Bilateral breast carcinoma in a sample of Iraqi patients

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Abstract

Background: Bilateral breast cancer has a rising incidence due to the widespread adoption of bilateral mammography and improved management of breast carcinoma leading to increase in life expectancy and development of a second primary metachronous or synchronous breast cancer.

Objective: To determine the clinical picture of Bilateral breast carcinoma in a sample of Iraqi patients

Patients and Methods: A cross-sectional study was performed in AL-Imamain AL-Khadumain Teaching hospital to determine the clinical features of bilateral breast carcinoma in a sample of Iraqi patients. Data ollection was done in a period of five years, from April 2018, to April 2023. At first, the process was explained to the patients and informed consent taken from all enrolled individuals. The patients were divided into two groups; Group A patients with unilateral breast carcinoma that have nosynchronous tumor, nor they develop metachronus tumor in 5 years. While group B patients they were either hadsynchronous tumor or they develop metachronus tumor in the course of their routine follow up or in case of any breast complaint.

Results: Breast carcinoma was diagnosed in 386(2.29%) patients. Group A (unilateral breast carcinoma) was found in 373(2.21%) while Group B (bilateral breast carcinoma) was found in 13 (0.07%) patients; 8(0.04%) of them were patients withmetachronous tumor, and the other 5(0.02%) patients were synchronous tumor. Family history for breast carcinoma was positive in 66 (17.09 %%) in Group A patients, while family history was positive in 11 (84.61%) in Group B patients which is significant (p value $\leq$ 0.05). Patients on hormonal treatment and developed breast carcinoma was 35(9.38%) in Group A patients, while there were 9 (69.23%) patients in Group B which was significant (p value $\leq$0.05).

Key words: Synchronous or Metachronous Bilateral breast carcinoma.

Introduction

Improved management of breast carcinoma leads to increase in life expectancy and development of a second primary metachronous (MBBC) or synchronous (SBBC) breast cancer. Some patients after having been treated for breast carcinoma may develop a histologically different carcinoma in the contralateral breast. Although there have been very few cases reported about synchronous bilateral breast carcinoma with different histopathological types. Breast cancer may arise from the epithelium of the duct system anywhere from the nipple end of the major lactiferous ducts to the terminal duct unit, which is in the breast lobule. The disease may be entirely in situ, an increasingly common finding with the advent of breast cancer screening, or may be invasive cancer. Ductal carcinoma is the most common variant with lobular carcinoma occurring in up to 15 per cent of cases. Occasionally, the picture may be mixed with both ductal and lobular features. If there is doubt whether a tumour is predominantly lobular in type, immunohistochemical analysis will help in diagnosis. The degree of differentiation of the tumour is usually described using three grades: well differentiated, moderately differentiated or poorly differentiated[1,2].

Magnetic resonance imaging (MRI) is becoming the standard of care when a lobular cancer is diagnosed to assess for multifocality and multicentricity and can be used to assess the extent of DCIS (ductal carcinoma in situ).Recent studies have clarified the role of exogenous hormones, in particular the oral contraceptive pill and Hormone replacement therapy (HRT), in the development of breast cancer. The recent fall in use of HRT in USA and UK has seen a reduction in the incidence of breast cancer in the 50- to 60-year-old cohort. The incidence of synchronous bilateral breast cancer (BBC) is1–3% among newly diagnosed patients, and it has a rising incidence due to the widespread adoption of bilateral mammography as part of the work-up for newly diagnosed unilateral breast cancer (UBC), leading to the early detection of contralateral disease.[3,4,5]

