



Case series

Osteoclast-like stromal giant cells in invasive ductal breast cancer: A case series

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ABSTRACT

Introduction: Breast Cancer with osteoclast-like stromal giant cells (OLGCs) is a rare pattern of invasive non-special type ductal carcinoma. The OLGCs are specific type of macrophage and are likely distinct from true osteoclasts. The aim of this case series was to describe the characteristics of this invasive ductal carcinoma rare histotype.

Presentation of cases: The authors present the cases of two young women that, during national screening, discovered with mammography X-ray a breast lump suspected for malignancy. The core needle biopsy confirmed the malignancy of both nodule and in one patient the histological analysis revealed pre-operative OLGCs. In both cases the sentinel lymph node biopsy was negative therefore a quadrantectomy without axillary lymphadenectomy was done. The definitive histopathological examination was positive for invasive ductal carcinoma with OLGCs and CD 68 marker positivity. After surgery, patients underwent adjuvant therapy and multidisciplinary follow-up.

Discussion: The origin and mechanism for developing osteoclast-like giant cells is unknown. The OLGCs directly descend from the precursors of the monocyte-macrophage. The rarity of this entity often promotes a misleading diagnosis, with >50 % of erroneous diagnosis of benign lesion. The prognostic significance of OLGCs in breast cancer is controversial, however it doesn't seem to influence the axillary lymph nodes spread. The presence of preoperative OLGCs didn't modify our surgical and oncological approach.

Conclusion: Breast Cancer with OLGCs is a rare tumour that has a similar prognosis to other carcinomas of identical grade and stage in most cases. The rarity and characteristics of this neoplasm require personalized treatments, discussed by a multidisciplinary team.

1. Introduction

Breast Cancer with osteoclast-like stromal giant cells (OLGCs) is a rare pattern of invasive ductal carcinoma, in the WHO classification with an incidence between 0.5 and 1.2 % [1]. This distinct subtype of breast carcinoma was first described in the French medical literature by Leroux 1932 [2].

This tumour is characterized by the presence of multinucleated giant cells, associate with an inflammatory, fibroblastic, hypervascular stroma or within tumour glandular lights. The OLGCs are specific type of macrophage, likely distinct from true osteoclasts. The origin and nature of multinucleated OLGCs in extra-skeletal tumours are not yet defined.

However, the OLGCs have similar characteristics to bone osteoclast, in fact without cytonuclear atypia these cells are morphologically like the osteoclastic cells [3]. Moreover, when these OLGCs are isolated from breast carcinomas, and placed in cell cultures over bone slices, they performed a bone resorption, a classical function of osteoclast [4].

The origin and mechanism for developing OLGCs is unknown. One hypothesis suggests that the migration of macrophages in the tumour is favoured by the angiogenesis, developed thanks to the vascular endothelial growth factor, produced by cancer cells [5]. Furthermore, the secretion of cytokines, such as VEGF, determines an inflammatory and hyper vascular stroma and promotes macrophage migration. Then, the differentiation of macrophages in OLGCs is a response of the

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microenvironment [6]. The OLGs directly descend from the precursors of the monocyte-macrophage, so they probably have a hematopoietic origin [7].

The aim of this case series was to describe this rare histotype of invasive ductal carcinoma, highlighting the low incidence and discussing diagnosis, management, and prognosis of these patients.

This case series was written according to SCARE guidelines [8].

2. Presentation of cases

We reported two cases of invasive ductal carcinoma with OLGs treated in our Breast Unit between July 2019 and January 2022.

2.1. Case 1

A 38-year-old female patient performs breast cancer national screening. The ultrasound and the mammography X-ray showed presence of a nodule of 7 mm in equatorial inner quadrant of right breast, which was highly suspect for malignancy (Fig. 1). The core needle biopsy, of the suspect nodule, was positive for highly differentiated invasive ductal carcinoma with OLGs and haemorrhagic stroma. The histotype was confirmed by immunohistochemical determination of markers: CD68 stained tumour cells (Fig. 2).

Patient was in premenopausal, no smoker, with negative oncological familiar history, without BRCA mutation, without comorbidity and with negative oncological markers.

