



Case report

Excellent long term oncological outcome in a patient with rare glycogen rich clear cell carcinoma of breast following breast conservation surgery



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ABSTRACT

Introduction: We present a case report of excellent oncological outcome after 7-year follow up in a female Indian patient with pT2N3aM0 rare GRCC of the breast following breast conservation surgery and appropriate adjuvant treatment. Glycogen rich cell carcinoma (GRCC) is a rare subtype of primary malignant neoplasm of the breast which is not commonly discussed. Only approximately 288 cases have been reported since its first description globally with reports of varying prognosis. Even less (4 patients), which have been reported from India have described only clinic pathological features. This is first case report of patient from India discussing long term oncological outcome of a patient with rare GRCC (pT2N3aM0) of the breast following breast conservation surgery and appropriate adjuvant treatment.

A 41-year-old lady presented to us with history of 2 × 2 cm right breast lump for 2 weeks. A BIRAD IV hypochoic lesion with slightly irregular margins in the upper outer quadrant of the right breast and right axillary lymphadenopathy was reported in mammogram. PET CT showed metabolically active lesion 2.3 × 1.3 cm enhancing nodule with spiculated margins at the same site (SUV-10.8) with metabolically active right axillary metastatic lymphadenopathy (SUV-11) with no distant metastases. Core biopsy indicated Ductal carcinoma. Patient underwent right breast conservation surgery (Wide local excision and oncoplasty with axillary clearance) uneventfully followed by appropriate adjuvant treatment (Chemotherapy, Targeted treatment, Radiotherapy). The final pathological stage was Glycogen rich clear cell carcinoma, pT2N3a M0 with Her2 positive but negative for ER and PR with Ki 67–50 %. The patient had excellent outcome and was alive and cancer free even after 7 years follow up.

Conclusion: The purpose of reporting this case is to increase the knowledge about this rare subtype of breast cancer which underwent organ preservation. This case report reveals that clinical behavior and oncological outcome of GRCC breast can be unexpected, unusual, varied and even good, contrary to recent 2019 SEER data (Zhou Z, Kinslow CJ, Hibshoosh H, et al. Clinical features, survival and prognostic factors of glycogen-rich clear cell carcinoma (GRCC) of the breast in the US population. J Clin Med. 2019; 8: pii: E246).

1. Introduction

Glycogen rich clear cell (GRCC) carcinoma is a rare subtype of breast cancer in which >90 % of the neoplastic cells have abundant clear cytoplasm containing glycogen according to WHO classification [1]. GRCC of the breast make up 1.4–3 % of all breast malignancies [2,3]. First case was reported in 1981 by Hull et al [4]. Only 4 case reports of GRCC breast have been published from India. All of these discuss mainly

clinicopathological features [5–8].

Most common surgical approach reported in the literature for cases of GRCC carcinoma was mastectomy with sentinel lymph node biopsy or axillary dissection regardless of the tumor size. Breast conservative surgery was uncommon [9–18].

There have been conflicting reports that have been published regarding differences in tumor biology, natural history and prognosis of GRCC carcinoma in comparison to conventional ductal carcinomas.

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[9,12–18]

We report excellent surgical outcome after 7-year follow up in a female Indian patient with rare pT2N3aMO GRCC of the breast who had breast conservation surgery and appropriate adjuvant treatment.

This case report has been formulated according to 2020 updated SCARE guidelines [19].

2. Patient information

A 41-year-old Indian housewife with known Diabetes and Body Mass Index (BMI) of 28.6 kg/m² presented to us with history of 2 × 2 cm upper outer quadrant right breast lump in a 36C cup breast for 2 weeks which was mobile and overlying skin free with single clinically mobile palpable lymph node in right axilla in a tertiary cancer care hospital. Left breast appeared normal. There was no family history of breast cancer. She was premenopausal and breastfed both her children. She did not suffer from any comorbid illness and was not taking any medication. Her psychosocial history was normal.

FNAC report was suggestive of ductal carcinoma. Mammogram showed a BIRAD IV hypo echoic lesion with slightly irregular margins in the upper outer of the right breast and right axillary lymphadenopathy (Fig. 1).

PET CT indicated metabolically active lesion 2.3 × 1.3 cm enhancing nodule with speculated margins (SUV-10.8) at the same site with metabolically active right axillary metastatic lymphadenopathy (SUV-11) with no distant metastases. Patient underwent right breast conservation surgery (lumpectomy followed by oncoplasty with axillary

clearance) on 4.5.2013 uneventfully (Fig. 2) by a senior consultant surgical oncologist in a tertiary cancer hospital.

