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Breast lumps: Types, biomarkers and prognosis

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Abstract

Introduction: The breast is a dynamic organ in the female and the symptoms related to it considered a major cause enrolled the women to get medical intension, a complete physical, radiological, and cytological examination should be accomplished until the symptoms resolved or benign\ malignant condition established, there were many types of benign tumor in the breast: solid or cystic, painless or painful with different ways for management either by close surveillance or by surgical removal. But the breast cancer required hard work to establish the histological and pathological grade.

Conclusion: to treat the breast cancer properly the cancer should stratify into molecular entities by using hormonal biomarker (ER, PR) and using of oncoprotein HER2 and proliferating index Ki-67, usage of these markers is satisfying for grouping the breast cancer subtypes into four major entities which are Luminal A, Luminal B, HER2+, and triple negative tumor.

Keywords: Breast; Cancer; Lipoma; Adenoma; Biomarkers

1. Introduction

The breast of the adult human composed of three main elements; skin, subcutaneous fat and tissue of the breast (stromal and parenchymal tissue), where the skin contains; sebaceous glands, sweat glands and hair follicles and the glandular tissue of the breast consist of 15-30 lobes or segments where each lobe made of 20-40 lobules that had 10-100 alveoli drained their milk into collecting duct measured approximately 2mm, at the nipple 5-10 major collecting duct opened [1]. Symptoms related to the breast are the commonest cause prompting the women to get medical evaluations that tailored according to the age and women complains, A through medical history focusing upon breast cancer risk factors, a complete physical, radiological, and cytological examination should be accomplished until symptom resolved or benign\malignant condition established [2]. In this review; the most frequent tumors seen in Iraq are summarized whether are benign or malignant in addition to their prognosis and biomarkers used to identify them or identify their prognosis.

2. Benign breast disease

Most of the women seeking medical evaluation for being have breast related symptom; may have benign breast conditions, and only 1 from 10 women referred to the breast clinics may have breast cancer [3,4].

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2.1. Fibroadenoma

Previously called benign breast neoplasms, but nowadays should be considered aberration of normal breast development, the third decade of a women life considered the age of peak incidence although there was increased number of fibroadenomas recorded among the fifth and sixth decade may be due to wide use of hormonal replacement therapies and mammographic testing. Fibroadenomas arise from lobule rather than single cell that explores elevated level of estrogen and sulfate in addition to enzymes responsible of making estrogen like sulfatase and aromatase that make thought the fibroadenomas are hormones dependent neoplasm [5]. The fibroadenomas considered as a polyclonal lesion after clonal analysis [6]. 72% of fibroadenoma resolved over the period of 7 years [7] and there is no risk of developing breast cancer except for some pathological subgroups like complex fibroadenomas (cysts greater than 3mm in diameter with sclerosis adenosis and epithelial calcification) where the relative risk (RR) of 3:1 for breast cancer. It can undergo into vascular infraction during pregnancy and lactation and calcification [8].

2.2. Fibrocystic changes

Fibrocystic changes (FCCs) are multifocal and bilateral disease that known by many names over years (Fibrocystic disease, Chronic cystic disease, Cystic mastopathy, Mazoplasia, and Reclus s disease), the name of "Fibrocystic changes" is preferred now because 50% of these changes diagnosed clinically and up to 90% histologically in women [9,10]. These changes consider the most frequent changes affecting premenopausal women from 20-50 years [11]. The more frequent presentation is breast pain and tender nodule with unknown exact etiology, although hormonal imbalance; especially estrogen over progesterone imbalance have an important role in its development [12]. FCCs contain both cyst (micro or macro) and solid lesions (Adenosis, Epithelial hyperplasia with or without atypia, apocrine metaplasia, radial scar and papilloma), using of mammography and facilities used to identify benign breast conditions; it's important to identify women at increasing risk of development of breast cancer, so it is important to evaluate FCCs under a classification system first proposed by Dupon and Page (Fig. 1) [13]. This classification includes (non-proliferative lesions, proliferative lesions without atypia, and proliferative lesions with atypia) whereas 70% of breast biopsies are of non-proliferative type [14]. According to different studies women with non-proliferative lesion have no elevated risk of developing breast cancer, while women with proliferative lesion without atypia and women with a typical lobular or ductal hyperplasia have increasing risk of developing breast cancer with relative risk (RR) ranging from 1.3-1.9 and 3.9-13 respectively [14,15,17]. However; absolute risk of developing invasive breast cancer from non-atypical and atypical proliferative lesions is very low and in about 80% of women with FCCs [16].

