Virchows Archiv (2024) 485:749–753
https://doi.org/10.1007/s00428-024-03898-2

BRIEF REPORT

YAP1::NR4A3 and *YAP1::NCOA2* fusions in poroma: expanding the spectrum of molecular alterations in poroid tumors

Léo-Paul Secco[1] · Louis Libbrecht[1,2] · Michiel Bonny[3] · Charles Lepine[4,12] · Marián Švajdler[5] · Anne Tallet[6] · Paul-Louis Chantreau[6] · Benedicte Cormier[7] · Bernard Cribier[8,9] · Vasiliki Siozopoulou[1] · Thibault Kervarrec[9,10,11]

Received: 15 July 2024 / Revised: 30 July 2024 / Accepted: 11 August 2024 / Published online: 23 August 2024

Introduction

Poromas are benign adnexal tumors differentiating toward the upper portion of the sweat gland apparatus [1]. Four histological variants, namely hidroacanthoma simplex, classical poroma, poroid hidradenoma, and dermal duct tumors, are described [1, 2]. Although most of the poroma cases are from the eccrine type, apocrine as well as folliculo-sebaceous differentiation may be observed [1, 3]. Porocarcinoma constitutes the malignant counterpart of poroma and may be difficult to distinguish in current practice from squamous cell carcinoma [1, 4].

In 2019, Sekine et al. demonstrated the presence of recurrent *YAP1::MAML2* and *YAP1:: NUTM1* in the majority of the poromas and porocarcinomas [5]. Interestingly, *YAP1::NUTM1* fusion seems to be more prevalent in poroid hidradenoma [5, 6] and porocarcinoma [5] suggesting that the *NUTM1* part contributes to the tumor morphology and behavior as previously described for NUT ex-middle line carcinoma. More recently, our group evidenced *PAK2* fusions in poroma tumors with follicular and sebaceous differentiation [3], and a case of porocarcinoma with *YAP1::MAML3* fusion and an unusual spindle cell cytology has been described [7] suggesting again a correlation between the genetic background and tumor phenotype.

To expand the morphologic and genetic spectrum of poromas, in the present study, we report three cases of poroma tumors with distinctive morphologic features and previously undescribed *YAP1::NCOA2* or *YAP1::NR4A3* fusion transcripts.

Methods

Patients

Among the 73 cases of poromas ($n=53$) and porocarcinomas ($n=20$) registered since 01 January 2022 in consultation files of one of the authors (TK) (including 17 cases analyzed by RNA sequencing as described below), three poroma tumors with either *YAP1::NR4A3* or *YAP1::NCOA2* fusions were identified and included in the present study. The design of this study was in accordance with the requirements for the use of biological material in research

✉ Thibault Kervarrec
thibaultkervarrec@yahoo.fr

1 Department of Pathology, Cliniques Universitaires Saint-Luc, B-1200 Brussels, Belgium

2 Department of Pathology, AZ Groeninge, B-1200 Kortrijk, Belgium

3 Department of Dermatology, AZ Groeninge Kortrijk, Kortrijk, Belgium

4 Department of Pathology, University Hospital of Nantes, Nantes University, Nantes, France

5 Department of Pathology, Faculty of Medicine in Plzen, Charles University, Prague, Czech Republic

6 Platform of Somatic Tumour Molecular Genetics, Université de Tours, Centre Hospitalier Universitaire de Tours, Tours, France

7 IHP Groupe, Tours, France

8 Clinique Dermatologique, Hôpital Civil, Hôpitaux Universitaires, Université de Strasbourg, Strasbourg, France

9 CARADERM, French Network of Rare Cutaneous Cancer, Lille, France

10 Department of Pathology, University Hospital of Tours, 37044 Tours Cedex 09, France

11 "Biologie Des Infections À Polyomavirus" Team, UMR1282 INRAE, University of Tours, Tours, France

12 Immunology and New Concepts in ImmunoTherapy (INCIT), Inserm, CNRS, UMR 1302/EMR6001, Nantes, France

proposed by our institutional ethics guidelines (Local Ethics Committee in Human Research, Tours, France; No. ID RCB2009-A01056-51).

