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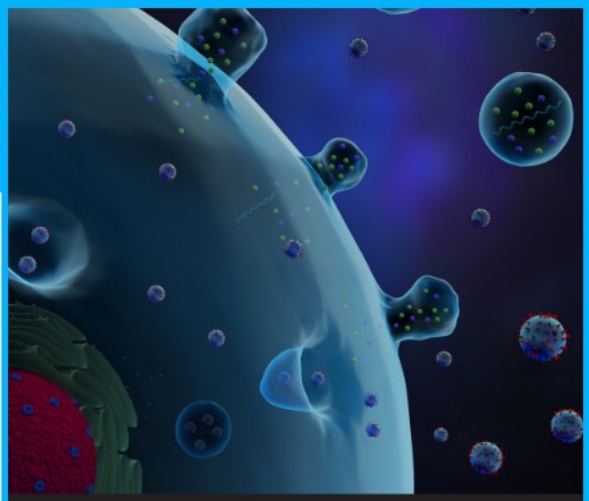

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Recurrent *PAK2* rearrangements in poroma with folliculo-sebaceous differentiation

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Recurrent *PAK2* rearrangements in poroma with folliculo-sebaceous differentiation

Aims: Poroma is a benign adnexal neoplasm with differentiation towards the upper portion of the sweat gland apparatus. In 2019, Sekine *et al.* demonstrated recurrent *YAP1::MAML2* and *YAP1::NUTM1* fusion in poroma and porocarcinoma. Follicular, sebaceous and/or apocrine differentiation has been reported in rare cases of poroma and whether these tumours constitute a variant of poroma or represent a distinctive tumour is a matter to debate. Herein we describe the clinical, immunophenotypic, and molecular features of 13 cases of poroma with folliculo-sebaceous differentiation.

Methods and results: Most of the tumours were located on the head and neck region ($n = 7$), and on the thigh ($n = 3$). All presented were adults with a slight male predilection. The median tumour size was 10 mm (range: 4–25). Microscopically, lesions displayed features of poroma with nodules of monotonous basophilic cells associated with a second population of larger eosinophilic cells. In all cases, ducts and scattered sebocytes were identified. Infundibular cysts were

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Maxime Battistella and Arnaud de la Fouchardière equally contributed to the present study.

present in 10 cases. In two cases high mitotic activity was noted, and in three cases cytologic atypia and areas of necrosis were identified. Whole transcriptome RNA sequencing demonstrated in-frame fusion transcripts involving *RNF13::PAK2* ($n = 4$), *EPHB3::PAK2* ($n = 2$), *DLG1::PAK2* ($n = 2$), *LRIG1::PAK2* ($n = 1$), *ATP1B3::PAK2* ($n = 1$), *TM9SF4::PAK2* ($n = 1$), and *CTNNA1::PAK2* ($n = 1$). Moreover, fluorescence *in situ* hybridisation (FISH) analysis revealed *PAK2* rearrangement in an additional case. No *YAP1::MAML2* or *YAP1::NUTM1* fusion was detected.

Conclusion: Recurrent fusions involving the *PAK2* gene in all analysed poroma with folliculo-sebaceous differentiation in this study confirms that this neoplasm represents a separate tumour entity distinct from *YAP1::MAML2* or *YAP1::NUTM1* rearranged poromas.

Keywords: apocrine poroma, folliculo-sebaceous differentiation, holocrine poroma, infundibular adenoma, PAK2

Introduction

Skin adnexal tumours constitute a heterogeneous group of neoplasms differentiating towards the apocrine-folliculo-sebaceous unit or the eccrine sweat gland apparatus. The majority of these neoplasms are benign, but a rare small number of tumours are malignant.[1] The latter lesions may derive from a benign counterpart or arise *de novo* without any identifiable precursor.[2] In recent years a common oncogenic driver has been demonstrated in benign adnexal tumours and their malignant counterparts and these include *YAP1::MAML2* and *YAP1::NUTM1* fusion in poroma/porocarcinoma.[3]

The identification of recurrent genetic alterations in several sweat glands tumours has largely contributed to our understanding of the biology of these neoplasms, leading to a more accurate classification.[1] By contrast, the genetic background of most of the adnexal tumours with follicular differentiation remains poorly characterised.

In 1981, Grosshans *et al.* reported the first description of the "infundibular adenoma",[4] a tumour with close morphologic similarities with poroma but also harbouring follicular and/or sebaceous differentiation. Tumours with similar morphologic features including follicular, sebaceous, and/or apocrine differentiation were later reported as apocrine/holocrine poroma, referring to the common embryologic origin of all apocrine-folliculo-sebaceous unit components.[5–7] The question as to whether these lesions represent a variant of poroma or a distinct entity is still a matter of debate.[5,7]

In this report we describe recurrent *PAK2* gene fusion in thirteen cases of poroma with folliculo-sebaceous differentiation.

Methods

PATIENTS

Thirteen poroma cases with folliculo-sebaceous differentiation and six poroma cases with apocrine differentiation were retrospectively identified from the consultation files of the authors. The design of this retrospective study was in agreement with the requirements for the use of biological material in research proposed by our institutional ethics guidelines (Local Ethics Committee in Human Research, Tours, France; no. ID RCB2009-A01056-51).

