

Case Report

Intergluteal Cleft Eccrine Porocarcinoma with Metastasis to Inguinal Region and Lung: Case Report and Review of the Literature

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Keywords

Intergluteal cleft · Eccrine porocarcinoma · Metastasis · Chemotherapy

Abstract

Eccrine porocarcinoma (EPC) is an infrequent cutaneous neoplasm, and was described in 1963 by Pinkus and Mehregan. It is a rare type of skin tumor (0.005–0.01% of all skin tumors). Less than 300 cases have been described in the entire world medical literature. To our knowledge, no case of intergluteal cleft EPC has been reported in the literature in English and Spanish to date, so this would be the first reported case of such pathology. Metastatic EPC is less frequent, since only <10% of metastatic type have been reported and the rest as localized disease. The primary treatment of choice is surgical wide local excision of the tumor with histological confirmation of tumor-free margins. Prognosis is difficult to determine because of the rarity of EPC and the variations in natural history. There are no data to support the use of adjuvant chemotherapy or radiotherapy, and there are currently no agreed criteria to define patients at high risk of relapse. We present a 67-year-old man with intergluteal cleft eccrine tumor by biopsy. Metastasis to left inguinal region and lung was reported by contrasted abdominal and chest computed tomography. He started chemotherapy based on etoposide, vincristine, carboplatin. A review of pertinent literature is provided.

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Introduction

Eccrine porocarcinoma (EPC) is an infrequent cutaneous neoplasm, which derives from the eccrine sweat glands and was described in 1963 by Pinkus and Mehregan [1]. It is a rare type of skin tumor (0.005–0.01% of all skin tumors). It is located more frequently in the lower extremities (44%), other common sites are the trunk (24%) and head (18%) in elderly patients with a slight predominance in women [2, 3]. This tumor can appear de novo or as a progression of a benign poroma, of very slow growth in its onset that after its malignancy, its behavior is aggressive, with rapid growth. Macroscopically, EPC can appear as a nodule, a polypoid ulcerating lesion, or a plaque with an infiltrative or erosive pattern [2, 4].

Less than 300 cases have been described in the entire world medical literature, with incidence being rare in Europe. 20% of these tumors recur, 10% metastasize to solid organs and 20% to regional lymph nodes and can have epidermotropic pagetoid diffusion, with a mortality rate of almost 70% in the latter [2, 5, 6].

The treatment of this type of tumor has been through extensive surgical excision, Mohs surgery, or radiotherapy. Surgical treatment is curative in 80% of non-metastatic cases [7, 8]. Chemotherapy is reserved for the treatment of metastatic EPC, there are no standard protocols, and there are varying degrees of response [9, 10]. The radiation is of little benefit, leaving for palliative care since the response is partial. The role of sentinel lymph node biopsy is unknown, and prophylactic lymphadenectomy is controversial [11].

To the best of our knowledge, no cases of intergluteal cleft EPC have been reported in the English-language literature to date. We report a new rare case of a 67-year-old man affected by an intergluteal cleft EPC, with inguinal and lung metastasis. We discuss the clinical presentation and the histopathological findings and review the literature.

Case Report

A 67-year-old man presented with a mass on the intergluteal cleft and lymphadenopathy in both inguinal regions. There was no history of pain, fever, malaise, nausea, vomiting, constipation, bloody diarrhea, or abdominal distension. Past medical history included Systemic arterial hypertension in treatment. He first noticed it 1 year before and it had progressively increased in size to 2.5 × 2.5 cm. The mass was soft, non-tender, and freely mobile in the subcutaneous tissue with normal-appearing overlying skin. Examination revealed bilateral inguinal lymphadenopathy (right of 1 cm and a ganglionic conglomerates of 4.5 × 7 cm in left inguinal region). Mohs surgery was performed, and a tumor and ganglion biopsy was taken, histopathological examination revealed high-grade malignancy of primary cutaneous appendages of skin with basaloid differentiation of squamous cells, glandular and alveolar tubule, in some areas myxoid degeneration, microcalcifications, lymphatic and vascular permeation; the tumor was less than 1 mm from the edges of the section and from the surgical bed and ganglion right inguinal lymphatic with metastasis of malignant neoplasm mixed with high skin grade (Fig.1 and 2).

