

Paget's Disease of the Breast*

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= 국문초록 =

페제트 유방암에 대한 임상적 고찰

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페제트 유방암은 희유한 질환으로 담양의 (pale)의 세포질과 저명하고 불규칙한 핵을 가진 비교적 큰 세포인 “페제트”세포들이 간혹 유사핵 분열을 보여주기도 하면서 유두 표피내에서 단독 혹은 응집된 상태로 나타나는 것이 특징으로, 이 페제트 유방암은 일반적으로 유두와 유두윤의 습진양 피부염으로 나타나는데 소양증과 따가움 정도 동반하여 환자에게 이상이 있음을 빨리 알려주어 조기진단이 가능 할것 같은데 실제로는 진단 및 치료가 일반적인 유방암보다 더 늦어지는 것이 보통이다. 문헌상 이 질병의 평균연령은 54세였고, 대부분 6개월 혹은 1년이상 지체한 후에 의사를 찾는다고 했다. 진단시 질환이 유두와 유륜에 국한되고 유방내에 축지되는 종괴가 없는 경우가 약 45%이고 유방내 종괴가 있으면서 눈으로 볼수있는 유두변화가 없는 경우는 5~28%로 보고되어 있다. 치료방법은 여러가지로 권고되어 왔는데 일반적으로 다른 유방암의 치료 방법과 같이 하면 되겠다. 치료결과는 유방내에 축지되는 종괴의 유무 및 액와 임파선 전이의 유무에 따라 달라진다고 하였다.

계명대학교 동산의료원에서는 1979년 1월부터 1988년 12월까지 만 10년사이에 총 317명의 유방암 환자를 수술하였는데 그중 11명(3.5%)이 병리조직검사 결과 페제트씨 유방암으로 진단되었다. 이들의 평균연령은 44.6세였고, 유방암 환자 전체의 평균연령은 46세였다. 평균 증상기간은 15.5개월이었다. 3명은 유두변화만 있었고, 4명은 유방내에 종괴만 있었으며, 4명은 유두변화와 종괴를 동반했다. 5명이 액와 임파선전이를 일으켰으며, 이들 모두에서 유방내에 종괴를 축지 할수 있었다.

단순 유방절제술 및 하위 액와 임파선 청소술을 3명에서, 근치적 유방절제술을 3명에서, 그리고 변형 근치유방절제술을 5명에서 시행하였는데, 현재 6명이 재발없이 생존하여 있고 그중 3명은 수술후 10년, 1명은 수술후 3년, 1명은 수술후 1년반, 1명은 수술후 8개월 동안 생존하였다. 3명이 사망했는데, 1명은 수술후 2년만에, 그리고 2명은 1년만에 사망하였다. 이들 3명 모두 유방내 종괴 및 액와 임파선 전이가 있었다. 2명은 추적조사가 불가능하였다.

Key Words: Paget's disease, Breast Carcinoma

Introduction

Paget's disease of the nipple represents an intra-

epidermal proliferation of neoplastic cells in the skin and adnexa of the nipple and areola and clinically it commonly presents as a chronic eczematoid dermatitis of the nipple¹⁾. According to Haagensen, Da-

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rier²⁾ first described Paget cells in 1889 but did not recognize their neoplastic nature and mistakenly regarded them as degenerated epidermal cells³⁾. Paget cells are large cells with pale cytoplasm and prominent irregular nuclei, occasionally in mitoses, occurring singly or in clumps in the nipple epidermis. The histogenesis of the Paget cells in the epidermis is still not entirely resolved and are divided into those suggesting that the cells are derived from the underlying carcinoma⁴⁾, represent a separate local intraepidermal carcinoma^{5, 6)}, or are degenerated melanocytes⁷⁾. The vast majority of cases of Paget's disease of the nipple are associated with underlying breast carcinoma constituting 97% of the series of 214 cases reported by Ashikari et al.⁸⁾. The incidence of Paget's disease has been reported to be between 0.7 and 4.3% of all breast cancers^{9, 10, 11)}.

This review reports the experience of the Paget's disease of the breast in the Department of Surgery, Keimyung University Dongsan Medical Center between January 1, 1979 and December 31, 1988.

Materials and Methods

During the period 1979 through 1988, a total of 11 cases of histologically proven Paget's disease of the breast were treated surgically by the Department of Surgery at Keimyung University Dongsan Medical Center. During the same period, the total number of patients treated surgically for all breast cancers was 317 patients and these 11 patients represented 3.5% of the entire breast cancer patients. All 11 patients were female and patient age ranged from 31 to 61 years, with an average age of 44.6 years. At the time of diagnosis, three patients presented with disease confined to the nipple and areola characterized by eczematoid dermatitis, erosion, crust formation, or ulceration without palpable mass in the breast. Eight patients had palpable breast masses, four patients without visible nipple changes and the diagnosis of Paget's disease was confirmed only by the microscopic examination of the resected specimen, so that the disease was incidental to an obvious malignant neoplasm of the breast. Five of eight patients with

palpable breast masses had axillary lymph node metastases.

