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Case Series

Interesting Breast Tumours: A Tripod of Cases

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Abstract

Knowledge regarding the lesser common breast tumours, including malignant papillary neoplasms and glycogen-rich clear cell carcinoma, is limited. Overall, cases of papillary carcinoma of the breast fare better than invasive breast carcinoma, from the data available in literature. Glycogen-rich clear cell carcinoma is characterized by the presence of clear cells, having mostly a poorer prognosis. We hereby present three such cases which would add to the existing available information. ***Case 1*** is a 79-year-old female who presented with a left breast lump and bloody nipple discharge. Mammography suggested malignant lesion, with FNAC suspicious of malignancy. Surgery was done and histopathological examination showed irregular islands of tumour cells having papillary fronds with absence of myoepithelial layer. Immunohistochemically, the tumour was GATA3, CK7, ER, PR positive, HER2 negative, with Ki67 index 10%. The case was diagnosed as Solid papillary carcinoma. ***Case 2*** is a 57-year-old female presenting with a left breast lump along with bloody nipple discharge. Mammography and FNAC were in favour of malignancy. Trucut biopsy was done, microscopy revealing a tumour having >90% papillary architecture with infiltrative pattern. Features were suggestive of Invasive breast carcinoma with papillaroid features. The tumour was GATA3, CK7, ER, PR positive, HER2 negative, with Ki67 index 15%. ***Case 3*** is a 70-year-old female presenting with a right breast lump with nipple retraction. Mammography and FNAC were suggestive of malignancy. Trucut biopsy followed by microscopy revealed polygonal tumour cells with clear cytoplasm in nested pattern, showing positive staining for Periodic Acid Schiff. Immunostaining showed GATA3 positive, PAX8 negative, ER and PR positive, HER2 negative, and Ki67 index 20%. A diagnosis of Invasive breast carcinoma with Glycogen-rich clear cell pattern was made. Identifying these rare entities is important along with assessing hormone status for avoiding overtreatment and undertreatment and applying appropriate targeted therapies.

Keywords: Breast Cancer; Solid Papillary Carcinoma; Invasive Papillary Carcinoma; Glycogen-Rich Clear Cell Carcinoma.

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Introduction:

Among the malignant breast tumours, rare entities like papillary lesions constitute <0.5-2% and include Solid papillary carcinoma (SPC) and the even rarer Invasive papillary carcinoma (IPC) among others.[1] Microscopically, determining the status of the myoepithelial layer is key, which helps distinguish *in-situ* from invasive forms. Prognostically, they are better than Invasive breast carcinoma (IBC), from the limited available data.[2]

Glycogen-rich clear cell carcinoma (GRCCC) comprises 1.4-3% of all breast malignancies and is characterized by clear cells mimicking clear cell metastatic tumours, having mostly a poor prognosis.[3]

We hereby report three such cases which would add to the existing available information.

Case Series

Case 1

A 79-year-old female patient presented with complaints of a left breast lump along with bloody nipple discharge for the last 12 months. Physical examination revealed a firm lump of size 3.0cm x 2.5cm in the retroareolar region of the left breast, along with crusting and retraction of the nipple. Mammography showed an irregular high-density lesion of size 2.8cm x 2.6cm x 2.5cm in the central quadrant with partial spiculation and micro-lobulated margins, which was suggestive of a Breast Imaging Reporting and Data System Category 5 (BIRADS-5) lesion (Figure 1A). PET-CT scan showed a fluorodeoxyglucose (FDG) avid mass in retroareolar location in the central region of the left breast, with overlying skin and underlying pectoralis muscle unremarkable, and no significant axillary lymphadenopathy. Fine needle aspiration cytology (FNAC) was done which showed atypical ductal cells in clusters, singly dispersed and occasional papillary pattern with complete absence of myoepithelial cells, which were suggestive of a papillary lesion, suspicious for papillary carcinoma.