Final pathology of specimen showed 2.2 × 2.8 cm tumor with surrounding fibrocystic tissue. It had grey, white appearance with infiltrating margins. Margins were free. Histology showed glycogen rich clear cell carcinoma, grade 2 with a very focal area of grade 2 invasive ductal carcinoma with high grade DCIS and no lymph-vascular invasion being present.

Microscopically, the tumor showed solid sheets of >90 % large clear

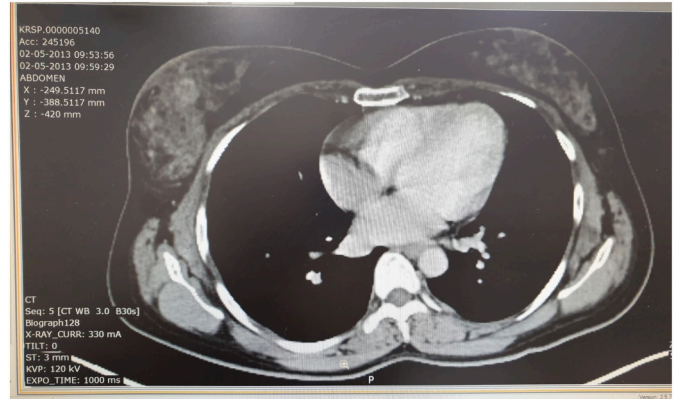


Fig 2. CT scan image indicating right upper quadrant breast lump.

