Case Report

A brother and sister with breast cancer, BRCA2 mutations and bilateral supernumerary nipples

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Abstract: We describe a 54-year-old man with breast cancer and a BRCA2 mutation who was also found to have bilateral supernumerary nipples. His sister, also with a BRCA2 mutation, was diagnosed with breast cancer in her late forties; she also had bilateral supernumerary nipples. We address the significance of breast cancer arising in breast tissue underlying supernumerary nipples; the known association between supernumerary nipples and genitourinary malignancies/malformations and the possible link between BRCA2 and supernumerary nipple development. We believe that this is the first described case of the latter. We then outline an approach to further management for supernumerary nipple cases.

Keywords: Supernumerary nipples; ectopic; breast cancer; familial; genitourinary malformations

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Introduction

Supernumerary nipples are congenital malformations of nipples or their related tissue that arise in addition to the normal bilateral nipples of the chest. Their prevalence is between 0.22% and 5.6% (1), although there may be under-reporting. Supernumerary nipples typically appear along the embryonic milk lines from axillae to inguinal regions. *Ectopic* supernumerary nipples may be found beyond the milk lines. Supernumerary nipples may arise sporadically or through familial inheritance via autosomal dominant, X-linked dominant or X-linked recessive transmission (1-3). Their main significance lies in the potential for malignancies to arise in underlying breast tissue, especially in ectopic locations (4) and, in the association between supernumerary nipples and genitourinary malformations and malignancies (5).

Case presentation

A phenotypically normal 54-year-old man was diagnosed with infiltrating ductal carcinoma of the right breast for which he underwent right mastectomy and right axillary clearance. Seven of ten right axillary lymph nodes were positive for metastatic disease. His histopathological staging was pT1pN2M0.

He received postoperative chemotherapy and radiotherapy to the right chest wall and right supraclavicular fossa. He was subsequently commenced on tamoxifen.

There was no evidence of cancer recurrence at follow up 12 months after completing radiotherapy. However, at the follow up examination he was incidentally noted to have bilateral supernumerary nipples along the milk line on the lower chest/upper abdomen (*Figure 1*). Clinically, the patient or his relatives had no genetic syndrome. However, his family history was significant for one sister having had breast cancer diagnosed at age 40 (*Figure 2*). Interestingly, the same sister also had bilateral supernumerary nipples, which had previously been removed for cosmetic reasons, and a BRCA2 mutation, as had our case.

Ultrasound in the region of the supernumerary nipples revealed elevation of the skin with a little underlying hypoechoic tissue. No convincing mass was seen and there was no connection to deeper structures. The soft tissues of the anterior abdominal wall appeared normal. We recommended removal of the two supernumerary nipples, which were subsequently resected. The macroscopic and

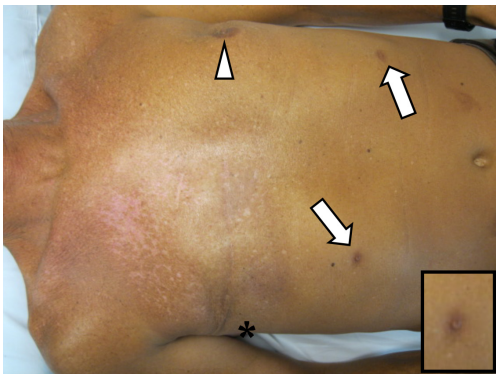

Figure 1 Image of the patient showing bilateral supernumerary nipples along the milk line on the lower chest and abdomen. Bottom right: magnified view of left accessory nipple and areola.

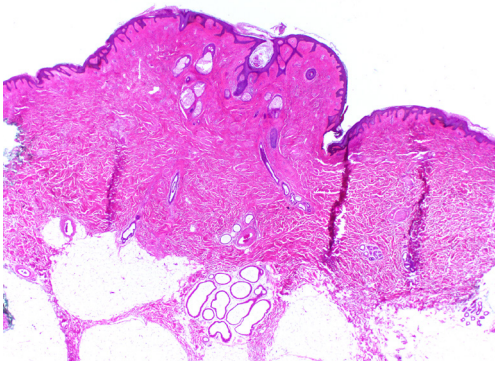

Figure 3 Low power (×4) histological view of one of the accessory nipples from the male case. Macroscopically and microscopically normal nipples, with a very small amount of underlying glandular tissue.

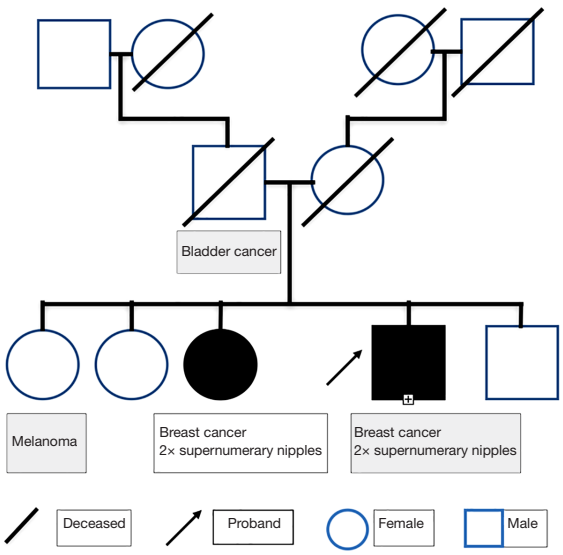

Figure 2 Patient's family tree demonstrating pattern of disease.

microscopic appearance of the nipples was normal. The histological appearance of the resected specimen is shown in *Figure 3*.

