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Surgical and Clinical Pathology of Breast Diseases

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1. Introduction

Histopathology plays an important role in management of breast diseases. It is a necessary component of diagnosis, treatment and prognosis in most breast disorders. Also, when assessing the adequacy of treatment in breast cancer, pathologic assessment is the main criterion. The importance of the role of histopathology in treatment of breast cancer has encouraged the researchers to investigate the impact of pathology review on treatment of breast cancer. Kennecke HF and colleagues studied the impact of pathology review in treatment of 405 patients with breast cancer. A total of 102 pathology changes were documented among 81 patients (20%). These changes resulted in 27 treatment modifications among 25 patients (6%) (1). It seems that before decision making for treatment of breast disease, the pathology should review by an expert breast pathologist.

2. How to achieve tissue?

Fine needle aspiration or core needle biopsy versus surgical biopsy has remained a challenge in breast lesions suspicious to malignancy. An article published in December 2011 resulted from a report from the National Cancer Data Base concluded that tumor stage, hospital volume, and hospital location were the most statistically significant predictors of biopsy type (2). Rates of needle biopsy at high-volume hospitals suggest that appropriate utilization of this preferred diagnostic method should approach 90%. A meta-analysis has shown that FNA cytologic analysis of palpable breast masses is highly accurate in the diagnostic differentiation of benign from malignant tumors (3).

Sampling of nonpalpable or indistinct breast lesions can be done using stereotactic breast needle biopsy, a technique that enable the spatial localization of the lesion within the breast.

3. Estrogen receptor (ER) and progesterone receptor (PR) status

Receptors are proteins in or on certain cells that can attach to certain substances, such as hormones, that circulate in the blood. Normal breast cells and some breast cancer cells contain receptors that attach to estrogen and progesterone. These 2 hormones often fuel the growth of breast cancer cells.

An important step in evaluating a breast cancer is to test a portion of the cancer removed during the biopsy (or surgery) to see if they have estrogen and progesterone receptors. Cancer cells may contain neither, one, or both of these receptors. Breast cancers that have estrogen receptors are often referred to as *ER-positive* (or ER+) cancers, while those containing progesterone receptors are called *PR-positive* (or PR+) cancers. If either type of receptor is present, the cancer is said to be hormone receptor-postive.

Women with hormone receptor–positive cancers tend to live longer and are much more likely to respond to hormone therapy than women with cancers without these receptors.

All breast cancers, should be tested for these hormone receptors either on the the biopsy sample or when they are removed with surgery. About 2 of 3 breast cancers have at least one of these receptors. This percentage is higher in older women than in younger ones.

4. HER2/neu status

About 1 of 5 breast cancers have too much of a growth-promoting protein called *HER2/neu* (often just shortened to HER2). The HER2/neu gene instructs the cells to make this protein. Tumors with increased levels of HER2/neu are referred to as*HER2-positive*.

Women with HER2-positive breast cancers have too many copies of the HER2/neu gene, resulting in greater than normal amounts of the HER2/neu protein. These cancers tend to grow and spread more aggressively than other breast cancers.

All newly diagnosed breast cancers should be tested for HER2/neu because HER2-positive cancers are much more likely to benefit from treatment with drugs that target the HER2/neu protein, such as trastuzumab (Herceptin) and lapatinib (Tykerb).

Testing of the biopsy or surgery sample is usually done in 1 of 2 ways:

1.   Immunohistochemistry (IHC): In this test, special antibodies that identify the HER2/neu protein are applied to the sample, which cause cells to change color if many copies are present. This color change can be seen under a microscope. The test results are reported as 0, 1+, 2+, or 3+.
2.   Fluorescent in situ hybridization (FISH): This test uses fluorescent pieces of DNA that specifically stick to copies of the HER2/neu gene in cells, which can then be counted under a special microscope.

Many breast cancer specialists feel the FISH test is more accurate than IHC. However, it is more expensive and takes longer to get the results. Often the IHC test is used first. If the

results are 1+ (or 0), the cancer is considered HER2-negative. People with HER2-negative tumors are not treated with drugs (like trastuzumab) that target HER2. If the test comes back 3+, the cancer is HER2-positive. Patients with HER2-positive tumors may be treated with drugs like trastuzumab. When the result is 2+, the HER2 status of the tumor is not clear. This often leads to testing the tumor with FISH.

A newer type of test, known as chromogenic in situ hybridization (CISH), works similarly to FISH, by using small DNA probes to count the number of HER2 genes in breast cancer cells. But this test looks for color changes (not fluorescence) and doesn't require a special microscope, which may make it less expensive. Right now, it is not being used as much as IHC or FISH.

5. Benign breast lesions
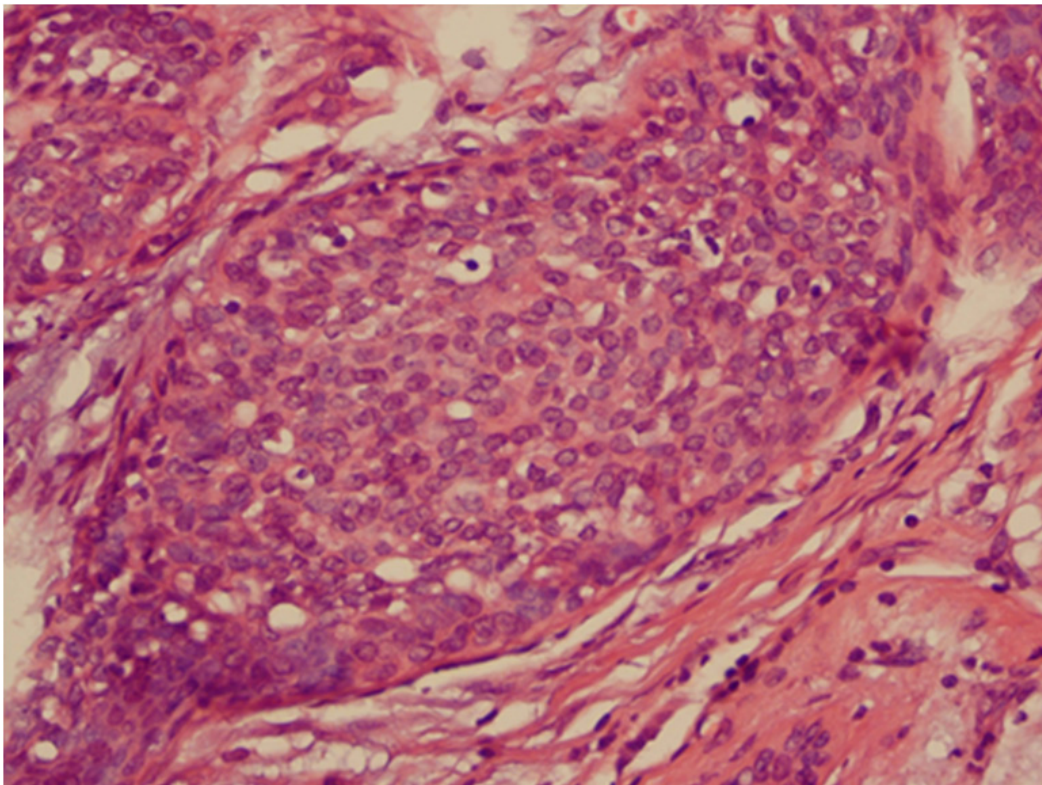
5.1. Fibrocystic disease

Fibrocystic disease is one of the most common benign breast lesions. The breast tissue in response of imbalanced estrogen and progesterone stimulation over time, undergoes a various morphologic changes of fibrocystic disease. The peak incidence is between 35 and 50 years of age. It is rare before 25 years. The term embraces a spectrum of histologic changes, and may encompass many patients who have cystic lesions detected clinically or sclerotic breast lesions detected on mammography as discussed elsewhere. Histologically it is characterized by overgrowth of both fibrous stroma, and of epithelial elements i.e. ducts and lobules, in differing proportions. These changes may be considered as aberrations of normal breast involution and not part of a disease process. The basic morphologic changes in the fibrocystic disease are cysts formation, apocrine metaplasia and fibrosis (4, 5, 6, 8,) Cysts may be grossly visible or evident in microscopic examination, usually contains yellow to clear fluid. The cyst lining may be flattened, or shows apocrine metaplasia and epithelial hyperplasia (5, 8). Apocrine metaplasia is characterized by abundant granular eosinophilic cytoplasm with apical snouts (5). Stromal fibrosis is also a common finding (5). Epithelial hyperplasia whether typical or atypical may be occurred in fibrocystic disease and put the patient in a higher risk of cancer development especially in patients accompanied by atypical ductal hyperplasia (Figure 1A &B) (4, 5, 6, 7).

Other rare morphologic variations include calcification and fibroadenoma-like picture, so called fibroadenomatoid mastopathy (9).

In most cases, symptoms of fibrocystic changes include breast pain and tender lumps or thickened areas in the breasts. These symptoms may change as the woman moves through different stages of the menstrual cycle. Sometimes, one of the lumps may feel firmer or have other features that lead to a concern about cancer. When this happens, a needle biopsy or a surgical biopsy may be needed to make sure that cancer is not present. Most women with fibrocystic changes and no bothersome symptoms do not need treatment, but closer follow-up may be advised. Women with mild discomfort may get relief from supportive bras or over-the-counter pain relievers. For a very small number of women with painful cysts,
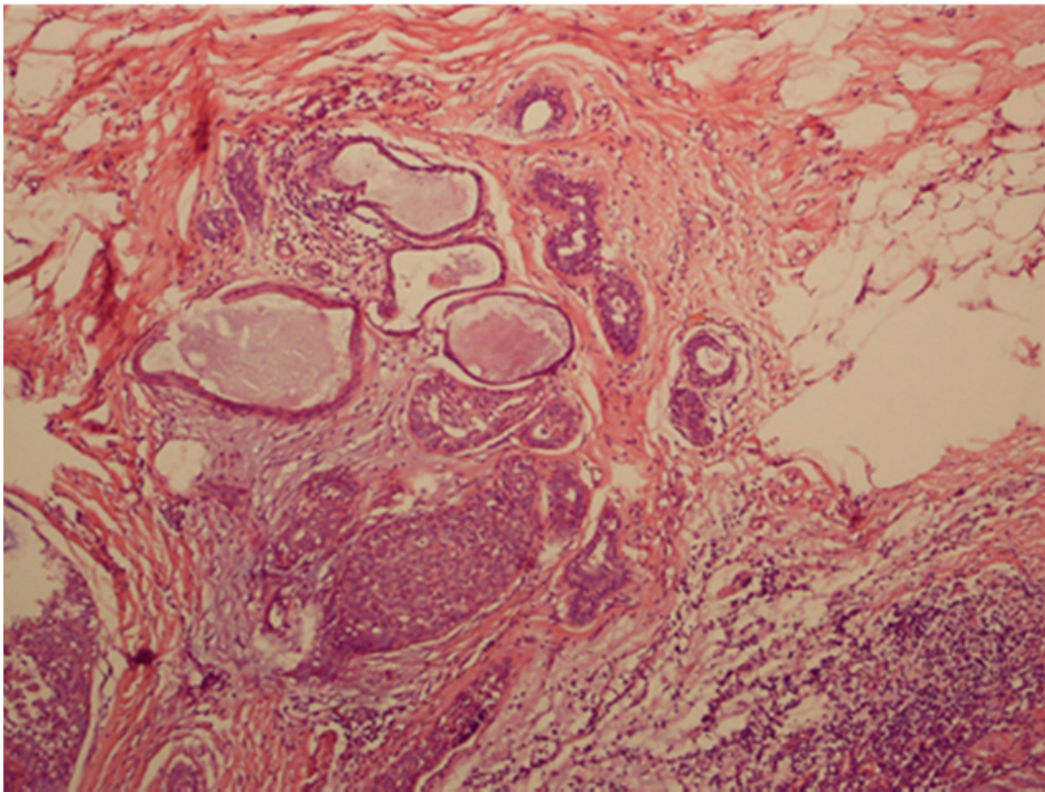
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Figure 1. A: fibrocystic disease showing typical ductal hyperplasia, H & E, x100. B: typical ductal hyperplasia. The duct is obliterated by uniform cells with indistinc cytoplasmic border, H & E, x400.

draining the fluid with a needle can help relieve symptoms. Some women report that their breast symptoms improve if they avoid caffeine and other stimulants (called *methylxanthines*) found in coffee, tea, chocolate, and many soft drinks. Studies have not found those stimulants to have a significant impact on symptoms, but many women feel that avoiding these foods and drinks for a couple of months is worth trying. Because breast swelling toward the end of the menstrual cycle is painful for some women, some doctors recommend that women reduce salt in their diets or take diuretics. But studies have not found diuretics to be better than placebos. Many vitamin supplements have been suggested, but so far none are proven to be of any use, and some may have dangerous side effects if taken in large doses. Some doctors recommend hormones, such as oral contraceptives (birth control pills), tamoxifen, or androgens. But these are usually used only in women with severe symptoms because they can have serious side effects (10).

5.2. Breast cysts

Breast cysts are fluid filled, round or ovoid masses derived from the terminal duct lobular unit (TDLU). Cysts begin as fluid accumulation in the TDLU as a consequence of distension and obstruction of the efferent ductule (11). Breast cysts are influenced by hormonal function and therefore typically develop in premenopausal and perimenopausal women as a consequence of lobular development, cyclic changes, and lobular involution (12). Microscopically the cyst inner lining is flat or completely denuded and myopeithelial layer is recognizable.

Cysts are mostly occurs in women between 35-50 years old. It is uncommon for postmenopausal women to develop breast cysts, unless they are taking postmenopausal hormone replacement therapy. Breast cysts can present as gross palpable masses or as microcysts, usually found as an abnormality on an imaging examination. Acute enlargement of cysts may cause severe, localized pain of sudden onset. Cysts usually prompt women to seek medical attention because of a palpable mass or associated discomfort. FNA biopsy can confirm the diagnosis of a cyst and, at the same time, drain the cyst fluid. Removing the fluid may reduce pressure and pain for some time, but it is not necessary to remove the fluid unless it is causing discomfort. If removed, the fluid may come back later. Because needle biopsy of breast masses may produce artifacts that make mammography assessment more difficult, many radiologists prefer to image breast masses before performing needle biopsy (13, 14).

