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Report

Porocarcinoma: an epidemiological, clinical, and dermoscopic 20-year study

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Abstract

Background Porocarcinoma (PC) is a rare cutaneous adnexal tumor with a variable metastatic potential. Given the paucity of data, guidelines and specific recommendations for PC are not yet well-established. In this study, we evaluate the disease-specific characteristics and outcome of this rare and often underestimated tumor.

Materials and method A retrospective study of the epidemiological, clinical, and dermoscopic characteristics among cases of histopathologically diagnosed PC, collected from the database of two skin cancer clinics in Italy (Firenze, Pistoia) from 2000 to 2020, was conducted.

Results Among the 52 patients with 53 tumors, 31 were men (59.6%) and 21 were women (40.4%) with an age range of 49–96 years (median age 82 years). The most common locations were the head/neck region in men (34% in men vs. 17% in women) and the lower limb in women (17% in women vs. 9% in men). Forty-eight cases (91%) underwent local excision. Of these patients, two (4%) experienced local recurrence, and one (2%) developed a second PC on a different anatomical site 1 month after the primary tumor's excision. Lymph node metastases were present in three cases (6%). Two of them have been treated surgically with adjuvant radiotherapy (both are disease-free after a 2-year follow-up period), whereas the third case developed visceral metastases followed by PC-related death.

Conclusions This study, with 52 patients with 53 tumors covering a follow-up period of more than 5 years, shows a less aggressive behavior of PC with 4% local recurrence, 6% nodal metastases, and 2% mortality.

Introduction

Porocarcinoma (PC), previously known as malignant eccrine poroma, was first described as a separate entity in 1963 by Pinkus and Mehregan.[1] PC is rare, with an incidence rate of 0.005–0.01% of all cutaneous tumors.[2] It is one of the most frequent malignancies of the eccrine gland, representing 7% of the skin adnexal tumors in the Netherlands.[3]

The exact etiology of PC remains unknown. However, some cases have been related to previous radiotherapy, chronic light exposure, Merkel cell polyomavirus, human papillomavirus DNA, and immunosuppression.[4,5] PC may appear de novo or develop on a previous poroma. The exact frequency of malignant transformation of poroma into PC remains unknown. Histopathological studies indicate that up to 18–50% of PCs may have developed from preceding benign poromas.[4] Clinical modifications, such as bleeding, ulceration, and accelerated growth of a preexisting poroma, can be indicative of malignant transformation.[6] Porocarcinomas can be either in situ (about 10% of cases) or invasive.

PC is a typical cancer of the elderly and usually occurs between the sixth and seventh decades of life[7–9], with a debatable gender predilection.[9–11] The most common location for PC is the lower limbs, followed by the head, scalp, and upper

limbs.[4,12] Occasionally, the tumor may appear on the face (eyelids, ear, or lips)[13] or the genitalia.[14]

Clinically, PC can present as a slow or rapidly growing ulcerated nodule or verrucous plaque, ranging from 1 to 20 cm in size.[12,15] It can have a pedunculated growth or appear as a partially eroded multinodular plaque. Its color can vary (red, purplish, or brown). Given its heterogeneous clinical presentation, PC may be confused with a broad spectrum of malignant neoplasms, particularly squamous cell carcinoma (SCC) or, more rarely, benign tumors.[16]

The latency between the appearance of the tumor and its diagnosis is usually quite long, from several months to dozens of years, with considerable therapeutic delay.[17,18] According to a recent metanalysis, the duration of the presentation is more than 5 years.[19] Dermoscopy is usually not diagnostic due to its nonspecific features, such as a polymorphic vascular pattern characterized by convoluted and forked and linear vessels.[20]

Histopathologically, invasive PCs show intraepidermal nests of basaloid cells, reminiscent of poroma, with nuclear hyperchromasia, nuclear pleomorphism associated with intradermal proliferation cords and aggregates of atypical cells (Fig. 1a). As in poromas, poroid cells are the predominant neoplastic cells, while the few cuticular cells are seen around dermal structures. Necrosis en masse (Fig. 1b) and ductal differentiation in the form of intracytoplasmic lumina are often observed in association with perineural spread and vascular invasion. Rare additional findings include clear cell changes and squamous cell differentiation, and intratumoral melanin deposits. Recently, clear cell differentiation seems to be associated with a greater tumor depth.[21]