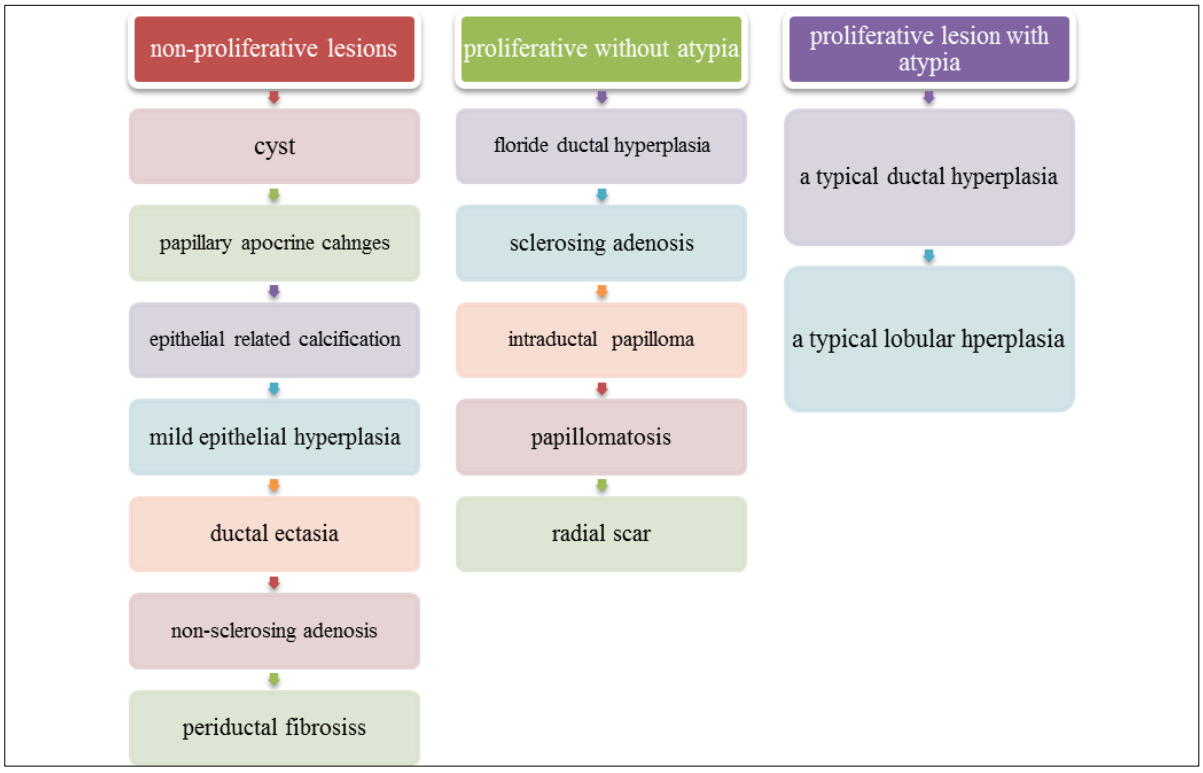

Figure 1 Schematic classification of FCCs according to Dupon and page 1985

2.3. Lipoma

It is a benign solitary mass of breast composed from mature fat cells, it considered a challenging condition because it sometime difficult to discriminate from other breast conditions clinically [18]. Lipoma present clinically as well circumscribe or lobulated mass, soft and not tender, ultrasound and mammography gave a negative result except in large masses, while FNA is mandatory to see fat cells with or without normal epithelium [19]. Normally; women should be followed after 6 months and if the mass grow in a rapid manner or the diagnosis was not certain the mass should be removed surgically [18].

