Histopathology

Histopathology 2020

Correspondence

Polymorphous sweat gland carcinoma found to have *MYB* rearrangement

DOI: 10.1111/his.14025

Sir: Polymorphous sweat gland carcinoma (PSGC) is a rare low-grade malignant cutaneous neoplasm that presents as a slow-growing, skin-coloured nodule in middle-aged to older patients, with no sex preference.[1,2] Histologically, PSGC is a well-circumscribed multinodular neoplasm composed of epithelioid cells arranged in an admixture of growth patterns within the same lesion, including trabecular, solid, pseudopapillary and cylindromatous (adenoid cystic carcinoma-like) patterns, although not all patterns must be present, and the proportions of the patterns vary from tumour to tumour.[3] The histological differential diagnosis of PSGC includes metastatic adenocarcinoma, other adnexal neoplasms with ductular differentiation, and, most importantly, adenoid cystic carcinoma (ACC), given that focal areas of PSGC can be indistinguishable from the cribriform pattern present in ACC.[3] In contrast, primary cutaneous ACC has a more infiltrative border and shows perineural invasion in up to 60% of cases.[4] In addition, genomic rearrangements involving the MYB family of proteins, particularly *MYB–NFIB* fusions, are considered to constitute the molecular hallmark of ACC.[3] The *MYB* locus encodes a master transcription factor involved in both cellular proliferation and differentiation.[5]

MYB rearrangements have not been previously described in PSGC.[2] This is the first report to determine a *MYB* rearrangement associated with PSGC. This gene rearrangement is distinct from the *MYB–NFIB* fusion characteristically seen in ACC.

We report on a man in his 60s with no pertinent past medical history who presented with an asymptomatic pea-sized papule in the left axilla that grew to become a 20 × 30-mm, skin-coloured, mobile, firm tumour within 6 months. After surgical removal, histopathological examination revealed a well-circumscribed, unencapsulated, multinodular neoplasm composed of epithelioid cells arranged in various architectural patterns, including tubular, trabecular and cylindromatous (adenoid cystic-like) patterns, with foci of intraluminal mucin and hyalinised stroma (Figure 1). Approximately eight mitoses per square millimetre were present. Perineural invasion was not seen. Anti-MYB antibody (1:200 dilution; Abcam, Cambridge, UK) detected diffuse and strong nuclear expression of MYB in >75% of tumour cells (Figure 1E,F). The tumour cells were diffusely positive for p63 (1:150 dilution; Biocare Medical, Pachecho, CA, USA) and negative for CD117 (1:1500 dilution; Dako, Santa Clara, CA, USA) and S100 (1:400 dilution; Cell Marque, Rocklin, CA, USA), consistent with the results found for PSGC,[2] but distinct from those obtained in primary cutaneous ACC (often S100-positive and CD117-positive).[4] Fluorescence *in-situ* hybridisation evaluation for *MYB* rearrangement was performed on 5-μm tissue sections, with break-apart probes that were specific for the 5′ (centromeric) and 3′ (telomeric) regions of *MYB* at 6q23.3 (Abbott Molecular, Chicago, IL, USA) (Figure 2). An unbalanced *MYB* rearrangement, involving loss of the 3′ probe, was identified in 39 of 50 nuclei (normal range: up to 2% rearranged). RNA sequencing (RNA-seq) was performed on the specimen, and *MYB* mRNA was highly expressed (>10 000 reads in several exons), in contrast to the absence of *MYB* mRNA expression in control formalin-fixed paraffin-embedded non-tumour tissues from placenta, bone marrow, and lung. RNA-seq did not identify a *MYB–NFIB* fusion transcript.

Currently the patient is asymptomatic. Positron emission tomography–computed tomography and brain magnetic resonance imaging did not reveal metastatic disease.

The tumour *MYB* rearrangement resulted in loss of its 3′-end, which is a well-described mechanism of increased MYB activity, because the *MYB* 3′-untranslated region contains a microRNA regulatory site that down-regulates *MYB* expression.[5] In ACC, increased *MYB* expression is coordinated with *TP63* expression in myoepithelial cells and *Notch* expression in luminal epithelial cells to orchestrate the characteristic cribriform histological pattern seen in ACC.[5] *MYB–NFIB* fusions have been found in ACC and, to a lesser degree, in cylindroma, which shares histological features with ACC.[6]

We hypothesise that primary cutaneous adnexal neoplasms, including primary cutaneous ACC, cylindroma, and PSGC, that show a cribriform histological pattern also show MYB activation, either through gene rearrangements or though other mechanisms, and have a similar biological behaviour. Given the significant clinicopathological and molecular overlap, ACC and PSGC may represent histological variants of the same disease process, although further study and comparison are warranted. Nevertheless, recognition

