



ORIGINAL ARTICLE

Eccrine Porocarcinoma: A Multicenter Retrospective Study with Review of the Literatures Reported in Korea

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Background: Eccrine porocarcinoma (EPC) is a rare malignant cutaneous adnexal tumor. Other than several scattered case reports, no comprehensive review on EPC has been conducted in Korea. **Objective:** To clinicopathologically review all EPC cases from our institutions as well as those reported in Korea. **Methods:** Medical records and histopathological slides of EPC cases in the skin biopsy registries of our institutions were retrospectively reviewed. Additionally, EPC cases reported in Korea before June 2019 were retrieved by searching the PubMed, KoMCI, KoreaMed, and KMBase databases. **Results:** Nine EPC cases from our institutions were included in the study. In addition, 27 reports of 28 patients with EPC were reported in Korea. A total of 37 patients with EPC were identified, consisting of 19 males (male:female ratio, 1.06:1; mean age at diagnosis, 65.6 years). The most common site of primary tumor was the head and neck (29.7%). Wide excision was the most common (78.4%) treatment method. Initial metastasis work-up imaging studies were performed in 18 patients (48.6%), and metastasis was confirmed in eight patients (21.6%). **Conclusion:** EPC is a rare cutaneous carcinoma in Korea. EPC usually affects elderly patients, with no sexual predilection. Due to possible

metastasis, careful diagnosis and appropriate metastasis work-ups are warranted in EPC. (*Ann Dermatol* 32(3) 223~229, 2020)

-Keywords-

Eccrine porocarcinoma, Malignant eccrine poroma, Porocarcinoma

INTRODUCTION

Eccrine porocarcinoma (EPC) is a rare malignant cutaneous adnexal tumor^{1,2}. The reported frequency of EPC is 0.005% to 0.01% of all cutaneous tumors, making it the most common malignant eccrine tumor³. Since EPC is notoriously known for being mis- or overdiagnosed, its actual prevalence remains unknown¹. It can arise *de novo* or from long-standing pre-existing eccrine poroma (EP)^{2,4}. Chronic light exposure and immunosuppression have been suggested as factors that contribute to the transformation of EP to EPC². Malignant transformation is often heralded by spontaneous bleeding, ulceration, itching, pain, and sudden growth⁵.

According to a recent systematic review of 206 cases, which included only two Korean patients, the mean age at diagnosis was 63.6 years, and EPC occurred in both sexes equally². The most common location was the lower limbs (33%), followed by the head and neck (32%)². Since the two official case reports in 1998^{6,7}, only scattered reports of EPC have been made in Korea, and no overall review has been conducted. This study aimed to comprehensively review EPC cases in Korea.

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MATERIALS AND METHODS

Multicenter retrospective study: patient and data collection

The skin biopsy registries of department of dermatology at three university hospitals (Korea University Anam, Guro, and Ansan Hospital) were searched for patients with EPC from January 2000 to June 2019. Medical records and clinical photographs were reviewed retrospectively. Data on patient age, sex, tumor location, tumor size, duration, clinical impression, metastasis work-up imaging studies, surgical methods with results, follow-up duration, and any pre-existing lesions were identified. All available histopathological slides were re-examined by an experienced dermatopathologist (AK). EPC is diagnosed when a proliferation of medium-sized cells with intercellular bridges, duct formation (including intracytoplasmic ducts), nuclear atypia, increased mitoses, and apoptosis are observed⁵. For the histopathological review, the following features were evaluated: mature duct formation, necrosis (comedonecrosis or diffuse necrosis), melanocytic colonization, squamous/clear cell/spindle cell/mucus cell differentiation, associated benign components, mitotic counts, perineural/lymphovascular invasion, and immunohistochemistry results.

Review of the literatures in Korea: search strategy and data collection

Two authors (HJK, YSB) searched for reports of EPC in Korea before June 2019 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines. Literatures were searched in the PubMed, KoMCI, KoreaMed, and KMBase databases. The search terms were “porocarcinoma” and “malignant eccrine poroma.”

Two authors (HJK, YSB) independently assessed the eligibility of each study. Any type of study from Korea in English or Korean regarding EPC was initially included. The following were excluded: 1) any studies without information on the individual patient or tumor character-

istics; 2) cases with collision of EPC and other carcinomas; 3) *in situ* cases. Data on patient age, sex, primary tumor site, initial metastasis work-up imaging studies, confirmed metastasis (lymph node or distant), treatment method with results, and any associated benign lesion were collected from the literature. Since this literature search identified only case studies, we were unable to assess the risk of bias of individual studies.