PC shows a variable metastatic potential. The prognosis is difficult to determine accurately because of its rarity. It is reported that about 20% of PC can recur and involve regional lymph nodes, while metastatic disease has been described in 10% of cases. When metastatic, PC may be fatal, with a mortality approaching 70%.[22]

This study evaluated the epidemiological, clinical, dermoscopic, and histologic features of a long retrospective cohort of PC patients collected over a period of 20 years.

Materials and methods

We undertook a retrospective, descriptive study of the epidemiological, clinical, and dermoscopic characteristics of histopathologically diagnosed PC, collected from the databases of two skin cancer clinics in Italy (Firenze, Pistoia) from January 2000 to October 2020. Data on clinical and dermoscopic characteristics, histopathology, local extension, therapy and follow-up, lymph node staging (clinical involvement, sentinel lymph node [SLN] procedure, complete lymph node dissection), and outcome were analyzed. The Institutional Review Board approved this retrospective study. The inclusion criterion was the availability of the data of histopathologically diagnosed PC. Patients without complete medical records were excluded. A hand-held dermatoscope (Heine Delta 20; Heine Optotechnick, Herrsching, Germany) was used for the dermoscopic examination.

Both clinical and dermoscopic images of all lesions were captured with a high-resolution compact digital photographic camera (Olympus Digital model no. E-520, a 7.1-megapixel digital photo camera with a 3.8 optical zoom lens, a focal length of 28–105 mm in a 35 mm format, and a maximum lens aperture of f/2.8-f/5.8). In vivo dermoscopic images assessment was captured via Dermaphot (Heine Optotechnick), which connects the dermatoscope to the camera to generate reproducible, high-quality dermoscopic pictures at 10-fold magnification in the joint photographic expert group (JPEG) format. These clinical and dermoscopic images and the data were stored on a standard Windows-based personal computer.

Three investigators (VDG, IS, and FS) with expertise in dermoscopy analyzed the archived digital dermoscopic images and completed a printed questionnaire to categorize the lesions

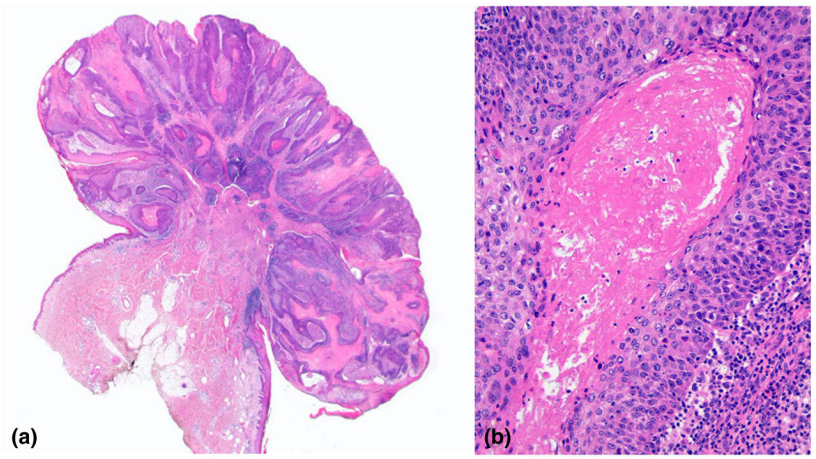

Figure 1 Histopathology of the lesion: (a) scanning power shows an exophytic ulcerated nodular lesion composed of aggregates of atypical basaloid cells involving the dermis (hematoxylin and eosin, original magnification ×5). (b) Necrosis en masse is observed. Tumor cells exhibit large and hyperchromatic nuclei (hematoxylin and eosin, original magnification ×40)

according to the typical dermoscopic pattern analysis. These dermatologists possessed comparable levels of training and experience in dermatology, each with more than 5 years of practice in dermoscopy. The dermatoscopic criteria applied are those indicated in internationally proposed classifications and algorithms. All histological specimens were reexamined by dermatopathologists specialized in the diagnosis of skin cancer (DM, VM).