Immunohistochemistry

Immunohistochemical staining for EpCAM (Ber-EP4, Dako, 1:200), EMA (E29, Dako, 1:200), p40 (BC28, Biocare, 1:100), SOX10 (SP267, Cell Marque, prediluted), YAP1 (C-terminal part) (D8HIX, Cell Signaling, 1:200), and NUT (C52B1, Ozyme, 1:200) was performed using a VENTANA BenchMark platform according to the instructions.

RNA sequencing

Next-generation sequencing libraries were prepared with anchored multiplex PCR-based methodology using the Archer® FusionPlex® Sarcoma Panel (ArcherDX, Boulder, CO, USA). Libraries were generated according to the manufacturer's protocol using 250 ng of total RNA. Amplifiable cDNA quality was assessed using the PreSeq RNA QC assay. Final libraries were quantified on the LightCycler® 480 Instrument II, using the KAPA Library Quantification Kit (Kapa Biosystems, Roche; Wilmington, MA, USA) for Illumina (San Diego, CA, USA) Platforms. Illumina paired-end indexed libraries were sequenced 8-plex on a MiSeq with the MiSeq Reagent Kit v2 (300 cycles) from Illumina, and sequencing data were analyzed via the Archer® automated analysis pipeline.

Results

Case #1

An 8-mm skin tumor arose on a scar of the chest wall in a 74-year-old man. Histological examination revealed a superficial dermal neoplasm organized as micronodules with multiple connections to the surrounding epidermis. In the superficial part of the lesion, an intraepidermal component composed of small, monotonous poroid cells was present associated with few cuticular cells forming a duct resulting in a hidroacantoma simplex appearance (Fig. 1). The dermal component harbored numerous glands filled with an eosinophilic secretion material. Such glandular structures were composed of tall luminal cells with abundant eosinophilic cytoplasms and evidence of decapitation secretion. Such population was surrounded by poroid cells with frequent nuclear pseudoinclusions.

