

Importance of Prostate-Specific Membrane Antigen in Paget's Disease of the Breast

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ABSTRACT

In this study, the relationship of prostate specific membrane antigen (PSMA), a type-2 transmembrane glycoprotein, with the Her-2 Receptor and prognosis of the disease in cases with Paget's Disease of the Breast was investigated.

The data of 14 patients diagnosed and treated with Paget's disease of the breast between July 2013 and March 2020 in the General Surgery Clinic were evaluated retrospectively.

After the pathological diagnosis was made, all patients underwent modified radical mastectomy. Paget's disease was found together with invasive ductal carcinoma in one patient, and Paget's disease was found together with ductal carcinoma in situ in 7 patients (50%). Staining in malignant tissue with PSMA was detected in only two patients. The normal dermis venules of other patients were stained with PSMA. In the subsequent follow-ups, lung and bone metastases were detected. The other patient stained with PSMA showed weak PSMA expression in malignant epidermal cells in the epidermis (The patient's tumor invasion grade was T2, there was no axillary lymph node metastasis, ki-67 expression was 10%, estrogen, progesterone and HER2 receptor were positive.

Although studies showing the relationship between PSMA and breast malignancies are limited and there is no literature information; In our study, two patients with staining with PSMA had high grade and distant metastases with ki-67. Larger studies are needed to establish a link between PSMA and Paget's disease of the breast.

Keywords: Paget's Disease of the Breast, Prostate Specific Membrane Antigen, Human Epidermal Growth Factor-2

Introduction

Prostate specific membrane antigen (PSMA) is a type-2 transmembrane glycoprotein consisting of 750 amino acids, known as glutamate carboxypeptidase 2 or N-acetyl-L-aspartyl-L-glutamate peptidase, with folate hydrolase activity expressed by the prostatic epithelium. PSMA activates signaling cascades that ensure cell survival, cell proliferation and migration (1). In addition, PSMA initiates the penetration of therapeutic agents into the cell by receptor-related endocytosis (2).

Physiologically, it is known to be present at low levels in the salivary and lacrimal glands, spleen, liver, kidney proximal tubule, central nervous system, duodenal mucosa and colonic crypt neuroendocrine cells, as well as in prostate secretory epithelial cells. However, in recent studies, PSMA has also been found to be exposed

in the neovascularization of many solid organ tumors (2).

In our study, the relationship between PSMA and HER-2 receptor, grade, lymphovascular invasion, and lymph node metastasis in Paget's disease of the breast was evaluated.

Material and Method

The data of 14 patients diagnosed and treated with Paget's disease of the breast between July 2013 and March 2020 in the General Surgery Clinic were evaluated retrospectively. The study protocol was approved Local Ethics Committee.

Result

All of the patients were women. The mean age was 52.2 (min: 36-max: 81). Two of the patients presented with a palpable mass in the breast, the others with a

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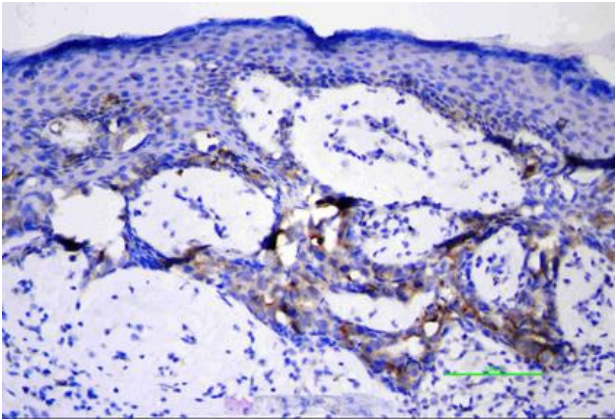


Fig. 1. PSMA Staining In Normal Dermis Venules

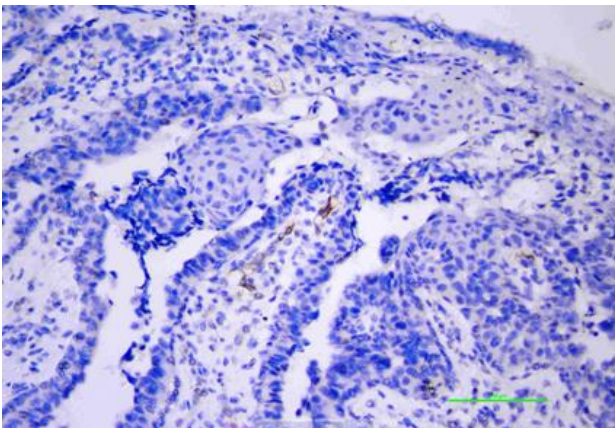


Fig. 2. Strong PSMA Staining In Malignant Tissue

palpable mass on the nipple with an eczematous lesion. The diagnosis was made by tru-cut biopsy who presented with only the mass, and the others were diagnosed by skin biopsy together with tru-cut. After diagnosis, all patients underwent modified radical mastectomy (MRM). Paget's disease in the mastectomy specimen was detected with invasive ductal carcinoma in one patient and with ductal carcinoma in-situ in 7 patients (50%). When tumor histology was examined, the degree of invasion of the tumor was T1 in 4 patients, T2 in 7 patients, and T3 and T4 in one patient each. Axillary lymph node metastases were detected in only 3 of the patients. The tumor was determined as grade 3 in 7 patients, grade 1 in one patient and grade 2 in 6 patients. Estrogen and its receptor were positive in 9 patients and negative in the rest. HER2 receptor was positive in 8 patients. Triple negative was detected in only one patient. The ki-67 index was 15% in 42.8% of the patients, the ki-67 index was 25% in 28.5%, 50% in two patients, and 75% in one patient. Staining in malignant tissue with PSMA was detected in only two patients.