Discussion

Supernumerary nipples most commonly arise along the milk lines, which extend from the axilla to the groin bilaterally. However, they may also appear in other regions of the chest and abdomen, as well as the thighs, upper limbs, posterior thorax and head (4,6,7). Supernumerary nipples may be associated with underlying breast tissue. This breast tissue can have many, if not all, the histologic characteristics of normal breast tissue. As a result, breast adenomas and malignancies can arise in the breast tissue underlying supernumerary nipples. Furthermore, ectopic breast tissue is more prone to malignant change than normal breast tissue. Evidence also exists that ectopic breast cancer carries a poorer prognosis than cancer arising in normal breast tissue; recommendations have been made for regular cancer screening in ectopic breast tissue and consideration of prophylactic resection (8,9).

Of further significance is the association between supernumerary nipples and genitourinary tract cancer, as well as possibly increased genitourinary tract malformations (10). As a result, our patient underwent ultrasound of the genitourinary tract. The ultrasound findings were normal.

Our patient's family tree is consistent with an autosomal dominant pattern of breast cancer inheritance, a mode characteristic of BRCA2 mutations and which has also been reported previously for supernumerary nipples (10). The pattern would also be consistent with a X-linked pattern of inheritance with variable penetrance. There are a number of syndromes associated with supernumerary nipples. Those with known gene mutations are summarised in *Table 1*. Supernumerary nipples have also been associated with syndromes due to aneuploidy or partial aneuploidy and include Turner syndrome, trisomy 8, partial chromosome 3p trisomy (10) and trisomy 2p syndrome (11). Fleisher's syndrome is another very rare syndrome associated with supernumerary nipples (10).

Male breast cancer accounts for about 1% of all incidents of breast carcinoma. Approximately 20% of men with

Table 1 Genetic mutations and related syndromes associated with supernumerary nipples

Syndrome or disease	Genetic basis	Comments	Refs
Char syndrome	Missense transcription factor AP-2 beta defects	The AP-2 family appears to regulate expression of genes required for development of tissues of ectodermal origin	(11-13)
Simpson-Golabi-Behmel syndrome type 1	Frequently due to a mutation in the gene encoding glypican-3	Main function of membrane-attached glypicans is to regulate the signaling of Wnts, Hedgehogs, fibroblast growth factors and bone morphogenetic proteins	(11,14-15)
Neurofibromatosis type 1	Mutations in neurofibromin 1 gene	Neurofibromin 1 gene has capacity to regulate RAS-cyclic AMP pathway, ERK/MAP kinase cascade, adenylyl cyclase and cytoskeletal assembly	(10,16-17)
Hailey-Hailey disease	Defect in gene ATP2C1 on chromosome 3q21–24	ATP2C1 is a high affinity Mn^{2+} pump in the Golgi	(11,18-19)
Bartsocas-Papas syndrome	Homozygous mutation in the RIPK4 gene on chromosome 21q22	RIPK4 is a direct transcriptional target of p63, a known regulator of stratified epithelial development	(11,20-21)
Some spondylocostal dysostosis syndromes with different patterns of inheritance	Five subtypes of SCDO are recognized, based on the underlying gene involved	SCDO subtype not specified in ref 17 nor ref 18	(11,22-24)

breast cancer have a family history of the disease. Genetic risk factors for breast cancer in men include Klinefelter syndrome and BRCA1 and BRCA2 mutations, with the latter a more characteristic predisposing factor. Mutations in the PTEN tumour suppressor gene and the mismatch repair gene human mutL homolog 1 (hMLH1) have been associated with, but not clearly shown, to increase breast cancer risk in men (25).

Conclusions

The kindred we describe here carries the breast cancer predisposition gene, BRCA2. It is anyway a 'high risk' kindred for having a BRCA1 or BRCA2 mutation, in that one female had breast cancer at an early age and there was a breast cancer-affected male in the kindred. Given the rarity of male breast cancer and supernumerary nipples, the possibility exists that a mutation in the BRCA2 gene affected its associated functions and is responsible for both the breast cancer and the supernumerary nipples. Should this be the case, wild-type BRCA2 would be acting as a suppressor of supernumerary nipple formation.

Given the risk of breast cancer arising in ectopic breast tissue we believe that consideration should be given to removal of supernumerary nipples and any associated breast tissue, in patients previously diagnosed with breast cancer and in patients for which there is a family history of breast cancer.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Ethics approval for this study was given by North Coast Area Health Region Ethics Committee (ID: 08-16) and the patient who was the subject of the case report gave consent for reproduction of a de-identified photograph of himself.

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