INTRODUCTION

Breast cancer is the most common invasive cancer in females worldwide. It accounts for 16% of female cancers and 22.9% of invasive cancers in women. Also it is the cause of 18.2% of all cancer deaths worldwide, including both males and females ***(Nordqvist, 2016).***

Breast cancer rates are higher in developed nations compared to developing ones due to longer life-expectancy, the different lifestyles and eating habits between females in both rich and poor countries ***(Nordqvist, 2016).***

Mammography is the preferred screening examination for breast cancer as it is widely available, well-tolerated and inexpensive. The earliest sign of breast cancer can be an abnormality depicted on a mammogram, before it can be felt by the woman or her physician ***(Dongola, 2016).***

In mammogram the breast composition is classified into A- The breast are almost entirely fatty. B- There are scattered areas of fibroglandular density. C- The breasts are heterogeneously dense and small masses could be obsecured. D - The breasts are extremely dense, which lowers the sensitivity of mammography ***(Zonderland and Smithuis, 2014).***

Asymmetry in mammogram is caused by superimposition of normal breast fibroglandular tissue, **focal asymmetry** visible on two projections, is considered a real finding rather than superposition and this has to be differentiated from a mass, **global asymmetry** which is usually considered as a normal variant; is an asymmetry over at least one quarter of the breast; and **developing asymmetry** is a new, larger and more conspicuous asymmetry than on a previous examination ***(Zonderland and Smithuis, 2014).***

Sensitivity for breast cancer detection is inversely related to density. It is as high as 98% in fatty breasts (category A) and 50-65% in dense breasts (category D). In addition, the risk of breast cancer increases with increased density. The relative risk of breast cancer in women with very dense breasts "category D" is 4 times greater than in women with fatty category A breasts ***(Dongola et al., 2016).***

Possible causes for missed breast cancers are dense parenchyma obscuring a lesion, poor positioning or technique, perception error, incorrect interpretation of a suspect finding, subtle features of malignancy, and slow growth of a lesion ***(Dongola et al., 2016).***

False-positive results may arise when benign microcalcifications are regarded as malignant. Tissue summation shadows may cause local parenchymal distortion and this may be erroneously called suspicious tissue. A benign circumscribed lesion may show signs suggestive of malignancy, in association with other findings, such as an irregular border and no halo sign ***(Dongola et al., 2016).***

CEDM is one of the contrast studies; it provides both morphologic and functional information of breast lesions. According to the strength of enhancement and morphological characteristics malignant lesions could be distinguished from benign lesions. Sometimes, it picks up abnormal enhancing lesions when digital mammography and ultrasounds are negative ***(Liao et al., 2014).***

Technically dual energy contrast enhanced digital mammography (CEDM) provides dual energy acquisitions by emitting low and high energies at the end of the 2nd minute after injection of a non-ionic contrast media with breast compression to avoid motion artifact. Then subtraction is obtained by preprogrammed software, allowing any enhancing abnormality to be more obveious ***(Bhothisuwan and Kimhamanon, 2014).***

In dense breast, CEDM has better diagnostic accuracy than mammography alone and sono-mammography ***(Mokhtar and Mahmoud, 2014).***

Microcalcifications which may be the only finding in ductal carcinoma in situ (DCIS) are seen in CEDM as white spots in low energy images and dark spots in high energy CEDM. CEDM might provide added value in assessing the non-mass screened breast microcalcifications, with enhancement is favorable of cancers or lack of enhancement is diagnostic of non-malignant lesions or noninvasive cancers ***(Cheung et al., 2016).***

In the symptomatic patients with palpable suspicious abnormalities, CEDM provides immediately available, clinically useful information. Sensitivity, specificity, and size accuracy for breast cancer detection and staging are improved using CESM as the primary mammographic investigation ***(Tennant et al., 2016).***

In addition CEDM can be easily performed for clinical assessment after positive breast cancer screening and may change the diagnostic and treatment strategy significantly through breast cancer staging ***(Tardivel et al., 2016).***

As regards radiation exposure and possible side effects of the already known iodinated contrast medium, CESM is not used as a routine initial study, instead of mammography ***(Bhothisuwan and Kimhamanon, 2014).***

A comparison between CEDM and MRI shows a very high sensitivity for the lesion with both modalities, but MRI detects more satellite tumors and CEDM had fewer false positives**.** Quality of tumor size measurement using CEDM is good and additional measurements by breast MRI did not improve the quality of tumor size measurements. CEDM is also characterized by easier accessibility, shorter time of examination and fewer costs ***(Lobbes et al., 2015).***

AIM OF THE WORK

Assessment of the role of contrast enhanced digital mammography in characterization of mammographically detected focal asymmetric density in terms of determination of normal tissue, benign and malignant lesions.

