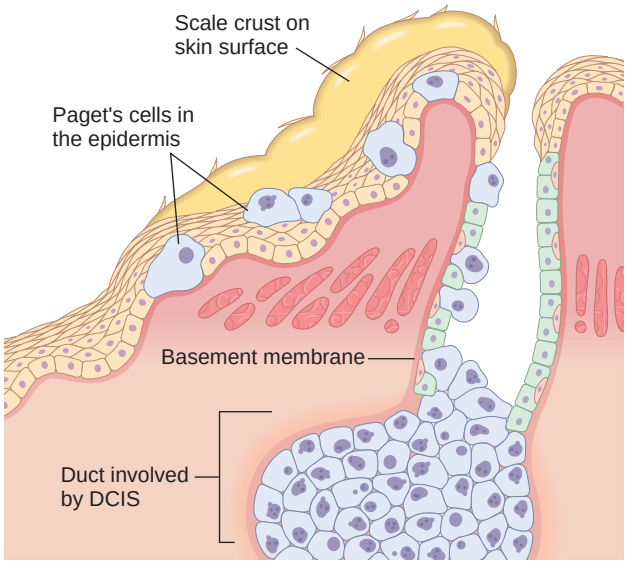

Figure 23-18 Paget disease of the nipple. Ductal carcinoma in situ arising within the ductal system of the breast can extend up the lactiferous ducts and into the skin of the nipple without crossing the basement membrane. The malignant cells disrupt the normally tight squamous epithelial cell barrier, allowing extracellular fluid to seep out and form an oozing scaly crust.

Lobular Carcinoma in Situ

LCIS is a clonal proliferation of cells within ducts and lobules that grow in a discohesive fashion, usually due to an acquired loss of the tumor suppressive adhesion protein E-cadherin. The term "lobular" was used to describe this lesion because the cells expand but do not distort involved spaces and, thus, the underlying lobular architecture is preserved. LCIS is always an incidental biopsy finding, since it is not associated with calcifications or stromal reactions that produce mammographic densities. As a result, its incidence (1% to 6% of all carcinomas) did not increase after the introduction of mammographic screening. When both breasts are biopsied, LCIS is bilateral in 20% to 40% of cases, compared with 10% to 20% of cases of DCIS.

The cells of atypical lobular hyperplasia, LCIS, and invasive lobular carcinoma are morphologically identical. In most cases, loss of cellular adhesion is due to dysfunction of E-cadherin, a transmembrane protein that contributes to the cohesion of normal epithelial cells in the breast and other glandular tissues. E-cadherin functions as a tumor suppressor protein in such tissues, and may be lost in neoplastic proliferations through a variety of mechanisms, including mutation of the E-cadherin gene (*CDH1*). In rare cases, there is dysregulation of other proteins, such as catenins, that are also needed for E-cadherin–mediated cellular cohesion.

MORPHOLOGY

LCIS consists of a uniform population of cells with oval or round nuclei and small nucleoli involving ducts and lobules (Fig. 23-19*A*). Mucin-positive signet-ring cells are commonly present. The lack of E-cadherin results in a rounded shape without attachment to adjacent cells (Fig. 23-19*B*). The cells cannot form cribriform spaces or papillae, such as are seen in DCIS. Pagetoid spread, the presence of neoplastic cells between the basement membrane and overlying luminal cells, is commonly seen in the breast, but LCIS does not involve nipple skin (Fig. 23-19*B*). Necrosis and secretory activity are not seen with classic LCIS and, thus, substrates for calcification are not present. LCIS almost always expresses ER and PR. Overexpression of HER2 is not observed.

LCIS is a risk factor for invasive carcinoma. Invasive carcinoma develops in 25% to 35% of women over 20 to 30 years time, or at a rate of about 1% per year, similar to that observed for untreated DCIS. However, unlike DCIS, the risk is almost as high in the contralateral breast as in the ipsilateral breast. Invasive carcinomas developing in women after LCIS are three-fold more likely to be lobular carcinoma; however, most are of other morphologies. Treatment choices include bilateral prophylactic mastectomy, tamoxifen, or, more typically, close clinical follow-up and mammographic screening.

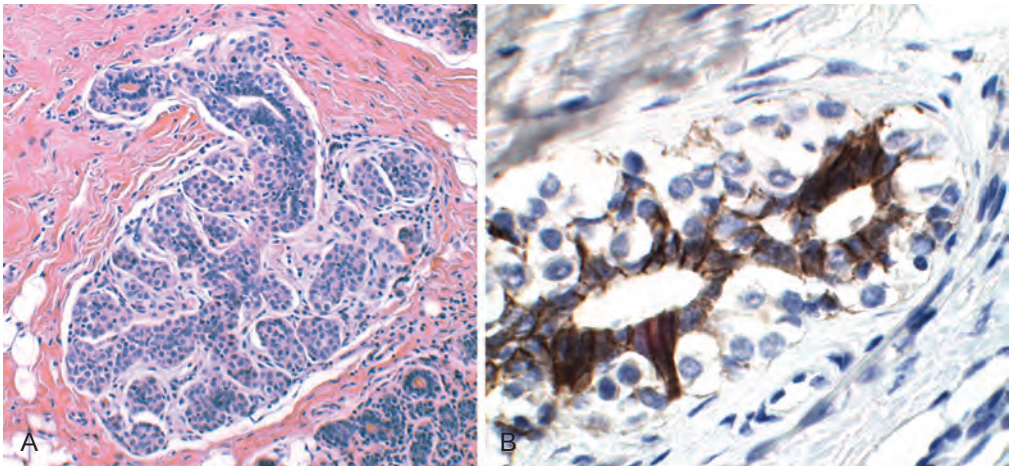

Figure 23-19 Lobular carcinoma in situ. **A,** A monomorphic population of small, rounded, loosely cohesive cells fills and expands the acini of a lobule. The underlying lobular architecture can still be recognized. The cells extend into the adjacent lobule by pagetoid spread. **B,** An immunoperoxidase study shows E-cadherin–positive normal luminal cells that have been undermined by E-cadherin-negative LCIS cells spreading along the basement membrane.