REVIEW ARTICLE

Current concepts in breast pathology
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Abstract
Breast is a hormone-regulated organ with a myriad of lesions, both detected and undetected, and visualized by light microscopy after numerous changes at molecular level. With the advent of newer modalities of investigation, an emerging challenge to pathologists is to identify these lesions and avoid diagnostic pitfalls. We need to pay attention to the emerging concepts to meet practical expectations of clinicians and patients.

Introduction
Rosai wrote, as a preface to seminars in diagnostic pathology in February 2010, “I read on a long plane trip, Prof. John G. Azzopardi’s classical monograph, problems in breast pathology, after having practiced surgical pathology for 15 years, and I found it a revelation, a sort of road to Damascus. Breast lesions that I had encountered countless times appeared now in a totally different light, as if I were confronting them for the first time. This was nowhere more evident than with the proliferative intraductal lesions, which never looked the same after that reading.”[1] In 2009, 30th anniversary of this publication was celebrated. Every breast pathologist admires this book and is influenced by his insights.

I wish to acknowledge and thank many pathologists and clinicians who have sent interesting and challenging cases and the many patients whose material I have had the opportunity to view. Without the thought-provoking questions they posed, I would not have been interested in this exhaustive information from peer-reviewed articles in the current concepts and this review would not have been possible. In this article, I have reviewed terminology, histopathological features, new insights, and treatment options. I have illustrated a few of my cases in Figures 1 and 2.

The progressive use of image-detected biopsies has created a challenge for pathologists and led to increased diagnosis of ductal carcinoma in situ (DCIS) and high-risk proliferative breast lesions in small and often fragmented tissue samples. These entities are difficult to diagnose even from surgically excised lesions. Some of the gray areas in diagnostic pathology of image-detected biopsies include the differentiation of atypical ductal hyperplasia (ADH) from low-grade DCIS, lobular neoplasia from solid low-grade DCIS, the correct interpretation of papillary lesions with atypia, atypical apocrine proliferations, and classifying the spectrum of columnar cell changes.[2]

Columnar Cell Lesions
A spectrum of columnar cell lesions in the terminal duct lobular units of the breast include columnar cell change, columnar cell hyperplasia, and columnar cell change or columnar cell hyperplasia with atypia. The latter is designated by the World Health Organization as flat epithelial atypia (FEA). To increase diagnostic agreement on these lesions among pathology residents and presumably general pathologists in practice, a training tutorial on the ability to distinguish various types has been advocated.[3]

FEA, a distinctive lesion, commonly associated with mammographically suspicious microcalcifications represents one of the earliest morphologically recognizable neoplastic alterations of the breast. Herein, mild-to-severe atypical cells simply replace the single layer of native epithelial cells in a flat fashion without appreciable proliferation; tufting, intraluminal bridging, micropapillary structures, and so forth are not seen
or are very focal and minimal, if present. Based on the degree of
cytologic atypia, low- and high-grade FEA need to be separated.
Surgical pathologists need to view the involved cell populations
using high-power magnification to detect the cytologic
alterations of these lesions. [4]

Several types of benign alterations may superficially resemble
FEA due to the presence of cysts, enlarged lobules, and/or
columnar ductal cells. The benign changes that most frequently
cause problems in differential diagnosis include microcysts in
fibrocystic changes, blunt duct adenosis, and early usual ductal
hyperplasia. The lack of cytologic atypia is the key criterion that
distinguishes these lesions from FEA. [5]

FEA frequently coexists with several types of low-grade
neoplasia: Low-grade DCIS, lobular neoplasia (atypical lobular
hyperplasia and lobular carcinoma in situ), and invasive tubular
carcinoma. The histologic triad of tubular carcinoma, columnar
cell lesion, and lobular carcinoma in situ has been recognized,
but yet not fully characterized. The “Rosen Triad,” named
after the eponymous pathologist who first categorized it is an
observation that may have important clinical and pathologic
implications. [6]

Myoepithelial Lesions
Identification of the myoepithelial cell (MEC) layer is
essential in the routine practice of diagnostic breast pathology,
for distinguishing invasive from noninvasive neoplasms
and to establish microinvasion. It is needed for identifying
pseudoinvasion from infiltrating carcinoma, in sclerosing
papillary lesions, and when differentiating a benign papilloma
from the stratified spindle cell variant of papillary FEA1 (DCIS
Grade 1, papillary type) which lacks epithelial proliferation in
the papillary processes. [7]

