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Clear Cell Carcinoma of the Breast: A Rare Breast Cancer Subtype – Case Report and Literature Review

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Key Words
Breast cancer · Glycogen-rich clear cell carcinoma

Abstract
Background: Glycogen-rich clear cell breast carcinoma is a rare histological breast cancer subtype. Its prognosis may vary depending on specific clinical and pathological characteristics such as low grade, strong positivity of estrogen receptor (ER) expression and early diagnosis. ***Case Presentation:*** We present the case of a 53-year-old woman with a bleeding 10-cm-diameter mass in the left breast. The histological examination showed a poorly differentiated tumor with malignant cells characterized by abundant clear cytoplasm. The diagnosis of clear cell carcinoma was based on the histological characteristics of the tumor, and a non-mammary origin was initially ruled out. The tumor was triple negative [i.e. ER, progesterone receptor (PR) and HER2 negative]. Four months after the initial locoregional treatment, the patient developed lung and distant lymph node metastases. ***Conclusions:*** Glycogen-rich clear cell carcinoma of the breast is a rare tumor. Early diagnosis, absence of lymph node metastases and ER/PR positivity are associated with a better prognosis, as in other common breast cancer subtypes.

Case Report

A 53-year-old female patient presented with a 2-month history of a mass in the left breast. A physical examination at the first consultation revealed a massively bleeding, stiff and ulcerated palpable mass (10 cm maximum diameter). No locoregional nodes were palpable. Mammography (fig. 1) showed a round, high-density mass of approximately 8.5 cm.

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Ultrasound of the right breast showed a solid, heterogeneous mass with no axillary involvement.

A core needle biopsy of the mass was performed. The microscopic examination showed a poorly differentiated carcinoma of the breast composed of malignant cells with abundant clear cytoplasm (fig. 2, fig. 3). At immunohistochemistry, many cells were positive for keratins AE1/AE3, E-cadherin and p53, but negative for PAX8, vimentin and HER2 (score 0). Ki-67 was at 80%. The tumor was weakly positive for estrogen receptors (ER) and negative for progesterone receptors (PR). PET-CT revealed suspicious lymph node metastases in the homolateral axilla, but no distant metastases or other primary tumors.

The patient had no serious concomitant diseases or significant systemic symptoms, but the tumor continued to bleed, with fast development of symptomatic anemia, requiring several blood transfusions. The patient initially underwent hemostatic radiotherapy, without any local improvement. Therefore, a left mastectomy with axillary dissection was performed.

The definitive histology confirmed the initial diagnosis. Extensive areas of tumor necrosis were detected, consistent with significant tumor regression after radiotherapy. No angiolymphatic invasion or nodal involvement was observed and the surgical margins were tumor free. The final pathological stage was ypT4 (8.5 cm maximum diameter) ypN0 (0/22).

Wound healing was long and complicated, delaying the start of adjuvant chemotherapy and chest wall radiotherapy. Three months after the surgery, another PET-CT was carried out, which showed lung and mediastinal node metastases. The patient started palliative chemotherapy with cisplatin and vinorelbine, which elicited a partial disease response after 3 and 6 cycles. Ototoxicity (grade 1) and peripheral neurotoxicity (grade 2) developed at the end of the 6th cycle, which prevented the continuation of treatment. The radiological evaluation after 12 weeks showed progressive disease at all sites. A second-line chemotherapy with epirubicin was started (no phase I trial available, because of the persistent neuropathy). We observed a rapid disease progression with endobronchial infiltration. Despite endobronchial laser therapy, the patient died of respiratory failure within a few weeks.

Discussion

Invasive breast cancer is a heterogeneous disease, both in its pathological classification and clinical course. Most tumors derive from the mammary ductal epithelium, principally the terminal duct-lobular unit, and up to 75% of invasive carcinomas are classified as ductal carcinomas. The second most common epithelial subtype is lobular carcinoma (5–15% of cases). In addition, there are several less common variants, well defined by the World Health Organization classification [1].