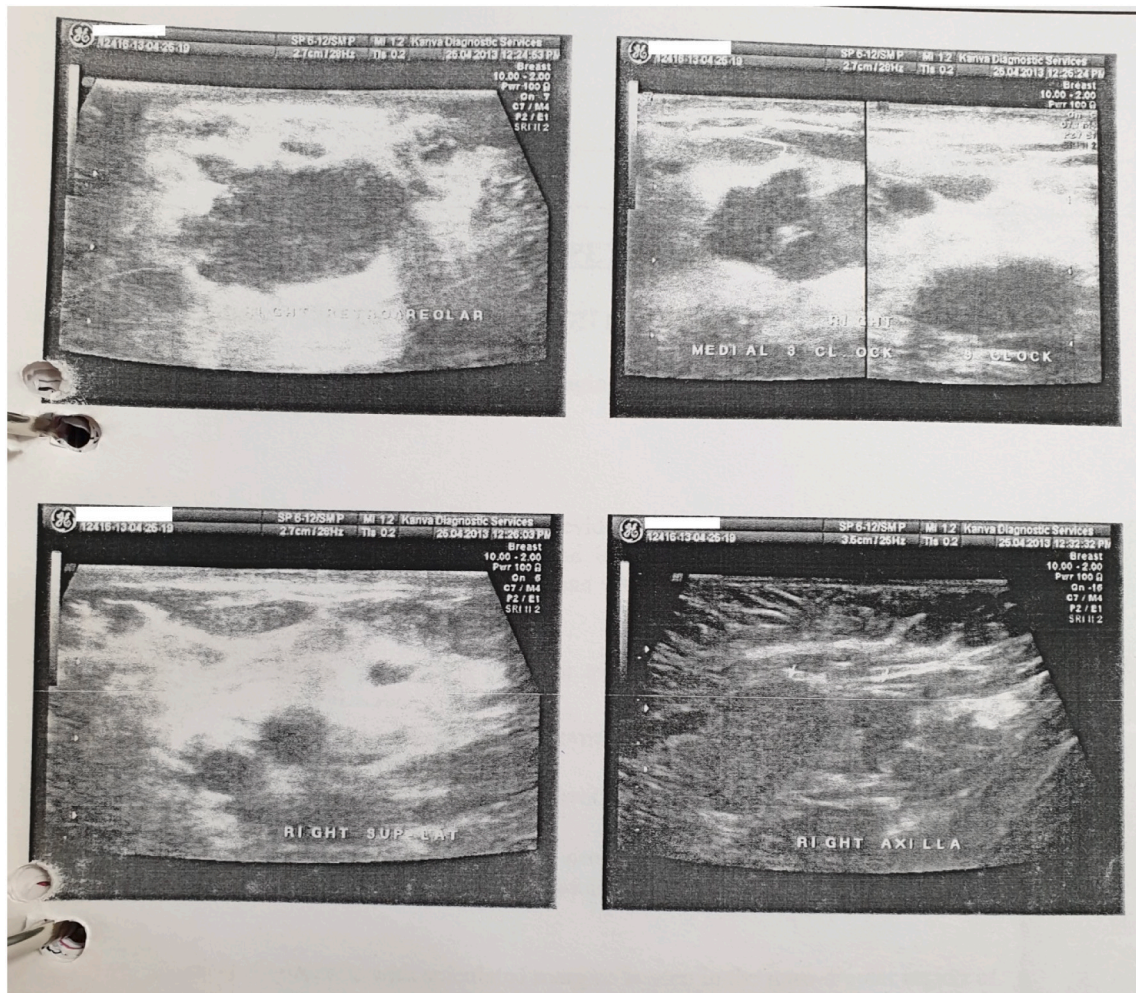


Fig 1. Sonomammogram showing BIRADS IV right upper quadrant breast lesion.

cells with distinct cell borders and clear cytoplasm (Figs. 3–5). There was extensive intra ductal component of comedo and solid type with the cells showing clear cytoplasm in intra ductal component. No cytoplasmic vacuoles were appreciated. The cytoplasmic glycogen was highlighted by PAS stain and diastase stain (Fig. 6).

13 out of 26 lymph nodes showing metastasis with extra capsular extension. The tumor cells showed clear cytoplasm containing glycogen which is PAS positive and diastase sensitive. The immunohistochemistry profile showed many cells were positive for Her2 (Fig. 7) but negative for ER and PR with Ki 67–50 %. The final pathological stage was pT2N3a.

Patient received chemotherapy with TAC regime according to her BSA 1.43 (Doxorubicin 80 mg + Endoxan 800 mg + Inc. Docetaxel 110 mg) for 6 cycles and Trastuzumab 330 mg every 3 weeks for 52 weeks and external beam radiotherapy using IMRT technique to a dose of 45Gy/25# to CTV breast, right supraclavicular and axilla followed by boost to a dose of 15 Gy/7# to CTV. Patient had a regular 3 monthly follow up for 2 years, 6 monthly follow up for the third year and subsequently yearly mammogram and clinical examination which showed no evidence of any recurrence (local, regional and distal) for 7 years.

3. Discussion

Since GRCC's first description in 1981 by Hull et al. [4], incidence is unclear. However, most researchers agree that they are quite rare. Surveillance, Epidemiology and End Results (SEER) database which was the most comprehensive study until now revealed 155 cases of GRCC out of 1,251,584 cases of other (non-GRCC) breast carcinomas (incidence-0.01 %) [20]. There have been only 4 case reports of GRCC breast from India and their discussion pertains mainly to clinico pathological features [5–8]. This is the first case report from India discussing a patient with pT2N3a GRCC breast who underwent Breast Conservation surgery having longest follow-up of 7 years.

Our patient was 41 years old while many patients presenting GRCC were >50 years [9–14,17,20]. Most patients presented with a breast lump accompanied by skin and nipple changes in about 50 % of patients [4,11,13,21]. Mammographic and PET Scan in this case was no different from conventional ductal carcinoma. There were no characteristic mammographic findings specific to GRCC [13,16].

Most GRCCs demonstrate a nested, sheet-like or corded growth pattern like IDC-NST [9]. Most GRCC are diagnosed as invasive carcinomas. Sometimes, the clear cells may exhibit solid, papillary, cribriform, lobular, and/or tubular patterns. [4,9,22–26]. Rarely cases of neuroendocrine, mucinous and apocrine differentiation have also been described [9,23,27].

The cancer cells of GRCC have well marked borders with polygonal contours (Fig. 1). The cytoplasm that is clear or finely granular contains the diastase-sensitive Periodic Acid Schiff (PAS)-positive glycogen [28]. The cell nuclei are oval with a prominent nucleoli and clumped

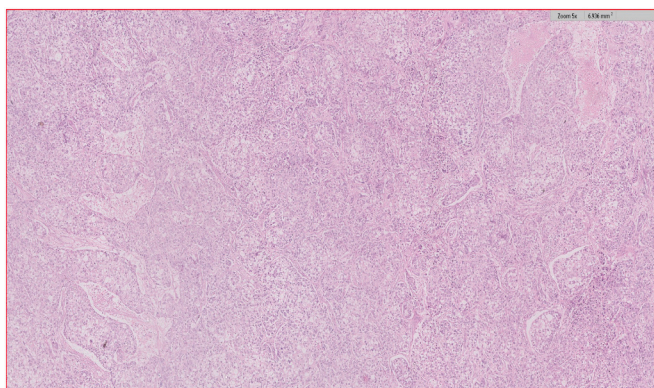


Fig 3. shows tumor cells in nests and sheets (H&E stain, 5×).

