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Molecular basis and review of literature of eccrine porocarcinoma

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Abstract: *Eccrine porocarcinoma (EPC) is a rare potentially lethal neoplasm of the skin that arises from the intraepidermal portion of the eccrine sweat glands. It was previously known as eccrine adenocarcinoma or malignant eccrine poroma. In the past they were known by different terminologies such as malignant hidroacanthoma simplex, sweat gland carcinoma, malignant intra-epidermal eccrine poroma, eccrine poroepithelioma, dysplastic poroma, malignant syringe-acanthoma and porocarcinoma. It commonly occurs between 60 to 80 years of age. There is no sex predilection. It is commonly seen arising from hands and feet. Review of literature shows involvement of rare sites such as scalp, face and eyelids. We report an unusual case of porocarcinoma arising on the upper anterior chest wall. Treatment includes wide local excision but metastatic lesions can be treated with chemotherapy as well.*

Keywords: *Skin cancer, eccrine porocarcinoma, sweat gland tumor, Porocarcinoma.*

I. Introduction

According to the World Health Organization (WHO) consensus classification cutaneous appendageal carcinomas are classified as apocrine-eccrine, follicular, and sebaceous carcinomas, taking into account the clinical, histologic, and molecular genetic features [1].Eccrine Porocarcinoma, also known as malignant eccrine poroma is a rare adnexal tumor arising from the intraepithelial ductal parts of the sweat gland. These tumors account for 0.005% to 0.01% of all epidermal skin neoplasms [2].It may arise denovo as a primary tumour or develop from pre- existing benign poromas after a long period of latency. They may develop as a malignant transformation of an eccrine poroma, nevus sebaceous, chronic lymphatic leukemia and actinic lesions. The tumour was first described by Pinkus and Mehregan in 1963 as an epidermotropic eccrine carcinoma [3]. The term eccrine porocarcinoma was introduced by Mishima and Morioka in 1969. Since then fewer than 300 cases have been reported worldwide. It is a rarely seen tumour and usually mistaken as a case of Squamous cell carcinoma. There have been fewer than 20 cases of porocarcinoma arising on scalp with fewer than 10 cases seen in younger age group reported previously in the literature. Only three cases occurring specifically on the ear have been documented. The largest series of cases to date in the literature was by Robson et al., from St Thomas' Hospital, presented a series of cases with a poor prognosis in 30% of patients with lymph node (20%) or distant metastases (10%) [4].They suggested four histopathological findings as prognostic factors in EPC patients such as

- Lymphovascular invasion,
- depth of invasion greater than 7mm,
- mitosis greater than 14/10 high power field and
- Lymph node involvement.

The infiltrative growth pattern rather than the pushing border is a prediction of local recurrence.
More than 50% of the tumors are usually located in the lower extremities, but may rarely occur on scalp, face and ear (<20%), upper extremities 11%, trunk and abdomen 9%.A variety of different presentations have been reported in scalp, ear, cheek, nose, scapular region, back and hand. Clinically, it may present as a verrucous plaque, polypoid growth or an ulcerative lesion of long duration. Local recurrence and metastasis to skin, lymph nodes, viscera and bone may occur. Treatment includes wide local excision while metastatic lesions can be treated with chemotherapy**.**

II. Clinical case presentation

A 74 years old male patient presented to the plastic surgery out-patient department with the history of an ulcerative growth on the upper part of the anterior chest wall just below the medial third of right clavicle for the past 2 years. It is a slow growing tumor with history of ulceration. The patient was referred to us as basal cell carcinoma from the department of Dermatology. On examination there was an elevated black nodular lesion measuring 2.5cm X 1.5 cm with areas of ulceration.[Figure.1].

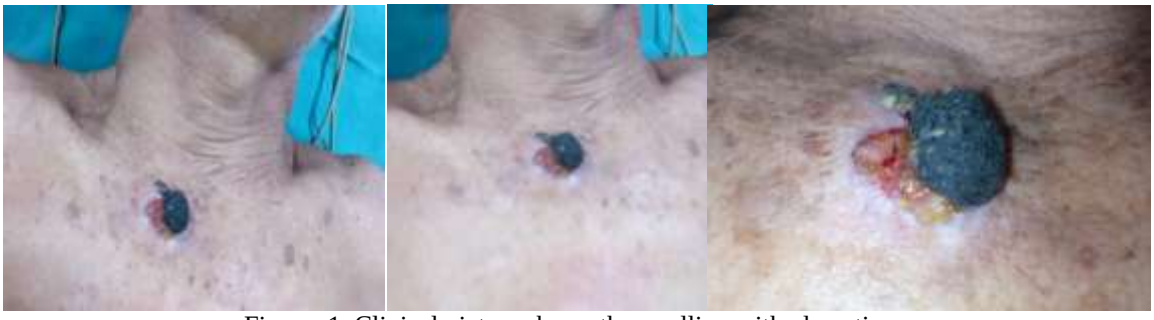

Figure: 1. Clinical picture shows the swelling with ulceration.