Descriptive analyses were performed to summarize the number and proportion of patients by demographics, tumor characteristics, clinical management, and outcome.

Statistical analysis

Demographic and clinical-pathological characteristics were expressed as relative frequencies and percentages for categorical and median and interquartile ranges for continuous variables. Univariate models were performed to evaluate the associations of potential prognostic factors with clinical outcomes. Survival curves were estimated using the Kaplan–Meier method, and differences between groups were investigated with Log-rank tests.

Results

Fifty-two patients with 53 PC tumors were studied. Thirty-one patients were men (59.6%), and 21 were women (40.4%), with ages ranging from 49 to 96 years (mean, 79.7 years; median, 82 years).

Most of the cases (94%) were localized to the skin at the time of diagnosis, while three cases (6%) had involvement of regional lymph nodes. One patient with lymph node involvement also had distant metastases at the time of presentation.

The most frequent localization was the head/neck region, with 25 (47%) cases, including the face with 20 cases, the scalp with three cases, and the neck with two cases (Fig. 2), followed by the trunk with eight (15%), upper limb with five (9%), lower limb with 13 (25%), and two cases not otherwise specified (4%) (Table 1).

The head and neck region, particularly the face, was the most frequently involved area in men (34% in men vs. 17% in women), whereas there was a predilection for the lower limb in women (17% in women vs. 9% in men) (Fig. 3).

Two patients (4%) had local recurrence, one man and one woman, after 2 years and 1 year from the initial diagnosis, respectively. The local recurrences were primitively located on the upper limb and the face, respectively, and both of these were treated with local surgical excision. In one case, the patient developed a second primitive PC (lower limb) after 1 month from the primary tumor's excision (trunk). Only one case of PC arising from a preexisting benign eccrine poroma was noted.

In our series, most of the PCs (98%) were nonpigmented or partially pigmented lesions (pigment in <30% of lesions), in accordance with larger published series (97%).[11]

Clinically, the most common observed morphology was the erythematous nodular form with 34 cases (64%), followed by the verrucous form (six cases [11%]), the plaque form (two cases [4%]), the scaly crusty surface form (four cases [8%]), and seven (13%) not specified cases. About 50% of the lesions were clinically ulcerated.

Upon histopathological examination, ulceration was observed in 58% of cases. *In situ* PC was observed in three (6%) cases and invasive PC in 50 (94%) cases (Table 1).

The dermoscopic analysis showed three distinct patterns (Fig. 4). In particular, 20% of cases revealed round-to-oval pink-red structureless areas surrounded by white-to-pink halos and an orange-yellowish background. A polymorphous vascular pattern was present, including branched vessels with rounded endings, dotted, and linear irregular vessels. This pattern has been categorized as a poroma-like lesion and clinically presents as an erythematous ulcerative lesion, sometimes with a scaly or crusty surface.

