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Case Report

Mammary carcinoma with osteoclast-like giant cells: a case report

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Abstract: Mammary carcinoma with osteoclast-like giant cells is rare, and comprises less that 2% of breast carcinoma cases. Herein, we present a case of a 45-year-old woman who underwent breast lumpectomy and sentinel lymph node biopsy for a solitary well defined breast tumor. Histological examination revealed an invasive tumor composed of ducts, small nests and cribriform formations intermixed with a prominent osteoclast like giant cell component. The background stroma is hemorrhagic with conspicuous hemosiderin deposition. The paper will outline the clinico-pathologic characteristic features of this uncommon subtype as well as the current understanding on the pathogenesis of the osteoclast-like giant cells. The invasive carcinoma and the osteoclast-like giant cells staining patterns using immunohistochemical stains for estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, receptor activator of nuclear-kB, RANK ligand, and matrix metalloproteinase 1 are reported.

Keywords: Mammary carcinoma, osteoclast like giant cells, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (Her2/neu), receptor activator of nuclear-kB expression (RANK), RANK ligand (RANKL) expression, matrix metalloproteinase 1 (MMP1)

Introduction

Mammary carcinoma with osteoclast-like giant cells is uncommon, comprising less that 2% of breast carcinoma cases [1, 2]. The current paper does not address osteoclast rich mammary carcinoma in association with granuloma or foreign body material. Receptor activator of nuclear-(RANK) & RANK ligand (RANKL) are vital regulators of osteoclastic differentiation and activation. RANK is a transmembrane protein type I and RANKL is the sole ligand for RANK [3]. There is a correlation between positive RANK immunohistochemical stain and development of bone metastases (P = 0.023) [4]. Moreover, RANK transcript expression is reduced in estrogen receptor positive cancer cases and vice versa (P = 0.026). RANK/RANKL expression might serve as prognostic marker [3]. Matrix metalloproteinases (MMPs), including MMP1 are endopeptidases that degrade extracellular matrix proteins and thus have a role in tumor invasion and metastasis. MMPs have higher expression in breast carcinoma compared to normal mammary tissue, and an association between strong expression and short relapse free survival is documented [5, 6]. MMP1 is one of the bone metastasis related genes using human breast cancer cells [7]. This paper explores the expression of RANK, RANKL and MMP1 in this osteoclast-like giant cells rich histological variant.

Report of a case

A 45-year-old female presented with left sided breast lump. Left breast mammography confirmed the presence of a lobulated and hyper dense round mass that measures 3 cm in greatest dimension. Ultrasound study documented the well circumscribed round hypoechoic mass, measuring 2.6 cm in greatest dimension and confined to the lower outer quadrant. CT scan showed no evidence of distant metastasis. The patient underwent left breast lumpectomy and sentinel lymph node biopsy. Resection specimen showed a well circumscribed soft fleshy brown tumor. The tumor measured 3 cm in

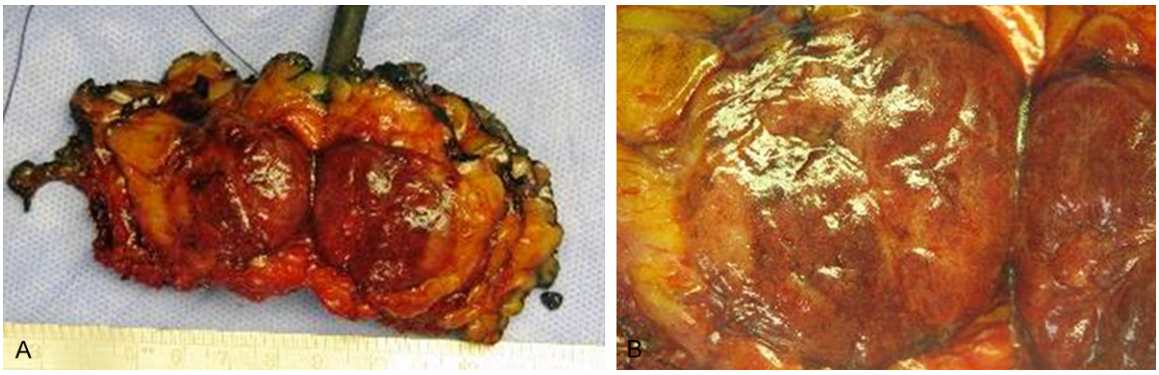

Figure 1. Breast. A. Gross picture of a well circumscribed tumor. B. The tumor is soft, brown and fleshy.

