Carcinomas that accumulate abundant glycogen arise in many organs, including the lungs, endometrium, cervix, ovary, and salivary glands. Extraction of the water-soluble glycogen during histologic processing causes the cytoplasm to become vacuolated or completely clear in conventional hematoxylin and eosin (H&E)–stained sections, and this phenomenon has led pathologists to designate such tumors as clear cell carcinomas. In 1981, Hull et al. described an in situ and invasive mammary carcinoma composed of cells with clear cytoplasm and proposed the diagnosis of glycogen-rich clear cell carcinoma of the breast for this variant of mammary duct carcinoma. These writers did not establish criteria for this diagnosis, nor did they estimate the frequency of the lesion; however, subsequent observers have commented on both points. Fisher et al. required that 50% or more of the cells contain “optically clear cytoplasm and, usually, centrally placed nuclei” to make the diagnosis of glycogen-rich clear cell carcinoma. Having done so, the authors classified 45 of 1,555 breast carcinomas (3%) as glycogen-rich clear cell carcinoma. Kuroda et al. used the same threshold and discovered 20 glycogen-rich clear cell carcinomas in a group of 723 primary breast carcinomas (2.7%). Toikkanen and Joensuu required that 90% of the carcinoma cells contain clear cytoplasm to make the diagnosis of glycogen-rich clear cell carcinoma. They found 6 of 439 breast carcinomas (1.4%) met their criteria for this diagnosis. Hull and Warfel did not specify their diagnostic criteria, but they regarded only 9 of 936 breast carcinomas (1%) as glycogen-rich clear cell carcinomas. These findings indicate that glycogen-rich clear cell carcinoma is an exceedingly rare form of primary breast carcinoma. Fewer than 150 well-documented examples have been described since the first case was reported in 1981.

CLINICAL PRESENTATION

The patients, whose ages ranged from 32 to 81 years, presented with a mass accompanied by skin dimpling, nipple retraction, or pain in some cases. Both in situ and invasive lesions may be detected by mammography and sonography. The imaging studies reveal an irregular spiculated mass that may contain calcifications. The nuclei appear hyperchromatic and

GROSS PATHOLOGY

Glycogen-rich carcinomas resemble conventional breast carcinomas to the unaided eye. Distinctive macroscopic features have not been recorded. Most tumors measured between 2 and 5 cm; the largest spanned “about 15 cm.” In one series, the mean size was 3 cm. Observers have described the masses as “brownish pink-gray or whitish-gray.” The carcinoma can form multifocal or multicentric masses, and macroscopically evident involvement of the skin occurred in several cases. The seminal authors could appreciate an in situ papillary component during macroscopic examination.

MICROSCOPIC PATHOLOGY

Glycogen-rich clear cell carcinomas have basic structural features of ductal carcinoma in situ (DCIS) alone or of DCIS and infiltrating duct carcinoma. The intraductal component can grow in papillary, solid, cribriform, micropapillary, and “intra-cystic” patterns. Cytoplasmic clearing appears most evident in solid areas that also exhibit moderate nuclear atypia (Fig. 28.1). The cells in cribriform and micropapillary regions usually have low-grade atypia and less often appear water-clear. The neoplastic cells can undergo focal necrosis, but abundant, comedo-like necrosis associated with high-grade nuclear atypia does not occur commonly. In most cases, one can detect small regions in which the cells contain eosinophilic and granular cytoplasm or exhibit other clear-cut apocrine features. The invasive component usually exhibits the histologic growth pattern of a conventional invasive duct carcinoma, but it can also display the patterns seen in lobular, medullary, and tubular carcinomas. The tumor cells typically form cords, solid nests, or papillary structures (Fig. 28.2). The formation of ductular or tubular structures occurs only rarely. The cells exhibit sharply defined borders and polygonal rather than rounded contours. The cytoplasm is clear or, less often, finely granular or foamy. Like the noninvasive component, the invasive carcinoma sometimes contains foci in which the cells have eosinophilic and granular cytoplasm that suggests an apocrine nature, and these cells often form a continuum with the clear cells. Observers have noted PAS-positive, diastase-resistant, intracytoplasmic hyalin droplets in rare cases. The nuclei appear hyperchromatic and
FIG. 28.1. Glycogen-rich carcinoma. A, B: DCIS and invasive carcinoma composed of cells with clear cytoplasm and small, dark, punctate nuclei. C: The tumor is strongly positive with the PAS reaction. D: After treatment with diastase, PAS reactivity is almost entirely abolished. The same pattern of PAS staining occurred in the intraductal carcinoma.