PSMA staining was observed in the normal dermis venules of other patients (Figure 1).

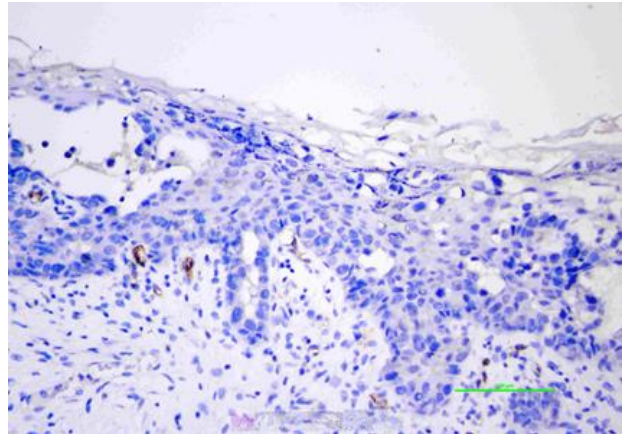


Fig. 3. Weak PSMA Staining In Malignant Tissue

The patient with strong PSMA expression in the malignant epidermal cells in the epidermis had tumor invasion grade T4, axillary lymph node metastasis was present, ki-67 expression was 75%, estrogen, progesterone and HER2 receptor were detected as triple positive. In the follow-up of the patient, lung and bone metastases were detected approximately 2 years later (Figure 2).

In the other patient stained with PSMA, weak PSMA expression was present in the malignant epidermal cells in the epidermis. The tumor invasion grade of the patient was T2, there was no axillary lymph node metastasis, ki-67 expression was 10%, estrogen, progesterone and HER2 receptor were detected as triple positive (Figure 3). No local or systemic recurrence was detected in this patient's 5-year follow-up.

Discussion

Paget's disease of the breast is usually detected clinically as an eczematous and erythematous lesion with irregular borders. The diagnosis is made by demonstrating the invasion of Paget cells into the epidermis in the biopsy taken from these lesions. Paget cells are malignant glandular epithelial cells with pale, transparent cytoplasm containing mucin, enlarged pleomorphic and hyperchromatic nuclei (3).

Two theories exist to explain the oncogenesis of Paget's disease. In one of them, Paget cells originating from ductal malignant cells migrate to the basement membrane of the nipple and HER-2 protein is detected in these Paget cells in immunohistochemically studies. The motility factor expressed by epidermal keratinists called Heregulin-a binds to the HER-2 receptor and attracts Paget cells to the basement membrane. Depending on Heregulin-a, chemotaxis and invasion of Paget cells into the epidermis occurs

(4). This theory explains the synchronous detection of Paget's disease with ductal carcinoma in-situ or with invasive ductal cancer.

The second theory for the development of Paget's disease is that Paget cells arise from malignant keratinocyte cells in situ. Therefore, Paget's disease is considered as an in-situ cancer that does not invade the deep layer (5).

Many studies show that Paget's disease of the breast frequently expresses HER-2 (6,7).HER-2 is an epidermal growth factor receptor with tyrosine kinase activity. It encodes a transmembrane receptor protein that plays a role in cell growth and proliferation, cell differentiation, apoptosis, adhesion, and migration-like functions with its intrinsic tyrosine kinase activity. PSMA is a type-2 transmembrane glycoprotein like HER-2.It has also been detected in breast tissue other than normal prostate epithelial cells (8,9). In this case, it has been suggested that PSMA can be used as a prognostic factor in breast malignancies such as HER-2.In the study of Kinoshita et al., moderate staining was detected in the terminal duct epithelium of normal breast parenchymal cells, while PSMA staining was not observed in 4 of 5 ductal carcinomas, and weak staining was detected in only one (10). There are no studies in the literature showing PSMA staining and the prognostic feature of PSMA in Paget's disease of the breast. In our study, PSMA staining was detected in normal dermal venules in 14 patients (Figure 3), and PSMA staining was detected in malignant tissue in only 2 cases. Observation of HER-2 receptor positive in both cases with PSMA positive suggested a relationship between PSMA and HER-2. In addition, although distant metastases were not detected in the other patients during the follow-up, the presence of lymph node at the time of diagnosis and both lung and bone metastases during the follow-up in the patient with strong staining with PSMA was evaluated as a bad prognostic factor for PSMA.

As a result, the information showing the relationship between PSMA and breast malignancies is limited, there is no literature on PSMA and Paget's disease of the breast; Despite the small number of patients in our study, the high grade and distant metastasis with ki-67 in patients with PSMA staining supports the view that PSMA is considered as a bad prognostic factor and included in routine immunohistochemically studies in Paget's disease.

Conflict of Interest: No conflict of interest was declared by the authors.

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Informed Consent: Retrospective study

Ethics: The study were approved by the Isparta Süleyman Demirel University Medicine Faculty Clinical Researchs Local Ethics Committee Date:11.09.2020, Decision no:250

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