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CASE REPORT

Porocarcinoma "A Masquerader as Left InfraClavicular mass" A case report with review of literature

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ABSTRACT

Porocarcinoma, dermal duct tumor or malignant eccrine poroma also called malignant hidrocanthoma simplex is an infrequently reported skin malignancy that arises from the terminal ducts of the sweat gland. First described in 1963 by Pinkus & Mehregan. The term eccrine Porocarcinoma was coined by Mishima & Morioka. The reported incidence less than 1 per 100,000 persons years. Although commonly described in the palms and soles of the feet, it is the head neck followed by the lower extremities that are most affected. The etiology is unknown possible causes include radiation therapy, prolonged solar UV exposure and immunosuppression. The presentation is a painless slow growing red or pink nodular or ulcerative growth seen in the elderly males or females. The diagnosis therefore is delayed as it relies on the sum of Clinical, Histopathology and Immunohistological findings. Clinicians worldwide continue to be unfamiliar with this clinical condition. Masquerading as a benign appearing skin lesion they continue to deliberate on a myraid differential diagnosis from Bowen's disease, amelanotic melanoma, seborrheic keratosis, fibroma, verruca vulgaris, pyogenic granuloma, and squamous cell carcinoma. Once advanced the prognosis of patients with metastatic Porocarcinoma (PC) continues to be grim, with little evidence based medicine on optimal management case reports will continue to highlight literature on this Masquerader.

Introduction

The human skin consists of sebaceous glands and sweat glands. The glands are broadly divided into exocrine and endocrine glands. The exocrine glands pour their secretions into a duct system that leads up in to the blood stream. The endocrine glands on the other hand pour their secretions directly into the blood. On the basis of their secretions these glands are further classed as Holocrine glands like the sebum producing sebaceous glands in which secretory cells burst releasing the cytoplasmic content along with their membranes into the duct system. Merocrine glands like the salivary glands and sweat glands that pour secretions via exocytosis into the duct system without damaging the cell structure and finally the Apocrine glands like mammary glands the ceruminous glands of the external auditory canal that store the secretory product on the cells apical surface. It is this portion that pinches off from the rest of the apical cell to release their secretions.

The Sweat glands are further sub classified into the apocrine & eccrine gland variety. Eccrine and apocrine sweat glands originate from the epidermis. The Eccrine glands were the first type of sweat gland to be discovered & were named by Schiefferdecker a 100 years later[1].Eccrine glands begin as epithelial cellular buds that grow into the underlying mesenchyme. Eccrine sweat glands first appear during the fourth month of gestation & become functional soon after birth. These glands are complete at birth therefore no new glands are formed after birth. The skin in humans has two three million eccrine sweat glands distributed over the body. The eccrine glands are primarily responsible for thermoregulation through sweat excretion.

The Eccrine glands are found on the palms of the hands, soles of the feet, head, trunk and extremities all except the genital prepuce, glans penis, clitoris & labia minora[1]. Apocrine glands on the other hand are located in axilla and the anogenital region of the body[2]. Their function is augmented with the onset of puperty.

The glands terminate as long, unbranched, closely coiled secretory tubules. The ducts are located in the dermis and epidermis. Their openings into the epidermis are called pores. The straight intradermal portion of the duct is called the syrinx.

Tumours that arise from the syrinx are called syringomas. The coiled intradermal portion opening onto the skin surface is the acrosyringium[3,4]. The tumours that arise from the acrosyringium are designated as poromas. Porocarcinoma is the malignancy that arises from a poroma. The name was coined by Mishima and Morioka in 1969[5] after Pinkus reported his case.

Eccrine sweat glands receive sympathetic innervation. The thermoregulatory center of the hypothalamus mediates sympathetic innervation to the sweat glands. The Cholinergic stimulation of muscarinic receptors induces sweating.

The apocrine sweat glands on the other hand require hormonal stimulation during puberty to become functional. Their ducts do not open onto the skin surface directly, Instead, the ducts open into hair follicles, and sweat is released through the hair opening in the skin. The canals of these apocrine sweat gland ducts secrete protein rich sebum sweat that enters the hair follicle superficial to the sebaceous gland.

Pathogenesis

Porocarcinomas arise de novo or are the result of the histopathological transformation of a benign eccrine poroma into a malignant porocarcinoma[6]. Poromas are benign neoplasms & account for 10% of eccrine sweat gland tumors[7-9]. The ratio of malignant transformation of an eccrine poroma into an eccrine porocarcinoma is 18%[10]. Porocarcinoma takes on various names like malignant hidraocanthoma simplex, eccrine porocarcinoma, malignant eccrine poroma. The cell of origin is the acrosyringium the intraepithelial coiled part of the eccrine duct.