5.3. Intraductal papilloma

Papillomas are benign breast lesions usually affecting the lactiferous ducts, but smaller peripheral ducts may also be involved (4, 5, 6). The larger lesions may present with intramural fragile masses but smaller ones may be evident only on microscopic examination (4, 5). Microscopically, the papilloma consists of proliferation of ductal epithelium rested on fibrovascular stroma. Epithelial component consist of cuboidal to columnar cells without pleomorphism, nuclear atypia or mitotic figures (Figure 2A & B). Myoepithalial layer is also
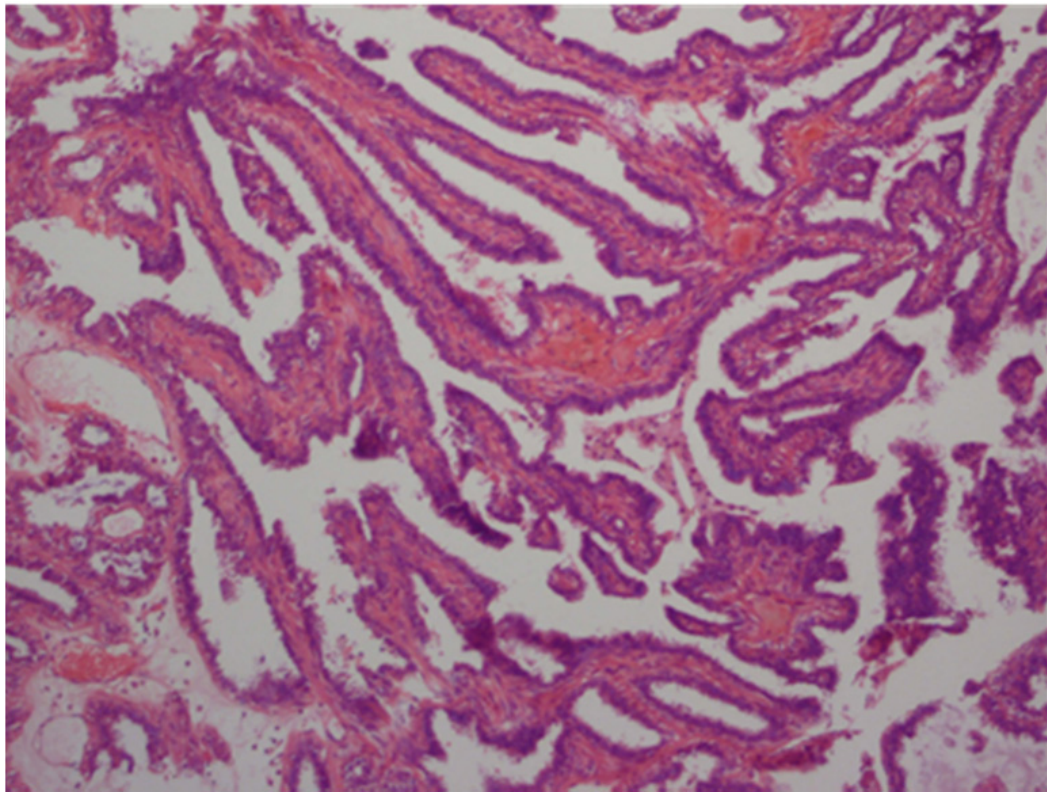
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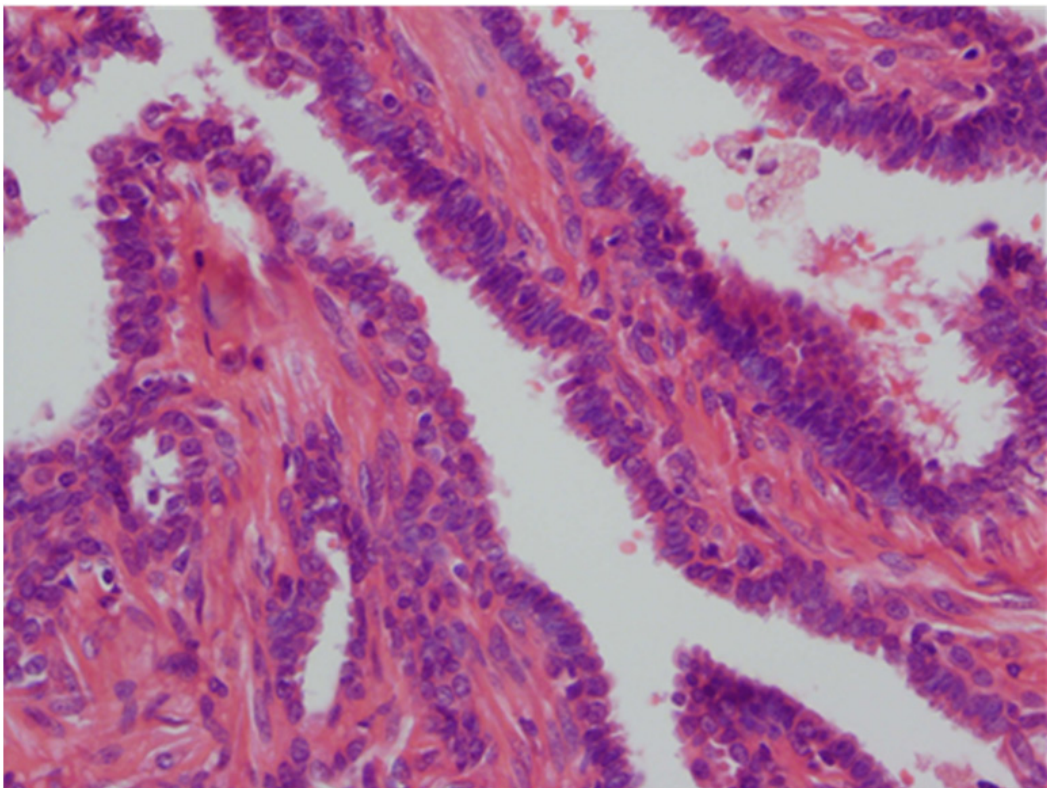
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Figure 2. A & B: Papilloma. The epithelial cells are laying on fibrovascular core showing no atypia, H & E, x100 and x400

preserved (4, 5). Some papillomas have more complex structure accompanied by epithelial hyperplasia (4, 5, 6, 15). Atypical ductal hyperplasia and carcinoma in situ may occur in the setting of papillomas. Absence of myoepithelial layer is a useful marker for recognition of the malignant transformation (4, 5, 15). Papillomatosis (multiple papillomas) are usually bilateral with higher probability of association with carcinoma (6).

5.4. Sclerosing adenosis

Adenosis of breast is a proliferative lesion, characterized by increase number of glandular components. Various types of adenosis has been described: sclerosing, tubular, microglandular, and apocrine adenosis. Sclerosing adenosis is a kind of hyperplastic proliferation of glandular component of breast (5). It can occur as a focal or generalized proliferation of ducts and it may be accompanied by various forms of hyperplasia and even carcinoma (4, 6). Microscopically, the lesion has an oval to round configuration with central accentuation of cellularity. High power examination shows elongated and compressed glands formed by atrophied epithelial cells with preservation of myoepithelial layer, surrounded by sclerosed stroma (Figure 3A &B) (4, 5).

Some other morphologic variations include apocrine metaplasia and perineural invasion. Presence of myoepithelial layer distinguishes this lesion from an invasive carcinoma (4, 5, 16). The patients with sclerosing adenosis have a higher risk of subsequent development of malignancy, especially in patients that their lesion is accompanied by atypical lobular hyperplasia (4, 5). The clinical significance of sclerosing adenosis lies in its mimicry of cancer. It may be confused with cancer on physical examination, by mammography, and at gross pathologic examination. Excisional biopsy and histologic examination are frequently necessary to exclude the diagnosis of cancer. The diagnostic work-up for radial scars and complex sclerosing lesions frequently involves stereoscopic biopsy. It usually is not possible to differentiate these lesions with certainty from cancer by mammographic features, so biopsy is recommended. The mammographic appearance of a radial scar or sclerosing adenosis (mass density with spiculated margins) will usually lead to an assessment that the results of a core-needle biopsy showing benign disease are discordant with the radiographic findings. Breast radiologists will therefore often forego image-guided needle biopsy of a lesion suspicious for radial scar and refer the case directly to a surgeon for wire localized excisional biopsy.

5.5. Epithelial hyperplasis

Breast ducts are lined by two layers of epithelial cells, luminal and basal cells. Any increase in cell number within ductal space regarded as epithelial hyperplasia. Based on cytomorphology and presence of nuclear atypia, the lesion sub-classified as typical or atypical hyperplasia. The diagnosis of atypical epithelial hyperplasia (AEH) increases with breast cancer screening. AEH is divided in three groups: atypical ductal hyperplasia, columnar cell lesions with atypia, lobular neoplasia.
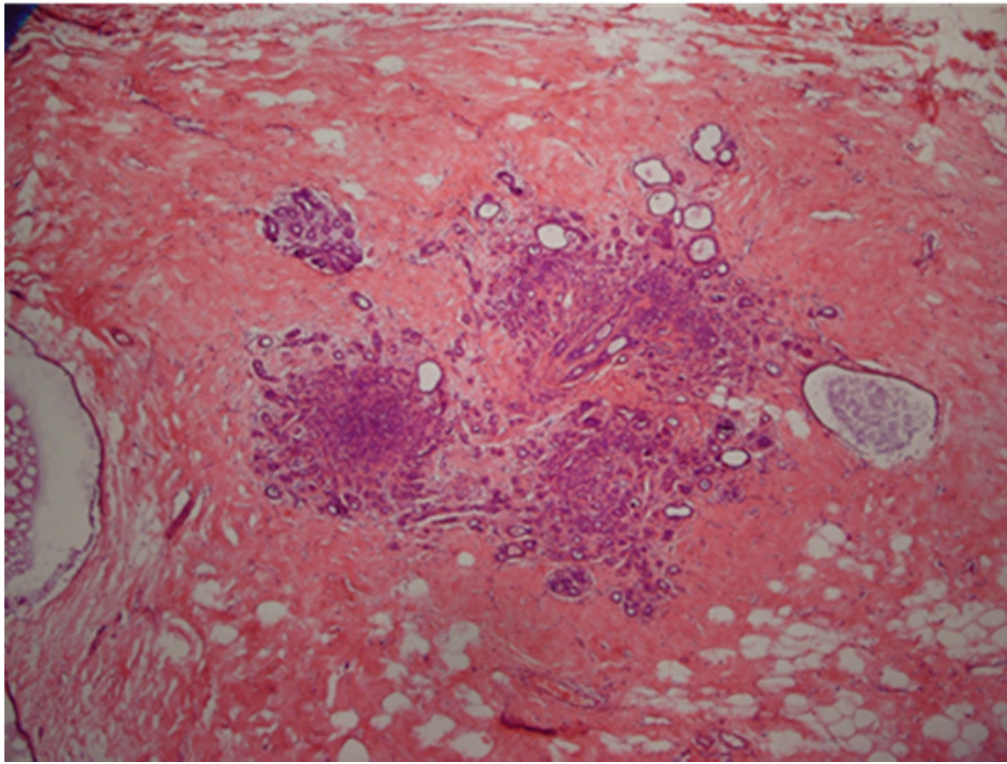
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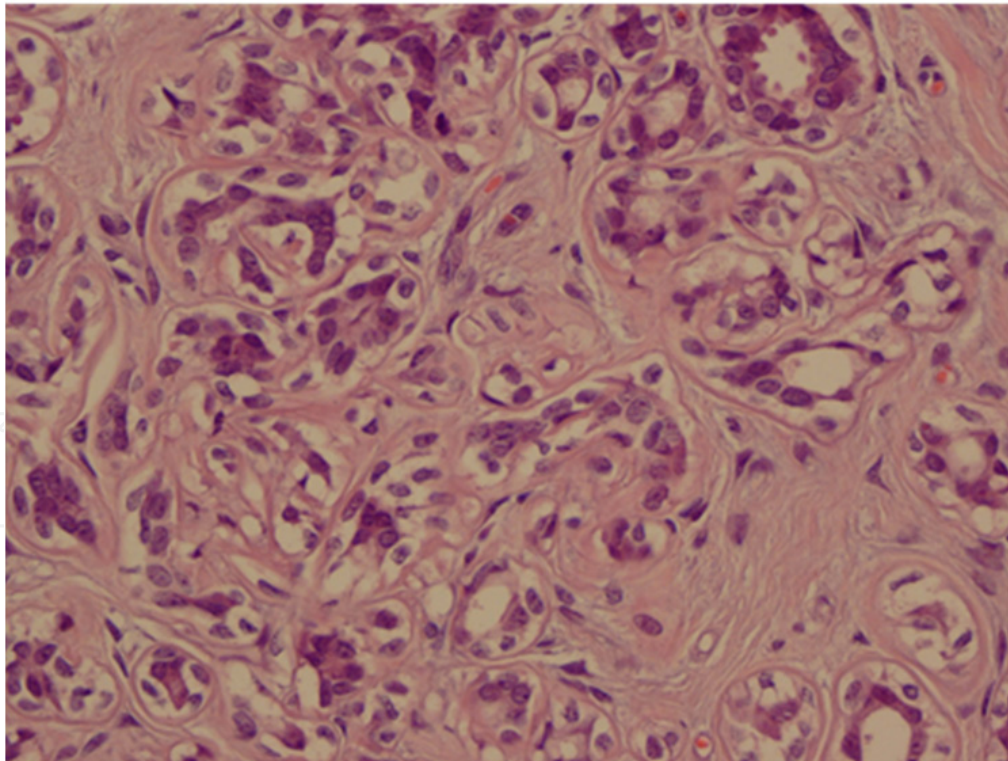
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Figure 3. A & B: sclerosing adenosis. Glandular proliferation surrounded by sclerosed stroma. The glands are lined by two layer of epithelial and myoepithelial cells. The latter shows clear cell changes, H & E, X40 and X400

5.6. Ductal hyperplasia

Ductal hyperplasia is characterized by proliferation of ductal epithelium, resulting in increased cellularity and multi layering of ductal epithelium (4, 5). The pattern of growth varies greatly from case to case leading to different types of ductal hyperplasia (4, 5).

