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CLINICAL CASE

Fluoroscopy and Paget's disease of the breast

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Summary

A case report concerning a 36-year-old woman having developed Paget's disease of the breast subsequent to multiple fluoroscopies as a child for the investigation of Fallot's anomaly/pulmonary atresia is presented. This case is discussed with a brief review of the relevant literature regarding current theories as to the pathogenesis of Paget's disease of the breast, ionizing radiation and its role in dysplastic breast disease and their possible interrelation.

Key words: breast, Fallot's anomaly, fluoroscopy, nipple, Paget's disease

Case presentation

A 36-year-old woman with a history of Fallot's anomaly/pulmonary atresia presented with a 3-month history of a "dry scab" on the right nipple with no associated breast lump. The patient had not had any corrective surgery for her Fallot's anomaly/pulmonary atresia but she had extensive cardiac fluoroscopy immediately after birth and then at age 7 years. It was calculated that she would have received a total dose of at least 5.4 Gy.

Biopsy of the right nipple showed epidermal proliferation of single cells and groups of epithelial cells with eosinophilic cytoplasm and prominent nucleoli. No invasion of the dermis was seen and immunohistochemistry showed these atypical cells to be positive for epithelial membrane antigen (EMA), appearances consistent with Paget's disease of the nipple. The patient underwent right central quadrantectomy and a Grisotti flap. Histology confirmed Paget's disease of the nipple and the underlying subareolar ducts and breast tissue showed a single duct containing high-grade ductal carcinoma *in situ* (DCIS) extending for 6mm. The patient is currently undergoing adjuvant radiotherapy.

Discussion

Paget's disease of the breast (PDB) is a malignant disorder of the nipple and areola accounting for less than 5% of all breast carcinoma [1]. The clinical appearance is usually a well-defined, slightly raised, red scaly plaque which is frequently fissured and ulcerated [2,3]. A small proportion of PDB can be clinically occult and diagnosed on histology of mastectomy or nipple excision specimens for other diagnoses [4]. The histological hallmark of PDB is infiltration of the epidermis by malignant cells referred to as Paget cells which are large pleiomorphic cells with abundant pale-staining cytoplasm and hyperchromatic nuclei with conspicuous nucleoli [3]. These cells often contain mucin (diastase-resistant, periodic-acid-Schiff (PAS) positive reaction) [5] and are immunoreactive for low-molecular weight keratins [6,7] and epithelial membrane antigen c-erb-B2 (HER2/neu) [8].

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PDB was first described by Sir James Paget in 1874 when he reported a series of 15 cases of chronic ulceration of the nipple occurring in women aged 40-60 and in every case cancer appeared in the affected breast within 2 years [9]. Patients with PDB who present with an associated palpable mass in the breast, are most likely to harbour invasive disease whereas patients who present without a clinical mass most often have non-invasive disease [4,10]. When a breast mass is present, this is not always adjacent to the nipple. Kollmorgen et al. [4], observed that only 61% of tumors were centrally located (within 2cm of the areolar margin).

There are two theories to explain the histogenesis of PDB. The most favoured one is the epidermotropic theory where Paget cells are cells that have migrated/extended from underlying DCIS or invasive ductal carcinoma (IDC) along lactiferous ducts to the epidermis. This theory is based on: a) the frequent association of PDB with underlying DCIS and the presence of direct extension of the tumour cells into the overlying epidermis via ducts [11-13]; b) the cytological, immunohistochemical and genetic similarities between the atypical cells in the epidermis and the underlying breast carcinoma [14-19]; and c) the chemotactic effect of keratinocyte secretory factors on malignant cells [20,21]. The second theory known as the *in situ* transformation theory suggests that Paget cells arise from the malignant transformation of basal cells in the epidermis secondary to field effects. Cells in this field effect are believed to "belong to the same type of tissue, to be susceptible to oncogenic alteration and to be predisposed to the same factors that induce genetic alterations such as heredity, hormones and possibly mutagenic factors released from adjacent tumour cells" [13]. This theory is supported by: a) the presence of desmosomes or desmosome-like structures between Paget cells and adjacent keratinocytes [13,22]; b) skip lesions characterized by foci of DCIS in the same duct separated by a long portion of duct without epithelial hyperplasia [13]; and c) Paget cells being most prominent in the lower part of the epidermis may suggest that they arise from pluripotent cells of the basal layer.

