READING ASSIGNMENTS:

Robbins: Pathologic Basis of Disease, pp 1089-1111

OBJECTIVES:

Upon completion of this segment of the course the student should:

1. Comprehend the microscopical changes which are represented by the term, “Fibrocystic Changes,” and should know which of these relate to the risk of subsequent carcinoma.

2. Understand which breast lesions may be responsible for a nipple discharge, and which lesions most often present as a mammographic or palpable abnormality.

3. Be able to distinguish between invasive and noninvasive carcinoma of the breast, and the clinical implication of these diagnoses. The prognostic significance of these terms must be appreciated, as must their implication for treatment of the patient.

4. Appreciate the pathologic findings of a breast carcinoma which impact on the patient’s prognosis.

MICROSCOPIC SLIDES

Slide 148: Fibrocystic Changes in Breast

This biopsy is from the breast of a 45-year-old woman. A variety of changes are present on this slide, indicating the heterogeneity of the findings in this condition. Cystically, dilated ducts containing eosinophilic fluid are present, as are foci of intraductal epithelial proliferation (intraductal hyperplasia). Prominent fibrosis, blending intralobular and interlobular connective tissue, is focally present. A small area of sclerosing adenosis is evident in most sections, is relatively circumscribed, and contains small spindled cells and attenuated ducts centrally and somewhat more normal ducts at the periphery. Another component of this complex of findings, apocrine metaplasia of the ductal epithelium, is present in only scattered cystic ducts, although it may be absent in some sections. Note the microcalcifications in some of the ducts with intraductal hyperplasia as well as in some seemingly normal ducts.
Compare are foci of intraductal hyperplasia with the neoplastic ducts in slide 152.

Would this lesion have been evident on mammography? Why?

Yes. Fibrocystic changes of the breast are often associated with microcalcifications and fibrosis. These areas of fibrosis and the microcalcifications would appear radiographically. In addition, larger cystic lesions may also be apparent.

Which of the microscopical findings in this section, if more extensive, would result in a palpable mass in the breast?

Both the fibrosis and the cystic changes would result in palpable masses in the breast. Cyst size is dependent on the hormonal cycle and tends to be most significant toward the end of the cycle (approximately 1 week prior to menses). Extensive fibrosis of the breast is referred to as “fibrous mastopathy” and would result in very firm, dense breast tissue.

Why is it important that both epithelium and myoepithelium can be identified around the ducts in this lesion?

Scelosing adenosis, a key component in fibrocystic disease of the breast, often attenuates the duct lining epithelium. The importance of the myoepithelial layer is in excluding the possibility of invasive carcinoma. In fact, if myoepithelium is not convincingly present on histologic exam alone, immunohistochemical stains for S100 and smooth muscle specific actin can be attained to assure its presence.

Which of the microscopical abnormalities in this section would constitute a somewhat increased risk of subsequent carcinoma for this patient?

In general, fibrocystic disease itself does not increase a woman’s risk of developing breast cancer. The presence of duct hyperplasia (a common component of fibrocystic changes) represents approximately 1.5 times increased risk over the normal population. Some of the slides that you have contain areas of atypical duct hyperplasia (more rounded nuclei). This alone carries a five times increased risk of development of breast carcinoma in this patient.

Slide 149: Gynecomastia

This 49-year-old man had enlargement of both breasts, more pronounced on the left. The characteristic feature of this tissue is the absence of lobule development. Also, note the pale, basophilic, connective tissue immediately
surrounding the ducts, which is in contrast to the dense collagen elsewhere in the breast. The epithelium lining some of the ducts is hyperplastic and is thrown into small papillae. This mild intraductal hyperplasia is a common feature of gynecomastia and is unassociated with an increased risk of subsequent carcinoma.

What are the usual causes of gynecomastia?

**Drugs, estrogen excess, chronic liver disease, and peripubertal asymmetric breast enlargement.** Klinefelter’s syndrome patients are at increased risk. **Note:** Florid duct hyperplasia is a common finding in gynecomastia. An increased risk of developing infiltrating carcinoma has not been statistically noted, perhaps due to the extreme rarity of this neoplasm in the male breast.

This patient had asymmetrical breast enlargement. Is gynecomastia usually unilateral or bilateral?

