Bahrain Medical Bulletin, Vol.25, No.1, March 2003

Paget's Disease of The Breast in Nigeria

Lawrence C Chiedozi,MD, FACS* Jonathan U Aligbe,MD, FMCPath**
John A Aghahowa, MB BS, MSc DCP**

Background: Breast cancer in Nigeria often presents at incurable stage. Paget's disease of the breast is rare but carries a good prognosis if recognized early.

Objective: To heighten awareness of the problem, to improve its recognition in its early stages.

Methods:The clinical presentation and the course of disease of twenty-two patients were seen in our breast clinic over a 10-year period with Paget's disease of the breast were reviewed. Five patients (Group 1) without associated mass were compared with 17 (Group 2) with an associated mass.

Results: Misdiagnosis due to non-recognition added 6.2 months to the mean delay of 18.4 months prior to definitive management. Patients without associated mass were alive at a mean of 104 months compared to 46.8 months in patients with associated mass ($p< 0.001$). Survival was 50 months for Paget's disease with a mass, but negative axillary lymph nodes versus 32 months when a mass and positive axillary nodes were present ($p < 0.05$).

Conclusions: Familiarity with Paget's disease of the breast is mandatory for all medical personnel. Its visibly symptomatic presentation provides a chance for early diagnosis, early management, and an excellent prognosis.

Bahrain Med Bull 2003: 25(1):26-29.

Although epidemiologically, Africans and residents of Africa and Asia have a low risk for breast cancer[1,2], breast cancer in Africa and Asia occurs at a relatively younger age than in Europe and America. In Nigeria and in many African countries, breast cancer has a very bleak prognosis[2-4]. Factors suggested as contributing to this abysmal prognosis include late presentation, (60-90% in TNM stages III and IV), tumour of a different biological behaviour, non-availability of appropriate medical facilities, and ignorance[1-4]. One form of breast cancer, which if diagnosed in its early stages could be guaranteed to yield excellent results, is Paget's disease of the breast.

---

* Departments of surgery
** Morbid anatomy
College of Medical Sciences
University of Benin
Benin City
Nigeria

Paget's disease is carcinoma of the nipple ducts which deceptively presents like a benign areolar skin lesion. Recognized and diagnosed early it carries an excellent prognosis with survival of up 100% five-year survival in some series[5-7]. The presentation of this disease misdiagnosed in its early stages and consequently presenting when advanced among our patient population prompted this study. The study aims to look at this disease as it occurs in our patient population, to heighten awareness of the problem, to improve its recognition in its early form, and hopefully to improve its management and prognosis. No study to date has focussed on Paget's disease in Africa.

METHODS

All women admitted to the Breast Clinic of the University of Benin Teaching Hospital, Benin City, Nigeria between 1979 and 1989 with biopsy proved carcinoma of the nipple ducts were included to this study. Patients who met the criteria for Paget's disease namely: history of a nipple/areolar lesion at the onset of the disease and a finding on histology of intra-epidermal infiltration of the nipple and/or areolar by Paget's cell were admitted to this study. There were 22 women. They were divided into two groups: clinical Paget's disease without a palpable mass 5 patients, designated Group 1, and those with associated mass 17 patients, designated Group 2. Excluded from the study were patients who were pregnant or had rapidly progressing breast cancer.

Detailed history of disease onset, diagnosis, treatment, treating personnel, time till presentation, and time till definitive diagnosis and treatment were recorded for all patient. Physical examination and limited metastatic evaluation, including bone survey (radiography of the skull, chest, spine, pelvis and the long bones), and liver function tests including alkaline phosphatase were obtained for each patient. (Brain, bone and liver scans are unavailable). All patients were staged by the UICC-TNM system[8] and underwent total mastectomy and levels 1 and II axillary dissection. Follow up was from admission to the study till death or loss to follow up, a period of 36 to 100 months. Statistical analysis was by Students' t test, and chi square test as appropriate. $P < 0.05$ was considered significant.