IMMUNOHISTOCHEMISTRY

Immunohistochemical staining for CD15, EMA, BerEP4, PHLDA1, CK7, CK18, CEA, P63, SOX10, YAP1, and NUT was performed using a BenchMark XT Platform as instructed. Antibodies and dilutions are provided in the Supplementary Material.

FISH ANALYSIS

Fluorescence *in situ* hybridisation (FISH) was performed on 4-µm sections of formalin-fixed paraffin-embedded (FFPE) tissue using the ZytoLight FISH-Tissue Implementation Kit (#Z-2028-20; Zytovision, Bremerhaven, Germany) and with an adapted break-apart probe (PAK2 Break Apart FISH Probe, Empire Genomics, Buffalo, NY, USA; PAK2BA-20-ORGR). FISH signals were determined from at least 50 nonoverlapping, intact nuclei. A specimen was considered positive if >20% of nuclei demonstrated a signal pattern consistent with a balanced or unbalanced gene rearrangement.

DETECTION OF *YAP1::MAML2* AND *YAP1::NUTM1* FUSIONS

The presence of *YAP1::MAML2* and *YAP1::NUTM1* fusions was investigated by real-time polymerase chain reaction (PCR) as previously described.[8]

RNA SEQUENCING

RNA sequencing was performed in all cases as previously described.[9] Briefly, total RNA was extracted

from FFPE tissue sections. For each sample, 100 ng of total RNA was used to prepare the library with the TruSeq RNA Access Library Prep Kit (Illumina, San Diego, CA, USA). Fourteen libraries were pooled at 4 nM with PhiX Control in a low-concentration spike-in (1%). Sequencing was performed (75 cycles paired-end) with NextSeq 500/550 High Output V2 Kit in NextSeq 500 (Illumina). The samples were analysed with the BaseSpace sequence Hub (Illumina) with RNA-Sequencing Alignment application. The alignments were realised with Star and TopHat2 on the GRCh37 reference genome. The fusion transcript was called with Manta, EricScript, and TopHat2 fusion.

Results

Thirteen cases of poroma with folliculo-sebaceous differentiation were studied. Clinical, histological, immunohistochemical, and molecular features of all cases are summarised in Table 1. Briefly, there were eight females and seven males. The median age at the diagnosis time was 61 years (range: 23–90). Seven tumours were located on the head and neck region, three presented on the thigh, one on the axillary area, and one on a finger (tumour site was unknown for case #13). One case arose from a preexisting sebaceous nevus (case #10). The median tumour size was 10 mm (range: 4–25 mm). Follow-up data were available in eight cases (mean duration: 11 months [2–36]) and no recurrence was observed.

Microscopic features of the cases are highlighted in Table 1, and Figures 1 and 2. All tumours were connected with the epidermis and located in the dermis with focal extension into the subcutaneous tissue in four cases. All lesions were circumscribed and displayed solid lobules of monotonous small- to medium-sized cells with basophilic cytoplasm, and round to oval nuclei with a typical "poroid" cytology. A second population of larger cells with eosinophilic cytoplasm, a squamoid appearance, and arranged in clusters or with formation of squamous eddies were identified in most cases. Cystic structures were observed in eight cases. Ducts with frequent eosinophilic cuticles were associated with infundibular cysts displaying lamellar keratin in 10 cases. Calcification within the keratin was seen in three cases. Scattered sebocytes were present and focal aggregates of melanin were seen in three cases. Glandular formation harbouring decapitation secretion was observed in one case (case #10). The stroma surrounding the tumour lobules was frequently hyalinised. Mitotic count was low (median count: 1/mm^2) except in two cases (cases #8 and 13). Necrosis *en masse* and cytologic atypia were observed in three cases (Figure 2). No perineural or vascular invasion was seen.

Immunohistochemistry showed (Table 1, Figure 3) negative or focal expression of BerEP4 or PHLDA1 in most cases. Ducts were highlighted by EMA, CEA, and cytokeratin 7. The sebocytes highlighted by EMA and SOX10 demonstrated focal colonisation by melanocytes in the superficial part of the tumours. In contrast to *YAP1::MAML2* or *YAP1::NUTM1* poromas, YAP1 (C -terminal) expression was preserved in all cases and no expression of NUT was detected.

Whole transcriptome RNA sequencing revealed in-frame fusion transcripts involving *RNF13::PAK2* in four cases, *EPHB3::PAK2 and DLG1::PAK2* in two cases, *LRIG1::PAK2*, *ATP1B3::PAK2*, *TM9SF4::PAK2* and *CTNNA1::PAK2* in one case (Figure 4). Moreover, FISH analysis using a break-apart probe revealed *PAK2* rearrangement in one additional case (case #5) in which no *PAK2* gene fusion was detected by RNA sequencing, possibly due to severe RNA degradation in this sample. Importantly, although the position of the breakpoints in *PAK2* gene changed from one sample to another, the protein kinase domain was constantly preserved, while the p21 − Rho−binding and regulatory domains were lost. As loss of the regulatory N-terminal part of the PAK2 protein through caspase 3 cleavage has been identified as a main contributor of PAK2 activation,[10] these findings suggest a constitutive activation of the PAK2 catalytic domain in the fusion protein. Interestingly, in addition to the *PAK2* fusion *HRAS* activating mutations (G13V and G13R) were detected in three cases (cases #5, 10, and 13) including the tumour arising from nevus sebaceous. Moreover, gene expression analysis revealed high levels of epidermal growth factor receptor (eGFR) expression when compared to other previously analysed cutaneous tumours (Figure S1).