Paying detailed attention to morphologic features resolves the
differentials considered in most of the scenarios. However,
myoepithelial markers are valuable diagnostic adjuncts, especially
in core biopsies, and can facilitate the accurate categorization of
a given proliferation. Because of the cross-reactivity patterns
and the fact that lesional foci are typically minute, none of the
myoepithelial markers enjoy a 100% sensitivity and specificity
for MECs. As such, at least two markers should be used to
evaluate any given focus. Several factors should go into the
choice of a myoepithelial marker, including published evidence
on its diagnostic utility, its availability, optimal reactivity that has
been achieved in a given laboratory, and the specific diagnostic
scenario. The absence of MECs is often the diagnostic goal
with the use of these markers, so care must be taken to ensure that
lesional foci remain on the sections that are stained, positive
and negative controls show expected patterns of reactivity,
and the final diagnosis is compatible with the hematoxylin-
eosin (H and E) diagnosis. When its use is deemed necessary,
immunohistochemistry (IHC) for MECs in breast pathology is
most effective when seen as supplemental, rather than central to
routine morphologic interpretation. [8]

The IHC for distribution of MECs using p63 and calponin in
metaplastic and intraductal proliferative apocrine lesions showed
frequent heterogeneity. Benign and noninvasive apocrine lesions
show can reduction and occasional complete loss of MECs
which may lead to overdiagnosis of atypia and/or malignancy
in apocrine papillary proliferations. Hence, when evaluating
apocrine lesions, at least two myoepithelial markers should be
used, and a malignant diagnosis should be based on the features
of the proliferating cells until more data become available. [9]

The range of lesions with proliferation of both epithelial and
myoepithelial elements may be quite diverse. The diagnostic
classification surrounding the entity of adenomyoepithelioma
(AME), defined as a proliferation of both epithelial and
myoepithelial elements, and its prognostic implications have led
to its diagnosis by default as malignant and to overtreatment.
A review of the varied histology of AME and similar lesions
and their immunohistochemical properties will assist
general pathologists in evaluating these sometimes difficult
lesions. Follow-up and treatment information demonstrate
their benignity. Architecture and histologic features should
be combined with IHC when determining categorization
[Figure 1]. [9] AME, an uncommon benign tumor, may be
mistaken for a carcinoma in core biopsies. [10]

AME may undergo malignant transformation, which
may be biphasic or may show either ductal or myoepithelial
differentiation. The metastatic potential seems to depend on
the grade of the malignant component of the lesion. [10]

Mucinous Lesions
Mucin production is seen in a range of breast lesions. Both
intracytoplasmic and intraluminal acid or neutral mucins can
be seen in up to 95% of infiltrating ductal carcinomas. Usually,
those breast lesions with significant amounts of extracellular
mucin pose diagnostic challenges. They are a continuum
from benign mucocele-like lesions (MLLs) which refers to
distended mucin-filled ducts with mucin extrusion into the
stroma to invasive mucinous carcinoma of the breast. In MLLs,
the accompanying epithelial alterations have to be separately
evaluated, and may range from benign changes to ADH and
DCIS. The displaced epithelium in MLL associated with DCIS
can be misdiagnosed as early invasive mucinous carcinoma.
If few detached epithelial nests are accompanied by MECs, or
observed in apparent contiguity with the duct wall, invasion
is unlikely. A useful histological clue to the diagnosis of solid
papillary neuroendocrine DCIS is the accompanying mucin
production. [11]

Papillary Lesions
The assessment of papillary lesions is one of the most challenging
areas in breast pathology. Guidelines are needed to diagnose the
various papillary lesions based on H and E morphology with
adjunctive use of IHC. [12-14]
The controversy whether or not all papillary lesions identified on core biopsies should be surgically excised remains. When a papillary lesion is identified on a core biopsy, correlation with clinical, mammographic, and sonographic findings is essential. Complete excision is necessary in many, regardless of the findings on an initial core biopsy that has not removed the lesion in its entirety because of histologic variability in papillary lesions.[12]

Evaluation of papillary lesions is based primarily on morphologic features, and IHC could be reserved as an adjunct to diagnosis both on core needle biopsy and excision biopsy. Combination of diffuse estrogen receptor (ER) positivity, with absence of high molecular weight cytokeratin staining, is found to be the most useful adjunctive test in discriminating ADH/low-grade DCIS within a papilloma from florid hyperplasia of usual type within a papilloma.[13]