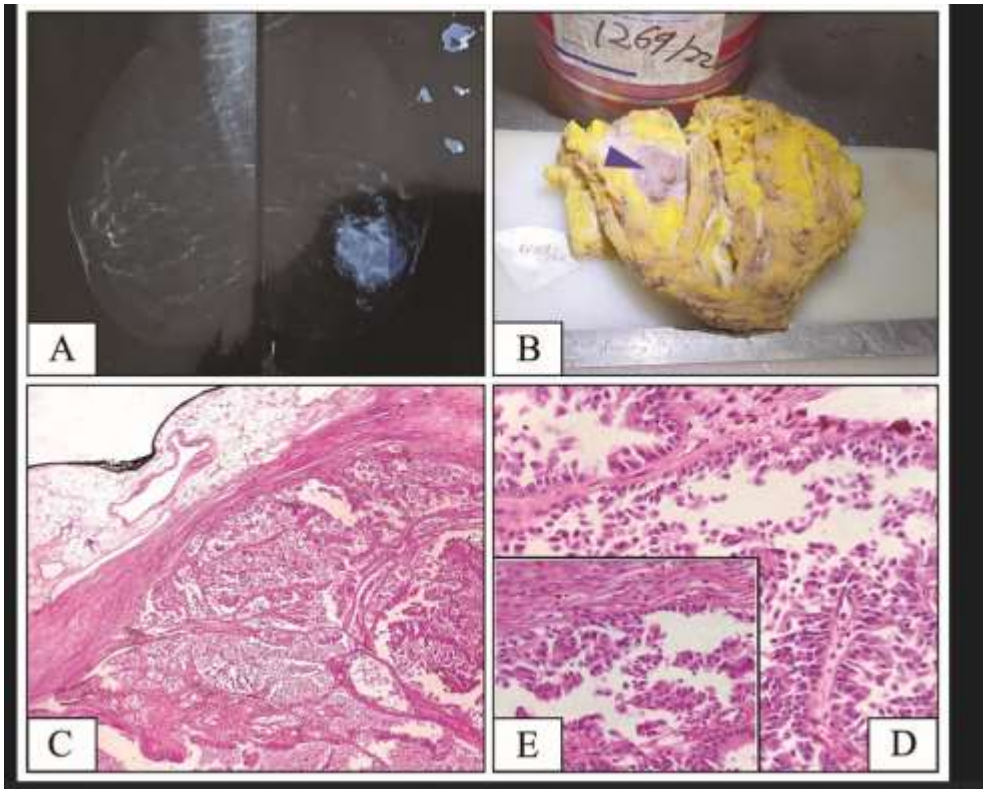

Figure 1:

A – Mammography showing lesion in the left breast
B – Arrowhead depicting grey-white tumour
C – Tumour cells in nests with papillary architecture, 10x, Haematoxylin-Eosin (HE) stain
D – Papillary fronds lacking myoepithelial cells, 40x, HE stain
E – Inset showing absence of myoepithelial layer at the periphery, 40x, HE stain

Left modified radical mastectomy (MRM) was done and the specimen was sent to the Pathology Department. Grossly, we received a specimen of the left breast with a grey-white solid tumour of size 4.0cm x 4.0cm x 3.0cm located in the central region (Figure 1B). Microscopic examination showed a tumour with irregular jigsaw-shaped islands and lobules of tumour cells, having compactly formed papillary fronds with branching networks of fibrovascular cores (Figure 1C). Myoepithelial cells were absent along the internal fibrovascular cores and around the perimeter of the lobules (Figure 1D**, 1E).** Individual tumour cells had a moderate amount of cytoplasm with fine nuclear chromatin, moderate nuclear pleomorphism, and occasional mitotic figures. No area of necrosis was seen. Nottingham's overall grade assigned was Grade 2. Lymphovascular and perineural invasion were not identified. The tumour showed infiltration into the surrounding breast tissue with the involvement of the nipple-areolar complex, but the skin was free of tumour. The adjacent breast parenchyma showed features of ductal carcinoma *in-situ*.

