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Glycogen-rich clear cell breast carcinoma in a luminal-Her2 molecular subtype: is it only a pathologic feature or is there a gap in therapy?

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Summary

Introduction: Glycogen-rich clear cell carcinoma (GRCC) of the breast is a rare variant of primary breast carcinoma that is characterized by carcinoma cells containing an optically clear cytoplasm and intracytoplasmic glycogen. An ongoing debate exists whether it harbors aggressive clinical features. *Case Report:* The authors report the case of a 41-year-old Greek female patient, who had noticed a lump in the upper inner quadrant of the left breast. The patient underwent a left radical mastectomy with sentinel lymph node excisional biopsy and the histopathological diagnosis revealed a pT3pN0cM0R0 luminal-HER2 GRCC invasive carcinoma of the breast. Although the patient received aggressive multimodal adjuvant chemoradiation, as well as hormone therapy, she recurred 31 months after the operation with cervical, supraclavicular, and mediastinal lymph node metastasis on the left side. *Conclusions:* The biological behavior of GRCC is difficult to predict. According to the presented data, a gap in therapy might exist regarding the treatment of GRCC. Larger studies should be performed in order to refute or confirm this hypothesis.

Key words: Glycogen rich clear cell carcinoma; HER2; GCDFP-15; Ductal breast carcinoma; In situ component.

Introduction

Glycogen-rich clear cell carcinoma (GRCC) of the breast is a rare histological subtype of breast carcinoma occurring with an incidence between 1.4% and 3% of all breast cancers [1]. The vast majority of this tumor type is characterized by carcinoma cells containing optically clear vacuolated cytoplasm and intracytoplasmic glycogen, whereas it has been supported that it tends to have an aggressive clinical course and poor outcome [2]. However an ongoing debate regarding its clinical behavior continues to occur with those supporting the latter and those supporting that no difference exists compared to ordinary breast cancer.

Case Report

A 41-year-old Greek female patient presented in January 2012 to the present clinic with a lump in her left breast after having noticed it on self-examination a few months ago. Physical examination revealed a palpable mass, hard in consistency, with no tenderness to the touch in the upper inner quadrant of her left breast. The lesion was not mobile, had no evidence of dermal invasion, and axillary lymph nodes were not palpable. Mammography showed a high-density irregular mass, with no skin thickening (Figure 1). Ultrasound scanning of the left breast showed a solid, hypoechoic mass, measuring 6.4 cm in diameter that was interpreted as BI-RADS 5 in the 11th hour of the left breast (Figure1).

Ultrasound-guided core needle biopsy (CNB) of the mass was performed, which showed carcinoma cells seen in clusters with distinctly abnormal chromatin pattern. The cells appeared pleomorphic with abnormal nuclear margins and micronucleoli suggesting a case of ductal carcinoma.

Full staging investigations performed, showed no signs of metastatic disease, and thereafter a left modified radical mastectomy with sentinel lymph node excisional biopsy was performed. The mastectomy specimen showed a whitish pale tumor with irregular borders and hard consistency measuring 6.2×5×2.5 cm. The two axillary lymph nodes that were removed, measured 0.8-1.3 cm in diameter and were histologically free of tumor.

Microscopic examination (Figure 2.) revealed a low differentiated invasive ductal adenocarcinoma, composed mainly of large polygonal cells with clear, empty or finely granular cytoplasm, arranged in a solid pattern. The clear cells occupied 60% of the tumor; the remaining 40% showed features of ductal adenocarcinoma not otherwise specified. The two components were intermingled. Clear cells were loaded with glycogen (PAS+/diastase -). The non-clear cells also contained glycogen in lesser quantities. The in situ component had a compact growth pattern with comedo necrosis and high-grade nuclear features. Inside the neoplasm there were no areas of necrosis, while the authors observed areas with columnar cell changes as well as papillary apocrine metaplasia. Immunohistochemistry showed: ER(-), PR(+) 5%, cerbB-

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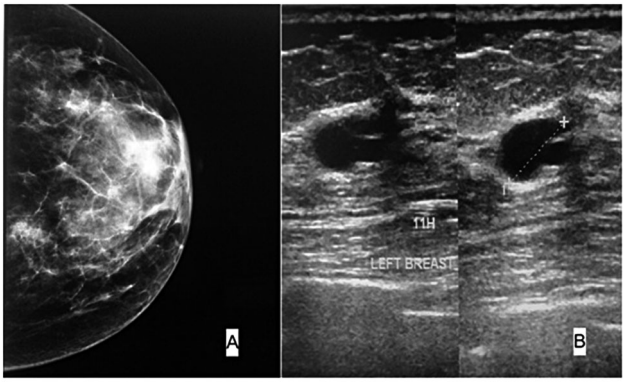