Ethics

All clinical investigations were conducted in accordance with the Declaration of Helsinki principles. This study protocol was approved by the Institutional Review Board (IRB) of the Korea University Medical Center (K2019-1634-001). Requirement of informed consent was waived by the IRB. However, we received the patient’s consent form about publishing all photographic materials.

RESULT

Multicenter retrospective study

Nine patients with EPC were identified through the skin biopsy registries (Supplementary Table 1, Fig. 1)⁸⁻¹⁰. Among them, three cases⁸⁻¹⁰ have already been reported in the literature, consisting of five males (male:female ratio 1.25:1), and the mean age at diagnosis was 65.9 ± 16.0 years. The most common tumor site was the head and neck (3 patients). Squamous cell carcinoma (SCC) was the most common clinical impression, and EPC was not initially suspected in all cases. Interestingly, all patients had a unique clinical history indicating that the lesion had persisted for several years and had changed recently (bleeding, size growth, or ulceration). Five patients had metastasis work-up imaging studies. However, none had metastatic disease. Two patients were treated with Mohs micrographic surgery (MMS), and the remaining patients underwent wide excision.

In the histopathological review, mature duct formation (66.7%), necrosis (66.7%), and squamous differentiation

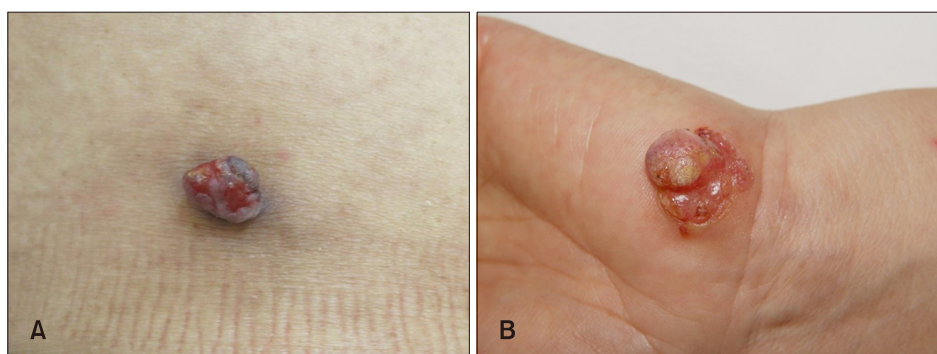


Fig. 1. Representative clinical examples of eccrine porocarcinoma. (A) Case 1, a 61-year-old male patient with an erythematous erosive pedunculated mass on the right flank. (B) Case 5, a 62-year-old male patient with an erythematous protruding nodule on the left palm.

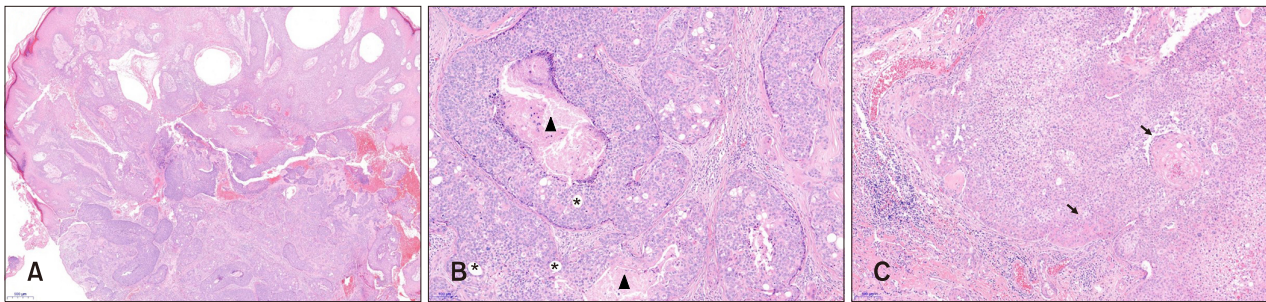


Fig. 2. Representative histopathological features of eccrine porocarcinoma. (A) Note the infiltrative irregularly shaped basaloid tumor nests (H&E, original magnification: $\times 20$). (B) Cellular pleomorphism, mature duct formation (asterisks), and comedonecrosis (black arrowheads) can be noted in a high-power field (H&E, original magnification: $\times 100$). (C) Squamous differentiation (black arrows) was also noted (H&E, original magnification: $\times 100$).