Breast cancer in women surpassed lung cancer as the most common cancer type, in 2020, according to the most recent Global Cancer Incidence, Mortality and Prevalence report[6]. In situ carcinoma is preinvasive cancer that has not breached the epithelial basement membrane. This was previously a rare, usually asymptomatic, finding in breast biopsy specimens but is becoming increasingly common because of the advent of mammographic screening. In situ carcinoma may be ductal (DCIS) or lobular (LCIS), the latter often being multifocal and bilateral. Both are markers for the later development of

invasive cancer, which will develop in at least 20 per cent of patients. Staining for oestrogen and progesterone receptors is now considered routine, as their presence will indicate the use of adjuvant hormonal therapy with tamoxifen or an aromatase inhibitor If bilateral breast carcinoma (BBC) is diagnosed in both breasts virtually simultaneously, it is referred to as synchronous bilateral breast cancer (SBBC). Successive diagnosis of BBC is called metachronous bilateral breast cancer (MBBC). A meta-analysis showed that the incidence of SBBC and MBBC in patients with breast cancer was 2% and 3%, respectively [(7)]. The time interval to distinguish between SBBC and MBBC is still controversial, ranging from 3 months to 5 years [(8-11)]. The World Health Organization (WHO) defined the threshold as 3 months [(12)].

The prognosis of SBBC patients is significantly worse than that of those with MBBC. In addition, the prognostic difference between patients with BBC and unilateral breast cancer (UBC) is also controversial [(13)].

Paget's disease of the nipple is a superficial manifestation of an underlying breast carcinoma. It presents as an eczema-like condition of the nipple and areola, which persists despite local treatment. The nipple is eroded slowly and eventually disappears. If left, the underlying carcinoma will sooner or later become clinically evident. Inflammatory carcinoma is a fortunately rare, highly aggressive cancer that presents as a painful, swollen breast, which is warm with cutaneous oedema. This is the result of blockage of the subdermal lymphatics with carcinoma cells. Inflammatory cancer usually involves at least one-third of the breast and may mimic a breast abscess. A biopsy will confirm the diagnosis [(14)].

The aim of the study is to determine the clinical bilateral breast carcinomain a sample of Iraqi patients.

Patients And Methods

A cross-sectional study was performed in AL-Imamain AL-Khadumain Teaching hospital to determine the clinical features of bilateral breast carcinoma in a sample of Iraqi patients. Sample collection was done in a period of five years, from April 2018, to April 2023. At first, the process was explained to the patients and informed consent taken from all enrolled individuals. The study was approved by the Institution Review Board in the College of Medicine Al-Nahrain University. The study population included 16358 patients attending the breast clinic in the hospital in five years with breast problems (mass, nipple discharge, and/or pain). Triple assessment of the patients was done by detailed history (including family history and any hormonal therapy) and clinical examination, image study including ultrasound, mammography (and magnetic radio image study when indicated), and the preoperative histopathological examination by fine needle aspiration and/or trucut biopsy.

Staging of the patients with breast carcinoma using TNM (T = Tumor N=Node; and M=Metastasis); and the patients were operated upon according to their stage of the diseases, with or without adjuvant therapy (chemotherapy, hormonal therapy and radiotherapy according to their stage of disease. Breast carcinoma was diagnosed in 386 patients, and bilateral breast carcinoma in 13 patients. Follow up of the patients to detect the progress of the disease and to exclude recurrence and/or development of metachronous breast carcinoma. The patients were divided into two groups; Group A patients with unilateral breast carcinoma that have no SBBC, nor they develop metachronus tumor in 5 years. While group B patients they were either had SBBC or they develop metachronus tumor in the course of their routine follow up or in case of any breast complaint. The study was compared with other studies in the word.

Analysis of data was done using the available statistical package of SPSS-27 (statistical packages for social sciences- version 27). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values) accordingly whether they were categorical or continuous.

Results

All the patients were females. The total number of patients attending the breast clinic in the AL-Imamain AL-Khadumain Teaching hospital was 16853 patients in the period of five years, complaining of breast mass, nipple discharge, and/or pain. Breast carcinoma was diagnosed in 386(2.29%) patients. Group A (unilateral breast carcinoma) was found in 373(2.21%) while Group B (bilateral breast carcinoma) was found in 13 (0.08%) patients.

