

Paget's Disease of the Breast: Study of 5 Cases with Review of Literature

Sumalatha K¹, SanthoshBabu R², Pradeep Kumar Ch³, Ravinder Thota⁴, Shanmuga Raju P⁵

¹Assistant Professor
Department of Pathology
²Associate Professor
Department of Radiology
³Associate Professor
Department of Surgery
⁴Professor
Department of Pathology
⁵Associate Professor
Department of Physiotherapy
and Rehabilitation
Chalmeda Anand Rao
Institute of Medical Sciences
Karimnagar-505001
Telangana, India

CORRESPONDENCE:

¹Dr.Sumalatha Kasturi
DCH, MD(Pathology)
Assistant Professor
Department of Pathology
Chalmeda Anand Rao
Institute of Medical Sciences
Karimnagar-505001
Telangana, India
Email:
sumalathakasturi97@gmail.com

ABSTRACT

Paget's disease of the breast has been recognised as a distinct clinical entity. It is defined as the presence of malignant glandular epithelial cells within the squamous epithelium of the nipple and is almost always associated with underlying intraductal or invasive carcinoma of breast or both. It accounts for 1-4% of all cases of breast carcinoma. Its clinical significance, pathogenesis are topics of controversy. The main aim of this review is to describe its clinical features, pathological features, pathogenesis and differential diagnosis.

Keywords: Paget's disease of breast, carcinoma in situ, invasive carcinoma

INTRODUCTION

Paget's disease of the breast is seen as a red, weeping, often crusted lesion of the nipple and may be clinically indistinguishable from eczema.^[1] Paget's disease (MPD) occurs in 1-4% of all patients with mammary carcinoma.^[2,3] Classically the underlying carcinoma is invasive in nature, although in 40-45% of cases the underlying pathology is DCIS. MPD may be asymptomatic and unsuspected clinically and may be diagnosed as a histologic finding by a pathologist on a mastectomy specimen. Mammary Paget's is almost always associated with an underlying breast carcinoma in 92-100% of cases.^[4,5] MPD is much more frequent in women because of the predominance of breast cancer in females.^[6] It occurs most commonly in women, often during the 6th decade of life

(mean age 57 years), but it has been observed in adolescents and in elderly patients also.^[7,8]

MATERIALS AND METHODS

Five cases of MPD were collected over a period of 3 years in the Department of Pathology, Guntur Medical College, Guntur from March 2009 to February 2012.

Specimens studied were modified radical mastectomy specimens. Age of the patients ranged from 32-58 years. Paraffin embedded, haematoxylin and eosin stained tissue sections were studied for the presence and histologic type of paget's disease of breast and its underlying carcinoma. The results were analysed.



Figure 1: Clinical photograph showing nipple ulceration and retraction

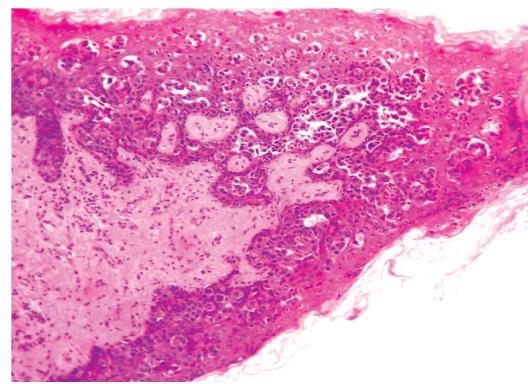


Figure 2: Low power view showing clusters of Paget cells in the basal layer of epidermis H&E, x100

