

Glycogen-Rich Clear Cell Carcinoma of the Breast: Report of Two New Cases and an Updated Literature Review*

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Abstract

Objective. To report two additional cases of glycogen-rich clear cell carcinoma (GRCC) of the breast – detailing their clinicopathologic features, immunophenotypes, and follow-up – and to provide an updated literature review since 2020. **Case Reports.** Two patients (66 and 52 years old) had GRCC confirmed morphologically and histochemically. Case 1 was ER-positive/HER2-positive (luminal B/HER2-positive) and was managed with surgery, followed by adjuvant chemotherapy, endocrine therapy, and anti-HER2 therapy (trastuzumab). Case 2 was triple-negative and received neoadjuvant chemoimmunotherapy (pembrolizumab-based) with marked pathologic tumor regression at resection. Both patients were disease-free at one and 12 months, respectively. **Conclusions.** GRCC is heterogeneous and should not be regarded as a single clinicopathologic entity within invasive breast carcinoma of no special type or assumed to have a uniform prognosis. Management should be biomarker-guided, as illustrated by these cases. The role of targeted and immune therapies in GRCC warrants multi-institutional studies.

Key Words: Breast Cancer ■ Special Patterns ■ Glycogen-Rich Pattern ■ Biomarkers ■ Outcome.

Introduction

Invasive breast carcinoma is the most common malignancy in women worldwide (1). It is a biologically and morphologically heterogeneous disease that comprises more than 20 histologic subtypes, of which invasive breast carcinoma of no special type (IBC-NST) is the most frequent (≈70–80%) (2). Special types account for approximately 10–20% and include lobular, tubular, mucinous, medullary, and several rarer variants, each with distinctive morphologic and molecular features that may influence clinical management and prognosis (2, 3).

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Within this spectrum, a subset of rare tumors exhibits clear-cell cytomorphology—so-called breast carcinomas with clear-cell features or patterns. Importantly, this appearance is etiologically diverse: cytoplasmic clearing may indicate different intracellular contents or even a processing artifact (2, 3). Determining the nature of the optically clear cytoplasm is critical for at least two reasons: (1) clear change can be artifactual, and (2) when clearing involves more than a few cells, understanding its biochemical basis helps guide classification. Upon confirmation, invasive carcinomas with clear cytoplasm can be further categorized as lipid-rich carcinoma, secretory carcinoma, apocrine carcinoma with clear (histiocytoid) cytoplasm,

and glycogen-rich clear-cell pattern of IBC-NST (2, 4-7).

Glycogen-rich clear cell carcinoma (GRCC), first described by Hull et al. in 1981 (8), is characterized by tumor cells with abundant intracytoplasmic glycogen that is Periodic Acid-Schiff (PAS)-positive and PAS-diastase-sensitive (i.e., PAS staining is abolished after diastase digestion) (2, 4). Because clear cytoplasm alone does not prove the presence of glycogen and glycogen is not the sole cause of clearing, both morphology and histochemistry are required. Evolving diagnostic criteria stipulate demonstration of PAS positivity and PAS-D sensitivity in $\geq 90\%$ of tumor cells to assign a glycogen-rich pattern (2).

Although early reports labeled GRCC highly aggressive, accumulating series suggest a variable clinical course (9). A population-based SEER analysis (155 GRCC vs >1.2 million non-GRCC breast cancers) found that GRCCs are more often high-grade, present at advanced stage, more frequently triple-negative, and are associated with worse survival than non-GRCC cancers (9), underscoring their distinct prognostic profile (2, 10). GRCC/

clear-cell pattern of IBC-NST is rare, with reported incidences ranging from 0.01% to 3% (9, 11-13). Owing to its rarity and a literature dominated by case reports and small series, GRCC remains understudied relative to other subtypes.

Here, we report two new GRCC cases of the breast, detailing their clinicopathologic features, immunoprofiles, and follow-up. We also provide an updated literature review (PubMed/MEDLINE, Google Scholar, Web of Science, and Scopus) of GRCC that have been published since our previous review in 2020 until October 2025 (Table 1) (4).