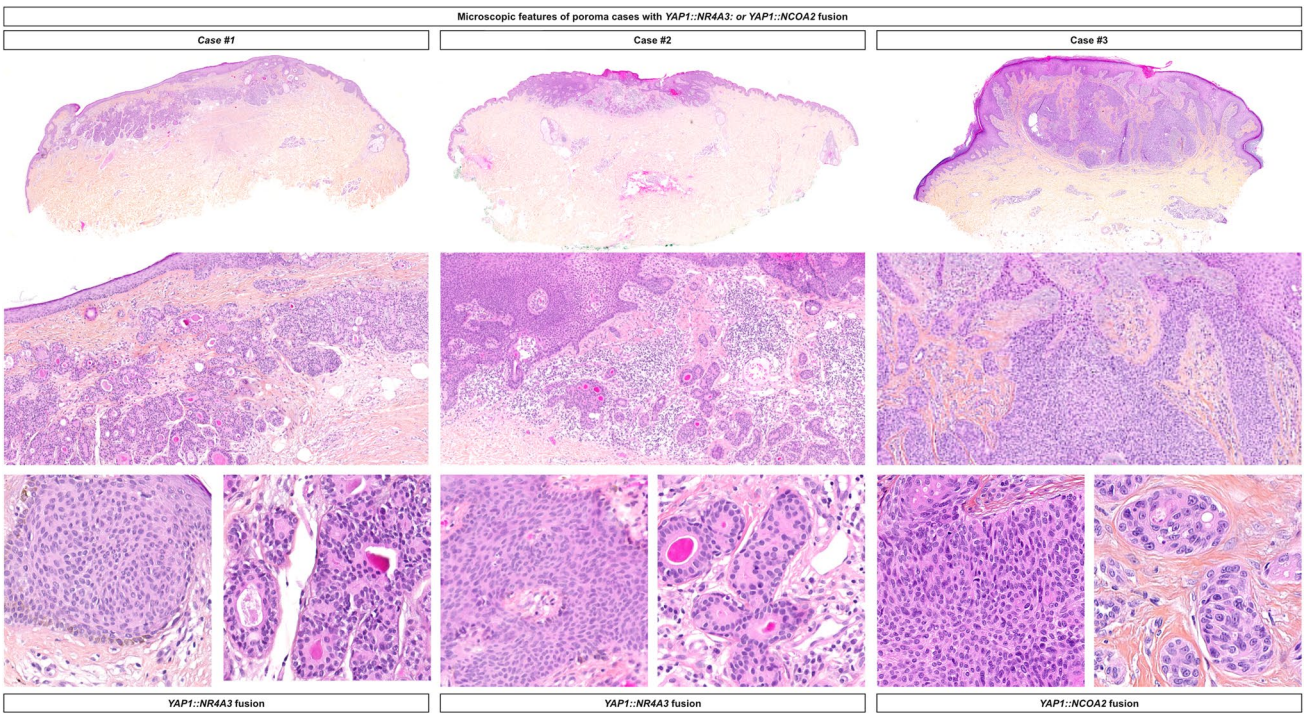

Fig. 1 Microscopic feature of *YAP1::NR4A3 and YAP1::NCOA2* rearranged poromas. Microscopic examination revealed well-demarcated tumors with multiple connections with the epidermis, harboring a biphasic appearance. In the superficial portion, the neoplasm was composed of small poroid cells and large eosinophilic cuticular cells forming ducts. Micronodules containing numerous glandular formations were present in the deepest part

Neither cytologic atypia nor mitotic activity was observed. Immunohistochemical staining with EMA and CEA highlighted the presence of ducts and glands, YAP1 (C-terminal extremity) expression was lost suggesting a rearrangement of the *YAP1* gene, while no NUT positivity was detected. The molecular analysis evidenced a *YAP1* (exon 4)::*NR4A3* (exon 3) fusion (Fig. 2).

Case #2

This 10-mm diameter neoplasm was excised from the back of a 33-year-old woman. This specimen consisted of a superficial biphasic tumor proliferation located in the superficial dermis (Fig. 1). The upper part of the tumor harbored a classical poroma appearance with interconnected strands of