Review of Literature

Anatomy & Radiologilogical Anatomy

Structure of the Breast

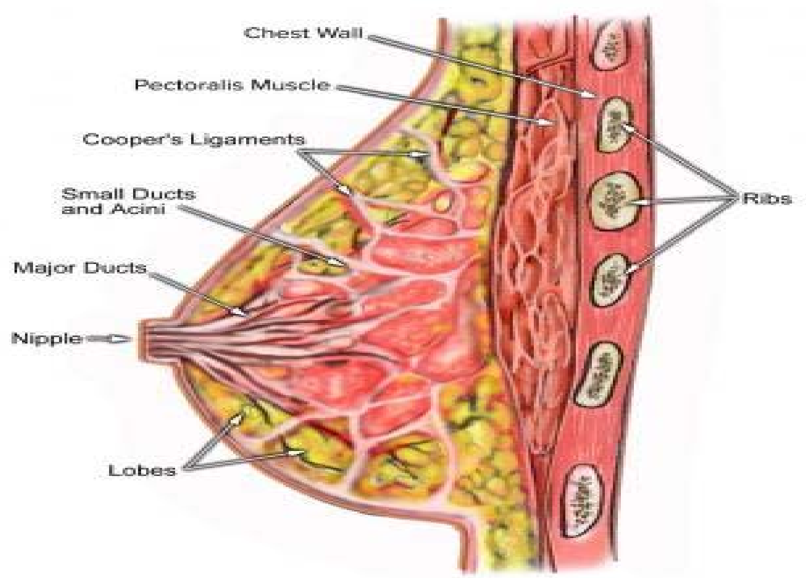

Fig. (1): Breast anatomy ***(Gabrial and Long, 2016).***

Skin and Subcutaneous Fat

Skin thickness depends on subcutaneous fat which may be absent in 44%of patient. It is variable from 0.5 mm up to 2.1 mm. Camper's fascia separates subcutaneous fat from the fat surrounding the glandular tissue. Both superficial and deep fasciae merge at the inferior border of the breast ***(Rusby and Agha, 2017).***

Glandular Tissue

The glandular structure is composed by 15-20 lobes arranged in radial pattern around and behind the nipple as in fig.2. Each lobe is made of numerous lobules, constituted by alveoli, which are the secreting units. The alveolar ducts converge into the lobular ducts which in turn converge into the milk ducts which converge to the nipple with the lactiferous sinus dilatation ***(Benedetto, 2016).***

Fig. (2): Mammary ducts injected with *red, yellow, black, green,* and *brown* ***(Rusby and Agha, 2017).***

Supporting Structures

The stroma is composed of dense fibrous and adipose tissues that surround the entire gland and penetrate between the lobes. The breast parenchyma is enveloped by the anterior facial layer that covers the gland and fibrous septae of Cooper's ligaments, which penetrate and support the gland parynchyma, and the posterior layer, which covers the posterior portion of the gland and separates it from the underlying superficial fascia of pectoralis major muscle ***(Jesinger, 2014).***

Nipple and Areola

The nipple-areolar complex contains the Montgomery glands, that are transitional between sweat glands and mammary glands. They open at the Morgagni tubercles, which are papules on the areola. The complex contains smooth muscle, sensory nerves and abundant lymphatic. Skin of the nipple is continuous with the epithelium of the ducts so, cancer of the ducts may spread to the nipple ***(Nicholson et al., 2009).***

Blood supply and lymphatics

The main blood supply to the breast is the medial perforating branches of the internal mammary artery and vein after traversing through the pectoralis major muscle. Lymphatic drainage of medial aspect of the breast is the internal mammary chain of lymph nodes within the chest; however, this is quite variable. The majority of the lymphatic from the breast drain to the axillary lymph nodes. Some node/s may be located in atypical locations within the breast such as axillary tail, upper outer quadrant or very low on the lateral chest wall ***(Doreen & Agnese, 2016).***

