CASE REPORT

AN UNUSUAL LARGE SIZE DUCTAL CARCINOMA IN SITU IN A PATIENT ON LITHIUM THERAPY: A CASE REPORT WITH LITERATURE REVIEW

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Background: Ductal carcinoma in situ (DCIS) is the earliest and most curable form of breast cancer. Patients who harbour this disease for quite some time usually have micro invasion by virtue of high-grade disease or big size. Herein, we report a case of 56-year-old postmenopausal woman presenting with a one-year history of blood-stained nipple discharge from right breast. She was a known case of depression receiving oral anti-depressants containing lithium for 20 years. Her mammogram was performed followed by ultrasound breast. Mammogram identified suspicious clusters of micro calcifications hence subjected to stereotactic core biopsy which revealed two separate foci of high-grade DCIS. Therefore, based on her clinical, radiological, and pathological findings she was subjected to mastectomy and sentinel node biopsy. Final histopathology showed big DCIS (10×8×3 cm in size) with immunohistochemical stains confirmed no invasive focus on extensive sampling. Therefore, we postulated that it might be correlated to the use of Lithium which has anti-cancer properties.

Keywords: Ductal carcinoma in situ; Lithium; Breast

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INTRODUCTION

Ductal carcinoma in situ (DCIS) comprises about 20 to 25% of all breast malignancies having a propensity to transform into an invasive ductal carcinoma in approximately 13–50% of cases over a time of 10 years or more after initial diagnosis.[1] Numerous epidemiological studies have discovered that patients with mental illnesses like schizophrenia or bipolar disorder are more likely to suffer from malignancies of various sites (lung, prostate, colorectal).[2] Similarly, bipolar disorder confers an increased risk of breast malignancy in women when compared to general population.[3] This may be attributed to unhealthy behaviours like smoking, alcohol abuse, malnutrition, or lack of exercise and, possibly, medication side effects.[2] Data linkage studies have also proved a positive correlation between bipolar disorder and the breast cancer-related genes BRCA2 and PALB2.[4] Lithium was found to be the most efficacious drug for the treatment of this disorder and so far, research has not demonstrated any relationship between its use and incidence of invasive breast cancer.[3] Moreover, literature search has proven the role of lithium in not just using it as an anti-maniac agent but also possessing properties that make it a useful adjunct in treating different malignancies.[5] However, the anti-invasive potential of lithium in ductal carcinoma in situ (DCIS) or breast carcinoma has not been explored. We would like to report a case of a woman on lithium who had a very large ductal carcinoma in situ (DCIS). A very large DCIS is an infrequent presentation. Hence, we hypothesized that lithium use might be responsible for halting the invasive potential of a large DCIS. To the best of our knowledge, this is the first case report speculating potential of lithium containing medications having anti-cancer potential, particularly in breast.

CASE REPORT

A 56-year-old postmenopausal woman, unmarried, known case of depression receiving oral anti-depressants containing lithium (600 mg once daily) for 20 years, presented with a one-year history of blood-stained nipple discharge from right breast on and off. An ill-defined area was palpable in retro-areolar region of right breast with copious, blood-stained nipple discharge from a single duct. The patient had not sought consultation previously for this complaint nor had undergone any breast imaging. Her mammogram was performed which revealed diffusely spread clusters of pleomorphic microcalcifications particularly involving upper outer quadrant and retro-areolar region of right breast (Figure-1). An ultrasound scan of the breast showed dilated ducts with no intraductal lesion and benign appearing ipsilateral axillary lymph node. Subsequently, two clusters of micro calcifications (5.5 cm apart from each other) were subjected to stereotactic core biopsy which revealed high grade comedo ductal carcinoma in situ (DCIS). Based on clinical, radiological and histological findings, patient was subjected to mastectomy with sentinel lymph node biopsy. Final histopathology revealed high grade DCIS