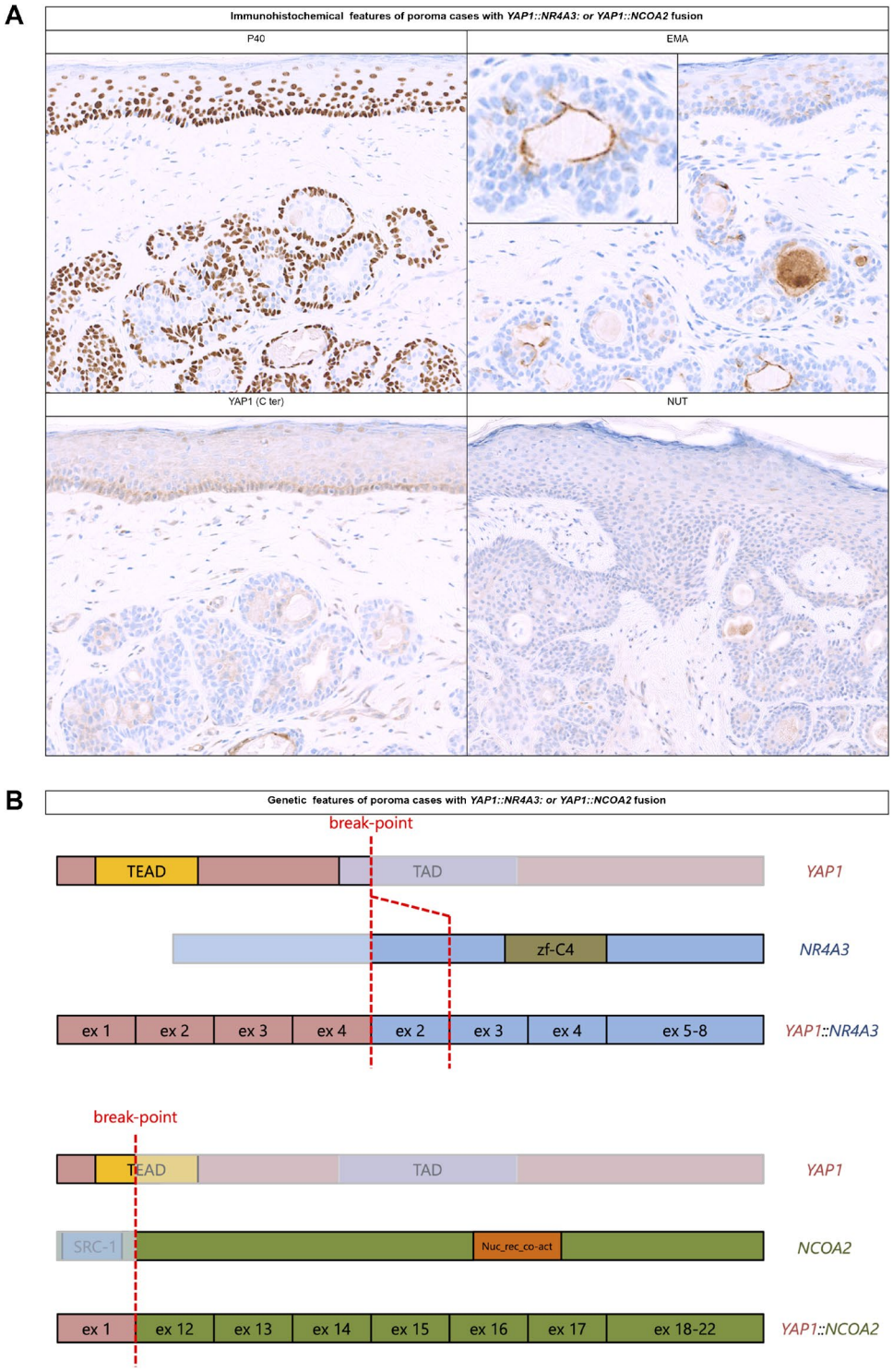

Fig. 2 Immunohistochemical and genetic features of the cases. **A** Immunohistochemical features. Case #2 is depicted. Immunohistochemical investigation of the case confirmed the presence of ducts and glands highlighted by EMA. P40 was diffusely positive excepted in the glandular component. The lack of YAP1 (C terminal) expression suggested a rearrangement of the *YAP1* gene. No NUT expression was observed. **B** Schematic representation of the *YAP1::NR4A3* and *YAP1::NCOA2* fusion transcripts

poroid cells and few melanin deposits. In the deepest part, the neoplasm was organized as micronodules harboring prominent glandular formations filled by an eosinophilic material. Immunohistochemical investigation confirmed the presence of ducts and glandular structures highlighted by CEA and EMA (Fig. 2). Loss of YAP1 (C-terminal extremity) expression was observed, while no NUT positivity was detected. Accordingly, next-generation sequencing revealed a *YAP1* (exon 4)::*NR4A3* (exon 2) fusion (Fig. 2).

Case #3

This neoplasm arose as a 6-mm nodule located on the back of the left foot. Microscopic examination of the case revealed a well-demarcated tumor with multiple connections with the epidermis harboring a solid growth pattern as observed in classical poroma but also in the deepest part a micronodular architecture similar to the one observed in dermal duct tumor (Fig. 1). The tumor was composed of small poroid cells with scant cytoplasm and round nucleus associated with large eosinophilic cuticular cells forming ducts but also glands with focal decapitation secretion. Few degenerative cytological atypia and rare multinucleated tumor cells were present. No sebaceous or follicular differentiation was observed. Immunohistochemical characterization of the case demonstrated heterogeneous expression of EpCAM (Ber-EP4) and EMA. Moreover, YAP1 (C-terminal part) expression was lost, while no positivity was observed for NUT suggesting again a *YAP1* gene rearrangement with another partner than *NUTM1*. Accordingly, molecular investigation evidenced a *YAP1 (exon 1)::NCOA2 (exon 12)* fusion (Fig. 2).