The age of the patients with breast carcinoma attending the breast clinic in AL-Imamain AL-Khadumain Teaching hospital ranged from 18 -79 years, their mean age was 36.16±76 years . Bilateral synchronous (SBBC) and metachronous (MBBC) breast carcinoma was 13 (0.08%) patients; 8(0.04%) of them were patients with MBBC, and the other 5(0.02%) patients were SBBC. Family history in Group A patients waspositive in 66

(17.09 %%) patients, while family history was positive in 11 (84.61%) in Group B patients which is highly significant (p value < 0.0001). All the five patients with SBBC had positive family history of breast carcinoma, while 6 of the 8 patients with MBBC had positive family history of breast carcinoma. Table 1 shows the number of patients in both groups.

Table 1: shows the number of patients and the incidence of positive family history in both groups.

	Group A (unilateral breast carcinoma)	Group B (bilateral breast carcinoma) 13 (0.08%)	
		metachronous breast carcinoma (MBBC)	synchronous breast carcinoma (SBBC)
Number of patients	373(2.21%)	8(0.05%)	5(0.03%)
Positive family history	66 (17.69 %%)	11 (84.62%) significant (p value<0.0001)	

The patients with SBBC were diagnosed by MRI study of the breast (Magnetic Radio-Image) , and they were on heavy doses of hormonal therapy, four patients were infertile patients on prolonged treatment of infertility and heavy doses of hormonal therapy for stimulation of ovaries, and one patient was on contraceptive pills. There were 4 patients with MBBC were on postoperative tamoxifen (anti –estrogen treatment) developed second breast carcinoma less than five years postoperatively, while the other four patients with MBBC were complete their postoperative treatment and developed the second breast carcinoma more than five postoperative year following their management of breast carcinoma.

Patients on hormonal treatment (contraceptive pill or stimulatory of ovaries for treatment of infertility) and developed breast carcinoma was 35(9.38%) in Group A patients, while there were nine (69.23%) patients in Group B were taking hormonal therapy and developed second breast carcinoma which was highly significant (p value < 0.0001).Table 2 shows the number of patients taking hormonal treatment (contraceptive or stimulatory of ovaries for treatment of infertility) before their affection by breast carcinoma.

Table 2: shows the number of patients taking hormonal treatment before their affection by breast carcinoma.

	Group A	Group B	significant
hormonal treatment (contraceptive or stimulatory of ovaries for treatment of infertility)	35(9.38%)	9 (69.23%)	(p value < 0.0001)

The patients with MBBC were presented with another breast carcinoma during their follow up in the period from 2.5-6 years following their management of the first breast carcinoma.

One of the patients in Group A was died due to pulmonary metastasis less than 2 years postoperatively. The total mortality in Group A was 18 (4.66%) patients in the five years of the study while there was one 1(7.69%) patient died in Group B may be due to shorter period of follow up than Group A (P value=0.639) . Table 3 :shows the mortality in both groups.

Table 3 shows the mortality in both groups.

	Group A	Group B	Significant
Mortality	18 (4.83%)	1(7.69%)	P value=0.639

Regarding histopathological examination results, in Group A; there were 135(36.19%) patients had Ductal carcinoma in situ, 176(47.18%) patients had invasive ductal carcinoma, 49(13.14%) patients had Lobular carcinoma, 6(1.61%) patients had Inflammatory carcinoma, and 7(1.88%) patients had Paget's disease. While in Group B; there were 6 (46.15%) patients with ductal (DCIS), 3(23.08%) patients with invasive ductal carcinoma, and 4(30.77%) patient with Lobular carcinoma (P value=0.184). Table 4 shows the histopathological examination results in both groups.

Table 4: The histopathological examination results in both groups.