Features indicative of benign nature of the lesion includes oval nuclei with indistinct cytoplasmic border and eosinophilic rather than pale cytoplasm, arrangement of the cells in parallel bundles, presence of peripheral elongated clefts in ducts, presence of myoepithelial layer, apocrine metaplasia and absence of necrosis (4, 5). Ductal hyperplasia has been subdivided into mild, moderate and florid categories (4). In mild ductal hyperplasia, the epithelial thickness is 3 to 4 cell layer. In moderate hyperplasia, the thickness of epithelium is more than 4 layers and in florid hyperplasia, the gland lumen is often obliterated by proliferative epithelium and the affected duct is enlarged. Atypical ductal hyperplasia shares some features with intraductal carcinoma. The cells are monomorphic with round nuclei and distinct cytoplasmic border. Cytologic atypia is defined by high nuclear – to – cytoplasm ratio, hyperchromasia of nuclei and enlarged nucleoli. Mitotic activity is more seen in atypical ductal hyperplasia (Figure 4A & B). Presence of intermingled typical ductal hyperplasia or partial involvement of ducts aid in differentiating these lesions from ductal carcinoma insitu. (4, 5, 17). Patients with ductal hyperplasia especially with atypical ones have a higher risk for cancer development (4, 5, 6, 17, 18).

5.7. Columnar cell hyperplasia

The lesion is composed of ducts lined by tall columnar epithelial cells. Intraluminal secretion and calcification do occur. Atypical changes may be also encountered (4, 5, 6, 17).

5.8. Lobular hyperplasia

Lobular hyperplasia is a lesion in which lobules are larger and more cellular (4, 5). The lobular hyperplasia may occur in the setting of hormonal stimulation as in pregnancy (5). Atypical lobular hyperplasia characterized by proliferation of abnormal cells similar to the cell of lobular carcinoma in situ in one or more lobules. Atypical lobular hyperplasia increases the risk of cancer development (4, 5).

The management of women with AEH is not consensual because of uncertainty about their diagnosis related to the type of the biopsy sampling (core needle biopsy or surgical excision) and their controversial clinical signification between risk marker and true precursor of breast cancer. A systematic review performed by Lavoué V and colleagues showed that although according to immunohistochemistry and molecular studies, atypical epithelial hyperplasia (AEH) seems to be precursor of breast cancer; But, epidemiological studies show low rate of breast cancer in women with AEH. AEH were still classified as risk factor of breast cancer.
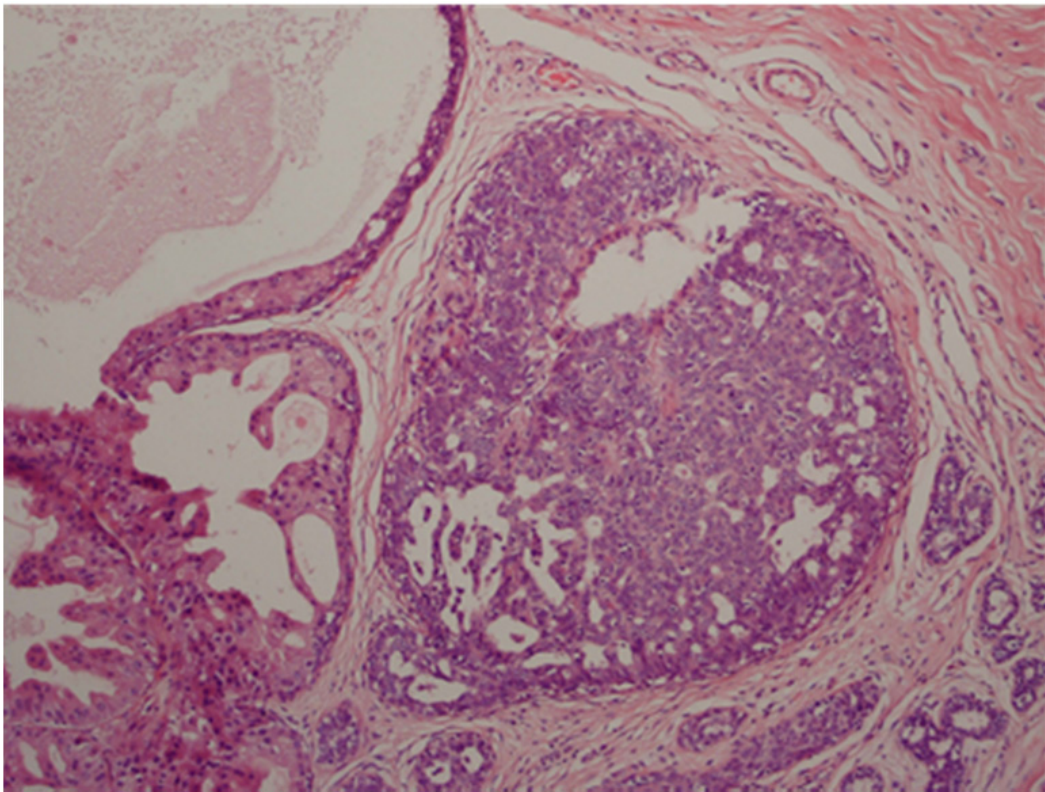
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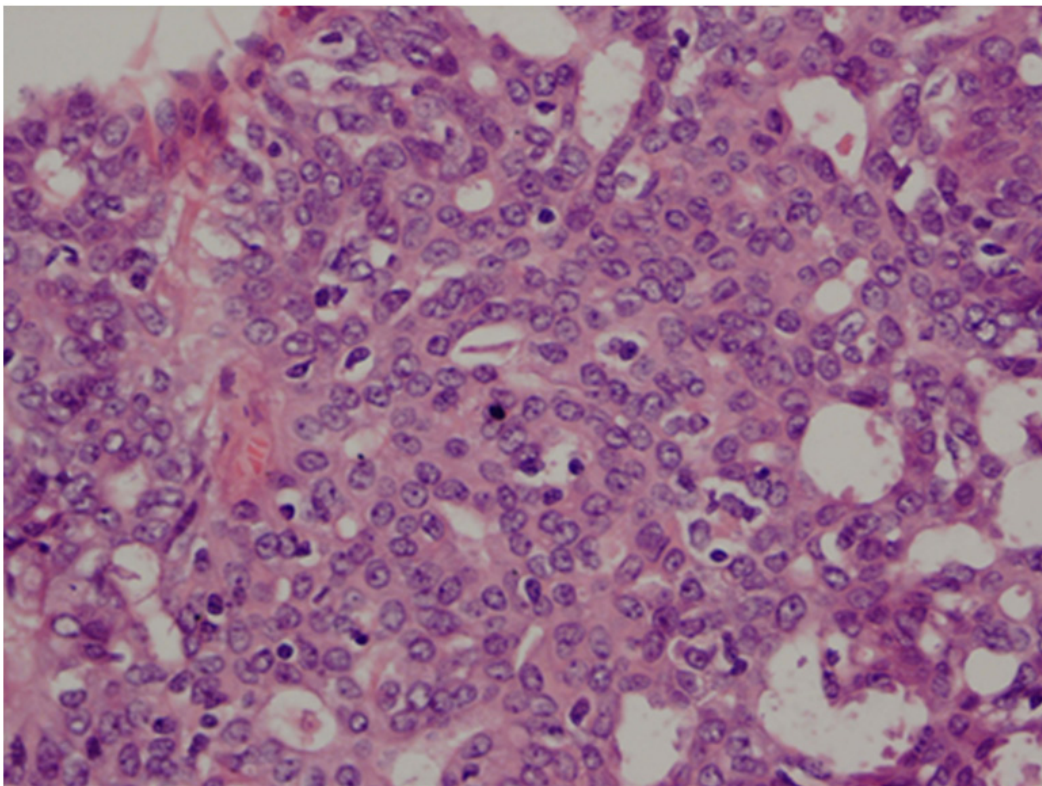
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Figure 4. A & B: Atypical ductal hyperplasia. The duct is filled by atypical cells with pleomorphism and conspicuous nucleoli, H & E, x400.

5.9. Inflammatory lesions

Mastitis: inflammation of breast may caused by many etiologies, including infectious agents, local reaction to systemic disease, localized antigen-antibody reaction and idiopathic. Acute mastitis usually occurs in first 3 months of postpartum. The disorder is a cellulitis of the interlobular connective tissue within the mammary glands which can result in abscess formation. Granulomatous mastitis caused by infectious etiology, foreign material or systemic autoimmune disease. Idiopathic granulomatous mastitis can be diagnosed only when other causes were excluded. Histologically, chronic non-caseating granuloma confining to the lobule exist (Figure5A & B). Mammary duct ectasia or periductal mastitis characterized by dilatation of major ducts in the subareolar region. These ducts contain eosinophilic granular secretions within the duct epithelium or lumen.

Fat necrosis: is a benign non-suppurative inflammatory process secondary to trauma, surgery or radiation therapy. Microscopically, the lesion is characterized by infiltration of foamy histiocytes, lymphocytes, plasma cells and giant cells around anuclear fat cells (Figure 6) (4, 5, 6).

6. Neoplasms

Fibroadenoma is a common benign breast tumor, mostly occurs in second and third decade of life (4, 5). Grossly the tumor is circumscribed and firm. Microscopically, the fibroadenoma is a biphasic mass composing of epithelial and stromal components. The epithelial part is usually made up of tubules consisting of cuboidal to low columnar cells, resting on a myoepithelial cell layer. Stroma with varying degree of cellularity, contains loose connective tissue (Figure 7A & B) (4, 5, 6, 13).

Some morphologic variation exists in fibroadenoma including hyalinization, mixoid change, calcification, apocrine metaplasia and sclerosing adenosis. fibroadenoma showing cysts, sclerosing adenosis, apocrine neoplasia are called camplex fibroadenoma (4, 5).

Proliferative epithelial changes including ductal hyperplasia whether typical or atypical and lobular hyperplasia, are also noted in fibroadenoma (4, 5, 6, 13).

Malignant transformation in fibroadenoma do occur but it is rare, usually involving the epithelial component in the form of carcinoma in situ and invasive carcinoma (lobular and ductal) (4, 5, 13, 14).

The main differential diagnosis of fibroadenoma is phylloides tumor . The latter is usually occurring in older ages, has more cellular stroma with stromal overgrowth .