Discussion

In the present article, we reported the detection of *YAP1::NR4A3* and *YAP1::NCOA2* fusion transcripts in a rare morphologic variant of poromas.

Description of new alterations in poroid tumors might contribute to improve our understanding of poroma physiopathology. Indeed, it is clearly established in in vitro and also in mice models that *YAP1* fusions result in the activation of the YAP1 protein that acts together with TAZ and TEAD factors to promote cell proliferation (reviewed in [1]). However, to which extent the fusion partner impacts tumor biology remains to be determined. *NR4A3* and *NCOA2* are genes encoding for nuclear receptors and involved in oncogenic fusions in several tumor entities. Notably, *NCOA2* rearrangements are observed in rhabdomyosarcoma [8], while *NR4A3* fusions are detected in acinic cell carcinoma [9], extraskeletal myxoid chondrosarcoma [10], and gynecologic leiomyosarcoma [11], *NR4A3* being even proposed as a therapeutic target in this context [12]. In *GREB1*-rearranged uterine sarcomas with variable sex-cord differentiation, a rare gynecologic tumor, mutually exclusive *GREB1* gene rearrangements with either *NCOA2* or *NR4A3* are observed [13] suggesting an overlap in the biological behavior of these two proteins at least in a context of gene fusions.

Accordingly, in this article, we reported three cases of poroma tumors harboring either *YAP1::NR4A3* or *YAP1::NCOA2* fusions and specific morphologic features. Indeed, although four histologic variants of poroma are described depending on the tumor location (epidermis or dermis) and architecture, the association of several patterns may be observed in one specimen [14]. Moreover, although most of the specimen harbor eccrine differentiation, apocrine as well as folliculosebaceous differentiation [3] may also be detected in some cases [14]. Interestingly, the three tumors presented in this article harbored a biphasic appearance with a superficial component of classical poroma or hidroacantoma simplex, while the deepest portion harbored unusual micronodular growth pattern with reminiscence of thus observed in dermal duct tumors as well as numerous glandular formations harboring apocrine differentiation. In the two specimens with *YAP1::NR4A3* fusion, such glands were filled with an eosinophilic secretion material. Interestingly, by investigating a large series of 384 poroid neoplasms, Ito et al. suggested that apocrine differentiation was more frequently observed in composite tumors than in the others [14], especially the one combining a dermal duct component together with poroma or hidroacanthoma simplex. Thus, it is possible that such composite specimens harboring dermal duct component and apocrine differentiation are enriched in *YAP1::NR4A3* or *YAP1::NCOA2* fusions.

To note, although the distinction between *YAP1::NR4A3* and *YAP1::NCOA2* rearranged tumors and other poromas has no impact for the patients, these findings may be of interest for the distinction between porocarcinoma and poorly differentiated non-keratinizing squamous cell carcinoma [1]. Indeed, it is well established that porocarcinoma may arise from poroma [1, 4], these two neoplasms sharing the same oncogenic drivers mostly fusion genes [1, 4], while secondary genetic events contribute to the progression. In this context, identification in a malignant tumor of a fusion gene previously detected in poroma would constitute a strong argument in favor of a porocarcinoma.

In addition, it is possible that among poroid tumors, characterization of the initial oncogenic driver has some prognostic values. Indeed, a higher incidence of *YAP1::NUTM1* over *YAP1::MAML2* fusion transcripts has been reported in porocarcinoma and might suggest a distinct potential of transformation depending on the *YAP1* partners [5]. Accordingly, the recent description of *PAK1/2/3* fusions in a subset of porocarcinomas with frequent metastatic spreading [15] when compared to *YAP1*-fused cases also supports the view of distinct behaviors depending on the genetic backgrounds.

