recent metanalysis including a total of over 5000 patients also supports the association of solar elastosis and improved patient outcome[14].

Our results indicate that solar elastosis deserves attention as predictive biomarker for cutaneous melanoma as its assessment is available worldwide wherever routine histopathology is practiced without extra cost to the patient and healthcare system.

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Table 1

Descriptive associations between solar elastosis and other variables of interest.

	Absent		Mild/Moderate		Severe		
	Count	**Row %**	**Count**	**Row %**	**Count**	**Row %**	**p-value**[**]
Total N	218	46.5 %	144	30.7 %	107	22.8 %	
Age at Diagnosis[*]	59	48–70	64	53–75	74	69–79	<0.001
Sex							0.011
Female	95	54.9 %	49	28.3 %	29	16.8 %	
Male	123	41.6 %	95	32.1 %	78	26.4 %	
Group							0.007
Died from melanoma within 5 years of diagnosis	98	46.9 %	76	36.4 %	35	16.7 %	
Lived more than 5 years after diagnosis	120	46.2 %	68	26.2 %	72	27.7 %	
Mutant Subtype							<0.001
BRAF_V600	80	56.3 %	44	31.0 %	18	12.7 %	
NRAS_Q61	36	42.4 %	32	37.6 %	17	20.0 %	
NF1	25	26.0 %	30	31.3 %	41	42.7 %	
WT	70	54.7 %	31	24.2 %	27	21.1 %	
BRAF_Other	7	38.9 %	7	38.9 %	4	22.2 %	
Breslow thickness							0.065
1–2 mm	35	57.4 %	21	34.4 %	5	8.2 %	
2.1–4 mm	82	45.8 %	52	29.1 %	45	25.1 %	
>4 mm	101	44.1 %	71	31.0 %	57	24.9 %	
Stage							<0.001
II	93	35.8 %	90	34.6 %	77	29.6 %	
III	125	59.8 %	54	25.8 %	30	14.4 %	
Histological Subtype							<0.001
ALM	19	100.0 %	0	0.0 %	0	0.0 %	
LMM	0	0.0 %	4	18.2 %	18	81.8 %	
NOS	88	43.1 %	70	34.3 %	46	22.5 %	
Nodular	20	38.5 %	16	30.8 %	16	30.8 %	
SSM	78	59.1 %	43	32.6 %	11	8.3 %	

	Absent		Mild/Moderate		Severe		
	Count	Row %	Count	Row %	Count	Row %	p-value**
Other	12	30.8 %	11	28.2 %	16	41.0 %	
Site							<0.001
Arms	26	30.6 %	33	38.8 %	26	30.6 %	
Head&Neck	20	16.5 %	32	26.4 %	69	57.0 %	
Legs	91	70.0 %	34	26.2 %	5	3.8 %	
Other	1	100.0 %	0	0.0 %	0	0.0 %	
Trunk	79	60.3 %	45	34.4 %	7	5.3 %	
Ulceration							0.022
Absent	92	47.9 %	47	24.5 %	53	27.6 %	
Present	126	45.7 %	96	34.8 %	54	19.6 %	
Mitoses							0.288
Absent	15	60.0 %	7	28.0 %	3	12.0 %	
Present	202	45.6 %	137	30.9 %	104	23.5 %	
TMB Category							<0.001
Low	160	61.3 %	65	24.9 %	36	13.8 %	
High	24	20.3 %	45	38.1 %	49	41.5 %	
Mutations*	8	3–19	20	9–31	33	28–38	<0.001

ALM= acral lentiginous melanoma, LMM= lentigo maligna melanoma, NOS= melanoma subtype not specified/not evaluable, SSM=superficial spreading melanoma, TMB= tumor mutation burden

*Median and IQR shown for continuous variables

**P-values for categorical variables were determined by Fisher's exact test where feasible and chi-squared test otherwise. Kruskal-Wallis used for continuous tests.

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Table 2

Logistic regression models predicting odds of dying.

	Univariable model				Multivariable model			
	Odds Ratio	**5 %**	**95 %**		**Odds Ratio**	**5 %**	**95 %**	
(Intercept)	0.82	0.65	1.02	.	0.01	0.00	0.05	***
Solar Elastosis - Mild/Moderate	1.37	0.96	1.95		1.86	1.09	3.21	.
Solar Elastosis - Severe	0.60	0.39	0.89	*	0.42	0.20	0.83	*
Age at Diagnosis	-	-	-		1.03	1.01	1.05	**
Stage - III	-	-	-		4.27	2.67	6.95	***
Sex - Male	-	-	-		1.81	1.15	2.86	*
Site - Head/Neck	-	-	-		3.16	1.59	6.41	**
Site - Legs	-	-	-		1.28	0.64	2.56	
Site - Trunk	-	-	-		1.72	0.86	3.47	
Breslow - 2.1–4.0 mm	-	-	-		2.17	1.06	4.61	.
Breslow - >4 mm	-	-	-		3.91	1.94	8.22	**
Ulceration - Present	-	-	-		3.02	1.94	4.77	***

. $p < 0.1$,

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.001$