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Glycogen Rich Clear Cell Carcinoma (GRCC) of the breast may not have a poor prognosis

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ABSTRACT

INTRODUCTION: Glycogen Rich Clear Cell Carcinoma (GRCC) is a rare variant of breast carcinomas and believed to be linked with a poor prognosis.**CASE SUMMARY:** We are presenting a 60-year-old Saudi lady with a 2 cm GRCC carcinoma associated with clear cell ductal carcinoma in situ (DCIS) and no axillary lymph node involvement. The tumor was Estrogen and Progesterone receptors (ER & PR) positive and HER 2-neu negative. She underwent mastectomy with sentinel lymph node biopsy followed by hormonal therapy. She is alive and free of disease for 35 months.**CONCLUSION:** The prognosis of GRCC may not be different from other types of invasive breast cancer.
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1. Introduction

Glycogen Rich Clear Cell Carcinoma (GRCC) is a rare variant of breast carcinoma [1]. It is considered a member of a heterogeneous group of neoplasms, including signet-ring, secretory and lipid-rich carcinomas of the breast [2]. Contradicting reports were published discussing the aggressive nature of this entity and its poor prognosis; others concluded that the behavior of GRCC carcinoma carries a comparable prognosis to the conventional ductal carcinomas [3–10,12,13].

We report a case of GRCC carcinoma with no axillary lymph node involvement. A literature review is included.

This work has been reported in line with the SCARE criteria [14].

2. Case summary

A 60-year-old Saudi lady presented with a right breast mass noticed few weeks back. She is a known case of hypothyroidism on Thyroxin tablets. She is a mother of 9 children whom she breast-fed for an average period of 18 months. No family history of malignancy was documented. Examination showed a healthy lady with a right breast 10 o'clock firm oval slightly nodular mass measuring 2 × 1.5 cm with no palpable axillary lymph nodes. Mammogram showed a fatty breast with an asymmetric density in the right upper

outer quadrant with no calcifications (Fig. 1A); spot magnification compression view revealed an ill-defined elongated mass with faint calcifications (Fig. 1B). Right breast ultrasound showed a hypo-dense lobulated horizontally oriented lesion (Fig. 2A) measuring 1.3 × 0.8 cm with mild increased peripheral vascularity (Fig. 2B). Magnetic Resonant Imaging (MRI) of the breast showed an irregularly enhancing lesion with distortion and benign looking axillary lymph nodes (Fig. 3). Ultrasound guided tru-cut needle biopsy showed invasive ductal carcinoma; grade II with polygonal cells that contain clear cytoplasm consistent with the diagnosis of Glycogen Rich Clear Cell Carcinoma (GRCC).

She underwent simple mastectomy with sentinel lymph node biopsy. Final pathology confirmed the diagnosis of GRCC carcinoma with extensive solid type clear cell ductal carcinoma in-situ (Fig. 4A). The malignant cells were round to polygonal, forming cords and nests, containing clear cytoplasm and constitute more than 90% of the tumor (Fig. 4B). The glycogen granules in the clear cytoplasm are positive (Fig. 4C) for Periodic Acid-Schiff staining (PAS) and negative for diastase-periodic acid stain (d-PAS). Immunohistochemistry assessment of the tumor showed positive estrogen (ER) and progesterone receptors (PR). Allred score for ER was 7 (proportion score of 4 and intensity score of 3) which reflects a 75% chance of benefit from hormonal treatment. The tumor cells showed negative HER 2-neu receptors and >15% Ki 67 positivity. The sentinel lymph node showed no metastatic malignant cells. The patient was treated with hormonal therapy in the form of Aromatase inhibitors; Letrozole 2.5 mg daily. She is alive and free of disease for 35 months.