An abdominal computed tomography (CT) with intravenous contrast was performed in which a solid tumor lesion in intergluteal cleft of 2.3 cm, as well as a giant adenopathy in left inguinal region (4.5 cm conglomerate) was reported. Contrast chest CT reported bilateral pulmonary nodules (right 6.4 mm and left basal 1.1 cm) and bilateral axillary and cervical adenopathies. The diagnosis was EPC with areas of epidermoid, basal cell and sebaceous differentiation. No perineural lymphatic invasion, lymph node with carcinoma metastasis (Fig.1 and 2). He started chemotherapy based on etoposide, vincristine, carboplatin.

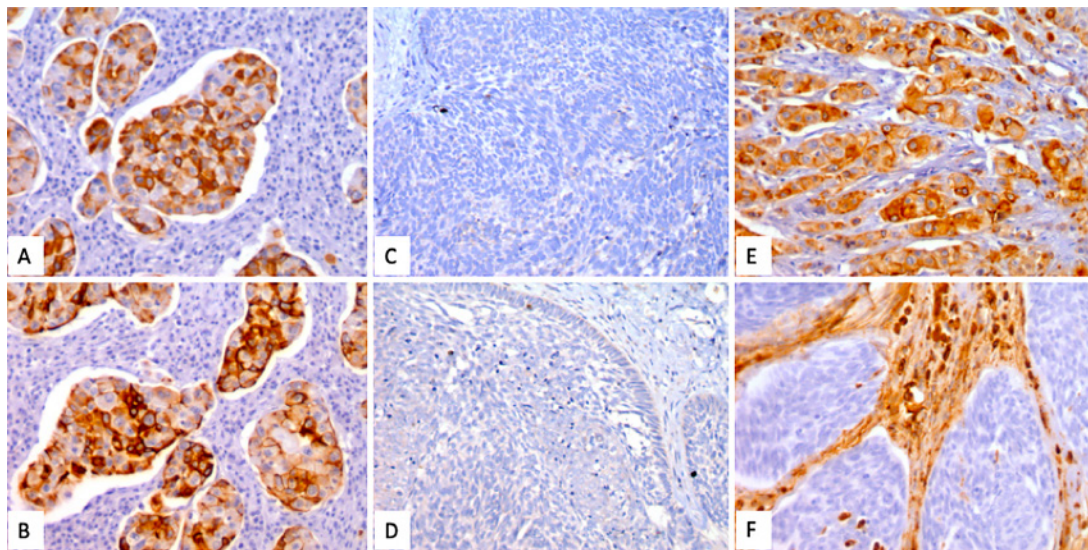
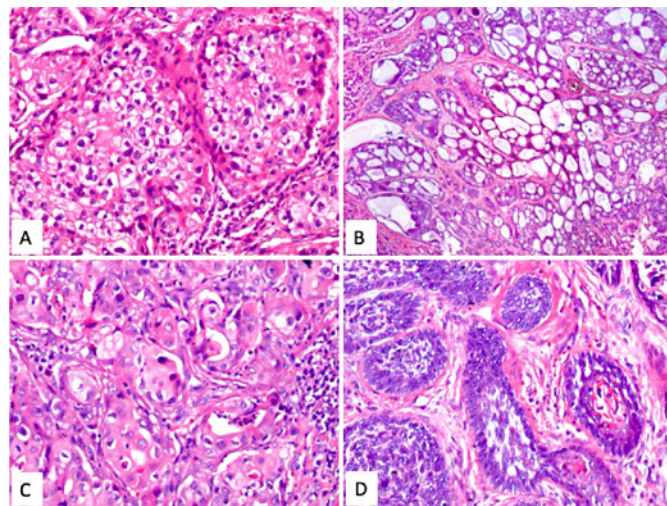


Fig. 1. Immunohistochemistry: In spite of the different morphologies, most of the cells showed reactivity to immunostains with AE1/3, CK7 (A) and CK19 (B), which confirms their epithelial lineage. The spindle cell areas were negative for vimentin (E, F), which only marked the accompanying stroma. Chromogranin (C) and synaptophysin (D) were also negative.