Overall, it is possible that, in porocarcinomas, characterization of the oncogenic driver might help to define the prognosis of the tumor and may even contribute to develop new therapeutic options [12].

To conclude, we report the detection of *YAP1::NR4A3* and *YAP1::NCOA2* fusions in a variant of poroma morphologically characterized by composite patterns combining poroma/hidroacanthoma simplex together with dermal duct tumor and prominent glandular differentiation.

Author contribution LPS, LL, and TK performed study concept and design; LPS, LL, TK, AT, and VS performed development of methodology and writing, review, and revision of the paper; MN, CL, MS, AT, PLC, BCor, and BCri provided acquisition, analysis and interpretation of data, and statistical analysis. All authors read and approved the final paper.

Data availability Not applicable.

Declarations

Ethics approval The local Ethics Committee in Human Research of Tours (France) approved the study (no. ID RCB2009-A01056-51).

Conflict of interest The authors declare no competing interests.

References

1. Kervarrec T, Pissaloux D, Tirode F et al (2024) Gene fusions in poroma, porocarcinoma and related adnexal skin tumours: an update. Histopathology 84:266–278
2. Kervarrec T, Sohier P, Pissaloux D et al (2023) Genetics of adnexal tumors: an update. Ann Dermatol Venereol 150:202–207
3. Kervarrec T, Pissaloux D, Paindavoine S et al (2023) Recurrent PAK2 rearrangements in poroma with folliculo-sebaceous differentiation. Histopathology 83:310–319
4. Robson A, Greene J, Ansari N et al (2001) Eccrine porocarcinoma (malignant eccrine poroma): a clinicopathologic study of 69 cases. Am J Surg Pathol 25:710–720
5. Sekine S, Kiyono T, Ryo E et al (2019) Recurrent YAP1-MAML2 and YAP1-NUTM1 fusions in poroma and porocarcinoma. J Clin Invest 129:3827–3832
6. Macagno N, Kervarrec T, Sohier P et al (2021) NUT is a specific immunohistochemical marker for the diagnosis of YAP1-NUTM1-rearranged cutaneous poroid neoplasms. Am J Surg Pathol 45(9):1221–7
7. Li P, Busam KJ (2023) Spindle cell porocarcinoma with a novel YAP1::MAML3 fusion. J Cutan Pathol 51:226–229
8. Watson S, LaVigne CA, Xu L et al (2023) VGLL2-NCOA2 leverages developmental programs for pediatric sarcomagenesis. Cell Rep 42:112013
9. Lee DY, Brayer KJ, Mitani Y et al (2020) Oncogenic orphan nuclear receptor NR4A3 interacts and cooperates with MYB in acinic cell carcinoma. Cancers 12:2433
10. Wilbur HC, Robinson DR, Wu Y-M et al (2022) Identification of novel PGR-NR4A3 fusion in extraskeletal myxoid chondrosarcoma and resultant patient benefit from tamoxifen therapy. JCO Precis Oncol 6:e2200039
11. Momeni-Boroujeni A, Mullaney K, DiNapoli SE et al (2024) Expanding the spectrum of NR4A3 fusion-positive gynecologic leiomyosarcomas. Mod Pathol Off J U S Can Acad Pathol Inc 37:100474
12. Safe S, Karki K (2021) The paradoxical roles of orphan nuclear receptor 4A (NR4A) in cancer. Mol Cancer Res MCR 19:180–191
13. Lee C-H, Kao Y-C, Lee W-R et al (2019) Clinicopathologic characterization of GREB1-rearranged uterine sarcomas with variable sex-cord differentiation. Am J Surg Pathol 43:928–942
14. Ito K, Ansai S-I, Fukumoto T et al (2017) Clinicopathological analysis of 384 cases of poroid neoplasms including 98 cases of apocrine type cases. J Dermatol 44:327–334
15. Kervarrec T, Westphal D, Pissaloux D et al (2024) Porocarcinomas with PAK1/2/3 fusions: a series of 12 cases. Histopathology