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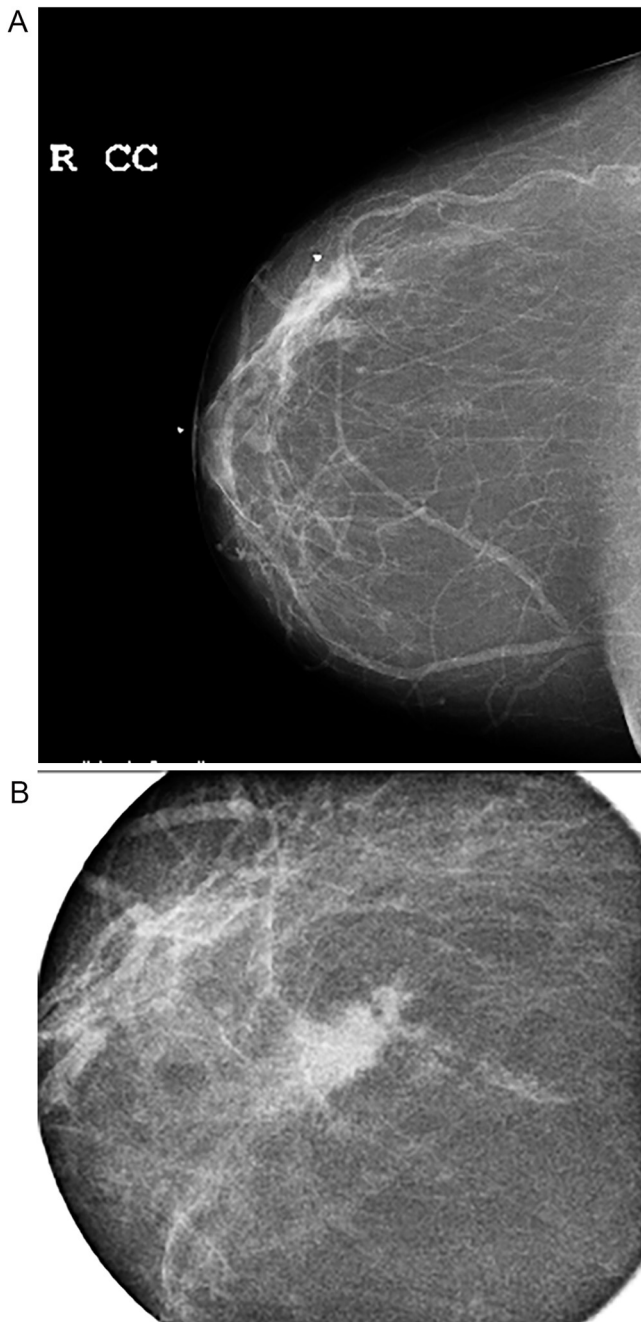


Fig 1. A. A right mammogram, crano-caudal view showing an area of asymmetric density. B. A spot magnification compression view shows an elongated mass with irregular margins and faint calcifications.

3. Discussion

Glycogen Rich Clear Cell Carcinoma (GRCC) is a rare variant of breast carcinoma with an incidence of 1.4–3% [1]. It is the commonest cause of clear cell morphology in breast malignancies [3].

The originally reported case by Hull et al. in 1981 was a slowly growing mass over 20 years and has no axillary lymph node involvement [1]. In 1985, Fisher et al. published their series of 45 cases of GRCC with a disease-free survival that was significantly less (p value = 0.0038) than the commonly encountered breast carcinomas. They considered the case reported initially by Hull a benign breast tumor analogous to dermal eccrine acrospiromas like hidradenoma, spiradenoma or myoepithelioma [6].

