Pathologic Quiz Case

A 62-Year-Old Woman With a 4.5-cm Nodule in the Right Breast

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A 62-year-old woman presented with a hard lump in the right breast and palpable nodes in the right axilla. Mammography and ultrasound disclosed a 4.5-cm, irregular, dense mass with lobulated borders in the upper outer quadrant of the right breast. Results of staging investigation, including chest radiographs and bone scans, were normal. The patient underwent a right modified radical mastectomy with axillary dissection. Gross examination revealed a 4.5-cm, well-circumscribed, lobulated, firm, white-to-yellow tumor. Microscopic examination disclosed a tumor with pushing borders surrounded by and admixed with a massive lymphoplasmacytic and eosinophilic infiltrate (Figure 1). The tumor was characterized by sheets and anastomosing cords of large polyhedral cells with ill-defined borders, fine granular, eosinophilic cytoplasm, and large nuclei with coarse chromatin and prominent nucleoli. These cells were located in the central aspects of the neoplasm (Figure 2), merging imperceptibly with large, clear cells with univacuolated, multivacuolated, or foamy cytoplasm, eccentric to peripheral scalloped nuclei with coarse chromatin and conspicuous nucleoli (Figure 3). Scattered, abortive, ductlike structures were also observed. The mitotic index was 33 mitoses/10 high-power fields, with frequent atypical mitotic figures. In the adjacent breast tissue, high-grade solid and comedo ductal carcinoma in situ (Figure 1, arrow), as well as foci of lymphovascular invasion, were observed. Sudam III staining performed on cryostatic sections of formalin-fixed, wet, unprocessed tissue disclosed neutral fat in nearly all clear cells. Periodic acid–Schiff (PAS) with and without diastase revealed rare cells with PAS-positive, diastase-sensitive granules. Alcian blue, mucicarmine, and toluidine blue were consistently negative. The tumor cells were strongly immunoreactive for cytokeratin MNF116 and negative for S100 protein, α-smooth muscle actin (α-SMA), and cytokeratins 14 and 5/6. Gross cystic-disease fluid protein 15 (GCDFP-15) was focally positive in eosinophilic cells. Estrogen receptor (ER) was weakly positive in approximately 15% of the tumor cells, and progesterone receptor (PgR) was strongly positive in approximately 25% of them. No membrane staining for HER-2/*neu* in neoplastic cells was observed. p53 (clone DO-7) immunoexpression was observed in 60% of the tumor cells. Four out of 14 lymph nodes were involved by metastatic disease, which resembled the primary tumor, being composed of eosinophilic cells in central areas and clear, vacuolated cells at the periphery (Figure 4 and inset). No local recurrence or distant metastases were observed. The patient was lost to follow-up 7 months following surgery.

What is your diagnosis?

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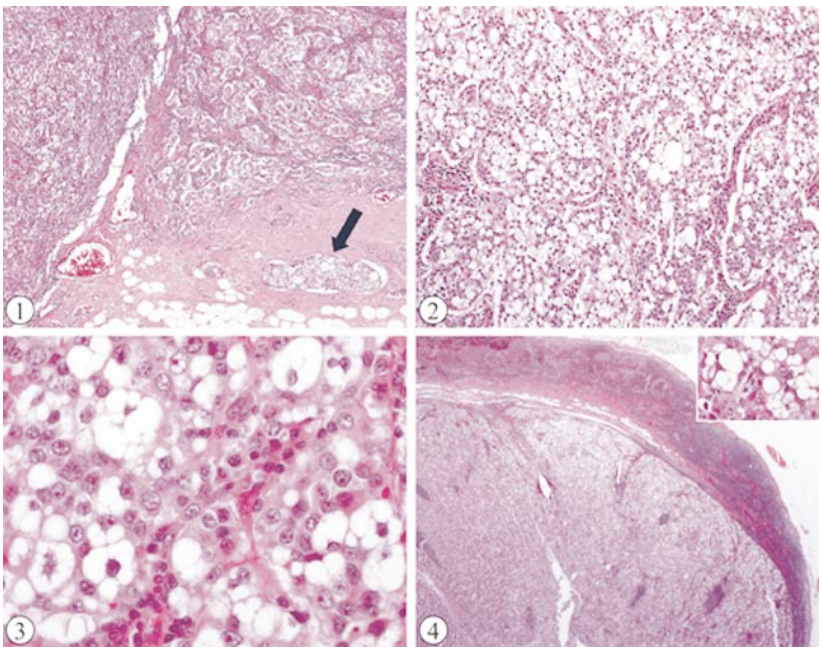

