

Significance of Eczema in Paget's Disease of the Breast*

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Abstract—The records of 108 patients with Paget's disease of the breast were reviewed. Patients were separated into two groups according to presence or absence of nipple eczema. Seventy-five patients were "nipple positive," while the rest had "silent" or "negative" nipples. Axillary nodal involvement was found in 28% of patients with eczema and in 78% of patients belonging to the "silent" group (overall 41%). The 5-yr survival was 70 and 47.2% in the "positive" and "silent" groups, respectively (overall 63.6%). Patients with eczema were on the average, 8.7 yr older. The data corroborates our hypothesis that the presence or absence of an inflammatory response in the nipple to the Paget cells separates the patients into two prognostically different groups. Tumors eliciting an inflammatory response are associated with a protracted course, accounting for the superior prognosis in Paget's disease compared to breast cancer in general.

INTRODUCTION

THE TYPICAL Paget cells found near the basal layer of the nipple epidermis are viewed today as malignant cells originating in an intraductal carcinoma [1-3]. Skin invasion by breast cancer is known to worsen prognosis and is considered a grave sign, but Paget's disease of the breast is an exception to this rule [4]. Moreover, study of the major clinical series of patients with Paget's disease suggests a better prognosis in patients with this disease than in the average breast cancer patient. Ashikari *et al.* [5] found 41% involvement of the axillary nodes in 214 patients with Paget's disease, appreciably less than the 58% figure found in the other breast patients treated at Memorial Hospital in New York. Kister *et al.* [6] report a 37% involvement, vs 49.4% in Haagensen's [7] personal series. (See Table 1 for data reported by Maier *et al.* [8] and Salvadori *et al.* [9]).

With reference to the next most important prognostic factor in breast cancer, tumor size,

it is commonly known that Paget's disease is often associated with tumors too small to be palpated (Table 1).

With a lower rate of axillary involvement and smaller tumor size, it is not surprising that the survival rate in patients with Paget's disease is superior than that in other breast cancer patients. One could argue that Paget's disease is not a more benign form of breast cancer, but is diagnosed at an earlier stage because of its skin manifestations. This amounts to stating the same fact in different words; lower-grade malignancies tend to present at lesser stages. Moreover, the delay in diagnosis of Paget's disease is longer than other forms of breast cancer.

A biologic factor speaking strongly against the possibility of early discovery in Paget's disease is the patient's age. According to Muir [3], Paget's disease is just the common type of breast cancer affecting the ducts near the nipple, enabling the tumor to invade the epithelium. Accepting this view, one would expect the same etiological factors to be involved and to cause cancer at the same age. By this logic and by comparison to *in situ* cancer of the uterine cervix, since Paget's disease is an earlier-staged tumor, it should be diagnosed in a younger population. But Paget's disease is diagnosed at an older age than other forms of breast cancer patients. The mean age in Haagensen's [2] women with

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Table 1. Age, major prognostic factors and survival in Paget's disease of the breast

Author (hospital)	Number of patients	Mean age (yr)	Involvement of axillary nodes (%)	Tumor not palpable (%)	<i>In situ</i> tumors (No.)	10-yr survival (%)
Ashikari (Memorial, N.Y.)	214	54	41	45	63	60
Kister (Columbia Presb., N.Y.)	133	53.9	37	43	8	58
Salvadori (Ist. Naz., Milan)	82	54	50	45		44
Maier (Temple, Phil.)	66	58.5	45	41	14	(52.3 at 5 yr)

Paget's carcinomas is 3.9 yr older than in breast cancer of no special type. Haagensen was alerted to the fact that patients with "earlier" nonpalpable Paget's tumor were significantly older—by 9 yr. Maier [8] found a difference of 9 yr between his patients and the mean age of breast cancer patients in Philadelphia County. Thus, Paget's disease is biologically a more benign form of breast cancer. It affects an older population and is diagnosed at a lesser tumor size and degree of axillary involvement.

The logical next step would be to identify the factor associated with or responsible for the superior prognosis in Paget's disease. In most patients the diagnosis is suspected clinically and confirmed histologically. In a minority of patients, the pathological diagnosis of Paget's disease comes as a surprise. Evidently it is not the Paget's cells *per se* that cause the eczema, but lymphocytic infiltration in the dermis underlying the invaded epidermis [10]. The proportion of patients diagnosed as having Paget's disease without the accompanying inflammatory response varies between 9% in Memorial Hospital, NY and 39% in Columbia Presbyterian. It is conceivable that some of these patients are not diagnosed if nipples are not histologically examined as a routine. Those patients with the "silent" nipple must have had palpable tumors, which are associated with higher rates of axillary metastasis and worse prognosis [5–9]. Thus, the favorable outcome of Paget's disease is associated with the type of disease causing eczema of the nipple.