Figure 1. — **A**: Mammography showing a high density irregular mass with calcifications suspicious of malignancy, with no skin thickening. **B**: Ultrasound scanning of the left breast showing a solid, hypoechoic mass, measuring 6.4 cm in diameter BI-RADS 5 in the 11th hour of the left breast.

2 score 3+, p53 < 5%, partially positive GCDFP15 (gross cystic disease fluid protein), Ki-67 (90%), CK14(-), CK5/6(-), EGFR (-) (Figure 2). The histopathological diagnosis was pT3pN0cM0R0 GRCC-infiltrating ductal carcinoma, Stage IIB according to UICC. According to the classification of this study [3] the case was classified as exhibiting the luminal-HER2 molecular subtype.

The patient received adjuvant chemoradiation: four cycles of cyclophosphamide + 5FU + epirubicin with pegfilgrastim for white blood cell support and four cycles of docetaxel + trastuzumab, with one year trastuzumab therapy and radiotherapy of the chest wall, and lymph nodes within the axillary and supraclavicular regions (50 Gy). Moreover the patient received hormone therapy consisting of tamoxifen and goserelin. During the follow-up of the patient, a CT scan of the chest revealed at two years and seven months after the operation, enlarged mediastinal, supraclavicular, and cervical lymph nodes of the left side. FNA of the supraclavicular and cervical lymph nodes confirmed lymph node metastases. After three cycles of additional chemotherapy with pertuzumab, trastuzumab, and docetaxel, a new CT scan of the chest showed no pathological enlargement of the lymph nodes. One year after the first disease recurrence, there were no signs of a new disease recurrence.

Discussion

GRCC is recognized as a distinct carcinoma according to the WHO classification and is defined as a carcinoma with neoplastic cells which exhibit more than 90% abundant clear cytoplasm-containing glycogen [4]. In most of the GRCC cases, cells might obtain a tubular, papillary, and/or solid well differentiated, sometimes associated with an intraductal component form, while apocrine features are often observed. More specifically, the cells have a clear cytoplasm that contains PAS-positive diastase-labile material, consistent with glycogen [2]. Carcinomas of clear cell phenotype of the breast are of several different types including furthermore glycogen rich, lipid rich, secretory, mucinous, and signet-ring cell carcinomas, or they are consistent of myoepithelial apocrine, or neuroendocrine differentiation.

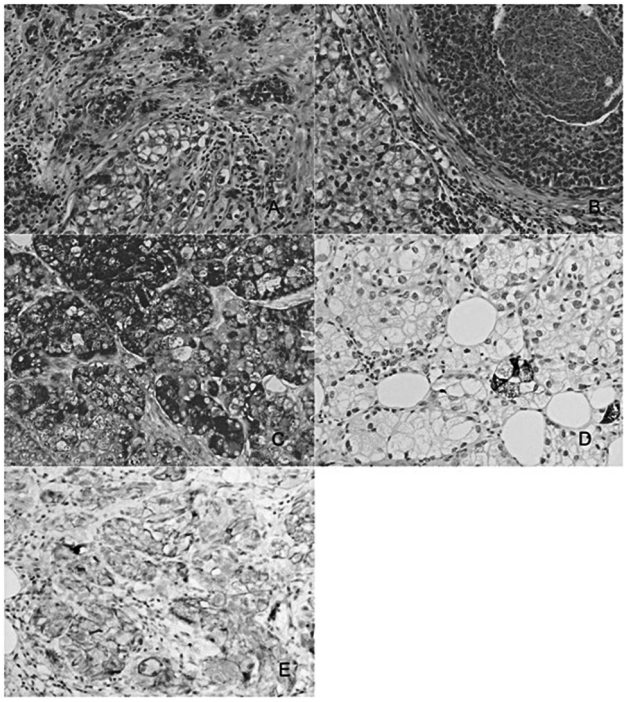

Figure 2. — **A**: Infiltrating atypical neoplastic cells with clear cytoplasm adjacent to an area of ductal carcinoma NOS. **B**: High grade DCIS with comedo necrosis adjacent to infiltrative carcinoma with clear cell morphology. **C**: Large amounts of intracellular glycogen in neoplastic clear cells. **D**: GCDFP-15 positive staining. A few scattered neoplastic cells are immunoreactive for gross cystic disease fluid protein 15. **E**: C-erb2score 3+ in areas with clear cell morphology.