**Unilateral. Reason: unknown.**

What would be the appropriate treatment if this breast enlargement occurred in a 12-year-old boy?

**Observation.**

**Slide 150: Fibroadenoma**

This slide is from a solitary, well circumscribed, freely mobile mass removed from the left breast of a 23-year-old woman. Most distinctive is the presence of elongated and compressed ducts surrounded by connective tissue of varying cellularity. This growth pattern has been termed “intracanalicular.” The connective tissue surrounding the ducts has a pale, basophilic, appearance. Note that the connective tissue cells (fibroblasts) lack any atypism, cellular crowding or increased mitotic activity. Compare these cells with those in slide 154. The blue or black ink at the edge of the biopsy represents the margin of surgical excision.

What is the most common age of occurrence of these lesions?

**Fibroadenomas tend to occur in post-pubertal and young reproductive age women more often than other age groups.**
Does this lesion imply a clinically significant increased risk of subsequent carcinoma for this patient?

No.

Since the lesional tissue extends to the inked margin of excision, should this patient have a re-excisional lumpectomy?

No, not unless there is a regrowth of the fibroadenoma.

Is mammography useful for detection of these lesions in this age group?

Routine mammographic screening, unless otherwise indicated because of a strong family history, is not recommended for women under the age of 35. Since fibroadenomas are benign neoplasms, self breast examination is an adequate monitoring technique.

**Slide 151: Intraductal Papilloma**

This large papillary lesion was present in a cystically dilated duct in the left upper outer quadrant of the breast of a 41-year-old woman. In this setting it is often termed an intracystic papilloma. Such lesions more commonly present in a subareolar location where they produce a nipple discharge. The papillary lesion consists of fibrovascular stalks of varying thickness, and these are covered by a single layer of epithelial cells which lack nuclear atypism. In some sections foci of apocrine metaplasia of the epithelial cells are present. The surrounding cystic duct is partially represented in your section. It is lined, in part, by a single cell layer of attenuated epithelium and manifests chronic inflammation. The dense connective tissue at the point of origin of the papilloma in the cystic duct seemingly subdivides the lesion giving the false appearance of more than one lesion.

How would this lesion have been clinically recognized?

**Nipple duct discharge, usually sanguinous (bloody) or serosanguinous.**

Would ultrasonography have been a useful adjunct to diagnosis?

Yes. Often there is cystic dilatation around the solid papillomatous lesion. Ultrasound can be useful in noting the papillation.

Does this lesion imply an increased risk of breast malignancy?

No. This is a specific type of lesion usually noted around the nipple duct. This should not be confused with other “papillary” lesions of the breast
away from the nipple, which may be associated with hyperplasia and an increased risk of carcinoma.

What is the age range of most patients with intraductal papillomas?

Peri- and post-menopausal patients are at a higher risk for intraductal papillomas (5th and 6th decade of life). Of importance is that their clinical presentation is often a bloody nipple discharge which raises the concern about possible breast malignancy. The finding of an intraductal papilloma is a reassuring finding in these cases.

Is the character of the nipple discharge important in distinguishing between benign and malignant lesions?

No.

Slide 152: Ductal Carcinoma in situ

Some of the ducts in this biopsy material from the right breast of a 52-year-old woman manifest abnormal epithelial proliferation, while other areas of the biopsy lack abnormality. Much of the abnormal proliferation has a papillary configuration, and in other areas the abnormal cells bridge across duct lumens, resulting in a cribriform pattern of growth. The neoplastic cells are large, have variably sized irregular nuclei with nucleoli and occasional mitotic figures. This can be considered as a neoplasm of high nuclear grade. There is focal necrosis of these cells in the center of ducts and occasional slides have dystrophic calcification in this necrotic material. Compare this abnormal proliferation with the normal breast ducts on the slide. In some instances the neoplastic cells in large ducts can be seen to extend into branching lobular ducts. Occasional slides may have a thin rim of blue ink at an edge of the tissue. Painting the gross specimen in this manner allows determination of the proximity of carcinoma to the margin of surgical excision.

What clinical/mammographic finding likely led to this biopsy?

The most likely mammographic finding leading to a biopsy such as this is microcalcifications. Other findings may have included: irregular fibrosis and a mass effect.

Is there any evidence of stromal invasion in this biopsy material?