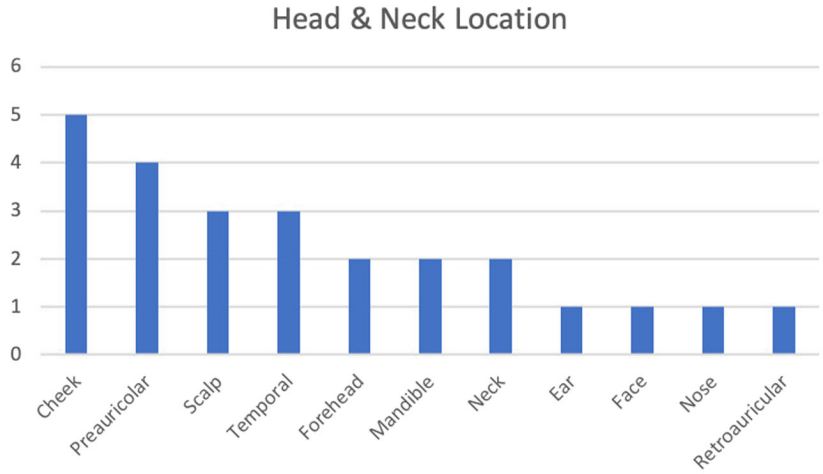

Figure 2 Anatomic head and neck location of primary eccrine porocarcinoma lesion

Table 1 Demographic and tumoral data for all patients included in the study

	n	Percent
Sex		
F	21	40.38
M	31	59.61
Age at diagnosis, years		
<70	10	18.87
>70	43	81.13
Primary site		
H&N	25	47.17
Trunk	8	15.09
Upper limb	5	9.43
Lower limb	13	24.53
NOS	2	3.77
Preoperative diagnosis		
SCC	14	26.42
BCC	13	24.53
EPC	5	9.43
Bowen	1	1.89
SK	2	3.77
CCA	1	1.89
Ulcerative cyst	1	1.89
KA	2	3.77
Pyogenic granuloma	1	1.89
NOS	13	24.53
Stage		
In situ	3	5.66
Localized	47	88.68
Regional	3	5.66
Distant	1	1.88
Treatment		
Surgery alone	51	96.22
Surgery and radiotherapy	2	3.77
Nodal dissection	2	3.77
Metastasis[a]		
Yes	3	5.66
No	50	94.34

BCC, basal cell carcinoma; CCA, clear cell acanthoma; EPC, eccrine porocarcinoma; H&N, head and neck; KA, keratoacanthoma; NOS, not otherwise specified; SCC, squamous cell carcinoma; SK, seborrheic keratosis.
[a]Includes at time of diagnosis and during follow-up.

A second pattern consisted of a homogenous pink structureless area with a polymorphous vascular pattern, including linear irregular or branched serpentine, glomerular and hairpin vessels, surrounded by a whitish halo. This pattern has been classified as SSC-like and was identified in 40% of cases. SCC-like PC appears clinically as a solitary pink-reddish nodule with a smooth surface. A peripheral hemorrhagic area was present in most of these cases.

Notably, in 10% of cases, the features of both dermoscopic patterns were present. In the last 20% of cases, a third pattern, categorized as basal cell carcinoma-like (BCC-like), was found. This pattern presented blue-gray globules of different dimensions surrounded by shiny white areas and partial pigmented areas. The vascular structures included prominent irregular arborizing vessels surrounding and crossing the surface of the lesions. The BCC-like pattern appears clinically as a round-to-oval, well-circumscribed pinkish, sometimes ulcerative, and partially pigmented nodule (Fig. 4a–f).

When specified, the primary referral diagnosis was SCC in 14 cases (26%) followed by BCC in 13 cases (25%), whereas other diagnoses (keratoacanthoma and seborrheic keratosis) were detected in two (4%) cases (one each). Bowen's disease, ulcerated cysts, and pyogenic granuloma were detected in one case (2%) each. PC was only suspected in five (9%) cases (Table 1).

Overall, 48 (91%) cases underwent local excision. Of these, four had wider local excision due to positive surgical margins, with one case experiencing a local recurrence after 2 years from the wider local excision with negative surgical margins. Five (9%) cases underwent incisional biopsy and electrodesiccation due to preoperative misdiagnosis.

Only one case underwent the Mohs Tubingen technique and experienced no local recurrence. SLNB was performed in none of the cases.

Three patients experienced lymph node metastases, two men and one woman.

In two cases, the metastases were present at the time of local excision of the primary tumor (head/neck), while in the third case, the patient developed lymph node metastases after 3 months from the initial diagnosis of PC. Of these patients, two suffered exclusive nodal metastases treated with lymphadenectomy (cervical) and parotidectomy followed by local radiation therapy. Neither of these two patients showed a disease progression after a 2-year follow-up period (Table 1).

The other case presented nodal and visceral metastases at the local excision of the primary tumor (hand). The patient was treated with a wide surgical excision followed by a CT scan that revealed nodal, hepatic, and pulmonary metastases. The patient died 4 months after diagnosis due to PC-related complications.

A total of 10 previous or concomitant cutaneous tumors were observed, including seven SCC, one Merkel cell carcinoma, and one Bowen's disease.

One patient developed PC during immunosuppressive therapy due to a previous renal transplant.

