Int J Clin Exp Pathol 2014;7(11):8266-8270
www.ijcep.com /ISSN:1936-2625/IJCEP0002318

Case Report

Cutaneous apocrine carcinoma in groin with bilateral lymph node metastasis: a case report and review of the literature

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Received September 4, 2014; Accepted October 18, 2014; Epub October 15, 2014; Published November 1, 2014

Abstract: Cutaneous apocrine carcinoma (CAC) is a rare type of malignant adnexal tumour with only scattered reports. We report a 52-year-old male patient of CAC in groin with bilateral lymph node metastasis. The patient had a left inguinal subcutaneous mass 3 cm × 2 cm in size for 4 years, and received a wide local excision of the tumour. Pathological sectioning suggested CAC. The immunohistochemical staining revealed GCDFP15 (+), 34BE12 (+), ER (+), PR (+), CK7 (+), Ki67 (5%-10%), HER2/Neu (-), P53 (-), P63 (-), and CK20 (-). Two subcutaneous masses of 2 cm × 1 cm were found below the original incision 10 months after the operation, and regional lymphadenectomy was performed. During the outpatient follow-up, B-ultrasound examination showed abnormal enlargement of the right inguinal lymph nodes 17 months later, and right inguinal lymphadenectomy was performed. No evidence of recurrent or metastasis disease has been seen after a follow-up period of 16 months till now. We review the literature on pathological and immunohistochemical study of CAC and discuss its diagnostic dilemma.

Keywords: Cutaneous apocrine carcinoma, pathology, immunohistochemistry

Introduction

Cutaneous apocrine carcinoma (CAC) is a rare primary adeno-carcinoma that commonly develops in the axillary and inguinal regions, the incidence ranged from 0.0049 to 0.0173/100,000 per year with no significant change in this trend over time [1]. CAC can exhibit a wide variety of clinicopathological presentations, making accurate diagnosis difficult. The tumour is often misdiagnosed and is not well known to either clinicians or pathologists [2, 3]. It can be diagnosed based on the clinical manifestations, the features of the skin lesions, the histopathologic characteristics, and immunohistochemistry. Immunostaining with giant cystic disease fluid protein-15 (GCDFP-15), epithelial membrane antigen (EMA), cytokeratin 7 (CK7), estrogen receptor (ER), progesterone receptor (PR), S100, and cytokeratin 20 (CK20) are useful, but none alone reliably distinguishes primary CAC from both benign and malignant disorders [4, 5].

Case report

A 52-year-old male patient had a left inguinal subcutaneous mass 3 cm × 2 cm in size for 4 years with a clear edge and good mobility, without rash, pain, ulceration, or change in skin colour. No abnormality was found in the external genitalia, anus, rectum, or prostate. The serum α-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 12-5 (CA12-5), carbohydrate antigen 19-9 (CA19-9), and prostate-specific antigen (PSA) values were within the range of the reference values. No abnormal swollen lymph nodes were observed by B-ultrasound examination of the bilateral inguinal area. A wide local excision of the tumour was performed. Pathological sectioning suggested that a large number of tumour cells with abundant eosinophilic cytoplasm were present in the collagen fibres of the skin. Certain tumour cells were arranged in nests, others in cords and still others in cribriforms with identical shape (**Figure 1**). The immunohis-

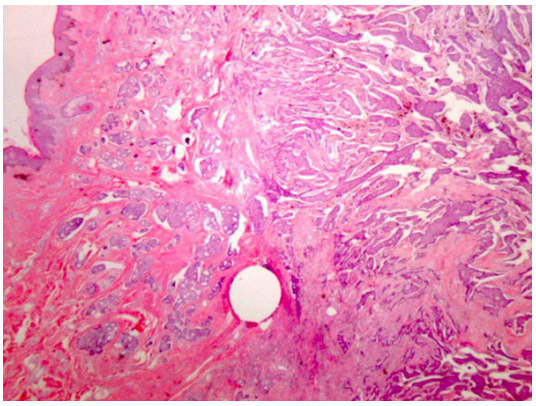

Figure 1. The histological findings of the metastatic lymph node of the CAC in the left groin area. The lymph node was well preserved in shape but damaged in structure; it was infiltrated with tumour cells, which were arranged in nests of identical shape. The tumour cells exhibited an increased ratio of cell nucleus to cytoplasm, and increased numbers of collagen fibres were found between the tumour cells. HE. Original magnification: × 100.

tochemistry revealed Ki67 (5%-10%), GCDFP15 (+), 34BE12 (+), oestrogen receptor (+), progesterone receptor (+), cytokeratin 7 (+), human epidermal growth factor receptor-2 (HER2/neu), P53 (-), P63 (-), and cytokeratin 20 (-). Combining the results of the immunohistochemistry with the clinical manifestations, the tumour was diagnosed as CAC. The results of PET-CT suggested that no elevation of FDG intake was found in the regional lymph nodes or the systemic organs two months after the operation.

