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Benign breast disorders: An insight with a detailed literature review

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Abstract

The term Benign Breast Disorders can be defined as any non malignant breast condition and includes a wide range of clinical and pathological entities. A clear understanding of BBDs is needed to provide appropriate counseling for the affected individuals, initiate treatment and avoid unnecessary anxiety and follow up.

This review aims to

- Provide comprehensive and concise account of BBDs.
- Highlight the current concepts regarding the pathogenesis of BBDs.
- Describe the accepted treatments for common BBDs.

Abbreviations

BBD – Benign Breast Disorder, ANDI – Aberrations in Normal Development and Involution.

Introduction

The vast majority of lesions that occur in the breast are benign. However they have less cared for as compared to their malignant counterparts. With increasing use of mammography, the chances of detection of asymptomatic accidental lesions have increased. Symptomatic lesions can cause considerable suffering to the affected individual. The affected individual suffers not just by the trouble symptoms like pain and nipple discharge but has to cope up with the fear of malignancy. Thus there is a need to accurately diagnose the BBDs, stratify the risk of malignancy and instill appropriate treatment.

Article Proper

BREAST DEVELOPMENT, CYCLICAL CHANGE AND INVOLUTION

The functional unit of the breast is called “the lobule”. The lobule has epithelial (ductal) and stromal components, which when acted upon by hormones such as estrogen, progesterone and prolactin undergoes development, maturation and differentiation (1, 2).The interaction between the hormones and the epithelial and stromal components of the lobule are responsible for many BBDs. The breast undergoes significant changes between adolescence and menopause (3). The lobules develop primarily between 15 to 25 years of age. The lobules in early reproductive years tend to be immature. They are subsequently replaced by more mature lobules particularly during pregnancy.

The lobules display changes with each menstrual cycle. A peak of mitosis can be observed in the late cycle followed by apoptosis (4). These changes provide a continuing opportunity for stromal or ductal components to deviate from their normal characters. Over time these deviations from normalcy produce marked differences in the structure and appearance of breast, which are described as ‘fibrosis’ or ‘adenosis’ in histopathology. It is noteworthy that such changes can even be observed in breasts of individuals without any clinical complaint or finding.

Involutional changes in the breast are apparent by 35 yrs of age. Thus cyclical and involutional changes can be simultaneously present for about 30 years. Involution affects both stromal and epithelial components of lobule. Loose hormone receptive connective tissue in the stroma is replaced by denser connective tissue. Involution of epithelial component results in gradual disappearance of the ductal elements. By menopause, involution will be extensive sparing very few ductal and lobular structures. Epithelial involution of the lobule is dependent on the continuing presence of surrounding specialized stroma.

Aberrations are common even in the involutional phase. Early stromal involution results in the formation of microcysts from the remaining epithelial acini. Obstruction of the draining ductule facilitates progression of microcysts to macrocysts. Microcyst formation is quite common and can be present in healthy breasts as well (5).

NOMENCLATURE

A flurry of terms has been used to describe the benign breast conditions. Most of these terminologies emphasize on one or the other sign, symptom or histological finding. Some of the common terms used

are, fibro cystic disease (FCD) (6), fibrocystic changes (FCC) (7) and benign breast disorders (BBD). In this review we have consistently used the term Benign Breast Disorder (BBD), as it is a broad term which encompasses all the entities except carcinoma. Also by using the term BBD, we have avoided the controversy of FCD versus FCC.

CLASSIFICATION

BBDs can be classified in the following ways.

1. Aberrations of Normal Development and Involution.
2. Pathological classification.
3. Clinical classification.
4. Classification based on the risk for malignancy.

Aberrations of Normal Development and Involution (ANDI)

The principles based on which BBDs are classified in ANDI are (8),

- BBDs are related to normal processes of reproductive life and involution.
- There is a spectrum of breast conditions that range from “normal” to “disorder” to “disease”.
- The ANDI classification encompasses all aspects of the breast condition, including the symptoms, signs, histology, physiology, pathogenesis and degree of abnormality.

The ANDI system of classification can be conveniently tabulated as shown in Table 1. (9). The horizontal component of the table defines ANDI along a spectrum from normal to mild abnormality (disorder) to severe abnormality (disease). The vertical component defines the period during which the condition develops.

The ANDI classification was accepted and recommended by an international multidisciplinary working group in 1992. (10).

PATHOLOGIC CLASSIFICATION SYSTEM OF BENIGN BREAST DISORDERS *(8)*

NON PROLIFERATIVE LESIONS OF THE BREAST

- Cysts and apocrine metaplasia.
- Duct ectasia.
- Mild ductal epithelial hyperplasia.
- Calcifications
- Fibroadenoma and related lesions

PROLIFERATIVE BREAST DISORDERS WITHOUT ATYPIA

- Sclerosing adenosis.
- Radial and complexing sclerosing lesions.
- Florid ductal epithelial hyperplasia.
- Intraductal papillomas.

ATYPICAL PROLIFERATIVE LESIONS

- Atypical lobular hyperplasia (ALH).
- Atypical ductal hyperplasia (ADH).