Finally, the presence of *PAK2* and *YAP1* rearrangements were evaluated by FISH and real-time PCR in an additional series of six apocrine poroma cases harbouring elongated ductal structures with decapitation secretion, but lacking follicular or sebaceous differentiation (Figure S2). This analysis revealed *YAP1::MAML2* fusions in all tested cases, while no *PAK2* gene fusion was observed.

Discussion

In a large series of 68 cases initially reported as follicular poroma/inverted keratosis, Grosshans *et al.*[4]

Table 1. Clinical, microscopic, and molecular features of the cases

	Case #1	Case #2	Case #3	Case #4	Case #5	Case #6	Case #7	Case #8	Case #9	Case #10	Case #11	Case #12	Case #13
Clinical features													
Age (years)	61	87	52	36	90	66	77	53	47	23	52	78	86
Sex	M	F	M	F	F	F	F	M	F	M	M	M	M
Location	Neck	Occiput	Finger (left hand)	Lip	Thigh	Thigh	Scalp	Scalp	Axillary area	Scalp	Scalp	Thigh	NA
Tumour size (mm)	10	10	11	6	10	11	17	10	14	5	15	4	25
Follow up (months)	2	18	NA	NA	144	12	6	3	NA	10	NA	36	NA
	No recurrence	No recurrence			No recurrence	No recurrence	No recurrence	No recurrence		No recurrence		No recurrence	
Morphologic features													
Epidermal connection	+ (multiples)	+ (multiples)	+	+ (hair follicle)	+ (multiples)	+ (multiples)	+ (multiples)	+	–	+ (multiples)	+ (muliples)	+ (multiples)	+ (multiples)
Location													
Dermis	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous	+	–	+	–	–	+	–	–	+	–	NA	–	–
Delimitation	Well	Well	Well	Well	Well	Well	Well	Well	Well	Well	Well	Well	Well
Architecture													
Macronodule	+	+	+	+	+	+	+	+	+	+	+	+	+
Cyst	+	Focal	+	–	–	+	–	+	+	Focal	Focal	–	–
Cytology													
Poroid	++	++	++	++	++	++	++	++	++	++	++	++	++
Squamoid	+	++	++	+	+	+	+	-	++	+	+	++	–
Atypia	-	-	-	-	-	-	-	-	+	+	-	-	+
Clear cell changes	Focal	+	Focal	Focal	–	Focal	–	–	–	–	–	–	–
Poroid differentiation													
Duct formation	+	+	+	+	+	+	+	+	+	+	+	+	+
Eosinophilic cuticle	+	-	+	+	+	+	-	+	+	+	+	+	+
Decapitation secretion	-	-	-	-	-	-	-	-	-	+	-	-	-

Table 1. (*Continued*)

	Case #1	Case #2	Case #3	Case #4	Case #5	Case #6	Case #7	Case #8	Case #9	Case #10	Case #11	Case #12	Case #13
Follicular differentiation													
Infundibular cyst	+	+	+	+	+	+	+	-	Focal	-	+	+	-
Squamous eddies	+	+	+	-	+	+	-	+	+	Focal	+	+	-
Keratin calcification	+	-	-	-	+	+	-	-	-	-	-	-	-
Sebaceous differentiation													
Sebocytes	+	+	+	+	+	+	+	+	+	+	+	+	+
Others													
Hyalinised stroma	-	+	–	–	+	-	+	+	+	+	-	-	-
Melanin aggregates	+	+	-	-	+	-	-	-	-	+	-	-	-
Necrosis	-	-	+	-	-	-	-	+	+	-	-	-	-
Mitotic count/mm^2	1	1	2	1	1	1	1	7	1	0	4	0	8
IHC features													
EMA	Duct+sebocytes	Duct+sebocytes	Duct	Duct	NA	Duct+sebocytes	Ducts	Duct+sebocytes	Duct+sebocytes	Duct+sebocytes	Duct+sebocytes	Sebocytes	Duct+sebocytes
BerEP4	–	–	–	Focal	NA	–	–	–	Weak	+(glands)	Diffuse	–	Weak
PHLDA1	Focal	Focal	Diffuse	Weak	NA	Weak	Weak	Weak	–	–	–	–	–
CK7	Ducts	Ducts	Ducts	Duct	NA	Ducts	Ducts	NA	Ducts	Ducts+ glands	Ducts+diffuse	Ducts	Heterogenous
CEA	Ducts	Ducts	Ducts	Duct	NA	Duct	Ducts	–	Ducts	Ducts+ glands	Ducts	–	Ducts
P63	Diffuse	Diffuse	Diffuse	Diffuse	NA	Diffuse	NA	Diffuse	Diffuse	Diffuse[a]	Diffuse	Diffuse	Diffuse
SOX10	Few melanocytes	Few melanocytes	–	Few melanocytes	NA	NA	–	Few melanocytes	–	Few melanocytes	Few melanocytes	Few melanocytes	Few melanocytes
YAP1 (C-Ter)	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved	Preserved
NUT	–	–	–	–	NA	–	NA	–	–	–	–	–	–
Genetic features													
FISH PAK2	+	+	NA	NA	+	+	+	NA	+	+	+	+	+
RNA sequencing	*EPHB3::PAK2*	*LRIG1::PAK2*	*RNF13::PAK2*	*EPHB3::PAK2*	NA	*DLG1::PAK2*	*ATP1B3::PAK2*	*TM9SF4::PAK2*	*RNF13::PAK2*	*DLG1::PAK2*	*CTNNA1::PAK2*	*RNF13::PAK2*	*RNF13::PAK2*