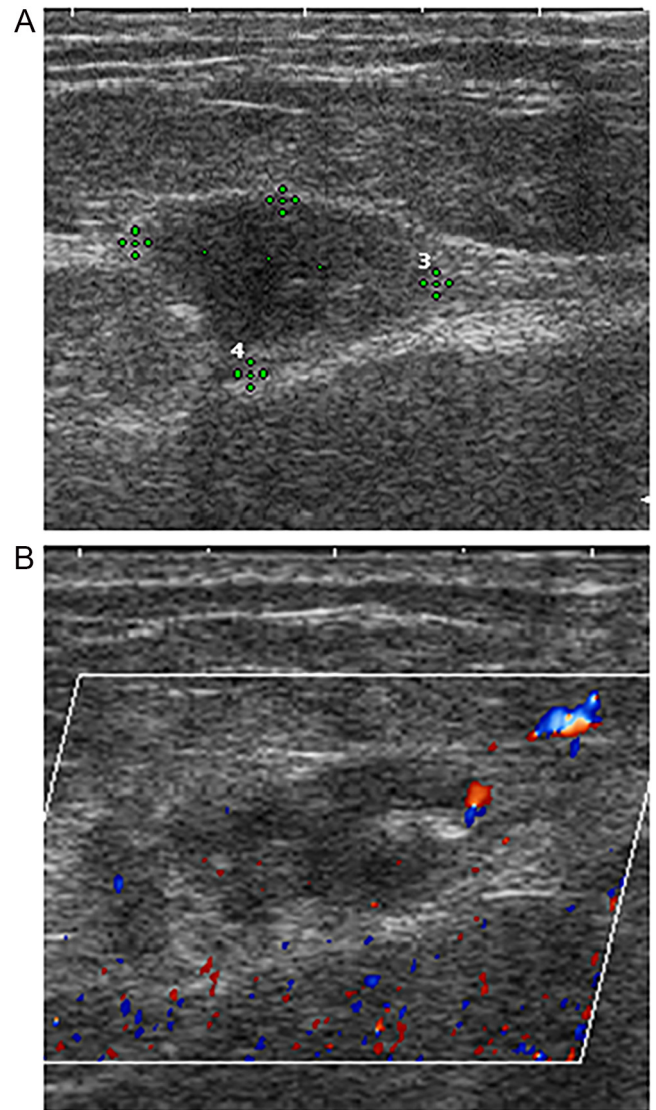


Fig. 2. A right breast ultrasound showing a hypodense lobulated horizontally oriented lesion (A) with peripheral vascularity (B).

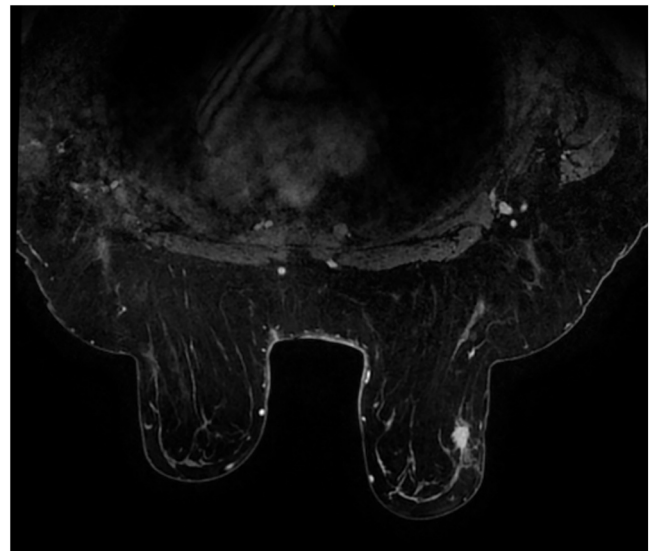


Fig. 3. MRI showed an irregular mass with distortion; it has an irregular enhancement at the margins. Multiple benign looking axillary lymph nodes are seen with preserved fatty hilum.

Table 1
Details of GRCC cases reported in previous publications arranged chronologically according to publication year.

	Number of Cases	Mean Age (years)	Surgical Intervention (%)	Mean Tumor Size (mm)	Clear Cell Changes (%)	Positive Hormone Receptors (%)	Her 2/ <i>neu</i> Overexpression (%)	AXLN Involvement (%)	Adjuvant Treatment (%)	Follow up (months)
Fisher et al. [6] USA, 1985	45	NA	M (90) CS (10)	NA	>50	NA	NA	26.6 ^a	NA	(144) Less DFS in GRCC
Hull et al. [4] USA, 1986	10	59.4	M (90) CS (10)	37.5 ^b	NA	20 ^c	NA	70	NA	(64) 5 cases DOD
Toikkanen et al. [5] Finland, 1991	6	58.3	M (100)	53 ^d	>90	NA	NA	83	RT (83)	(84) 5 cases DOD
Hayes et al. [3] USA, 1995	21	55.7	M (52) CS (48)	28 [§]	>90	57 ^e	NA	20 [§]	RT (23) ^e CH (15) ^e HT (7.6) ^e	(38.5) ^e 3 cases DOD
Gövrüz et al. [13] Turkey, 2003	1	45	M (100)	30	90	0	NA	0	NA	(27) DF
Varga et al. [12] Switzerland, 2003	12	66.9	NA	37	NA	75	25	66.6	NA	NA
Kuroda et al. [8] Japan, 2005	20	52	M (85) CS (15)	26	>50	35	20	35	RT (75)	(60) 5 cases DOD
Markopoulos et al. [10] Greece, 2008	1	59	M (100)	35	NA	100	0	0	HT	(48) DF
Kim et al. [9] Korea, 2012	3	58	M (33.3) CS (33.3)	17.5	NA	33.3	33.3	NA	CH (66.6) RT (33.3)	(16) 2 cases DF
Ma et al. [7] China, 2014	28	50.8 (median)	M (96.4) CS (3.6)	32	>90% in 24 cases	61.5	12	46.4	CH (89.3) RT (28.6) HT (61.5)	(56.5) 21 cases DF
Baslaim et al. Saudi Arabia, 2016	1	60	M (100)	13	>90	100	0	0	HT	(35) DF

NA: Not Available, M: Mastectomy, CS: Conservative Surgery, AXLN: Axillary Lymph Nodes, CH: Chemotherapy, RT: Radiotherapy, HT: Hormonal Therapy, DF: Disease Free, DFS: Disease-Free Survival, DOD: Died of Disease.