Of the 52 patients (53 tumors) followed up for a mean of more than 5 years, there were two patients (4%) with local recurrence, three patients (6%) with nodal metastases, and one patient (2%) who died of tumor-related causes.

Univariate analysis shows that clinical ulceration was associated with a significantly better prognosis ($P = 0.04$, Fig. 5). At the same time, the site of the upper limbs was borderline significantly associated with shorter disease-free survival ($P = 0.08$, Fig. 5), compared to the head/neck and other sites.

Discussion

Porocarcinoma is a rare malignant adnexal tumor with eccrine differentiation. For this reason, there is a paucity and different

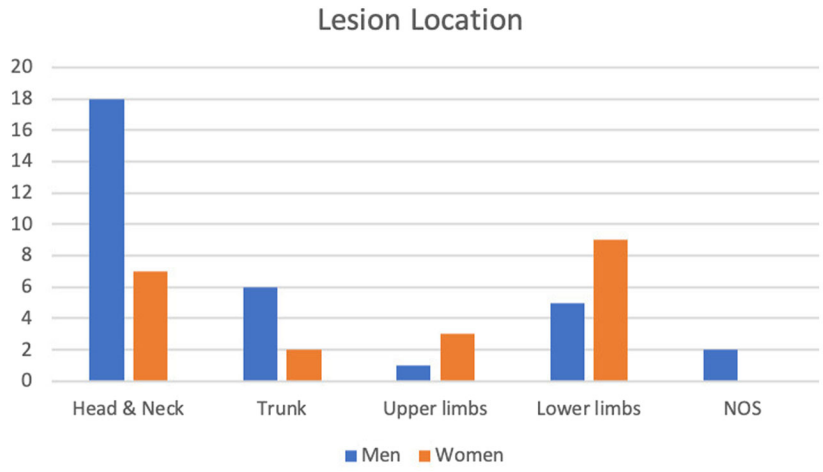

Figure 3 Gender-related anatomic location of primary eccrine porocarcinoma lesion