Mitotic figures may be seen in phylloides tumor, but they are usually absent in fibroadenoma (4, 13).
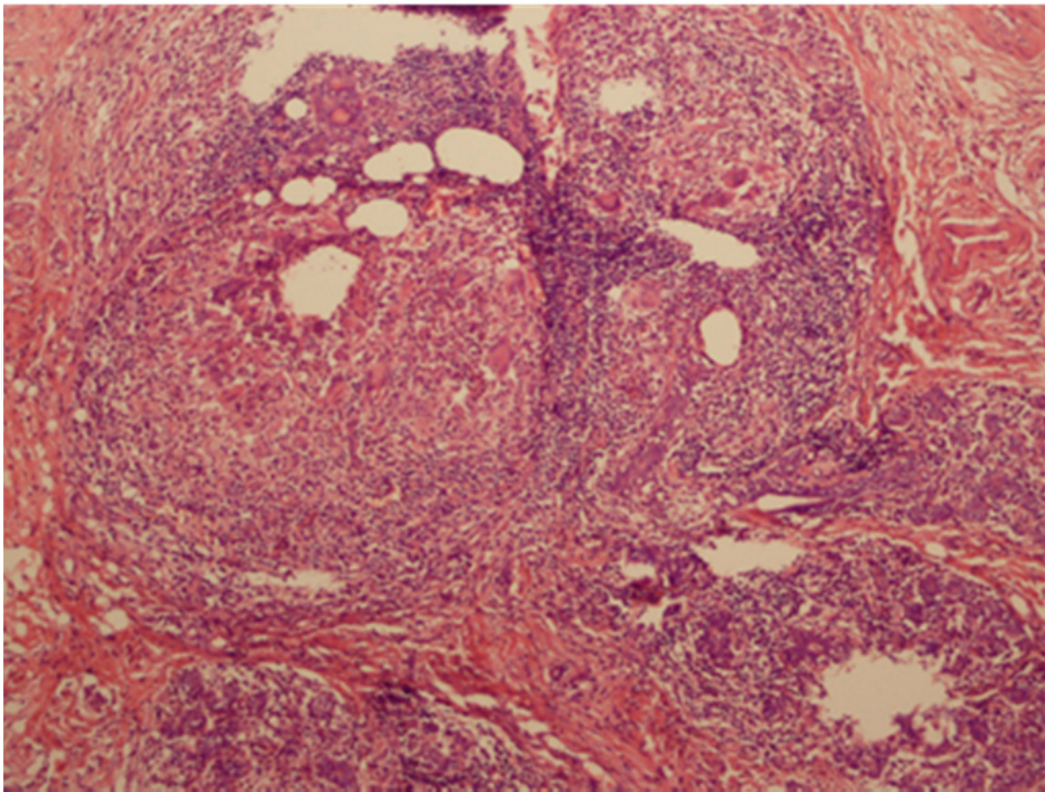
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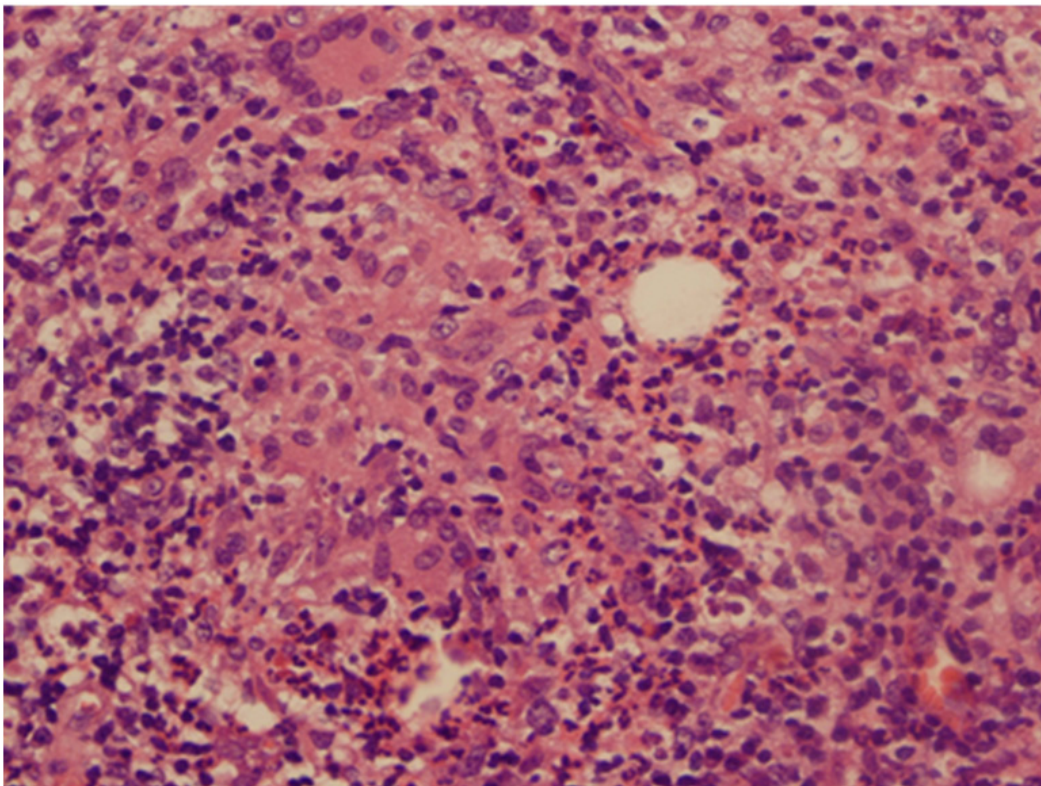
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Figure 5. A & B: Granulomatous mastitis. The granulomatous reaction consistiong of epitheloid histiocytes, giant cells and inflammatory cells surrounds the breast lobules, H & E, x 100 and x400.
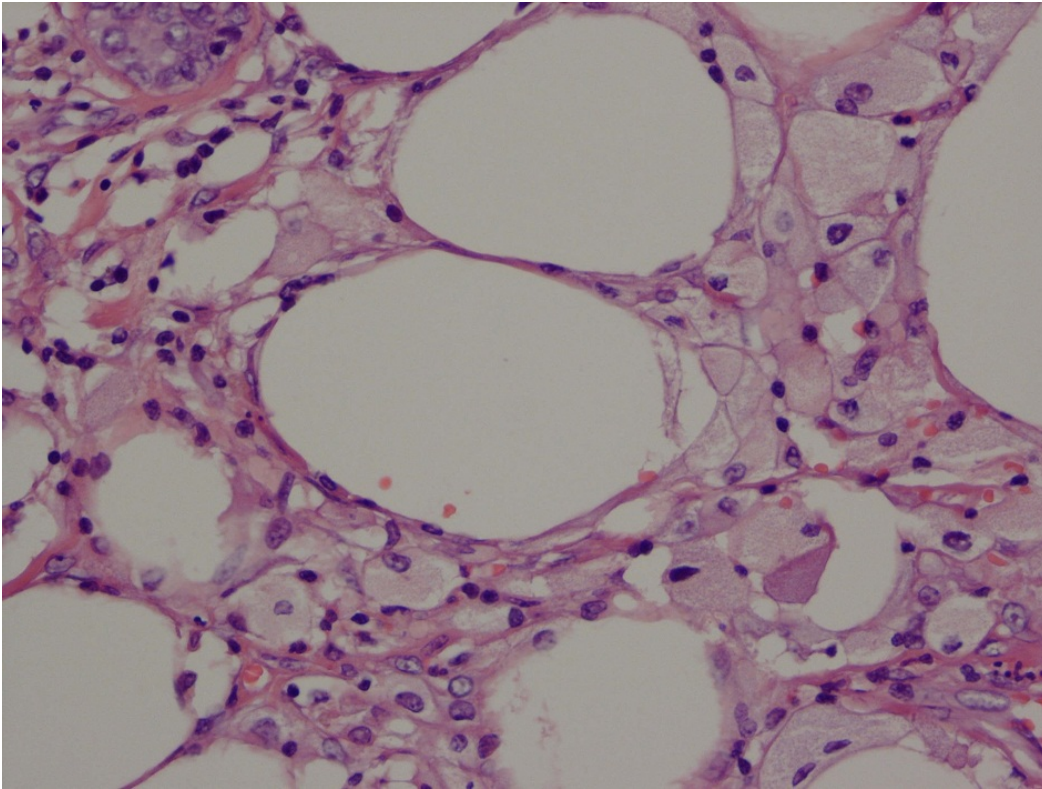
Figure 6. Fat necrosis. The breast parenchyma is infiltrated by foamy macrophages and inflammatory cells, H & E, X400.
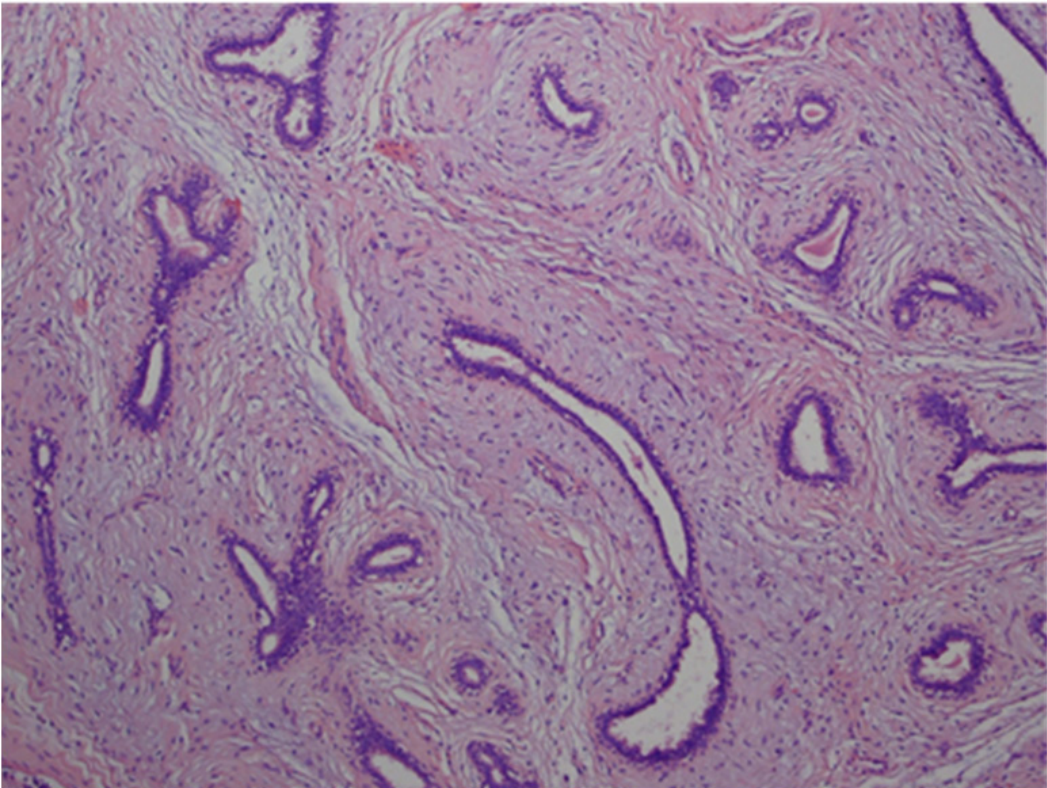
7. Breast cancer

Breast cancer is the most common female cancer in the US, the second most common cause of cancer death in women, and the main cause of death in women ages 40 to 59. About 1 in 8 (12%) women in the US will develop invasive breast cancer during their lifetime (19). The American Cancer Society's most recent estimates for breast cancer in the United States are for 2012:

- About 226,870 new cases of invasive breast cancer will be diagnosed in women.
- About 63,300 new cases of carcinoma in situ (CIS) will be diagnosed (CIS is non-invasive and is the earliest form of breast cancer).
- About 39,510 women will die from breast cancer (20).

Many early breast cancers are asymptomatic. Among the symptomatic cases ,painless mass is the most common symptom. Pain or discomfort is not usually a symptom of breast cancer; only 5% of patients with a malignant mass present with breast pain. Diagnosis of the breast cancer is made based on history, physical examination, mammograms and/or ultrasound findings and the pathologic assessment of specimens. Once a diagnosis of breast cancer is made, the type of therapy offered to a breast cancer patient is determined by the stage of the disease. Laboratory tests and imaging studies are performed based on the initial stage.
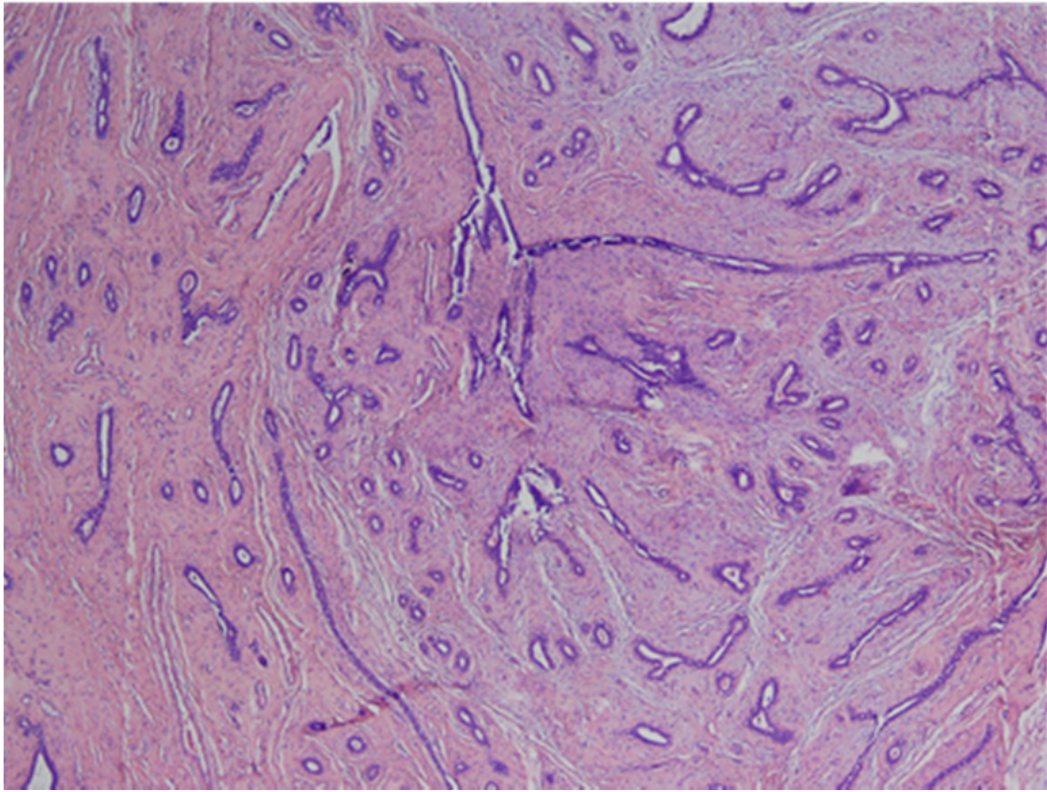
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Figure 7. A & B: Fibroadenoma. The tumor is biphasic consisting of glanduar and stromal parts, H & E,x 40 and x100.

8. Pathology of the breast cancer

8.1. *In situ* carcinoma

8.1.1. Ductal carcinoma in situ (DCIS)

In situ ductal carcinoma is a malignant proliferation of epithelial cells, confined to the lumen of ducts, which was categorized into two grades: High grade comedocarcinoma, composed of pleomorphic cells showing central necrosis and low grade solid, cribriform and micropapillary group with uniform cells without area of necrosis. Clinging carcinoma, based on cytologic features was placed in either groups (4, 5, 21).

Recently, in situ carcinomas were divided into three grades, comedocarcinoma has been placed in grade 3, solid, cribriform and micropapillary carcinomas were designated as grade 1 if they and bland cytologic morphology and classified as grade 2 if they had intermediate cytomorphology (5).

8.2. Comedocarcinoma

Comedocarcinoma is characterized by solid growth of pleomorphic cells within the ducts with area of central necrosis and dystrophic calcification. Mitosis may be abundant. Grossly, thick walled ducts filled with creamy White necrotic material is a characteristic finding. Some comedocarcinoma may present with a palpable mass (4, 5, 22). Myoepithelial layer is usually present but it may have a discontinues fashions (Figure 8A & B) (4, 5).

8.3. *In situ* papillary carcinoma

In situ papillary carcinoma is defined by proliferations of epithelial cells resting on a fibrovascular core. The most important differential diagnosis of this lesion is papilloma. The proposed criteria in favor of in situ papillary carcinoma are older age, larger size, presence of uniform cells, lack of myoepithelial layer, presence of nuclear atypia (hyperchromasia and high nuclear-to-cytoplasmic ratio), high mitotic activity and absent intervening stroma (4, 5, 23, 24).

8.4. Solid *in situ* carcinoma

Solid In situ carcinoma is characterized by filling of the ducts lumen by malignant cells. These cells are uniform with distinct cytoplasmic border and pale cytoplasm (4, 5).