This review is an attempt to elucidate the characteristics of patients with this disease, its clinical manifestations, pathology, treatment, and results of therapy.

Results

Eleven patients in this series of Paget's disease represent 3.5% of all breast cancers treated surgically in the Department of Surgery at the Keimyung University Dongsan Medical Center during the period 1979 to 1988. All 11 patients were female and the age of patients ranged from 31 to 61, with an average of 44.6 years. The average age of the entire patients of 317 with all breast cancers was 46 years. Only two patients were postmenopausal at the time of diagnosis and eight of 11 patients (72.7%) were in their forties (Table 1).

Table 1. Distribution of patients by age

Age distribution	Number of patients	Per cent
30-39	1	9.1%
40-49	8	72.7%
50-59	1	9.1%
60-69	1	9.1%

Clinical manifestations at the time of diagnosis are summarized in Table 2. Typical nipple changes including eczematoid lesions, oozing, nipple and areolar ulceration, itching, nipple excoriation were the primary symptoms in 7 patients (63.6%). One of these patients showed nipple enlargement. Three patients did not have any breast lump at the time of diagnosis, and of eight patients with mass in the breast, two patients presented with two masses in each breast. Four patients who presented with breast lump did not have typical nipple changes seen in Paget's disease of the breast. Nipple retraction independent of typical nipple changes was seen in four patients and all these patients had palpable breast lumps. Axillary lymph nodes were positive in five patients. Abnormal nipple discharge was present in four patients,

and in three, the discharge was bloody. Since three of these four patients also had typical nipple changes, only one can be considered to have true bloody nipple discharge. Pain was present as a symptom in only one patient who came with a 7cm breast lump and edema of breast skin (1/3) and a large, 2cm, palpable axillary node.

The interval between the onset of overt symptoms and signs of Paget's disease and diagnosis by a surgeon ranged from 2 weeks to 260 weeks (5 years) with an average of 66.5 weeks (15.5 months).

Two patients had Paget's disease only on microscopic examination of the breasts. Two patients had Paget's disease and non-infiltrating intraductal carcinomas, and one of these two patients had a large

elongated firm mass, measuring 4.0×3.0cm in size, located in the subepithelial region, and one patient did not have any mass on gross examination. Seven patients had associated infiltrating ductal carcinomas and one of them also had coexisting lobular carcinoma in situ. Four of these patients with infiltrating carcinomas had lymph node metastasis, most of them extensively. Pathological findings, presence of mass, lymph node status, and operation performed are summarized in Table 3.

Surgical treatment varied with simple mastectomy with low axillary dissection in three patients, modified radical mastectomy in five patients and radical mastectomy in three patients. The decision regarding the type of surgery performed was made by the indi-

Table 2. Clinical manifestations at the time of diagnosis

Symptoms and signs	Number of patients	Per cent
Nipple changes	7	63.6%
Breast mass	8	72.7%
Multifocal lesions	2	
Nipple changes+Breast mass	4	36.4%
Breast mass alone	4	36.4%
Nipple change alone	3	27.3%
Palpable axillary nodes	4	36.4%
Pain	1	9.1%

Table 3. Pathological findings, mass, lymph node status, and operation

Microscopic findings	Mass	Lymph node status	Operation performed	Results
Paget's disease alone	None	0/4	SM*	Alive
Paget's disease alone	None	0/20	RM**	Alive
Paget's+intraductal carcinoma	None	0/12	MRM***	Alive
Paget's+intraductal carcinoma	4.0cm	1/11	MRM	Dead
Paget's+infiltrating ductal ca +lobular carcinoma in situ	3.0cm 2.0cm	0/28	MRM	Alive
Paget's+infiltrating ductal ca	7.0cm	42/45	RM	Lost
Paget's+infiltrating ductal ca	3.5cm	0/17	MRM	Alive
Paget's+infiltrating ductal ca	3.0cm	11/11	MRM	Dead
Paget's+infiltrating ductal ca	8.0cm	0/10	SM	Alive
Paget's+infiltrating ductal ca	8.0cm	6/27	RM	Lost
Paget's+infiltrating ductal ca	6.5cm 2.0cm	6/6	SM	Dead

*SM: Simple mastectomy with low axillary dissection.

**RM: Radical mastectomy

***MRM: Modified radical mastectomy

vidual surgeon involved and was not always determined by the extent of the disease.