Abbreviation: NA, not available.

[a]Diffuse p63 positivity except in the glandular structures.

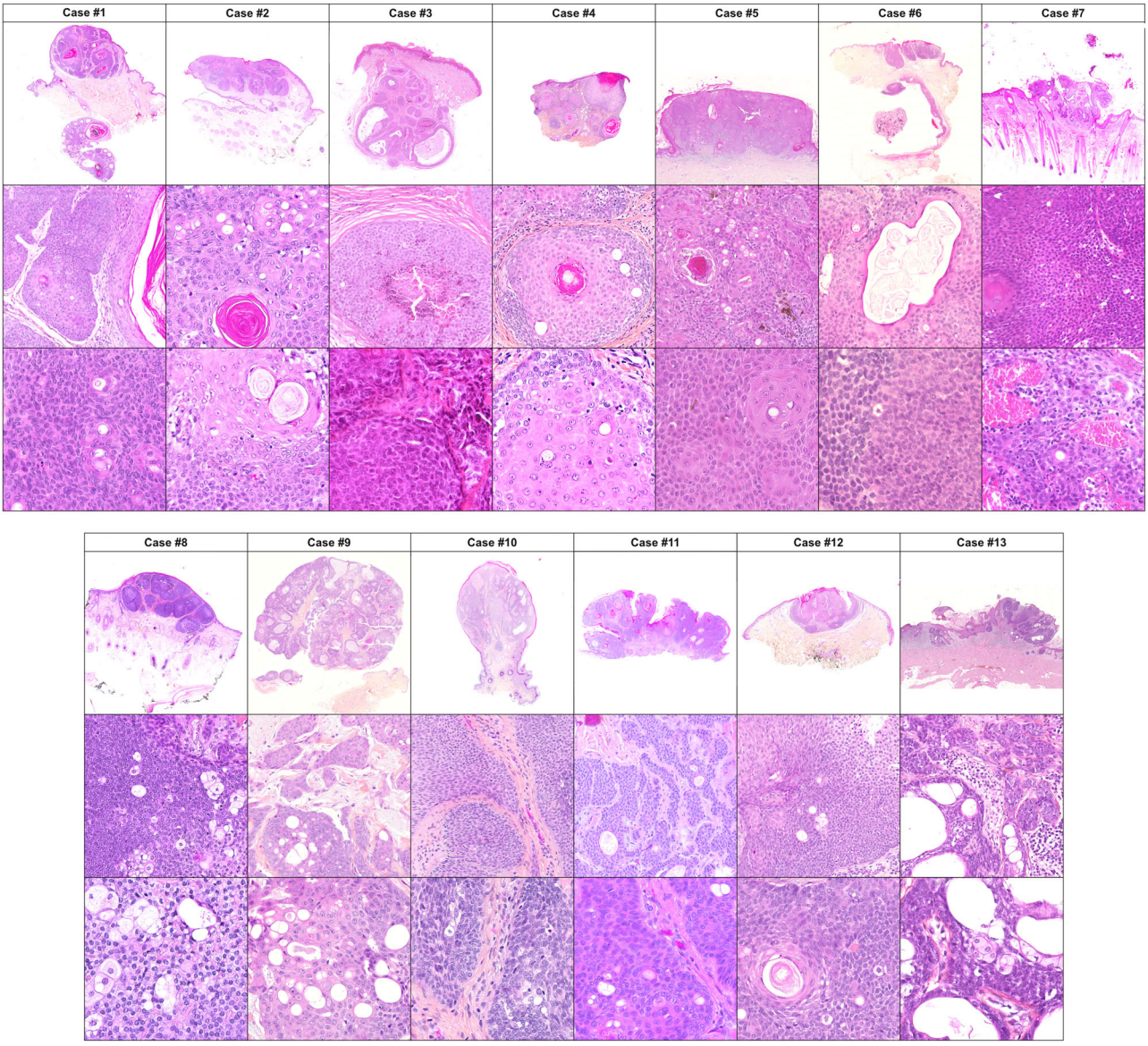

Figure 1. Microscopic features of *PAK2*-rearranged poroma. Microscopic features of the 13 cases included in the present study. The tumours were connected with the epidermis and located in the dermis, with some displaying extension into the subcutaneous tissue. The neoplasms consist in solid nodules of monotonous basophilic cells associated with a second population of larger squamoid cells with eosinophilic cytoplasm.

