majority of pDCs developing from interleukin 7 receptor^{+} lymphoid progenitor cells and a minor population of myeloid-derived pDC-like cells. Both groups were able to secrete type 1 interferons, but only myeloid-derived pDCs had the ability to process and present antigens. The lack of lymphoid-origin SPMs in our study supports the current myeloid classification of BPDCN.

Limitations include a retrospective design, coding errors, and inability to adjust for tumor characteristics, treatment, lifestyle/modifiable risk factors, and socioeconomic status.

Overall, our study's findings may help in the surveillance of patients with BPDCN, especially as new, lifespan-increasing treatments such as tagraxofusp become available.

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Merkel cell carcinoma of lymph nodes without a skin primary tumor: A potential metastatic neoplasia associated with a brisk immune response

To the Editor: Merkel cell carcinoma (MCC) is a rare neuroendocrine cutaneous carcinoma frequently caused by Merkel cell polyomavirus. In 10% of cases, MCC presents as lymph node metastasis (LNM) without a primary skin tumor (MCCWOP).[1] We and others[1] confirmed that MCCWOPs share a common phenotype with their cutaneous counterparts. However, whether MCCWOP constitutes an intranodal primitive neoplasia or a nodal metastasis from an occult or totally regressive skin MCC remains unknown.

The metastatic process is related to the epithelial-mesenchymal transition (EMT) characterized by a loss of epithelial markers such as E-cadherin and acquisition of a mesenchymal phenotype, with expression of N-cadherin or vimentin.[2] In addition, zinc finger E-box binding homeobox 1 (ZEB1)[3] is a crucial determinant of EMT. We hypothesized that investigating EMT markers in MCCWOP would help determine whether they constitute a primary neoplasia or a metastatic process. Expression levels of 4 EMT markers were evaluated by immunohistochemistry (Supplemental Methods and Supplemental Fig 1; available via Mendeley at https://data.mendeley.com/datasets/sn964fs2dp/draft?a=d6fc7ff0-f4d7-40f2-9658-f4cbdb7b0cd1) in 60 cutaneous primary MCCs, 18 LNMs from cutaneous MCCs, and 15 MCCWOPs. In the whole cohort (N = 93), loss of E-cadherin, aberrant expression of N-cadherin and vimentin, and expression of ZEB1 were observed in 91% (n = 82), 88% (n = 75), 6% (n = 5), and 74.5% (n = 61) of interpretable cases, respectively (Supplemental Tables I and II and Supplemental Fig 2; available via Mendeley at https://data.mendeley.com/datasets/sn964fs2dp/draft?a=d6fc7ff0-f4d7-40f2-9658-f4cbdb7b0cd1). Among the 78 MCC cases with an identified primary tumor, only ZEB1 harbored a significant differential expression between primary tumors and LNM (P = .047) and was therefore considered as a surrogate of metastatic process in MCC. As such, 74% of the LNMs from cutaneous MCCs (n = 11/15) but only 36% of primary tumors (n = 19/52) showed high and diffuse expression of ZEB1 (score 2) (P = .017). We found a similar pattern of ZEB1 (score 2) in 67% of MCCWOP cases (n = 10/15) (Table I and Fig 1), suggesting that MCCWOPs result from a metastatic process. Such a scenario would therefore imply a complete regression of a skin primary tumor, as a result of an efficient antitumoral immune response.[4] We investigated this hypothesis

Table I. Immunohistochemical detection of ZEB1 expression and immune infiltrates in primary cutaneous MCC, LNM from cutaneous MCC, and MCCWOP

Metastatic marker	All MCC cases (n = 93)	Primary MCC (n = 60)	LNM from cutaneous MCC (n = 18)	MCCWOP (n = 15)	*P*
ZEB1*					
Score 0-1, n (%)	42 (51)	33 (64)	4 (26)	5 (33)	.01
Score 2, n (%)	40 (49)	19 (36)	11 (74)	10 (67)	
Missing data, n	11	8	3	0	
Immune infiltrates					
CD8 infiltrates					.03
Absent, n (%)	34	19 (34)	11 (69)	4 (27)	
Present, n (%)	53	37 (66)	5 (31)	11 (73)	
Missing data, n	6	4	2	0	
$CD33^{brisk}/CD8^{+}$ infiltrates					.001
No, n (%)	42	24 (52)	14 (93)	4 (31)	
Yes, n (%)	32	22 (48)	1 (7)	9 (69)	
Missing data, n	19	14	3	2	

LNM, Lymph node metastasis; *MCC*, Merkel cell carcinoma; *MCCWOP*, Merkel cell carcinoma presenting as lymph node metastasis without a primary skin tumor; *ZEB1*, zinc finger E-box binding homeobox 1.
*Score: 0, lack of expression; 1, low staining of tumor cells or high staining of less than 50% of the tumor cells; 2, high staining of more than 50% of tumor cells.