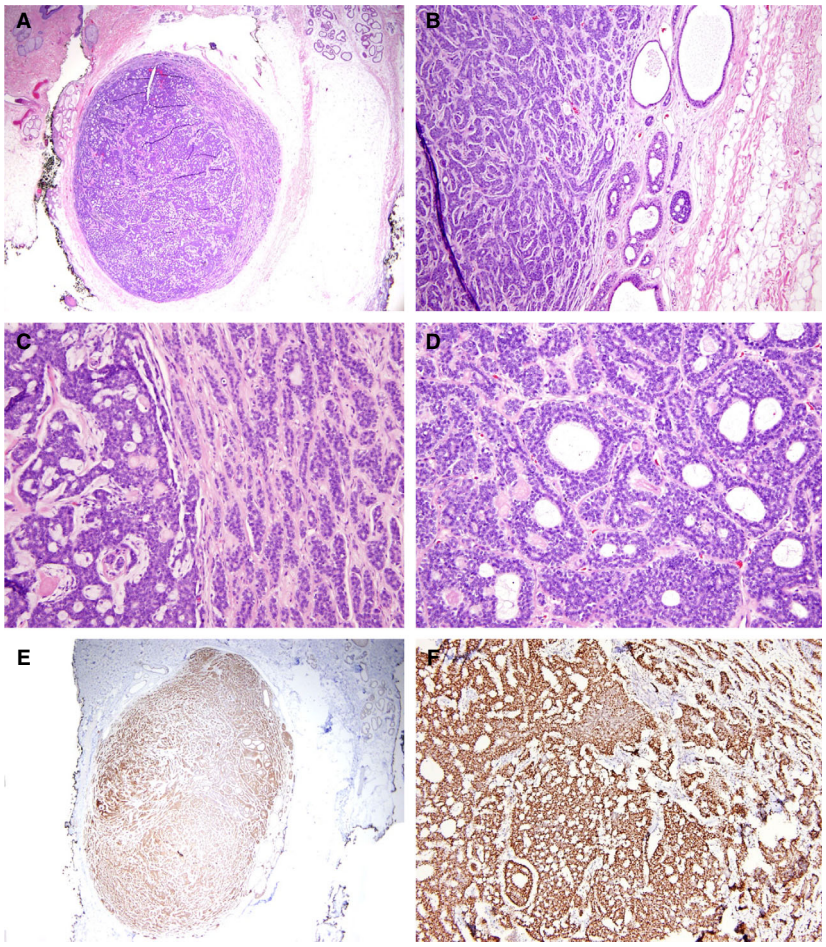

Figure 1. **A**, Well-circumscribed nodular neoplasm (haematoxylin and eosin). **B**–**D**, Diversity of architectural patterns with an adenoid cystic-like pattern in (**D**) (haematoxylin and eosin). **E**,**F**, Diffuse MYB expression in the neoplasm.

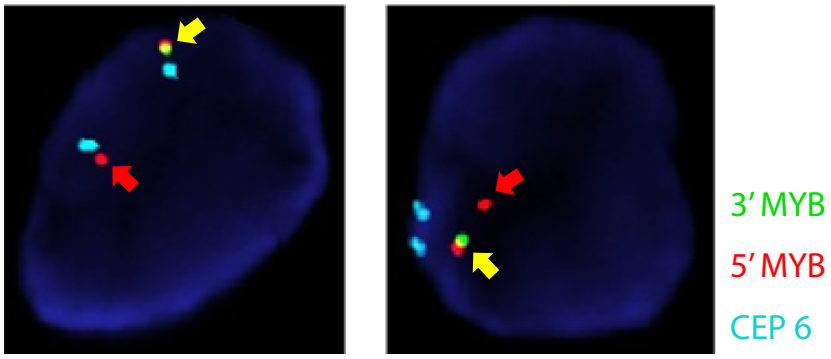

Figure 2. Fluorescence *in-situ* hybridisation evaluation for *MYB* rearrangement performed with a break-apart probe set mapping to the *MYB* locus on 6q23.3 (the 5′-end probe is highlighted in red, and the 3′-end probe is highlighted in green). In addition, a probe (highlighted in aqua) targeting the centromeric portion of chromosome 6 was used to track the number of copies of chromosome 6 present. The yellow arrow points to a normal, unaffected *MYB* locus, and the red arrow points to a *MYB* locus with loss of the 3′-end.

of MYB activation is clinically relevant, as small-molecule inhibitors of MYB have shown promise in a variety of preclinical experiments.[6]

Conflicts of interest

The authors state that they have no conflicts of interest.

Author contributions

Conceptualisation: F. Hafeez. Methodology and investigation: F. Hafeez, S. Xiao, P. D. Cin, J. F. Krane, P. Chen, J. Hayek, and C. L. Lian. Writing: F. Hafeez. Review and editing: F. Hafeez, P. D. Cin, and C. G. Lian.

Farhaan Hafeez[1,2]
Sheng Xiao[1]
Paola Dal Cin[1]
Jeffrey F Krane[1]
Ping Chen[3]
Jihad Hayek[4]
Christine G Lian[1]

[1]*Department of Pathology, Brigham and Women's Hospital,Harvard Medical School, Boston, MA,* [2]*Department of Dermatology, St Luke's University Health Network, Temple/St. Luke's School of Medicine, Bethlehem, PA, USA,* [3]*Suzhou Sano Precision Medicine Ltd, Suzhou, China, and* [4]*Department of Pathology, New England Baptist Hospital, Boston, MA, USA*

1. Suster S, Wong TY. Polymorphous sweat gland carcinoma. *Histopathology* 1994; **25**; 31–39.
2. Ronen S, Aguilera-Barrantes I, Giorgadze T, Steiner P, Grossmann P, Suster S. Polymorphous sweat gland carcinoma: an immunohistochemical and molecular study. *Am. J. Dermatopathol.* 2018; **40**; 580–587.
3. Walker A, Mesinkovska NA, Emanuel PO *et al*. Polymorphous sweat gland carcinoma: a report of two cases. *J. Cutan. Pathol.* 2016; **43**; 594–601.
4. Ramakrishnan R, Chaudhry IH, Ramdial P *et al*. Primary cutaneous adenoid cystic carcinoma: a clinicopathologic and immunohistochemical study of 27 cases. *Am. J. Surg. Pathol.* 2013; **37**; 1603–1611.
5. Drier Y, Cotton MJ, Williamson KE *et al*. An oncogenic MYB feedback loop drives alternate cell fates in adenoid cystic carcinoma. *Nat. Genet.* 2016; **48**; 265–272.
6. Corda G, Sala A. Cutaneous cylindroma: it's all about MYB. *J. Pathol.* 2016; **239**; 391–393.