Pathologic Diagnosis: Lipid-Rich Breast Carcinoma

Lipid-rich carcinoma (L-RC) is one of the rarest histological types of breast carcinomas, accounting for only 1% to 2% of breast cases.[1–3] It was first described by Aboumrad, Horn, and Fine[3] in 1963, as lipid-secreting carcinoma, but it was Ramos and Taylor[1] who coined the term lipid-rich breast carcinoma. At gross examination, L-RCs are described as lobulated, well or poorly circumscribed, and firm, and range in size from 1.5 to 15.0 cm.[1–8] Histologically, the tumor is composed of nests, cords, and solid sheets of large polygonal cells, with abundant foamy or multivacuolated cytoplasm, which may confer a clear-cell or lipoblast-like appearance to neoplastic cells. The nuclei are fairly irregular, with moderate atypia, usually containing one or more nucleoli of varying size.[1–8] Occasionally, the large pleomorphic cells are arranged in an alveolar pattern with a hobnail-like appearance, or they may show oxyphilic cytoplasm, reminiscent of oncocytic or apocrine change. As a rule neoplastic cells stain strongly for neutral lipid, as observed in the present case.[1–8] Mucin and glycogen, when present, are far less conspicuous and usually unevenly distributed.[2,4–6] This is reflected in the negative or only focally positive results of special histochemical stains for mucin and glicogen in L-RC. These tumors are usually PgR-positive and show varying immunoreactivity for the ER.[2,5–7] To the best of our knowledge, there have been no previous reports on the immunohistochemical analysis of p53 and HER-2/*neu*.

Ultrastructural analysis has been performed in a small number of cases,[1,2,4–6,8] with divergent results. All authors demonstrated the presence of intracytoplasmic lipid droplets and globules isolated by distinct membranes surrounded by a dense, osmiophilic cytoplasmic rim.[1,2,4–6,8] However, Ramos and Taylor, Vera-Sempere and Llombart-Bosch, and Lim-Co and Gisser found evidence in support of secretory activity of neoplastic cells (exemplified by the presence of abundant rough endoplasmic reticulum with prominent Golgi apparatus),[1,4,6] whereas Wrba et al failed to find any feature suggestive of secretory activity.[2] Ramos and Taylor[1] also described the presence of peculiar 125 to 200 μm intramitochondrial crystalloids, a feature that has not been described by other groups.

Regardless of the small number of cases reported so far, the prognosis of L-RC seems to be poor.[1–3] Of the 20 female patients who underwent axillary dissection,[1,2,5,7,8] and who were reported in the English-language literature, 14 (70%) showed lymph node metastasis at presentation. In those patients with a follow-up longer than 2 years,[1–4,6] 12 of 15 (80%) developed distant metastasis (two thirds of these had either shown distant metastasis at presentation or developed it in the first year of follow-up). Moreover, in the largest series published so far,[1] a 38.5% first-year mortality rate was reported.

The differential diagnosis of L-RC includes other breast carcinomas composed of vacuolated or clear cells, such as secretory carcinoma,[4,5,9] glycogen-rich carcinoma,[4,5] apocrine carcinoma,[4] oncocytic carcinoma,[4] myoepithelial carcinoma,[5,6] and epithelioid liposarcoma.[10]

Secretory carcinoma, also referred to as juvenile carcinoma, frequently affects young women and, unlike L-RC, has a better prognosis than the other histological types of breast neoplasms.[9] Neoplastic cells of secretory carcinoma contain PAS- and Alcian blue–positive, acid mucopolysaccharides, which are not stained by histochemical preparations for lipids.[4,9] Most importantly, secretory carcinoma has recently been shown to harbor the chromosomal translocation t(12;15)(p13;q25), involving the genes *ETV6* and *NTRK3*, which appears to be fairly specific for this neoplasm in the breast.[9]