In July 2019, an equatorial inner quadrantectomy of right breast with sentinel lymph node biopsy was performed. The sentinel lymph node, analysed with One-Step Nucleic Acid Amplification method (OSNA), was negative therefore no axillary lymphadenectomy was performed. The definitive histopathological examination showed a moderately differentiated invasive carcinoma with OLGs of 6 mm, 20 mm far from deep level and 1 cm from other levels. There was an immunoreactivity for oestrogen receptor (ER > 95 %) but absence for progesterone receptor with Ki67 equal to 7 % and Her2\neu clone CB11 score 0. According to the TNM staging of tumour [9], the overall stage was pT1aN0. Margins of lesion were free of the carcinoma.

After surgery, the patient underwent adjuvant therapy with radiotherapy and hormone therapy with aromatase inhibitor. At two years and 11 months to diagnosis of cancer, at the last follow-up, the patient was in good clinical conditions without evidence of clinical and radiological disease recurrence.

2.2. Case 2

The second case was a 41-year-old female patient with a medical

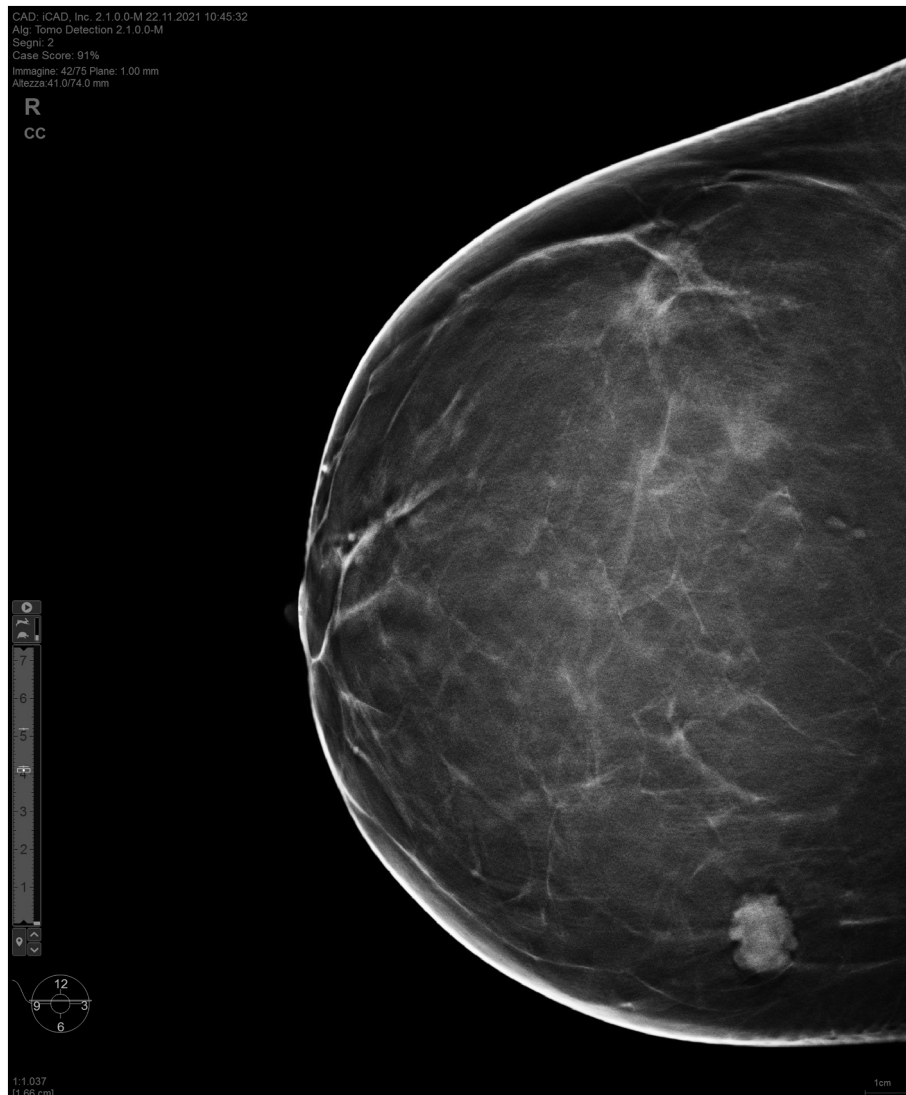


Fig. 1. Mammography X-ray showing a nodular lesion with irregular margins of 7 mm in equatorial inner quadrant of right breast.