(55.6%) were common findings (Fig. 2). In contrast, melanocytic colonization (22.2%) and clear cell differentiation (11.1%) were observed less often. No spindle cell differentiation, mucus cell differentiation, or perineural or lymphovascular invasion were observed in our case series. Associated benign components were found in 77.8% of our series, with EP as the most common (Table 1). Mitotic counts ranged from 3 to 22 mitoses per high-power field. Five patients underwent additional immunohistochemical stains. Epithelial membrane antigen (EMA) and periodic acid-Schiff (PAS) stains were positive in four patients. Carcinoembryonic antigen (CEA) also tested positive in three patients, whereas S-100 in three patients was all negative (Fig. 3).

Review of the literatures in Korea

The initial search revealed 524 articles after removing duplications. After a screening process, 38 articles from Korea regarding EPC were assessed for eligibility in full-text. However, eight articles were excluded because they met the exclusion criteria (Supplementary Fig. 1). As a result, 30 articles were included in the study. Since three reports⁸⁻¹⁰ were from our institutions and were previously included in the multicenter retrospective study, 27 reports of 28 patients with EPC were analyzed in this section (Supplementary Table 2)^{6,7,11-35}. Twenty-six patients presented with a primary skin lesion. The other two presented with symptoms of metastatic lesions (one with mental change and the other with dyspnea). There were 14 males (male:female ratio 1:1), with a mean age at diagnosis of 65.5 ± 16.6 years. The most common site for primary tumors was the head and neck (8 patients) and trunk (8 patients), followed by the lower limb (seven patients). Thirteen patients had initial metastasis work-up imaging studies. The majority of patients were initially managed with wide excision. Other treatment methods included

Table 1. Summary of histopathological features of nine patients with eccrine porocarcinoma (EPC) from our institutions

Histopathological feature	Number (%)
Mature duct formation	6 (66.7)
Necrosis (comedonecrosis/diffuse necrosis)	6 (66.7)
Melanocytic colonization	2 (22.2)
Differentiation	
Squamous	5 (55.6)
Clear cell	1 (11.1)
Spindle cell	0 (0)
Mucus cell	0 (0)
Associated benign component	
Eccrine poroma	5 (55.6)
Hidroacanthoma simplex	1 (11.1)
Epidermal nevus	1 (11.1)
Perineural invasion	0 (0)
Lymphovascular invasion	0 (0)

partial excision, chemotherapy, and palliative care. Metastasis was eventually diagnosed in eight patients (six during initial work-up, and two during the follow-up period at three months and 17 months, respectively). Six patients had distant and regional lymph node metastases. Associated benign lesions were EP (5 patients), hidroacanthoma simplex (2 patients), seborrheic keratosis (1 patient), and ganglion cyst (1 patient).

Summary of 37 cases

Combining nine cases from our institutions and 28 from the literature search, a total of 37 patients with EPC were analyzed, which consisted of 19 males (male:female ratio 1.06:1), with a mean age at diagnosis of 65.6 ± 16.4 years. The most common site for a primary tumor was the head and neck (11 patients, 29.7%), followed by the trunk (10 patients, 27.0%) and lower limb (9 patients, 24.3%). Initial metastasis work-up imaging studies were performed