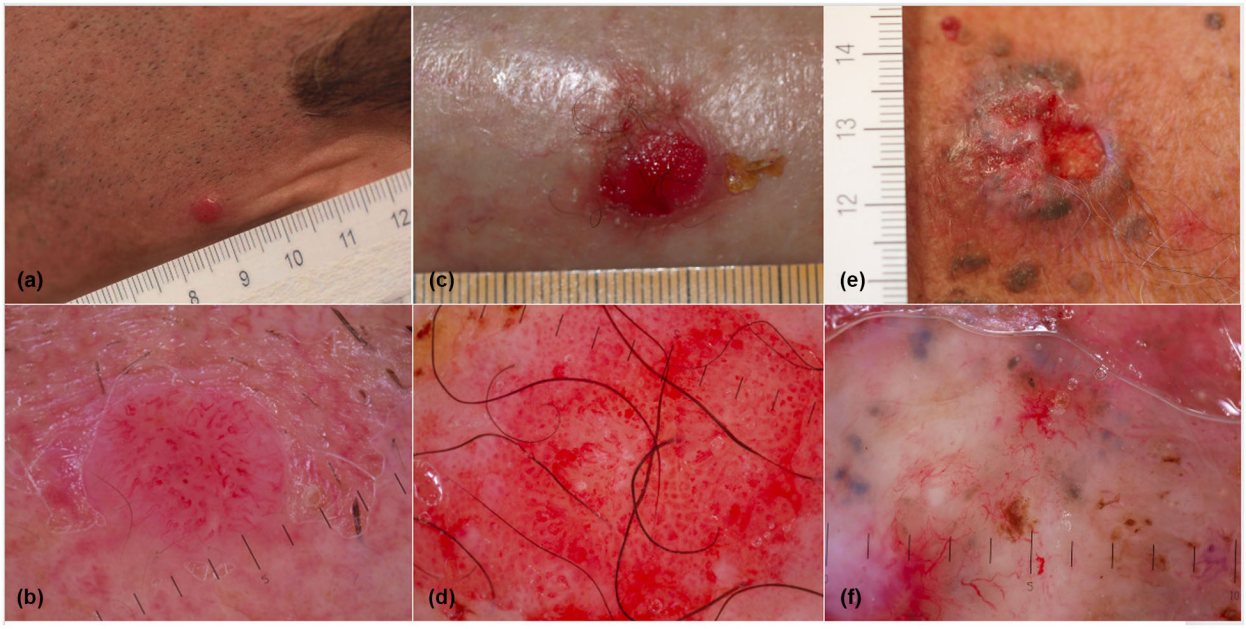

Figure 4 The dermoscopic analysis showed three distinct patterns of porocarcinoma. (a) Clinical view of a well-circumscribed, dome-shaped, pink nodule measuring 5 mm in diameter with a smooth surface without ulceration in the left preauricular area of a 49-year-old male patient. (b) Dermoscopy of the lesion: A round homogenous pink structureless area with polymorphous vessels including linear irregular serpentine or branched serpentine and glomerular vessels with convoluted morphology (center of the lesion) and thinner hairpin vessels surrounded by a whitish halo (periphery of the lesion) (SCC-like pattern). (c) Clinical view of a well-circumscribed, round, ulcerative red nodule measuring 14 mm in diameter with a peripheral superficial crust (lower right part) in the left pretibial area of a 64-year-old female patient. (d) Dermoscopy of the lesion: round-to-oval pink-red structureless areas surrounded by white-to-pink halos and an orange-yellowish background. The polymorphous vascular pattern included branched vessels with rounded endings, dotted, and linear irregular vessels (poroma-like pattern). (e) Clinical view of a well-circumscribed, round-to-oval pinkish nodule measuring 13 mm in diameter with superficial ulcers surrounded by multiple small seborrheic keratoses on the trunk of an 82-year-old male patient. (f) Dermoscopy of the lesion: blue-gray globules of different dimensions surrounded by shiny white areas. The vascular structures included prominent irregular arborizing vessels surrounding and crossing the surface of the lesions (BCC-like pattern)

center-based findings of disease characteristics, management, and prognosis. Indeed, most literature descriptions are case series, meta-analyses and case reports broadly grouping together malignant cutaneous adnexal tumors. Our study specifically focuses on PC characteristics, evaluating epidemiological, clinical, dermoscopic, and histopathological findings. We report a series of 53 PC cases diagnosed in 20 years with a mean follow-up time of 5 years. Our series of PCs may be