Histopathology	Group A	Group B
Ductal carcinoma in situ	135(36.19%)	6 (46.15%)
invasive ductal carcinoma	176(47.18%)	3(23.08%)
Lobular carcinoma	49(13.14%)	4(30.77%)
Inflammatory carcinoma	6(1.61%)	None
Paget's disease	7(1.88%)	None
Total	373	13

Discussion

The youngest female patient with breast carcinoma in this study was a 28 years old female, she was unmarried with negative family history and presented with a breast mass (2.6 centimeter in diameter), irregular suspicious mass which proved to be invasive ductal carcinoma of the breast. Another patient was 29 years old female developed breast carcinoma 3 months after a single injection of contraceptive drug, and unfortunately she was died 1.5 year after diagnosis (because she refused any surgical interference).

This study shows that hormonal treatment (contraceptive and drugs used for stimulation of ovaries for treatment of infertility) was significant in development of breast carcinoma (there were 9 (69.23%) patients in Group B were taking hormonal therapy and developed second breast carcinoma which was significant (p value < 0.05).

Also this study shows that the genetic factor and family history was significant in development of breast carcinoma. Family history in Group A patients was positive in 66 (17.09 %%) patients, while family history was positive in 11 (84.61%) in Group B patients which is significant (P-value < 0.05).

In review of literatures, one study shows that the interval between the diagnosis of the first carcinoma of the breast and metachronous breast carcinoma was 45.62 months [(15).] Recently, a study on a Western population reported that the median time interval in patients with MBBC was as long as 111 months the peak onset of breast cancer in Asian populations is earlier than that in Western population [(16)].

First Medical Center of Chinese PLA General Hospital, showed that 98 patients had SBBC, and 25 patients had MBBC, accounting for 1.6% and 0.4% of the breast cancer population, respectively. Some studies from Western countries found that the incidence of MBBC was higher than that of SBBC [(17-20)].

Some studies have also reported similar incidences of MBBC and SBBC [(21-23)] .A meta-analysis showed that the incidence of SBBC and MBBC in patients with breast cancer was 2% and 3% respectively [(17)].

Previous data showed that an absolute risk of development of BBC is 0.5–0.75% per year [(23)] .In recent years, the widespread use of endocrine therapy, such as estrogen modulators and aromatase inhibitors, has significantly reduced the risk of MBBC. Population-based studies have shown that the incidence rate has dropped to 0.1–0.3% per year [(24)]. A study from the Tianjin Medical University Cancer Institute and Hospital, China, showed a prevalence of 1.8% among patients with BBC .However, the study did not divide the BBC group into SBBC and MBBC groups for further analysis. A study based on Indian population data showed a higher incidence of SBBC (0.38%) than MBBC (0.18%).[(25)]

An infiltrative lobular carcinoma is more prone to multicentricity and bilaterality as compared to infiltrative ductal carcinoma [(25)].Regarding prognosis of BBC, Most authors indicate that SBC and MBC diagnosed within 5 years of index cancer are associated with poorer prognosis. Hartmann and colleagues analysed the mortality rates of over 100,000 breast cancer patients from Swedish cancer data base[(26)] .They found that women with SBC and MBC occurring within 10 years are more likely die of breast cancer compared to unilateral patients. In contrast population based studies from Australia, Switzerland and

Geneva demonstrated that BBC was not associated with impaired survival [27].

Some studies showed that patients with (Estrogen/Progesterone) ER/PR (−) breast cancer were more likely to develop MBBC than those with ER/PR (+) breast cancer probably because patients with ER/PR (+) breast cancer received endocrine therapy, resulting in the reduction of metachronous breast carcinoma[28].

Other studies proved that the prognosis of SBBC was significantly worse than that of MBBC [29]. Histopathologically, lobular carcinoma as a risk factor for BBC was found in only one of 60 patients in some studies, while two other studies in India evaluating bilateral breast carcinoma BBC found no lobular carcinomas in their patients [30].

Patient with breast carcinoma should be informed about the risk of development of metachronous breast carcinoma so strict follow up is essential.

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