Case Presentations

We report two invasive breast carcinomas with clear-cell morphology on hematoxylin-eosin sections. Intracytoplasmic glycogen was confirmed by periodic acid-Schiff (PAS) positivity that was diastase-labile on PAS-D. Immunohistochemistry for estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67 was performed using standard protocols (14, 15). The tumor-infiltrating lymphocytes (TIL) were assessed following

Table 1. Review of the Clinicopathologic Characteristics of Glycogen-rich Clear Cell Carcinomas Published in the Previous Five Years (2020-2025)

Author (year)	No of cases	Age (yrs)	Diagnosis	AJCC TNM	Grade	IHC profile	Ki-67	PAS/PAS-D
Liu et al. (2020)	6	46-57	GRCC	n/a	n/a	ER-, PR-, HER2 0 (3/6)	n/a (%)	Positive/sensitive
Georgescu et al. (2021)	2	64 54	GRCC	pT1cN2a pT1cN0	G3 G2	ER+, PR+, HER2 0 ER+, PR+, HER2 1+	25 5	Positive/sensitive
Demyashkin et al. (2021)	9	n/a	GRCC	pT1 (1/9) pT2 (6/9) pT3 (2/9)	G3	ER and PR negative (9/9) ~80% HER2 3+	26*	Positive/sensitive
De la Sancha et al. (2021)	1	69	GRCC	pT1cN0	G2	ER+, PR-, HER2 0	n/a	Positive/sensitive
Sanjeeviah et al. (2022)	1	41	GRCC	pT2N3a	G2	ER-, PR-, HER2 3+	50	Positive/sensitive
Singh et al. (2022)	1	70	GRCC	pT1N0	G2	ER+, PR+, HER2 0	20	Positive/sensitive
Lee et al. (2022)	1	79	GRCC	pT2N0	n/a	ER+, PR-, HER2 0	n/a	Positive/Sensitive
Braganza et al. (2025)	1	75	GRCC	pT2	G3	ER+, PR-, HER2 2+ (not amplified)	25	Positive/sensitive

GRCC = Glycogen-rich clear cell carcinoma; TNM = Tumor node metastasis; IHC = Immunohistochemical; PAS = Periodic acid-Schiff; PAS-D = PAS diastase; ER = Estrogen receptor; PR = Progesterone receptor; HER2 = Human epidermal growth factor receptor 2; n/a = Not available; *The study reported the average Ki-67 values.

the recommendations of the International TILs Working Group 2014 (16). Tumors were classified as GRCC when $\geq 90\%$ of tumor cells exhibited clear cell morphology and contained intracytoplasmic glycogen, confirmed by special stains (PAS and PAS-D) (2). None of the cases were sequenced by next-generation sequencing (NGS) for targeted treatment purposes.

Case 1 (GRCC, Luminal B, HER2+)

A 66-year-old woman with a positive family history detected a left breast mass on self-examination. Ultrasound demonstrated a suspicious anechoic focus in the upper outer quadrant (~ 10 mm), and mammography confirmed a poorly circumscribed mass with microcalcifications. Because of a documented allergy to local anesthetics, a core biopsy was not performed; at the patient's request, a total mastectomy with axillary dissection was undertaken. Grossly, a 13 mm tumor was identified in the upper outer quadrant near the deep margin. Microscopically, the carcinoma was predominantly solid, with clear-cell morphology in $>90\%$ of cells (Figure 1A-C). Immunohistochemistry showed that the tumor cells were diffusely (100%) and strongly positive for ER (Figure 1D), negative for PR (0%), while HER2 protein exhibited a complete, intense membranous expression in $>90\%$ of cancer cells (IHC score 3+) (Figure 1E); the proliferating marker Ki-67 was positive in $\sim 10\%$ of cancer cells. Tumor-infiltrating lymphocytes were low ($\sim 1\%$) (Figure 1A). The tumor cells were strongly and diffusely PAS-positive and PAS-D-sensitive, consistent with intracytoplasmic glycogen (Figure 1F). An associated solid clear-cell ductal carcinoma in situ (DCIS) comprised $\sim 10\%$ of the lesion (Figure 1A arrow). All axillary nodes were negative (AJCC stage pT1cN0Mx). Adjuvant therapy included 12 weekly cycles of paclitaxel combined with trastuzumab (administered every three weeks) for one year, followed by radiotherapy. Endocrine therapy with letrozole was initiated after the completion of both adjuvant chemotherapy and radiotherapy. The patient remains disease-free at 1-year follow-up.

