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Male breast neoplasia in association with selective serotonin re-uptake inhibitor therapy: a report of three cases

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Male breast cancer is a rare condition with very poorly understood risk factors. We report three cases of men witl malignant and pre-malignant breast disease who had all been prescribed selective serotonin re-uptake inhibitor (SSRIs) for depression. Concerns about an association between this group of drugs and breast cancer in wome have been previously raised and experimental evidence has suggested that these drugs could influence regulation o cellular proliferation acting through internal cellular messengers. Risk factors for the development of breast cance are likely to be multifactorial, possibly more so in women given the complex physiological changes that occur in th female breast. Whilst the cases we report are anecdotal and other risk factors may be present, we suggest tha assessment of any possible contribution that SSRI therapy may make to the development of breast neoplasia ma be more easily assessed in a male population.

Key words: male; breast cancer; anti-depressant therapy; risk factors.

INTRODUCTION

Carcinoma of the male breast is a rare malignant lesion and accounts for less than 1% of all breast cancers.[1] Risk factors for the development of the disease in men are poorly understood with the exception of Kleinfelter's Syndrome which appears associated with an increased risk.[2] Other risk factors including gynaecomastia, testicular disorders, exogenous oestrogen therapy, radiation, obesity, alcohol abuse, diet, exercise and occupational exposures have all been previously postulated.[1,3,4] A family history of breast cancer has also been noted as a risk factor and recent studies have shown BRCA2 germ-line mutations in men with breast cancer indicating a probable genetic link.[5]

Selective serotonin re-uptake inhibitors (SSRIs) represent a relatively new class of anti-depressant drugs first developed in the 1970s. This group, which includes the drugs paroxetine, fluoxetine, fluvoxamine and setraline have come into wide clinical use in the late 1980s anc 1990s largely due to having fewer side-effects than the more traditional tricyclic anti-depressant group of drugs and their relative lack of toxicity in overdose.[6,7]

Reports in the scientific literature have suggested that anti-depressant drugs, including SSRIs, may be associated with accelerated tumour growth in rodent models.[8] The possibility of an association between anti-depressant therapy and breast cancer risk has been previously considered in women. Studies have raised concerns about SSRI usage and the risk of developing breast cancer.[9–11] No reports of any studies of SSRI usage in men with breast disease have, however, to our knowledge been published. In this paper we report three men presenting with neoplastic or pre-neoplastic breast disease to our hospital all of whom were on prescribed SSRIs prior to presentation.

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CASE REPORTS

Case 1

A 71-year-old man presented to the breast clinic in August 1999 with a 2-month history of a right breast

lump. There was no family history of breast disease. He had been taking fluoxetine 20 mg daily since 1996 and immediately prior to his referral had been commenced on finasteride 5 mg daily for prostatic symptoms. The lesion was clinically regarded as suspicious and a fine needle aspirate performed in the clinic was reported as equivocal. A subsequent core biopsy confirmed the presence of invasive carcinoma and he underwent a right Patey mastectomy and axillary clearance. This showed a grade 1 invasive ductal carcinoma of no special type with no evidence of metastatic carcinoma in 14 lymph nodes. The carcinoma was oestrogen receptor positive as assessed by immunohistochemistry. He was commenced on tamoxifen and remains well with no evidence of recurrence.

Case 2

A 58-year-old man presented to the breast clinic in June 1995 with a 2–3-week history of a lump behind the left nipple. He had a family history of breast cancer with his mother and maternal aunts dying of the disease. He also had a sister and uncle who had both died of bronchial carcinoma. He had been treated with paroxetine 20 mg daily periodically for the previous year. He drank 20–30 pints of beer per week but there were no features to suggest liver disease and liver function tests were normal. A fine needle aspirate was reported as showing malignant cells and subsequently a left Patey mastectomy and axillary clearance was performed. This revealed a grade 2 invasive ductal carcinoma of no special type with focal ductal carcinoma *in situ* (DCIS) present as a minor component. Metastatic carcinoma was identified in one of seven lymph nodes. The carcinoma was oestrogen receptor positive as assessed by immunohistochemistry and he was commenced on tamoxifen and given post-operative radiotherapy to the skin flaps. He currently remains well with no evidence of recurrence.

Case 3

A 62-year-old man presented to the breast clinic in April 1999 with a history of intermittent bloody nipple discharge since 1998. This had been treated by his general practitioner with antibiotics but this had recurred. There was no family history of breast disease. He had been prescribed fluoxetine since 1998 for depression. On examination a bloody nipple discharge was observed but no mass was detectable. A left major duct excision (Hadfield's procedure) was performed. Examination of the specimen revealed atypical ductal epithelial hyperplasia (ADH) within a large duct but no evidence of malignancy. He has been kept under review with no evidence of any further symptoms.