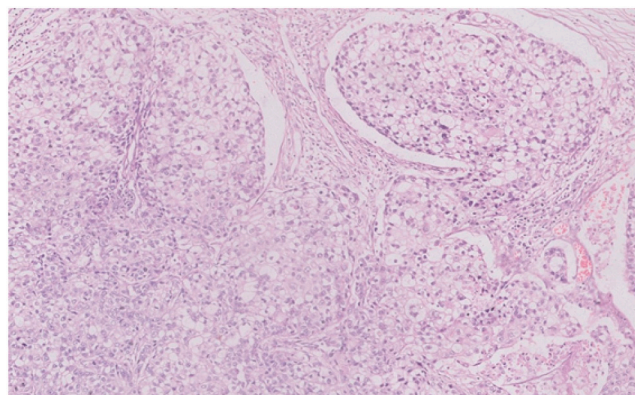


Fig 4. depicts tumor cells with abundant clear cytoplasm and well-defined cytoplasmic borders. (H&E stain, 10×).

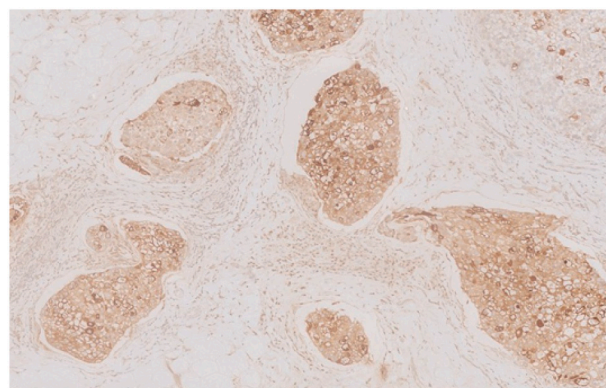


Fig 5. Tumor cells express GCDPF-15.

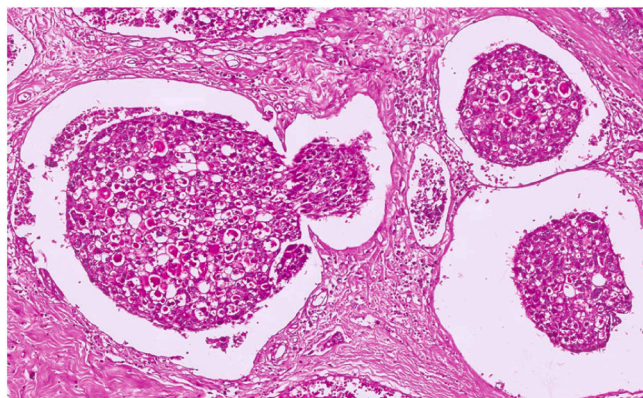


Fig 6. PAS stained GRCC breast cancer cells.

chromatin. The nuclear atypia is usually moderate to marked which is equivalent to grade 2 or 3 [29].

Breast cancers with clear cell cytoplasm like secretory carcinoma, lipid rich carcinoma, histiocytoid carcinoma and sebaceous carcinoma must be considered in the differential diagnosis [30]. Apocrine carcinomas containing cells with foamy cytoplasm ("type B" cells) and focal clear cell changes in other growth patterns of IDC including papillary, micropapillary, mucinous, and neuroendocrine carcinomas should be differentiated from GRCC [31]. Benign and malignant myoepithelial lesions of the breast which have prominent clear cell differentiation may be rarely encountered. [32–34]. PAS and PAS diastase along with an appropriate immunohistochemical special stains are helpful to confirm