RESULTS

A total of 22 women with histologically proven Paget's disease of the breast were evaluated in this study. Table 1 shows details of the patient characteristics. Breast lesion had been present for a mean period of six to 14 months before the patients sought initial treatment at a medical clinic. Misdiagnosis resulted in further delay for a mean period of 6.2 months. Of 22 patients, 15 were initially misdiagnosed and treated as an eczema or chronic inflammation. There was thus total mean delay of 18.4 months from the onset of the lesion before the correct diagnosis was made and definitive treatment instituted. By this time, 17 of the 22 (77.3%) patients (group 2) had an associated mass. Of these, 14 patients were TNM stage 1 and three, Stage 11. The mean tumour size in the latter three was 1.7 cm.

Table 2 shows the clinical findings and progression of the disease as gleaned from the patient's history, and defines the criteria for recognition of the disease. An isolated but persistent nipple itchiness was the earliest symptom noted by all 22 patients. When an itchy eczematoid lesion showed up (19 patients), followed by a weepy ulceration (15 patients), the patients assumed that ulceration had resulted from scratching their breasts. At presentation many months later, the itchiness and burning sensation were no longer an isolated finding but were present in association with other findings. Most of the areas on the areola that had had a dry crusty itchy eczematoid lesion had been replaced by superficial weepy ulceration. The most easily recognizable clinical finding at this point was a weepy or eczematoid lesion of the nipple and the areolar present in 19 (86.4%) of the patients. Figure 1 shows the histology of a biopsy specimen with a plethora of intradermal Paget's cells. Histologically the Paget's cell is a large cell with an abundant cytoplasm and irregular hyperchromatic nuclei, the pathogpnomomic finding in Paget's disease of the breast[5].

Figure 1. Biopsy specimen showing Paget's cells

Table 3 shows that all group 1 patients (5, 100%) who presented with clinical Paget's disease without an associated mass, were still alive at a mean period of 104 months. In contrast, the 17 patients of group 2 (associated mass) had a mean survival of 46.8 months ($p < 0.001$). In group 2 patients with negative axillary nodes, mean survival was 50 months compared to only 32 months in those with positive nodes ($p < 0.05$).

Table 1. **Patient characteristics**

	Group 1 n = 5(100%) n (%)	Group 2 n = 17(100%) n (%)	p value
No. of patients	5(100)	17(100)	
Mean age (years)	42.2	44.5	ns
Premenopausal	5(100)	15(88.2)	
Postmenopausal	0(0)	2(5.9)	
Delay prior to any RX (months)	6	14	
Mean length misdiagnosed care	7	6	ns
Mean total duration breast lesion	13	20	<0.05
Treated as eczema	5(100)	10(58.8)	
TNM Tis	5(100)	0(0)	
TNM stage 1(T1N0M0)	0(0)	14(82.4)	

TNM stage II (T1N1M0)	0(0)	3(17.6)

Group 1 = Paget's disease no associated mass
Group 2 = Paget's disease with associated mass

Table 2. **Clinical Presentation**

	Group 1 n = 5(100%) n(%)	Group 2 n =17(100%) n(%)	Total N =22(100%) N(%)
Initial itchiness nipple and areolar	5(100)	17(100)	22(100)
Weepy areolar and nipple lesion	2(40)	13(76.5)	15(88.2)
Eczematoid lesion Nipple + areolar	1(20)	3(17.6)	4(23.5)
Ulcerated nipple only	1(20)	1(5.9)	2(11.8)
Burning sensation + itchiness	1(20)	0	1(5.9)
Mean tumour size (cm)	1.3		
Axillary mass	0	3(17.6)	3(17.6)
Mean duration RX under misdiagnosis	7	6	6.2
Mean total delay prior to definitive Rx (months)	13	20	18.4

Table 3. **Results of Management**

N = 22(100%)

	Group 1 (%)	Group 2 n(%)	p value
Negative axillary nodes	5	14	
Positive axillary nodes	--	3	
Mean survival (months)	104	46.8	< 0.001
Mean survival -ve nodes (months)	--	50	)
		)	< 0.05
Mean survival +ve nodes (months)	--	32	)