The patient was evaluated to rule out metastasis and planned for excision of the lesion with a wide margin and flap cover. The tumor was excised with a margin of 1 cm all around and the defect was covered with a local fascio-cutaneous flap cover based on the 2nd internal mammary perforator. The specimen was sent for histopathology and was reported as eccrine porocarcinoma**.** The patient was referred to the department of Oncology for further management.

III. Histopathological features

Macroscopic appearance: External surface appears to be a nodular black out pouching growth measuring 1.5x1 cm. Cut section through the growth is grey white and extends to a depth of 1.3 cm. The margins were reported to be free of the tumor.

Microscopic findings: The neoplasm extends from epidermis to dermis (to a maximum depth of around 1.1 cm. The tumor is composed of marked ulcerated polypoidal lesion with asymmetrical, infiltrative growth pattern. Large islands and small irregular shaped nests seen connected to the epidermis at multiple places [Figure: 2A].Cells are large, atypical with hyper chromatic markedly pleomorphic nuclei [Figure: 2B] and clumped chromatin. Brisk mitotic activity (3-4 per HPF) is seen. [Figure: 2C].

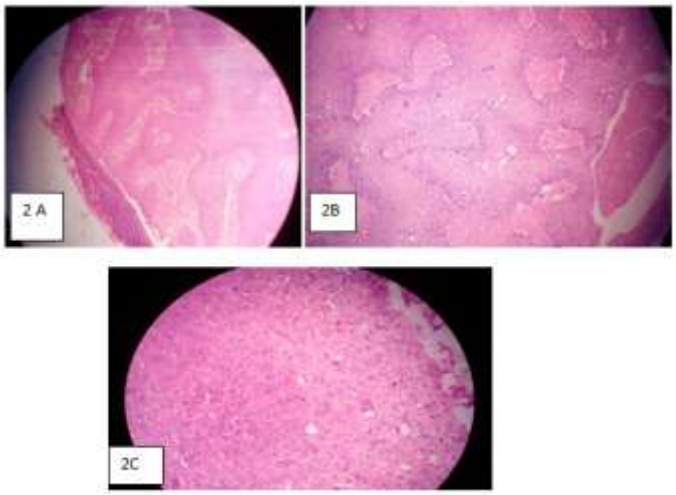

Figure: 2.Microscopic pictures with H & E staining 4x {2A and 2B} and 10x {2C} magnifications.

Cytoplasm is moderate with eosinophilic character. Squamous differentiation is seen in places with foci of keratinization.There is marked surface neutrphillic debris seen. However the infiltrative border has lymphoplasmacytic infiltration. No benign poroma component is seen. No definite ductal differentiation is evident. The tumor is roughly 1 cm from the base. Areas of focal necrosis are seen. No evidence of perineural or vascular invasion seen.

IV. Molecular genetics and histological features of eccrine porocarcinoma

4.1. Molecular genetic basis of eccrine porocarcinoma:

A striking inverse correlation between p16 and RB expression was noted in all of the eccrine porocarcinomas and poromas. Strong immunoreactivity for p16 protein was observed in both nuclei and cytoplasm of the tumor cells in eccrine porocarcinomas. RB expression was negative in these cases. Conversely, cases of eccrine porocarcinoma did not show immunoreactivity for p16 protein, whereas RB

protein was positive in the scattered nuclei. On the other hand, immunostaining of p16 was negative in all cases of poromas, whereas RB-positive nuclei were sparse. No p16 gene mutation was detected in the eccrine porocarcinoma cases.