DISCUSSION

Neoplastic disease of the male breast is rare.[1] Since 1991 in this hospital, including the cases described above, we have seen only six cases of invasive carcinoma, one of DCIS and one case of ADH. The case notes of seven of these patients were retrieved and reviewed and only in the cases described above was there any evidence of prescribed anti-depressant therapy prior to presentation. Although this represents a small sample, the proportion of these patients on treatment with SSRIs at presentation attracted our attention.

Concern about the possible association between anti-depressant therapy and the development of breast cancer in women has been stimulated by animal studies demonstrating a high incidence of mouse mammary tumours in animals treated with fluoxetine and amitriptyline using the dimethylbenzanthracene (DMBA) model of mouse carcinogenesis.[8] Not only have these studies shown an increase in the number of tumours developing but also a reduction in the tumour latency. These drugs have also been shown to stimulate DNA synthesis in fibrosarcoma cell lines[8] at similar relevant clinical concentrations suggesting possible effects on cell cycle regulation. A possible mechanism for this effect may be that the chemical structures of these drugs are similar to the anti-oestrogen binding site/intracellular histamine receptor (AEBS) ligand N,N-diethyl-2-[4-phenyl–methyl)phenoxy]ethanamine HCL (DPPE) which is recognized as promoting tumour growth *in vivo*.[8,12]

Male neoplastic breast disease is considered to be pathologically and biologically the same as that in women.[1] The possibility of an association between breast carcinoma and anti-depressants in women has been suggested and articles have even reached the lay scientific literature.[13] Recent epidemiological studies in women with breast cancer have found that the relative risk for regular use of SSRI in the year prior to diagnosis was 1.8 with 95% confidence intervals (CI) of 1.0–3.3.[9] These authors concluded that these results were 'far from reassuring' but other studies have suggested that the risk may be even more substantial. A study, based on the Ontario Cancer Registry,[11] showed an odds ratio of 7.2 with 95% CI of 0.9–58.3 for breast cancer in women who had used paroxetine compared with controls. Earlier studies examined use of anti-depressants, anxiolytics and hypnotics in women with breast cancer and found a higher incidence of metastases at presentation, or recurrence within 12 months, in those treated.[10] This author, however, did not specifically look at the group taking anti-depressants in isolation and others have found no evidence of an increased risk of recurrence or the development of second lesions, in women with breast cancer subsequently treated with SSRIs.[14]

We can find no reports of any previous description of male neoplastic breast disease in association with SSRI therapy. Our description of two from six cases of invasive

male breast cancer identified in our hospital since 1991 and a further patient with ADH in association with SSRI therapy raises further interesting questions about a possible association. We fully accept that this represents anecdotal evidence and that there may be other factors in these cases, such as other therapeutic agents (finastaride in case 1) and a heavy alcohol intake or family history (case 2), that could be postulated to play a role in the development of carcinomas in these cases. In case 1, however, the finasteride was commenced immediately prior to referral and in case 2 there were no clinical features to suggest liver disease and liver function tests were normal.

Risk factors for the development of breast cancer, in men and women are likely to be complex and multifactorial. Even in large epidemiological studies the relative contribution of minor risk factors may be difficult to detect. Although male breast cancer is rare the absence of the complex physiological changes in the breast throughout life may make elucidation of such lesser risk factors more obvious and we would suggest that a study of anti-depressant usage in relation to male breast cancer may be easier to interpret than in women.

ADDENDUM

Following submission of this manuscript an 87-year-old man presented to the breast clinic in July 2000 with a right breast mass. A core biopsy confirmed an invasive carcinoma consistent with a primary lesion in the breast. Immunohistochemical staining revealed the tumour to be strongly positive for oestrogen receptor and he was commenced on primary tamoxifen therapy. He had a past history of phaeochromocytoma and depression for which he had been treated with paroxetine.

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Metastatic malignant acrospiroma of the hand

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We present the case of a 37-year-old man with multiple pulmonary metastases of a primarily unknown primar tumour. Thorough revision of the medical history yielded that he had already passed three resections of a righ palmar mass, which had been described as a benign tumour. Clinical examination showed a thickened scar with suspicious palpable mass in the right hand. Excision of this scar and the tumour mass with histopathologic examination now revealed a malignant acrospiroma. Resection of the pulmonary metastases histologically als confirmed a malignant acrospiroma. The following radical resection of the metacarpals II and III with the index an middle finger under the assumption of a wide compartment resection achieved tumour free margins and proved t be efficient with the patient being relapse free for 4 years from this operation.

Although the prognosis of this tumour is generally unfavourable this particular case demonstrates the value of radical surgical resection as the mainstay of treating such highly malignant sweat gland tumours of the hand.

Key words: acrospiroma; radical resection; hand tumour; metastasis.