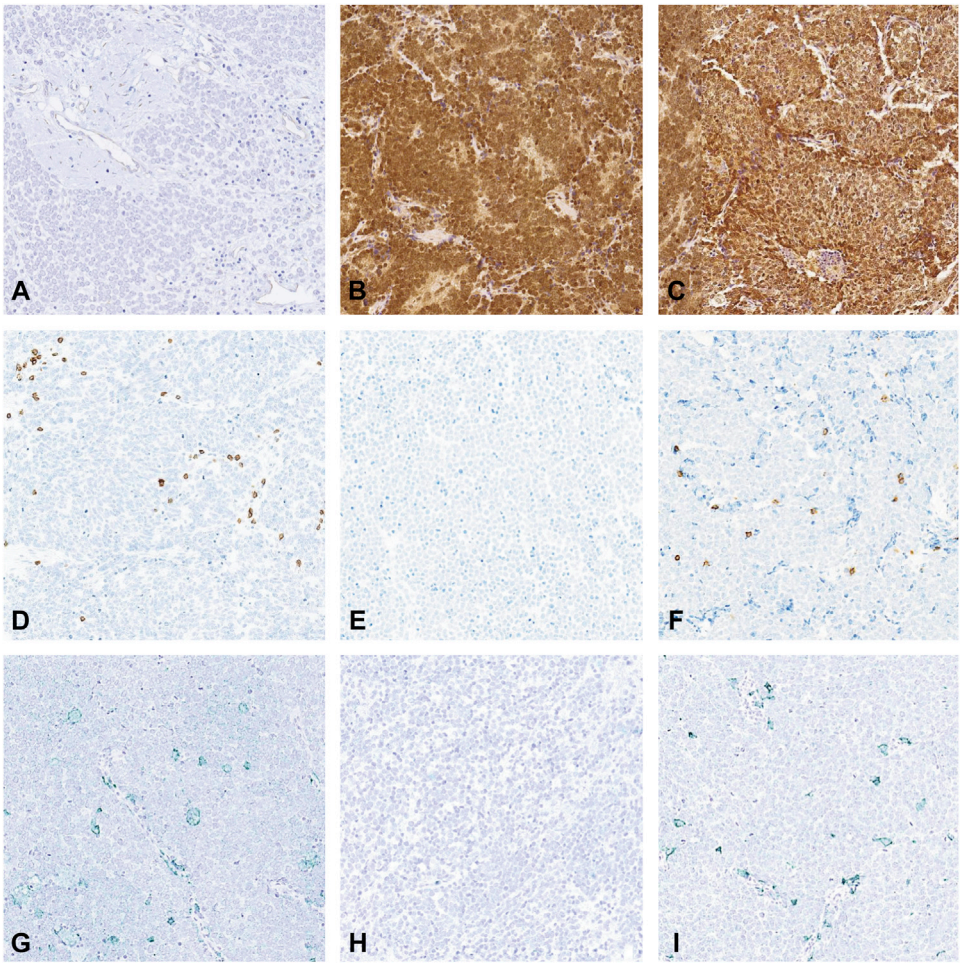

Fig 1. Representative immunohistochemical stainings of (**A-C**) zinc finger E-box binding homeobox 1 (ZEB1), (**D-F**) CD8, and (**G-I**) CD33 infiltration in (**A, D, G**) primary cutaneous tumor, (**B, E, H**) metastasis of cutaneous Merkel cell carcinoma, and (**C, F, I**) Merkel cell carcinoma presenting as lymph node metastasis without a primary skin tumor.