Ten months later, two subcutaneous masses of 2 cm × 1 cm were found below the original incision in the left groin. A B-ultrasound examination showed abnormal enlargement of the left inguinal lymph nodes, which retained their full shape but exhibited a thickened cortex and rich blood flow, suggesting regional lymph nodes metastasis. Regional lymphadenectomy was performed on the left groin. The pathological section showed that the lymph nodes were well preserved in shape but damaged in structure. Most of the regional lymph nodes were infiltrated by tumour cells, which were arranged in nests with identical shape and exhibited an increased ratio of cell nucleus to cytoplasm and increased numbers of collagen fibres between the tumour cells. Three of the seven left inguinal lymph nodes were metastasised.

During the outpatient follow-up, B-ultrasound examination showed abnormal enlargement of the right inguinal lymph nodes 17 months later, which retained their full shape but exhibited low, weak internal echoes and rich blood supply. The biopsy of a right inguinal lymph node showed adenocarcinoma metastasis. Subsequently, right inguinal lymphadenectomy was performed. The pathological results showed three metastases in eleven right inguinal lymph nodes. No evidence of recurrent or metastasis disease has been seen after a follow-up period of 30 months till now.

Discussion

CAC is a rare adnexal carcinoma with only scattered reports with the largest series to date describing 24 cases [6-10]. There is a lack of consensus regarding definition and little information about the clinical or pathologic characteristics of this tumor [10]. CAC can exhibit a wide variety of clinicopathologic presentations, making accurate diagnosis difficult [2, 3, 11]. There was a long duration of time between the initial identification of a mass and the subsequent diagnosis and initiation of treatment [11]. Although the incidence is extremely rare, both clinicians and pathologists should be alert to the possibility of synchronous double primary apocrine carcinoma in cancer patients with malignant cutaneous lesions [12].

At birth, the apocrine sweat glands are located primarily on the axilla and in the anogenital region. However, modified apocrine glands exist in the eyelid (Moll's gland), in the ear canal (ceruminous glands), and in the breast as mammary glands [3]. Apocrine glands are characterized by an excretory duct with a straight intradermal component that is lined by stratified squamous epithelium, typically opening into a hair follicle, and a secretory tubular component that is lined by a single layer of secretory cells with eosinophilic cytoplasm surrounded by an outer layer of myoepithelial cells [13]. The inner layer of epithelial cells is characterized by decapitation secretion, a feature considered pathognomonic for apocrine differentiation [14]. The malignancy arises at sites of apocrine glands, which have a relatively limited distribution in the body and are found in the axillae, the medial aspect of the upper arm, the areola, the lateral aspects of the breasts, the ear canals, the eyelids, and the anogenital region [15]. The

disease is primarily diagnosed in the fifth to seventh decade of life, with similar incidence observed in men and women and without racial predilection [1, 11]. Generally, this disease shows no obvious symptoms, grows slowly, presents single or multiple lesions that consist of nodular or cystic plaques of different sizes, and results in a red or purple skin surface and occasional ulceration [1]. Although there is always local invasion in CAC, several published cases have demonstrated metastasis to regional lymph nodes or even to the lungs, bone, and brain [11, 16].

The correct interpretation of CAC is often a conundrum: at one end of the spectrum, there are highly differentiated malignant neoplasms, which are frequently difficult to differentiate from benign adnexal lesions, and at the other end of the spectrum, the lesions can be less well differentiated and require differential diagnosis of adenocarcinoma metastasis from a variety of organs [2]. Morphologically, CAC shows variable growth patterns such as tubular, cribriform, or papillary occasionally with solid sheets of cells. However, cystically dilated glands that show atypical cells lining the glandular spaces with features of decapitation secretion are the most common histologic finding [6]. Histological diagnosis criteria of CAC are not standardized. Rabson et al. suggested the criteria of CAC were: A tumor with an infiltrative margin and/or cytologic pleomorphism unacceptable for a benign neoplasm; At least focal decapitation secretion into luminal space by glandular epithelial cells with abundant granular, eosinophilic cytoplasm; and no history or clinical evidence of breast cancer [10]. The diagnosis of malignancy in apocrine tumors is based upon architectural and cytological criteria, but they are largely subjective [17]. Paties et al. believed that the most reliable criteria for the diagnosis of CAC are decapitation secretion, PAS-positive diastase-resistant material in the cells or lumina, and positive immunostaining for GCDFP-15 [18]. Moreover, this tumour type showed various forms, such as papillary, complex glandular and tubular forms, solid cellular sheets and cord-like arrangements, according to the degree of differentiation [13].