Fig. 2. Hematoxylin & eosin: Some of the tumoral nests show clearing of the cytoplasm, with a foamy appearance and with small vacuolar formations. (A) The zones with eccrine differentiation (B) show ductular formation with mucoid content. Other areas exhibit squamous differentiation (C), whose cells are large, with broad and eosinophilic cytoplasm. Histologically, the neoplasm is heterogeneous, composed predominantly of compact nests of small, basaloid cells (D) with scant cytoplasm; some of these cells displayed mild spindling.



Discussion

EPC, also known as malignant eccrine poroma, forms in the intraepidermal ductal portion of the sweat gland and was first described by Pinkus and Mehregan in 1963, who used the term epidermotropic eccrine carcinoma as the tumor arises from the intraepidermal portion of the eccrine sweat glands [1]. The term EPC was introduced by Mishima and Morioka in 1969, since then fewer than 300 EPC cases have been reported worldwide [2, 5, 12]. This rare malignant adnexal tumor has been termed as malignant hidroacanthoma simplex, malignant intra epithelial eccrine poroma, eccrine poroepithelioma, malignant syringoacanthoma, dysplastic poroma, and sweat gland carcinoma [13–15].

It is a rare tumor, representing only 0.005–0.01% of all malignant epithelial neoplasms. However Goon et al. [16] showed that EPC diagnosis, although rare, has been rising in the East of England, and has risen rapidly over the last 10 years, possibly due to histological diagnostic factors, and more precise registration together with a possible real increase in incidence [2, 4].

The majority of the patients are older, with a peak incidence at 67 years of age (mean age 74 years), but it can affect children or young adults. Although it does not seem to have a predilection for sex or race, some studies indicate a slight prevalence in women. The exact etiology of EPC is unclear. Some authors suggested a possible association with radiation exposure and immunosuppression, although an excessive sun exposure does not seem to be a significant risk factor [17–19].

EPC arises most commonly (33–50%) on the lower extremities, but can also be found in other cases series in 18%, followed by the trunk (14.7–24%), head and neck (23–32%), upper extremities (7.4–11%), genitalia/buttocks (<11%), and rarely involves other areas (e.g., scalp <5%, lips, mandible, nose, occiput, parietal, parieto-occipital, preauricular, temporomandibular, temporoparietal, crus, thorax, flank, breast, axilla, finger, hand, palm, shoulder, calf, heel, knee, sole, tibia, toe, mons pubis, prepuce, penis, scrotum, inguinal, vulva, etc.) [2, 4, 5, 8, 13, 15, 18–58].

In Mexico, Riera-Leal et al. [4], reported 33 cases, the most frequent localization was the head (37%), followed by the trunk (30%), upper extremities (15%), lower extremities (18%). As to the clinical form, the most frequently observed was nodular (46%), followed by exophytic tumor (21%). This contrasts with reports from other authors, who mention that polypoid or ulcerated tumors were the most common form. Other reported forms of presentation include verrucous plaque similar to a cauliflower, firm erythematous-violaceous nodule, zosteriform variant, such as reticulated erythema, carcinomatous lymphangitis with lymphedema and mimicking a venous leg ulcer [21, 59, 60].

The size can also vary from less than 1 cm to up to 10 cm in diameter, with a 2.4 cm average [4, 34]. The low degree of clinical suspicion of EPC could be due to the low incidence rate, non-specific macroscopic appearance, and vague dermoscopic pattern of neovascularization. As a result, the diagnosis and appropriate treatment are often delayed, thereby providing time for the cancer to spread throughout the body, with lethal consequences [61]. Histopathologically, metastatic adenocarcinoma, trabecular carcinoma, Merkel cell carcinoma, benign nevi, warts, angiomas, clear cell hidradenocarcinoma, basal cell carcinoma, squamous cell carcinoma, seborrheic keratosis, amelanotic melanoma, and verruca vulgaris should be considered as some of the differential diagnoses. Later, as their growth accelerates, these lesions are submitted to biopsy to reveal the correct diagnosis [2, 4, 5, 18–20, 60–62].