CLASSIFICATION OF BENIGN BREAST DISEASE BASED ON CLINICAL FEATURES *(8)*

- Physiologic swelling and tenderness.
- Nodularity.
- Mastalgia (breast pain).
- Dominant lumps

  -Gross cysts

  -Galactocele

  -Fibroadenoma

- Nipple discharge

  -Galactorrhoea

  -Abnormal nipple discharge

- Breast infections

1. Intrinsic mastitis

   -post partum engorgement

   -lactational mastitis

   -lactational breast abscess

1. Chronic recurrent sub areolar mastitis
2. Acute mastitis associated with macrocystic breasts
3. Extrinsic infections

CLASSIFICATION OF BBD BASED ON THE RISK FOR MALIGNANCY

The importance of BBDs lies in their risk for malignant transformation. Thus it would be practical to have a classification system for BBDs which takes into consideration the risk of malignant transformation. One such classification system (11) is as follows.

ABERRATIONS IN NORMAL DEVELOPMENT AND INVOLUTION

DISORDERS OF DEVELOPMENT

Fibroadenoma

Fibroadenoma is due to aberration in normal lobular development. It is commonly seen in 15-25 years age group. Parks demonstrated that hyperplastic lobules histologically resembling fibroadenomas can be found virtually all breasts **(5).** All the cellular elements of fibroadenomas are normal on conventional and electron microscopy and the epithelium and

myoepithelium maintain a normal relationship. (12). Fibroadenomas usually grow to the size of 1 or 2 cms and then remain constant in size. They show hormonal dependence similar to that of normal lobules. They lactate during pregnancy and involute to be replaced by hyaline connective tissue in the perimenopausal period. A fibroadenoma is usually less than 3 cms in size. Very rarely a fibroadenoma can attain a size of 5 cms or more when it is termed giant fibroadenoma. Equally rare are multiple fibroadenomas, a term employed when more than 5 fibroadenomas are found in the same breast. Fibroadenomas fit well in ANDI system. Small fibroadenomas are normal, fibroadenomas between 1-3 cms in size are considered as disorder and giant/ multiple fibroadenomas fit in the disease end of the spectrum.

Adolescent Hypertrophy

Adolescent hypertrophy is due to gross stromal hyperplasia occurring during thelarche. Even though a precise cause is not described, a hormonal etiology is quoted as the probable cause. Adolescent hypertrophy is considered as a disorder, while gigantomastia, the extremity of the spectrum is considered as a disease, thereby qualifying the entity into ANDI.

DISORDERS OF CYCLICAL CHANG

A certain degree of premenstrual enlargement of the breast is a normal phenomenon. This is usually followed by postmenstrual involution. However, pronounced cyclical mastalgia with nodularity persisting for more than a week is considered as a disorder (8). When the symptoms become severe and distressing thereby affecting the daily activities, the condition is termed “incapacitating mastalgia” which is considered as a disease entity. The cause for cyclical mastalgia, nodularity and incapacitating mastalgia is excess prolactin release from the pituitary following stimulation of hypothalamic-pituitary axis (13).

DISORDERS OF INVOLUTION

Cyst formation: The exact mechanism of involution is not well understood, but it appears that involution of lobular epithelium is dependent on specialized stroma around it (14). Normally, involution of breast is characterized by synchronous involution of stromal and lobular epithelium. However such synchronicity is not always seen. Early involution of stroma as compared to lobular epithelium results in microcyst formation. Microcysts progress to macrocysts if there is an obstruction to the draining ductule. Since the macrocysts are frequently found even in asymptomatic and clinically normal breasts, they are considered as a disorder rather than a disease.

Sclerosing adenosis: Sclerosing adenosis can be considered as a disorder of either proliferative phase or involutional phase or both. This is because the histological changes in sclerosing adenosis can be both proliferative and involutional in nature. The detailed histological description is provided else where in this article.

Duct ectasia and periductal mastitis: Periductal fibrosis represents a part of normal involutional process of the breast (15). Duct ectasia and periductal mastitis thus represent the disorders of involution. The pathogenesis of these entities has been explained by two theories. Haagensen (16) suggested that the primary event in the pathogenesis of duct ectasia-periductal mastitis complex is dilation of the ducts which results in stagnation of the secretions, epithelial ulceration and extravasation of the secretions. This results in a local inflammatory process and fibrosis. An alternative theory suggests that the primary event is periductal mastitis which leads to weakening of ducts and secondary dilation. The spectrum of features seen in this condition includes nipple discharge, nipple retraction, inflammatory masses and abscesses.

Epithelial hyperplasia: Parks showed that lobular and ductal papillary hyperplasia is common in the premenopausal period and tends to regress spontaneously after menopause (5). However Page and colleagues (17) and Wellings, Jensen and Marcum (18) have shown that the other end of the spectrum i.e. atypical lobular hyperplasia and atypical ductal hyperplasia are associated with malignancy. There is insufficient evidence to determine whether these conditions represent a continuous spectrum.

PATHOLOGY OF BENIGN BREAST DISORDERS

Pathologically, benign breast disorders can be classified as non-proliferative lesions and proliferative lesions. The proliferative lesions associated with or without atypical changes.

NON-PROLIFERATIVE LESIONS OF THE BREAST

Non-proliferative lesions account for benign lesions of the breast (8). Cysts and apocrine metaplasia, duct ectasia, mild ductal hyperplasia, calcifications, fibroadenomas and related lesions are included in this category.

Cysts and apocrine metaplasia: Cysts are fluid filled epithelialized spaces (19) (20). They are mostly multifocal, bilateral and almost never malignant (21, 22). Cysts originate from the terminal duct lobular unit or from an obstructed ectatic duct. They may contain fluid of variable color like green or gray or brown. The epithelial lining the cyst is often flattened. There could be occasional apocrine metaplasia. The surrounding

stroma is generally fibrotic and contains lymphocytes, plasma cells and histiocytes.