Nerve supply

Nerve supply of breast and nipple is from the lateral and anterior cutaneous branches of the 2nd to the sixth intercostal nerves, and from the supraclavicular nerves ***(Rusby and Agha, 2017).***

Developmental Abnormalities

Ectopic breast (mammary heterotopia), which is both supernumerary and aberrant breast tissue is the most common congenital abnormality of the breast, **Ectopic nipple (polythelia), areola, and glandular tissue (polymastia)** may occur along or outside the milk line. Identification of an accessory breast tissue is difficult in absence of nipple. It responds to physiological influences as the normal tissue. Absence of a duct system may cause obstruction symptoms during lactation and clinical mistake for a carcinoma. A variety of benign and malignant lesions may occur in the ectopic breast tissue as the normal breast. **Excessive breast growth (macromastia)** can be seen during pregnancy and adolescence. **Underdevelopment of the breast (hypoplasia),** may be *congenitally* associated with genetic disorders, such as ulnar-mammary syndrome, Poland's syndrome, Turner's syndrome, and congenital adrenal hyperplasia or *acquired* hypoplasia, usually iatrogenic, mostly due to trauma or radiotherapy. **Complete absence of both breast and nipple (amastia)** or presence of **nipple without breast tissue (amazia)** is rare ***(Guray & Sahin, 2006).***

Radiological anatomy

***CEDM Appearance of anatomic structur*es**

Normal tissues in CEDM are cancelled by image subtraction. However, a number of factors can lead to incomplete cancellation; including the x-ray spectrum, the presence of contrast agent in the breast, the time after contrast agent administration, and subject breast density (fig 3) ***(Hill et al., 2013).***

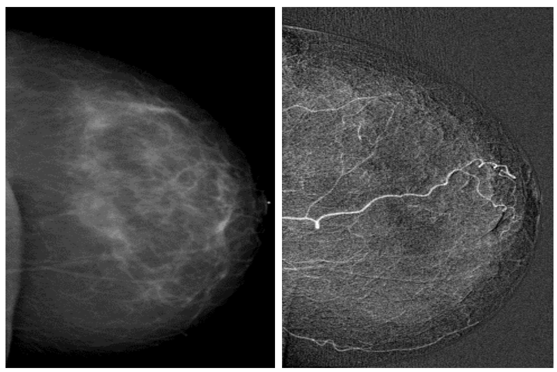

Fig. (3): Images from CEDM of two different females illustrate appearance of normal tissue in subtracted images. Left image is conventional mammography and right image is subtracted CEDM image show no suspicious enhancement ***(Hill et al., 2013).***

Anatomic structures in subtracted image of CEDM

1. ***Skin*** appearance is variable. Predominately, it is none or faintly enhancing. Any variable skin enhancement and thickening should be correlated with the standard low-energy mammography (fig. 4).

2. ***Nipple*** is commonly not enhanced due to compression technique. Right place of nipple in profile prevents misdiagnosis as enhanced mass. A marker should be used in case of retracted nipple to localize nipple if it is not applicable to be in profile (fig. 5).

3. ***Pectoralis major*** *muscle* is not enhanced.

4. ***Vessels*** enhance more prominently with early wash out on the first view, the number of enhancing vessels increases in breast cancer.

5. ***Lymph nodes*** are seen in up to 47% of breasts commonly seen in the upper outer quadrants. Lymph nodes enhancement is not necessarily indicative of pathologic characteristics. Enhancement may be secondary to necrosis or metastatic implants and is usually more heterogeneous with increased lymph node size.