EPCs are histologically diverse; however, common characteristics on hematoxylin & eosin staining include nuclear atypia, increased mitotic activity, and necrosis [20, 63]. From the histopathological point of view, the tumor is characterized by pleomorphic cells with nuclear hyperchromasia and important mitotic activity, surrounded by ductal lumen. It can be intraepidermal, an in situ variation, grows horizontally, and produces an extensive pagetoid infiltrate. This epidermotropic or intraepidermal type has been reported to have local recurrences. The invasive dermal type usually presents as nodular aggregates associated with a broad deep margin pushing down into the dermis (pushing type) or with an infiltrative growth pattern (infiltrative type) [64]. Immunohistochemical stains used for the diagnosis of EPC include carcinoembryonic antigen, cytokeratin (CK) (pan-CK and CK5/6), epithelial membrane antigen, p53, and p63 [12, 65]. In addition, a recent study by Mahalingam et al. [65] showed that the diagnostic sensitivity and specificity for EPC significantly improved by using a selected panel of stains including CK7, CK19 (specificity, 82%), and nestin. Little is known about metastatic cutaneous adnexal neoplasms, but it seems that p63 continues to be

Table 1. Eccrine carcinoma pathological stages

Eccrine carcinoma pathological stages (pTNM)
pTX: Primary tumor not assessable
pT0: No evidence of primary tumor
pTis: Carcinoma in situ
pT1: Tumor 2 cm or less in the largest dimension
– pT1a: Limited to the dermis or 2 mm or less in thickness
– pT1b: Limited to the dermis and more than 2 mm in thickness, but not more than 6 mm in thickness
– pT1c: Invading the subcutis and/or more than 6 mm in thickness
pT2: Tumor greater than 2 cm but not more than 5 cm in its greatest dimension
– pT2a: Limited to the dermis or 2 mm or less in thickness
– pT2b: Limited to the dermis and more than 2 mm in thickness but not more than 6 mm in thickness
– pT2c: Invading the subcutis and/or more than 6 mm in thickness
pT3: Tumor over 5 cm in its greatest dimension
– pT3a: Limited to the dermis or 2 mm or less in thickness
– pT3b: Limited to the dermis and more than 2 mm in thickness, but not more than 6 mm in thickness
– pT3c: Invading the subcutis and/or more than 6 mm in thickness
pT4: Tumor invades the deep extradermal tissue (e.g., cartilage, skeletal muscle, bone)
– pT4a: 6 mm or less in thickness
– pT4b: More than 6 mm in thickness
Regional lymph nodes (pN)
– pNX: Regional lymph nodes not assessable
– pN0: No regional lymph node metastasis
– pN1: Regional lymph node metastasis
Distant metastasis (pM)
– pMX: Presence of distant metastasis not assessable
– pM1: Distant metastasis

expressed in these tumors, thus making their histological differentiation from metastatic adenocarcinomas to the skin potentially easier [66]. Expression of p53 protein may have a role in the carcinogenesis of EPC. The time to malignant transformation of a benign poroma is highly variable and can range from months to decades. A long period of clinical history is often encountered (up to 50 years), but rapid development within few months has also been reported [67].

Radiology may be useful for surgical planning and evaluation of regional or distant metastasis, including the detection of occult metastases. Ultrasound, CT, or magnetic resonance imaging of the regional lymph node basins should be considered for primary tumors on the trunk, extremities, and genitalia. PET (positron emission tomography)/CT scan might be considered in these patients. In addition, a mitotic index of more than 14 mitotic cells per 10 high-power fields, lymphovascular invasion, and a tumor depth exceeding 7 mm and poorly differentiated tumor may suggest the need for diagnostic imaging and often predict a worse prognosis [20, 65].

An interesting detail is the fact that certain clinical data have been reported as suggestive of poor prognosis, such as presence of ulceration, sudden growth in a few months, spontaneous bleeding, pain, multinodularity, and pruritis. Organ spreading is only found occasionally, but with a very poor prognosis [68].