Other skin gland tumors like eccrine spiroadenoma or cylindroma[11] also carry the risk for transformation to a Porocarcinoma.

The cellular pathogenesis begins with the

acquirement of fused genes that are a hybrid gene a product of two independent genes the end result of translocation, inversion, or deletion and the byproducts of these genes that lack regulatory domains, leading to their overexpression & a series of events that involve genetic alterations of oncogenic drivers and tumor suppressor genes like *TP53* (tumor protein p53), *CDKN2A* (cyclin-dependent kinase inhibitor 2A), *HRAS* (HRas protooncogene,Gtapse), *EGFR* (epidermal growth factor receptor), and the *Rb1* (Retinoblastoma 1) gene. The dysregulation of signaling pathways like the mitogen activated protein kinase pathway (MAPK) and the phosphatidylinositol AKT serine/threonine kinase (PI3K-AKT)[12,13] result in production of cellular proteins responsible for transformation into carcinomas[14,15].

Porocarcinoma in Children & Pregnancy

Porocarcioma have been reported both in children and pregnancy as well. It has been reported to arise from a pre existing poroma in children[16] Pregnancy and the altered hormonal profile of the body trigger a sudden spurt of eccrine poromas[17]

Metastasis of porocarcinoma is through lymphatics to distant organs. The recurrence rates are high especially after local excision in which positive margins involvement.

Metastasis is to regional lymph nodes followed by lungs and bones. The Mortality reaches 67% with regional lymph node metastasis[18] .Once metastasized the Survival is anywhere from 5-24 months.

Case Presentation.

A 61 year old Middle eastern Male presented with a history of gradually increasing left clavicular nodular plaque like mass 5cm by 4cm for few years and a recent history of itchiness, bleeding with ulceration. Clinically there were no palpable regional lymph nodes. Motor and sensory examinations were normal.

He had undergone wide excision of this mass. The histopathology was reported as Porocarcinoma with clear surgical margins. He was taken up for a MDT meeting and is on follow up discharge up at the regional Oncology Centre.

HPE- Poorly differentiated Porocarcinoma in situ with squamous features. Margins clear.

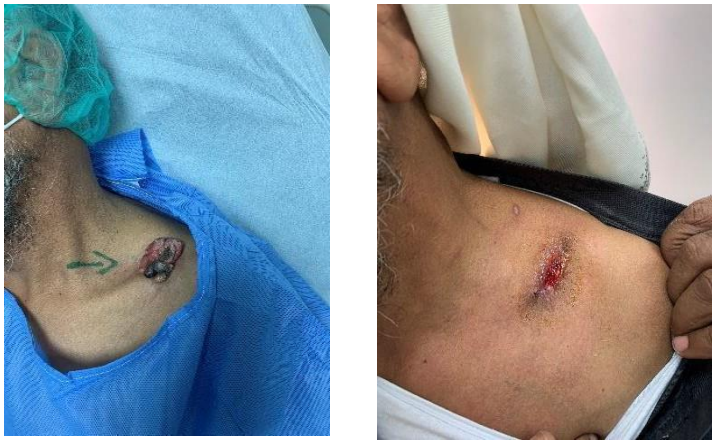

Fig (1). Left Clavicular ulcerative plaque preoperative & Fig (2) Post Operative.

Clinically a nodular ulcerative lesion with necrosis suggest heightened mitotic activity within the skin growth more so if the history is suggestive of a change in size or a history of recent bleeding from the growth. Red flags on histology include more than 7mm depth of the tumor, an increase in number of mitoses, and presence of lymphovascular invasion. An infiltrative margin is associated with more local recurrence in comparison to a broader margin.

Discussion.

The incidence of porocarcinoma 0.05 to 1.8 per 100,000 person years[19]. It affects mainly the elderly

population. The incidence increases with age, and those affected are in their seventh or eight decade of life[20]. It affects the Males more than females and even children are not spare[21]. There is a tendency for porocarcinomas to rapidly grow during pregnancy. The most common region reported is the head & neck[22].

Other common sites include the face, Scalp, Palms, soles and abdomen. One possible explanation for the preference for head and neck is chronic exposure to sunlight and radiation. Chronic Dermatologic diseases states who are immunocompromised are other risk factors for the development of porocarcinoma[23]. On an average the diagnosis of porocarcinoma is often delayed from a few years to five years[23]. Eccrine poromas are benign and arise from the intraepidermal region of the eccrine sweat duct.

Porocarcinoma are thought to arise De novo. A history of Polychemotherapy for cancer produces direct sweat duct cytotoxicity & remodeling of the sweat gland apparatus these toxic metabolites is thought to be responsible for multiple porocarcinoma development.

The predominant reported symptoms in porocarcinoma include pain and itching[15]. As with other skin lesions a history of sudden growth and or ulceration with bleeding heralds malignant degeneration.