with comedo necrosis, measuring 10×8×3 cm. Solid and cribriform patterns were also seen. (Figure-2). Sentinel nodes were benign. Immunohistochemical analysis was also performed with the following immunohistochemical markers: cytokeratin AE1 / AE3 (CKAE1/AE3) and p63. Tumour cells were positive for CKAE1/AE3 while positive p63 immunostaining indicated intact myoepithelial cell layer of ducts supporting the diagnosis of ductal carcinoma in situ with no invasive focus on multiple serials and levels. As her oestrogen and progesterone receptor status were strongly positive, she was started on Tamoxifen 20 mg daily. Subsequent follow up visits showed that she is doing well.

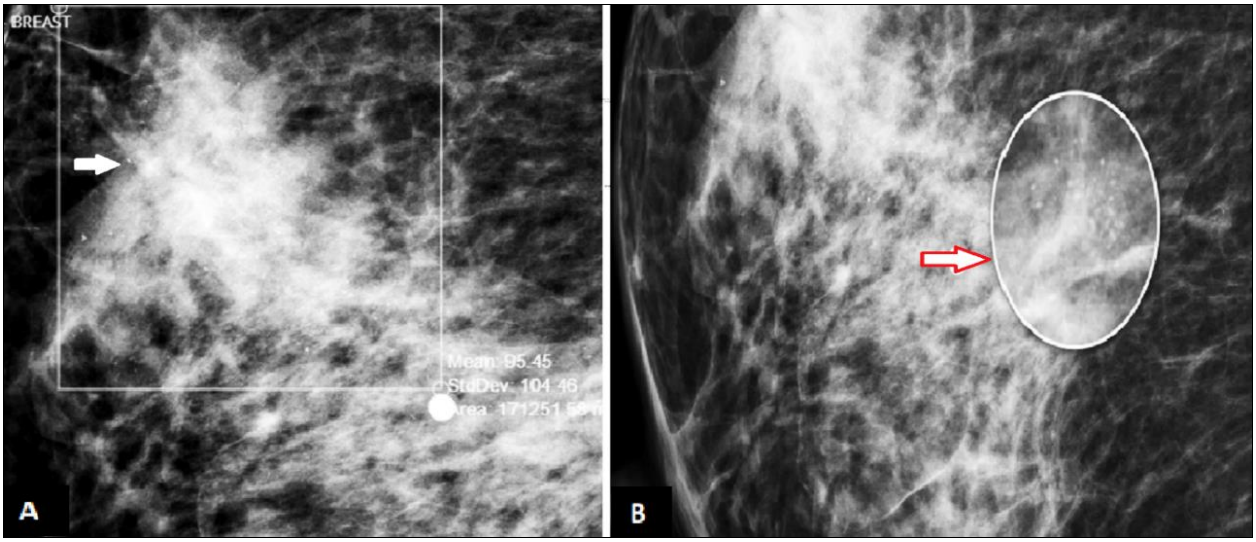

Figure-1: Mammogram of the right breast (Magnified View)

This magnified view of the mammogram shows diffusely spread clusters of pleomorphic micro calcifications particularly involving upper outer quadrant and retro-areolar region (circled).

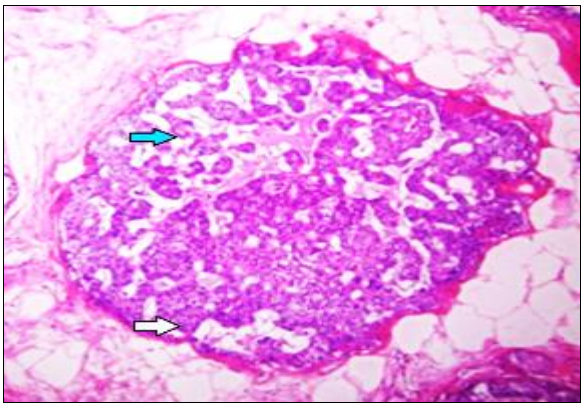

Figure-2: Haematoxylin and Eosin (H&E) stain (Mastectomy Specimen)

This demonstrates ductal carcinoma in situ. The dilated duct shows intraluminal proliferation of ductal epithelial cells in cribriform configuration (blue & white arrows).

