Cutaneous squamous cell carcinoma is associated with Lynch syndrome: widening the spectrum of Lynch syndrome-associated tumours

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Dear Editor, Lynch syndrome (LS) is caused by a germline mutation in one of the mismatch repair (MMR) genes. Individuals with LS have an increased risk of developing colorectal and many other tumours including skin tumours.[1] Sebaceous neoplasms and keratoacanthomas are skin tumours associated with LS, also known as Muir–Torre syndrome.[2] For cutaneous squamous cell carcinoma (SCC), an association with LS has been suggested.[3–5] Recently, a 12-fold increased risk for sebaceous carcinoma and SCC has been described in individuals with LS compared with the Dutch general population at the age of 60 years.[6]

Our aim was to evaluate whether cutaneous SCC is part of the LS tumour spectrum by evaluating the MMR status of cutaneous SCCs diagnosed in a cohort of individuals with LS. Furthermore, we evaluated the concordance between MMR immunohistochemistry (IHC) and microsatellite instability (MSI) polymerase chain reaction (PCR) testing.

Cutaneous SCCs were identified within a cohort of 331 individuals with LS, with a proven germline mutation, from 194 families, derived from two Dutch hospitals (January 2000 to October 2016), as described previously.[6] The study was approved by the institutional review board of the Netherlands Cancer Institute (IRBm19-123).

Pathology reports and formalin-fixed paraffin-embedded tissues were obtained for histopathological reassessment. IHC was performed according to standard protocols on slides for MMR proteins for the Ventana immunostainer (Roche Diagnostics Limited, Burgess Hill, UK). The proteins studied were MLH1 (clone ES05; Agilent, Santa Clara, CA, USA), MSH2 (clone G219-1129; Roche), MSH6 (clone EP49; Epitomics, Burlingame, CA, USA) and PMS2 (clone A16-4; Roche). Cutaneous SCCs with absent staining of one or more MMR proteins were considered MMR deficient.

DNA was isolated using a Qiagen extraction kit (Qiagen, Venlo, the Netherlands). A pentaplex PCR-based assay for MSI was performed using fluorescent-labelled primers of five mononucleotide repeat targets (BAT25, BAT26, NR24, NR21 and NR27), followed by fragment analysis. MSI was defined as instability in two or more markers.

In 331 individuals with LS, in total 13 cutaneous SCCs were diagnosed in eight patients (2·4%) (11 SCCs as described earlier and two additional SCCs identified in 2015 and 2017 within this cohort). Tissue from 10 of these 13 cutaneous SCCs in seven patients was available for further analyses. Three patients were diagnosed with two SCCs each. Two patients were male (29%) and the majority were diagnosed with an *MSH2* germline mutation (86%; Table 1). Five patients had a history of dermatological neoplasms prior to SCC diagnosis. The median age at diagnosis of the first cutaneous SCC was 52 years (range 33–60).

MMR IHC and MSI PCR testing were performed in the 10 and nine available cutaneous SCCs, respectively (from one sample there was not enough DNA available). MMR deficiency was detected in all 10 cutaneous SCCs by IHC, with the deficiencies corresponding to the LS germline mutations. MSI PCR demonstrated MSI in three of nine cutaneous SCCs, resulting in a discordance of 67% between MMR IHC and MSI PCR. All of these three patients had two cutaneous SCCs, with both concordant and discordant results between MMR IHC and MSI PCR (Table 1).

We showed that all cutaneous SCCs diagnosed in individuals with LS were MMR deficient, with loss of staining of MMR proteins corresponding to the known germline mutation, suggesting that SCC is an LS-associated tumour. We assume that MMR-deficient cutaneous SCCs develop by a germline mutation in one of the MMR genes, followed by a second hit of the wildtype copy.

Concordance between MMR IHC and MSI PCR is high for colorectal and endometrial cancer, but a low concordance has been described for other (skin) malignancies.[7,8] Explanations can be that high tumour turnover is necessary to induce enough detectable MSI or that the standard pentaplex panel is not effective for all tumours.[8] Therefore, we suggest performing only MMR IHC to detect LS in cutaneous SCC.

Table 1 Immunohistochemistry (IHC) of mismatch repair (MMR) genes and microsatellite instability (MSI) polymerase chain reaction (PCR) in cutaneous squamous cell carcinoma (SCC) diagnosed in patients with Lynch syndrome

Patient no. and sex	SCCs	Lynch mutation[a]	Year of dx	Age at dx (years)	Location of SCC	MMR IHC	MSI PCR	Dermatological history	History of malignancy
1, F	1	MLH1	2010	52	Neck	MLH1/PMS2 deficient	MSS	Sebaceous adenomas	No
2, M	1	MSH2	2015	49	Unknown	MSH2/MSH6 deficient	MSI	Keratoacanthoma	Yes (CRC)
2, M	2	MSH2	2017	51	Arm	MSH2/MSH6 deficient	MSS		
3, F	1	MSH2	2004	55	Hand	MSH6 deficient	MSS	No	Yes (cervical and endometrial cancer)
4, F	1	MSH2	2008	57	Chin	MSH2/MSH6 deficient	MSS	Keratoacanthoma	No
4, F	2	MSH2	2009	58	Thorax	MSH2/MSH6 deficient	MSI		
5, F	1	MSH2	2016	51	Hand	MSH2/MSH6 deficient	NA	Sebaceous adenomas, basal cell carcinoma, hidrocystoma	No
6, M	1	MSH2	2015	60	Cheek	MSH2/MSH6 deficient	MSI	Sebaceous carcinoma	Yes (CRC)
6, M	2	MSH2	2015	60	Cheek	MSH2/MSH6 deficient	MSS		
7, F	1	MSH2	Unknown	33	Cheek	MSH2/MSH6 deficient	MSS	No	No

CRC, colorectal cancer; dx, diagnosis; F, female; M, male; MSS, microsatellite stable; NA, not available. [a]The pathogenic variant of the germline mutation is available upon request.

We recommend that especially for individuals with a pathogenic mutation in *MSH2* or *MLH1*, information about sun exposure, self-examination and the risk of cutaneous malignancies is important, and a single dermatological consultation may be helpful. Further research is necessary to determine whether it is cost-effective to routinely test MMR status in newly diagnosed cutaneous SCC in the general population, especially when diagnosed at a young age. Moreover, the effect of immunotherapy on MMR-deficient cutaneous SCC is being investigated by ongoing trials, which could also influence the need for MMR testing.

To conclude, cutaneous SCC seems to be part of the LS tumour spectrum. Individuals with LS should be informed about their risk of cutaneous cancers including SCC, and preventive measurements should be provided.

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