On HPE the characteristics of parocarcinoma are nuclear atypia, hyperchromatic nuclei, foci of necrosis and frequent mitoses. It is challenging for the pathologist to differentiate a squamous cell carcinoma from a porocarcinoma, due to the histological similarities between the two conditions.

The histological features of PC in hematoxylin and eosin (HE) are poromatous basaloid cells that display ductal differentiation with marked cytologic atypia.

Porocarcinoma is distinguished from poroma by the presence of an infiltrative border and cytologic pleomorphism with atypia.

The terms Infiltrative, pagetoid or pushing elaborated. Infiltrative is characterized by an ill-defined lower margin of malignant clusters infiltrating the dermis. Pushing PC lesions often have polypoid tumors with distinct dermal limits[24]. Pagetoid is identified by the intraepidermal spread of tumor cells mimicking Paget's disease.

Immunohistochemistry (IHC) in principle involves identifying antigens by exploiting the principle of antibodies binding specifically to antigens in biological tissues.

Immunohistochemical staining for markers like carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA) are used to identify ductal structures, this in combination with a positive for CD117 is almost diagnostic for porocarcinoma[25] .A negative CD 117 however with a positive EMA & carcinoembryonic antigen (CEA) is an indicator of eccrine ductal Squamous cell carcinoma. Further staining for cytokeratin 19, KIT proto oncogene receptor tyrosine kinase, and epithelial antigen (BerEP4) aids in differentiating a Porocarcinoma from a Squamous cell carcinoma[13].

S100 protein is employed for recurrent and metastatic porocarcinoma[26].

Immunohistochemistry can aid in diagnosis and stains for EMA, carcinoembryonic antigen (CEA), and S-100 protein aid in the diagnosis.

The genetic theory states that a fused gene (*YAP1-MAML2* gene *YAP1* fusion) overexpression induces oncogenesis or put simply a hybrid gene the result of translocation, deletion and or inversion that is devoid of regulatory domains, lead to defective protein production with subsequent transformation to carcinoma[27,28].

The tumor suppressor gene TP53 is the most common site for mutations[29] followed by the tumor suppressor gene APC (Adenomatous polyposis coli).

ROLE OF SENTINEL LYMPH NODE BIOPSY (SLB): In cases where the histopathology is reported as aggressive tumor with features of a depth of 7mm with mitosis and or lymph vascular invasion, there is a role for Sentinel lymph node Biopsy. The reported success rate for detecting occult lymph node metastasis is 81%[30].

PROGNOSIS, RECURRENCE & DISEASE FREE SURVIVAL: The Overall 5-year survival is stage dependent 96% for stage I or II. The local recurrence rate is reported 20%, even when clear margins are confirmed at primary resection. The chances of Disease free survival increase with uninvolved margins. The most common metastatic site are regional lymph nodes (58.5%), followed by the lungs (12.8%).

The average Surgical safe margin is 2 mm for lesions on the face and Neck & 3 cm at other parts of the body[31].

The prognosis of patients with metastatic Porocarcinoma is guarded, with mortality rates of approximately 60–70%. Adjuvant RT is reserved for advanced porocarcinoma those with positive resection margins, high-grade tissue, multiple lesions or recurrent disease.

TREATMENT

Surgical resection is curative if performed in the early stages for localized PC tumors. Complete excision with clear surgical margins ensures the best prognosis[31,32].

Treatment using Micrographically Oriented Histographic surgery (MMS) is an alternative surgical technique. The principle is microscopic control of margins by utilizing tangentially cut frozen section histology. The disadvantages include multiple sessions, the cost and experience of the team.

ROLE OF CHEMOTHERAPY & MOLECULAR THERAPY.

The most common employed Chemotherapy are Platinum based drugs carboplatin (CBDCA) and cisplatin (CDDP) in combination with Fluorouracil (5-FU).

Most common side effect include peripheral neuropathy through dorsal nerve ganglion neuronal apoptosis, ototoxicity and nephrotoxicity.

Biological therapy with pembrolizumab, which is a monoclonal immunoglobulin G4 (IgG4) antibody that blocks the programmed cell death protein 1 (PD-1) receptor on the cell surface. The cancer cells use these to their advantage by preventing T cells from killing cancer cells. Therefore, the inactivation of the PD-1 pathway via pembrolizumab allows activation of the T cell mediated immune response against tumor cells[31].

Conclusion:

It is imperative for the treating Clinicians to be familiar with Porocarcinoma as the Disease specific mortality is low if picked up early. Surgery will continue to be a curative form of treatment for localized disease. Advanced or metastatic porocarcinoma will require referral to a Tertiary care Centre for MDT management.

Conflict of Interest:

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