Ackerman's

SURGICAL PATHOLOGY

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EIGHTH EDITION
with 3295 illustrations, 898 in color
are probably more closely related to ductal carcinoma of
either invasive588 or in situ type.587

The intracellular mucin accumulation resulting in the
signet ring appearance is probably the result of a blockage
in secretion resulting from deletion of one or more of the
enzymes needed for this extremely complex process. Ultra-
structurally it is manifested in its more extreme form by a
large membrane-bound vacuole of varying but usually low
electron density.593 This is a different process from that of
intracellular lumen formation, which is characterized ultra-
structurally by a microvillus-coated cavity and which appears
as a bull’s-eye on light microscopic examination.

Other types. Some authors restrict their diagnosis of ILC
tumors having the features described for the classic type
and for some of the signet ring carcinomas. Others have
expanded considerably the concept and include in this
category tumors that traditionally have been placed into the IDC
category.594,597,599 Cases having closely aggregated cells,
solid pattern, trabecular pattern, loose alveolar pattern, and
spindle-cell chains have been accepted as ILC, as long as
the relatively bland and homogeneous cytologic appearance
was maintained. Perhaps the most distinctive of these forms
is the alveolar variant, in which the tumor cells are arranged
in sharply outlined groups separated by fibrous tissue som-
times containing osteoclast-like giant cells.600,601 Yet another
variation is represented by tubulolobular carcinoma,598 in
which typical areas of ILC merge with small tubules with a
minute or undetectable lumen ("closed" or "almost closed"
tubules). A converse approach has been taken more recently,
and that consists of including tumors with pleomorphic
nuclear features into the ILC as long as the infiltrating pat-
tern of classic ILC is maintained. Such tumors have been
designated as the pleomorphic variant of ILC602; the further
suggestion has been made that this tumor shows apocrine
dermatization.596

The cytologic and/or architectural similarities between
these various forms and classic ILC are undeniable. The
problem, however, is that the more the concept of ILC is
widened and to some extent diluted, the less distinct the
entity becomes and the less significant (or at least the less
uniform) its clinical connotations are.595

Mixed ductal and lobular carcinoma

Biphasic carcinomas composed in part of a component
with definite features of invasive ductal carcinoma and in
part of a component with definite features of invasive lobu-
ar carcinoma do occur, but they are very rare. These tumors,
of course, should be distinguished from the cases in which
two separate neoplasms of different microscopic appear-
ances are present in the same breast.

Undetermined (unclassified) carcinoma

This category includes all cases of invasive carcinoma in
which features of ductal or lobular type are not definite
enough to place it into either category. Azzopardi603 places
3% to 4% of the invasive breast carcinomas in this category.

HORMONE RECEPTORS

A very important development in the evaluation of breast
carcinoma is the realization that the presence of hormone
receptors in the tumor tissue correlates well with response to
hormone therapy and chemotherapy.613 The hormone (estro-
gen and progesterone) receptors can be measured by the
standard dextran-coated charcoal and sucrose gradient
assays or by immunohistochemical techniques using mono-
clonal antibodies directed against the receptor molecule
(Fig. 20-70). Fresh tissue is needed for the biochemical
methods, whereas sensitive and reproducible techniques are
now available for the immunohistochemical detection of the
receptor in formalin-fixed, paraffin-embedded material.4 The
method can be semiquantitated by computer-assisted image
analysis.603,610 Estrogen receptors can also be detected by the
in situ hybridization technique, which is actually a more sensitive method than either
immunohistochemistry or the biochemical assay.612

Not much correlation exists between the cytoarchitectural
type of breast carcinoma and presence of hormone receptor
protein; specifically, no statistically significant difference
has been found between ductal-type and lobular-type tumors.
However, most series have shown that most medullary car-
cinomas and intraductal carcinomas of the comedocarcin-
toma type are negative.614,621,624,626 whereas mucinous car-
cinomas have the highest rates of positivity.617 In DCIS, a pre-
dominance of large cells is the best morphologic predictor of
estrogen receptor–negative status.608

Generally, estrogen receptor concentrations are lower
in tumors of premenopausal women than in those of post-
menopausal women.624 Fisher et al.611 found the presence

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References 615, 616, 618, 619, 620, 622, 623, 625.
of estrogen receptors to be significantly associated with high nuclear and low histologic grades, absence of tumor necrosis, presence of marked tumor elastosis, and older patients’ age groups. Hormone receptor positivity also correlates with bel-2 immunoreactivity and absence of p53 mutations, and it correlates inversely with the presence of epidermal growth factor receptors.

**SPREAD AND METASTASES**

Breast carcinoma spreads by direct invasion, by the lymphatic route, and by the blood vessel route. Some of these metastases are already present at the time of diagnosis, and others become manifest clinically months, years, or decades after the initial therapy. Local invasion can occur in the breast parenchyma itself, nipple, skin, fascia, pectoralis muscle, or other structures of the chest wall. The frequency of microscopic invasion in the breast outside the gross confines was evaluated by Rosen et al. by performing a “local excision” with a 2-cm gross margin in specimens of radical mastectomy and studying microscopically the remainder of the breast. Of eighteen mastectomy specimens for carcinoma measuring less than 1 cm, residual invasive carcinoma was found in 11% and residual in situ carcinoma in an additional 22%. The importance of a proper pathologic evaluation of local invasion in breast carcinoma is now greater because of the increasing number of conservative surgical procedures being performed.

A somewhat related problem is that of microscopic involvement of the nipple by breast carcinoma, since this structure would obviously be left in the patient if a local excision of the lump were carried out. Nipple invasion has been found in 23% to 31% of all invasive carcinomas; the large majority are seen in tumors located less than 2.5 cm from the nipple.

Local recurrence following mastectomy appears as superficial nodules in or near the surgical scar or as subcutaneous parasternal nodules. Their malignant nature should always be documented by biopsy because the condition can be closely simulated by foreign body granulomas and infectious processes. Although women with local recurrences have an increased risk of distant metastases, these seem to represent partially independent events that occur at different times.

Tumor recurrence following local excision often develops in the same segment, a fact that has led some authors to recommend a primary excision technique that removes en bloc the tumor mass and the associated duct system.

The most common site of lymph node involvement is the axilla, followed by the supravacular and internal mammary region. Axillary node metastases are present in 40% to 50% of the cases and are divided into levels according to their topographic relation with the insertion of the pectoralis minor muscle: low or proximal, medium, and high or distal. When extensive they are clinically detectable, but the margin of error with clinical palpation is high. Careful dissection of the submitted nodes by the pathologist is of importance. The yield of nodes will increase if they are searched for after the axilla is cleared with an organic solvent, but this seems hardly worth the trouble and expense. The yield of...