- Mitotic figures are easily identified in most cases. One group found as many as 70 mitotic figures per 10 high-power fields. Patches of necrosis often occur in large tumors. A linear pattern consisting of strands of cells resembling invasive lobular carcinoma may be seen, and glycogen-rich variants of tubular, medullary, and endocrine carcinomas have been described.

Differential Diagnosis

The differential diagnosis of glycogen-rich carcinoma includes benign and malignant mammary and extramammary neoplasms. The clear cell type of hidradenoma (eccrine acrospiroma) shares the presence of many glycogen-laden clear cells with glycogen-rich carcinoma. However, hidradenomas are centered in the dermis, they have well-defined, smooth contours, and they consist of uniform bland cells. Atypical and malignant hidradenomas pose greater challenges in differential diagnosis (see Chapter 42). Myoepithelial cells with clear cytoplasm can dominate uncommon examples of mammary adenomyoepithelioma. Detection of a second population consisting of glandular cells and immunohistochemical demonstration of proteins characteristic of myoepithelial cells will distinguish this tumor from glycogen-rich carcinoma.

The detection of glycogen in a mammary carcinoma does not establish the diagnosis of glycogen-rich clear cell carcinoma, for Fisher et al. found that 58% of breast carcinoma lacking clear cells contained intracytoplasmic glycogen. Among the types of primary mammary carcinomas, lipid-rich, secretory, histiocytoid lobular, and apocrine carcinomas exhibit certain features that may bring to mind the appearance of glycogen-rich carcinoma, but one can usually distinguish these tumors without difficulty. Lipid-rich carcinomas contain lipid rather than glycogen (see Chapter 27). Secretory carcinomas feature microcystic spaces containing eosinophilic secretions (see Chapter 22). Invasive lobular carcinomas of the histiocytoid type possess intracytoplasmic mucin rather than glycogen. Apocrine carcinomas can contain clear cells (see Chapter 19), and focal apocrine features are identified in the majority of glycogen-rich carcinoma. This association
Glycogen-Rich Carcinoma

FIG. 28.2. Glycogen-rich carcinoma. A: This tumor has moderate cytoplasmic clearing and a gland-forming structure. B: PAS reactivity is strong. C: PAS reactivity is abolished by diastase treatment. D: Strong nuclear reactivity for ER is present.

suggests that that glycogen-rich carcinoma might constitute a variant of apocrine carcinoma. These overlapping findings and the possibility of an etiological relationship notwithstanding, the usual apocrine carcinoma contains intracytoplasmic, diastase-resistant eosinophilic granules or droplets, a finding that does not characterize glycogen-rich carcinomas.

Metastatic clear cell carcinomas can mimic the appearance of glycogen-rich carcinoma. Carcinoma of the kidney is the most notable culprit in this regard (see Chapter 34).

### CYTOLOGY

Descriptions of the cytological characteristics of specimens obtained by fine-needle aspiration vary somewhat from case to case depending on the attributes of the carcinoma. Most authors report that the smears appear cellular and that the carcinoma cells form loosely cohesive groups. The aggregates sometimes display a branching architecture, and papillary formations can occur. At least a few intact dissociated cells can be seen in the background of the smears in most cases. The cells typically exhibit distinct cell membranes, but syncytial groups can be seen. The cytoplasm usually appears finely granular and eosinophilic or vacuolated; however, the degree of vacuolization and clearing of the cytoplasm varies and it sometimes represents only an inconspicuous cellular feature. The oval or round nuclei vary in size. They have irregular membranes and prominent nucleoli. In many cases, the nuclei demonstrate obvious pleomorphism and anaplasia. One can sometimes appreciate occasional mitotic figures.