identified six poroid tumours with apocrine and sebaceous differentiation and labelled them "infundibular adenoma". Similar poroid tumours with folliculosebaceous and apocrine differentiation were later reported as "apocrine poroma" or "holocrine poroma" with fewer than 100 published cases.[5] Horenstein *et al.* published a series of 48 "holocrine poroma" harbouring follicular and sebaceous differentiation.[6] These lesions were more common on the head and neck (62.5%) as shown in our study and in contrast to eccrine poroma, which favour the extremities.[11] Microscopically, "holocrine poroma" displayed both, a solid-cystic architecture, and most but not all tumours were connected to the epidermis. Infundibular cysts, ducts with "steatocystoma-like cuticles" and sparse sebocytes were present in most of the cases. No apocrine decapitation secretion was observed. The authors concluded that "holocrine" poroma constitutes a distinctive neoplasm derived from the sebaceous duct and different from eccrine poroma. Other authors, however, regard this neoplasm as part of the spectrum, and a variant of poroma .[7] Importantly, Horenstein *et al.* proposed the term of "holocrine poroma" due to lack of apocrine secretion and due to the presence of an eosinophilic cuticle in the

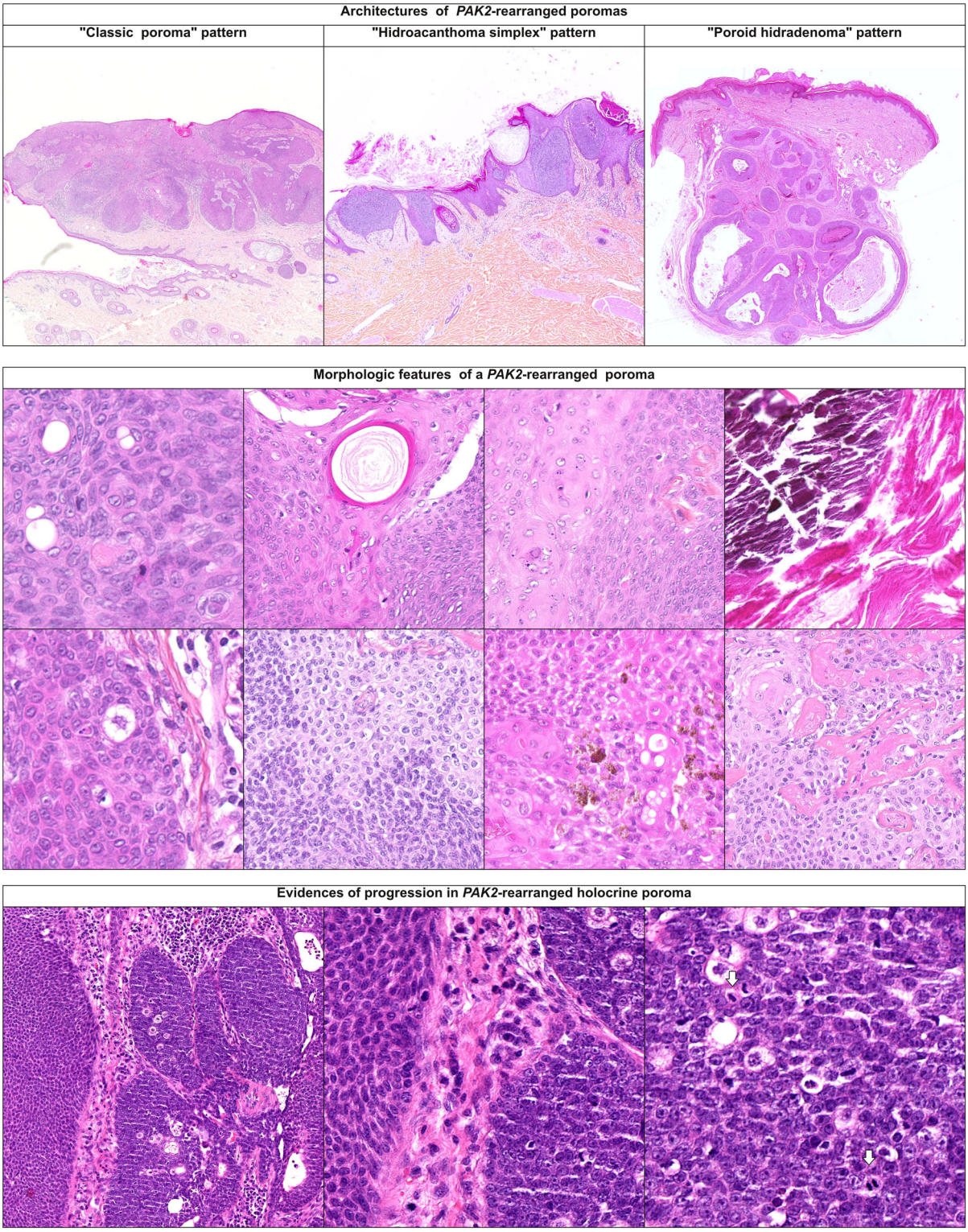