Six patients are alive without evidence of disease, ten years after surgical treatment in three patients, three years after surgery in one patient, one and half years after surgery in one patient and eight months after surgery in one patient. Among these six patients, five did not have any lymph node involvement and two patients had Paget's disease only on microscopic study, and one patient had an associated intra-ductal carcinoma, and one patient had infiltrating ductal carcinoma. Three patients died of the disease, two years after surgery in one patient and one year after surgery in two patients. All three patients had a palpable mass in the breast and axillary lymph node metastasis. One of these patients had an associated intraductal carcinoma with only one of 11 lymph nodes was involved but developed recurrent local carcinoma within a year and microscopic study at that time showed an invasive ductal carcinoma and this patient eventually died of generalized metastatic disease 2 years after the initial surgical therapy. Two patients were lost to follow up study.

Discussion

Several theories have been proposed to explain the origin of the Paget cells and three possible sources of malignant cells in the epidermis of the nipple have been described: 1. The Paget cells may begin in the mammary ducts secondarily involving the skin and areola of the nipple. 2. The Paget cells may originate in the skin and descend along the ducts, causing invasive cancer within the breast. 3. Paget's disease may be an in situ carcinoma arising from keratinocytes, melanocytes, or clear cells in the skin of the nipple. The most widely accepted concept considers these Paget cells to be neoplastic cells that migrate through ducts from an underlying carcinoma to the nipple and this view has been supported primarily by early histologic studies of Muir and Inglis^{4, 12}. Toker provided evidence for epidermotropic migration of Paget cells by examining more than 1000 serial sections of the ductal system from a breast con-

taining a tumor located 3cm from the surface of the nipple. Haagensen stated that the fact is now established beyond any reasonable doubt that they are carcinoma cells that have invaded the epidermis of the nipple from carcinoma in the subjacent nipple ducts³. But this epidermotropic theory has been challenged by the autochthonous theory of origin, that is, Paget cells arise in the nipple epidermis independent from the underlying carcinoma either through in situ malignant transformation or degeneration from existing cells. Lagios and colleagues combined information from electron microscopy with the immunoperoxidase staining pattern from an antiestradial antibody to conclude that Paget cells arise in situ¹³. Desmosomes between Paget cells and between adjacent epidermal cells were reported by Sagami¹⁴, Sagebiel¹⁵, and Lagios and colleagues¹³, and Sagebiel¹⁵ concluded that alteration of epidermal cells adjacent to Paget cells suggested in situ transformation of epidermal cells to Paget cells. Summarizing these theories, Os-teen stated that, at present, the origin of Paget cells is still controversial and it is possible that several of these explanations are correct and that the clinical and microscopic appearance of Paget's disease can arise from multiple circumstances¹⁶.

The incidence of Paget's disease in patients with breast cancer is low, ranging from 0.7% to 4.3%^{9, 10, 11, 17, 18}, and the incidence of 3.5% in this series compares well with these figures.

The average age of patients with Paget's disease has been reported as about 54 years^{3, 8, 10, 19} and a few authors also reported that this age was slightly higher than that of patients with breast cancer of no special type^{3, 9}. The average age in this series was 44.6 years, about 10 years younger than that of reported series, and the average age of entire patients with breast disease in the same period was 46 years.

Paget's disease of the breast is the easiest form of breast carcinoma to detect because the nipple lesion frequently produces itching or burning and it often takes the form of eczema, erosion, and crusting. Nevertheless, long delays in diagnosis are common, with an average duration of symptoms greater than

6~12 months in most series^{8, 10, 16, 18, 19, 20}. The duration of symptoms in this series ranged from 2 weeks to 5 years with the average delay of 15.5 months. The average duration of symptoms in 80 patients with breast cancer of no special type seen recently at the out-patient department for follow up study was 11 months.

Clinical manifestations include a persistent eczematoid lesion of the nipple and areola, or a palpable mass in the breast, or both. In the report of Ashikari et al., the disease was confined to the nipple and areola with no palpable mass in the breast in 45%^{3, 8}, and Kister and Haagensen in 43%¹⁰, Osteen in 46%¹⁶, and Freund et al. in 45.5%¹⁹. The incidence of patients with palpable breast mass with no visible nipple changes ranged from 5%¹¹ to 28%¹⁰. In these patients, the diagnosis of Paget's disease was incidental to an obvious malignant neoplasm of the breast. The incidence of positive lymph nodes in patients who did not have a mass ranged from zero¹¹ to 20%⁹. Forty two to 69% of patients with palpable mass in the breast had axillary lymph node metastasis^{3, 8, 10, 11, 19}. In the present series, three patients(27.3%) had nipple changes alone and four patients(36.4%) had breast mass alone, and four patients(36.4%) had nipple changes and palpable breast mass. Axillary lymph node involvement was seen in five patients (45.5%) and all these patients had palpable mass in the breast.

