A STUDY OF NON-MELANOMA SKIN CANCER IN A SERIES OF WELL-CHARACTERIZED PATIENTS WITH KINDLER SYNDROME

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ABSTRACT

KS is a rare genodermatosis characterized by skin fragility, skin atrophy, premature aging and poikiloderma. Several reports in the literature have also shown the presence of SCC's arising in KS patients suggesting a predisposition of these patients to this neoplasia. However, no systematic study has been carried out investigating the frequency of SCC in KS and the outcome of the disease in these patients. Here, we studied the incidence of SCCs in a cohort of 44 well-characterized patients with KS by clinical and molecular techniques. A total of 10 patients developed SCC at different ages. The youngest patient with SCC was 33 years old. The cumulative risk increases up to around 50% at age 50 and plateau afterwards. This pattern is somewhat smaller than the cumulative risk of Recessive Dystrophic Epidermolysis Bullosa (RDEB) and remarkably, patients with KS appear to develop SCC 10-20 years later than patients with RDEB. Our study also showed that SCC developed in KS patients have the potential of becoming metastatic: In our cohort, SCC lead to death in one case and to amputation in the other. An additional patient (alive) presented multiple metastasis.

This study suggests that approximately 50% of patients with KS may develop SCC during their lifetime and 30% metastatic disease with the possibility of a lethal outcome.

INTRODUCTION

KS is a rare genodermatosis characterized by skin fragility, skin atrophy, premature aging and poikiloderma. It is caused by mutations in the *FERMT1* gene that codes for kindlin-1, a protein associated to integrin and focal adhesions [1]. Reports in the literature have documented the presence of SCCs in KS patients suggesting a predisposition of these patients to this neoplasia [2]. However, a systematic study of cancer frequency in a series of patients has not been carried out. Therefore, the relative risk of SCC at different ages cannot be predicted from the current published data. Furthermore, the literature has not provided a clear picture of natural history, the degree of aggressiveness and mortality of SCCs in KS patients.

We have previously reported the largest series of KS patients with the associated mutant *FERMT1* genotype [3]. That study showed a wide variety of *FERMT1* mutations in KS patients, and showed a lack of genotype-phenotype clear correlation. The development of cutaneous cancer was noted in patients older than 45 years; however, characteristics and follow-up data of the tumors were not provided [3].

We have revisited the previously described series by Has et al [3], added newly recruited patients and evaluated the risk of SCC for KS patients at different ages. In addition, we investigated the outcome of skin cancer in KS individuals.

MATERIALS AND METHODS

Patients for this retrospective study were recruited from different European institutions. Forty patients were described in the original study by Has et al. [3]. Some patients from the original report were not included in the present study, either because we could not carry out a proper follow-up or due to lack of reliable histopathologic records. Additionally, we added 7 new cases to the series, recruited since our previous study. All new patients were clinically and molecularly characterized as described previously [4;5].

Patient informed consents were obtained in agreement with the collaborative centers where the biopsies were obtained. Patients included in this study were older than 16 years, the age of the youngest KS patient with SCC described so far. The procedures followed were in accordance with the institutional ethical standards on human experimentation and the Helsinki Guidelines and further reviews including Seoul 2008. A calculation of cumulative risk was obtained by calculating the number of new cases over the population at risk (presently or in the past) for each age segment.

CONCLUSIONS

- *The risk of SCC development is very high compared to the general population but lower than RDEB which is the EB with a higher risk of SCC*
- *The accumulative risk appears to be shifted to 20 years later than RDEB*
- *The risk of the KS SCC to become metastatic is around 50% and in some cases it can be lethal*
- *Patients with KS should be carefully monitored for the development of SCC*

FUNDING

This work was partially supported by grants from the Science and Innovation Ministry of Spain (SAF2013-43475R), and Comunidad de Madrid (S2010/BMD-2420 and S2010/BMD-2359),

Table 1: Sex, age and genetic data from a total of 44 patients with well-characterized KS.