^a Information on axillary lymph node status were available only for 12 cases and found to be positive for metastases.

^b 50% of the cases with skin dimpling or nipple retraction.

^c Hormone receptors were available for 2 cases only.

^d 50% of the cases were T4 (with skin fixation or edema).

^e These numbers and percentages are for the 13 invasive GRCC; 8 cases of intra-ductal GRCC were not grossly identified. The % of Hormone receptors positivity was done only in 7 cases of invasive GRCC. No Follow up data available for 9 cases.

According to the world Health Organization (WHO) classification, in GRCC carcinoma, more than 90% of the neoplastic cells have abundant clear cytoplasm-containing glycogen [11]. Table 1 summarizes the published studies from different countries on GRCC with variability in the % of clear cells used to classify the lesion. This might explain the variability in reporting GRCC cases as well as their prognosis. Most of the GRCC cases were above 50 years of age. The duration of symptoms was not clearly stated. The commonest reported presenting symptom was a breast mass [7]. Some reported skin involvement (dimpling, edema, fixation or nipple retraction) in 50% of their cases [4,5]. There were no specific radiologic characteristics associated with GRCC carcinoma, the commonest finding was a calcified mass that is relatively well defined on breast ultrasound [7,10]. Our case had a relatively benign appearance that can mimic a fibro-adenoma. The lobulated appearance combined with the peripheral vascularity in a 60 years old lady warranted biopsy. MRI showed an irregularly enhancing lesion typical of a mammary carcinoma.

Microscopically, the growth pattern is that of the usual infiltrating ductal carcinoma however other patterns may be seen like papillary, lobular or tubular ones. The neoplastic cells are characterized by an optically clear cytoplasm which contains glycogen but no lipids or mucin [1]. Within the cytoplasm, there are fine glycogen granules which are stained by Periodic Acid Schiff stain (PAS) but not stained by diastase-periodic acid stain (d-PAS). They have a relatively low nuclear and cytoplasmic ratio, irregularly thickened nuclear membranes and prominent nucleoli [9]. The glycogen in the cell is extracted during tissue processing for histologic assessment leaving the vacuolated cytoplasm; hence the differential diagnosis

includes lipid rich carcinoma, signet-ring cell carcinoma, histiocytoid carcinoma, adenomyoepithelioma, clear cell hidradenoma and eccrine spiradenoma [1,2,10].

Intra-ductal clear cell component is commonly present as seen in our case. Hayes et al. reported 21 GRCC cases; 8 of them were intraductal GRCC showing different histologic subtypes like solid, papillary, micropapillary and cribriform [3].

Kim et al. reported 3 cases of GRCC seen over 10 years. They Used 12 different antibodies to study the phenotype of these tumors and concluded that the immune-phenotype of GRCC is not uniform and might be similar to that of the conventional carcinoma. In their cases, P53 – which is considered a poor prognostic marker – was variably present with variable percentage (15–60%) of Ki-67 [9].

Varga et al. studied Her 2 overexpression in aggressive histologic subtypes of invasive breast cancer. Among his series, there were 12 cases of GRCC, 3 of them displayed Her 2 overexpression [12]. The reported amplification rate of the Her 2 gene in GRCC was similar to that among breast cancers generally from 0 to 33% [9,12].

The commonest surgical approach reported in the literature for cases of GRCC carcinoma was in the form of mastectomy with sentinel lymph node biopsy or axillary dissection regardless of the tumor size, conservative surgery was less practiced [3–10,12,13]. The role of neo-adjuvant chemotherapy was not discussed in the published literature as well. This might be related to the poor understanding of this rare entity and the conflicting reports about its therapeutic response and prognosis.