Figure 2. Microscopic details of *PAK2*-rearranged poroma. Tumours harbour "classic poroma", "hidroacanthoma simplex", or "poroid hidradenoma" architectures. Ducts with frequent eosinophilic cuticles were associated with infundibular cysts containing lamellar, sometimes with calcification. Sparse sebocytes, melanin deposits, and clear cell changes were observed. A hyalinised stroma was also present in some cases. An atypical component harbouring enlarged hyperchromatic nuclei and enhanced mitotic activity was detected in two specimens, suggesting tumour progression (case #13 is depicted).

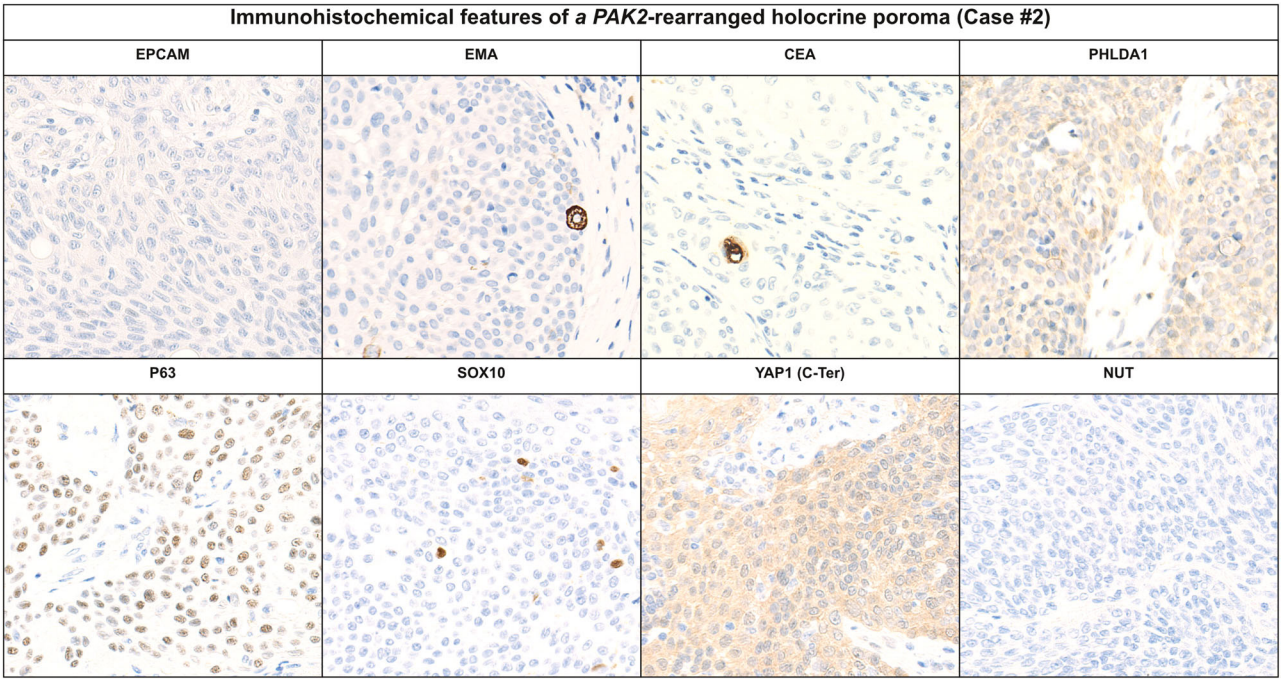

Figure 3. Immunohistochemical features of a *PAK2*-rearranged apocrine poroma. No expression of EpCAM was observed. EMA and CEA staining highlight duct formations. In addition, EMA also demonstrated the presence of sparse sebocytes. Only focal and weak expression of PHLDA1 was detected, while p63 expression was diffuse. Sparse SOX10-positive melanocytes were detected in the superficial part of the tumour. In contrast to eccrine poroma, preserved expression of YAP1 (C-terminal) and lack of NUT expression were demonstrated in *PAK2*-rearranged poroma cases with folliculo-sebaceous differentiation.

ductal structures. However, although frequently observed, this feature is not always present in all cases, while follicular or sebaceous differentiation is a constant. In our series, we confirmed that apocrine differentiation with decapitation secretion is rarely observed in poroma tumours with follicular and sebaceous differentiation (n = 1/13).