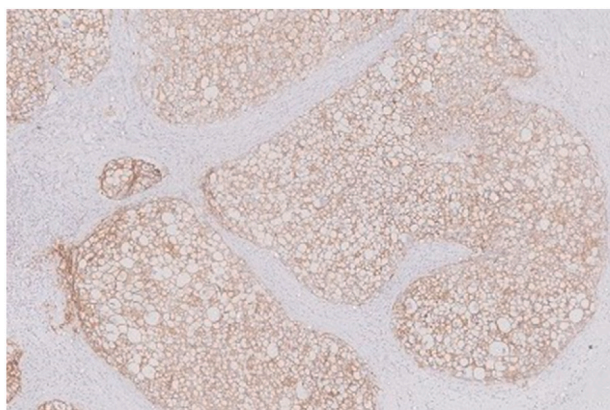


Fig 7. Tumor cells are positive for Her-2.

correct diagnosis in most of these cases. Identification of chromosomal translocation t (12;15) (p13; q25), resulting in the ETV6-NTRK3 fusion gene will rule out the GRCC in case of secretory carcinoma [35]. Detailed clinical history of the primary site, imaging along with an appropriate immunohistochemical panel will help in differentiating metastatic cancers with clear cell histology involving the breast (e.g., melanomas, clear cell, renal cell carcinoma, and soft tissue tumors) which are very rare.

ER positivity and PR positivity has been reported in 35 % to 100 % and <30 % of cases, respectively (Table 1). This aligns with the data from the SEER database, where the ER positivity rate in GRCC was ~47 % and 27 % for PR [20]. The expression of androgen receptor (AR) was recently reported in 88 % of GRCC cases [36].

There have been varying reports of HER2 expression in GRCC (Table 1). In SEER cohort of GRCC, HER2 expression was observed in only ~7 % of GRCC [20]. Highest rate (44 %) of HER2 positivity in GRCC was reported by Akbulut et al. [37]. In addition, HER2 gene mutations have not been reported in GRCC [36].

Many case series reporting >3 GRCC patients have had more mastectomies irrespective of tumor size than breast conservation surgery

Table 1

Details of case series with >3 GRCC cases reported in literature whose details of surgical intervention included breast conservation surgery.

Studies	Number of patients	Average age (years)	Surgery (%)	Average tumor size (mm)	Clear cell changes (%)	Positive hormone receptors (%)	Her2/neu over expression (%)	AXLN involvement (%)	Adjuvant treatment (%)	Follow up (months)
Zhou et al, US, 2019 [20]	155	62 (median)	M (37.8) CS (55.1)	NA	>90	46.3	6.9	41.3	RT (45.5)	(54) 92 cases DF (56.5)
Ma et al. China, 2014 [13]	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)	21 cases DF (16)
Kim et al. Korea, 2012 [15]	3	58	M (33.3) CS (33.3)	17.5	NA	33.3	33.3	NA	CH (66.6) RT (33.3)	2 cases DF (60)
Kuroda et al. Japan, 2005 [14]	20	52	M (85) CS (15)	26	>50	35	20	35	RT (75)	5 cases DOD (38.5) e
Hayes et al. USA, 1995 [9]	21	55.7	M (52) CS (48)	28	>90	57e	NA	20	RT (23) CH (15) HT (7.6)	3 cases DOD (84)
Toikkanen et al. Finland, 1991 [11]	6	58.3	M (100)	53	>90	NA	NA	83	RT (83)	5 cases DOD (64)
Hull et al. USA, 1986 [4]	10	59.4	M (90) CS (10)	37.5	NA	20	NA	70	NA	5 cases DOD (144)
Fisher et al. USA, 1985 [12]	45	NA	M (90) CS (10)	NA	>50	NA	NA	26.6	NA	Less DFS in GRCC

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

[Table 1]. However, in contrast, recent SEER database indicated GRCC patients underwent less mastectomies (37.8 % vs 55.1 %) [20].

There are conflicting reports of studies regarding prognosis of GRCC. Some studies have indicated that when matched for TNM status, the prognosis was not significantly different from that of IDC-NST [13,38–40].

In the most comprehensive SEER database study on GRCC Breast of US population, incidence, demographics and prognostic factors of 155 cases of GRCC of the breast were compared to 1,251,584 cases of other (non-GRCC) breast carcinomas. High grade (mainly grade 3), triple negative receptor status and advanced stage are more likely to be present in GRCC. GRCC patients had a poorer prognosis than non-GRCC carcinomas of the breast irrespective of age, AJCC staging, tumor grade, joint hormone receptor/human epidermal growth factor receptor 2 (HER2) status, and treatment. Surgery and radiation were associated with improved survival. Radiation, specifically in the setting of breast-conserving surgery, further improved survival compared to surgery alone [20].