2.4. Adenoma

Adenoma considered as a pure epithelial tumor of the breast that contains range of variety includes; tubular, lactating, ductal, apocrine, and pleomorphic varieties, only tubular and lactating adenoma that occurred at reproductive age are common and the rest considered uncommon adenomas [20]. The lactating adenoma considered as the most prevalent adenoma in women during pregnancy and postpartum period, that tend to be solitary or multiple and discrete and usually small <3cm that characterized grossly by lobulation, and by hyperplastic lobule that lined by actively secreting cuboidal cells, lactating adenoma some time developed in an axilla, chest wall or vulva as ectopic adenoma [21]. This tumor resolved spontaneously but if it caused pressure effect may be removed surgically, lactating adenoma had no risk of development of breast cancer [22]. On the other hand, tubular adenoma tends to be well circumscribed solitary nodule that similar to noncalcified fibroadenoma in radiological appearance, but histologically it consist of tightly adherent of a very regular tubular or acinar structures that appeared sparely in stroma [23].

2.5. Nipple adenoma

Also called by other names as; florid papillomatosis or erosive adenomatosis that resemble Paget's disease, and sometime missed as adenocarcinoma, even though it considered as a benign tumor of the nipple duct, present as a palpable, discrete tumor of the papilla accompanied by nipple discharge [24]. Appear histologically as a proliferation of duct structures invades the surrounding stroma with keratin cysts which consider as distinguishing feature of this disease [24, 25]. It is benign lesion, but some malignant changes have been reported, so biopsy needed to confirm the diagnosis and treated surgically with complete excision and safe margin [24].

2.6. Hamartoma

Benign tumor of the breast contains a variable amount of adipose, glandular, and fibrous tissue, so it sometime called fibroadenolipoma and lipofibroadenoma or adenolipoma [26]. It is an uncommon benign tumor that present as palpable well encapsulated, discrete painless lump of unknown etiology, may be due to dysgensis rather than complete tumor process in addition; some case linked to a genetic defect named Cowden's disease [24]. The mammographic presentation typically as a well encapsulated mass contains soft tissue and lipoma elements surrounding by clear zone [27]. The proper management of this tumor, first by confirming diagnosis through biopsy that appears histologically; normal breast and fat tissue distributed as nodules surrounded with fibrous stroma and spreads between individual lobules that obliterate normal specialized loose stromal fashion, then surgical removal [28].

2.7. Granular cell tumor

It is uncommon benign breast neoplasm originated from Schwan cells of a peripheral nerve that occur only 5-6% in the breast, the rest commonly found in the neck and oral cavity [29]. The mammography and ultrasound revealed a fibrous consistency, fixation to the pectoral fascia and an ulceration and retraction of the skin that give a wrong idea of carcinoma [30]. By examination the tumor < 3cm, well encapsulated tumor, histological examination revealed nets of polygonal cells with a clear border and granular eosinophilic cytoplasm that considered characteristic to this tumor [31]. Some studies reported malignant changes in this tumor that characterized by tumor size >5cm, cellular and nuclear pleomorphism, present of nucleoli, increased mitotic activities with local necrosis and local recurrence [24, 32]. The current treatment is wide local excision of the tumor with muscle and adjacent structure to give tumor free margin for preventing the recurrence [31].

3. Breast cancer

Globally human cancer has been become as the main cause of morbidity and mortality in recent decades due to various demographical, economical or epidemiological factors [33, 34]. Among females the breast cancer considered the most common malignancy and the leading cause of mortality, in 2018 there were 2.1 million cased newly diagnosed with breast cancer among the world with roughly 626,600 death annually [35].

3.1. Histological types

Histological study must reveal whether the tumor is limited to epithelial cells of the breast or it infiltrated to the stroma, or whether this tumor appear in the duct or lobe of the mammary gland [36]. Since the cell type characteristics, cells numbers, type and location of secretion in addition to immunohistochemical profiles which determined the tumor ductal or lobular [37]. About 50-80% of breast cancers newly diagnosed are invasive ductal carcinoma (IDC), while the rest are invasive lobular carcinoma (ILC) [38]. IDCs sometime classified into "no specific type" if there is no sufficient morphological characteristic to be classified as a distinct histological type, or it recognized as "special type" if there is special cellular characteristic and special molecular behavior [39], the most common special types of IDCs are: medullary carcinoma, apocrine carcinoma, metablastic carcinoma, mucinous carcinoma, tubular carcinoma, classical lobular carcinoma, pleomorphic lobular carcinoma, neuroendocrine carcinoma, mucinous carcinoma, cribriform carcinoma [38]. Prognostic factors traditionally includes; histological grade, nuclear grade, tumor size and axillary lymph node involvement [40].