A tumor subtype with a distinct morphology different from common breast cancers is glycogen-rich clear cell carcinoma (GRCCC) of the breast. The first case of GRCCC was reported by Hull et al. [2] in 1981. In GRCCC, >90% of the neoplastic cells are polygonal with abundant clear cytoplasm, containing glycogen. The histological structure usually resembles ductal carcinoma, but lobular, tubular and mixed ductal-tubular features have also been reported [3–5]. Pure intraductal GRCCC is very rare [6]. GRCCC may form solid and papillary structures [7]. Clear cell breast carcinoma can be easily missed or misdiagnosed in a breast core biopsy specimen because it tends to show a papillary pattern with clear cell and pseudolactating changes, especially in young female patients [8]. Normal breast tissue may include clear cells as a consequence of physiological changes during pregnancy, and a clear cytoplasm may be found in myoepithelial cells and/or apocrine metaplasia.

Clear cell carcinoma of the breast is rare, accounting for 1.4–3% of all breast tumors [7, 9] and commonly affecting women in the 5th decade of life [10]. The tumor size usually ranges from 1 to 6.5 cm; in our case, the clinical mass measured >10 cm (histologically 8.5 cm), and in one case report a tumor mass of 15 cm was palpable [11]. The tumor growth period in the breast before clinical diagnosis may vary between 2 months and 2 years [6]. There are no sufficient published data about the imaging characteristics of GRCCC. Mammography may be inconclusive in case of a dense breast; however, MRI is important in preoperative patient evaluation and surgical planning [6].

A differential diagnosis of GRCCC includes secretory carcinoma, lipid-rich carcinoma, apocrine carcinoma and mucinous carcinoma [1]. Several other 'clear cell' entities may primarily or secondarily involve the breast, e.g. clear cell hidradenoma, sebaceous neoplasm, clear cell papulosis and malignant melanoma. Primary GRCCC may also arise in the lung, endometrium, salivary gland, cervix and kidney [12]. It is therefore mandatory to discriminate between a breast primary and a breast metastasis, especially in case of a renal clear cell carcinoma.

In the series of Kuroda et al. [10] (20 cases, the majority with small tumor sizes), ER and PR positivity was less than in other breast cancer subtypes (ER and PR positive in 35 and 30% of the cells, respectively, as compared with 65 and 35% in invasive ductal carcinomas). No significant correlation was found between histological type and HER2 status (HER2 positivity in 20% of GRCCC and 31% of the other invasive carcinoma subtypes). In this series, lymph node metastases were detected in 7 out of 20 cases, but more small-sized carcinomas were present than in a previous series. In 28 patients reported on in 2014 by Ma et al. [13], ER and PR were positive in 61% of the cases, and HER2 was positive in 12%. According to the molecular subtypes, 56% of the patients were luminal A, 12% were luminal B, and 32% were triple negative.

Because of the rarity of this disease (<150 cases reported so far), it is difficult to define a prognosis of GRCCC. A poor prognosis was reported in a small Finnish series (6 cases) [14], in which 80% of the patients had axillary metastases at diagnosis and died within 7 years. This outcome is in contrast with earlier reports, in which GRCCC showed a better prognosis [9]. Hayes et al. [15] published 21 cases of breast GRCC and suggested the prognosis is not different from that of other common breast cancers when tumors were matched by size, grade and lymph node status, as confirmed by other authors [5, 14]. In the series of Ma et al. [13], follow-up data were available for 24 patients: 21 women were disease free, and 3 cases had local recurrences or distant metastases. The median overall survival was 56.5 months. The number of positive nodes at diagnosis was significantly related to the risk of local or distant disease relapse. When compared to controls in their database (matched by age, year of diagnosis, tumor size, nodal status and phenotype), the authors found that overall survival and disease-free survival were not significantly different between GRCCC and control cases. In this series, a high proportion of carcinomas were ER and PR positive.

To better clarify the specific characteristics and prognosis of breast GRCCC and improve treatment strategies and outcomes, systematic study of a large number of cases with long-term follow-up will be of paramount importance.

Statement of Ethics

We declare that the patient gave her oral consent to publishing her clinical story. She was treated outside of a clinical trial, so no ethics committee approval was required.