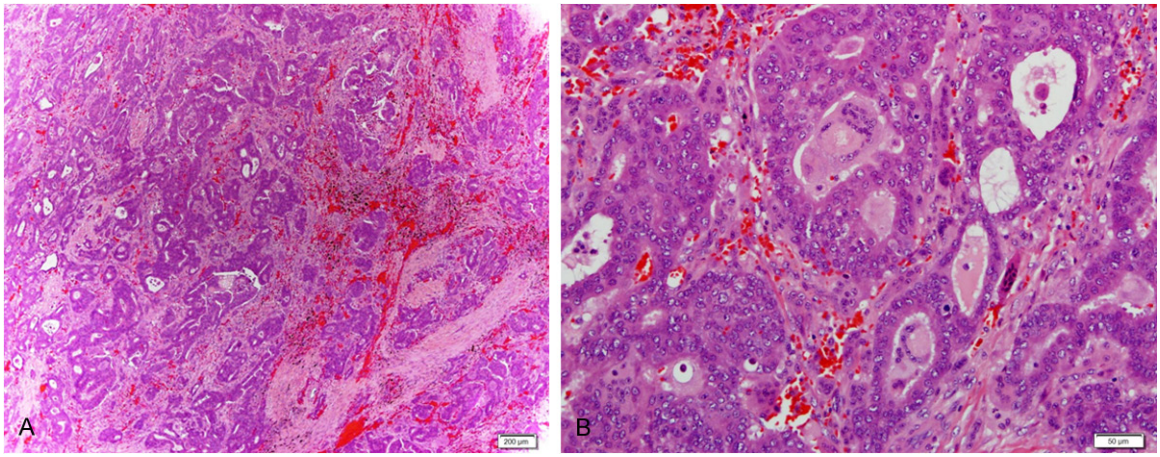

Figure 2. Breast. A. Low-power view of an infiltrative mammary tumor arranged in ducts, nests and cribriform formations in a prominent hemorrhagic background. B. High-power view highlight the intimate association between the tumor and the abundant osteoclast like giant cells.

greatest dimension (**Figure 1A**, **1B**). The tissue was fixed in 10% buffered formalin and embedded in paraffin. Hematoxylin-eosin-stained sections revealed a tumor composed of ducts, small nests and cribriform formations intermixed with a prominent osteoclast like giant cell component. The background stroma revealed hemorrhage and hemosiderin deposition (**Fiure 2A**, **2B**). The invasive ductal component was of Nottingham Combined Histological grade 2. Left axillary sentinel lymph node was free of malignancy (pN0). Tumor cells stained positive for estrogen receptor (SP1, Roche Ventana) and progesterone receptor (1E2, Roche Ventana) with Allred score of 7 and 8 respectively. The osteoclasts like giant cell nuclei were negative for both hormonal markers. Ki-67 was approximately 5%. Her2/neu was equivocal (2+) (4B5, Roche Ventana) on immunohistochemistry. Re-assessment by FISH technique showed no gene amplification, with HER-2/CEP17 ratio of 1.1.

In addition, immunohistochemical stains for RANK/RANKL and MMP1 is performed. For RANK protein, a mouse monoclonal antibody is used (clone 80707, R&D Systems, Inc.). Tumoral tissue staining intensity was graded as negative, mild (1+), moderate (2+) or strong (3+). RANK overexpression is considered when the score is moderate (2+) or strong (3+) [4]. Normal ducts lobular units show moderate staining with RANK immunostain, while the invasive ductal carcinoma component in the current case is negative, and the osteoclast like giant cells exhibited focal mild (1+) staining, thus not overexpressed (**Figure 3A**). RANKL immunostain is negative in normal ducts lobular units, but display focal mild (1+) staining in invasive tumor including the osteoclast likes giant cells