Treatment of Paget's disease of the breast has been controversial and still is. Many authors recommended standard radical mastectomy for all Paget's disease with or without palpable breast mass^{2, 9, 10, 21}. Other authors recommended modified radical mastectomy for patient without a palpable mass or palpable axillary lymph nodes with immediate examination of the specimen and removal of the pectoral muscles if invasion of the breast parenchyma or lymph node metastasis is found^{13, 22}. Some authors recommended radical mastectomies for patients with a mass and simple mastectomies for patients with only nipple changes^{11, 23, 24}. More recently, modified radical mastectomy was recommended in patients with a mass and simple mastectomy for patients with

nipple changes without a palpable mass²⁰. Helman and Kliman²⁵ reported such dismal results for the treatment by radical mastectomy of patients with a mass that they believed that all such patients should be treated with simple mastectomy and radiation therapy. Osteen¹⁶ summarized 46 patients who had been treated for cure with breast conserving surgery with or without radiation therapy. These patients were treated with excisions less than mastectomy. Among the 46 patients, three local recurrences were noted and all patients who were followed for five years or longer were still alive and, except for the one local recurrence, were free of disease. Lagios and colleagues¹³ reported a series of patients selected for breast conservation in patients with nipple changes without a mass and negative mammograms. Patients underwent excision of the nipple-areolar complex and a wedge of underlying breast tissue. Histologically, the disease was found to be limited to the nipple in all cases. With an average follow-up of 50 months, all five of these highly selected patients were free of disease. Paone and Baker²⁰ recommended adjuvant chemotherapy in premenopausal patients with lymph node metastases and also thought that adjuvant chemotherapy may be of benefit to postmenopausal patients, particularly when combined with tamoxifen.

In the present series, three patients had simple mastectomies, two for palliative procedures and one for Paget's disease confined to the nipple and areola. Three patients had standard radical mastectomies and five patients had modified radical mastectomies.

The most significant aspects influencing survival in Paget's disease of the breast are related to the presence or absence of a mass and to the presence of lymph node metastasis^{3, 9, 11, 23, 24, 25}. Ten year survival rates for the Paget's disease without a palpable mass ranged from 75 to 100% and ten year survival rates for the Paget's disease with a palpable mass ranged from 22 to 47%^{8, 19, 10, 20, 26, 27}. In Paget's disease with a palpable mass and lymph node metastases, the ten year survival rate was 25 to 28% and those without a palpable mass and with lymph node metastases, the rate was 33 to 75%^{3, 8, 10}. In the present

series, the total number and the follow-up period are both inadequate to give any conclusive statement, but from the review of the literature and the present concept of breast carcinoma and its treatment, most of the Paget's diseases should be treated by modified radical mastectomy and very selected patients with Paget's disease with no evidence of palpable mass in the breast and axilla by clinical examination and mammography can be treated with simple mastectomy.

Summary

Paget's disease of the breast is a rare disease and characterized by the presence of Paget cells which are large cells with pale cytoplasm and prominent irregular nuclei, occasionally in mitoses, occurring singly or in clumps in the nipple epidermis. It generally appears as an eczematous lesion of the nipple or areola, and frequently produces itching or burning which should call the patient's attention to it but the diagnosis is missed more often, and treatment delayed longer, than in ordinary breast carcinoma.

Average age of patients was 54 years and average delay in diagnosis was longer than six months to one year in the literature. The disease was confined to the nipple and areola with no palpable mass in the breast in about 45% of cases and the incidence of patients with palpable breast mass with no visible nipple changes ranged from five to 28%. Various treatment methods have been recommended and the prognosis was related to the presence or absence of a palpable mass in the breast and to the presence or absence of axillary lymph node metastases.

The salient features of 11 cases of Paget's disease of the breast encountered in a major university hospital in Korea over a 10-year period are presented. Eleven patients in this series represented 3.5% of all breast cancers and the average age of the patients was 44.6 years compared to 46 years in all breast cancer patients in the same period. The average duration of symptoms prior to surgical treatment was 15.5 months. Three patients had nipple changes alone, four patients had palpable mass in the breast

alone, and four patients had nipple changes and palpable breast masses. Five patients had axillary lymph node metastases and all these patients had a palpable mass in the breast. Simple mastectomy with low axillary dissection was performed in three patients, radical mastectomy in three patients, and modified radical mastectomy in five patients. Six patients are alive without evidence of disease, ten years after treatment in three patients, three years after surgery in one patient, one and half years after surgery in one patient and eight months after surgery in one patient. Three patients died of the disease, two years after surgery in one patient and one year after surgery in two patients. Two patients were lost to follow up study.

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