8.5. Cribriform *in situ* carcinoma

Cribriform in situ carcinoma is characterized by proliferation of uniform cells with distinct cytoplasmic border and pale cytoplasm forming round spaces. (Figure 9)(4, 5).
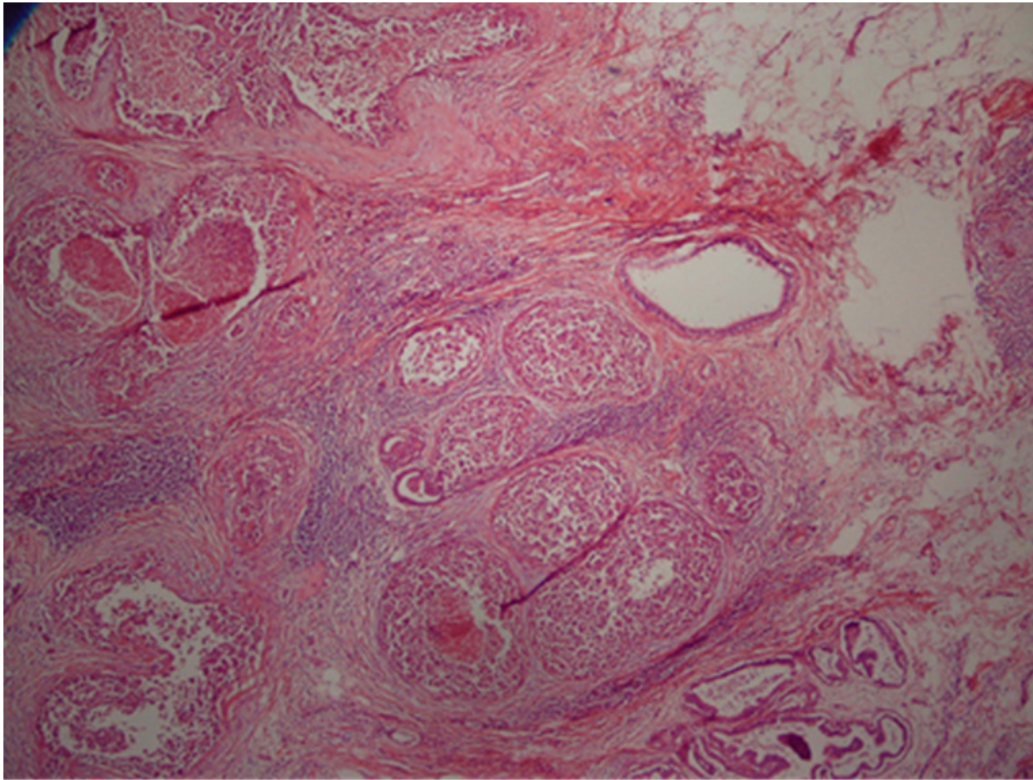
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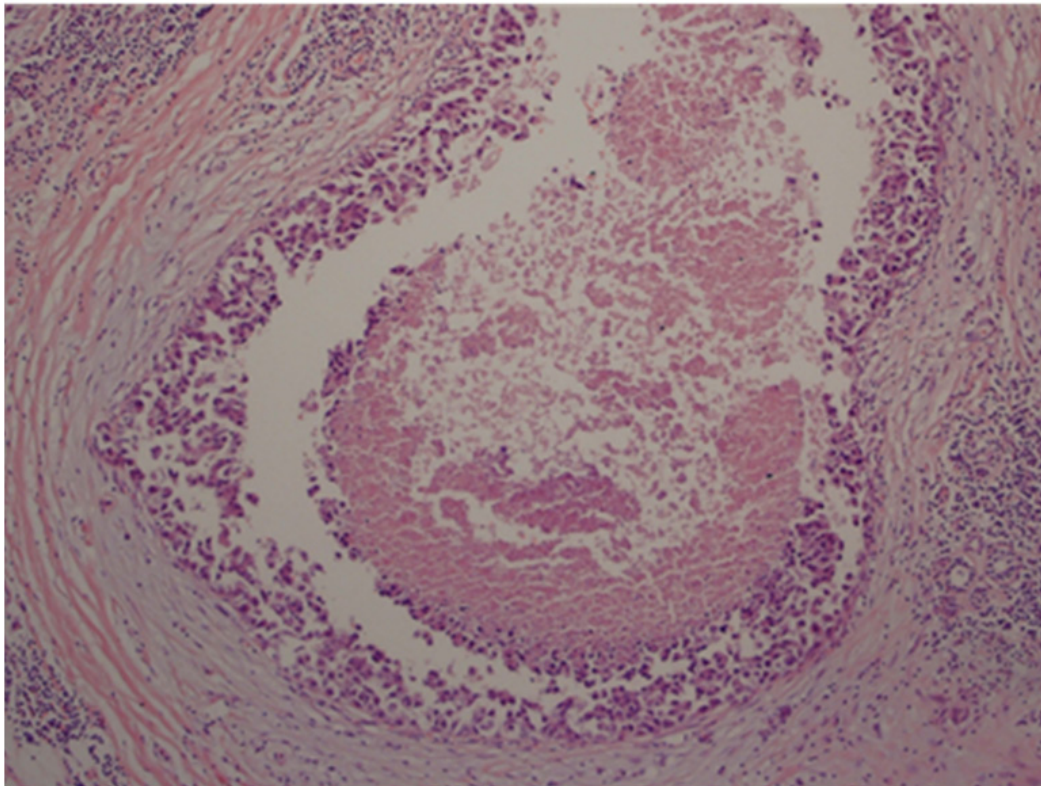
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Figure 8. A & B: *In situ* comedo carcinoma. The dilated ducts are filled by atypical cells showing central necrosis, H & E, X40 and X100.
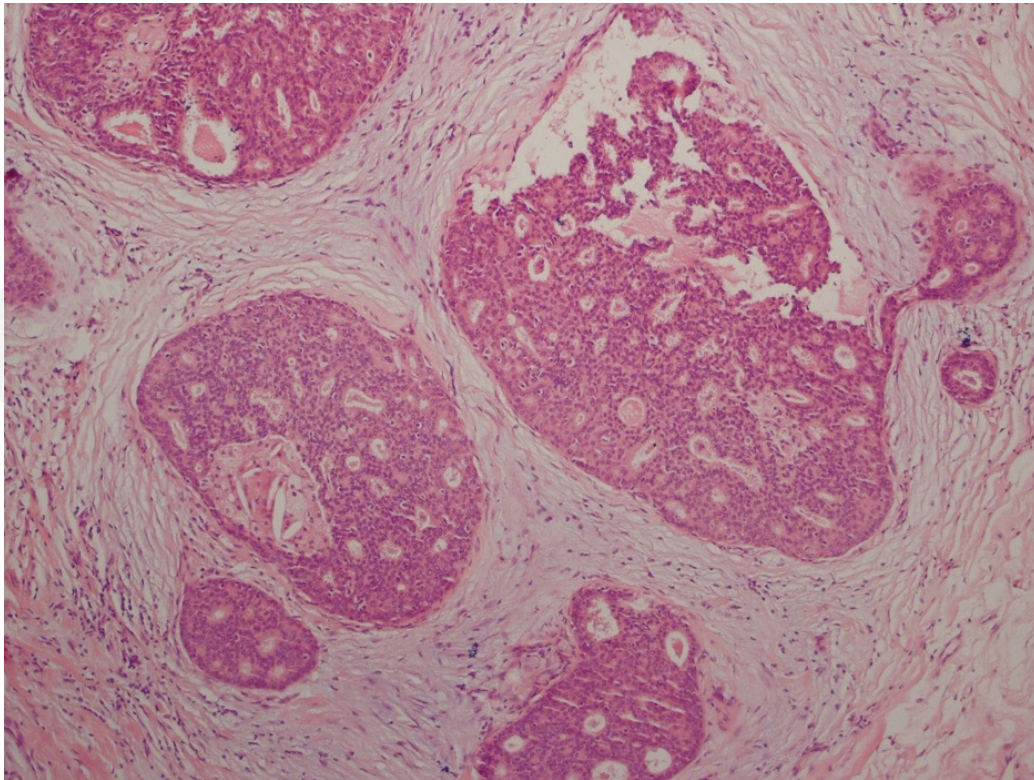
Figure 9. Ductal carcinoma in situ of cribriform type. The ducts are filled by cells forming round spaces, so called cribriform pattern, H & E, x100.

8.6. Micropapillary *in situ* carcinoma

Micropapillary in situ carcinoma is defined by intraluminal epithelial papillary projections. In contrast to papillary carcinoma, fibrovascular stroma is absent.

Pure micropapillary in situ carcinoma is significantly associated with foci of microinvasion and multicentricity (4, 5, 25).

8.7. Clinging *in situ* carcinoma

Clinging in situ carcinoma is a type of intraductal carcinoma in which one to two layer of malignant cells lined the ducts periphery (4, 5).

All types of in situ carcinomas have potential to transform into invasive carcinoma. It has been stated that the risk of subsequent invasive carcinoma development is related to cytologic grade of tumor (5, 21, 22).

8.8. Lobular carcinoma *in situ* (LCIS)

Lobular carcinoma in situ characterized by proliferations of neoplastic cells replacing the normal epithelial of breast lobules (4, 5, 26, 27, 28). Microscopically, the lobules are enlarged, filled with uniform, round, small to medium sized cells usually obliterating the lumen (Figure 10 A & B). The cells lost their cohesion. As a general rule the cells are more uniform
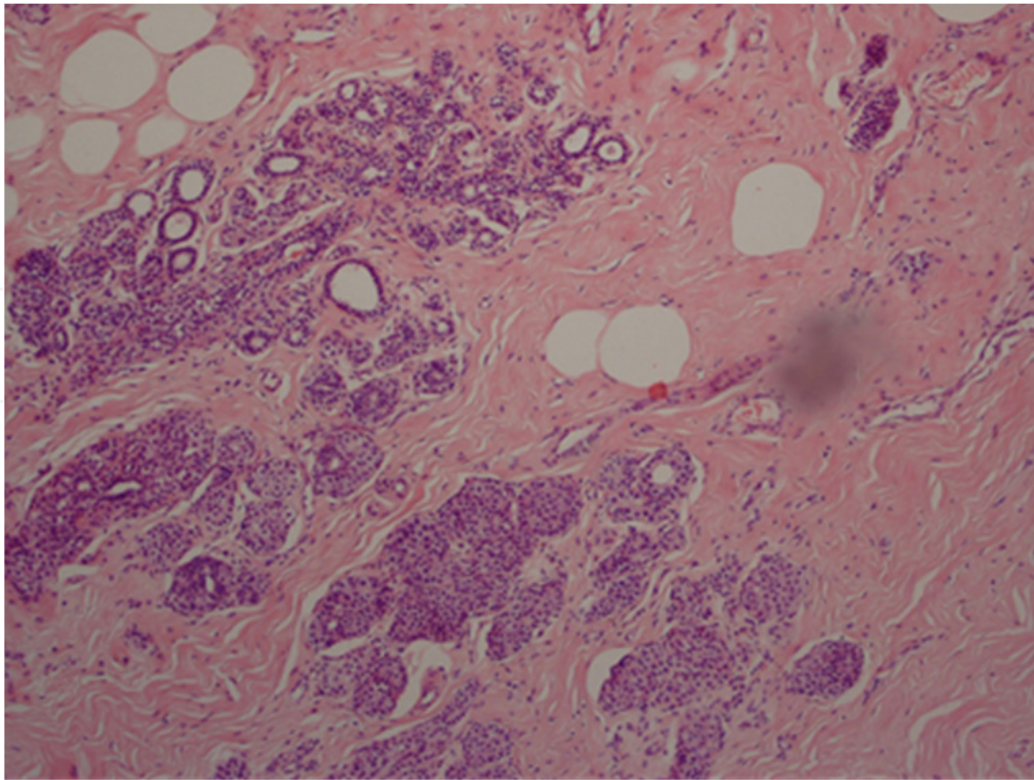
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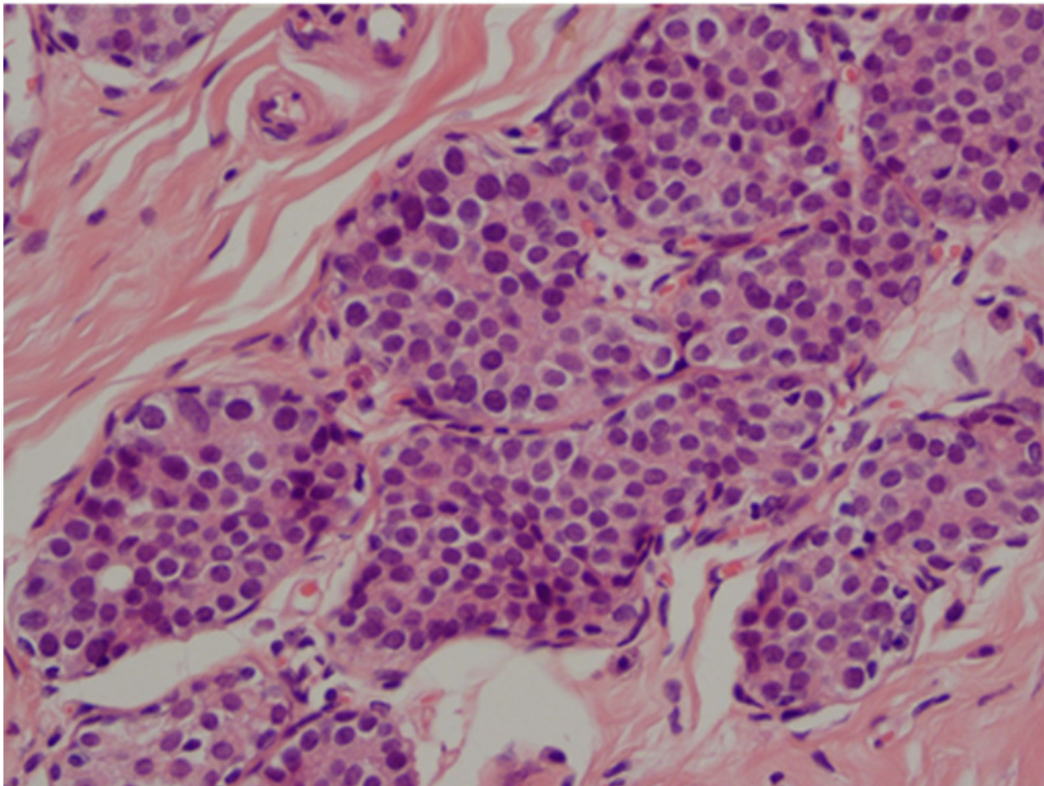
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Figure 10. A & B: Lobular carcinoma *in situ*. The distended lobules obliterated by small and relatively uniform cells, H & E, X100 and X400.

and smaller than cells of DCIS, although cases with pleomorphic and large cells are present which are called " pleomorphic LCIS". So differentiation of this variant of LCIS from solid DCIS is an important task. Positive E-cadherin immune staining in DCIS distinguishes these two lesions (4, 5, 26, 27). Risk of invasive carcinoma development in breast harboring LCIS is significantly increased (4, 5).