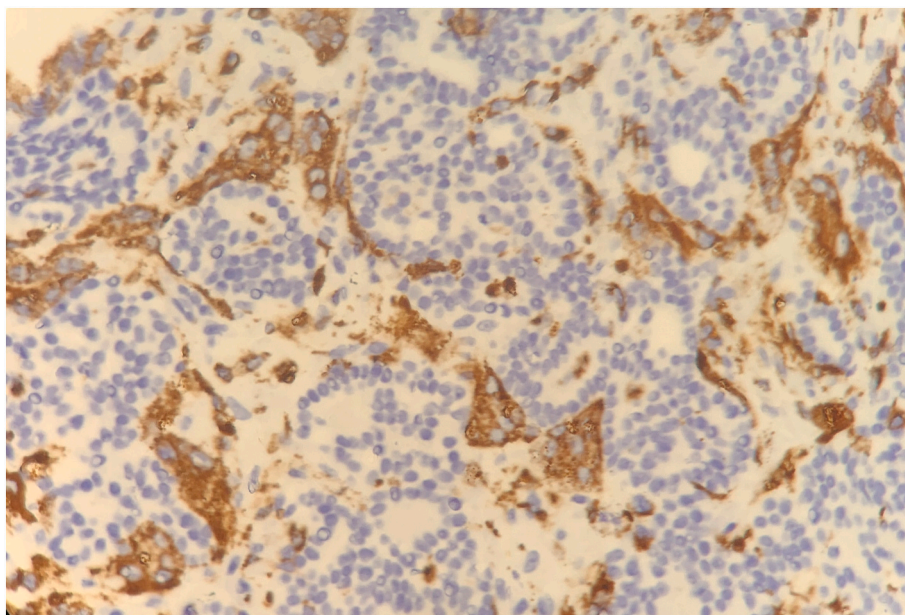


Fig. 2. Immunohistochemistry 400× magnification with CD68 immunostain highlights macrophages and the stromal osteoclast-like giant cells.

history of type II diabetes in treatment from April 2021 and Hashimoto's thyroiditis. She was no smoker, with negative oncological familiar history, without BRCA mutation and negative oncological markers. In January 2021 she underwent ultrasound thyroid follow-up for her thyroiditis, discovering in the right lobe two nodules of 5 and 6 mm then analysed with FNA (fine-needle aspiration) with diagnosis of a high-risk indeterminate nodule (TIR3B).

In November 2021, during the national screening, the mammography X-ray showed an irregular nodule of 7 mm in the upper inner quadrant of the right breast (Fig. 3); the ultrasound showed the same lesion, but of 17 mm, suspected for malignancy. The core needle biopsy of the suspect nodule confirmed malignancy: invasive non-special type ductal carcinoma, without OLGs (Fig. 4).

In January 2022, the patient underwent total thyroidectomy and quadrantectomy of upper inner quadrant of right breast without axillary lymphadenectomy because the sentinel lymph node biopsy was negative at OSNA assay. The final anatomopathological examination was positive for invasive non-special type ductal carcinoma of 2,4 cm, 15 mm far from all levels, with OLGs pattern with peritumoral vascular invasion. The tumour had immunoreactivity for oestrogen and progesterone receptors (90 %) with Ki67 equal to 16 % and positive Her2\neu clone CB11 (score 1+). The overall stage was pT2N0, according to the TNM staging of tumour [9]. The immunohistochemical determination of markers showed CD68 stained tumour cells. After surgery and multidisciplinary evaluation of our Breast Unit, patient underwent adjuvant chemo/radiotherapy (Adriamycin and cyclophosphamide (AC) scheme followed by hormone and radiotherapy on the residual breast). At five months to diagnosis of cancer, at the last follow-up, the patient was in good clinical conditions without evidence of clinical and radiological recurrence.

3. Discussion

OLGs is a rare tumour mainly affects postmenopausal women [10], with rare cases in young women (<45 years old), as in our experience.

The rarity of this entity promotes often a misleading diagnosis: in >50 % of cases the mammography suggests an erroneous diagnosis of benign lesion [5]. However, for our patients, mammography showed presence of lesion with malignant characteristics, suggestive of heteroplastic tissue. Furthermore, the fine needle aspiration usually makes

diagnosis of this type of tumour due to the presence of large osteoclast-like giant cells in addition to the neoplastic epithelial component [11]. In our experience only in one of two cases, OLGs were found pre-operative; but, in both cases, the core biopsy described tumour cells, allowing the correct therapeutic process.