In 2019, Sekine *et al.* described a recurrent *YAP1::MAML2* and *YAP1::NUTM1* fusion in poroma/porocarcinoma.[3] If poroma with folliculo-sebaceous differentiation were part of the spectrum of poroma/porocarcinoma, one would have expected to find similar fusion transcripts in these tumours, but we did not detect this feature any of our cases. In contrast, our molecular analysis revealed distinct fusions consistently involving the *PAK2* gene. PAK2, i.e. p21 (RAC1) activated kinase 2, is a serine/threonine protein kinase forming a complex with the GTPases CDC42 and RAC1 and physiologically involved in cell motility, growth, angiogenesis, and development.[12,13] In cancer, PAK2 activation is associated with advanced stages, drug resistance, and poor outcome in several malignancies.[14] Accordingly pharmacologic inhibition of PAK2 has been proposed as a potential therapeutic target.[15]

Amplification or mutation of the *PAK2* gene seems to be the most prevalent genetic mechanism leading to its activation in tumours,[16] while fusions are rare. Among the 10,967 cancers registered in the Tumour Fusion Gene Data Portal (https://tumorfusions.org, last accessed 7/9/2022),[17] only seven cases harboured *PAK2* rearrangements. Of note, no *PAK2* rearrangement was detected in cases of poroma previously analysed by whole RNA sequencing,[3] as well as in the six apocrine poroma cases lacking follicular or sebaceous differentiation tested in our series. Therefore, the detection of *PAK2* gene fusions in the 13 poroma cases with folliculo-sebaceous differentiation analysed in the present study strongly suggests that *PAK2* gene fusions may constitute the oncogenic driver in this neoplasm.

Importantly, an *RNF13::PAK2* in-frame fusion transcript has already been reported in one case of metastatic tumours diagnosed as "eccrine porocarcinoma" but lacking the canonic *YAP1::MAML2* or *YAP1::NUTM1* fusion.[18] This tumour arose on the scalp of a 64-year-old man. Rapid metastatic spread to the lymph nodes and central nervous system led to the death of the patient. Although no folliculo-sebaceous differentiation was detected in this case, it could suggest a malignant transformation arising in

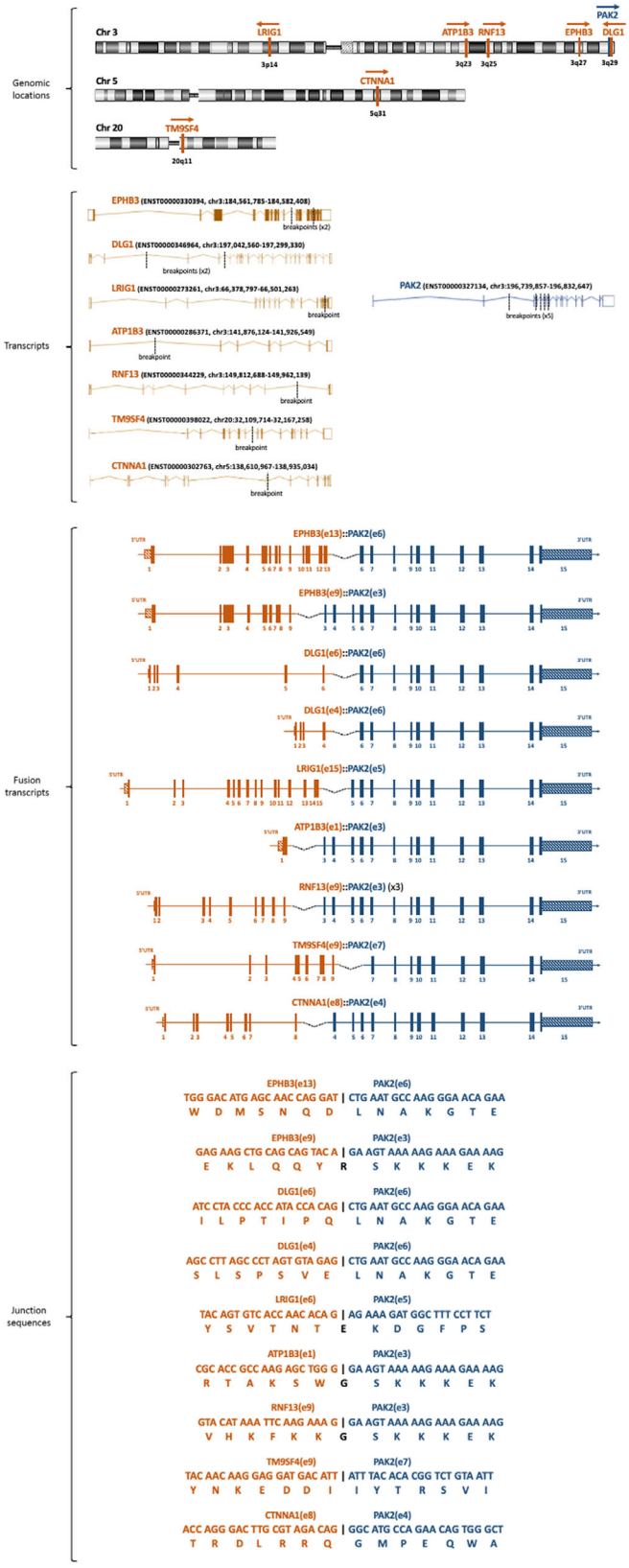

Figure 4. Schematic representation of fusion transcripts involving PAK2.

a benign folliculo-sebaceous poroma through the accumulation of additional oncogenic events, as previously suggested.[7] Of note, malignant/sarcomatoid transformation has been reported in a single case of apocrine poroma with sebaceous differentiation.[7] Accordingly, detection of an atypical component harbouring cytologic atypia and increased mitotic activity in cases #8 and #13 might suggest a progression in these tumours. Although no recurrence or metastasis were observed, short-term follow-up constitutes a main limitation of our study.

