Merkel cell carcinoma in a patient with Birt-Hogg-Dubé syndrome

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INTRODUCTION

Merkel cell carcinoma (MCC) is a rare but aggressive neuroendocrine skin cancer, caused by either clonally integrated Merkel cell polyomavirus (MCPyV) or UV mutagenesis. Although MCC has an estimated incidence of 0.7 cases per 100,000 person-years,[1] it is highly metastatic, with a disease-specific mortality of 33% to 46%.[2] Birt-Hogg-Dubé (BHD) syndrome is a rare autosomal dominant genodermatosis characterized by the presence of cutaneous fibrofolliculomas, as well as extracutaneous manifestations including kidney tumors, lung cysts, and spontaneous pneumothoraces.[3] BHD results from germline mutations in the tumor suppressor gene *FLCN*, wherein loss of heterozygosity (LOH) activates the mTOR pathway to promote tumorigenesis.[4] Here, we present a rare case of MCC occurring in a 58-year-old patient with BHD.

REPORT OF THE CASE

A 58-year-old man with clinically and histopathologically confirmed BHD, hypertension, and hyperlipidemia presented with a painful nodule on his right forearm that had been present for 10 days. His BHD history was notable for longstanding fibrofolliculomas on the face, neck, back, and limbs (Fig 1).

Abbreviations used:

BHD:	Birt-Hogg-Dubé syndrome
CT:	computed tomography
ES:	exome sequencing
H&E:	hematoxylin and eosin
LOF:	loss of function
LOH:	loss of heterozygosity
MCC:	Merkel cell carcinoma
MCPyV:	Merkel cell polyomavirus
PET:	positron emission tomography

He had undergone a left partial nephrectomy to remove 2 chromophobe tumors, followed by 2 additional left kidney resections, each removing an additional tumor. He also had lung cysts on computed tomography (CT) scan but no history of pneumothorax. Both his mother and maternal grandmother had BHD. The patient had no personal or family history of skin malignancy.

At the time of presentation, there was a 1.4 cm dark pink, tender nodule on the right proximal dorsal forearm (Fig 2, *A*). The review of systems was otherwise unremarkable. Histopathology of a punch biopsy from the forearm lesion demonstrated sheets and trabeculae of small, hyperchromatic basophilic cells with numerous mitotic figures.

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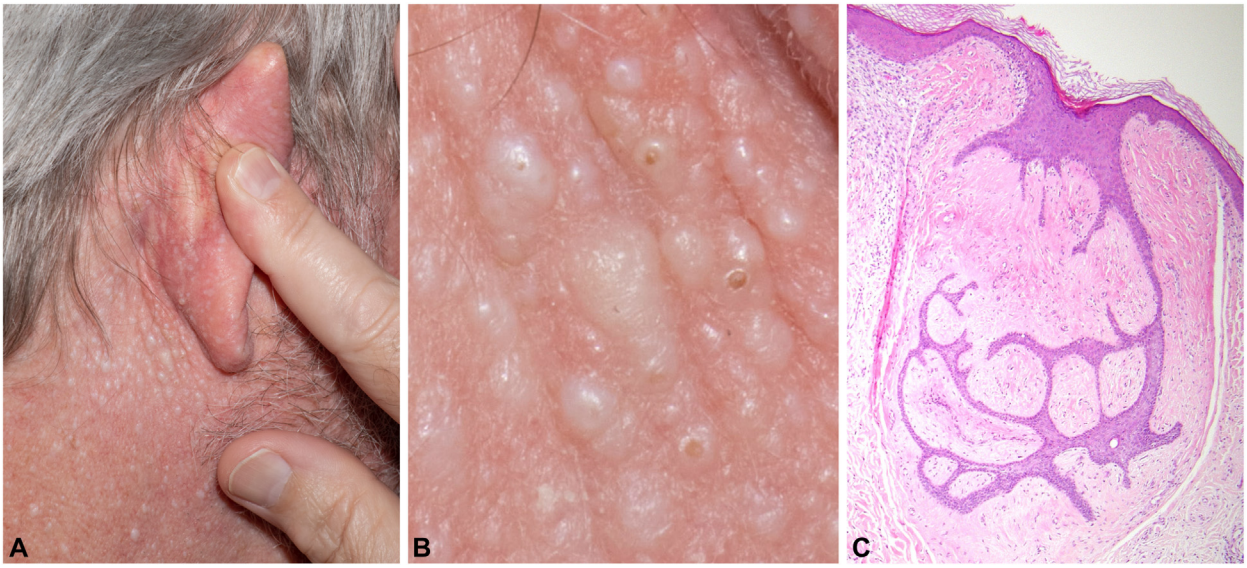

Fig 1. Clinical and histopathologic findings of fibrofolliculomas in our patient with Birt-Hogg-Dubé syndrome. **A** and **B,** Fibrofolliculomas on the neck and posterior auricular skin: 1-2 mm skin colored, dome shaped papules including some with central comedonal plugs. **C,** hematoxylin and eosin (H&E) staining of a fibrofolliculoma biopsied from supraclavicular skin showing epidermal strands extending from a central hair follicle with prominent perifollicular connective tissue. Original magnification 100×.

