SHORT COMMUNICATION

YAP1-NUTM1 Gene Fusion in Eccrine Porocarcinoma with Late Metastatic Recurrence: A Case Report

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Eccrine porocarcinoma (EPC) is a rare malignant neoplasm that arises from the intraepidermal part of the sweat duct gland and frequently manifests as a solitary nodule or plaque on the limbs or the head and neck area in elderly patients (1, 2). EPCs exhibit invasive growth and may have high morbidity and mortality potential (1, 2). Because of its low incidence, lack of distinct clinical features, variable histomorphological appearance, and absence of specific immunohistochemical methods, EPC diagnosis is often challenging (1–4). Recently, highly recurrent *YAP1* and *NUTM1* gene rearrangements have been described in cases of poromas and EPCs, highlighting the potential usefulness of immunohistochemical and molecular studies in the diagnosis of these neoplasms (3).

CASE REPORT

Clinical history. An otherwise healthy 51-year-old woman was referred to the department of Dermatology for evaluation of a 3-month history of enlarged and swollen lymph nodes on her right groin. Past medical history included the diagnosis of an EPC on the right popliteal fossa that was completely excised 15 years previously (at this time, a sentinel lymph node biopsy was not considered), with no signs of locoregional recurrence after a 10-year clinical follow-up period (**Fig.** 1a–b). Physical examination disclosed several tender erythematous subcutaneous nodules located on the right groin corresponding to enlarged lymph nodes. The rest of the physical examination, including a complete gynaecological and pelvic examination, was unremarkable, and no signs of local recurrence were detected in the postsurgical scar on the right popliteal area.

Histological, immunohistochemical and fluorescence in situ *hybridization findings.* A core-needle biopsy was obtained and the observed histopathological features were diagnosed as consistent with diffuse infiltration by moderately-differentiated squamous cell carcinoma (SCC). A positron emission tomography-computed tomography ruled out visceral involvement and no other hypermetabolic foci were detected. An inguinal lymphadenectomy was performed, and histopathological examination showed a diffuse lymph node infiltration by large pleomorphic round and oval cells arranged in groups and lobules with capsular rupture in 2 out of 6 lymph nodes removed (Fig. 1c, d). These malignant cells expressed the immunohistochemical markers cytokeratin AE1/AE3 and epithelial membrane antigen (EMA). YAP (C-terminus) and NUT immunohistochemistry were also performed on both the original EPC cutaneous specimen and the lymph node sample. The same results were observed in both specimens: a diffuse strong nuclear positivity for NUT, along with a total loss of YAP1 expression, which was consistent with the presence of an underlying YAP1-NUTM1 translocation (Fig. 1e). The fluorescence in situ hybridization (FISH) analysis confirmed the YAP1 gene rearrangement (Fig. 1f).

Treatment and follow-up. With the diagnosis of surgically resected metastatic EPC, and based on a multidisciplinary tumour board decision, adjuvant radiotherapy on inguinal region was recommended and the patient is currently undergoing a close clinical and imaging surveillance every 3 months.

DISCUSSION

New molecular pathways involved in the pathogenesis of poroid neoplasms have been described recently (3, 5–7). Thus, cytogenetic translocations involving *YAP1*, specifically the *YAP1-MAML2* and *YAP1-NUTM1* fusions, have been identified in approximately 89% of poromas and 64% of EPCs (3). The tumorigenic role of *YAP1* fusions might be explained by the activation of transcription factors and promotion of anchorage-independent growth in epithelial cells (3). Such genomic rearrangements seem to be specific of poromas and EPCs, since *YAP1* fusions have not been identified in other skin neoplasms (3). The current patient, to our knowledge, represents the first description of *YAP1-NUTM1* fusion in a metastatic EPC, demonstrating the presence of the genetic rearrangement in both the primary tumour and its metastasis. As in the current patient, the detection of a *YAP1-NUTM1* gene fusion in cases of metastatic lymph node involvement from a malignant neoplasm with unknown origin favours the poroid nature of the primary tumour.

The demonstration of specific molecular rearrangements in poroid neoplasms also represents a diagnostic opportunity to use immunochemistry as a useful diagnostic tool for these neoplasms. Thereby, recent studies have postulated that NUT immunohistochemistry might be considered as a potential histological marker of poromas and EPCs, since NUT would be overexpressed in *YAP1-NUTM1*-rearranged tumours (3, 5, 8). In this sense, it has been shown that this marker could have a high specificity (close to 100%) in the diagnosis of poroid neoplasms, since other skin tumours (including histological mimics of EPC, such as SCC or hidradenocarcinoma) do not express NUT (5, 8). Therefore, and given the high degree of concordance between the molecular and immunohistochemical results found in recent investigations (3, 5), NUT immunohistochemistry may represent a simpler, faster and more accessible technique than the molecular approach to better characterize EPC cases.