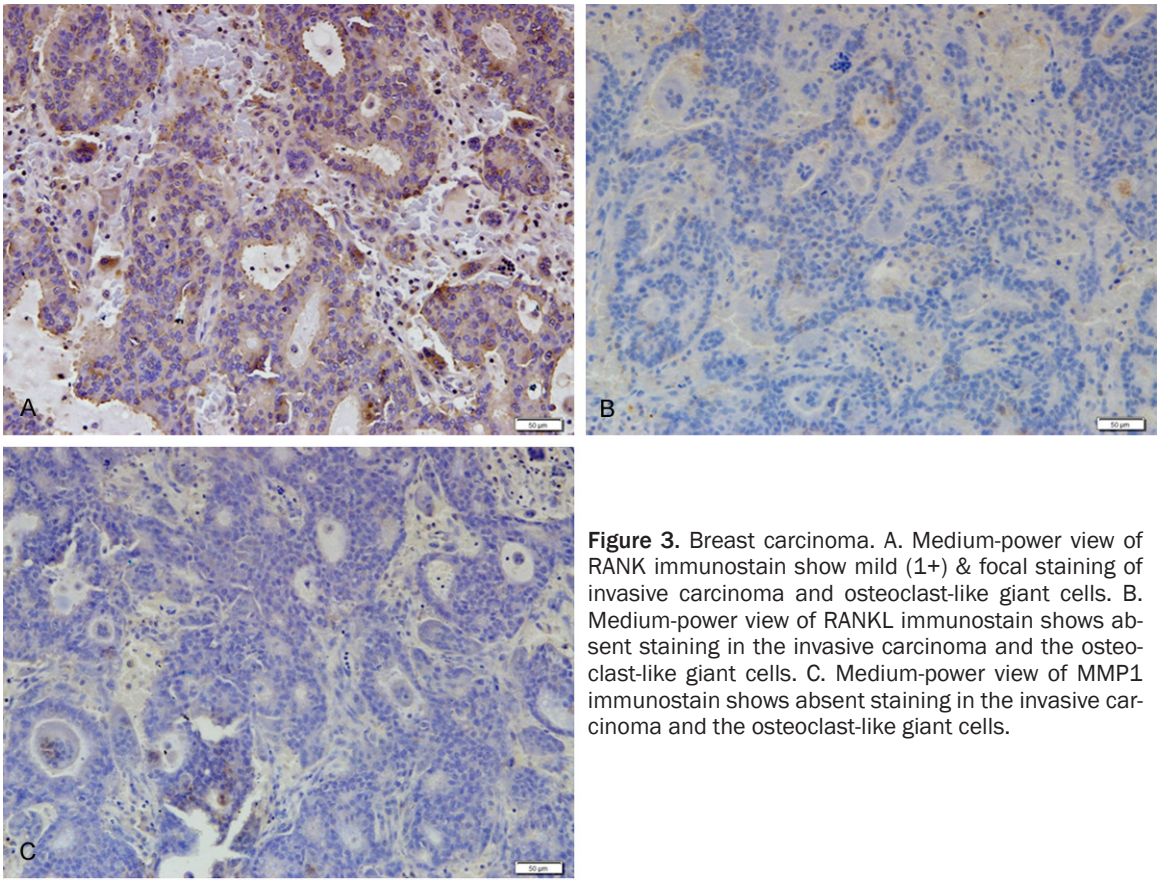

Figure 3. Breast carcinoma. A. Medium-power view of RANK immunostain show mild (1+) & focal staining of invasive carcinoma and osteoclast-like giant cells. B. Medium-power view of RANKL immunostain shows absent staining in the invasive carcinoma and the osteoclast-like giant cells. C. Medium-power view of MMP1 immunostain shows absent staining in the invasive carcinoma and the osteoclast-like giant cells.

Table 1. Gross differential diagnoses of current case

Gross Pathologic Differential Diagnoses
Carcinoma with medullary features
Juvenile (secretory) carcinoma
Malignant melanoma
Haemangioma
Angiosarcoma
Lymphoma

(**Figure 3B**). MMP1 is negative in normal and tumoral tissue (**Figure 3C**). RANK immunostain is prepared using TRANCE/TNFSF11/RANK L antibody using Heat Induced Epitope Retreival (HIER) with Citrate buffer pH 6.0 for 20 minutes at 97 C, Ab. Incubation time of 25 minutes. MMP1 immunostain is prepared using MMP-14/MT1-MMP Antibody; Proteinase K enzyme applied for 7 minutes, Ab. Incubation time 25 minutes. Detection system FLEX-DAKO (5 min. H_2O_2, 20 min. Polymer and 5 min. DAB) was employed and counter stain was Hematoxylin for 1 minute.

The patient's stage was pT2N0M0. She received adjuvant radiotherapy and hormonal therapy. Twenty-months following date of operation, the patient is clinically free of disease and her most recent mammogram is unremarkable.