4.2. Differential diagnosis of eccrine porocarcinoma:

Differential diagnosis of eccrine porocarcinoma should include eccrine poroma, Squamous cell carcinoma, and malignant melanoma (although these do not test positive with CEA immunocytochemistry) as well as occult visceral neoplasms, occult breast cancer and salivary gland tumors [5]. A variety of conditions should be considered in the differential diagnoses including metastatic adenocarcinoma, trabacular carcinoma, merkel cell carcinoma, clear cell hidradenocarcinoma, basal cell carcinoma, Squamous cell carcinoma, seborrheic keratosis, amelanotic melanoma and verruca vulgaris [6].Other distinct variety of sweat gland carcinoma includes chondroid syringomas, malignant dermal cylindroma, malignant syringomas, malignant acrospiroma, malignant trichoepithelioma and apocrine carcinoma must also be excluded.

4.3. Histopathological findings in eccrine porocarcinoma:

Glandular or acinar pattern in epidermis and dermis with hyperplasia of the overlying Squamous epithelium is often seen in metastatic adenocarcinoma. Trabacular and merkel cell carcinoma exhibit trabacular pattern with classical nuclear features of fine granular chromatin, nuclear moulding, fragmentation and abundant mitosis Distinguishing between Porocarcinoma and hidradenocarcinoma is difficult since both have overlapping histologic features especially when the tumors are not well differentiated [7]. It is challenging to diagnose EP based purely on clinical presentation. Histopathology along with immunohistochemistry is always the mainstay for early diagnosis and better treatment**.** Two histopathological patterns were found with areas of eccrine porocarcinoma and Bowen disease. The majority of neoplastic cells expressed strongly EMA and CK5/CK6 markers. The tumour cells did not express HMB45, chromogranin, CD56, CEA, and vimentin but were focally positive for MNF116 and involucrine. Different cell types are found to be associated with eccrine porocarcinoma, such as

- Squamous cells,
- spindle cells,
- clear cells,
- mucin-producing cells and
- melanocytes

The presence of squamous cells in eccrine neoplasia is from the luminal cells of the acrosyringium that are Squamous in type. Melanocytes may colonize benign or malignant tumors with the melanin pigment also being present in the metastases, leading to a misdiagnosis of malignant melanoma. Melanocyte-containing benign eccrine tumors are possibly more prevalent in dark-skinned people and may be multiple and grossly pigmented [8]. One hypothesis is that sweat ducts have melanocytes during the 14th week of gestation that are lost later on in embryonic development. Two theories include:

- melanocytes persist in the sweat gland acrosyringium after fetal life or
- Secrete Melanocyte growth factors from tumor cells [9].

4.4. Prognostic indicators:

Tumour stage is very significant regarding prognosis, and positive lymph node involvement may indicate up to 65%mortality [10]. Several prognostic factors have been identified; mitotic index, Lymphovascular invasion, perineural invasion, necrosis, tumour size and depth and the character of the tumour margin.

4.5. Immunohistochemistry:

The best prognostic indicators pathologically for a poor outcome seem to be a high mitotic index, Lymphovascular invasion and a tumour size and depth greater than 7 mm [11]. Nearly all sweat gland carcinomas exhibit immunoreactivity for CK, CEA and EMA. Ductal differentiation with formation of PAS positive cuticle is strong evidence against metastasis, Squamous cell carcinoma and sebaceous cell carcinoma.[12]. S100, NSE and CK 20 are positive in trabacular carcinoma. Immunohistochemical studies, namely, P53 protein expression study, expression of angiotensin type 1 receptors and expression of CEA, if possible, should be done to confirm the diagnosis. Immunohistochemistry staining pattern of normal skin is given in Table: 1.

Antigen	Antibodies	Internal control
Pan-cytokeratin	AE1/3 (AE1-acidic CK; AE3-basic CK), Pan-K	Suprabasal keratinocytes
HMWCK	34βE12 (CK1, 5, 10, 14, 15), CK5/6	Suprabasal keratinocytes and adnexal Epithelia
LMWCK	CAM5.2, CK7	secretory portion of eccrine and apocrine glands
Muscle markers	SMA, des min	pilar smooth muscle
Eccrine and apocrine glands	CEA, EMA	sweat glands
Endothelial cell markers	CD31, CD34, VWF, ERG-1	endothelial cells in vessels
Melanocytic markers	S100, MART-1, MITF, HMB-45, tyrosinase	epidermal basal layer melanocytes
Langerin	CD1a, CD4	epidermal Langerhans cells
Axon	NPF, S100	nerve bundle
LMWCK = Low-molecular-weight cytokeratin; NPF = neuropeptide F; VWF = von Willebrand factor; Pan-K = pan-keratin.		

Table: 1. Immunohistochemistry staining patterns in normal skin.