8.9. Invasive carcinoma

Tumors, in which stromal invasions by malignant cells are evident, are called invasive carcinomas. Invasive tumors are categorized into two groups: ductal and lobular.

8.10. Invasive ductal carcinoma, Not-otherwise-specified (NOS)

This lesion is the most common malignant tumor of breast, consisting 75% to 80% of breast cancers. Grossly, the tumors are variable in size and consistency; in the prototype ones, the lesions are firm with ill-defined border and ''*chalky streaks*'' appearance on cut sections. Some tumors may have softer consistency with a better-defined border. Microscopically, the tumor cells may grow in sheets, nests, cords or single cell. Glandular formation varies between cases. The cells also show considerable variation, ranging from small cells with relatively uniform nuclei to markedly pleomorphic cells. Mitotic figures are evident and necrosis may occur (Figure 11). Myoepithelial cells are absent. Based on morphology some other subtypes of invasive ductal carcinoma are present (4, 5).
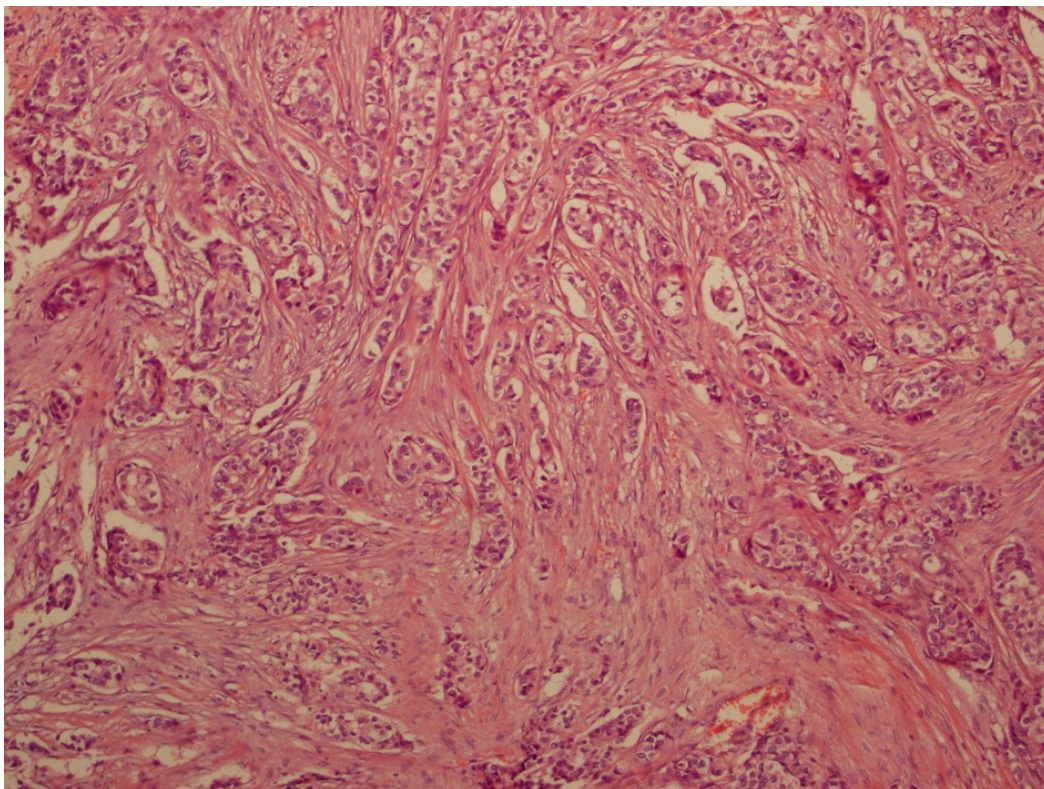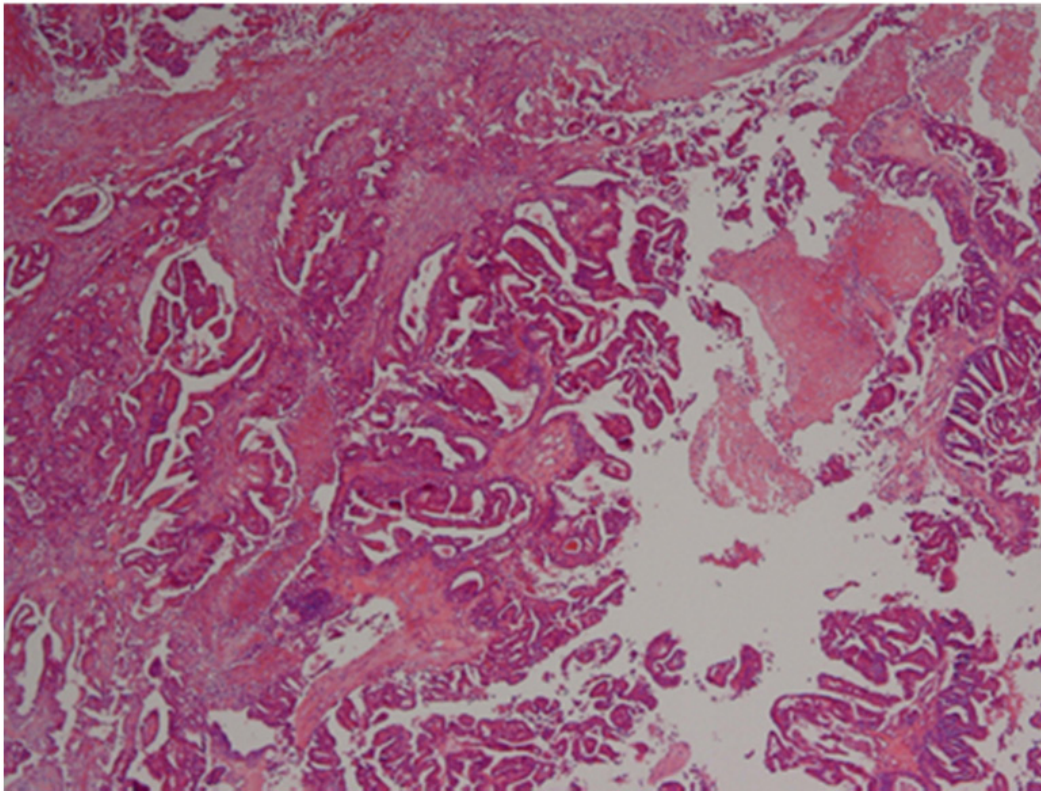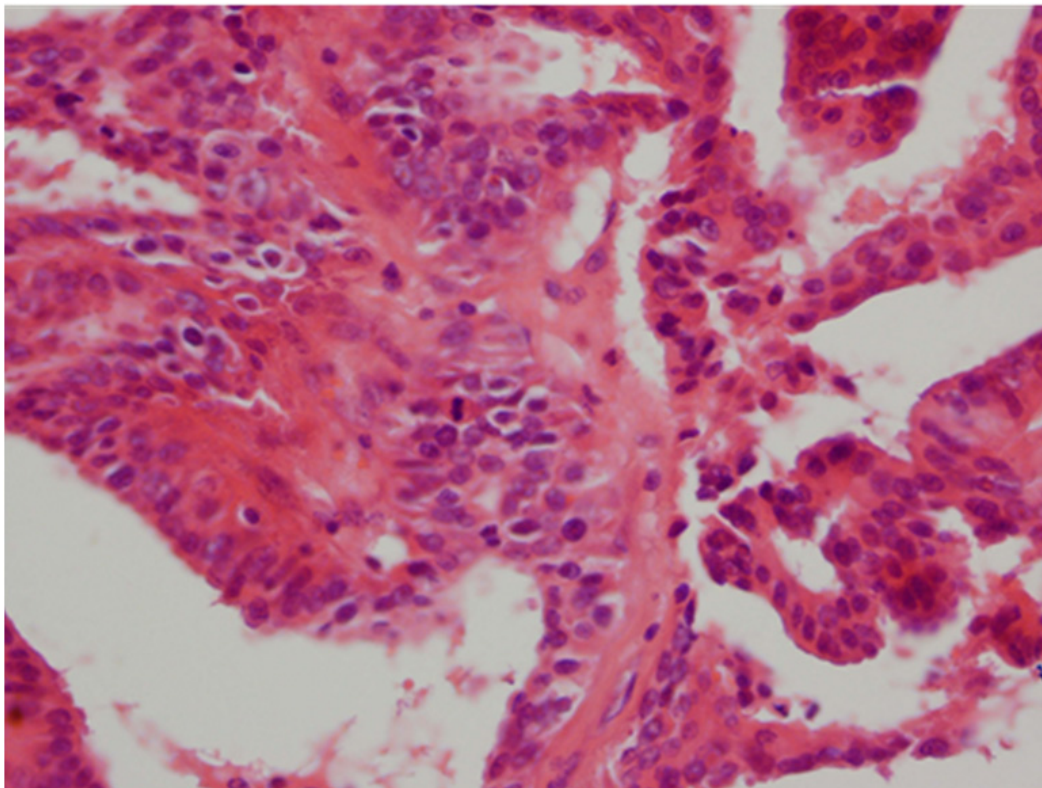

Figure 11. Invasive ductal carcinoma NOS. small nests of tumarl tissue infiltrating the breast stroma, H & E, X100.

(a)

(b)

Figure 12. A & B: Invasive papillary carcinoma. The invasive part of the tumor shows papillary proliferation of atypical cells showing pleomorphism. Mitotic figures are evident, H & E, x40 and x400.

8.11. Tubular carcinoma

The lesion is a distinctive type of breast cancer. Grossly, the lesion is firm with ill-defined border. Microscopically, the tumor composed of small glands or tubules with irregular contours, lacking myoepithelial layer. Basement membrane is also absent (4, 5, 29). This lesion has a better prognosis than invasive ductal carcinoma with lower risk of lymph mode metastasis (4, 5, 30).

8.12. Papillary carcinoma

Papillary carcinoma usually occurs in the central part of breast. Microscopically, the invasive component shows papilla formation, although in some area solid sheet proliferation of tumor cells is seen (Figure 12A & B). Myoepithelial cells are consistently absent (4, 5, 22, 24).

8.13. Medullary carcinoma

Medullary carcinomas are usually occur in young patients and are commonly associated with BRCA-1 mutation. Grossly, the tumor is relatively well circumscribed. Microscopically, the sheets of syncyial poorly differentiated large pleomorphic cells with prominent nucleoli are seen. Mitotic figures are numerous and the tumor border is of pushing type. Infiltration of lympho-plasma cells of the periphery of the tumor is a constant histologic picture (Figure 13). As a general rule gland formation is absent or minimal (4, 5, 31, 32). Prognosis of medullary carcinoma is too better than invasive ductal carcinoma (4).
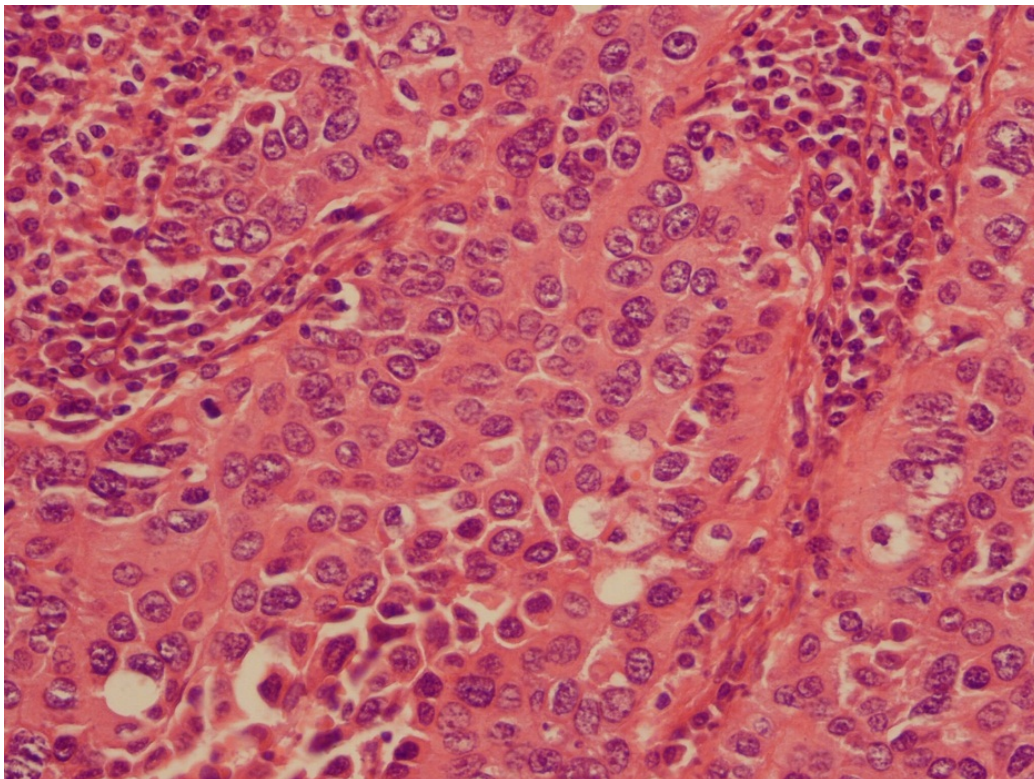

Figure 13. Medullary carcinoma. Sheet of atypical tumor cells infiltrated by lymphoplasma cells, H & E, X400.