Case 2 (GRCC, Triple-Negative)

A 52-year-old woman noted a left periareolar mass after a fall. Initial ultrasonography suggested a fibroadenoma, and short-interval follow-up (four weeks) was advised. During this period, the overlying skin became inflamed, prompting a second opinion. Mammography then demonstrated a circumscribed, lobulated mass measuring 31×28 mm. Core needle biopsy confirmed a high-grade, invasive breast carcinoma. Carcinoma was predominantly solid, with clear cell morphology in more than 90% of cells (Figure 2A-C), with a triple-negative immunophenotype (ER-/PR-/HER2 1+) (Figure D, E), and a high Ki-67 (90%). The cells were diffusely PAS-positive and PAS-D-sensitive, consistent with intracytoplasmic glycogen accumulation (Figure 2F). TIL levels were low ($\sim 5\%$, Figure 2B). PD-L1 testing was not performed. The multidisciplinary tumor board recommended neoadjuvant chemo-immunotherapy. The patient received paclitaxel and carboplatin for 12 weeks, followed by four cycles of the AC protocol (doxorubicin, cyclophosphamide). This was combined with the PD-1 inhibitor pembrolizumab, administered every three weeks. Of note, the patient obtained pembrolizumab through self-funding, as access to this therapy was restricted and subject to prolonged waiting periods under the Federal Solidarity Fund program. Subsequent clinical and ultrasound assessments showed marked tumor regression. The patient underwent segmentectomy with axillary dissection. Grossly, a 5-mm residual lesion was present between the lateral quadrants within a 31×28 mm tumor bed. The entire tumor bed was submitted for microscopic assessment. Postoperative pathology was evaluated using the MD Anderson Residual Cancer Burden (RCB) method (17, 18). The tumor response to neoadjuvant therapy was classified as RCB-II, indicating a partial pathologic response. The tumor bed showed treatment-related changes (inflammatory infiltrates, hemorrhage, fat necrosis). Residual invasive carcinoma was confined to a single block and displayed clear-cell morphology with therapy-related atypia (marked pleomorphism, hyperchromasia)

(Figure 3A-B). Ductal carcinoma in situ was not identified. All axillary lymph nodes were negative (AJCC ypT1aN0Mx). The patient is scheduled for

adjuvant radio- and systemic therapy, as recommended by the multidisciplinary tumor board (as of early October 2025).