**Fibroepithelial Lesions**

Phyllodes tumors (PTs) are uncommon mammary neoplasms, and their evaluation can constitute a diagnostic challenge when they focally resemble fibroadenoma (FA), leading to underdiagnosis, particularly on the evaluation of limited materials in fine-needle aspiration or needle core biopsy. Any fibroepithelial lesion that is large or is rapidly growing and shows one or more morphologic findings typical of PT, such as increased stromal cellularity, infiltrative borders, mitotic activity, stromal overgrowth, necrosis, cytologic atypia, and tissue fragmentation, in needle core biopsy material should be excised. The proliferation marker Ki-67 could be helpful in the distinction between FA and PT, but its expression tends to be low in benign and borderline PTs, and so it is not specific. Other markers such as CD10 and C-kit provide useful information, but it needs more studies involving a large number of cases and long-term follow-up before these markers gain a place in the workup of PT. However, IHC could play a role also in ruling out spindle cell carcinomas, which can occasionally masquerade as a PT [Figure 2a and c].[14]

**Vascular Lesions**

Vascular proliferations of the breast are uncommon and are more likely to be malignant when clinically apparent. A range of benign entities also exist which must be differentiated from angiosarcoma and radiation-associated vascular lesions which are of more clinical and pathological significance. Breast lesions of apparent vascular origin are pseudoangiomatous stromal hyperplasia [Figure 2b], and true lesions of vascular origin are benign and histologically bland perilobular, cavernous, and capillary hemangiomas. More diagnostically challenging are atypical hemangiomas, papillary endothelial hyperplasia, and epithelioid hemangioma.[14]

**Special Carcinomas**

New multistep pathways of breast cancer (BC) progression through genotypic–phenotypic correlations have been put forth as more intelligible data on the molecular characteristics of benign breast lesions, and BC precursors are described.[17]

In metaplastic carcinoma (MPC) of the breast, a rare carcinoma with various histologic types, metaplastic elements are heterogeneous and sometimes seen in mixtures next to glandular elements. The World Health Organization classifies MPC into epithelial type and mixed type. Multivariate analyses in the study of Okada et al. clearly demonstrated that MPC is
more aggressive than invasive ductal or lobular carcinoma. The subtypes had no prognostic significance, but an age not exceeding 39 years, the presence of skin invasion, and the presence of a squamous cell carcinoma component in nodal tumors were significant predictors of outcome.[14]

Basal-like BCs constitute a heterogeneous group that displays distinctive morphologic, genetic, and immunophenotypic features and are identified in routine clinical practice. Based on these features, although definitions vary and no consensus has been reached, they are associated with poor clinical outcome and specific patterns of distant metastasis and response to chemotherapy. The lack of ER and HER2 and positivity of one of the four basal markers (CK5/6, CK14, CK17, and epidermal growth factor receptor) are recommended for the identification of these cancers until a panel of markers that have a high degree of specificity and sensitivity that can correctly identify basal-like cancers are developed.[19]

Routine clinical management of BC relies on the availability of robust prognostic and predictive factors including morphologic and few individual molecular factors. Conventional classification need not to be replaced, instead, integration of multigene molecular classifiers seems more practical to support future targeted therapy. Gene expression profiling technology has transformed the BC research with unmatched speed and associated with a lot of publicity, but we cannot expect this technology to replace the classical BC classification systems.

It also remains to be seen whether more robust and simpler methods based on IHC will provide comparable information and be more suited to routine clinical practice.[20]

The pathologic examination of specimens of earlier stage operable breast carcinoma from women treated with chemotherapy or hormonal agents before surgery (neoadjuvant therapy) can be quite challenging. Clinical and radiologic assessments of tumor response by palpation or by breast imaging are useful techniques but often misjudge the amount of residual carcinoma present.

The gold standard, hence, is pathologic examination of the excised tumor bed and is needed for identifying typically 15-28% of the patients with a pathologic complete response to treatment, as well as the other 60-70% of patients who have a partial response to treatment. Pathologists have a key role in the evaluation of this pathologic response, which is a prognostic factor for individual patients, a short-term endpoint for clinical trials, and an adjunct for research studies. Hence, surgical pathologists must be familiar with the gross examination, sampling, and reporting of breast carcinomas after neoadjuvant therapy. Many systems with an explanation of the classification and categories of responses are available.[21]

Conclusion

Currently, there is much to do in the field of diagnostic breast pathology. There are data highlighting the deficiencies in our understanding of these lesions. It is necessary to attain adequate training in breast pathology, ensure uniformity in tissue processing, interpretation, diagnostic terminology, and incorporation of the pathologist in the clinical research and patient management.

References


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