8.14. Metaplastic carcinoma

Metaplastic carcinoma is a distinct type of ductal carcinoma in which the predominant growth pattern is nonglandular. The metaplastic change may be squamous or pseudosarcomatous (Figure 14A & B). Heterogeneous element such as bone or cartilage may also be found (4, 5, 33, 34). Metaplastic carcinoma is considered in differential diagnosis of any spindle cell lesions of the breast including primary breast sarcomas and phyllodes tumor. The behavior of metaplastic carcinoma is more aggressive than invasive ductal carcinoma (4).

Squamous cell carcinoma is a form of metaplastic carcinoma. Before establishing the diagnosis of primary squamous cell carcinoma, metastasis from extra mammary sites must be ruled out. Microscopically, this tumor is similar to squamous cell carcinoma of the other body organs in which keratinization may be evident (4, 5, 35).

8.15. Mucinous carcinoma:

Mucinous carcinoma also known as colloid carcinoma is a form of invasive ductal carcinoma, in which clusters of tumor cells floating in extracellular mucin lakes (Figure 15A & B). Grossly, the tumor is well circumscribed with a gelatinous cut surface. Some mucinous carcinomas may show neuroendocrine differentiation. Based on this observation mucinous carcinomas were categorized into type A and B with or without neuroendocrine differentiation, respectively (4, 5, 36, 37). Mucinous carcinoma has a better prognosis than invasive ductal carcinoma, NOS (4, 5, 36).

8.16. Secretory carcinoma

Secretory carcinoma was thought to occur in pediatric age groups but reported cases of this lesion in adults exist. Grossly, the tumor is well circumscribed and firm. Microscopically, the tumor shows glandular, cystic or papillary pattern. Individual tumor cells may be granular or vacuolated tend to form spaces containing a periodic acid-schiff (PAS) positive secretion. Atypia is minimal and mitotic activity is low (4, 5, 38, 39, 40). The prognosis is good and rate of lymph node metastasis is low (4, 5).

## 8.17. Inflammatory carcinoma

Inflammatory carcinoma is clinically present with edema and redness of the breast skin, resembling mastitis. Microscopically, inflammatory carcinoma is a type of ordinary breast cancer in which dermal lymphatic invasions by tumor is evident (4).

8.18. Paget's disease

Paget is an erythematous, eczema-like lesion of nipple and areola, accompanied by underlying breast carcinoma, which may be in situ or invasive. Microscopically, large cells with clear cytoplasm and atypical nuclei are seen in epidermis (Figure 16A & B). These cells
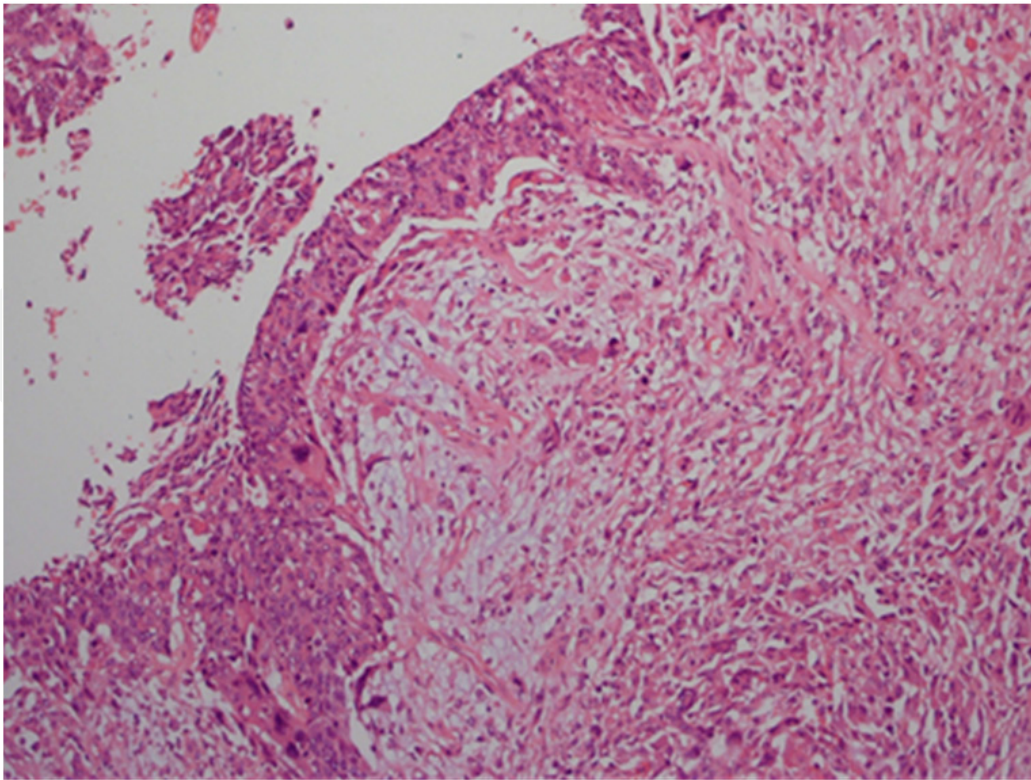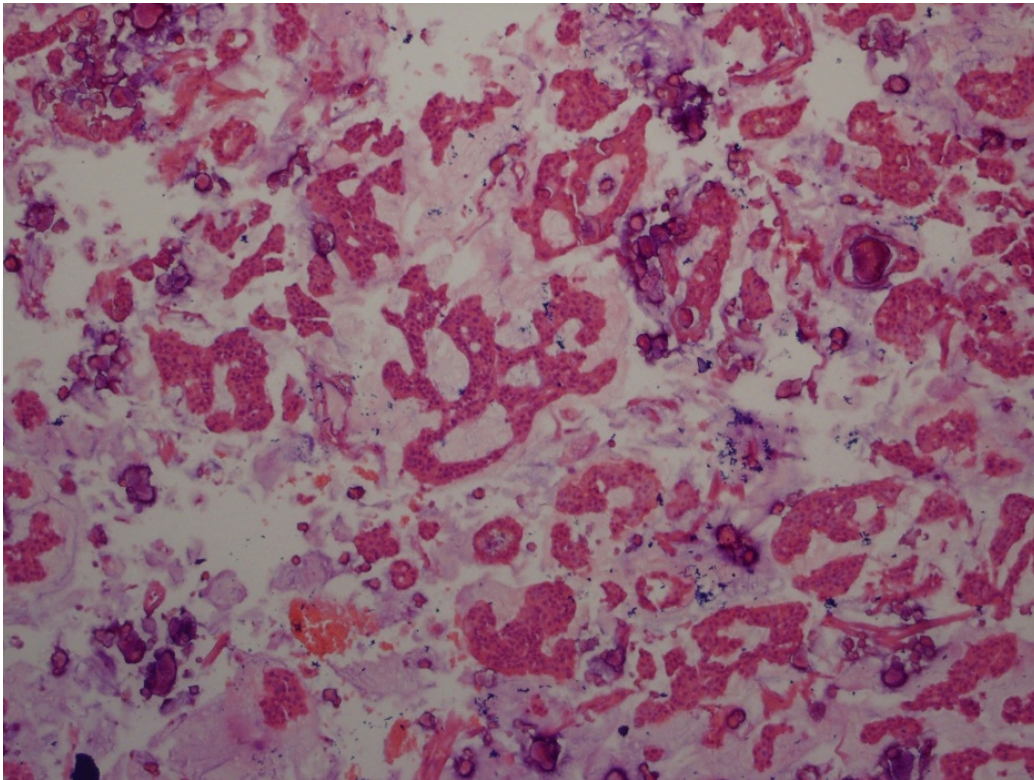
(a)
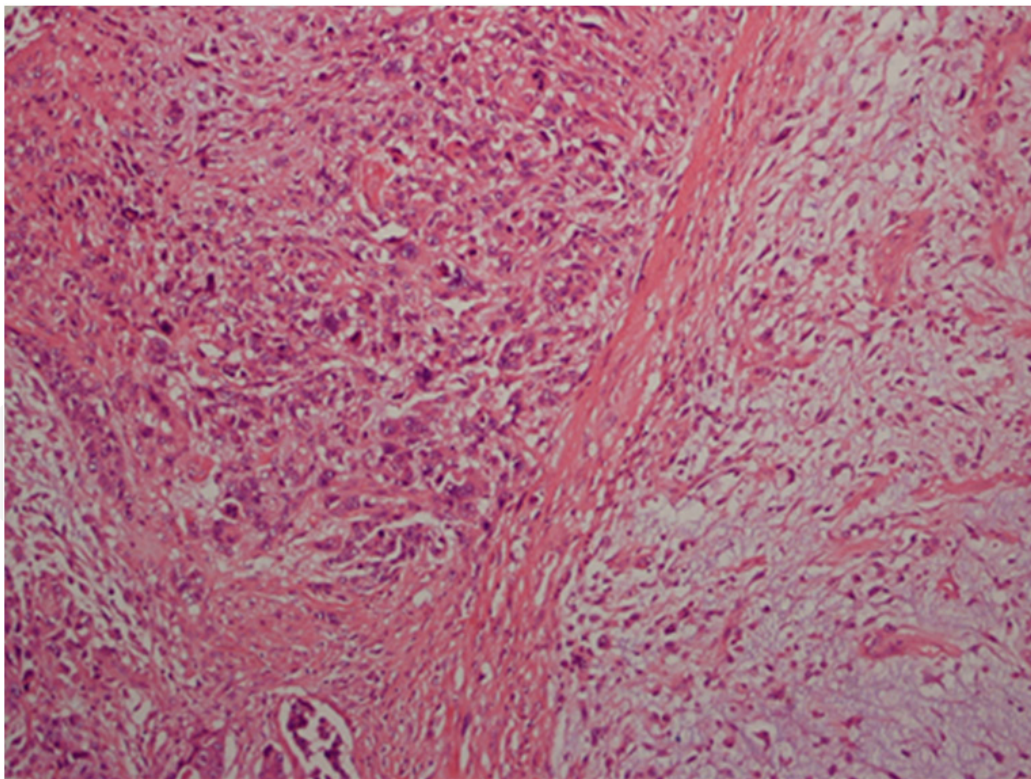
(b)