Pat #	Sex & age	Mutation	Protein	Epithelial Cancer/ Histopathology	Age of cancer (Cancer onset age)	Outcome
1.	F, 32	1714_1715in SA	Val572Aspfs X4	-	-	-
2.	F, 45	g.70250_741 68del	P381Rfs	-	-	-
3.	F, 27	g.70250_741 68del	P381Rfs	-	-	-
4.	M, 65	g.70250_741 68del	P381Rfs	Infiltrating SCCs, all WD	52 (53, 55)	Alive
5.	F, 29	1718-1G>A	AS	-	-	-
6.	M, 24	1161delA	Ala388Leufs X14	-	-	-
7.	M, 24	1161delA	Ala388Leufs X14	-	-	-
8.	M, 27	1161delA	Ala388Leufs X14	-	-	-
9.	M, 60	958-1G>A	AS	1-3 infiltrating SCC, all WD, 4, 5 in situ SCC	44 (44, 45, 45, 56)	Alive
10.	M, 40	958-1G>A	AS	Infiltrating SCC, WD	43	Alive
11.	M, 50	958-1G>A	AS	-	-	-
12.	M, 34	958-1G>A	AS	-	-	-
13.	M, 18	1051G>T	Glu351X	-	-	-
14.	F, 56	c.152-2delAGctcT	AS	-	-	-
15.	M, 20	g.70250_741 68del c.-20A>G	P381Rfs/RT	-	-	-
16.	M, 25	-711_1241d	RT	-	-	-
17.	M, 71	c.882C>T	Arg280X	-	-	-
18.	M, 71	328C>T	Arg110X	Multiple in situ SCC: Hyperkeratotic SCC in situ	Start at 50 years	Alive
19.	F, 79	328C>T	Arg110X	Invasive SCC, BCC, in situ SCC	Start at 66 years	Alive
20.	M, 49	910G>T	Glu304X	Metastasizing and undifferentiated SCC	48 years	Diffuse metastases (skin & lung)
21.	M, 22	1729delA	Ser577Alafs X14	-	-	-
22.	F, 36	1209C>G	Tyr403X	Breast cancer	39 years	-
23.	F, 58	96_97delAG	Arg32SerfsX 63	Undifferentiated SCC	-	Amputation of left arm
24.	M, 25	170C>A	Ser57X	-	-	-
25.	M, 42	373delT	Cys125Alafs X4	-	-	-
26.	M, 34	456dupA	Asp153Argfs	SCC: WD, early infiltrating	33	Deceased at 35 years
27.	F, 18	676dupC	Gln226Profs X17	-	-	-
28.	F, 24	676dupC	Gln226Profs X17	-	-	Deceased at 24 years NOT SCC related
29.	M, 18	910G>T	Glu304X	-	-	-
30.	F, 25	g.70250_741 68del	Pro381Argfs	-	-	-
31.	M, 37	1365_1371+3del	AS	-	-	-
32.	M, 34	1718+1G>A	AS	-	-	-
33.	M, 15	1718+2T>C	AS	-	-	-
34.	F, 43	IVS13_15del	-	-	-	-
35.	M, 47	IVS13_15del	-	-	-	-
36.	F, 53	IVS13_15del	-	1 SCC: WD, 2 SCC: WD & early invasive	45 (53, 56)	Deceased at 60 years
37.	M, 58	1209C>G	Tyr403X	1 SCC: WD	-	-
38.	M, 58	299_301del	Arg100del	-	-	-
39.	M, 61	IVS9+740G>A	pseudodexon	-	-	-
40.	M, 42	1179G>A	W393X	-	-	-
41.	F, 29	IVS9+740G>A	pseudodexon	-	-	-
42.	F, 16	190G>T	E64X	-	-	-
43.	M, 49	676dupC	Q226PfsX16	-	-	-
44.	F, 63	1761T>A	Y567X	-	-	-

SCC: Squamous Cell Carcinoma; WD: Well differentiated; AS: Altered splicing; RT: Reduced transcription.

Figure 1: Calculated cumulative risk of the first SCC in KS patients. For comparative purposes we have also plotted the calculated cumulative risk for RDEB and JEB taken from a study of Mallipeddi et al [6].

The incidence of carcinomas peaks between 40 and 60 years of age. This profile is different from RDEB (SCCs develop early and reach a higher cumulative risk). In contrast, patients with JEB, have a lower risk of developing non-melanoma skin cancer. Sex doesn't seem to affect the development of tumors in these patients and there was no correlation to a particular type of mutation.

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