Gastrointestinal malignancies in high-risk populations = Gastro-intestinale maligniteiten in hoog-risico populaties

Ykema, B.L.M.

10 CUTANEOUS SQUAMOUS CELL CARCINOMA IS ASSOCIATED WITH LYNCH SYNDROME; WIDENING THE SPECTRUM OF LYNCH SYNDROME ASSOCIATED TUMOURS

Berbel L.M. Ykema, Fieke Adan, Marianne B, Crijns, Fonnet E. Bleeker, Evelien Dekker, Marcel W. Bekkenk, Petur Snaebjornsson, and Monique E. van Leerdam

British Journal of Dermatology 2021

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

Cutaneous SCC 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 – 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 (FFPE) tissues were obtained for histopathological reassessment. IHC was performed according to standard protocols on slides for MMR proteins for Ventana immunostainer (MLH1 (MLH1 (Agilent/DAKO, clone ES05), MSH2 (Roche/Ventana, clone G219-1129), MSH6 (Epitomics, clone EP49) and PMS2 (Roche/Ventana, clone A16-4)). Cutaneous SCC with absent staining of one or more MMR proteins were considered MMR deficient.

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

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

MMR IHC and MSI PCR testing was performed in the ten and nine available cutaneous SCC, respectively (from one sample there was not enough DNA available). MMR deficiency was detected in all ten cutaneous SCC by IHC, with the deficiencies corresponding with the LS germline mutations. MSI PCR demonstrated MSI in 3/9 cutaneous SCC, resulting in a discordance of 67% between MMR IHC and MSI PCR. All 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 SCC diagnosed in individuals with LS were MMR deficient with loss of staining of MMR proteins corresponding with the known germline mutation, suggesting that SCC is part of LS associated tumours. We assume that MMR deficient cutaneous SCC develop by a germline mutation in one of the MMR genes followed by a second hit of the wild-type copy.

Concordance between MMR IHC and MSI PCR is high for colorectal and endometrium 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 for detecting LS in cutaneous SCC.

We recommend that especially for individuals with a pathogenic mutation in *MSH2* and *MLH1* information about the risk of cutaneous malignancies, sun exposure, and self-examination 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 diagnosed at a younger 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.

Acknowledgments: We would like to thank the NKI- AVL Core Facility Molecular Pathology & Biobanking (CFMPB) for supplying NKI-AVL Biobank material and lab support.

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

PtNr	NrSCC	Lynch mutation*	Sex	Year of dx	Age at dx	Location SCC	MMR IHC	MSI PCR	Dermatological history	History of Malignancy
1	1	MLH1	Female	2010	52	Neck	MLH1/PMS2 deficient	MSS	Sebaceous adenomas	No
2	1	MSH2	Male	2015	49	Unknown	MSH2/MSH6 deficient	MSI	Keratoacanthoma	Yes (CRC)
2	2	MSH2	Male	2017	51	Arm	MSH2/MSH6 deficient	MSS		
3	1	MSH2	Female	2004	55	Hand	MSH6 deficient	MSS	No	Yes (cervical and endometrial cancer)
4	1	MSH2	Female	2008	57	Chin	MSH2/MSH6 deficient	MSS	Keratoacanthoma	No
4	2	MSH2	Female	2009	58	Thorax	MSH2/MSH6 deficient	MSI		
5	1	MSH2	Female	2016	51	Hand	MSH2/MSH6 deficient	NA	Sebaceous adenomas and basal cell carcinoma and hydrocystoma	No
6	1	MSH2	Male	2015	60	Cheek	MSH2/MSH6 deficient	MSI	Sebaceous carcinoma	Yes (CRC)
6	2	MSH2	Male	2015	60	Cheek	MSH2/MSH6 deficient	MSS		
7	1	MSH2	Female	Unknown	33	Cheek	MSH2/MSH6 deficient	MSS	No	No

PtNr = patient number; NrSCC = number of cutanenous SCC for patient; dx = diagnosis; MSS = Microsatellite stable; CRC = colorectal cancer; NA; not available. * The pathogenic variant of the germline mutation is available upon request.

REFERENCES

1. Lynch HT, Snyder CL, Shaw TG, Heinen CD, Hitchins MP. Milestones of Lynch syndrome: 1895-2015. Nat Rev Cancer 2015;15:181-94.
2. Bhaijee F, Brown AS. Muir-Torre syndrome. Arch Pathol Lab Med 2014;138:1685-9.
3. Adan F, Crijns MB, Dekker E, et al. A squamous cell carcinoma in a young woman with Lynch syndrome. Fam Cancer 2019;18:193-6.
4. Sorscher S. A case of squamous cell carcinoma of the skin due to the molecularly confirmed Lynch Syndrome. Hered Cancer Clin Pract 2015;13:12.
5. Khaddour K, Fields RC, Ansstas M, Rosman IS, Ansstas G. Metachronous cutaneous squamous cell carcinoma in a young patient as the only presenting symptom to uncover Lynch syndrome with MLH1 Germline mutation. Hered Cancer Clin Pract 2020;18:23.
6. Adan F, Crijns MB, Zandstra WSE, et al. Cumulative risk of skin tumours in patients with Lynch syndrome. Br J Dermatol 2018;179:522-3.
7. Gray SE, Kay EW, Leader M, Mabruk MJ. Enhanced detection of microsatellite instability and mismatch repair gene expression in cutaneous squamous cell carcinomas. Mol Diagn Ther 2006;10:327-34.
8. Shia J. The diversity of tumours with microsatellite instability: molecular mechanisms and impact upon microsatellite instability testing and mismatch repair protein immunohistochemistry. Histopathology 2021;78:485-97.