MATERIALS, METHODS AND RESULTS

The M. D. Anderson Hospital records of 108 patients with Paget's disease of the breast

since 1950 have been reviewed. Seventy-five patients (69.4%) had some form of clinical Paget's disease, while the rest belonged to the "silent" nipple group. In 53 patients, no tumor could be palpated in the breast, while 36 patients had palpable tumors. No information relating to the presence of a mass could be found in 19 patients. Many patients presenting with eczema had nonpalpable tumors, whereas all patients with negative nipples had palpable tumors (Table 2). The

Table 2. Palpability of tumors vs presence of eczema

	All patients	Eczema	No eczema
Tumor palpable	36	13	23
Tumor non-palpable	53	53	0

mean age of the patients was 53.4 yr. The ages of the patients, separated according to presence or absence of palpable tumors and eczema, are shown in Table 3. The average delay from first symptoms to definitive diagnosis was 17.3 months. Eighty-seven patients had partial or complete excisions of the axillary nodes. Again separating the patients according to clinical nipple manifestations, the rate of axillary involvement was 28 and 78% for the "nipple positive" and "nipple negative" patients, respectively (Table 4). Table 5 shows the degree of axillary involvement in patients with palpable vs nonpalpable tumors.

The overall survival at 5 yr was 63.6% (Bergson-Gage). For patients with eczema the figure was 70%, whereas patients with negative nipples had a survival rate of 47.2% (Fig. 1).

Table 3. Age at diagnosis, MDAH

	Palpable tumors	Non-palpable tumors	Eczema	No eczema
Number of patients	36	53	75	33
Mean age (yr)	51.7	59.8	57.9	49.2

Table 4. Axillary involvement related to clinical eczema

	All patients (87)	Eczema (64)	No eczema (23)
Positive axilla	41% (36)	28% (18)	78% (18)
Involvement of a single node (No.)	(10)	(7)	(3)

Table 5. Axillary involvement related to palpable vs non-palpable tumors

	All patients (75)	Palpable tumors (27)	Non-palpable tumors (48)
Positive axilla	33% (25)	59% (16)	19% (9)
Involvement of a single node (No.)	(7)	(1)	(6)

No attempt was made to separate the patients according to treatment techniques.

DISCUSSION

Our clinical material conforms well to previously published series of cases of Paget's disease as judged by patient's age, delay, axillary involvement and survival.

Rather than separating our patients according to tumor size (palpable or nonpalpable), an obvious and known prognostic factor, we chose a new yardstick—presence of clinical eczema in the nipple. Patients with eczema had a lower rate and degree of axillary involvement than those in the "silent" nipple group. Patients presenting with eczema do particularly well and their benign course affects the overall prognosis. The clinically "silent" patients do worse than the average breast patient, but since they are a minority, this fact is overshadowed.

Lymphocytic infiltration at the site of the primary breast cancer is associated with a better prognosis [11-13]. Experiments performed by Black *et al.* [14-15] show the ability of the host to mount a lymphoreticular response to autologous breast cancer applied to the skin or *in vitro*. There was a negative correlation between stage and cellular response, the greatest being observed in pre-invasive tumors.

Paget's disease of the breast is unique among breast cancer in that the tumor invades the skin at an early stage, is microscopic in size and leaves an intact dermis under the micrometastasis. The combination of these factors might cause the host to react with lymphocytic infiltration at the site of inoculated autologous live tumor cells. This reaction separates "tumor positive" patients (69% MDAH, 61% Columbia Presbyterian Hospital) from "tumor negative" (31% MDAH, 39% Columbia). A much better prognosis has been shown to be associated with the "tumor positive" group. Whether the

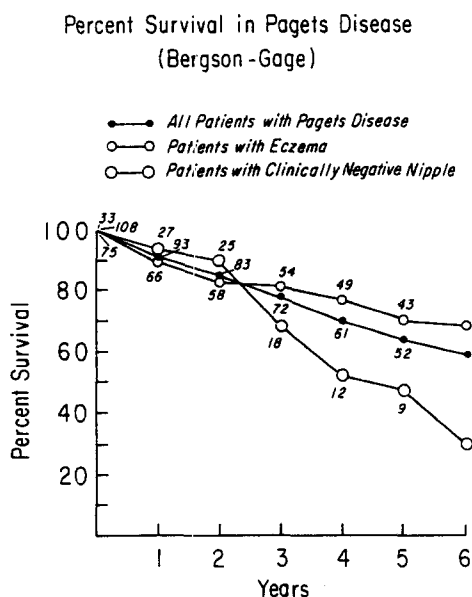


Fig. 1. Survival in Paget's disease as related to presence or absence of nipple eczema (Bergson-Gage).

results of this natural skin test correlated with the antigenicity of the tumor, the patient's general immune state, or the timing in the natural history of the tumor is not known [16].

An exciting possibility is that the nipple reaction has a restraining effect on the pri-

mary tumor and its ability to further metastasize. This would explain the few cases in which a primary tumor can not be found in the breast and solve the paradox of skin invasion coexisting with a benign course in this particular form of breast cancer.

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