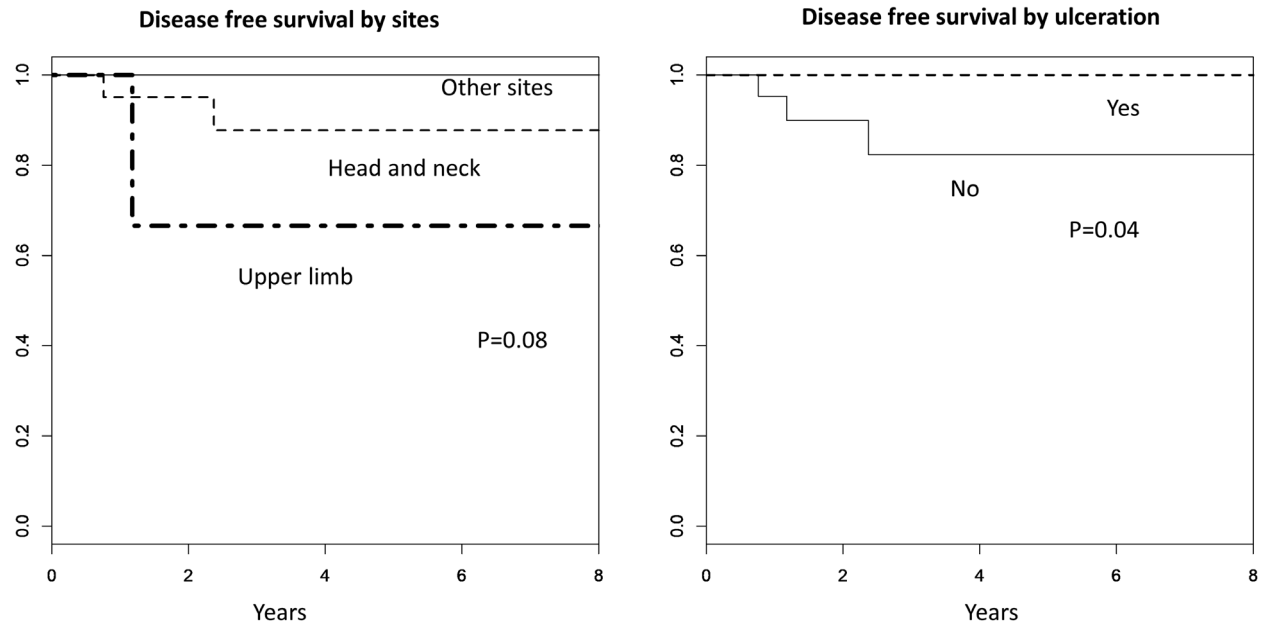

Figure 5 Kaplan–Meier survival curves for specific disease-free survival by the site of the lesion and ulceration

considered among the larger series with an added advantage of a reasonable follow-up period.

The incidence of PC is still not well-defined, varying widely in different national cancer registries. With a frequency of 0.005–0.01% among all malignant skin tumors in the initial studies, PC represents the most common malignant skin tumors of sweat glands.[3,23–27] In the last decade, there has been an increasing recognition of PC compared to the past[28], most likely reflecting increased accuracy in the histological diagnosis and population's progressive aging. Unfortunately, no specific immune profile is available.[3] However, carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA) highlight true ductal differentiation and may help in the differential diagnosis from poorly differentiated SCC. In addition, PC manifests various features (squamous cell areas, clear cells), and identification of a parent lesion (preexisting poroma or *in situ* PC) is crucial. Recent studies reported a variety of PC diagnostic markers in addition to CEA and EMA, which may highlight intracytoplasmic lumina as signs of ductal differentiation.[29–31] New potential additional markers include CD117[32], cytokeratin 7 (CK7), CK19 and nestin, YAP1 C-terminus and NUT, Engrailed Homeobox 1, and CK19, have been reported as helpful features in distinguishing PC from cSCC.[26,32–34]

In keeping with known data that PCs are more prevalent in older adults, the mean age in our series was 79.7 years (range 49–96 years). Male gender was prevalent (59.6%), although gender predilection is vigorously debated in other case series.[29–32] The most involved site was the head and neck region (47%). This was predominant in men (34% in men vs. 17% in women). Of note, all three of our scalp cases occurred in male patients with androgenetic alopecia, suggesting a possible correlation between lifelong sunlight exposure and the development of PC, as well as other more common sun-induced skin cancers.

Conversely, lower limbs were the most common site in women (17% in women vs. 9% in men), similarly with female melanoma body sites. Lower limbs also represent the second most common site in all cases (25%). This finding may suggest a possible role of ultraviolet radiation in the etiology of PC as recently demonstrated with the whole-exome sequencing analysis.[35] Other locations include the trunk (15%) and the upper limb (9%). Although the authors have no universal agreement on PC predilection sites, most reported lower extremities as the most common site.[31,32,36]

The management strategies and prognostic factors of PCs have still not been established.

In particular, early smaller series and various case reports suggest an aggressive natural history with reported local recurrence rates of up to 70% and metastases occurring in up to 60% of patients.[24,27,30,31,37] Of note, larger series reported less aggressive tumor biology, with 17% local recurrence rates, 19% nodal metastasis, and 11% distant metastasis or death,[3,11,26,30,37–39] suggesting that local and distant metastases and mortality rates are not as high as previously documented. This higher disease progression in previous studies can be explained by the fact that in the past, only histologically invasive and advanced lesions were diagnosed as PC, which expressed (at most) the known diagnostic parameters. This diagnostic bias caused both a lower incidence and a worse prognosis over time.