Duct ectasia: Duct ectasia involves the large and intermediate ductules of the breast (14). This condition is characterized by the presence of dilated ducts filled with desquamated ductal epithelium and proteinaceous secretions. Periductal inflammation is the characteristic histological feature of this condition. There is no demonstrated relationship between duct ectasia and breast cancer (23) (16).

Mild ductal epithelial hyperplasia: Normally two layers of cells are present over the basement membrane of ductal system. Epithelial hyperplasia is defined by the presence of three or more cell layers over the basement membrane (17) (24). Epithelial hyperplasia should be differentiated from adenosis. Adenosis is characterized by increase in the glandular cells relative to the basement membrane. Epithelial hyperplasia could be mild, moderate or florid. Florid epithelial hyperplasia carries an increased risk for breast cancer (17) (25)

Calcifications: Calcium deposits are frequently encountered in the breast. Most are benign and are caused by cellular secretions and debris or by trauma and inflammation. Benign calcifications should be differentiated from calcifications associated with breast cancer. Calcifications associated with breast cancer usually small, linear calcifications with branching.

Fibroadenomas: Fibroadenomas are benign tumors composed of fibrous and epithelial elements (26). They are well-circumscribed spherical lesions which may be unilocular or multilocular. The cut surface is white or yellow and on gross examination a fibroadenomas is pseudoencapsulated and sharply delineated from the surrounding normal breast tissue. Microscopically fibroadenomas have both epithelial and stromal components. Fibroadenomas have a doubling time of approximately one year and usually cease growing once they attain a diameter of around 3 cms (8). Other less common non-proliferative lesions of breast include adenoma, hamartoma and adenolipoma.

PROLIFERATIVE BREAST LESIONS WITHOUT ATYPIA

Proliferative breast disorders without atypia include sclerosing adenosis, intraductal papillomas and florid epithelial hyperplasia (27).

Sclerosing adenosis: Sclerosing adenosis is characterized by proliferation of the glandular and stromal elements resulting in enlargement and distortion of lobular units (28) (29). Microscopic characters of sclerosing adenosis include,

- Maintenance of lobular architecture.
- Maintenance of normal two cell population along the basement membrane.
- Increased number of acinar structures.
- Fibrosis of the lobular stroma.

Sclerosing adenosis can be associated with multiple microscopic cysts and diffuse microcalcifications (30) (31). The clinical significance of sclerosing adenosis is its resemblance to cancer (31). However it has no proven premalignant implications. Excisional biopsy and histological study of these lesions become necessary to exclude the diagnosis of malignancy.

Radial scars and Complex sclerosing lesions: Radial scars and complex sclerosing lesions of the breast are characterized by central sclerosis and varying degrees of epithelial proliferation, apocrine metaplasia and papilloma formation (32). The histological features of radial scar radiate from a central white area of fibrosis, which contains elastic elements. The term radial scar is reserved for smaller lesions up to 1cm in diameter while complex sclerosing lesion is the term used to describe larger masses. Radial scars originate at the point of terminal duct branching (33). Complex sclerosing closely resemble radial scar but on a larger scale.

Florid ductal epithelial hyperplasia: It is the most common proliferative lesion of the breast (17).

Intraductal papillomas: This entity is characterized by an increase in cell number within the ducts. Florid hyperplasia consists of a proliferation of cells that occupy at least 70% of the duct lumen (8). Epithelial hyperplasia is either solid or papillary and is characterized by intracellular spaces that are irregular, slit like and variably shaped. Intraductal papillomas can be solitary or multiple. Solitary Intraductal papillomas are common among premenopausal women. They are usually small (< 0.5 cm). They are pinkish, tan friable lesions usually attached to the wall of the involved duct by a stalk. Microscopically these lesions are composed of multiple, branching papillae with a central fibrous vascular core, which is lined by a layer of epithelial cells. Multiple Intraductal papillomas tend to occur among younger patients. They are often peripheral and can be bilateral. Solitary Intraductal papillomas rarely undergo malignant transformation. On the contrary, multiple Intraductal papillomas are more likely to undergo malignant transformation (8).

ATYPICAL PROLIFERATIVE LESIONS

They can be ductal or lobular lesions. They share a few common features with carcinoma in situ.

Atypical lobular hyperplasia: This lesion is characterized by the presence of round cells with

lightly stained eosinophilic cytoplasm. The uniformity and roundness of the cell population is pathognomonic of atypical lobular hyperplasia. The lobular unit is less than half filled with these cells and the architecture of the lobular unit is preserved (17). The histology of atypical lobular hyperplasia can mimic lobular carcinoma in situ. The spectrum of disease ranging from atypical lobular hyperplasia to lobular carcinoma in situ was termed lobular neoplasia by Haagensen and colleagues (34). The role of subsequent invasive cancer in women with atypical lobular hyperplasia is four times that of general population (35).

Atypical ductal hyperplasia: Atypical ductal hyperplasia is diagnosed when atypia is present and either cytological or architectural criteria for ductal carcinoma in situ (DCIS) are absent. Following are the criteria suggested (36) for the diagnosis of DCIS;

- A uniform population of cells.
- Smooth geometric spaces between cells or micro papillary formation with uniform cellular placement.
- Hyperchromatic nuclei.

Women with atypical ductal hyperplasia have about four times increased risk for breast cancer as compared with general population.