by assessing intratumoral immune populations previously associated with better outcome and/or regression (CD8,[4] $CD33^{brisk}/CD8^{+}$[5]) in the MCC cases from the same cohort (n = 93) (Table I, Fig 1, and Supplemental Table I; available via Mendeley at https://data.mendeley.com/datasets/sn964fs2dp/draft?a=d6fc7ff0-f4d7-40f2-9658-f4cbdb7b0cd1). Among the 87 interpretable cases, 34 did not harbor CD8 lymphocytes (score 0, 39%), 45 displayed low infiltrates (score 1, 52%), 8 had brisk infiltrates (scores 2-5, 9%), and $CD33^{brisk}/CD8^{+}$ immune infiltrates were identified in 32 cases (42%). Among the 78 MCC cases with an identified skin primary tumor, primary tumors more frequently harbored CD8 infiltrates (scores 1-5) (66% vs 31%; $P = .04$) and $CD33^{brisk}/CD8^{high}$ infiltrates (48% vs 7%; $P = .005$) than LNM (Supplemental Table I; available via Mendeley at https://data.mendeley.com/datasets/sn964fs2dp/draft?a=d6fc7ff0-f4d7-40f2-9658-f4cbdb7b0cd1). However, MCC cases with an identified primary tumor were less frequently immune-infiltrated than MCCWOPs. Indeed, CD8 and $CD33^{brisk}/CD8^{+}$ infiltrates were observed in 73% and 69% of MCCWOPs ($P = .03$ and .001, respectively) (Table I and Fig 1), reflecting a brisker immune response in such cases. To conclude, this descriptive study favors the view of MCCWOP as a metastatic process, associated with a marked immune response that may account for the regression of a primary skin tumor.

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Novel mutations identified by whole-exome sequencing in acral melanoma

To the Editor: There have been few studies examining mutational backgrounds for acral melanoma (AM) and different aspects of genetic alterations between nail apparatus melanoma (NAM) and non-nail acral melanoma (NNAM).[1-3] The aim of this study was to uncover previously unidentified novel mutations in patients with AM and compare genetic mutational profiles between NAM and NNAM.

We carried out paired whole-exome sequencing (WES) of saliva and affected tissue samples, collected from Korean patients with AM pathologically confirmed at Samsung Medical Center (Seoul, Korea) from September 2016 to March 2019, as described in our previous study.[4] Detailed methods are presented in Supplemental Appendix 1 (available via Mendeley at https://doi.org/10.17632/9kbh6p3cft.2).

The clinical details of patients included in this study are shown in Supplemental Appendix 2 (available via Mendeley at https://doi.org/10.17632/9kbh6p3cft.2). Among the 31 AMs tested, 6 were melanoma in situ; 24 patients had NNAM, and 7 patients had NAM. Through WES, single nucleotide variations (SNVs) and small insertions/deletions were identified (Supplemental Appendix 3; available via Mendeley at https://doi.org/10.17632/9kbh6p3cft.2). In NNAM, mutations were identified in *BRAF* (16.67%), *NRAS* (12.50%), and *KIT* (8.33%). In NAM, only 1 patient (14.29%) showed an alteration in *BRAF*, and no patients showed *NRAS* or *KIT* mutations. Fifty-three genes were repeatedly detected (≥2 times) as having somatic mutations in AMs (Fig 1). Of them, 11 genes have been previously reported to be associated with melanoma (Supplemental Appendix 4; available via Mendeley at https://doi.org/10.17632/9kbh6p3cft.2). Among SNVs, mutations in 25 genes were predicted to be significantly deleterious[5] in developing melanomas. Fisher's exact test showed that *CES1*, *CSMD3*, *EHMT1*, and *MAGI1* did not appear in NNAM but were distinct mutations in NAM ($P = .045$). We also identified genomic regions affected by copy number alterations (CNAs) (Fig 2). The CNA analysis was based on WES data. CNAs were relatively infrequent in NAMs but common in NNAMs.

In the present study, the frequencies of *BRAF* and *NRAS* mutations in patients with AM, especially in NAM, were lower than those in a previous study on cutaneous melanoma patients.[3] This suggests that NAM might require genetic alterations other than *BRAF* and *NRAS*. Hayward et al[2] reported, based on whole genome sequencing, that the frequencies of SNVs and insertions/deletions were lower but the frequency of structural variants was higher in AM and mucosal melanoma than in cutaneous melanoma. The present study is limited by the small number of cases and by using WES rather than whole genome sequencing.

Based on the results of analysis of significantly deleterious mutations, *CSMD3* and *EHMT1* might have an important role in the pathogenesis of NAM but not in NNAM. Previously, there have been several reports on the association of these genes with malignancies (Supplemental Appendix 5; available via Mendeley at https://doi.org/10.17632/9kbh6p3cft.2). Because our study used only WES, it is currently difficult to know the potential roles of these genes. Therefore, protein work or interaction analysis through transcript analysis may be helpful in the future.

In conclusion, we found possible pathogenic mutations previously unidentified in AM and identified differences between NAM and NNAM. Also, mutations in *CSMD3* and *EHMT1* could play a distinct oncogenic role in NAM. Further studies are needed to validate this result.

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