DISCUSSION

The findings and management of 22 Nigerian women seen over a 10 year period with Paget's disease of the breast has been presented. The mean age of the patients 42.8 was within the age range of all other breast cancer patients in this hospital and was in keeping

with findings elsewhere in Nigeria and Africa for breast cancer patients[2-4,9]. Breast cancer in Nigeria, as in other third world countries, is mostly a pre and perimenopausal disease and occurs about one decade before the reported age of occurrence in Europe and America[3,9,10]. The mean age of Paget's disease patients in the US and Europe falls within the age of other breast cancers in these countries[12,12]. Thus, as found in our study, the age of onset of Paget's disease falls within the age range for other breast cancers in a given population. In Haagensen's series[5], the mean age of his Paget's disease patients was greater than that of his other breast cancer patients. Although more common in middle aged women, Paget's disease has been reported at least twice in women under 30 years of age and in males[13-15.]

In western countries, the incidence of Paget's disease with an associated mass ranges from 29% to 49%[7]. In our study 17 (77%) of our 22 patients presented with an associated mass. The disease was first mentioned by Vespeau in 1856 and was later given a clear clinical description by James Paget in 1874. Now well over a hundred years later, Paget's disease is not always recognized when it presents.

In our patients, the most diagnostic finding at presentation was a weepy or eczematoid nipple and areolar ulceration that stained the patients clothing (86.4%). Nineteen of 22 patients had gone through a stage they described as an "itchy eczema" only 4 (18.2%) of these presented with a persistent crusty eczematoid lesion, two had isolated nipple ulcer and one a distressing burning sensation of the nipple. These findings are consonant with the various reported descriptions of the disease as a crusty psoriasis-like lesion, a recurrent erythematous and eczematoid lesion, and moist weepy nipple and areolar lesion[5,12].

Although the differential diagnosis of the lesion does include contact dermatitis, eczema, amelanotic melanoma, subareolar duct papillmatosis, erosive adenomatosis, basal cell carcinoma, intraductal papilloma, and duct ectasia[12,16] the disease is most often mistaken for a less ominous chronic skin disease like eczema or other chronic skin lesions. Unfortunately the mistaken lesion may respond temporarily to topical treatment[5,17]. The serious import of the disease went unrecognised by our patients for six to 14 months before help was sought at a medical clinic. Misdiagnosis added a further six to seven months for a total mean delay of 18.4 months before definitive diagnosis was made. A high index of suspicion for all areolar lesions, followed by a nipple areolar biopsy under local anaesthesia is needed to make a correct and early diagnosis of Paget's disease.

In the past, surgical management of this disease ranged from simple mastectomy to radical mastectomy[5,17]. The treatment chosen for our patients was total mastectomy and levels 1 and II axillary dissection. However, with the modern trend towards more conservative management in breast cancer, the treatment of Page's disease is evolving towards breast conserving operations[6,12]. Nevertheless until the complete results of the European Organization for Research and Treatment of Cancer (EORTC) study now evaluating the adequacy of breast conserving treatments becomes available, some form of mastectomy will continue to be the treatment of choice.

Paget's disease diagnosed early is almost totally curable by mastectomy. Thus five (22.7%) of our patients (group 1) who presented with clinical Paget's disease without an accompanying mass were all alive at mean period of 104 months. The presence of progression to an associated mass dropped the mean survival to a mean of 46.8 months in group 2 patients ($p< 0.001$). Further progression to a positive axillary lymph node dropped the survival further to 32 months versus 50 months for patients with negative nodes ($p < 0.05$). Reported survival elsewhere varies form 80% to 100% 5-year survival for those without an axillary mass and 0% to 55% for those with axillary mass[9]. A confounding factor in our study is the absence of brain, liver and bone scintigram facilities. Nevertheless, in a medical environment such as ours where cancer management is handicapped by the dearth of oncologists and constraints in appropriate post-surgical diagnostic tools, our current management is considered optimal.