Figure 14. A & B: metaplastic carcinoma. The tumor composed of sarcomatous component (right side) and carcinomatous compnent (left side), so called carcinosarcoma, H & E, X100.
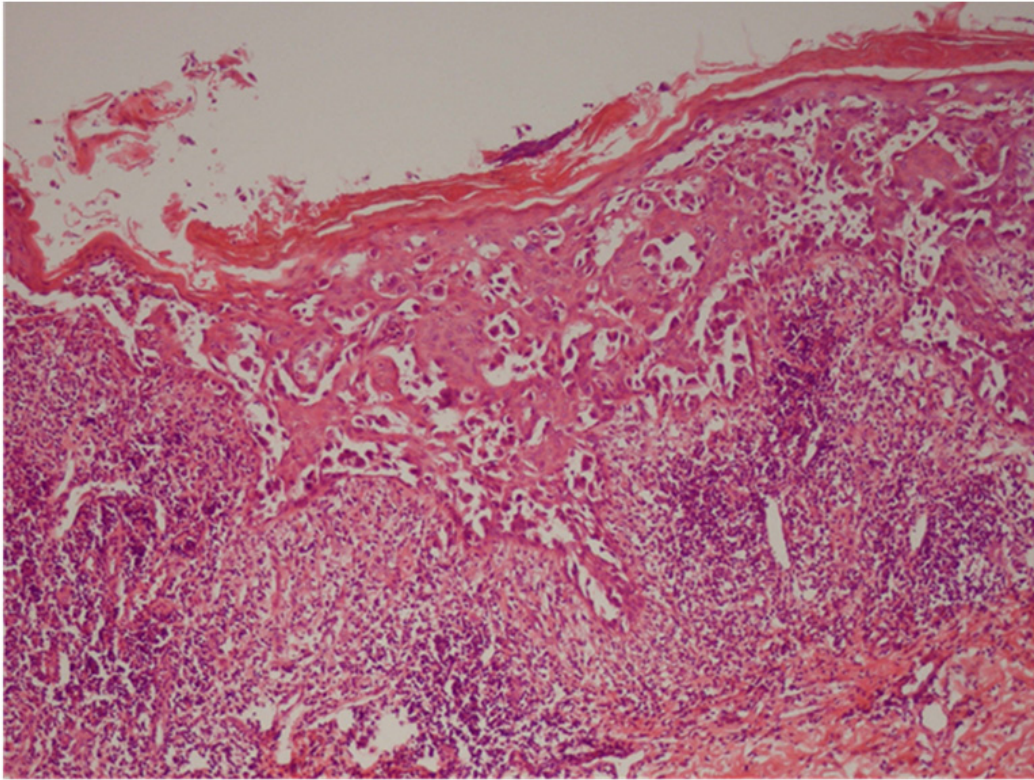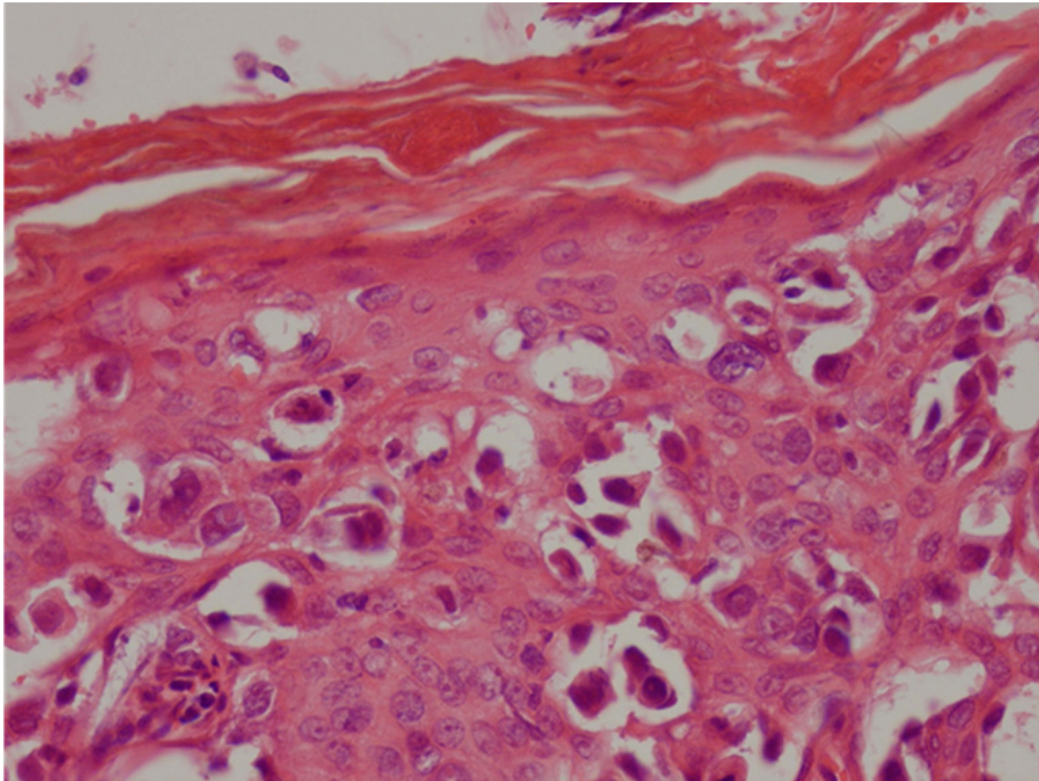
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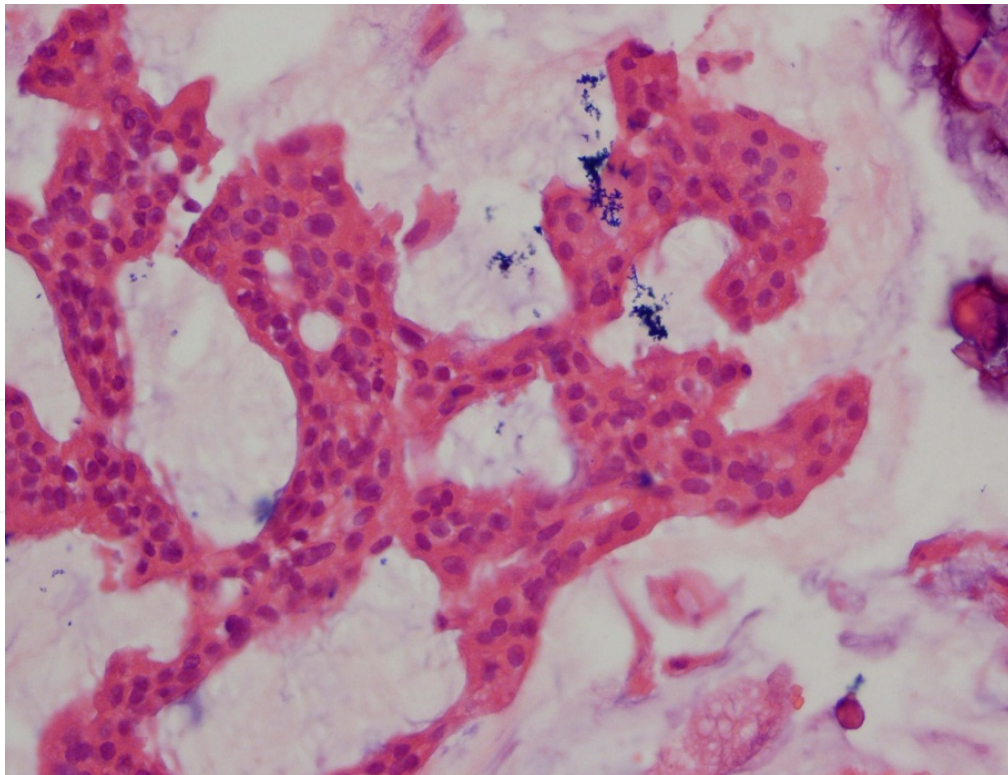
(b)

Figure 15. A & B: mucinous carcinoma. The tumor nests are floating in mucin lakes, H & E, X40 and X400.

(a)

(b)

Figure 16. A & B: Paget's disease. The atypical cells with clear cytoplasm are infiltrating the epidermis, H & E, X100 and X400.

may be isolated or appeared in clusters especially in basal layer of epidermis (4, 5, 41, 42). Important differential diagnosis is malignant melanoma. Immunohistochemistry is of great help to reach a correct diagnosis. Paget's cells are immune reactive for EMA, CEA, CK-7, HER-2/neu and GCPFP-15 but S100 is negative (4).

The other rare types of invasive ductal carcinoma are apocrine carcinoma, carcinoma with neuroendocrine differentiation and cribriform carcinoma.

8.19. Invasive lobular carcinoma

Invasive lobular carcinoma is characterized by infiltration of discohesive small, monotonous tumor cells grow in Indian file or singly (Figure 17). Concentric arrangement of tumor cells around lobules is seen (4, 5, 28, 43). Discohesion of cells is due to loss of E-cadherin. For purpose of differentiating these tumors from invasive ductal carcinoma, an attention to cytomorphology and immunohistochemistry is helpful. In general, cells of lobular carcinomas are smaller, more uniform and discohesive. Other morphologic variants of invasive lobular carcinoma exist (4, 5). Pleomorphic lobular carcinoma shows larger tumor cells with nuclear pleomorphism. Pattern of growth and loss of E-cadherin points to lobular nature of the lesion (4, 5).
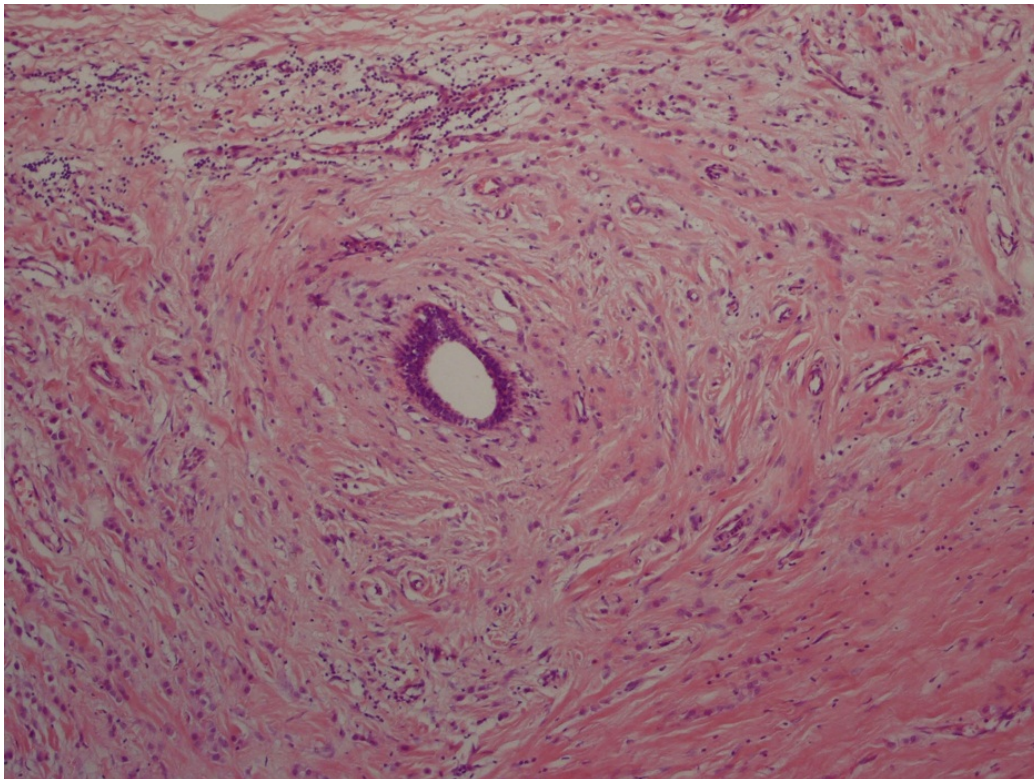

Figure 17. Invasive lobular carcinoama. The small tumoral cells infiltrating the stroma in indian file fashion concentrating around uninvolved duct, H & E, X100.

Other types of lobular carcinoma exist.

Histiocytic carcinoma is a type of lobular carcinoma in which tumor cells showing abundant foamy cytoplasm and apocrine differentiations. In signet ring carcinoma, accumulation of intracytoplasmic mucin pushes the nuclei to the periphery of cells (4, 5).

Tubulolobular carcinoma is characterized by small tubular formation in a tumor with typical appearance of lobular carcinoma. Immunohistochemical profile is intermediate between ductal and lobular carcinoma (4, 5).

8.20. Phylloides tumor

Phylloides tumor or cystosarcoma phylloides is a biphasic neoplasm usually affecting middle age woman. Grossly the tumor is firm, round and well circumscribed. Some cleft-like spaces may be evident on cut sections (4, 5).

Microscopically, the tumor is composed of epithelial and stromal components. Epithelial part is made of slit-like double layered ducts, surrounded by hypercellular stroma. The stromal hypercellularity and overgrowth distinguishes the phylloides tumor from fibroadenoma (Figure 18) (4, 5, 44, 45, 46, 47). Based on cytomorphology of stroma, mitotic count and status of margins, phyllodes tumor has been divided into three grades: benign, borderline and malignant.
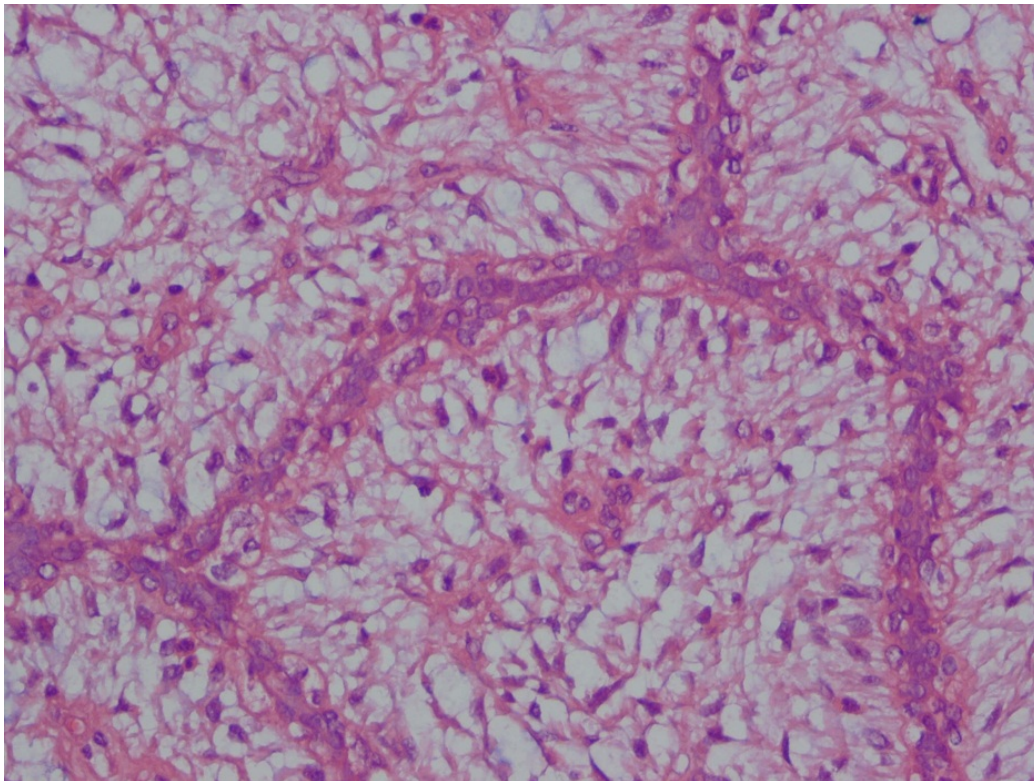

Figure 18. Phyllodes tumor. The biphasic tumor shows stromal hypercellularity surrounding the slit-like epithelial component, H & E, X400.

Benign phylloides tumor is characterized by less than two mitosis per ten high power field (HPF). The stroma is cellular with mild to moderate degree of cytologic atypia. The tumor border tends to be well defined.

Borderline lesions may have circumscribed or infiltrative margin. The stroma is hypercellular containing two to five mitosis per ten HPF (4).

Malignant phylloides shows marked degree of stromal hypercellularity and overgrowth. The border is usually invasive and mitotic count is more than five per ten HPF (4). Mitotic figure cut offs are different in various studies (44, 45, 46, 47).

Epithelial abnormalities ranging from hyperplasia to in situ carcinoma or rarely invasive carcinoma has been reported in phylloides tumor (4, 5).

Benign phylloides tumor has the potential for local recurrence but distant metastasis is a rare event in contrast to malignant phylloides tumor in which has the capacity for distant metastasis (5).

9. Conclusion

Histopathology plays an important role in management of breast diseases. It is a necessary component of diagnosis, treatment and prognosis in most breast disorders. When evaluating a breast lesion suspicious to malignancy pathologic assessment is a major consideration, because it not only differentiates the in situ lesions from invasive ones, but determines the grade and type of disease. An important step in evaluating a breast cancer is to test a portion of the cancer removed during the biopsy (or surgery) to see if they have estrogen and progesterone receptors; also All newly diagnosed breast cancers should be tested for HER2/neu because HER2-positive cancers are much more likely to benefit from treatment with drugs that target the HER2/neu protein, such as trastuzumab (Herceptin) and lapatinib (Tykerb). Fine needle aspiration or core needle biopsy versus surgical biopsy has remained a challenge in breast lesions suspicious to malignancy. Sampling of nonpalpable or indistinct breast lesions can be done using stereotactic breast needle biopsy, a technique that enable the spatial localization of the lesion within the breast.

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