Glycogen accumulation in tumor-associated stroma, Aberrant alternate glycogen fuel pathway in a nutrient-deprived tumor microenvironment (p38α-MAPK) signaling pathway, suppression of reactive oxygen species (ROS) levels and p53-dependent senescence due to hypoxia-induced glycogen phosphorolysis are various biomolecular theories proposed to explain poorer prognosis of GRCC [41,42].

4. Patient perspective

When I was first requested to write about my experience in dealing with my breast cancer, I had mixed feelings. I keep reliving all the raw emotions of my roller coaster ride of my cancer journey of the past 7 years: shock, uncertain nature of my rare cancer diagnosis, tears, pain, umpteen number of trips to the hospital, consultations with innumerable cancer specialists and of course the dreadful question of me being still alive after all this. I can now cheerfully state that my cancer journey has had happy ending as of now, despite all its tribulations.

How do I begin narrating my cancer journey? Well, it all started with this small right breast lump which I first noticed while having bath about

7 years back. Initially, I thought it was just nothing. I kept it to myself as the lump was painless and hoped it would go away by itself when it started slowly growing, I became worried and informed my husband. My husband immediately rushed me to see my cancer doctor (Dr MB). My cancer doctor took a detailed history and examined me thoroughly. He explained to me that my breast lump was suspicious and that I needed to undergo further tests in the form of breast needle biopsies and breast Xray and ultrasound. My breast biopsies confirmed that it was indeed cancer. My heart sank and thought I was going to die soon. I became very anxious and had so many questions to ask. My cancer doctor patiently sat me down and answered my queries calmly. He put me at ease by saying that my breast tumor was treatable while elaborating on various treatment options and that I needed to be very positive in dealing with it. I then underwent further tests and scans. Thankfully, tumor had not spread to other organs. I was pleasantly surprised to find that my surgery didn't entail removal of the whole breast. I was also told that results of removing the lump and preserving breast were same as removal of the whole breast. I was glad about this. My breast conservation operation was uneventful. But results of final pathology report of operative specimen were disconcerting. I was told that I had a rare type of breast cancer called Glycogen Rich Clear cell carcinoma and that tumor had spread to lymph nodes in my armpits. I became despondent and didn't want to proceed with the treatment. I was referred for psychooncology and multidisciplinary team assessment. I was informed that it was difficult to predict the course of my disease. Detailed discussion about pros and cons of various treatments followed. I was more concerned about disease and its spread than the side effects of the treatment. I resolved to fight back by completing my treatment in the form of chemotherapy and radiotherapy and hoping for the best. I have been closely monitored by entire team of cancer doctors since completion of my treatment.

It has been nearly 7 years after my first diagnosis of cancer. Now I feel absolutely fine and am back at work being a sales executive. I have been declared cancer free, although I still report to my cancer doctors. I can't tell you how much thrilled I am to say that I have been able to beat cancer. First of all, I thank my husband who stood beside me like a rock. I am also grateful to the entire oncology team of this wonderful hospital.

I am extremely thankful to have a second chance at life. I know that the cancer can come back at any time at the same or maybe different sites. But I plan to be positive. I hope to be a beacon of light for other cancer survivors and inspire them to conquer cancer. I have been appearing on cancer survivorship programmes on various forums like TV and social media to repay my debt.

I am happy that my cancer doctor decided to publish my case report. By gladly giving consent to publication of my case report in your journal, I sincerely believe that I will be contributing in my own small way in the fight against cancer.

5. Conclusion

Most recently conducted, comprehensive SEER database study of GRCC breast (2019) concluded that GRCC fared poorly compared to non GRCC breast. We however present patient with this relatively rare subtype (GRCC, ER-negative, PR-negative and HER 2 positive) breast carcinoma with multiple positive axillary lymph node involvement (N3) in clinical practice who underwent breast conservative surgery with a surprisingly good clinical outcome even after seven-years after the completion of therapy. This case highlights unusual, unexpected, varied clinical behavior of a GRCC breast tumor. We believe that further research is required in understanding its natural history and prognosis as it remains unclear due to its rarity and paucity of research. More sensitive molecular and histological methods may help to characterize important prognostic variables, that will aid in identifying GRCC breast patients who may benefit from additional novel therapies.

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Consent

Informed consent was obtained.

Author contribution

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Guarantor

First author.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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