INFLAMMATORY AND RELATED BENIGN BREAST LESIONS

A variety of inflammatory and reactive lesions can be seen in the breast. Inflammation of the breast is called mastitis. Mastitis can be,

- Due to infectious etiology.
- Idiopathic.

Breast infections can be classified as (37),

- Intrinsic breast infections / intrinsic mastitis – which are secondary to abnormalities in breast architecture or function.
- Extrinsic breast infections / extrinsic mastitis – which are secondary to infection in an adjacent organ or structure that involves the breast.

Most breast infections are intrinsic infections. Intrinsic breast infections include,

Acute mastitis (Syn. Puerperal mastitis, Lactational mastitis): Acute mastitis usually occurs during the first three months of post partal phase as a result of breast feeding. This disorder is essentially cellulites of the interlobular connective tissue within the mammary gland, which when left untreated can progress to abscess and sepsis. Factors predisposing to lactational mastitis include,

- Improper nursing technique leading to milk stasis.
- Cracks or fissures in the nipple – which facilitate the entry of micro organisms.
- Stress and sleep deprivation which lowers the immune status and inhibits the milk flow (38,39)

Because of the risk of abscess formation early diagnosis and treatment is of paramount importance (40). Since lactation mastitis is a process of subcutaneous cellulites, detection of pathogens in breast milk may not always be possible. Hence antibiotics should be started empirically. Breast emptying with frequent manual pumping is another essential component of management. When puerperal mastitis associated abscess occurs, incision and drainage of the abscess is recommended. Alternatively ultrasound guided aspiration of the abscess can be done with excellent cosmetic results (40).

Granulomatous mastitis: Granulomatous mastitis can result from

- Infectious etiology – tuberculous mastitis.
- Foreign body – silicone.
- Systemic auto immune diseases – sarcoidosis, Wegener's granulomatosis.

Tuberculous mastitis: Tuberculosis of the breast is a very rare disease. Clinical and radiological features of tuberculous mastitis are not diagnostic. And can easily be confused with mastitis or pyogenic breast abscess. Definitive diagnosis of the disease is based on identification of typical histological feature of caseating granulomas with chronic inflammatory cells under microscopy or detection of tubercle bacilli with mycobacterial culture (41).

Idiopathic granulomatous mastitis: This term is used for the granulomatous lesions of the breast without an identifiable cause. The diagnosis is arrived at after excluding all possible causes of granulomatous lesions. The etiology of the condition remains largely unknown (42). A localized auto immune response to retained and extravasated fat and protein rich secretions in the duct has been suggested as the probable etiology. Idiopathic granulomatous mastitis is histologically characterized by chronic non caseating granulomatous inflammation which is typically limited to lobules of the breast. The recommended therapy for idiopathic granulomatous mastitis is complete surgical excision whenever possible with steroid therapy. However even after appropriate treatment, persistence, recurrence and complications such as abscess formation, fistulae and chronic suppuration are seen in up to 50% of cases, thereby emphasizing the need for long term follow up (42,43) .

Foreign body reactions: Foreign materials such as silicone which are used for breast reconstruction may evoke a foreign body type granulomatous reaction in the breast. Silicone granulomas or siliconomas normally occur after direct injection of silicone into breast or following rupture of an implant (44).

Recurring subareolar abscess: Recurring subareolar abscess is a rare bacterial infection of the breast that is characterized by a triad of (45)

- Draining cutaneous fistulae from the sub areolar tissue.
- A chronic thick pasty discharge from the nipple.
- A history of multiple recurrent mammary abscess.

The disease is caused by squamous metaplasia of one or more lactiferous ducts in their passage through the nipple, probably induced by smoking (46). The ducts get obstructed by keratin plugs, which results in dilation of the proximal duct. Eventually there will be infection and rupture of the duct with abscess formation beneath the nipple. This abscess typically drains in the margin of the areola (45, 46). Treatment in the form of abscess drainage to facilitate resolution of the acute inflammation followed by complete excision of the affected duct and sinus tract is successful in most cases. But the condition may recur due to disease process developing in another duct (45, 47)

BENIGN BREAST DISEASE AND THE RISK OF BREAST CANCER

An increase in the number of mammographies in the recent times has increased the frequency of asymptomatic breast lesions and breast biopsies. Benign breast diseases are the most common entities discovered by such breast biopsies. Hence understanding the risk associated with BBD is important in appropriate treatment and counseling of the patient. Many studies have shown that women with BBD are at increased risk for breast cancer (25, 48, 49)**.** Some of risk factors that have been evaluated are as follows:

Histology: The histological appearance of the BBD is strongly is strongly associated with the risk of breast cancer. A classification system for BBDs based on the histological features has also been described (50).

Family history of breast cancer: It has been observed that there is no increased risk of breast cancer for women with non Proliferative BBDs with no family history or weak family history of breast cancer (25, 51)**.** However an NSABP study found a significantly increased risk of breast cancer among women with lower category benign breast disease including non Proliferative disease (52).

Age: The age at the diagnosis of BBD appears to modify the risks related to the histological appearance of BBD. Studies (51) have demonstrated that presence of atypia in women of pre menopausal age conveyed more risk as compared to post menopausal age group (49, 53**)**. However in another study (52) of women with lower category of BBD, the risk of breast cancer was greatest among post menopausal women.

CLINICAL FEATURES OF BBD

The clinical features of BBD can fall into one of the following categories (8)

1. Physiological swelling and tenderness: Tenderness associated with fullness, heaviness, and/or swelling in the breasts in the premenstrual phase of the menstrual cycle is a common symptom among many women. These symptoms are hormone related and they are limited to the reproductive years. Cyclical alterations in the breast structure, contour and size results from variations in the plasma concentrations of gonadotrophic and ovarian hormones (54).