Invasive carcinoma of the breast is the most common malignancy affecting women worldwide [19]. The differential between CAC from cutaneous metastases and breast carcinoma is one of the most difficult tasks in the field of dermatopathology; immunohistochemistry has only been partly helpful in solving this conundrum. Misdiagnosis of synchronous or metachronous apocrine carcinoma as a metastasis may allow the underlying disease to develop without proper local therapy because cutaneous metastases are classified as stage IV disease in patients with underlying primary carcinoma. Thus, a differential diagnosis of apocrine carcinoma from metastatic adenocarcinoma is very important. In some instances, the expression of certain markers, may give a clue to the possible, because immunohistochemistry was performed to help determine the origin of the cancer [15, 20]. The most commonly reported immunohistochemical markers included GCDFP15, EMA, lysozyme, CEA, ER, PR, CK7, Her2/Neu, P53, S-100, and CK20 in the literature [5, 10, 13, 18, 21-23].

GCDFP-15, from the family of giant cystic disease fluid protein (GCDFP), which is expressed in the cytoplasm of apocrine epithelium in the lacrimal glands, ceruminous glands, glands of Moll, submandibular glands, tracheal and bronchial glands, sublingual gland and minor salivary glands, is a tissue-specific marker of apocrine epithelium [24]. It can be observed that GCDFP-15 was negative in the report of Zelger et al. and Hall et al., but positive in the other reports [2, 6]. The full expression of GCDFP-15 in CAC was observed in 6 cases in the report of Paties et al. and 13 cases in the report of Robson et al. [10, 18]. Notably, enzyme histochemical determinations are useful to establish apocrine differentiation, but positivity for GCDFP-15 is not sufficient to determine apocrine differentiation because eccrine tumours and normal eccrine glands are sometimes positive for GCDFP-15 [13].

Epithelial membrane antigen (EMA) is a type I transmembrane glycoprotein of high molecular weight with a large number of variable terminal repetitive amino acid sequences and 0-glycosylation sites that is expressed at low levels in normal glandular cells. However, due to the abnormal and incomplete glycosylation found in cancer tissues, its core protein exposes new protein epitopes or carbohydrate antigens, thus becoming one of the specific antigens of epithelial cancer [25]. The study conducted by Paties et al. suggested that all CACs strongly

react with EMA [18]. However, further investigations will be needed to determine whether the EMA results are identical in apocrine adenocarcinoma and breast cancer, as the αSMA and cytokeratin characteristics are.

The S100 protein was found in the three nonaxillary CACs by Paties et al., and S100 was positive in two cases reported by Katagiri et al., but negative in the other reports [13, 18]. CK20 is different from other CKs in that its expression is limited to the gastrointestinal epithelium. Rutten et al. reported that CK20 was not expressed in 26 cases of primary cutaneous cribriform apocrine carcinoma [26]. The study conducted by Robson et al. found that 8 of 13 cases (62%) were oestrogen-receptor positive, 3 of 5 cases (60%) were progesterone-receptor positive, and 7 of 11 cases (64%) expressed androgen receptors [10]. Interestingly, most primary apocrine breast carcinomas are androgen receptor-positive, but these tumours are typically negative for oestrogen/progesterone [10]. HER2/neu overexpression has not been found in sweat gland carcinomas. However, HER2 expression was present in the case reported by several authors [5, 9, 27].

Other markers are, as well, of relative help when facing a possible CAC. CEA, B72.3, low molecular weight keratins, alpha-1-antitrypsin, lysozyme, Leu-M1, and LN5 are commonly expressed in CAC cells [6]. According the immunohistochemistry results of αSMA, cytokeratin, and p53, Miyamoto et al. suggested that apocrine carcinoma, apocrine adenoma, and apocrine hyperplasia are successive steps in a linear progression model terminating in apocrine carcinoma, as in invasive breast cancer and low grade sebaceous carcinoma [25]. It was once demonstrated as more frequently expressed in sweat gland carcinomas than in breast carcinomas [20].

In our retrieved English literature, Dai Ogata et al. recommend wide local excision for a primary lesion and prophylactic regional lymph node dissection at initial therapy because of the high frequency of regional metastasis of CAC [28]. Our case was rare and unique. By combining the histological finding, PET-C results, and immunohistochemical markers, the tumour could be confirmed as CAC. The patient exhibited bilateral metastases of the inguinal lymph nodes and underwent inguinal lymphadenectomy on each side in succession. The patient survived for 8 years and should be continuously followed up.

Disclosure of conflict of interest

None.

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