Disclosure Statement

Vilma Ratti and Olivia Pagani declare that they have no conflict of interest in relation to this paper.

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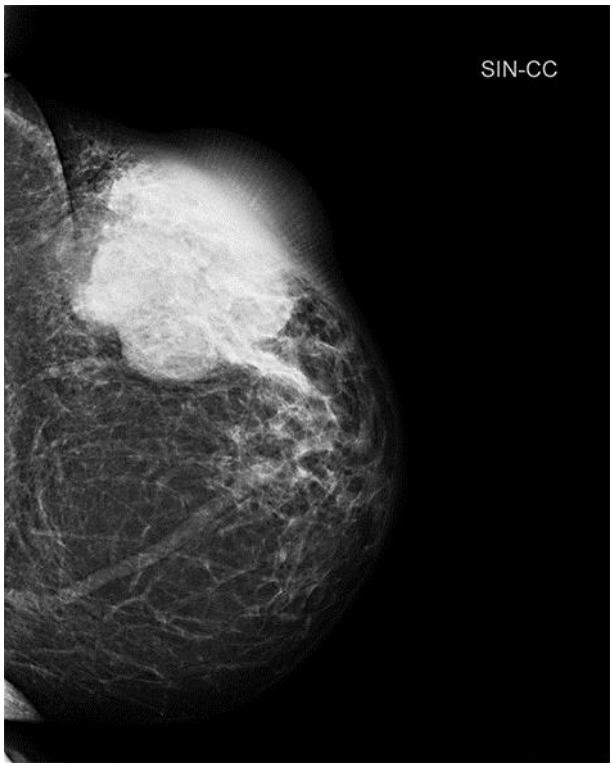

Fig. 1. Mammography image.

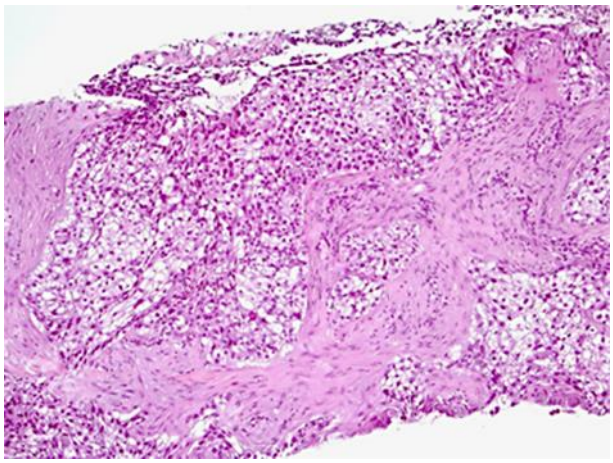

Fig. 2. Needle biopsy. Solid nests of clear cells in a background of desmoplastic stroma. HE. ×100.

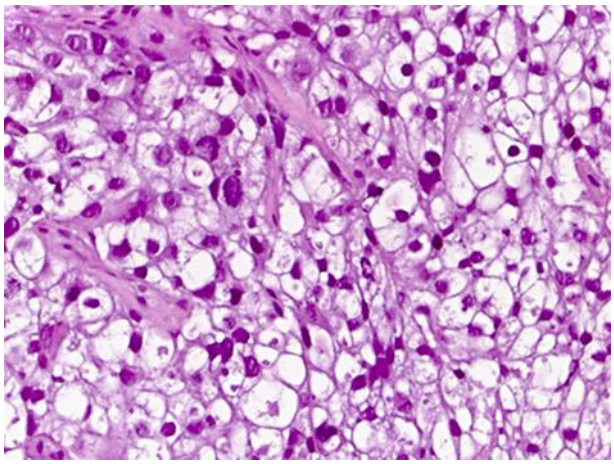

Fig. 3. Needle biopsy neoplastic cells with polygonal contours, sharply defined borders, clear or finely granular cytoplasm, hyperchromatic nuclei with prominent nucleoli and numerous mitotic figures. HE. ×400. With kind permission of U. Perriard, Istituto Cantonale di Patologia, Locarno, Switzerland.