2. Nodularity: Breast nodularity is another common symptom in BBDs. The nodularity could be finely granular or grossly lumpy and it can involve the entire breast or a specific portion. Patey coined the term pseudolump to describe a dominant area of lumpiness that coalesces into the surrounding breast tissue (55, 56). Breast nodularity can be cyclical due to the responsiveness to circulating estrogenic and progestational hormones.

3. Mastalgia: Pain in the region of breast is a common symptom. This pain could be “breast pain” or “non breast pain”. Breast pain could be cyclic or non cyclic. Cyclic breast pain usually occurs during the late luteal phase of the menstrual cycle and resolves with the onset of menses. In a study of 1171 healthy premenopausal American women, 11% had moderate to severe cyclic breast pain and 58% had mild discomfort. Breast pain interfered with usual sexual activity among 48% of patients, and among others it interfered with physical activities (37%), social activities (12%), and school activities (8%) (58, 59). Non cyclical breast pain is unrelated to menstrual cycle. It could be due to causes like, acute enlargement of a cyst, rupture of an ecstatic duct and periductal mastitis. Pain arising from the chest wall can be erroneously attributed to the breast. Causes of such pain include radicular pain from cervical arthritis and pain due to costochondritis.

4. Dominant masses and discreet lumps: Common causes of dominant masses and discreet

lumps include cysts (macro), galactocele and fibroadenomas (14)**.** The dominant breast masses can be cystic or solid. The cystic masses are differentiated from solid masses by needle aspiration. Cystic masses collapse and disappear on needle aspiration while solid lesions don't.

5. Nipple discharge: Nipple discharge can be classified as galactorrhoea or abnormal nipple discharge (24, 37). Galactorrhoea is the spontaneous discharge of milk like fluid as a result of stimulation of breast secondary to elevated prolactin secretion. Abnormal nipple discharge can be bloody or non bloody. The common causes of bloody discharge from the nipple are intraductal papilloma, duct ectasia and cancer. Takeda and colleagues noted that the presence of red blood cells or clusters of more than 30 ductal cells is suggestive of malignancy (60)**.**

6. Breast infections and inflammatory lesions: Mastitis and fat necrosis of the breast are included in this category. Diagnostic clinical features include, pain, local edema, erythema, tenderness and local rise of temperature. Differentiating these conditions from inflammatory carcinoma may be difficult. Mammographic or sonographic evaluation with/without biopsy may be required for such differentiation.

IMAGING OF BBD

The imaging techniques used to evaluate BBDs include

- Mammography.
- Ultrasonography.
- Ductography.

In addition to these imaging modalities Magnetic Resonance Imaging is also being used for evaluating breast lesions, particularly to screen for and evaluate breast cancer (9).

MAMMOGRAPHY

Mammography could be screening mammography or diagnostic mammography. Screening mammography is used to detect unexpected breast cancer in asymptomatic women. Diagnostic mammography is used to evaluate women with abnormal findings such as breast mass or nipple discharge. Xeromammography techniques are identical to those of mammography with the exception that the image is recorded on xerography plate which provides positive rather than a negative image. In xeromammography details of the entire breast and the soft tissues of the chest wall can be recorded with one exposure. It is not always possible to differentiate benign breast lesions from a malignant lesion by mammography. However such an attempt can be made with considerable success by analyzing the following characters of the lesions detected on mammography.

- Outline and shape.
- Radiographic density.
- Change with time.
- Calcification.

Outline and shape: A mass which is well defined has a high probability of being benign. However a few malignancies like medullary, mucoid or invasive ductal carcinoma have been reported to have well defined outlines (61**)**. "Halo sign" – is described as complete or a partial radiolucent ring surrounding the periphery of a breast mass. It is mostly seen in cysts and fibroadenomas.

Radiographic density: A lesion containing material with the density of fat has high probability of being benign.

Change with time: A mammographically detectable mass which changes little in size and shape over several years is most likely to be benign. However there have been reports of carcinomas which have not increased in size over years (62)**.**

CALCIFICATIONS

BBDs display the following patterns of calcifications on mammography.

- **Benign calcified masses:** This type of calcification is seen typically in an involuting fibroadenoma, which appears as dense large calcification within a lobulated mass. Usually the fibroadenomas calcify from the center. However the calcification can also start from periphery. The calcification in fibroadenomas resembles pieces of popcorn. Some fibroadenomas may display small, irregular calcification which is indistinguishable from cancer. Such lesions need biopsy for accurate diagnosis.

- **Benign masses with peripheral calcification:** Masses with peripherally distributed calcification in the wall or on the surface of the mass forming a "rim" or "egg shell" like calcification are almost always benign. Examples for such peripheral "rim" like calcifications include fibroadenomas, cysts and fat necrosis.

- **Calcified intraductal calcifications:** Rarely intra ductal papillomas may calcify. This probably results due to infarction. Such calcifications are characterized by,

  - shell like deposits which are lucent inside.
  - linear orientation along the course of a duct.
  - sausage like delineation.

- **Benign calcifications without associated masses:** Round, hollow spheres of calcium with lucent centers are always benign. They can be seen in the skin, areas of fat necrosis or in association with benign calcified debris in the ducts (63).