6. ***Moles and seborrheic keratoses*** do not enhance. ***Potentially enhancing skin lesions*** which mimic cancer, especially cherry angiomas enhances, so it is important to place a marker on such skin lesions as in (fig. 6) ***(Lewi et al., 2017).***

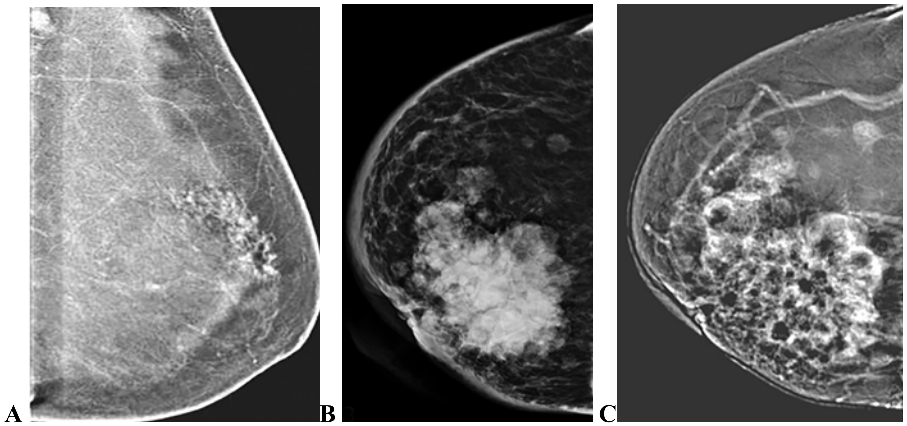

Fig. (4): Skin appearance: (A) Mediolateral oblique subtraction image illustrates a thin line of skin enhancement, which is a common benign finding. The low-energy (B) and subtraction craniocaudal (C) views show pathologic skin thickening and enhancement of a biopsy-proven breast carcinoma ***(Lewi et al., 2017).***

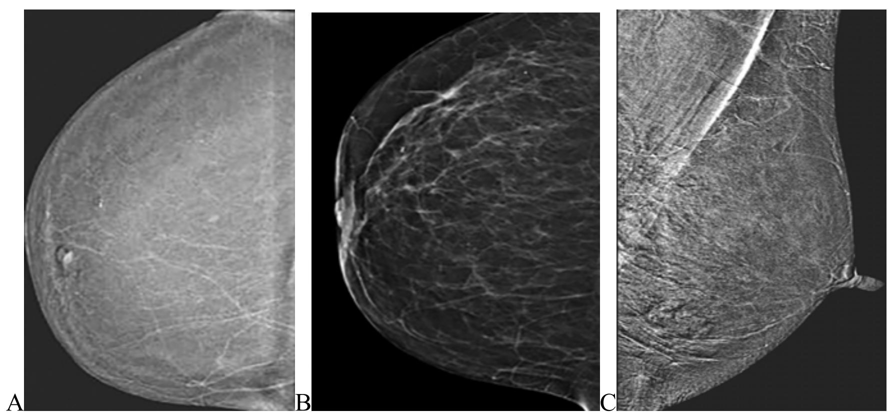

Fig. (5): Nipple out of profile: (A) the subtraction view shows a mass with corresponding enhancement in the anterior right breast. This was thought to possibly represent an out-of-profile nipple, mimicking an enhancing mass. (B) Craniocaudal view with the nipple in profile, confirming no retroareolar mass. (C) Mediolateral oblique subtraction image shows pectoral outlining ***(Lewi et al., 2017).***

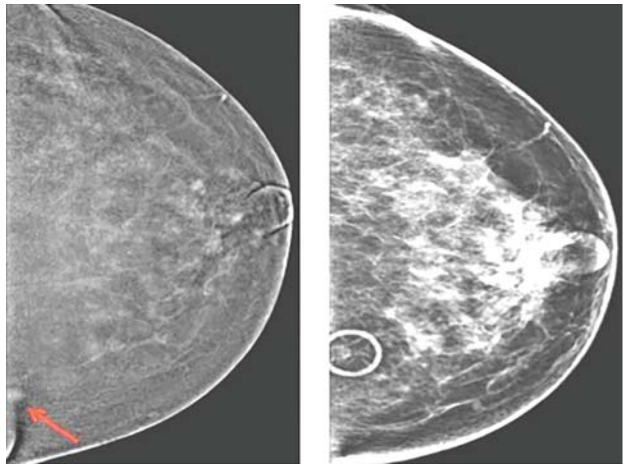

Fig. (6): Mole enhancement: (A) left craniocaudal subtraction image shows a small oval area of enhancement (arrow) in the medial, posterior breast. On further examination of the low-energy image, a rim of air appears to surround an oval density in this area, suggestive of a skin lesion. (B) Repeat craniocaudal 2-dimensional image of left breast taken after a mole marker was placed, confirming that the oval enhancing lesion corresponded to a cherry angioma ***(Lewi et al., 2017).***