Positivity for pan-macrophage markers (E-cadherine, CD68 and CD163) indicates the macrophage origin of the neoplasm [12]. In most cases the tumour is associated with an invasive ductal carcinoma with luminal A phenotype (89 %) and a minority of luminal B (11 %) [13]. Our experience confirms the literature data, both the patients had a Luminal A phenotype related to the primary breast cancer histotype.

In the literature this rare tumour has the same prognosis of other carcinomas with identical grade and stage [1]. However, the prognostic significance of OLGs in breast cancer is controversial: several authors reported less favourable prognosis related to OLGs [14]. Given this discrepancy, it is probably that the prognosis is more related to the type of cancer associated respect the presence of the OLGs [15]. Moreover, there isn't evidence of correlation between OLGs in breast cancer and positivity for metastasis in sentinel lymph node biopsy. In our experience, the biopsy of sentinel lymph node biopsy, analysed by OSNA method, was negative in both cases. Different authors reported cases with positive axillary lymph nodes [14], however the involvement wasn't related to the OLGs presence but to the breast cancer histotype. To date, the presence of OLGs doesn't seem to influence the axillary lymph nodes spread.

The complete excision of the tumour is the treatment of choice for OLGs in breast cancer as for OLGs in other sites [16]. Moreover, the prognosis seems to be related more to the type of cancer associated respect the presence of the OLGs, for this reason the presence of these cells didn't modify our surgical approach. In the two cases described we performed successfully a conservative surgical treatment with quadrantectomy followed by adjuvant chemo/radiotherapy. Furthermore, axillary staging shouldn't depend on the OLGs, in fact their presence doesn't seem to increase the risk of axillary lymph node metastasis as demonstrated in our experience.

This case series highlights the importance of multidisciplinary management of breast cancer. There are no well-defined guidelines for the treatment of this rare form of cancer, further studies are needed to gain more comprehension of the role of this rare tumour, to determine future personalized treatment strategies.