- **Milk of Calcium:** For unexplained reasons, calcium can precipitate in cystically dilated acini of the lobules. Since it looks like milk flowing in a container it has been termed “milk of calcium”. This calcium can form an insoluble powder or can actually form concretions in the lobular acini. These calcium deposits account for very small (< 1 mm), smooth, round deposits that are found tightly packed together. Such calcifications can be heterogenous and difficult to differentiate from cancer.

- **Vascular calcifications:** Vascular calcifications have the distinctive appearance of calcified arteries anywhere in the body. They have distinctive “train track” appearance and are rarely confused with malignant calcifications.

- **Large-Rod-shaped calcifications:** Rod shaped calcifications could be solid or tubular (lucent-centered). They are usually bilateral and mostly benign.

The presence of an extensive benign process does not preclude a simultaneous malignancy. Regardless of the presence of the benign findings a careful search should always be made for very few fine, linear, branching or heterogeneously clustered calcifications that may suggest the presence of a malignant process.

DUCTOGRAPHY

This modality is used primarily in nipple discharge (9)**.** Under sterile conditions the duct under investigation is gently dilated, cannulated and radio opaque contrast media is injected before obtaining mammographic films. Intraductal papillomas are seen as small filling defects surrounded by contrast media. Cancers may appear as irregular masses or as multiple intraluminal filling defects.

ULTRASONOGRAPHY

Ultrasonography is an important method used for resolving equivocal mammography findings, defining cystic masses, and demonstrating the echogenic qualities of specific solid abnormalities. Ultrasonography is also used to guide fine needle aspiration biopsy, core needle biopsy, and needle localization of breast lesions. It is highly reproducible and has a high patient acceptance rate, but is unreliable for subcentimeter lesions.

TREATMENT OF BENIGN BREAST DISORDERS

Since most BBDs are considered as minor aberrations of normalcy, they do not mandate specific treatment. Any active management of these conditions is based on considerations such as accurate diagnosis, the patient’s concern, and interference with the quality of life.

APPROACH TO FOCAL LESIONS IN THE BREAST

The lesions in the breast could be either dominant discreet lesions or vague nodularity.

Dominant discreet nodules: Women of less than 35 years of age are evaluated by sonography and biopsy to come to definitive diagnosis. Many experts omit biopsy for lesions with typical characters of fibroadenoma and opt to follow these patients with serial ultrasonography/ mammography. This is because a lesion that appears to be benign on sono/mammography will actually be benign on most of the occasions (64, 65). However other experienced surgeons disagree and believe that all fibroadenomas require core needle biopsy or fine needle aspiration to rule out malignancy. For patients with a diagnosis of atypical ductal hyperplasia on fine needle biopsy, excisional biopsy is required because more complete resection often changes the diagnosis to ductal carcinoma-in-situ.

APPROACH TO NIPPLE DISCHARGE

Nipple discharge could be galactorrhoea or discharge other than galactorrhoea. Galactorrhoea is evaluated by measurement of prolactin and thyrotropin levels (66, 67)**.** A discharge in the absence of galactorrhoea is considered to be ductal in origin and is classified as uniductal or multiductal (67). Further evaluation of the uniductal discharge could be by one of the following means.

- Galactography – This needs cannulation and insertion of dye into the discharging duct to facilitate visualization of the lesion.
- Surgical biopsy.
- Direct examination of the breast by means of fibre optic endoscopy (68)**.**

Management of Cysts of the breast: On most occasions the first investigation for easily palpable breast lump is needle aspiration. On inserting a needle, if the aspirate is not a fluid and the lump proves to be a solid, a cytologic specimen is obtained. If the aspirate is fluid then the lump under evaluation is considered cystic. If the aspirated fluid is not blood stained, the cyst is aspirated to dryness and the fluid is discarded. Routine cytological examination of all cyst fluid is considered unnecessary (69-72).

Following aspiration if there is a residual breast mass, an ultrasound guided needle biopsy is performed before contemplating excision biopsy. If the aspirated

fluid is blood stained, then about 1-2ml of fluid is sent for cytological examination. An ultrasound guided needle biopsy of any solid area in the cyst is performed. Presence of blood in the cyst fluid is considered synonymous with tumor. (8)

APPROACH TO CYSTIC LESIONS OF THE BREAST

Management of Mastalgia

Mastalgia is a common entity and thus commands a long list of treatment modalities. Mastalgia may resolve spontaneously and 19% of patients show marked response to placebo (73). Therefore double-blind placebo controlled trials are required to prove the effectiveness of drugs in the treatment of mastalgia. Treatment modalities available for mastalgia can be categorized as

Nutritional therapy

Endocrine therapy

Non endocrine therapy.

Nutritional therapy

This treatment modality has the advantage of being the least expensive modality and the modality with least side effects. However, initiating and sustaining the dietary modifications can be very difficult in non compliant patient.

Methyl xanthines: Methyl xanthines include caffeine, theophylline and theobromine. They are found in coffee, tea, chocolate and cola beverages, and in many respiratory medications and stimulants. There is literature which suggests that abstinence from diet containing methyxanthines can bring about beneficial effects on palpable nodules, pain, tenderness, and nipple discharge (74-76). However there are studies which contradict the beneficial effects of abstinence from methyl xanthines in treatment of mastalgia. (77-81).

Dietary fat: Reduction of dietary fat intake t less than 15% of total calories for 6 months significantly improves cyclic breast tenderness and nodularity (82). Studies (83) have demonstrated that

- Mastalgia is associated with significant elevations in high-density lipoprotein cholesterol (HDL-C), high ratio of HDL-C to low density lipoproteins and low total cholesterol to HDL-C ratio.
- Significant response to low fat diet in cyclical mastalgia group as compared with non-cyclic mastalgia suggesting that cyclic mastalgia may be due to aberrations in lipid metabolism

Because of these reasons it has been hypothesized that dietary fat manipulation may help in alleviating mastalgia.