Discussion

Mammary carcinoma with osteoclast like giant cells is a rare subtype of breast carcinoma, comprising less that 2% of carcinoma cases [1, 2]. As per the WHO classification of tumors of the breast, these tumors are designated carcinoma with osteoclast-like giant cells and are categorized under invasive carcinoma of no special type [8]. To date, more than 200 cases have been reported [9]. This distinct subtype of breast carcinoma was first described in the French medical literature by Leroux 1931 and Duboucher et al 1933 [10, 11]. In the English literature, Factor et al reported two similar cases in 1977 [12]. This was followed by a series of eight cases by Agnantis & Rosen in 1979. In the latter study, authors had a total of

eight cases; five ductal and three lobular phenotypes. Three patients had nodal metastasis. In their cohort patients seemed to have a less favorable prognosis acknowledging the limited clinical follow up period [2]. Subsequently, additional case reports followed [13-33]. The cases occurred over a wide age range 28-88 years [18]. Reported cases on non-metaplastic carcinoma associated osteoclast-like giant cells, showed that 34% of cases had lymph node involvement, and 86% of patients were free of disease on a mean follow up period of 2.4 years [9]. Bone -one case- and lung metastases -two cases- have been reported [9, 18]. The majority of the patients underwent modified radical mastectomy as the mainstay management option. Radiologically most tumors are solitary and well defined but rarely multiple [1]. Many of these tumors are readily diagnosed by fine needle aspiration. A task greatly facilitated by the presence of large osteoclast-like giant cells in addition to the neoplastic epithelial component. On cytological smears the osteoclast-like giant cells display branching cytoplasmic processes, voluminous cytoplasm, monomorphic oval nuclei and small nucleoli. Haemosiderin-laden macrophages are seen in a considerable number of the cases [25, 31, 32]. On gross examination, the previously reported tumors as well as the current case reveal circumscribed mass that is dark brown or red-brown in color. The tumor size varied from 0.5 to 10 cm [2, 18]. The gross differential diagnoses are listed in **Table 1**. On microscopic examination, the osteoclast-like giant cells are often seen admixed with other histological subtypes of invasive breast carcinomas most commonly ductal, but also lobular, mucinous, cribriform, papillary, and metaplastic [20, 26]. The majority of the tumors are ER, PR positive, and Her2 negative. Tumors studied with proliferation labeling index Ki-67, confirms luminal phenotype especially luminal A subtype [9]. Receptor activator of nuclear- (RANK), RANK ligand (RANKL), and matrix metalloproteinase 1 (MMP1) are absent or not overexpressed in the current case. This finding is in concordance with the reported favorable prognosis of this subtype. However, this finding is based on a single case, and would be prudent to validate it on a greater number of cases.

The osteoclast-like giant cells are of mesenchymal origin and are histiocytically derived as evidenced from immunohistochemical and ultrastructural data [9, 12-25]. It is postulated that the osteoclast-like giant cells form in response to tumor induced hypervascular microenvironment [27]. Others postulate that peripheral blood monocytes transformation into osteoclast-like giant cells in breast carcinoma is indeed virally induced [33]. The concept of virally induced breast carcinomas has been the topic of many recent studies, documenting an association likely causal between different oncogenic viruses and breast carcinogenesis, examples include Epstein Barr virus, and high risk human papilloma viruses 16/18 [34, 35].

Nonetheless, it is interesting to know that when these osteoclast-like giant cells are isolated from breast carcinomas, and placed in cell cultures over bone slices, they performed an osteoclast function resulting in bony resorption pits formation [33]. Their presence however, does not seem to influence the clinical outcome.

In summary, mammary carcinoma with osteoclast-like giant cells is a rare subtype of breast carcinoma. The pathogenesis of the osteoclast-like giant cells is not clearly understood and is at least partially attributed to tumoral induced angiogenesis and inflammatory cytokines. The mere presence of the osteoclast-like giant cells does not seem to alter clinical outcome. In view of the limited number of reported cases on this rare histological subtype and the relatively short follow up periods, it is difficult to establish patients' prognosis. However, current evidence suggests it is similar if not better than other common types of invasive carcinomas [8]. More studies are needed to establish the exact pathogenesis of the osteoclast-like giant cells, and to determine their role(s) -if any- in tumorgenesis.

Disclosure of conflict of interest

None.

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