Different reports were published discussing the aggressive nature of this entity. In these reports, the tumor grade was II–III, hormone receptors assessment was not always documented,

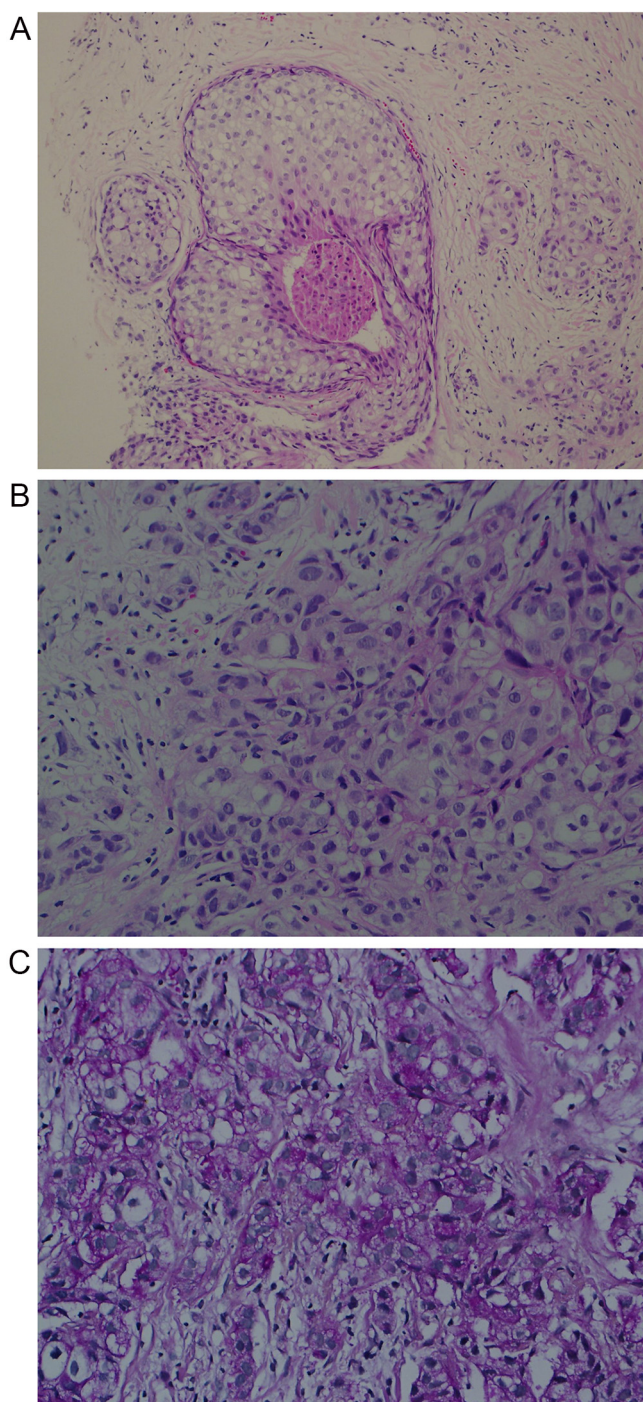


Fig. 4. A. DCIS of solid type, intermediate grade. Note the clear cytoplasm in the populated cells of the DCIS and the adjacent invasive area of ductal type (H&E \times 40). B. Invasive area of ductal type forming cords and nests made of malignant round to polygonal cells. These cells that exhibit clear cytoplasm constitutes more than 90% of the tumor (H&E \times 40). C. The granules in the glycogen component of the clear cell are positive for Periodic Acid-Schiff staining (PAS \times 40).

Her/2-neu tests were not mentioned and the use of adjuvant chemotherapy details were not available [4–6]. In one of them, adjuvant radiotherapy was provided for 83% of the patients but no mention of chemotherapy [5]. Fisher et al. concluded that the adverse influence of GRCC on survival is more related to their histologic grade and the presence of nodal metastases [6]. This was similar to the conclusions mentioned in other reports with a prognosis that is similar to other breast carcinomas [3,7–10,12,13].

4. Conclusion

The contradicting reports about the prognosis of GRCC carcinomas of the breast might be related to inconsistency in the classification and the percentage of clear cell changes reported in the tumor; a unified pathologic interpretation is crucial. Based on the tumor grade, axillary lymph node involvement and hormone receptor status, their management will be no different than the commonly seen infiltrating ductal carcinoma.

Conflict of interest

All authors declare no conflict of interest.

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Ethical approval

King Fahd Hospital approved this case report.

Consent

No consent was obtained from the patient in this case report.

Author contributions

Muna M. Baslaim: Study design, data collection, writing the paper.

Enaam M. Junainah: Pathologic assessment, images, literature review.

Hadeel H. Ahmad: Data collection, obtain images, literature review.

Anmar F. Semilan: Data collection, literature review.

Ahmed O. Al-Ghamdi: Writing the manuscript.

Noora O. Rahimuddin: Writing the manuscript.

Budoor A. Salman: Data collection, obtain images, review manuscript.

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