Evening Primrose Oil (EPO): EPO is essentially gamma-linoleic acid. Studies have shown that women with cyclic mastalgia have abnormal blood levels of some essential fatty acids (84). Essential fatty acids are implicated in the control of prolactin secretion and steroid hormone/ receptor alterations (85).EPO has very few side effects like mild gastrointestinal disturbances. Several studies have demonstrated encouraging clinical response when EPO is used in mastalgia (86, 87). Because of favourable clinical response in the absence of major side effects, EPO in the dose of 3 grams should be considered as the first line treatment for mastalgia.

Iodine: The exact influence of iodine on breast tissue is not understood. In contrast to iodides iodine is predominantly involved in extra thyroidal functions (88) particularly in breast. Studies (89) have shown that patient with mastalgia benefit from administration of molecular iodine. Molecular iodine is non thyrotrophic, without side effects and beneficial for breast pain.

Endocrine therapy

Hormones play an important role in the pathogenesis of mastalgia. This is evidenced by the fact that mastalgia primarily manifests during ovulatory years and symptoms fluctuate during the course of menstrual cycle (90).

ANDROGENS

Testosterone: Testosterone injections are one of the earliest effective hormonal treatments for mastalgia. A placebo controlled trial (91) using 40 mg twice daily of deaconate oral form of testosterone demonstrated beneficial effect on mastalgia. However the use of testosterone has been limited by its side effects.

Danazol: Danazol is 2, 3-isoxazol derivative of 17-α-ethinyl testerone. The precise mechanism by which danazol reduces mastalgia is not known. Recommended dose of danazol is 100 mg twice daily, while the patient maintains a breast pain record. In the event of no / incomplete response, the dosage may be increased to 200 mg twice daily. If there is still no response, then another drug should be tried. For the fear of side effects, therapy should not be continued for longer than 6 months and should be tapered (92, 93). Studies have reported favourable outcome for the use of danazol, even in patients with mastalgia refractory to other first line therapies (94). Side effects of danazol include amenorrhoea, weight gain, muscle cramps, acne, hirsuitism, voice change, depression and head ache. Danazol is contraindicated among women with history of thromboembolic disease.

Gestrinone: Gestrinone is an androgen derivative of 19-nortesterone. It has androgenic, antiestrogenic and

anti progestagenic properties and a side effect profile similar to danazol. A multicentric trial (95) has demonstrated a clinically favourable response to mastalgia in 55% and complete resolution of symptoms in 22%. The major side effect of gestrinone is contraception.

Luteinizing Hormone Releasing hormone agonist (LHRH agonist): LHRH agonists act by virtue of their anti gonadotrophic action and direct inhibition of ovarian steroidogenesis. Studies (96) have demonstrated the clinical efficacy of LHRH agonists given as intramuscular monthly depots for mastalgia. Side effects of LHRH agonists include hot flushes, myasthenia, depression, vaginal atrophy, decreased libido, visual disorders, hypertension and loss of trabecular bone (97). For this reason, only short courses of LHRH agonists should be administered.

Tamoxifen: Tamoxifen is an estrogen agonist-antagonist, commonly used in the treatment of breast cancer. It is thought to competitively inhibit the action of estradiol in mammary gland. Controlled trials using tamoxifen at dosages of 10 and 20 mg / day produced greater than 50% reduction in the mean pain scores in 90% of patients with cyclic mastalgia and 50% of those with non cyclical mastalgia (98). Major side effects of tamoxifen include hot flushes and vaginal discharge. Possible association between tamoxifen use and endometrial carcinoma has relegated its use only for patients in whom symptoms are severe and in whom all standard therapies have failed (99).

Non Endocrine therapy

BROMOCRIPTINE: Prolactin has been implicated as one of the factors responsible for mastalgia (100). Bromocriptine is an ergot alkaloid that acts as dopaminergic agonist on the hypothalamic-pituitary axis. One result of this action is suppression of prolactin secretion. Studies have demonstrated reduction in the prolactin levels with favourable clinical response following prolactin administration among patients with mastalgia (101-103). Side effects of bromocriptine can be serious and can include seizures, strokes and even deaths. Because of its serious side effects FDA has not approved the use of bromocriptine in mastalgia (104).

ANALGESICS: Oral analgesics have been tried for mastalgia. A study (105) **has** demonstrated favourable clinical response with the use of nimusulide for mastalgia. However prospective randomized trials evaluating the oral analgesics have not yet been reported.

SURGICAL APPROACHES: Surgery Such as sub-cutaneous mastectomy or excisional breast biopsy for mastalgia should be the last resort. In general, surgical excision of localized trigger spots is unsuccessful 20% of the time and runs the risk of replacing a painful area with a painful scar (106).

TREATMENT OF UNDIVIDUAL BENIGN BREAST PATHOLOGIES

FIBROADENOMA AND RELATED LESIONS

In spite of the fact that most fibroadenomas are self-limiting and many go undiagnosed, removal of all fibroadenomas was advocated in the past. At present, it is reasonable to adopt a more conservative approach (8).Conservative management of fibroadenoma requires

- Confirmation of the diagnosis by mammography/sonography and cytological examination.
- Regular monitoring to document if there is increase in the size of the lesion.