This particular intraductal carcinoma is of the comedo type. If you notice in your sections, there is an intense periductal stromal response to the intraductal carcinoma. Look for the myoepithelial layer surrounding the
ducts. If absent, your slide may indeed have a focus representing stromal invasion. However, most of the slides do not demonstrate this feature.

Assuming that the changes in other slides from this biopsy are the same as those evident in this section, what is the likelihood of axillary lymph node metastases?

Intraductal comedo carcinoma is the one intraductal carcinoma that may carry a higher likelihood of metastatic axillary nodal disease in the absence of obvious invasion. Consequently, careful examination and biopsy of a “sentinel” lymph node, if present, might be indicated. Full axillary node dissection is not recommended, however.

What are the therapeutic options for this patient? How will these be influenced by mammographic findings? By the results of a subsequent re-excisional lumpectomy?

Based on the size of the original mammographic lesion, the presence of suspicious findings for multifocal lesions, the therapeutic options may range from an excisional lumpectomy with wide margins to subcutaneous mastectomy to mastectomy with reconstructive surgery, sentinel lymph node biopsy and/or axillary dissection may be recommended of the lesion is in the tail of the breast or axillary metastases is suspicious clinically.

**Slide 153: Invasive Ductal Carcinoma**

There is diffuse invasion of breast stroma by carcinoma in this section. The invasive neoplasm lacks a myoepithelial investment. Surrounding the invasive carcinoma are foci of ductal carcinoma in situ with micropapillary and apocrine growth patterns, and with focal central necrosis. Compare the DCIS with the normal ducts present of this slide. Note the pleomorphism of nuclei in both the DCIS and in the invasive carcinoma. The invasive carcinoma is surrounded by a prominent lymphocytic infiltrate. This pattern of invasive carcinoma is often termed “NOS” (not otherwise specified), in contrast to some special growth patterns which have unique prognostic or therapeutic significance.

Is the diameter of the invasive carcinoma in this breast of prognostic importance?

Yes. Measurements of the tumor size are extremely important in the TNM and staging classification for breast disease. Obviously patients with larger lesions have a higher stage and an increased risk of subsequent findings of axillary nodal metastases and shorter disease-free intervals.
What other factors which can be seen in the breast biopsy material are of prognostic importance?

**Other prognostic features include histologic type, tumor grade, and lymphocystic response to the infiltrative tumor.**

What are the therapeutic options for the patient?

**Conservative lumpectomy with axillary node dissection is the most conservative approach. Some still recommend radical mastectomy and axillary node dissection however.**

What is the importance of the DCIS in planning for treatment of this patient?

**Patients with extensive DCIS in addition to an infiltrating component may indeed have a more aggressive tumor and may require a more aggressive surgical approach.**

**Slide 154: Periductal Sarcoma (Malignant Cystosarcoma Phyllodes)**

This tumor was removed from the left breast of a 56-year-old woman. On low power magnification this slide resembles a fibroadenoma, as it consists of variably sized ducts, some compressed and elongated, surrounded in most areas by a cellular stroma. On higher magnification the stromal component of this periductal stromal tumor is decidedly different from that of the fibroadenoma viewed in case 150. In most areas the degree of stromal cellularity is greater, there is variation in cell size and shape and considerable nuclear pleomorphism. Mitotic figures are plentiful, and some are bizarre. The epithelium lining the ductal component of the tumor is relatively normal, although there are some foci of minimal hyperplasia. This neoplasm is unique because of the presence of ducts amidst the stromal cell proliferation. In some areas the stroma lacks neoplastic change and resembles a fibroadenoma. The term “Cystosarcoma phyllodes” was coined before the era of microscopic pathology and relates to the gross appearance of the tumor. “Cystosarcoma” means a fleshy tumor with some grossly evident cysts, while “phyllodes” refers to the grossly evident leaf-like pattern.

Are all cystosarcomas malignant?

**Yes, but phyllodes tumors are considered low grade sarcomas. Rarely, they will metastasize beyond the local region.**

How should this patient be treated? Is axillary lymph node dissection necessary?

**These patients are treated with lumpectomy with a generous margin. Axillary node dissection is not required.**
How do malignant periductal stromal tumors metastasize?

For the most part, cystosarcoma phyllodes if it recurs, will recur in the local area. On rare occasions, hematogenous spread of phyllodes tumors has been known to occur.