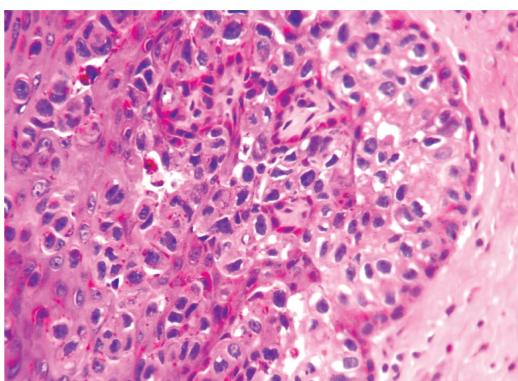


Figure 3: High power view showing clusters of atypical Paget cells. H&E, x400

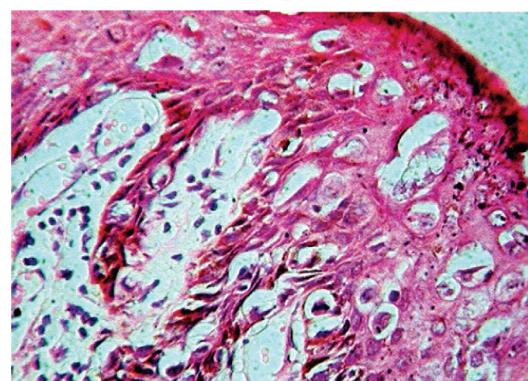


Figure 4: Paget cells showing enlarged, hyperchromatic, pleiomorphic nuclei with abundant clear cytoplasm. H&E, x400

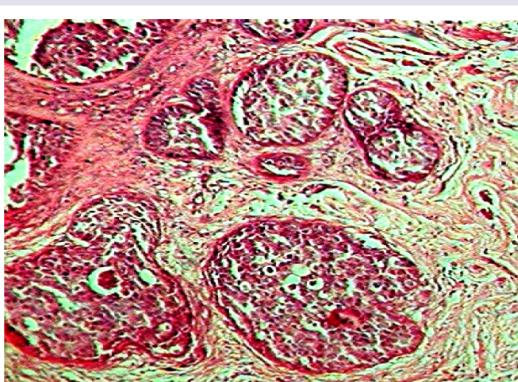


Figure 5: Underlying ductal carcinoma in situ H&E, x100

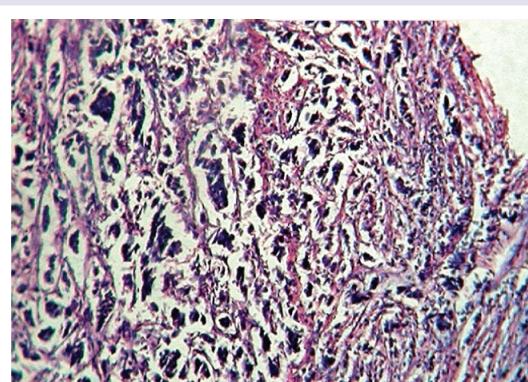


Figure 6: Associated invasive breast carcinoma in paget's disease of breast. H&E, x100

RESULTS AND DISCUSSION

Table 1: The details of the cases were as follows:

| S.No | Age of the patient | IDCC/ DCIS |
|------|--------------------|------------|
| 1 | 55 years | IDCC |
| 2 | 55 years | IDCC+DCIS |
| 3 | 32 years | DCIS |
| 4 | 50 years | IDCC+DCIS |
| 5 | 58 years | IDCC |

Paget's disease is the name given to eczematous, crusted lesion of the nipple as originally described by Sir James Paget in 1874.^[9] It is an uncommon disease accounting for 1-4% of all breast carcinomas.^[2] It is often associated with underlying ductal carcinoma in situ and / or invasive ductal carcinoma. The clinical appearance of MPD is usually a thickened, eczematoid, erythematous, weeping, itchy or crusted lesion with irregular borders, initially centred in the nipple. Later they rarely extend to the areola more than a few centimetres. In advanced cases it may be retracted or deformed.^[11] The lesions are almost unilateral and very rarely bilateral.^[10] MPD may also develop on ectopic breast and accessory nipples.^[7] In our study, all five cases presented with ulcerated and retracted nipples (Figure 1).

MPD is very often associated with an underlying breast cancer in 92-100% of cases.^[4, 5] Approximately 50% of the patients presents with an associated palpable mass in the breast.^[6, 11] In cases where mass is palpable, invasive carcinoma is present in over 90% of cases. Conversely, 66% of cases without a palpable mass are exclusively intraductal.

