PATHOLOGY
OF THE BREAST

SECOND EDITION

Fattaneh A. Tavassoli, MD, AFIP
Chairman
Department of Gynecologic & Breast Pathology
Armed Forces Institute of Pathology
Washington, DC

Adjunct Professor of Pathology
George Washington University
Washington, DC

Consultant in Pathology
National Cancer Institute
Bethesda, Maryland

APPLETON & LANGE
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Figure 9-22. Infiltrating lobular carcinoma, alveolar variant. (A & B) Closely packed islands of uniform small cells. ([BE] (A)×120; (B)×240)

Axillary Node Metastases

In Haagensen's series of 76 Columbia stage A small-cell carcinomas (comparable to infiltrating lobular carcinoma), the frequency of axillary node metastases was 39.7%, compared with 30.8% for similar stage carcinomas of all types. Two other studies also found a lower frequency of nodal metastases (32% in both studies) for lobular carcinoma compared with 37% and 35% for infiltrating ductal carcinoma. Fechner has suggested that the variant patterns may be associated with a lower frequency of axillary node metastases.

Infiltrating lobular carcinoma is notorious for simulating histiocytes in metastatic foci and when populating subcapsular and medullary sinuses in axillary lymph nodes. The sheet-like aggregation of the tumor cells and subtle distortion of the nodal architecture are helpful in arriving at the accurate diagnosis. When a distinction is difficult, special staining for mucin or immunostains for cytokeratin helps resolve the issue; a positive reaction for mucin or cytokeratin establishes the diagnosis of carcinoma. In the eyelids, the histiocytic appearance of the metastatic tumor cells may cause misinterpretation of the lesion as a chalazion.

The metastatic pattern of lobular invasive carcinoma differs from that of invasive ductal carcinoma with a higher frequency of skeletal, gastrointestinal tract, uterine, ovarian, meningeal, genitourinary, skin, diffuse serosal, peritoneal and retroperitoneal metastases observed in lobular carcinomas. The gastrointestinal, gynecologic, and peritoneal–retroperitoneal metastases are markedly more prevalent in lobular carcinoma. In the central nervous system, metastases from invasive lobular carcinoma form meningeal infiltrates, whereas ductal carcinomas show parenchymal deposits. Other investigators, however, found an equal proportion of lobular and ductal carcinomas among patients with meningeal carcinomatosis from breast cancer. Metastases to the ovary and uterus are common. In the endometrium, metastases cause bleeding, but because of the small cell size and diffuse pattern of infiltration in the endometrium, these metastases are easily overlooked. Furthermore, even when the cells are larger with pink cytoplasm, they are often misinterpreted as a decidual reaction to progestins, which many of the patients receive for their irregular bleeding prior to the cell age. Bone marrow metastases are particularly common, and constituted the most common site of metastases in DiCostanzo and colleagues’ series.

Hormone Receptors and Ploidy

About 70–92% of lobular carcinomas are ER-positive. ER positivity is observed in the classic form and all other variants, with the alveolar variant appearing to have a greater likelihood of ER positivity. Progesterone receptors are found in 63–67% of the tumors. Carcinoembryonic antigen (CEA) has been reported in 33–63% of cases. Milk-related proteins, such as lactalbumin and casein, have been detected in some cases. Also, 60% of these tumors show a positive reaction for S-100 protein, underscoring the lack of specificity of S-100 protein.
Figure 9–23. Infiltrating lobular carcinoma, pleomorphic variant. (A) At low magnification the lesion resembles typical infiltrating lobular carcinoma with isolated cells sometimes arranged in cords. (B) The nuclei display significant pleomorphism, and more variation is generally evident in cell size. (H&E, (A) x240; (B) x480)
Figure 9–23. (C) Pleomorphic lobular neoplasia (LN3) shows some highly atypical nuclei; curiously, this tumor was ER positive even in the highly atypical cells. (H&E, ×300)

Approximately 22% of infiltrating lobular carcinomas are aneuploid. Among ER-positive tumors, ploidy does not appear to influence the likelihood of PR positivity.

Treatment and Prognosis

Treatment of infiltrating lobular carcinoma should parallel that of infiltrating mammary carcinomas in general and depends on the stage of the lesion. Conservative treatment of invasive lobular carcinoma has been shown to be an appropriate alternative in selected cases. The results of limited excision and radiotherapy for 49 lobular carcinomas were compared with those of 561 cases of infiltrating duct carcinoma. The 5-year actuarial risk of local recurrence was similar for patients with infiltrating lobular or ductal carcinoma: 12% versus 11%. When the group with infiltrating duct carcinoma was divided into those with an extensive DCIS component and those without such a component, the 5-year actuarial survival of 12% for lobular carcinoma fell between the 5% rate for infiltrating duct carcinomas with extensive DCIS component and the 23% for those infiltrating duct carcinomas without extensive DCIS.

Another study comparing clinicopathologic features of infiltrating lobular carcinoma (726 cases), mixed infiltrating lobular/invasive ductal carcinoma (249 cases), and nonlobular infiltrating carcinomas (10,061 cases) also evaluated response of the three groups to conservative therapy. Conservative treatment was used in 480 cases (66%) of pure lobular carcinoma, 6797 cases (68%) of nonlobular infiltrating carcinomas, and 43 cases of mixed infiltrating lobular/invasive ductal carcinoma. With a median follow-up of 82 months, the overall survival rate, locoregional control, disease-free interval, and metastatic spread rate were not different among the three groups by either univariate or multivariate analysis; the investigators concluded that conservative therapy may be appropriate treatment for infiltrating lobular carcinoma.

The 5- and 10-year survival rate for node-negative women, is 86% and 74%, respectively. Following radical mastectomy, approximately 5.4% of the women develop local recurrences within 10 years. About 50% of patients with positive nodes eventually die from the disease compared with 14% of the node-negative women.

Although some studies have suggested a worse prognosis for infiltrating lobular carcinoma than for ductal cancer, several studies have found no significant difference in survival, or even a more favorable outcome for infiltrating lobular carcinoma. In some studies, the observed differences are not substantial; about 6% of women with T1N0M0 infiltrating lobular carcinomas treated by mastectomy died of the disease within 10 years, compared with 14% of those with infiltrating ductal carcinoma. In Haagensen’s experience and following radical mastectomy, women with Columbia stage A infiltrating small-cell carcinomas had a 75% probability of 10-year survival, compared with 72% for patients with all other types of breast carcinoma. In a comparison of survival between 217 women with invasive lobular carcinoma and 1121 women with infiltrating duct carcinoma, Toikkanen and coworkers found 5- and 30-year corrected survival rates of 78% and 50% respectively, among women with lobular carcinoma, compared with 63% and 37% survival rates, respectively, for those with infiltrating ductal carcinoma. Women with small pT1N0M0 infiltrat-