Clear cells of the nipple are considered to be ectopic mammary elements in the epidermis of the nipple and are only present in about 10% of women [23,24]. These cells, first described by Toker, express cytokeratin 7, a low molecular weight cytokeratin, also expressed in Paget cells and DCIS/IDC. In a minority of cases PDB can be present in the absence of underlying DCIS/IDC [9,25]. In such cases Toker cells have been suggested to be the precursor cells of PDB. Also Toker cells, due to their location, fall into the field effect with DCIS/IDC. In a recent study by Morandi et al. [14], microdissection and clonality analysis were used to compare the genetic profile of intraepithelial cancer cells to that of underlying DCIS/IDC. In only 20% of the cases intraepithelial cancer cells were genetically different from underlying carcinomas representing coincidental (collision) tumors.

The Her2/neu/c-Erb-B2 molecule is a transmembrane receptor tyrosine kinase of the epidermal growth factor receptor family [26]. Recent studies suggest that for Her2 to be activated it needs to form heterodimers with other ErbB receptor family members (Her1, Her3, Her4) [27]. The incidence of the Her2/neu protein overexpression in IDC is approximately 30% [28], whereas in PDB it was found in more than 70% of the cases [29,30]. It seems that in both IDC and PDB overexpression of the Her2/neu protein is caused by amplification of its gene [31]. The overexpression of Her2/neu protein in an unusually high percentage of patients with Paget's disease (Paget cells and their associated carcinomas) suggests that it may have an important role in the pathogenesis of this disease and the production of the Paget's phenotype. In a study by Schelfhout et al. [20], a motility factor was isolated from keratinocyte-conditioned medium named heregulin-α. Heregulin-α induces spreading, motility and chemotaxis of SK-BR-3 cells (human breast cancer cells overexpressing Her2/neu). Motility factor activities of heregulin-α are inhibited by a monoclonal antibody directed against the extracellular domain of Her2/neu. Normal epidermal cells produce heregulin-α mRNA, and heregulin receptors, Her3 and/or Her4 as well as their co-receptor Her2/neu, are expressed by Paget cells.

Exposure of the female breast to radiation has been shown to increase the risk of breast cancer. Evidence comes from studies of atomic bomb survivors and patients exposed to therapeutic/diagnostic ionizing radiation (pulmonary tuberculosis, scoliosis, acute post-partum mastitis, enlarged thymus, skin hemangiomas, Hodgkin's disease) [32].

The risk of breast cancer from exposure to ionizing radiation during infancy (<1 year of age) has been examined in a cohort of 1201 women who were exposed to low levels of scatter radiation to the breast as babies when they received thymic irradiation for an enlarged thymus gland [33]. Their 2469 non-irradiated sisters were used for comparison. The mean dose absorbed by the breast was 0.69 Gy and a relative risk of 3.48 for 1 Gy of radiation was noted (Excess Relative Risk (ERR)/Gy of 2.48). The first breast cancer was not diagnosed until 28 years after irradiation and most occurred after the age of 38 years and the median age

at diagnosis was similar for the irradiated and control groups (39 *versus* 39.5 years, respectively). Other studies have also investigated the risk of breast cancer from exposure to radiation in young age and include: 1) patients who underwent multiple fluoroscopic examinations during treatment for pulmonary tuberculosis (Massachusetts TB fluoroscopy study, <15 years old at time of first exposure, ERR/Gy=0.48) [34]; 2) patients with scoliosis exposed to multiple diagnostic X-rays (average age of diagnosis was 12.3 years, ERR/Gy=6.3) [35]; 3) patients who received radiotherapy for treatment of angioblastomas (mean age at first exposure was 6 months, ERR/Gy=0.35) [36]; 4) atomic bomb survivors (< 4 years of age at exposure, ERR/Gy=4.64) [37]; and 5) patients who were treated with radiation for childhood Hodgkin's disease [38]. In the latter case, the cohort consisted of children between 1-16 years of age when Hodgkin's disease was diagnosed. The median age at the time of diagnosis of breast cancers was 31.5 years. The risk of breast cancer was 75 times the risk in the general population and most breast cancers occurred in patients who had received at least 2Gy in the mantle region.

There is evidence that exposure to radiation is associated with increased incidence of breast cancer at all ages but not with earlier presentation of breast cancer [39]. It has therefore been hypothesized that "irradiation of the immature female breast acts as a tumor initiator by altering the cells to make them more susceptible to the subsequent tumor-promoting effects of hormones" [33]. Most studies have shown that PDB develops at an average age of 54-59 years [1], which is 5-10 years higher than that of overall breast carcinoma. In this case report the patient developed Paget's disease of the nipple and associated DCIS at the young age of 36 years. Radiation exposure during childhood may have increased the patient's risk of developing DCIS/IDC at such a young age. Radiation exposure might have also facilitated an early presentation of Paget's phenotype by altering the expression of genes such as c-erb-B2. The detail of the types of breast cancer and especially that of PDB have not been specifically addressed in the studies previously described investigating the association between radiation exposure and breast cancer. This may be worth considering further in future work.

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