In our study, four out of five cases presented with a palpable mass. All these 4 cases showed invasive ductal carcinoma. One case presented with retracted nipple without a palpable mass. Mammograph showed microcalcifications. On histopathological examination of mastectomy specimen revealed ductal carcinoma in situ of high grade (Figure 5).

It occurs most commonly in women, often during the sixth decade of life (mean age 57 years).^[6] But it has been observed in adolescents and in elderly patients also.^[7, 8] In this study, 4 out of 5 cases presented in the 6th decade. One case in 4th decade. MPD can also occur in men.^[12] Although there are no significant pathologic and clinical difference, prognosis seems to be worse in men compared with women.^[13] When MPD is suspected, imaging should be performed to detect the underlying carcinoma. Radiological findings are important to assess appropriate further management and treatment of the disease.

MPD is defined as the presence of malignant glandular

epithelial cells within the squamous epithelium of the nipple. The cells show enlarged, pleomorphic, hyperchromatic nuclei with discernible nucleoli and abundant clear or pale cytoplasm. They do not form intercellular bridges with adjacent squamous cells. They are more often located in the basal region of the epidermis either as single cells or as clusters of cells forming gland like structures(Figure-2,3,4). The cytoplasm may also contain melanin pigment. These granules have probably been transferred from neighbouring melanocytes by the process of cytocrinia.^[14]

Ultrastructurally, Paget cells cytoplasm lacks dense cytokeratin filaments, keratohyaline granules. No gap junctions or tight junctions are present. Ulceration is seen in advanced cases.^[2] The underlying carcinoma is always of ductal type and may be either purely DCIS or a combination of DCIS and invasive carcinoma.^[15] In this study, pure DCIS is found in one case, remaining 4 cases showed DCIS along with IDCC.

There are 5 histological variants of Paget cells are described

1. Adenocarcinoma like
2. Spindle cell type
3. Anaplastic type
4. Pigmented cell type
5. Acantholytic type

In the present study 2 cases showed conventional adenocarcinoma like Paget cells, 3 cases showed anaplastic variant.

Immunohistochemically, Paget cells show overexpression of CK 7 and do not express HMWCK like CK10, CK12, CK14. Paget cells also express other glandular antigens such as EMA, CEA, GCDFP-15, but do not express HMWCK, or melanocytic antigens.^[14] This immunostaining pattern and the presence of intracellular mucin favour the glandular origin. Hormone receptor reactivity is similar to underlying carcinoma also.

The histogenesis of MPD has remained controversial. There are two main hypotheses to explain its histogenesis.

According to one hypothesis, Paget cells originate from malignant ductal cells that have migrated along the basal membrane of the nipple. This is supported by immunohistochemical demonstration of Paget cells very similar to underlying malignant cells. A motility factor, hergulin-a binds to the her-2 family of receptors resulting in chemotaxis of breast ductal carcinoma cells and infiltration into the overlying epidermis of the nipple. Her-2 protein has a growth stimulating effect, furthermore it enhances the motility of tumour cells.

The second theory postulates that the Paget cells are the result of neoplastic transformation of multipotential cells located in the basal layer of the lactiferous duct and epidermis.

Differential Diagnosis

Clinical differential diagnoses include atopic/ contact dermatitis of nipple, chronic eczema, mammary duct ectasia, tumours such as benign intraductal papilloma, Bowen's disease, Basal cell carcinoma, superficial spreading malignant melanoma, Toker cell hyperplasia.^[16]

The characteristic feature is the presence of Paget cells, forming clusters in the basal portion of epidermis.^[17] In difficult cases, immunohistochemistry may be used. Toker cells are usually dispersed singly and small to medium sized cells with pale or clear cytoplasm which may consist of a large vacuole that appear clear on routine stains. Paget cells have larger, pleomorphic and cytologically atypical nuclei. Both Toker cells and Paget cells express CK7, CAM5.2, EMA, but do not express CK 20, GCFDP-15, HMWCK, s-100. CK7, Her-2 are specific and sensitive markers of Paget cells.^[10, 17]

The prognosis and management depend largely on the intraductal versus invasive nature of the underlying carcinoma and on the presence or absence of axillary lymphnode involvement, rather than on the presence or appearance of the intraepithelial component in the nipple.

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