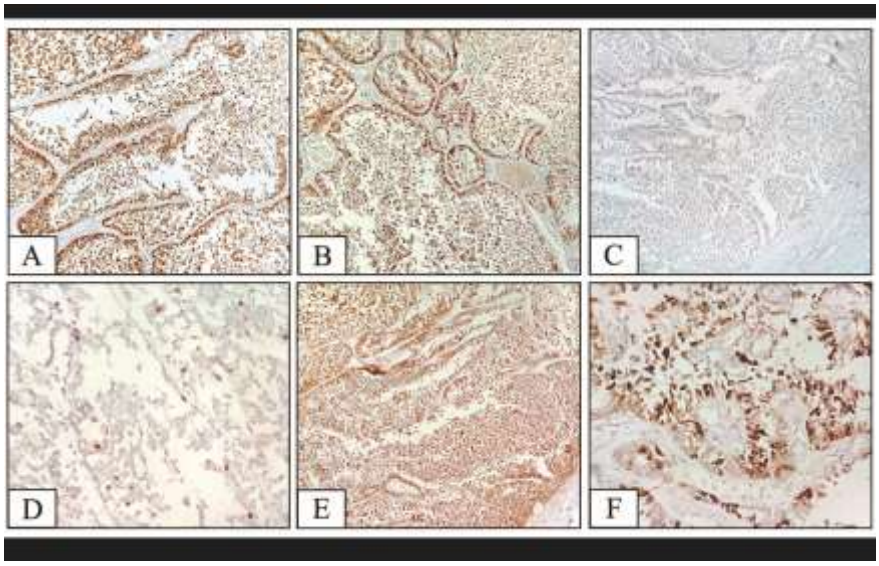

Figure 2:

A – ER strong nuclear positivity in tumour cells, 10x
B – PR strong nuclear positivity in tumour cells, 10x
C – HER2 negativity in tumour cells, 10x
D – Ki67 10%, 40x
E – GATA3 strong nuclear positive, 10x
F – CK7 strong membranous positive, 40x

Immunohistochemical findings were Estrogen receptor (ER) strongly positive in 100% tumour cells (Allred Score 5+3=8), Progesterone receptor (PR) strongly positive in 95% tumour cells (Allred Score 5+3=8), Human epidermal growth factor receptor 2 (HER2) negative (Score 0), and Ki67 index 10% (Figure 2A-D). GATA Binding Protein 3 (GATA3) was strongly nuclear positive, and Cytokeratin 7 (CK7) was strongly membranous positive in the tumour cells (Figure 2E, 2F). Based on the histomorphological and immunohistochemical findings, a diagnosis of SPC, invasive type, was made. Post-surgery, the patient has received 2 cycles of chemotherapy and hormonal therapy so far and is doing well.

Case 2

A 57-year-old female presented with a lump in her left breast and bloody nipple discharge for 4 months. Physical examination revealed a firm mass of size 5.0cm x 4.5cm in the upper outer quadrant of the left breast. Mammography showed an irregular high-density lesion of size 5.0cm x 4.4cm x 4.0cm with partially spiculated and partially lobulated margins (BIRADS-5) (Figure 3A). PET-CT scan confirmed the breast mass with no other abnormality elsewhere in the body. FNAC showed the presence of few atypical ductal epithelial cells and was suspicious for malignancy.

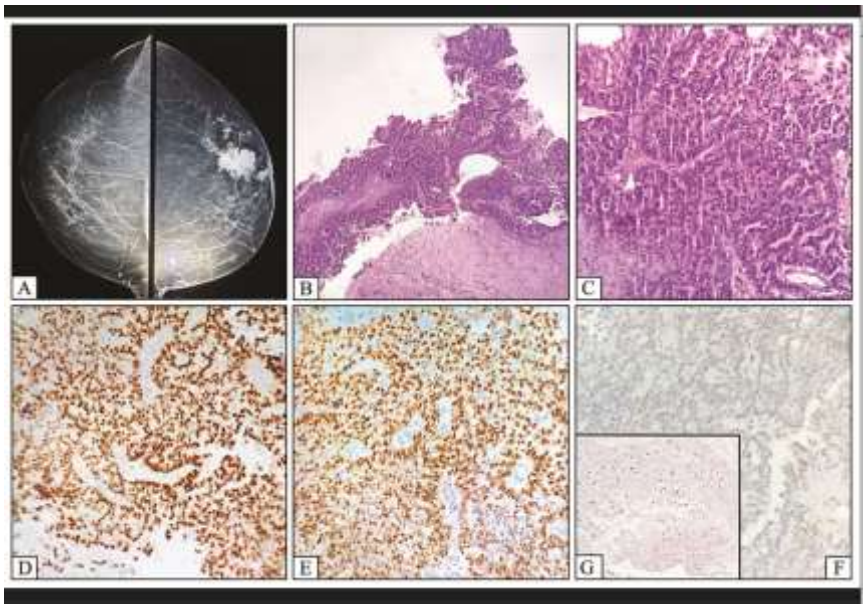

Figure 3:

A – Mammography showing lesion in the left breast
B – Papillary infiltrative architecture of tumour, 10x, HE stain
C – Papillary fronds with absent myoepithelial layer, 40x, HE stain
D – ER strong nuclear positivity, 40x
E – PR strong nuclear positivity, 40x
F – HER2 negativity, 40x
G – Inset showing Ki67 index 15%, 10x

A Trucut biopsy was done. Multiple fragmented linear cores were received, the largest measuring 0.5cm. Microscopy showed papillary fronds of tumour cells having fibrovascular cores and encompassing >90% architecture with an infiltrative pattern, lacking fibrous capsule or myoepithelial cell layer (Figure 3B, 3C). The histologic grade assigned was Nottingham grade 2. Lymphovascular and perineural invasion were not identified. Features were suggestive of IBC with prominent papillaroid features.

Immunostaining showed GATA3 strongly nuclear positive, CK7 strongly membranous positive in the tumour cells, ER strongly positive in 90% tumour cells (Allred Score 5+3=8) (Figure 3D), PR strongly positive in 90% tumour cells (Allred Score 5+3=8) (Figure 3E), HER2 negative (Score 0) (Figure 3F), and Ki67 index 15% (Figure 3G). The patient is now planned for MRM, with a plan for hormonal therapy depending on the stage.

***Case* 3**

A 70-year-old female presented with a painless palpable lump in her right breast. Physical examination revealed a 2.0cm x 2.0cm non-tender firm mass at the upper outer quadrant of the right breast, with crusting and retraction of the nipple, and no palpable axillary lymph nodes. Mammography showed an irregular high-density lesion of size 2.8cm x 2.6cm x 2.5cm with partial spiculation and micro-lobulated margins (BIRADS-5) (Figure 4A). PET-CT scan confirmed an FDG avid breast lesion and revealed no other abnormality. FNAC from the right breast lump demonstrated features suggestive of a malignant lesion.

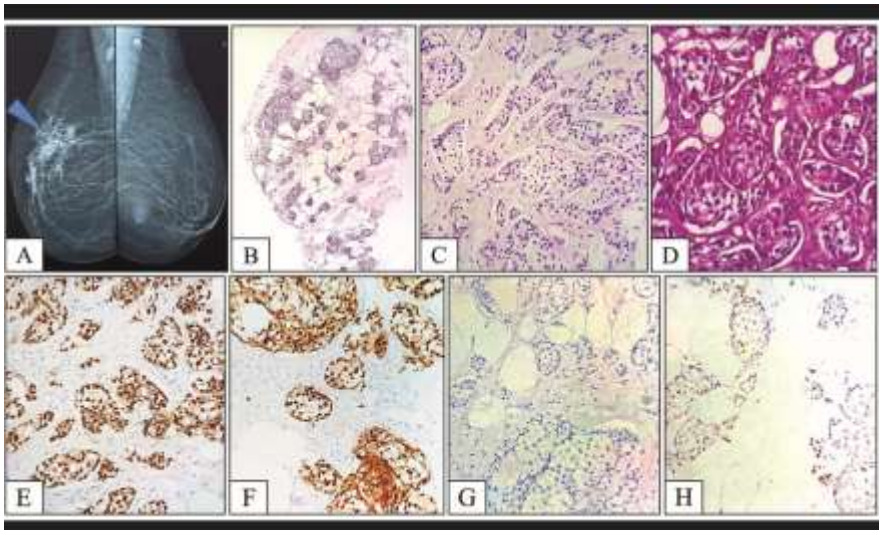

Figure 4:

A – Arrowhead depicting lesion in the right breast
B – Tumour cells in solid nests, 10x, HE stain
C – Polygonal cells with clear cytoplasm, 40x, HE stain
D – PAS highlighting glycogen within tumour cells, 40x
E – ER positivity, 40x
F – PR positivity, 40x
G – HER2 negativity, 40x
H – Ki67 index 20%, 40x