Invasive porocarcinoma shows extensive growth of cords or bands of polygonal tumorous cells with pleomorphic nuclei that proliferate asymmetrically inside the dermis with a large quantity of mitotic figures and necrotic areas with multiple ductal structures (90%). EPC often takes an aggressive clinical course. When invasive porocarcinoma affects the lymphatic

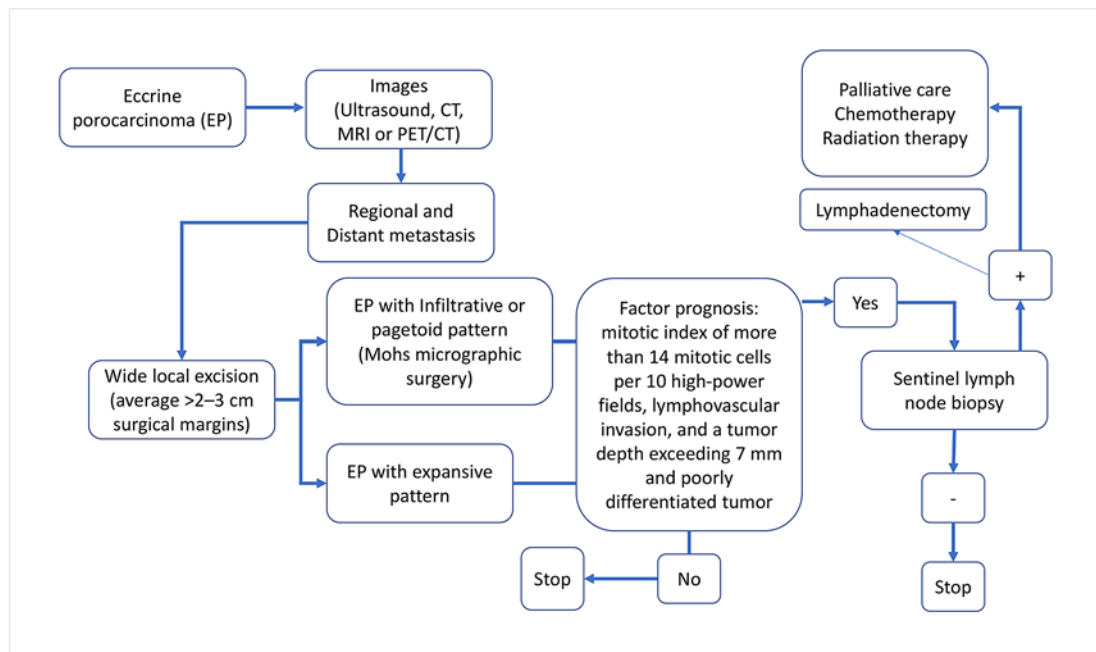


Fig. 3. Diagnostic and treatment algorithm followed in the series presented and based on the literature reviewed.

vessels, it reinvades the epidermis, which would explain the cutaneous metastasis, with a 20% rate of local recurrence, whereas distant metastasis occurs in approximately 10%. This lymphatic vessel invasion is rare, reported as present only in 15–20% of the cases however in patients with lymph node metastases, the mortality rate is high at 67%. The incidence of widespread cutaneous metastasis is unknown. According to other authors, this feature is unusual, and only 9 well-described case reports have been published. Multiple cutaneous metastases may develop or less commonly metastases occur in lung, retro-peritoneum, bone, liver, breast, bladder, peritoneum, or ovary [2, 5, 6, 9, 10, 18, 61, 69–74]. For eccrine carcinoma staging, see Table 1.

Treatment

According to what is reported in the literature, the diagnostic and treatment approach of EPC should be as shown in Figure 3.

The treatment of choice for a confirmed EPC is a wide local excision of the primary tumor, with curative rates from 70 to 80% of cases. Wide local excision (average >2–3 cm surgical margins) has been shown to have a 20% local recurrence rate, despite confirmation of clear margins from the primary excision [18, 75–80]. In cases of more infiltrative carcinoma, surgical resection should be performed with histological confirmation of the tumor-free margins by micrographic control of surgical margins, for example Mohs micrographic surgery. However, the size of the margins has not been clearly elucidated [7, 76, 81–83].