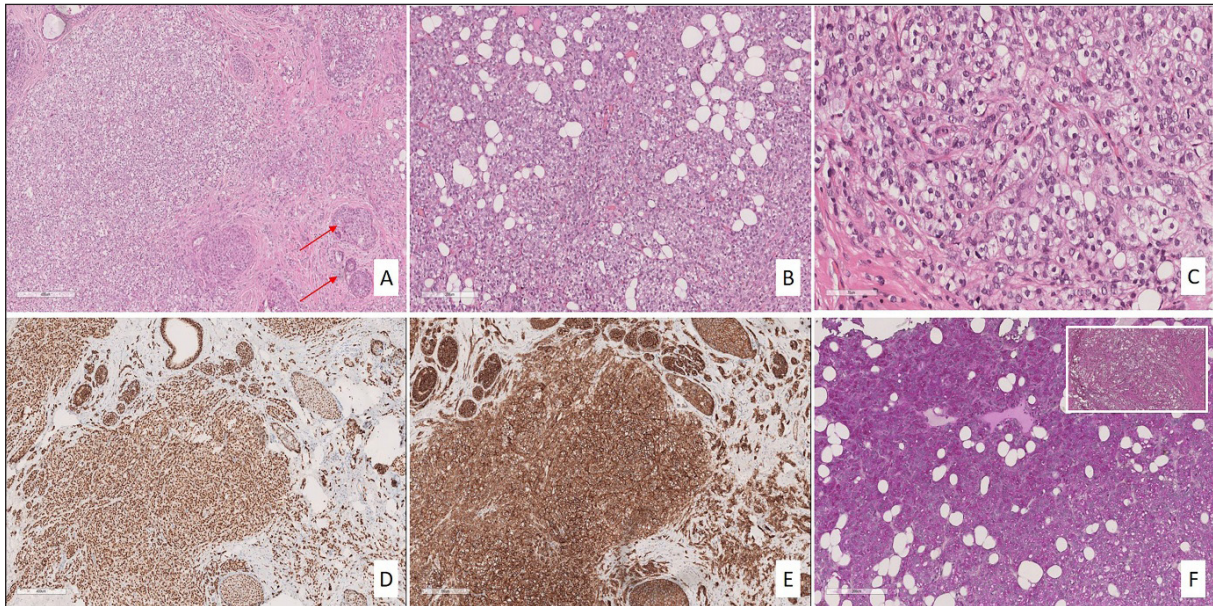


Figure 1A–F. Case 1. Clear-cell morphology in >90% of tumor cells on hematoxylin and eosin-stained slides (A, 4×; B, 10×; C, 20×). Tumor cells are diffusely and strongly ER-positive (D) and HER2-positive (E). Clear cells are strongly PAS-positive (F) and PAS-D-sensitive (inset in F), consistent with intracytoplasmic glycogen.

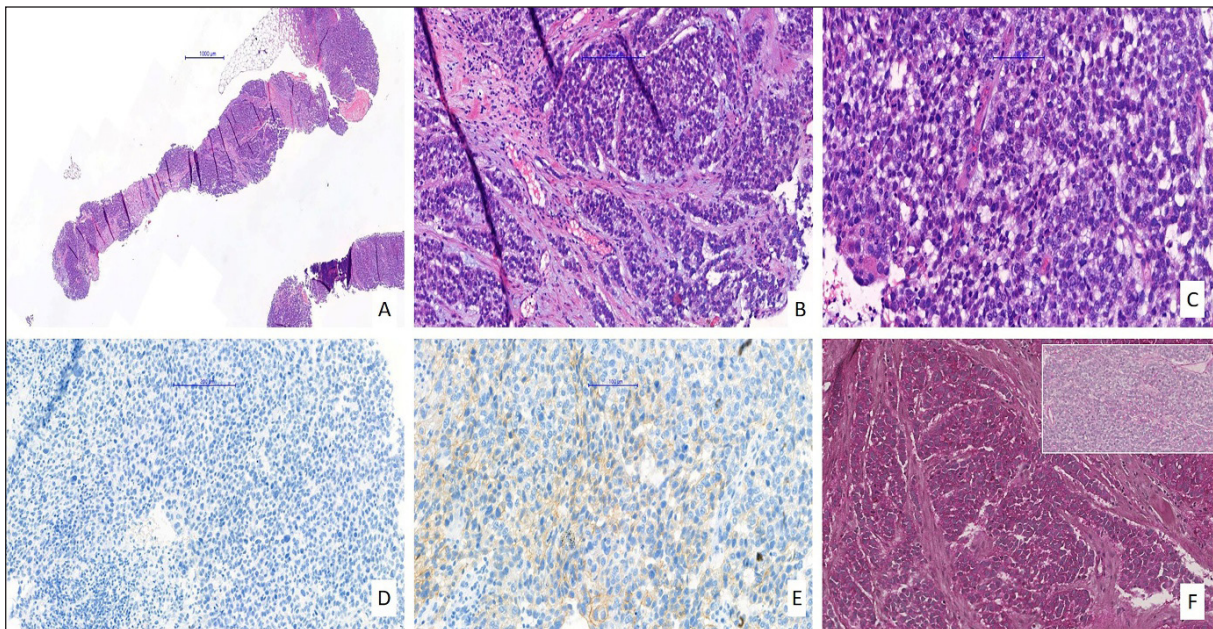


Figure 2A–F. Case 2. Core biopsy showing invasive carcinoma with predominant clear-cell morphology on hematoxylin and eosin-stained slides (A, 4×; B, 10×; C, 20×). Tumor cells are ER-negative (D) and HER2 negative/low (score 1+) (E). Clear cells are strongly PAS-positive (F) and PAS-D-sensitive (inset in F), consistent with intracytoplasmic glycogen.