3.1.1. Invasive ductal carcinoma - Nonspecific type (IDC-NST)

The most common type constitutes about 40-75% of IDCs, it usually has high range of morphological and behavioral variation [38], the characteristic features of the cells are pleomorphic with protruding nucleoli with active mitosis, an area of calcification and necrosis can be seen in more 50% of the cases [37].

3.1.2. Medullary carcinoma

Special type of breast carcinoma and account for 5% of all special subtypes, associated with better clinical outcome and minimal involvement of the axillary lymph nodes [41]. Usually affect female in a third or fourth decade of life and associated with mutation in breast cancer gene 1 (BRCA1) [38]. Microscopically this tumor characterized by well-circumscribed cancer, constitute of large pleomorphic cells and syncytial growth fashion with multiple mitotic activity in addition to lymphoplasmacystic infiltration, also it may associate with spindle cells metaplasia and giant tumor cells [42,43].

3.1.3. Metablastic carcinoma

This special subtype constitutes about 1% of all special type of breast carcinoma and mainly affect postmenopausal women, characterized by a presence of metablastic dominant component [44], this tumor had aggressive behavior with lymph node involvement, also it is poorly differentiated heterogeneous tumor that usually contained ductal carcinoma mixed with other histological metaplasia like squamous cells, spindle cells, chondroid cells, bone cells [42, 45].

3.1.4. Apocrine carcinoma

This tumor contains 90% of cells had differentiated to apocrine cells and constitute about 1-4% of carcinoma subtypes [37], it is affect a wide range of age but mostly postmenopausal women, it is of high grade poorly differentiated tumor with a poor prognosis [46]. Histologically; this tumor has large cells with abundant eosinophilic cytoplasm that positive for PAS (Periodic Acid-reactive Schiff) and contain prominent nucleoli and sometime bizarre shape cells [47].

3.1.5. Cribriform carcinoma

A good prognosis tumor affects women of about 50 years old, generally it constitutes about 2-3.5% of all subtypes of breast carcinoma [36], this carcinoma had no metastatic dissemination, histologically; this tumor has an island of similar cells with low atypia in 90% of cases and usually associated with Ductal carcinoma IN SITU (DCIS) without stromal invasion [48].

3.1.6. Tubular carcinoma

It affects postmenopausal women mainly 50-60 years, it is well differentiated tumor occurred in about 2 % of all cases of special subtypes of breast carcinoma [41], this subtype mainly associated with a wide range of premalignant proliferative lesions [49], characterized histologically by a proliferation of prominent tubules in more than 90% of all cases with unorganized elongated or oval cells and opened lumen covered by only one layer of epithelium without necrosis and mitosis [50].

3.1.7. Neuroendocrine carcinoma

This tumor resembles to neuroendocrine carcinoma of gastrointestinal tract, it constitutes about 0.5-5% of all cases, usually occur in postmenopausal age, at molecular basis; it expressed chromogranin A marker and synaptophysin in

more than 50% of tumor cells [51], histologically; the tumor cell infiltrate and aggregate in alveolar and trabecular pattern, the cells can be in different size and have fine granular eosinophilic cytoplasm [52].

3.1.8. Invasive lobular carcinoma

The second major biological type of breast cancer, constitute about 5-15% of all diagnosed cases, usually of postmenopausal age [41]. Histologically; this tumor constitute from small cells with low grade atypia that distributed throughout stroma in concentric pattern with hyperchromatic eccentric nucleus with mitoses and apocrine, usually it has TP53 mutation (tumor protein 53) [53].