However, in a prospective study (107), wherein 85 fibroadenomas were conservatively managed, 53 fibroadenomas came for subsequent excision and one was found to be malignant. Transformation of a fibroadenoma to a phyllodes tumor is an extremely rare occurrence. Identification of such a transformation is of paramount importance when a conservative line of management is being adopted for fibroadenoma. Noguchi and colleagues (108) have demonstrated that transformation of fibroadenoma to phyllodes can be accurately identified by clonal analysis of specimen obtained by fine needle aspiration.

SCLEROSING ADENOSIS, RADIAL SCAR AND COMPLEX SCLEROSING LESIONS

It is almost impossible to accurately diagnose these lesions by mammography (109). Hence the diagnostic work-up for these lesions need open or stereoscopic breast biopsy. Local excision is adequate management for benign lesions.

THE DUCT ECTASIA / PERIDUCTAL MASTITIS COMPLEX

This complex comprises of nipple discharge, nipple inversion, subareolar abscess and recurrent abscess with fistula. The duct ectasia/periductal mastitis present as painful tender masses behind the areola. Such lesions are initially explored with a 21 gauge needle and any fluid aspirated is submitted for cytological examination and culture. If the aspirate is purulent, empirical antibiotics can be started while awaiting the results of the culture. In the presence of considerable amount of pus, surgical treatment is recommended.

A subareolar abscess is usually unilocular and involves a single duct system. Ultrasound scan can be used for accurate delineation of the subareolar abscess. The surgeon may either undertake a simple drainage with a view towards formal surgery should the problem recur or may straight away proceed with the definitive surgery. The definitive surgery for the duct ectasia/periductal mastitis complex is either fistulectomy or total duct excision. The choice between fistulectomy and total duct excision depends upon the parameters summarized in the following table (8)**.**

Correction of nipple inversion: Nipple inversion could be congenital or acquired. The possibility that a woman comes for correction of congenital nipple inversion is much greater as compared to acquired nipple inversion. Nipple inversion is a result of shortening of the sub areolar ducts. Hence surgical treatment of nipple inversion encompasses divisions of these ducts. Complications of surgical correction of nipple inversion include, altered nipple sensation, nipple retraction and post operative fibrosis with nipple retraction.

CONCLUSIONS

- Breast is a dynamic organ which displays structural and functional changes through out the reproductive life of a woman.
- ANDI is a practical classification system. Most BBDs can be explained by the ANDI system.
- Few BBDs carry a risk of malignancy.
- The pathological classification aids in risk stratification of BBDs with respect to malignancy.
- Age, family history and histology are important risk factors determining the risk for malignancy.
- Imaging supplemented with biopsy in doubtful cases help in arriving at reasonably accurate diagnosis.
- Most BBDs can be managed non-surgically. However accurate diagnosis of the benign nature of the disease is an essential prerequisite and any suspicion of malignancy should be ruled out by biopsy.

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Illustrations

Illustration 1

ANDI classification of Benign Breast Disorders

ANDI classification of Benign Breast Disorders

	Normal →	Disorder →	Disease
Early reproductive years (age 15-25)	Lobular development Stromal development Nipple eversion	Fibroadenoma Adolescent hypertrophy. Nipple inversion	Giant fibroadenoma (Gigantomastia) Subareolar abscess
Later reproductive years (age 25-40)	Cyclical changes of menstruation. Epithelial hyperplasia of pregnancy	Cyclical mastalgia. nodularity Bloody nipple discharge	Incapacitating mastalgia
Involution (age 35-55)	Lobular involution Duct involution -dilation -sclerosis Epithelial turnover	Macrocysts Sclerosing lesions Duct ectasia Nipple retraction Epithelial hyperplasia	Periductal mastitis Epithelial hyperplasia with atypia

Illustration 2

Table 8: Treatment of Recurrent Subareolar Sepsis

SUITABLE FOR FISTULECTOMY	**SUITABLE FOR TOTAL DUCT EXCISION**
Small abscess- localized to one segment	Large abscess – Affecting > 50% of areolar circumference
Recurrence always at the same site	Recurrence involving a different segment
Mild or no nipple inversion	Gross nipple inversion
Patient unconcerned about nipple inversion	Patient requests correction of nipple inversion
Younger patient	Older patient
No discharge from other ducts	Purulent discharge from other ducts between episodes
	Recurre

Illustration 3

System 11

Risk	Proliferation	Histologic findings
No increase	Minimal	• Fibrocystic changes (within the normal range): cysts and duct ectasia, mild hyperplasia, nonsclerosing adenosis, and periductal fibrosis; simple fibroadenoma; and miscellaneous (lobular hyperplasia, juvenile hypertrophy, and stromal hyperplasia) • Benign tumors: Hamartoma, lipoma, solitary papilloma, neurofibroma, giant adenoma, and adenomyoepithelioma • Traumatic lesions: hematoma, fat necrosis • Infections: granuloma and mastitis • Sarcoidosis • Metaplasia: squamous and apocrine • Diabetic mastopathy
Small increase (relative risk, 1.5-2.0)	Proliferative without atypia	Usual ductal hyperplasia, complex fibroadenoma (containing cysts>3mm in diameter, sclerosing adenosis, epithelial calcifications, or papillary apocrine changes), papilloma or papillomatosis, radial scar and blunt duct adenosis
Moderate increase(relative risk, >2.0)	Proliferative with atypia	Atypical ductal hyperplasia and atypical lobular hyperplasia