Trucut biopsy was done, and we received six linear cores, ranging in length from 1.0cm to 2.0cm. Histopathological examination revealed fibroadipose tissue bits with nested and solid pattern of large neoplastic cells which were polygonal in shape with distinct cell borders, abundant clear cytoplasm and central hyperchromatic nuclei (Figure 4B, 4C). The histologic grade assigned was Grade 2. Lymphovascular and perineural invasion were not identified in the sections studied. The tumour cells showed positive staining with Periodic Acid Schiff (PAS) (Figure 4D) and were Diastase sensitive, and Sudan Black B was negative. Immunostaining showed GATA3 positive and PAX8 negative. Based on these morphological and immunohistochemical features, the diagnosis of IBC with Glycogen-rich clear cell pattern (GRCCP) was made.

The tumour cells were strongly nuclear positive for ER in 95% of tumour cells (Allred Score 5+3=8), strongly nuclear positive for PR in 60% of tumour cells (Allred Score 4+3=7), HER2 negative (Score 0) with no staining observed, and Ki67 index was 20% (Figure 4E-H), with above testing done using positive controls. The patient is now planned for MRM with axillary clearance, with a plan for hormonal therapy in the form of aromatase inhibitors.

Discussion

Papillary lesions of the breast range from benign entities to malignant IPC, with in-between *in-situ* papillary carcinoma. The *in-situ* papillary carcinomas include Encapsulated papillary carcinoma (EPC) and SPC *in-situ*. World Health Organization (WHO) Working Group provides guidelines for categorizing SPC as *in-situ* or invasive.[4] In our case, the tumour cells had multiple solid nodules with jagged, irregular borders and a complete absence of myoepithelial cell layer, which helped us classify it as an SPC invasive type.

SPC may often be confused with EPC which is well-encapsulated, and has a cystic space within, usually revealing a single nodule microscopically although occasionally can be multinodular, but lacks the jagged borders or back-to-back jigsaw-like pattern as in SPC.[5] There is a typical lack of myoepithelial cells in EPC, whereas SPC may show focal staining for myoepithelial cells in the *in-situ* type. Also, the tumour cells of EPC do not show neuroendocrine differentiation, unlike most SPC cases. However, neuroendocrine differentiation in SPC serves more as a diagnostic marker compared to other types of breast carcinomas where neuroendocrine differentiation acts as a poor prognostic marker.[5]

Another close differential of SPC *in-situ* is Papilloma with florid usual ductal hyperplasia (UDH). Compared to florid UDH, SPC has a monomorphic appearance of epithelial cells, absence of myoepithelial cell layer, mucin production, neuroendocrine differentiation highlighted by neuroendocrine markers like Synaptophysin or Chromogranin, strong and diffuse ER positivity and high molecular weight cytokeratin CK5/6 negativity.[5]

The distinction of SPC invasive type from SPC *in-situ* and EPC is important. Pure EPC is indolent and behaves like an *in-situ* carcinoma (pTis) with only a few reports of regional lymph node and distant metastasis. On the other hand, SPC *in-situ* has a better prognosis as it has not been found to metastasize at all to regional lymph nodes or distant sites, even with an absent myoepithelial layer. SPC invasive cases also have a favourable prognosis but are slightly worse than EPC and SPC *in-situ*.[6]

Comparison of SPC invasive with conventional IBC has revealed SPC to have better prognostic features like lower tumour grade, lower TN stage and lower chance of axillary metastasis than IBC. Thus, histopathological categorization is necessary because of the prognostic difference.[7] In patients with SPC, surgery can be followed by radiation and hormonal treatment, with avoidance of unnecessary systemic therapy.[8] However, in our case, the patient received additional chemotherapy because the invasive nature of the tumour had gone on to involve the nipple-areolar complex.

SPC is found to be mostly ER and PR diffusely and strongly positive but HER2 negative, and our patient revealed the same findings. At the molecular level, the genes RET, ASCL1, and DOK7 related to neuroendocrine differentiation have been found to be upregulated in SPC.[9]

IPC of the breast is a very rare subtype with limited data available in literature. However, WHO recognizes it as a distinct entity. The complete absence of myoepithelial cell layer in our case dismissed the possibility of DCIS, solid papillary pattern. Also, the growth pattern was frankly invasive without solid nodules or irregularly shaped islands, favouring IPC. Since we received only a core biopsy, we refrained from using the terminology IPC and signed out our report as IBC with prominent papillaroid features.