3.2. Biomarkers

Breast tumors represent a heterogeneous collection of biological and behavioral different disease with different clinical and treatment response [54], so triple test should be applied for every breast tumor that includes; proper physical examination, bilateral mammography and FNA (fine needle aspiration) of the mass [55], any suspicion in one of the triple test; open surgical biopsy should be done. A women age and reliability and ability of physical examination in addition to risk factors should be encountered [56]. The triple test should be reviewed strictly if a benign tumor is diagnosed and treated by close surveillance every 3 months initially then every 6 months if the disease is stable or surgical removal [55, 56], if breast cancer is diagnosed; the morphological or histological classification (histological grade, nuclear grade, mitotic index) and pathological characteristic (tumor size, lymph node involvement and metastasis) are deficient in determined clinical behavior and treatment outcome [57]. So many studies focused on reviewing the molecular basis of breast cancer to collect these tumors into groups to facilitate medical management and predict the outcome [58]. The breast cancer classified into molecular subtypes by Perou, Sorlie and their colleague based on similarities in gene expression [59, 60, and 61].

On this basis there are four distinct subtypes of breast cancer; Luminal A, Luminal B, HER2+ and triple negative (TN) [62], these molecular subtypes are related for IHC (immunohistochemical) panel of expression of ER (estrogen receptor), PR (progesterone receptor), HER2 (human epidermal growth factor-2) and cells proliferation regulator (Ki-67), these markers are considered sufficient in classifying breast disease into four molecular groups [63].

The luminal A considered more frequent and comprise of more than 50% of newly diagnosed cases that express ER >1%, PR in >20%, HER2+ in <10% and Ki-67 in <14% [64], this subtype exhibit luminal epithelial characteristics of high expression of cytokeratin's 7,8,18,19 and includes a wide range of breast cancer special types like low grade of cribriform carcinoma, tubular, mucinous, IDC-NST and classical ILC [65], this entity associated with better prognosis and less lymph node involvement, also the patient can use endocrine therapies due to positive endocrine receptor [66].

On the other hand, Luminal B subtype constitutes 20-30% of all invasive breast cancer and can be classified into two subtypes; Luminal B HER2- which exhibit ER+ >1%, PR+ in <20% or PR-, HER2- or HER2+ in <10% and Ki-67+ in more than 20%, or Luminal B HER2+ that exhibit ER+ >1%, HER2+ in >10%, any level of PR and any level of KI-67 [67]. This molecular subtype has moderate prognosis and considered as more aggressive hormone dependent subtype so the patient needed other treatment rather than endocrine based treatment like chemotherapy [57].

The molecular subtype HER2+ constitute 15-20% of all newly diagnosed breast cancer, characterized by highly expression of HER2+ >10%, ER- <1%, PR<20% and high expression of Ki-67 [68], the diagnosis is made for HER2+ if there was strong and complete immunostaining of cell membrane, while if the staining was mild to moderate then FISH (fluorescence in situ hybridization) is needed to confirm diagnosis [69]. This entity comprised ILC of pleomorphic variant only [70].

The triple negative variant comprised 10-20% of all newly diagnosed breast cancer, it is exhibit a negative hormonal receptor ER<1, PR<20 and negative HER2, but it expressed a high proliferative profile and so it considered a highly proliferative tumor where Ki-67 more than 30% [64], most variant in this entity; IDC-NST of high grade, mucinous, metablastic and apocrine carcinomas that associated with local recurrence and systemic relapse [71].

Nowadays the term serum biomarker or circulating biomarkers used to detect disease progression or treatment response, but it is not established in breast cancer management like CEA, CA15-30, CA 27-29 [72], where CEA is glycoprotein involved into cell-cell adhesion while the other two are carbohydrate work to prevent tumor cell lysis and reduce cell-cell interaction [73].

A lot of studies explain the importance of CEA at the time of diagnosis of primary breast cancer, whereas elevated serum CEA associated with a bad prognosis [74, 75, 76], while elevated CA15-30 at the time of diagnosis revealed a higher stage of breast cancer [77, 78, 79, 80].

4. Conclusion

The breast tumors comprise a heterogeneous group of disease that required a careful investigation and examination to classify the mass whether it is a benign or malignant tumor, and then stratify the malignant one into subtypes according to histological and pathological grade. Despite the development of clinical oncology and diagnostic tool; the breast cancer remains a major dilemma because it required proper molecular diagnosis to predict the treatment and outcome

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest in connection with the publication of this manuscript.

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