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Letter to the Editor

Glycogen-rich clear cell carcinoma of the breast showing carcinomatous lymphangiosis and extremely aggressive clinical behavior

To the Editor:

The World Health Organization (WHO) classifies mammary glycogen-rich clear cell carcinoma (GRCC) as an exceptionally rare variant among special types of invasive carcinoma and defines this tumor as >90% of neoplastic cells having abundant clear cytoplasm containing glycogen.[1,2] Although previous reports suggest that GRCC is more aggressive than invasive carcinoma of no special type,[3,4] some investigators have recently asserted that the prognosis is no different once GRCC and conventional mammary carcinomas are matched by tumor size, grade, and lymph-node status.[5,6] Herein, we describe, to our knowledge, the first case of a GRCC with extraordinary vessel invasion (lymphangitic carcinomatosis) in the breast, resulting in a very rapid and aggressive clinical course.

The patient, a 62-year-old postmenopausal Japanese woman, presented with a palpable mass in the upper outer quadrant of the right breast. She had no medical or familial history of breast disease. Ultrasonography revealed a well-marginated, hypoechoic right breast tumor showing heterogeneous internal echoes. Systemic CT and bone scintigraphy detected no other suspicious lesions. We performed ultrasound-guided, core needle biopsy of the breast lesion after obtaining informed consent, and the histological diagnosis was invasive carcinoma.

The cut surface of the mastectomy specimen contained a lobulated, solid tumor, with grey-whitish and brownish-red areas, measuring 34 × 32 mm. Histologically, this tumor was composed of expansive solid and/or infiltrating trabecular growths of carcinoma cells with geographical coagulation necrosis and hemorrhage (Fig. 1). Carcinoma cells were polygonal with abundant, clear, fine-granular cytoplasm (Fig. 1a) and rich glycogen granules were confirmed by the periodic acid–Schiff method employing diastase (Fig. 1b,c). The nuclei showing a granular chromatin pattern had irregular shapes, frequently with distinct nucleoli (Fig. 1a). Sixty-five mitotic figures were counted in 10 high-power fields. Marked lymphatic permeation (i.e. carcinomatous lymphangiosis) as well as vascular infiltration were detected (Fig. 2a,b). *In-situ* components composed of similar carcinoma cells with comedo-like necroses were observed near invasive cancer nests (Fig. 1d). Surgical margins of the right breast were negative for cancer. Metastases were identified in 12 of 23 excised right axillary lymph nodes (Fig. 2c).

Immunohistochemically, 0% of carcinoma cells were reactive for estrogen or progesterone receptors (Allred's total scores: 0 and 0, respectively). The HER2 score was 0, and the Ki67 (MIB-1) labelling index was 70.1%. Carcinoma cells were positive for cytokeratin (CK) AE1/AE3, CK7 and GATA3, focally positive for CK CAM5.2, mammaglobin, adipophilin and p63 and negative for CK5/6, CK14, CK20, gross cystic disease fluid protein 15 (GCDFP15), HMB45, Melan-A/MART-1, smooth muscle actin, muscle specific actin (HHF35), calponin, h-caldesmon, renal cell carcinoma marker (RCC Ma), PAX8, carbonic anhydrase IX, CD10 and androgen receptor. The lining endothelial cells, visualized by D2-40 and/or CD31 staining, were evident in vessels with tumor involvement (Fig. 2b). Myoepithelial markers showed the presence of myoepithelia along the periphery of *in-situ* carcinoma cell nests.

A month after surgery, three nodules were detected by palpation in the right chest wall and were diagnosed as local recurrence with carcinoma verification using fine needle aspiration cytology. On subsequent CT scans, multiple lung, liver, bone (Th5 and L1) and lymph node (right supraclavicular and internal thoracic) metastases were identified. The patient received paclitaxel (90 mg/m^2) and bevacizumab (10 mg/kg) every 4 weeks for seven cycles. She has remained alive with marked therapeutic effects for 8 months, to date, since surgery.

The possibility of metastatic clear cell carcinoma from another site, especially clear cell renal cell carcinoma, should be ruled out.[1] Imaging and clinical history confirmed that our patient had no lesions preoperatively in other organs, and an *in-situ* component accompanying the invasive breast cancer was demonstrated histologically. These are regarded as the two most important features for diagnosing primary clear cell mammary carcinoma.[1] In addition, GATA3 and mammaglobin immuno-expressions support a diagnosis of primary GRCC of the breast,[7] while negativity for RCC Ma, PAX8, carbonic anhydrase IX and CD10 and positivity for CK7 can rule out clear cell renal cell carcinoma.