EPC represents a cutaneous neoplasm with high rates of extracutaneous spread. It has been demonstrated that

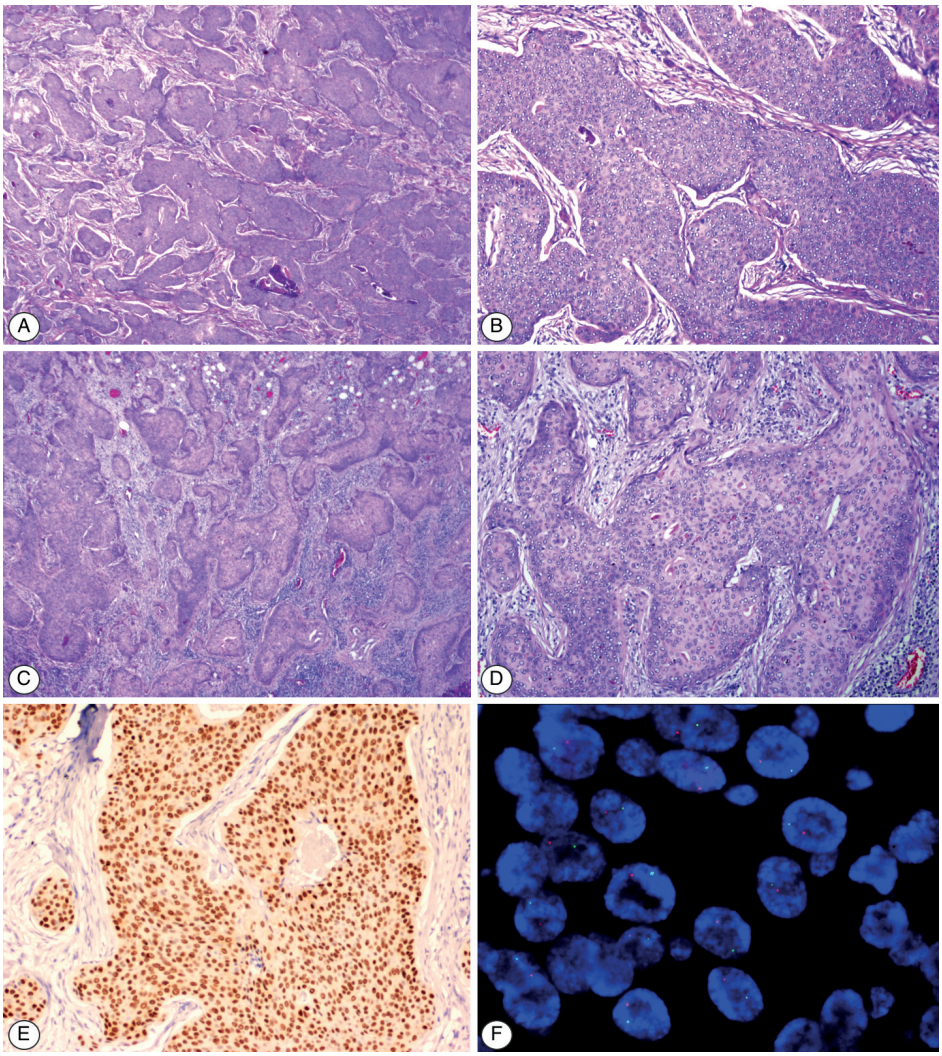

Fig. 1. (A–B) Histopathological examination of the primary eccrine porocarcinoma. (A) Low-power photomicrograph of haematoxylin and eosin (H&E)-stained tissue profile demonstrating a multilobulated malignant neoplasm with solid nests and anastomosing bands invading the dermis. The primary tumour measured 20 mm in diameter, with a depth of 10mm, and no perineural/vascular invasion or squamous/sarcomatoid differentiation was noted (original magnification, ×4). (B) Higher magnification showing the round-to-ovoid basaloid cells with pale eosinophilic cytoplasm, prominent nucleoli, and some mitotic figures (H&E, original magnification, ×20). (C–D) Histopathological examination of the lymph node metastasis. (C) Wide anatomical cords and nests of polygonal basaloid cells with asymmetrical invasion of the stroma (H&E, original magnification, ×4). (D) Closer view demonstrating the morphological similarity between the neoplastic cells within the lymph node and the primary tumour (H&E, original magnification, ×20). (E) NUT immunohistochemical stain showing strong diffuse nuclear positivity in lesional cells with no expression in the surrounding non-neoplastic cells (original magnification, ×20). (F) Fluorescence *in situ* hybridization analysis demonstrating the separate red and green signals indicating the YAP1 gene rearrangement and loss of fusion signal (YAP1 non-rearranged allele copy).

22.3% of EPC cases present as metastatic disease at the time of diagnosis, including regional lymph node (17%), distant (3.9%) and cutaneous metastases (1.5%) (1). Overall survival of patients with metastatic EPC has not been well characterized, but is probably poor (9). Moreover, the time from EPC diagnosis until the development of metastases is variable, but in most cases it has been estimated to be less than 1 year (1). Nevertheless, the present case demonstrates that late metastases could develop in EPC cases. Therefore, a long-term follow-up, with regular skin and lymph node examination, seems advisable for this malignancy.

Given its low incidence, little guidance is available in the literature regarding EPC management. For local disease, surgical resection represents the main treatment and may include wide local excision or Mohs micrographic surgery (10). Sentinel lymph node biopsy should also be considered in EPC cases exhibiting high-risk features (1). Systemic treatment of unresectable metastatic EPC has not been established, and several therapeutic regimens have been postulated in different case reports with variable results (radiotherapy, chemotherapy-based regimens, cetuximab, anti-PD1 agents, among others) (9, 11). The identification of the presence of *YAP1* fusions in EPC cases might also have therapeutic implications, representing a potential therapeutic target for this rare malignancy.

In conclusion, we present here a unique case of an aggressive EPC that developed regional lymph node metastasis after 15 years from the treatment of the primary tumour, in which the immunohistochemical pattern and FISH results were consistent with a *YAP1-NUTM1* rearrangement. A better understanding of the molecular pathways involved in the development of these neoplasms would help not only to improve the characterization and diagnosis of EPC cases, but also to the development of targeted therapies in the era of personalized medicine.

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