DISCUSSION

Ductal carcinoma in situ (DCIS) is an uncommon presentation of breast cancer in Pakistan because of limited cancer screening programmes.[6] Local data is unavailable for exact incidence of ductal carcinoma in situ (DCIS) in Pakistani population. The few cases that are diagnosed with DCIS, present with either suspicious findings on screening mammogram, symptoms of blood-stained nipple discharge, or a palpable mass. As far as natural history of disease is concerned DCIS, over a period of time, would progress to invasive carcinoma depending on grade, comedo necrosis and its size. Literature suggests that ductal carcinoma in situ (DCIS) with size $\geq$2.5 cm can be associated with areas of microinvasion or invasive carcinoma and axillary metastasis. Maffuz *et al* reported that the incidence of microinvasion and invasion bears a direct relationship to tumour size (10% for DCIS tumour size of 2.5–3.5 cm, 57% for 3.6–4.5 cm, and 71% for tumours between 4.5 and 6 cm).[7] In our reported case, despite a bigger tumour size (10×8 cm), no evidence of invasion was found. This absence of invasion in a very large DCIS could be because of long term lithium use. Literature search did not reveal any study reporting any therapeutic agent that caused in vivo ductal carcinoma in situ (DCIS) of breast from progressing to invasive carcinoma.

Lithium inhibits glycogen synthase kinase-3 beta (GSK-3b), an enzyme involved in the pathogenesis of cancer. It reduces the overall risk of cancer in patients with bipolar disorders as compared to anticonvulsant only exposure (HR=0.735, 95% CI).[5] In fact, it has been suggested as an anti-cancer agent for malignancies like

pancreatic cancer and glioblastoma multiforme.[8] In addition, it inhibits tumour lymphogenesis through the inhibition of transforming growth factor-β-induced protein (TGFBIp) expression in colon cancer cells thereby, limiting its metastasizing potential.[9] It may also help in maintaining the balance between oxidant and antioxidant states in hepatocellular carcinoma (HCC) cells, thus limiting the progression of precancerous condition towards malignancy.[9] It has been reported to promote apoptosis in human leukaemia NB4 cells in acute promyelocytic leukaemia (APL).[10]

Lithium not only inhibits initiation and development of certain cancers but can also be used as an adjunct with cytotoxic agents thus potentiating their actions. Examples include cancers of pancreas, prostate, ovaries, endometrium, breast, and the neuroendocrine tumours.[5,8,11] Evidence has also supported the role of lithium in decreasing melanoma risk and its associated mortality.[5]

Lithium chloride sensitizes breast cancer cells to ionizing radiation and has also been used in EGFR, PI3 kinase expressing cell lines. PI3 kinase and EGFR mutation may be predictors of response to lithium in breast cancer.[12] However, one study reported that it may increase the incidence of renal cancers.[13]

Lithium has also been proven to be neuroprotectant in cancer patients and is known to reduce chemotherapy induced cardiotoxicity and peripheral neuropathy. This could enable patients to tolerate more aggressive treatments.[14] Moreover, lithium use has been demonstrated to correct leukopenia during cancer treatment. Leukopenia is a common complication of chemotherapy and radiation and often results in delayed treatments. Studies have demonstrated that lithium can shorten the period of leukopenia in comparison to the control group.[15]

CONCLUSION

Considering the large size of the ductal carcinoma in situ, it was generally expected that it must be associated with invasive focus in the breast, however, histopathological examination revealed no such change. Therefore, keeping in mind the anti-proliferative effects of lithium in cancers, we speculated that it may be associated with its use. Further research is invited to investigate and prove the beneficial effects of lithium apart from its use in psychiatric and bipolar disorders.

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