4.6. Treatment:

Local excision with negative margins is the mainstay for treatment. If regional lymph nodes are involved then lymphadenectomy should be done. Peri lesional injection of interferon alpha and interleukin 2 has been reported to produce a partial response. DaSilva also mentioned successful outcome with post op radiotherapy in recurrent cases [13].

V. Discussion

Eccrine Porocarcinoma is a rare neoplasm arising from sweat gland from Intraepidermal and upper dermal eccrine ducts. It is commonly found in old people with a history of long duration. Matloub reported a case of ulcerative porocarcinoma of occipital region involving pericranium [14].Ritter et al. have reported one case of eccrine Porocarcinoma in occipital region with intracranial extension.[15]. Ribeiro et al reported EP with bone invasion and Lymph node metastasis [16]. They mentioned 6 cases of scalp porocarcinoma as described in literature. Porocarcinoma in frontoparietal without involvement of the underlying bone and pericranium has been reported. Clinically, the tumour may present as a

- verrucous plaque,
- polypoid growth or
- an ulcerative lesion of long duration

This has to be differentiated from cylindroma (turban tumor), eccrine poroma, sebaceous adenoma, sebaceous carcinoma, pilar tumor of the scalp and metastatic carcinoma. Local recurrence (25%) and metastasis to skin, local lymph nodes, breast, liver, bladder, ovary, adrenal glands, lung, peritoneum and bone may occur.

Microscopic appearance in a primary tumor will show an asymmetrical tumor with cords and lobules of polygonal cells. Tumor cells may be limited to epidermis or may extend into dermis. Some islands of tumor cells may lie free in the dermis and there will be cystic lumina within tumor nests. There is nuclear atypia with frequent mitosis and necrosis. Epidermis may show acanthosis. Eccrine differentiation is indicated by spiraling ductular structures, ducts lined by cuticular material, zones of cytoplasmic glycogenation, Intraepidermal cells in discreet aggregates often centered on acrosyringeal pores. Stroma may be fibrotic, hyalinised, highly myxoid or frankly mucinous. Malignant porocarcinoma in a poroma, on microscopy, will show areas composed of eccrine poroma cells with a benign appearance adjoining areas of anaplastic cells. Malignant cells have large hyper chromatic, irregularly shaped nuclei and may be multinucleated and are rich in glycogen. Infiltrating tumors present with lobular configuration, glandular and cribriform pattern, abnormal mitosis, keratinization and mucinous metaplasia of stroma [17].

The tumour spreads tangentially in the lower third of the epidermis and later infiltrates the dermis, subcuticular fat and lymphatic system. Hence the local recurrence rate is approximately 25% (18).The traditional mainstay of treatment has been surgical wide local excision with negative margins with lymphadenectomy if regional lymph nodes are involved. The role of sentinel node biopsy is unknown in eccrine porocarcinoma. Mohs micrographic surgery has been used successfully to treat five cases, with no reoccurrence over a five-year period in one of the cases. Retinoids and interferon have some isolated benefit and there have been no reports or trials in the literature regarding the successful use of radiotherapy or chemotherapy [19, 20]. Abenzo and Ackerman [21] have stated that it is difficult to distinguish primary tumour from metastasis with significant pagetoid spread. It could be that the nest of multiple lesions that are thought to be cutaneous metastases may be part of a true multifocal primary tumour rather than metastatic spread. This could explain the early local skin recurrence despite the clear resection margins and the treatment is wide local excision. Mohs

micrographic excision has also been reported with a successful outcome. If regional nodes are involved regional lymphadenectomy should be done. Metastatic lesions can be treated with chemotherapy. Oudit et al. have mentioned use of Melphalan, intra-arterial infusion of 5fluorouracil and hyperthermia. Peri-lesional injection of interferon alpha and interleukin 2 has been reported to produce a partial response [22].Arslan has mentioned use of docetaxel, interferon alpha 2a and isotretinoin [23]. DaSilva has reported a successful outcome with postoperative radiotherapy in recurrent cases. More than 100 cases of porocarcinoma have been described in literature, of which less than 10 cases have been of scalp porocarcinoma [24]. There is no case reported in literature of porocarcinoma on the frontoparietal region, not involving pericranium akin to our case.

VI. Conclusion

Eccrine porocarcinoma is a rare aggressive form of skin cancer with unknown etiology and little guidance available in the literature on exact protocols for treatment and follow up. It should be on the differential diagnosis of any suspicious skin lesion seen by the plastic surgeon. Close liaison with a pathologist is recommended to avoid incorrect diagnosis and delay in appropriate treatment.

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