Because most breast cancer usually presents late in Nigeria, management is almost always only a palliative battle to render the patient comfortable and socially acceptable[2-4]. In our patients the disease thus carries an ominous prognosis with survival measured in months[2-4,9]. In terms of presentation and survival, Paget's disease is an exception. These patients presented fairly early with a visibly recognizable problem. Secondly, 14 of our 17 patients presented with tumor masses less than 2 cm in size. This is much earlier than our usual patients who usually present with a bulky ulcerated tumor (mean 6 cm) after a delay of many months[2-4,18]. Large tumour size in breast cancer correlates with positivity on bone scan and poor prognosis[19,20]. Since Paget's disease is symptomatic, has an early visual manifestation and is so easily diagnosed, our low survival figures represent a missed window of opportunity for curative management. As in other malignant diseases of the breast, delay in diagnosis leads to a worse prognosis. Although the presence of Paget's cell has not been reported in the axilla[12], patients who present with clinical Paget's disease before progression to an associated mass are less likely to have cancer involvement of an axillary lymph node[7].

CONCLUSION

Although it is benign looking and easily mistaken for a less ominous skin lesion, Paget's disease of the breast is a malignant disease. Non recognition in its early stages leads to all the known consequences of late malignancy of the breast. It behooves all clinicians to become familiar with this disease in which early recognition and management leads to excellent results. A policy of mandatory biopsy of all nipple/areolar lesions would ensure the achievement of these aims.

REFERENCES

1. Kalache A, Vessey M. Risk factors in breast cancer In: Baum M ed. Clinics in Oncology VI London: Sanders 1982: 662–8.
2 . Chiedozi LC. Morbidity, mortality and survival in the management of cT4 cancer in Nigeria Saudi Med J 1995;15:227-30.
3 . Chiedozi LC. Breast cancer in Nigeria Cancer 1985;55:653 –57.
4. Chiedozi LC. The patient history: A source of prognostic data in breast

Cancer J Roy Coll Surg Edin 1987;32:142-44.
5. Haagensen CD. Diseases of the Breast. 2nd ed. Philadelphia: Saunders, 1971:545–69.
6. Greenall MJ. Cancer of the Breast. In: Morris PJ, Malt RA, eds. Oxford Textbook of Surgery. Oxford: Oxford University Press, 1994:808-36.
7. Lichter AS, Lippman ME. Special situations in the treatment of breast cancer. In: Lippman ME, Lichter AS, Danforth DN, eds. Diagnosis and Management of Breast Cancer. Philadelphia: WB Saunders, 1988:407–38.
8. UICC-TNM. Classification of Malignant Tumours. Geneva: UICC, 1979:7
9. Chiedozi LC. Dissection, sampling, and local excision in the management of the axilla in locally advanced breast cancer in Nigeria. The Breast 1995;4:96-9.
10. Sebai ZA. Breast Cancer in Saudi Arabia. Ann Saudi Med 1989;9:55–63.
11. Osteen RT. Special therapeutic problems: Paget's disease of the nipple. In: Harris JR, Hellman S, Henderson IC, eds. Breast Diseases. Philadelphia: JB Lippincott, 1987:589.
12. Duba RB. Paget's Disease. In: Harris JR, Lippman ME, Morrow M, et al eds. Diseases of the Breast. Philadelphia, Lippincott-Raven, 1996:870.
13. Martin VG, Pelletiere EV, Dress D, et al. Paget's disease in an adolescent arising in supernumerary nipple. J Cutan Path 1994;21: 283-6.
14. Decaussin M, Laville M, Nathevet, et al. Paget's disease versus Tocker cell hyperplasia in supernumerary nipple Virchows Arch 1998;432:289.
15 . Verniers D, Van der Bogaert W, van der Schueren E, et al. Paget's disease of the male breast treated by radiotherapy Br J Radiol 1991;64:1062-4
16. Miller, Tyler W, Maroon M, et al. III Erosive adenomatosis of the nipple: a benign imitator of malignant breast disease. Cutis 1997;59:91–2.
17. Dixon AR, Galea MH, Ellis IO, et al. Paget's disease of nipple. Br J Surg 1991;78:722-3.
18. Chiedozi LC. Breast cancer in young Nigerian women. Top Geog Med 1984;36:249-53.
19. Danforth DN, Lippman ME. Surgical treatment of breast cancer. In: Lippman ME, Lichter AS, eds. Diagnosis and Management of Breast Cancer. Philadelphia: Saunders, 1988:95-154.
20. Lee YT. Bone scanning in patients with early breast cancer. Cancer 1981;47:486-9.