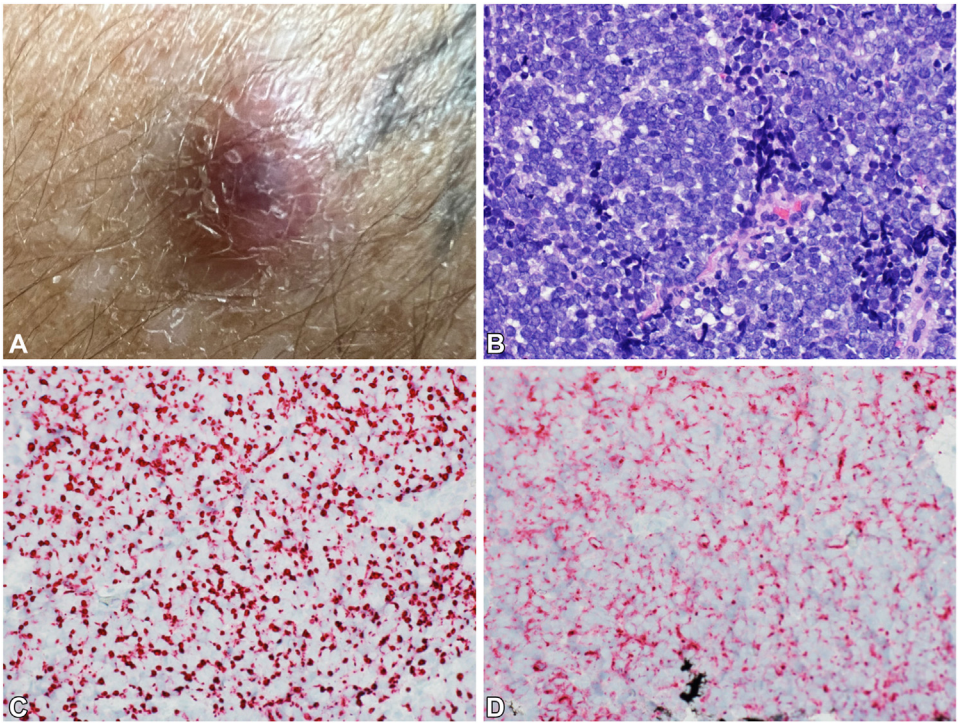

Fig 2. Clinical and histopathologic findings of Merkel cell carcinoma lesion. **A,** 1.4 cm nodule on the right proximal dorsal forearm. **B,** H&E section showing sheets and trabeculae of hyperchromatic basophilic cells. Immunohistochemistry stains were diffusely positive for (**C**) CK20 with a paranuclear dot staining pattern, and (**D**) chromogranin. Original magnification 100×. *H&E*, Hematoxylin and eosin.

Table I. Somatic mutations identified in the patient's Merkel cell carcinoma tumor

Gene	Transcript ID	cDNA change	Protein change	Type
OR10Z1	ENST00000641002	c.62G>C	p.Gly21Ala	Missense
C2orf16	ENST00000447166	c.15014C>T	p.Pro5005Leu	Missense
TTN	ENST00000589042	c.27887-1G>A	N/A	Splice site
CD96	ENST00000352690	c.548A>T	p.Asp183Val	Missense
MBLAC2	ENST00000316610	c.285C>G	p.Phe95Leu	Missense
MAK16	ENST00000360128	c.160A>G	p.Ile54Val	Missense
NOTCH1	ENST00000651671	c.4487G>A	p.Cys1496Tyr	Missense
MUC5B	ENST00000529681	c.16963G>A	p.Glu5655Lys	Missense
FLVCR2	ENST00000238667	c.5T>A	p.Val2Glu	Missense
ENST00000696174	ENST00000696174	c.1499G>A	p.Ser500Asn	Missense
PKD1L3	ENST00000620267	c.3956C>T	p.Ser1319Leu	Missense
CSNK1D	ENST00000314028	c.290C>T	p.Ser97Phe	Missense
POU2F2	ENST00000692977	c.427C>G	p.Gln143Glu	Missense

Sequence variants were identified by comparing exome sequencing reads from tumor and germline DNA. Nonsynonymous variants with predicted loss of function protein changes are listed.