Differentiation from other mammary neoplasms composed of clear cells is also necessary.[1] Clear cell 'sugar' tumor, one member of the family of neoplasms with perivascular epithelioid cell differentiation (so-called PEComas), shows solid proliferation of epithelioid tumor cells with glycogen-rich clear cytoplasm.[8] This tumor, originally described in the lung, is now being recognized at extra-pulmonary sites, including the breast. Immunohistochemically, the PEComa family is characterized by strong reactivity with the HMB45 antibody, variable expressions of muscle markers and negativity for cytokeratins,[8] unlike our present GRCC.

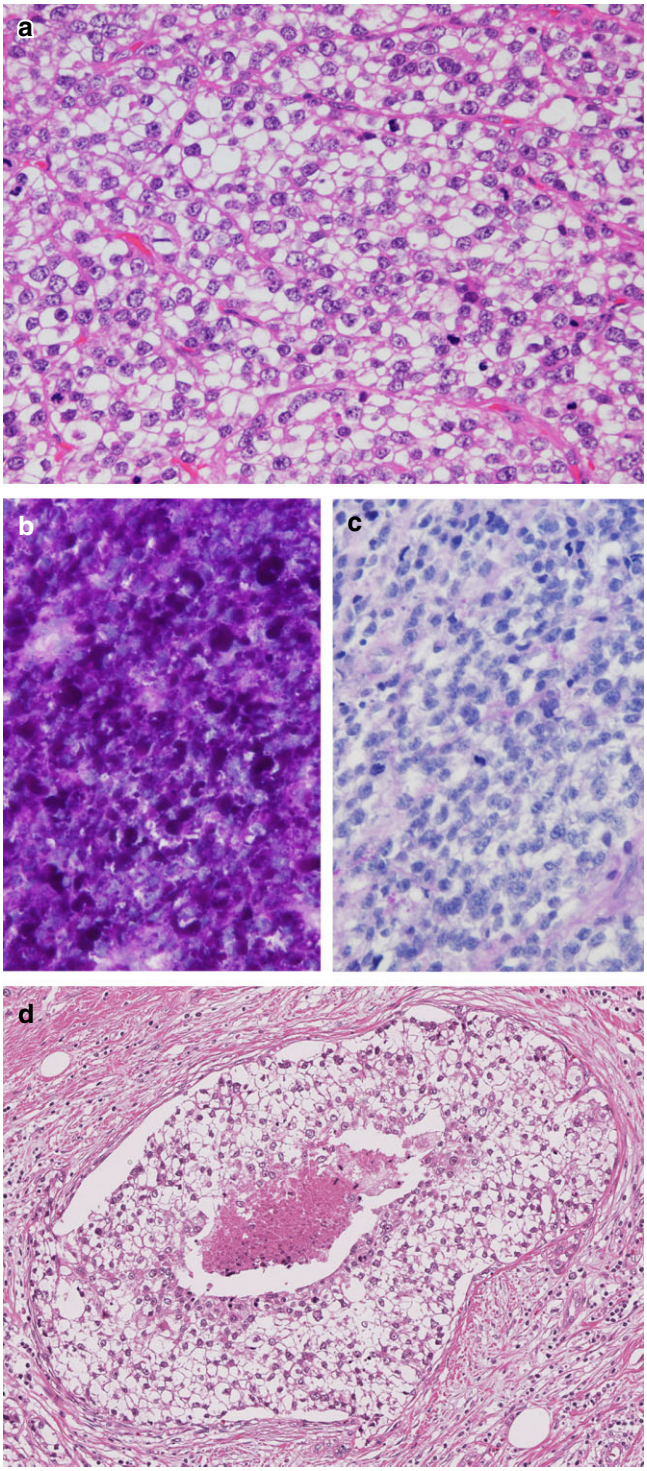

Figure 1 Histopathological findings of mammary glycogen-rich clear cell carcinoma. (**a**) Medullary invasive growth of polygonal cancer cells with clear and/or vacuolar cytoplasm and a capillary stroma. (**b, c**) Cancer cells show a strongly positive reaction with periodic acid–Schiff (**b**), eliminated by diastase digestion (**c**). (**d**) *In-situ* clear cell carcinoma focus, accompanied by comedo-like necrosis, indicative of a breast origin.