### IMMUNOHISTOCHEMISTRY

The cytoplasm gives a positive, diastase-labile reaction with the periodic acid–Schiff (PAS) stain (Figs. 28.1 and 28.2). The cells stain only focally or not at all with Alcian blue, mucicarmine, and colloidal iron stains, and the oil red O and Sudan black B stains for lipid are negative. The tumor cells are reactive for CK7, AE1/AE3, CK8/18, CAM5.2, and E-cadherin, variably or weakly reactive for carcinoembryogenic antigen (CEA) and epithelial membrane antigen (EMA), and only weakly reactive or unreactive for actin, smooth muscle actin (SMA), desmin, vimentin, S-100, α-lactalbumin, CK5/6,
CK14, CK20, CD31, and CD34. Several case reports document staining for gross cystic disease fluid protein-15 (GCDFP-15). Glycogen-rich carcinomas do not display a consistent pattern of staining for hormone receptors. Most authors report the absence of progesterone receptor (PR); however, Satoh et al. observed staining for PR in their single case, and Akbulut et al. detected PR in 43% of their cases. Researchers have observed staining for human epidermal growth factor 2 (HER2) in 20% to 43% of cases. The mean Ki67 score was 20% in one series, and a value of 48% was recorded in a single case. Observers have noted an elevated S-phase fraction (SPF) and nondiploid DNA content.

**ELECTRON MICROSCOPY**

At the ultrastructural level, the cells have polygonal to columnar shapes. The cytoplasmic borders can appear smooth or form complex interdigitations harboring junctional complexes and desmosomes. The cytoplasm contains intracytoplasmic lakes of non–membrane-bound glycogen and abundant small aggregates of glycogen intermixed with rough endoplasmic reticulum, mitochondria, ribosomes, lysosomes, and Golgi apparatus. In certain cases, the cytoplasm becomes distinctly segregated into two compartments: one containing the organelles and the other containing the glycogen. The nuclei appear oval to rectangular. Most exhibit smooth borders, but others have deep clefts. They contain moderate amounts of heterochromatin and nucleoli that vary from small to prominent, depending on the case. Lumens sometimes form among clusters of cells or within individual cells (intracytoplasmic lumens). The cells forming these primitive glands have short, broad microvilli on their luminal borders, and one can observe tight junctions and desmosomes between the cells.

**TREATMENT AND PROGNOSIS**

With rare exceptions, reported examples of invasive glyco- gen-rich carcinoma have been treated by mastectomy and axillary dissection. In one case, neoadjuvant chemotherapy resulted in the reduction of the cellularity of the infiltrating tumor by 30% or less. Approximately 30% of the patients had metastatic tumor in their axillary lymph nodes. In one series, 50% of the patients treated by mastectomy died of metastatic mammary carcinoma 1 to 175 months (median, 15 months) after diagnosis, and one patient was alive with recurrent carcinoma 36 months after local excision and lymph node dissection. Except for one woman who underwent simple mastectomy without axillary dissection, all patients with recurrent or fatal carcinoma had axillary nodal metastases. Toikkanen and Joensuu found axillary nodal metastases in five of six cases. All five of these patients died of metastatic carcinoma within 7 years from the time of diagnosis, and the single woman with negative lymph nodes died of intercurrent disease without recurrence. Among the group described by Kuroda et al., 5 of 15 patients followed for 1 to 72 months died within 5 years of the time of diagnosis. Hayes et al. reported that three of eight patients with follow-up information died of metastatic carcinoma. The length of follow-up was not reported. These data suggest that the prognosis of patients with glycogen-rich mammary carcinoma is not particularly favorable and that it may be similar to ordinary invasive duct carcinoma when analyzed on a stage- and grade-matched basis. The Senior Editor has examined slides from an unusual instance of glycogen-rich DCIS detected when calcifications

**FIG. 28.3.** Glycogen-rich carcinoma. A: DCIS with calcifications, which were detected by mammography. B: DCIS and invasive duct carcinoma with osteoclast-like giant cells (arrows) found in the breast 9 years after breast conservation treatment of the glycogen-rich DCIS shown in [A].
were found by mammography (Fig. 28.3). Nine years after breast conservation therapy with radiotherapy, the patient developed recurrent DCIS and invasive duct carcinoma with osteoclast-like giant cells in the same breast. The recurrent carcinoma was not glycogen rich.

REFERENCES