Glycogen-rich breast carcinoma (G-RBC) can be easily differentiated from L-RC by the presence of PAS + diastase–sensitive glycogen and lack of lipids in the cytoplasm of neoplastic cells.[4,5] Moreover, neoplastic cells of G-RBC have a water-clear cytoplasm at light microscopy level, whereas L-RC is composed of vacuolated or foamy cells.[4,5]

Apocrine carcinoma is a rare histological type of breast carcinoma, which is composed of large pleomorphic cells, with finely granular, eosinophilic cytoplasm, and large, round, vesicular nuclei, with prominent eosinophilic nucleoli.[4] The intracytoplasmic granules are usually PAS positive–diastase resistant, and the neoplastic cells are consistently and strongly decorated by antibodies for GCDFP-15. Occasionally, L-RC has a significant component of eosinophilic cells with finely granular cytoplasm that resemble cells of apocrine carcinomas.[4] However, apocrine carcinomas lack intracytoplasmic lipid and are consistently positive for GCDFP-15, whereas L-RCs show a rather focal expression of GCDFP-15, if any,[4] as observed in the present case.

Oncocytic carcinomas of the breast may be another source of confusion with L-RCs.[4] Histologically, these tumors are characterised by solid nests and glandular structures composed of round cells with eosinophilic and finely granular, toluidine blue–positive cytoplasm and centrally located, round nuclei having prominent nucleoli.[4] As clear-cell change in oncocytic tumors is a frequent phenomenon and, conversely, as L-RC may have cells with an oncocytic appearance, oncocytic carcinomas could be a source of confusion with L-RC. The differentiation can be achieved by immunohistochemical analysis with antimitochondrial antibody, which may corroborate the oncocytic nature of the cells. Ultrastructural analysis discloses numerous mitochondria, which may show abnormal morphology.

Myoepithelial carcinomas composed entirely of clear cells are exceedingly rare; the differential diagnosis with L-RC can be achieved by the immunoreactivity of neoplastic cells for myoepithelial markers, including high–molecular weight cytokeratins (eg, cytokeratin 14), α-SMA, S100 protein, calponin, smooth muscle–myosin heavy chain, and p63. It should be noted that in one case of L-RC, immunoreactivity of neoplastic cells for S100 protein was reported[5]; however, this case was rather unusual owing to the presence of metaplastic chondroid elements admixed with the lipid-rich component. In another case, ultrastructural features of myoepithelial differentiation were found[6]; in this instance, the tumor showed medullary carcinoma-like areas.

Epithelioid liposarcoma is an extremely rare histological variant of pleomorphic liposarcoma, which is histologically characterized by sheets of epithelioid cells with ample, variably eosinophilic cytoplasm, often arranged in a honeycomb-like pattern with scant, if any, collagenous extracellular matrix.[10] Presence of adipocytic differentiation is a rule, and scattered areas with spindle cells may also be found.[10] Interestingly, epithelioid cells consistently show ultrastructural features of adipocytic differentiation and have no features of true epithelial differentiation,

apart from occasional immunoexpression of cytokeratins (especially AE1/AE3).[10]

In their seminal study, Ramos and Taylor emphasized that the histological analysis of lymph nodes from patients with L-RC could be a major diagnostic pitfall if the observer is not aware of the presence of a breast tumor, because the neoplastic cells may resemble vacuolated histiocytes or a malignant histiocytic lesion instead of metastatic carcinoma.[1] In the present case, 2 of the 4 positive nodes showed a peculiar distribution of mono- or multivacuolated neoplastic cells resembling epithelioid and vacuolated histiocytes or even lipoblasts. These cells were strongly positive for cytokeratin MNF116, confirming their epithelial origin.

In conclusion, pathologists should bear in mind the diagnosis of this rather unusual and aggressive histological type of breast carcinoma. The differentiation of L-RC with less aggressive malignant breast neoplasms can be reliably achieved by careful histological examination combined with histochemical preparations for lipids, immunohistochemistry, and ultrastructural analysis.

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