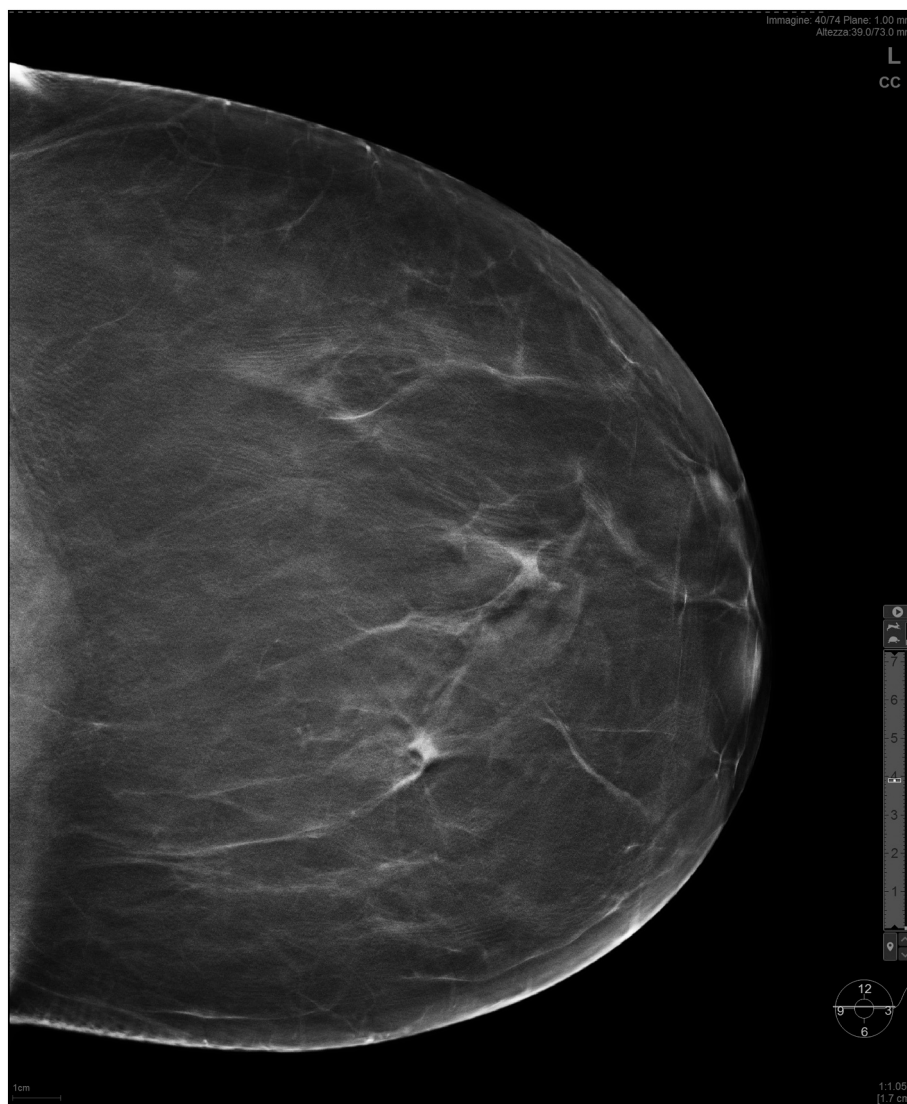


Fig. 3. Mammography X-ray showing an irregular nodule of 7 mm in the upper inner quadrant of the right breast.

4. Conclusion

This case series describes a rare histological type of invasive ductal breast cancer with OLGs. The cytologic features and growth patterns in combination with immunohistochemical studies are mandatory for correct diagnosis. The influence of OLGs presence on the treatment of this type of tumour is controversial, but in our experience, patients have the same prognosis of other patients with diagnosis of identical grade and stage carcinoma and the surgical approach shouldn't be modified by the presence of OLGs. The rarity and characteristics of this neoplasm require personalized treatments, widely discussed by a multidisciplinary team such as those in the Breast Units.

CRediT authorship contribution statement

C.P.: Senior advisor, supervision, performed surgery.

G.T., G.A.: data analysis, study concept and design, writing the paper.

M.G.M.: Data collection, data analysis, supervision.

A.E.M., M.T.: Data collection, data analysis.

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Ethical approval

The study is exempt from ethical approval in our institution.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Registration of research studies

Not applicable.

Guarantor

Prof. Clelia Punzo.

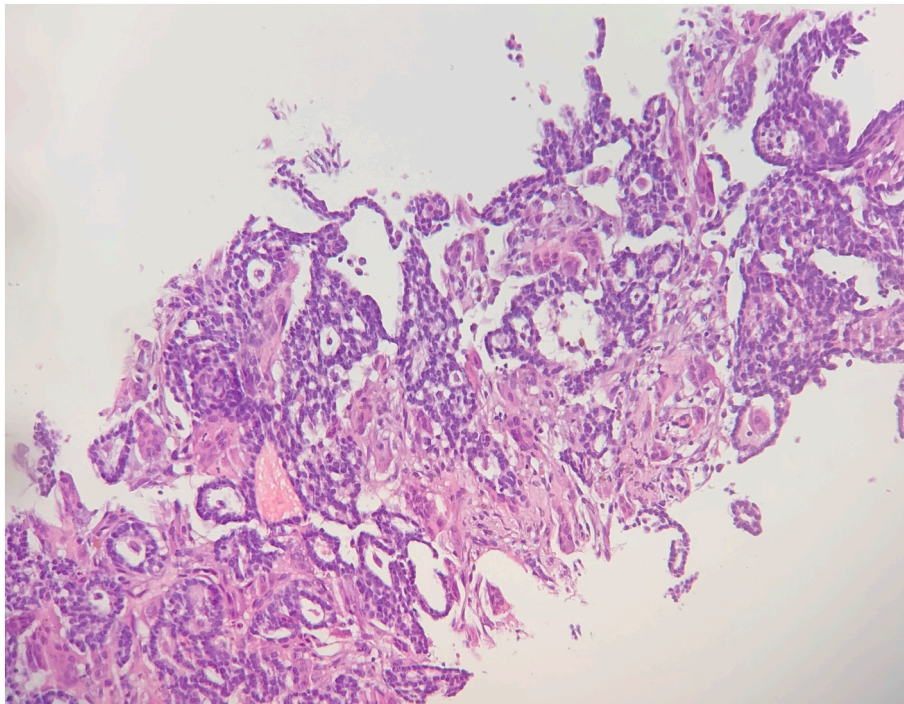


Fig. 4. Haematoxylin eosin staining 200× magnification with stromal osteoclast-like giant cells intermingled with invasive carcinoma cells.

Declaration of competing interest

All authors negate any conflict of interest.

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