Indeed, clear cell change has been described in the cytoplasm of neuroendocrine tumors of the breast, including pleomorphic lobular or ‘‘histiocytoid carcinomas’’ of the breast, which stain positive in some cells for chromogranin and synaptophysin though they lack glycogen [5, 6].

The differential diagnosis of clear cell lesions of the breast include myoepithelial lesions, such as myoepithelial hyperplasia, myoepithelioma, and adenomyoepithelioma which are all rich in glycogen [7]. The differential diagnosis includes however, metastatic lesions arising from tumors of other organs with clear cell features, such as kidney, pancreas, lung, adrenal gland, salivary gland, and the clear cell variant of melanoma [2, 8].

From a radiological point of view, the GRCC of this case was revealed with the presence of a high density irregular mass showing calcifications in mammography. According to current literature, GRCCs might exhibit these typical signs of malignancy in mammography [9], but according to other reports, calcifications and signs of malignancy might not be present [10]. The illustration of a solid hypoechoic mass on ultrasound scanning seems to be in accordance with other reports [11].

From a biological point of view, GRCCs might harbor

some aggressive features. In a study of six cases, it has been concluded that GRCC breast carcinomas are characterized by a peculiar "low proliferation-low apoptosis" cell kinetic profile which may possibly be accounted for ineffective apoptotic elimination of otherwise slowly proliferating tumor cells [12]. The study was based on the presence of MIB-1 genetic alterations, which are regulators of apoptosis. It was found that tumor size, lymph node metastases, and receptor status were correlated with neither proliferation nor apoptosis. There is however a strong limitation due to the limited cases, that were analyzed.

According to Ma *et al.* [4], in 28 cases of GRCC, only three cases were HER2 positive but expressed more often ER (16 patients) and PR (16 patients) receptors. The vast majority of these tumors at the time of diagnosis were at a maximum IIB disease stage. More studies focusing on treatment revealed that more than 50% of the patients, experienced early metastases in the axillary lymph nodes, exhibiting an aggressive behavior [1, 13]. Fisher *et al.* [6] reported in 45 cases of GRCC that there was worse prognosis compared to ordinary ductal carcinomas. On the other hand, Hayes *et al.* [2] supported that there is no difference in prognosis when the appropriate match between GRCC and ordinary ductal carcinoma is done in terms of tumor size, lymph node dissection, and grade of tumor differentiation. These results were in accordance with the results of Kuroda *et al.* presenting 20 cases of GRCC [8]. This debate can be partially explained due to the limited cases of GRCC presented in the literature, in order to provide a secure statistical analysis and due to the partial heterogeneity of the comparison groups in terms of clinicopathological features.

Voduc *et al.* [3] demonstrated that the ten-year regional relapse free survival of the luminal-HER2 subtype was 95% (95% Cl 83-99%). Interestingly to note is that more than a half of these patients had at the time of diagnosis, lymph node metastases, and despite this fact, after adjuvant treatment, the rate of regional relapse was too low in a ten-year period. On the other hand in the present case, although the patient had an R0 status and received a multimodal aggressive adjuvant treatment, she recurred with lymph node metastasis only 31 months after surgery. Therefore, the question raised here is if the presence of glycogen gives in some cases an aggressive clinical behavior with a risk of an early recurrence with lymph node metastases. If this hypothesis is to be confirmed, a different approach regarding treatment might be necessary in the near future. Interestingly, the results of a meta-analysis showed that even high-dose chemotherapy, eventually combined with an autologous bone marrow or stem cell transplantation, might give a benefit in the three-year event free survival but not in the long-term event free survival and/or overall survival [14]. The latter suggests that there might be a gap in therapy when it comes to treat breast cancers with aggressive biological behavior, based on specific histopathologic alterations.

Conclusions

Regarding current literature, it remains unclear whether GRCC breast cancer harbors aggressive clinical features. In the present case this hypothesis was confirmed with an early recurrence. However, the aforementioned hypothesis should be examined in larger series of patients as the current published studies refer to case series including less than 45 patients each time.

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