Sentinel lymph node sampling is controversial but may be helpful for prognosis in cases of thick tumors or with high mitotic rates. Thus, sentinel lymph node biopsy is recommended only in special cases such as those with aggressive tumor types, associated lymphadenopathy, or a depth of over 7 mm. Some authors have also advocated elective lymphadenectomy, but its clinical value remains controversial. Only radical lymphadenectomy of the affected territory will be performed if the sentinel lymph node biopsy is positive [2, 68, 83–87].

Table 2. General characteristics, treatment (surgical resection, radiation therapy, and chemotherapy), objective response, or global survival of metastatic EPC after chemotherapy

First author	Age, years	Sex	Site	Size, mm	Lymph node/distant metastasis	Surgical resection	Radiation therapy	Chemotherapy	Overall survival, months
Kurashige, 2013	50	M	Left arm	80	+	+	21 Gy	Docetaxel + cisplatin	8
Mandaliya, 2016	66	F	Right forearm	–	+	+	50 Gy	Docetaxel + cisplatin	Complete Response
Godillot, 2018	64	F	Pubic	50	+	+	57 Gy	Cetuximab + paclitaxel	Complete response
Ishida, 2011	72	M	Right thigh	17	+	+	–	Carboplatin and farmorubicin	8
Joseph, 2015	56	M	Anterior abdominal wall	100	+	–	–	Doxorubicin, mitomycin, vincristine, and 5-FU, bleomycin, paclitaxel, carboplatin, and docetaxel	14
Kim, 2007	42	M	Right palm	–	+	+	+	Cyclophosphamide, cisplatin, and doxorubicin	3
Grimme, 1999	47	M	Head	15	+	+	45 Gy	Bleomycin, 5-fluorouracil, carboplatin, interferon-alpha, and IL2	6
Shiohara, 2007	62	F	Head	98	+	+	50 Gy	Cisplatin, adriamycin, VDS/mitomycin, vincristine, and epirubicin	35
Permal, 2000	67	F	Left thigh	150	+	+	–	Tamoxifen	1
Gonzalez, 2003	71	M	Right thigh	40	+	+	60 Gy	Isotretinoin and tegafur	66
Plunkett, 2001	45	F	Left shoulder	10	+	+	BERT	Epirubicin and docetaxel	9
Swanson, 1989	78	M	Left shoulder	–	+	+	+	Continuous infusion 5-fluorouracil	Complete response
De Bree, 2005	69	M	Left thigh	150	+	+	–	Topical application of 3% 5-fluorouracil ointment, and docetaxel	25
Gutermuth, 2004	67	M	Left neck	100	+	+	–	Interferon-alpha and paclitaxel	7

While initial surgical treatment is curative for most of the cases, no standard treatment protocols exist for metastatic EPC. In the largest series of 24 evaluated patients with metastatic eccrine sweat gland carcinomas, the best results were achieved with combinations of cyclophosphamide, bleomycin, cisplatin, and 5-FU, leading to partial remissions lasting 5–8 months. Partial remissions lasting 2–4 months were achieved by combining cyclophosphamide, vincristine, and prednisone. Different therapeutic regimens have been proposed with varying results (Table 2). Among these, taxane-based regimens have been proposed for 50% of cases and have shown therapeutic efficacy [9, 88–104].

Single-agent or multi-agent chemotherapy with isotretinoin, interferon alfa, radiation therapy (usually as adjuvant postoperative palliative care), and electroporation (intralesional chemotherapy) have also been reported as being well tolerated but with varying responses [9–11, 64, 98, 99]. An electrochemotherapeutic approach for local recurrency or cutaneous metastases has been described, while radiation therapy is of little benefit [6].

Conclusion

This is the first reported case of intergluteal cleft EPC with metastasis to the left inguinal region and lung. Malignant sweat gland tumors are heterogeneous neoplasms of different biological behavior. The management of patients with metastatic EPC is difficult.

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Statement of Ethics

The patient gave his informed written consent to publish his case (including the publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

All authors thoroughly reviewed the topic.

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