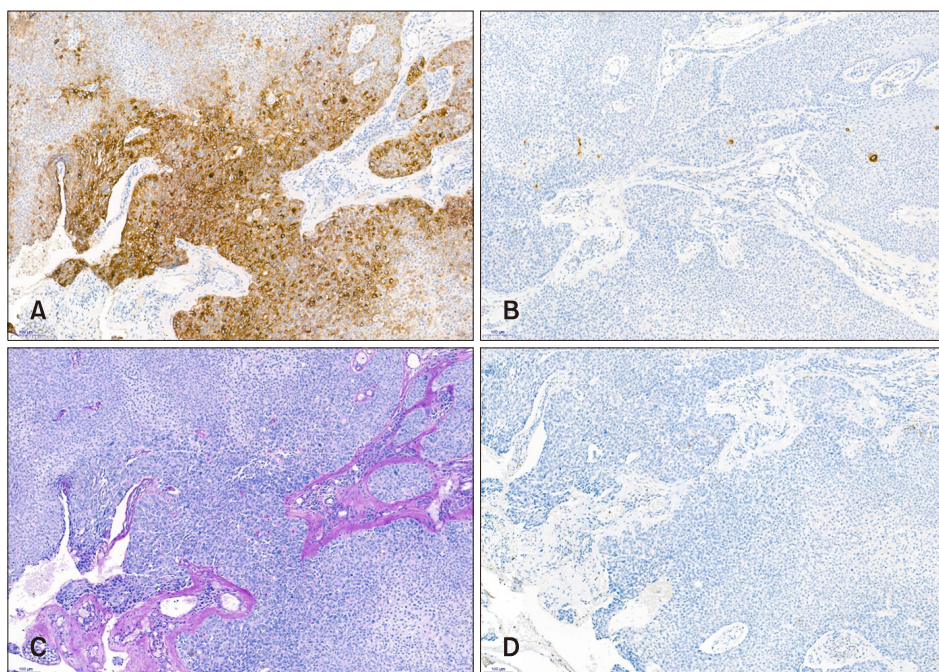


Fig. 3. Representative immunohistochemical staining results of eccrine porocarcinoma. (A) Epithelial membrane antigen staining showed focal positivity within the tumors nests as well as ductal differentiation (original magnification: $\times 100$). (B) Carcinoembryonic antigen staining highlighted ductal formation (original magnification: $\times 100$). (C) The presence of ducts was also shown in periodic acid-Schiff with diastase staining (original magnification: $\times 100$). (D) The tumor cells showed negative staining for S-100 ($\times 100$).

in 18 patients (48.6%). Wide excision was the most common surgical method (29 patients, 78.4%). Among them, only three patients (8.1%) underwent lymph node dissection (LND), and none underwent a sentinel lymph node biopsy (SLNB). MMS was performed in two patients (5.4%). Adjuvant radiation therapy was initiated in three patients (8.1%; two after wide excision and one after partial excision). One patient (2.7%) had adjuvant chemotherapy after wide excision and LND. Metastasis was confirmed in eight patients (21.6%). The most common metastatic site was the regional lymph node (8 patients), followed by the lung (5 patients) and bone, including the spine (3 patients). Associated benign lesions were found in 16 patients (43.2%), with EP (27.0%) as the most commonly found (Table 2).

DISCUSSION

In this study, EPC in Korea affected both sexes equally, with a mean age of 65.6 years. The most common primary locations of EPC are known to be the lower extremities and head and neck, with upper extremities as the least common sites². However, in our study, EPC in Korea most commonly occurred on the head and neck, followed by the trunk.

Due to its polymorphous presentation and rarity, it is generally difficult to suspect EPC as initial clinical diagnosis. For instance, none of patients with EPC in our institutions were clinically suspected as having EPC before biopsy, but were considered to have "SCC", "pyogenic gran-

uloma", or "EP". The clinical clue for EPC is a long-term history of a previously benign-looking lesions with recent secondary changes (size growth, bleeding, or ulceration). A prudent histopathological evaluation including immunohistochemical staining of EPC is therefore mandatory. Since a substantial percentage of EPC shows squamous differentiation, SCC is the most important differential diagnosis^{5,36}. In fact, > 50% of patient with EPC from our institutions showed squamous differentiation, which is a higher percentage compared with previous studies (5%~42%)^{4,36,37}. Mature duct formation, identified as the presence of ducts lined by cuboidal epithelial cells commonly with an eosinophilic cuticle, was found in 66.7% of our patients with EPC, which is similar to the findings of previous studies (62%~68%)^{4,36}. This characteristic is considered a significant indicator for a diagnosis of EPC⁴. However, caution is needed not to overlook the possibility of a poorly differentiated EPC that may not have easily recognizable mature ducts, but only less well-developed ducts^{4,37}. Immunohistochemical staining is necessary when EPC diagnosis is unclear³⁷. CEA, EMA, and PAS, which highlight ductal differentiation foci, are commonly performed^{2,36}. However, careful interpretation is required, because some SCC can be positive for these stains³⁶. EP is another important differential diagnosis of EPC. Invasive architectural patterns and significant cytological pleomorphisms are important findings that distinguish EPC from EP^{4,37}.