CEDM Artifacts:

- ***Ghosting Artifact*** results when a latent image from a prior exposure is superimposed on a newly acquired image (fig 7) ***(Kaur et al., 2018).***
- ***Skin line Enhancement Artifact and Enhancing Skin Lesions*** are thin, non-uniform lines of enhancement associated with the difference in skin thickness (fig 8) ***(Kaur et al., 2018).***
- ***Halo Artifact*** "breast-within a breast artifact" is thin curvilinear hyperdense area paralleling the edge of the breast ***(Kaur et al., 2018).***

- ***Negative Contrast Enhancement*** "eclipse sign" occurs in case of cyst, macrocalcification or post-biopsy haematoma. It appears as a rim-enhancing hypodensity (fig 9) ***(Kaur et al., 2018).***
- ***Misregistration artifact*** (***Ripple Artifact)*** is faint alternating black and white lines due to patient motion, and the short interval between the LE and HE exposures (fig 10 & 11) ***(Hill et al., 2013)***
- ***Transient Retention of Contrast in the Vein*** is common, transient and unilateral artifact. It is due to breast compression and disappears in the late phase (fig 12) ***(Kaur et al., 2018).***
- ***Abnormal Timing of the Contrast Bolus*** results in suboptimal image quality and false- negative examination ***(Kaur et al., 2018).***
- ***Antiperspirant Artifacts*****:** due to unclean axilla or skinfolds before image acquisition ***(Kaur et al., 2018).***
- ***Hair Artifacts*****:** it is important to ensure that the patient's hair is pulled back, to avoid obscuring important abnormalities (fig 13) ***(Kaur et al., 2018).***
- ***Motion*** results in blurring of radiopaque structures as well as lesion margins and improper parenchymal suppression (fig 14 & 15) ***(Kaur et al., 2018).***
- ***Clips and Microcacifications*** may be bright or dark according to CEDM software. The low-energy images are used for proper evaluation of microcalcifications (fig 16)

- ***Other high-attenuation artifacts***: Markers, pacemakers, and chest ports shows a dark halo around due to an image-processing artifact as in (fig 17)
- ***Air gap*** is the commonest artifact occurs due to improper contact between the skin and the compression paddle (fig 17) ***(Lewi et al., 2017).***
- ***Contrast contamination (Contrast Splatter)*** due to contamination of the patient by external contrast on the skin, paddle or detector artifacts which mimics in-situ carcinoma (fig 18) ***(Gluskin et al., 2017).***

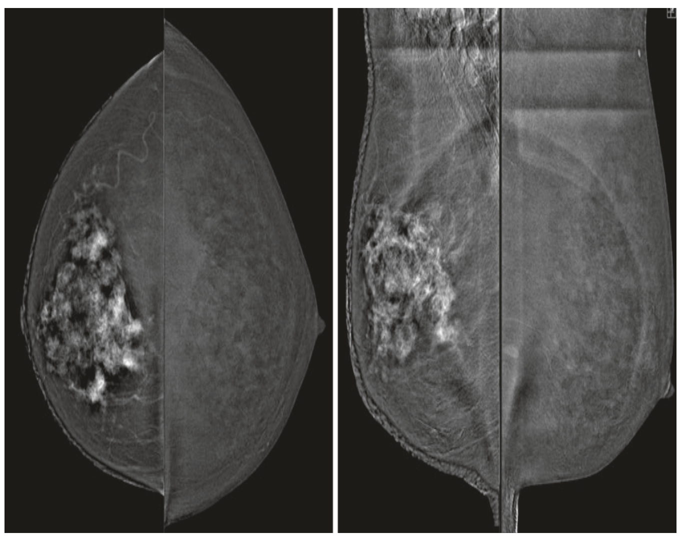

Fig. (7): Ghosting artifact: A single right axillary line was observed in the right MLO, and a double left axillary line ware observed in the left MLO due to shifting of the paddle i.e. CC, right MLO, and left MLO. Ghosting of the CC view of the previously imaged breast projected within the MLO images is also evident. The skin artifact in the diseased right breast is caused by a high detector signal ***(Kaur et al., 2018).***