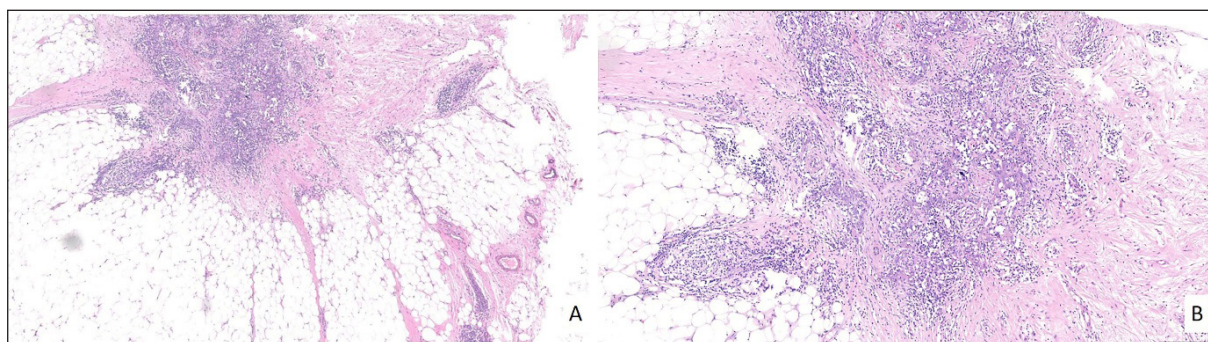


Figure 3A–B. Case 2, post-neoadjuvant therapy. Residual clear cell carcinoma with prominent inflammatory response and fibrosis on hematoxylin and eosin-stained slides (A, 4x; B, 20x).

Discussion

The two cases presented here illustrate the morphologic unity but biological diversity of GRCC of the breast—a rare histologic variant (pattern) of invasive breast carcinoma characterized by clear cytoplasm due to intracytoplasmic glycogen. Despite nearly identical H&E appearances, our patients showed strikingly different immunophenotypes and proliferation indices (Case 1: ER-positive, PR-negative, HER2 3+, low Ki-67; Case 2: triple-negative with 90% positive Ki-67). These observations reinforce that GRCC is not a biologically uniform entity but rather a heterogeneous group with potentially distinct molecular pathways and clinical outcomes (10). To contextualize our experience, we searched for newly diagnosed GRCCs from 2020 to 2025; results are summarized in Table 1 (13, 19–25).

Reported incidence varies widely, from <1% in population-based registries (SEER) to ~0.1–3% in some single-institution series from the 1980s–2020s (7, 9, 12, 13, 26–28). By definition, GRCC shows glycogen in ≥90% of tumor cells, documented by PAS positivity that is abolished after diastase digestion (PAS-D) (2). While most tumors show conventional ductal architecture, described patterns include solid papillary, tubular, mixed morphologies, and occasional neuroendocrine-like features (29). Radiologic findings are nonspecific; some reports note prominent microcalcifications on mammography and a peripheral “halo” on MRI, but no pathognomonic pattern has been established (30, 31).

Several case series report a predominance of luminal tumors (ER/PR positive, HER2 negative); for example, Kuroda et al. found ~56% luminal A among reviewed cases (28). Our series illustrates the spectrum, with one luminal B/HER2-positive (ER+/PR-/HER2+) carcinoma and one triple-negative tumor. Across studies, HER2 positivity varies widely—from rare/low (3/28 in Ma et al.) (32) to as high as ~44% in Akbulut et al. (33) and ~80% in the study of Demyashkin et al. (13) —likely reflecting differences in cohort selection, testing methodology, and sample size. Systematic, standardized studies are needed to clarify the molecular underpinnings of GRCC and its relationship to IBC-NST.