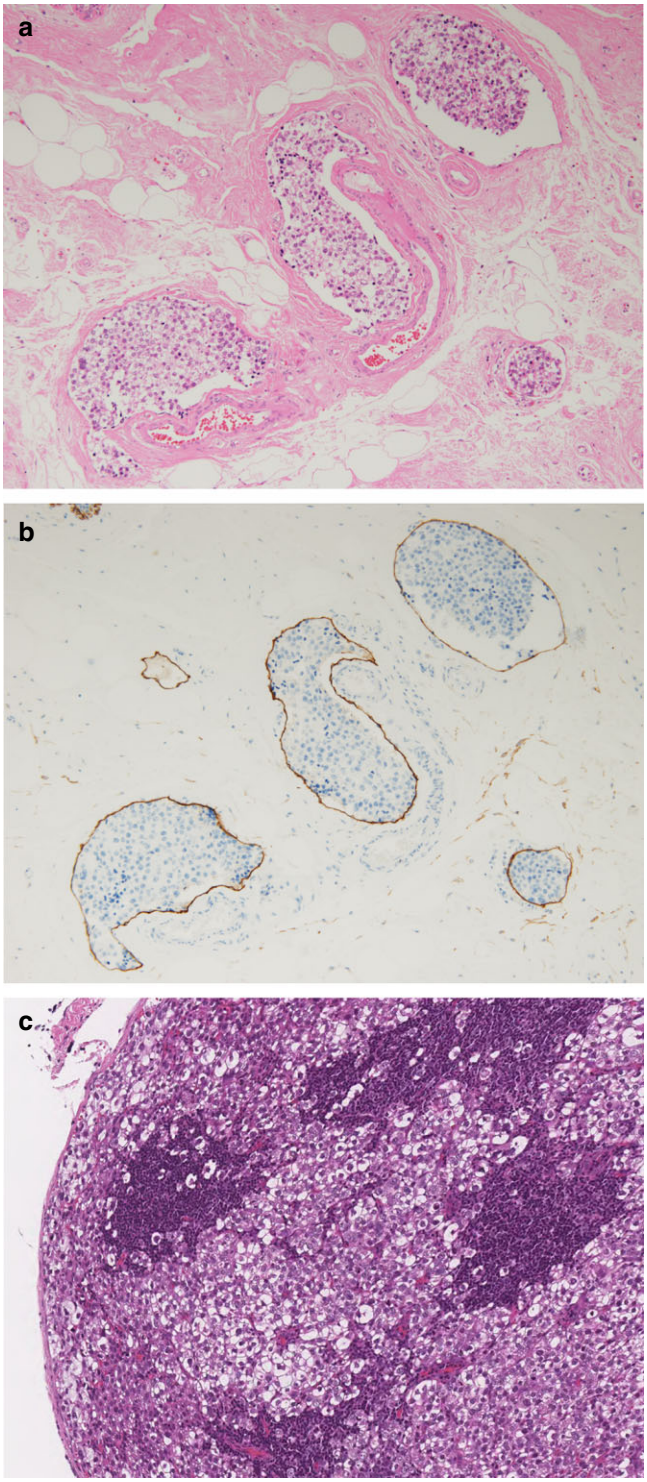

Figure 2 Histopathological findings of mammary glycogen-rich clear cell carcinoma with lymphangitic carcinomatosis. (**a**) Dilated lymph vessels filled with clear cancer cells. (**b**) Serial section demonstrates D2-40 positive lymphatic endothelia in this lesion. (**c**) Metastasis of clear cell breast carcinoma to a regional lymph node.

Kuwabara *et al*. reported a rare case of clear cell mammary malignant myoepithelioma with abundant glycogen suggesting GRCC to be a variant of malignant myoepithelioma (myoepithelial carcinoma).[9,10] In our current case, however, carcinoma cells did not show definite myoepithelial differentiation as demonstrated by immuno-staining for smooth muscle actin, HHF35, calponin, h-caldesmon, CD10 and high-molecular weight CKs, although the nuclei of a few cancer cells were positive for p63. Therefore, we can reasonably assume that the neoplasm in our patient essentially does not belong among the myoepithelial and epithelial-myoepithelial lesions.

Lipid-rich carcinoma of the breast is characterized by cytoplasmic vacuoles containing lipids in no fewer than 90% of the tumor cells.[1] On the other hand, two thirds to three quarters of mammary carcinomas including apocrine cancers contain intracytoplasmic lipid droplets to some extent. These lipid accumulations can now be demonstrated by immunohistochemistry for adipophilin and, in our present case, only some tumor cells were adipophilin immuno-reactive.

The biological behavior and prognosis of mammary GRCC remain controversial;[1] with some investigators demonstrating this tumor to be associated with frequent lymph node metastases and high mortality,[3,4] while others have emphasized that glycogen-rich clear cell features do not appear to influence the clinical outcome when stage and grade are taken into account.[5,6] Our patient, who had a GRCC not only of rather high stage (IIIc, pT2N3M0, at the time of operation) and high grade (nuclear/histological grade 3 and 'triple negative' immuno-subtype with a high MIB-1 index) but also with the unusual feature of intramammary carcinomatous lymphangiosis, followed a very aggressive clinical course with rapid recurrence and distant metastases.

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DISCLOSURE STATEMENT

None declared.

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