GATA3 and CK7 positivity and the absence of any other primary site, based on imaging evidence, confirmed the breast as the origin of the tumour and ruled out the possibility of metastatic tumours with papillary pattern.

Studies have found IPC to have a favourable prognostic and biomarker profile than IBC, with a higher frequency of ER, PR positivity and a lower frequency of HER2 positivity.[10]

The papillary breast neoplasms in descending order of prognosis from better to worse, based on currently available data, would be SPC *in-situ* followed by EPC, SPC invasive, IPC and finally IBC. However, sometimes, SPC or EPC may be complicated by an associated IBC, in which case the tumour staging would be dictated by the invasive component.[11] Hence, one has to be vigilant regarding this important finding.

WHO 5th edition has placed the previously recognised distinct rare entity of GRCCC under the broad umbrella category of IBC of no special type (NST) with GRCCP, among the other special morphological patterns recognised.[12] The tumour is reported as IBC NST with GRCCP if glycogen accumulation is noted in greater than 90% tumour cells. In case the GRCCP comprises 10-90%, the term "Mixed IBC NST and GRCCP IBC" may be used. Tumours with <10% glycogenated clear cells are however designated as IBC NST with focal GRCCP.[12]

IBC NST with GRCCP is a rare subtype of breast carcinoma and should be distinguished from other close differentials. Benign lesion like Clear cell hidradenoma (CCH) was considered due to the overlapping morphology. But GATA3, ER and PR positivity helped rule out CCH from our differentials. A diagnostic pitfall is that GATA3 may be variable or negative in IBC NST with GRCCP, and positive in adnexal tumours like CCH. Additionally, ER and PR may be negative in IBC NST with GRCCP. In that case, staining with p63 can be done to differentiate p63 positive CCH from p63 negative IBC NST with GRCCP.[13] However, we did not require p63 as a differentiating tool since our tumour turned out to be ER and PR-positive.

Other primary malignant breast tumours like Lipid-rich carcinoma, Signet ring cell carcinoma and Secretory carcinoma were ruled out as special staining with PAS-D and Sudan Black B demonstrated the presence of glycogen in the clear cells and the absence of lipid or mucin-containing vacuoles.

Finally, metastatic tumours which could be another differential, were excluded by imaging studies revealing the absence of primary in other organs. Also, PAX8 for renal cell carcinoma was negative.

IBC NST with GRCCP has a heterogeneous immunophenotypic profile, with the tumours mostly being ER positive, PR negative and HER2 negative. A review study done by Zhou et al on 155 cases of GRCCC using the U.S. Surveillance, Epidemiology and End Results (SEER) database revealed ER positivity in 46.5% cases, PR positivity in 27.8% cases and HER2 positivity in 6.9% cases.[14] However, ER-negative, PR-negative and HER2-positive cases as well as triple-negative cases have also been reported.[15] Our case showed ER and PR positivity with HER2 negativity.

The overall prognosis of IBC NST with GRCCP is controversial. However, from the data available to date, mostly it has an aggressive behaviour with poorer prognosis and late detection, compared to non-glycogen-rich breast carcinomas. The SEER database study by Zhou et al led to the conclusion that GRCCC is more aggressive than its non-glycogenated counterparts. Fisher et al found poorer outcomes in GRCCC cases with higher grades and greater nodal metastasis than the non-clear cell cases. On the other hand, Ma et al and Hayes et al found no significant prognostic difference between GRCCC and non-GRCCC in their studies.[16]

Conclusion

The varied morphological spectrum and overlapping features with other lesions make the diagnosis of these rare entities challenging. For papillary breast lesions, subtype categorization and identification of the myoepithelial layer are important, as is confirmation of breast as the primary. IBCNST with GRCCP is also a rare entity with contradictory information on its prognostic value, however, the consensus is that it is more aggressive than pure IBCNST. In all cases, hormone receptor and proliferation status assessment are essential, which can help in planning targeted treatment modalities and proper prognostication of these patients.

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