Only two of 52 patients (4%) experienced local recurrence in our series, and only one patient developed a second PC 1 month after the excision of the primary tumor. Lymph node metastasis was present in three cases (6%); in two of them, the nodal metastasis occurred preoperatively, and both patients have been treated surgically with adjuvant radiation therapy after resection. Notably, both patients are disease-free after a 2-year follow-up period, suggesting that removal of positive nodes, when present, if appropriately treated with surgery and radiotherapy, does not lead to an increased disease-related death rate. A third patient with preoperative lymph node involvement also developed distant metastases followed by PC-related death (1.9%).

By univariate analysis, the anatomical site of the upper limbs were predictive of a shorter disease-free survival ($P = 0.008$) than the head/neck and others. In addition, the presence of clinical ulceration was associated with a better prognosis ($P = 0.04$), Figure 5, possibly due to earlier diagnosis and treatment.

Generally, PC is considered a more aggressive tumor than cutaneous SCC (20% of all nonmelanoma skin cancers with 1.5–2.1% disease-specific death rate),[40] which represents the most clinical and dermoscopic misdiagnosis.[28] The data emerging from our study identified PCs with less aggressive behavior.

There is a lack of information about dermoscopic features in the literature, as the majority of case series of PC and, more generally for malignant adnexal tumors, are focused on histopathological features. The present study showed that the preoperative diagnosis was correct in only five cases (9%). The most frequent preoperative diagnosis was SCC (26%), emphasizing the need for histopathologically distinguishing these two entities. PC presents a variety of highly nonspecific dermoscopic patterns, making it difficult, if not impossible, to make a dermoscopy-based diagnosis of this tumor. In this study, we tried to identify some recurrent clinical and dermoscopic patterns to improve diagnostic accuracy. In particular, based on the similarity of clinical and dermoscopic features, we identified three types of pattern: poroma-like, SCC-like, and BCC-like lesions. Dermoscopically, our study highlights a crucial feature present in all PCs, showing an atypical and polymorphous vascular patterns, including dotted, linear irregular, branched, hairpin, and irregular arborizing vessels, which might increase the index of suspicion for the diagnosis of a growing malignant lesion and the need for excision of the lesion with histopathological examination.

Several limitations of this study need to be considered. First, our data are from only two centers, potentially limiting the generalizability of our results. Moreover, given the tumor's rarity, although this study is one of the largest cases in PC literature to date, the number of lesions included and noncomparative methodology limit a thorough evaluation of other possible variables.

In conclusion, in our study, PC had a less aggressive behavior with a significantly lower disease progression than currently reported in the literature. This finding could reflect an earlier tumor diagnosis and fine-tuning of cytoarchitectural histopathological criteria that, with the aid of additional IHC stains, may lead to increased recognition of this tumor compared with the past. Moreover, dermoscopy, even if it does not present specific or pathognomonic parameters, may enhance the diagnostic accuracy of these lesions along with clinical and histological features. In any case, PC clinical and dermoscopic presentation is remarkable for its polymorphism and consequent differential diagnostic challenge with melanocytic and nonmelanocytic skin tumors, both benign and malignant. Thus, histopathological examination is mandatory and represents the diagnostic gold standard. The incisional biopsy may not represent the tumor in its entirety, so it is preferable to an excisional biopsy. It is necessary to avoid inappropriate treatments, such as diathermocoagulation, given the risk of recurrence and diagnostic delay.

There are currently no recognized guidelines for PC follow-up, but it is cautious and advisable that these patients should be followed up every 6 months in the first 2 years and every year up to 5 years after the initial diagnosis. The follow-up visit must include skin examination with palpation of main lymph node stations; ultrasonography of locoregional draining lymph nodes; and instrumental investigation of the most common metastatic sites (i.e., lungs, chest x-ray at diagnosis and the following year).[9]

Authors' contributions

Dr. De Giorgi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: De Giorgi. Acquisition of data: Venturi, Silvestri, Trane, Scarfì, Zuccaro, Savarese. Analysis and interpretation of data: De Giorgi, Trane, Scarfì, Maio, Massi, Bellerba, Gandini. Drafting of the manuscript: De Giorgi, Massi, Gandini. Critical revision of the manuscript for important intellectual content: De Giorgi, Massi, Gandini. Study supervision: De Giorgi.

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