As for the metastasis work-up, 48.6% of EPC patients in Korea had undergone imaging studies, with computed tomography as the most common. Metastasis eventually oc-

Table 2. Summary of characteristics of 37 patients with eccrine porocarcinoma included in the present study

Variable	Value
Sex (male:female)	1.06:1
Age at diagnosis (yr)	65.6±6.4
Primary tumor site	
Head and neck	11 (29.7)
Trunk	10 (27.0)
Lower limb	9 (24.3)
Upper limb	4 (10.8)
Pelvis	3 (8.1)
Metastasis work-up imaging study*	
CT	11 (29.7)
PET-CT	7 (18.9)
MRI	3 (8.1)
None	19 (51.4)
Initial management	
Wide excision	24 (64.9)
Wide excision and adjuvant radiation therapy	2 (5.4)
Wide excision and lymph node dissection	2 (5.4)
Wide excision, lymph node dissection, and adjuvant chemotherapy	1 (2.7)
Mohs micrographic surgery	2 (5.4)
Others	6 (16.2)
Metastasis	
Regional lymph node metastasis only	2 (5.4)
Distant metastasis with regional lymph node involvement	6 (16.2)
Associated benign lesion	
Eccrine poroma	10 (27.0)
Hydroacanthoma simplex	3 (8.1)
Seborrheic keratosis	1 (2.7)
Epidermal nevus	1 (2.7)
Ganglion cyst	1 (2.7)

Values are presented as ratio, mean±standard deviation, or number (%). CT: computed tomography, MRI: magnetic resonance imaging, PET-CT: positron emission tomography-computed tomography. *Some patients had combination of imaging studies.

occurred in 21.6% of patients with EPC in Korea. Most of them were found initially; however, two metastases were found during the follow-up period (3 and 17 months). This is consistent with the results of recent studies demonstrating that approximately 20% to 30% of EPC patients had metastatic disease at the time of diagnosis^{2,38}. Also consistent with a previous study, the most common metastatic site of EPC was the regional lymph node followed by the lungs³⁸. Due to a relatively high risk of metastasis, we recommend initial imaging studies as work-up for EPC metastasis.

The majority of patients with EPC in Korea were managed with a surgical wide excision. Only two patients were managed with MMS, whereas 20% of patients worldwide are treated with MMS². Recent studies highlight the advan-

tages of MMS for EPC over a wide excision with fewer metastases (2.4% vs. 18%)^{1,2,5}. LND was performed in 8.1% of Korean patients with EPC. Although none of patients with EPC in Korea underwent SLNB, it was performed in 16 patients with EPC worldwide, achieving an 81.3% positive rate². Therefore, SNLB can also be considered in patients with EPC who are highly at risk for metastasis without palpable lymphadenopathy.

Chemotherapy and radiation therapy are less effective for EPC and are usually reserved for metastatic diseases. In this study, only three patients received chemotherapy, which was administered as an initial management (combination of 5-fluorouracil [5-FU] and cisplatin)¹⁹, adjuvant chemotherapy (5-FU)⁶, or management after the recurrence and metastasis (5-FU→adriamycin→paclitaxel)¹⁸. Radiation therapy was used as an adjuvant therapy^{7,17,18}, for palliative care^{18,24}, or for management of regional lymph node metastasis¹¹.

Associated benign components (EP, hydroacanthoma simplex, seborrheic keratosis, epidermal nevus, and ganglion cyst) were noted in 43.2% of 37 patients with EPC. This rate is much higher than that reported in two studies (12% and 18%)^{4,36}. The most common concomitant benign tumor was EP (27.0%), indicating that a substantial proportion of EPCs are malignant transformation of EP. In addition to the present study, EPC has been reported to arise within seborrheic keratosis^{39,43} or epidermal nevus⁴⁴. Although malignant transformation of these benign lesions is rare, dermatologists should be aware of the possibility. However, caution is necessary when diagnosing 'EPC arising from seborrheic keratosis'. It is possible to misdiagnose hydroacanthoma simplex as clonal seborrheic keratosis, especially when the lesion is pigmented and cystic or ductal structure is not definite. It might be reasonable to make a diagnosis of hydroacanthoma simplex rather than seborrheic keratosis if the lesion coexists with one of poroid neoplasms such as EPC⁴⁵.

In conclusion, EPC is a rare cutaneous adnexal tumor in Korea, found in only 37 cases in our institutions' data and literature search. EPC usually affects the elderly without sexual predilection. Although a wide excision was most commonly used to treat EPC in Korea, MMS can also be a useful alternative surgical method, considering recent studies showing its advantages over wide excision. Metastasis was eventually confirmed in 21.6% of patients with EPC. Due to the possibility of EPC metastasis, careful diagnosis and appropriate initial imaging studies are warranted.

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SUPPLEMENTARY MATERIALS

Supplementary data can be found via <http://anndermatol.org/src/sm/ad-32-223-s001.pdf>.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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