In conclusion, we report the recurrent detection of fusion involving the *PAK2* gene in poromas with folliculo-sebaceous differentiation, confirming it as a separate and distinct entity from *YAP1*-rearranged poroma.

Author contributions

TK, DP, MB, and AF substantially contributed to the conception, design, acquisition, analysis interpretation of data as well as article drafting. SP, FT, AO, SM, FJ, PS, EC, AP, EEL, KG, FD, EF, NM and BC substantially contributed to the acquisition of data, and revised the article. All authors approved the final version.

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Conflict of interest

All authors declare no conflicts of interest to disclose.

Data availability statement

Data are available upon request.

References

1. Macagno N, Sohier P, Kervarrec T *et al*. Recent advances on immunohistochemistry and molecular biology for the diagnosis of adnexal sweat gland tumors. *Cancers (Basel)* 2022; **14**; 476.
2. Robson A, Greene J, Ansari N *et al*. Eccrine porocarcinoma (malignant eccrine poroma): a clinicopathologic study of 69 cases. *Am. J. Surg. Pathol.* 2001; **25**; 710–720.
3. Sekine S, Kiyono T, Ryo E *et al*. Recurrent YAP1-MAML2 and YAP1-NUTM1 fusions in poroma and porocarcinoma. *J. Clin. Invest.* 2019; **129**; 3827–3832.
4. Grosshans E, Hanau D. The infundibular adenoma: a follicular poroma with sebaceous and apocrine differentiation (author's transl). *Ann. Dermatol. Venereol.* 1981; **108**; 59–66.
5. Horenstein MG, Sandoval MP, Lo Y, Jacob J. Holocrine poroma: a distinctive adnexal tumor. *Am. J. Dermatopathol.* 2018; **40**; 401–408.
6. Harvell JD, Kerschmann RL, LeBoit PE. Eccrine or apocrine poroma? Six poromas with divergent adnexal differentiation. *Am. J. Dermatopathol.* 1996; **18**; 1–9.
7. Kazakov DV, Kutzner H, Spagnolo DV *et al*. Sebaceous differentiation in poroid neoplasms: report of 11 cases, including a case of metaplastic carcinoma associated with apocrine poroma (sarcomatoid apocrine porocarcinoma). *Am. J. Dermatopathol.* 2008; **30**; 21–26.
8. Kervarrec T, Frouin E, Collin C *et al*. Distinct regulations driving YAP1 expression loss in poroma, porocarcinoma and RB1-deficient skin carcinoma. *Histopathology* 2023; **82**; 885–898.
9. Cellier L, Perron E, Pissaloux D *et al*. Cutaneous melanocytoma with CRTC1-TRIM11 fusion: report of 5 cases resembling clear cell sarcoma. *Am. J. Surg. Pathol.* 2018; **42**; 382–391.
10. Walter BN, Huang Z, Jakobi R *et al*. Cleavage and activation of p21-activated protein kinase gamma-PAK by CPP32 (caspase 3). Effects of autophosphorylation on activity. *J. Biol. Chem.* 1998; **273**; 28733–28739.
11. Moreno-Vílchez C, Torrecilla-Vall-Llossera C, Llobera-Ris C *et al*. Poroma: a retrospective series of 80 patients at a tertiary care hospital. *Actas Dermosifiliogr.* 2023; **114**; 102–107.
12. Zhao Z, Manser E. PAK family kinases: Physiological roles and regulation. *Cell Logist.* 2012; **2**; 59–68.
13. Radu M, Lyle K, Hoeflich KP, Villamar-Cruz O, Koeppen H, Chernoff J. p21-Activated kinase 2 regulates endothelial development and function through the Bmk1/Erk5 pathway. *Mol. Cell. Biol.* 2015; **35**; 3990–4005.
14. Gao C, Ma T, Pang L, Xie R. Activation of P21-activated protein kinase 2 is an independent prognostic predictor for patients with gastric cancer. *Diagn. Pathol.* 2014; **9**; 55.
15. Liu H, Shin SH, Chen H *et al*. CDK12 and PAK2 as novel therapeutic targets for human gastric cancer. *Theranostics* 2020; **10**; 6201–6215.
16. Bensen R, Brognard J. New therapeutic opportunities for the treatment of squamous cell carcinomas: a focus on novel driver kinases. *Int. J. Mol. Sci.* 2021; **22**; 2831.
17. Cerami E, Gao J, Dogrusoz U *et al*. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2012; **2**; 401–404.
18. Thibodeau ML, Bonakdar M, Zhao E *et al*. Whole genome and whole transcriptome genomic profiling of a metastatic eccrine porocarcinoma. *NPJ Precis Oncol.* 2018; **2**; 8.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Relative expression of *EGFR* among *PAK2*-rearranged poroma and other cutaneous tumours.

Figure S2. Morphologic, immunohistochemical and molecular features of the apocrine poroma cases without folliculo-sebaceous differentiation.