Our second case showed a triple-negative phenotype with low TILs but a high Ki-67 proliferative index. Given limited morphology-based evidence in the literature, treatment followed standards for triple-negative breast cancer (TNBC) rather than GRCC-specific features. Tumor-cell glycogen can function as an energy buffer that promotes therapeutic resistance and survival (34). This case illustrates that GRCC may occasionally present as high-grade, triple-negative, and TIL-low, suggesting a metabolically driven rather than immunogenic tumor. To our knowledge, this is among the first reported triple-negative GRCCs treated with neoadjuvant chemo-immunotherapy (pembrolizumab). The rationale for PD-1 blockade stems from the known immunogenicity of TNBC and the demonstrated benefit of adding pembrolizumab to multi-agent chemotherapy in the neoadjuvant setting (KEYNOTE-522), which improved response

rates and long-term outcomes versus chemotherapy alone (35). Recognizing this pattern is important, as its biology and therapeutic response may differ from classic basal-like TNBC (2, 28).

Neither of our cases showed lymph-node metastasis. Early reports (7, 8) and a population-based analysis by Zhou et al. (9) associated GRCC with higher grade, more advanced stage, a triple-negative shift, and poorer survival compared with non-GRCC breast cancers (7, 9). In contrast, Georgescu et al. found no significant prognostic differences between GRCC and non-GRCC cohorts (20). Individual long-term observations by Sanjeeviah et al. (19) further suggest that outcomes may be independent of clear-cell morphology per se and can be unexpectedly favorable. The follow-up in both cases presented in our study was short (1-12 months); therefore, long-term outcomes and prognostic assessments cannot be reported.

One of the important issues highlighted in our study is limited access to targeted drugs in the Federation of Bosnia and Herzegovina. Our patient (case 2, triple-negative carcinoma) had to obtain pembrolizumab through self-funding, given the limited utility and prolonged waiting period for access to immunotherapy in the Federation of Bosnia and Herzegovina. This common problem with a substantial adverse effect on cancer patient treatment and outcome requires urgent public action and has been previously discussed in the literature (36-40).

GRCC is heterogeneous and should not be regarded as a single clinicopathologic entity within IBC-NST or assumed to have a uniform prognosis. Management should be biomarker-guided, as illustrated by these cases. The role of targeted and immune therapies in GRCC warrants multi-institutional studies.

What Is Already Known on This Topic:

Glycogen-rich clear cell carcinoma (GRCC) of the breast is a rare morphologic variant characterized by clear cytoplasm due to intracytoplasmic glycogen, confirmed by PAS positivity that is diastase-sensitive; most series define GRCC when $\geq 90\%$ of tumor cells show this feature. Reported incidence is very low ($<1\%$), and the literature is dominated by small series and case reports. GRCC shows biologic heterogeneity: many cases are luminal (ER/PR-positive, HER2-negative), but HER2

positivity and triple-negative phenotypes have also been described; population-based data suggest higher grade, more advanced stage, and potentially worse survival than non-GRCC, although these findings are not uniform across studies. No pathognomonic imaging pattern is established, and management is not GRCC-specific – treatment generally follows biomarker-guided breast cancer standards.

What This Study Adds:

We describe two pathologically confirmed glycogen-rich clear cell carcinomas (GRCC) with contrasting biomarker profiles and clinical courses: One ER+/PR-/HER2 3+, low Ki-67 case and one triple-negative, high Ki-67 case treated with pembrolizumab-based neoadjuvant chemoinmunotherapy showing marked regression. These findings reinforce the biologic heterogeneity of GRCC and the need for biomarker-guided management. We document coexistent clear-cell DCIS in one case and low TILs in both cases. We also provide an updated 2020–2025 literature review, underscoring gaps that warrant larger, multi-institutional studies and prospective molecular profiling of this peculiar malignancy.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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