Immunohistochemistry was positive for CD56, chromogranin, neurofilament, and cytokeratin 20 with a paranuclear dot staining pattern, rendering a diagnosis of MCC (Fig 2, *B-D*). Twenty-four days after biopsy, the patient underwent a wide local excision of the MCC tumor, which had grown to 4.3 cm. A sentinel lymph node biopsy from the right axilla and positron emission tomography (PET)/CT scan were both negative. The patient received vacuum-assisted wound closure, followed by a split thickness skin graft. Anti-MCPyV oncoprotein serology was positive, with a titer of 76 standard titer units (normal: 0-74 standard titer units). Three months after his initial surgery, the patient received 56 Gy in 28 fractions of adjuvant external beam radiation to the primary site.

Five months after the initial surgery, a repeat anti-MCPyV oncoprotein serology serology showed a rising titer of 364 standard titer units, and recurrence of MCC was confirmed in the right axilla by PET/CT scan. The patient was subsequently started on combination immunotherapy with ipilimumab 1 mg/kg and nivolumab 3 mg/kg every 3 weeks. His immunotherapy course was complicated by immune related adverse events including thyroiditis, hepatitis, and type 1 diabetes mellitus, requiring treatment with thyroid hormone replacement, systemic steroid, and insulin therapy, respectively. Due to the adverse events, immunotherapy was held after cycle 2. Nonetheless, no detectable disease was found on a restaging PET/CT scan. Twelve weeks after the second infusion, the patient was restarted on nivolumab monotherapy 480 mg every 4 weeks, receiving 9 more infusions, followed by 3 infusions of pembrolizumab 400 mg every 6 weeks. Two and a half years after initial diagnosis, the patient continued to show a complete response, with PET/CT scans and circulating tumor DNA tests remaining negative.

As MCC has not been previously reported in association with BHD, we performed exome sequencing to evaluate the genetic drivers of our patient's tumor. Exome sequencing of peripheral blood DNA demonstrated a heterozygous variant in the *FLCN* gene (GRCh38 chr17:17216506-17216508, NM_144997.7: c.1177−5_1177-3del), consistent with a molecular diagnosis of BHD. This intronic deletion mutation is predicted to cause a splicing defect.[5] According to gnomAD v4.1.0 database, this variant is present in 7 heterozygotes and 0 homozygotes among 1,613,730 alleles.[5] The variant has been reported in multiple unrelated patients with BHD and is classified as pathogenic/likely pathogenic by 10 independent submitters.[5]

Sequencing DNA from the patient's MCC tumor identified the same germline *FLCN* mutation along with 13 somatic mutations (Table I), but there was no evidence of LOH or a second-hit *FLCN* mutation. Additionally, 2 MCPyV integration sites were identified — one on chromosome 1 and the other on chromosome 7 — further supporting the virus positive status of the patient's MCC.

DISCUSSION

BHD is caused by loss of function mutations in the tumor-suppressor *FLCN*. While *FLCN* haploinsufficiency is sufficient to cause fibrofolliculomas,[6] LOH or second-hit somatic mutations are implicated in the development of renal tumors.[7] Interestingly, not all BHD-associated renal tumors exhibit LOH or second-hit mutations because other mechanisms such as gene silencing or mutations in regulatory regions can also result in *FLCN* inactivation.[8]

Our patient is the first documented case of MCC developing in the setting of BHD. Early-onset MCC has been associated with mutations in cancer

predispositions genes such as *BRCA1/2, ATM*, and *TP53*.[9] However, to our knowledge, no previous association between MCC and germline *FLCN* mutations has been reported.

We initially hypothesized that our patient's MCC tumor may be related to his BHD. However, ES of the patient's tumor did not reveal any LOH or second-hit somatic mutations in *FLCN*. The 13 somatic variants identified, as well as the MCPyV integration sites, were either located on a different chromosome or distant from the *FLCN* locus, making it unlikely they would modify *FLCN* expression. Collectively, our genetic findings suggest that the oncogenesis of MCC in our patient was not due to complete *FLCN* loss. It remains possible that *FLCN* haploinsufficiency may have contributed to MCC oncogenesis.

In summary, we present an unusual case of co-occurrence of 2 rare cutaneous conditions in a single patient. Although no direct association between BHD and MCC was identified, further investigation may yet uncover epigenetic or other connections between the 2 conditions.

Conflicts of interest

None disclosed.

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