INTRODUCTION

Paget’s disease (PD) is an uncommon intraepithelial neoplasm first described by Sir James Paget in 1874 as nipple ulceration associated with an underlying breast carcinoma mass. There are two different subtypes of PD; one occurs in the nipple, which is called mammary Paget’s disease (MPD), and the other occurs in other sites and is better known as extramammary Paget’s disease (EMPD).

The origin of the neoplasm is not yet entirely understood, and there are several hypotheses concerning the origin of Paget’s cells. Some authors suggest that EMPD has an intraepidermal origin from adnexal structures, specifically from apocrine glands or multipotent stem cells in the epidermal basal layer. On the other hand, the origin of MPD is believed to originate from an intraductal cancer that has spread by upward migration to the nipple.

PD predominantly affects white women between 50 and 80 years old. Clinically, the disease presents as an erythematous well-demarked plaque, and the surface may have a scaly, grayish crust with erosion and ulceration. In some cases, pruritus and pain are found. The diagnosis is confirmed by a biopsy that presents a thickened epidermis, with papilomatosis, enlargement of the interpapillary ridges, hyperkeratosis or parakeratosis on the surface, and the characteristic Paget’s cells with a clear abundant cytoplasm. The cytoplasm of those cells are Acid-Schiff stain (PAS) positive and diastase resistant, whch indicates the presence of neutral polysaccharides and supports the glandular origin of the cells. Staining with antibodies to carcinoembryonic antigen (CEA), low molecular weight cytokeratin (Cam 5.2), and cytokeratin 7 (CK7) are also positive, they are markers of glandular epithelium.

MPD treatment is well established, as 80-98% of the cases are associated with ductal carcinoma. Surgical intervention is decided according to the oncological indication for the ductal carcinoma of the breast. It consists of the resection of the MPD with free margins. The MPD prognosis is good, with a low recurrence rate.

Even though the standard treatment for EMPD is also surgical, with intraoperative margin control, the prognosis is not satisfactory, and there is a high recurrence rate. For these reasons, new treatments, such as radiotherapy, CO₂ laser, Imiquimod and others, are being investigated. However, none of them has shown to be effective for treatment in most cases.

The objective of this study was to analyze the clinical evolution and interventions on patients with Paget’s disease followed in our ambulatory clinic between January 1991 and December 2007.

CASE DESCRIPTIONS

From January 1991 to December 2007, 14 patients were diagnosed with PD in our service. They represented 0.01% out of the total 114,646 patients registered in the department over the same period. Seven of these patients had MPD, and another seven patients had EMPD.

All seven patients with MPD were Caucasian women. The mean age at diagnosis was 56.7 years (range 34-84 years). The mean time between when the lesion was first noticed and the first consultation at our service was 3 years (range 1-4 years). All of these patients were investigated for underlying breast cancer. In five patients, invasive ductal...
carcinoma was diagnosed, one patient had an in situ ductal carcinoma, and one patient had no associated neoplasm.

The six patients with breast cancer were investigated to determine the staging of the disease. The surgery was planned according to the oncological indication of the ductal carcinoma. In patients who underwent conservative surgery, such as quadrantectomy, the MPD was excised in the same surgery, with either a 1-2 cm margin or intraoperative frozen-section of the margins. Treatment was also completed with radiotherapy or chemotherapy when indicated. No patients had recurrence after a mean follow-up time of 5 years (range 2-10 years).

Patient without breast cancer did not return for treatment and/or follow-up.

The seven patients with EMPD (Table 1) included three men and four women who were all Caucasians. The mean age at diagnosis was 68.4 years old (range 62-76 years). The women presented disease in the vulva, groin or perianal areas. Each man had a different compromised site; these sites included the scrotum, the penis and the axilla. The mean time between the initial lesion and the first consultation was 5.4 years (range 1-15 years). The six patients were previously treated in others hospitals with topical antifungals and corticosteroids, one of the patient did not remember the name of the medicaments that were previously used. None of them have had a therapeutic response.

All patients with EMPD underwent analysis of full blood cells count, renal function, hepatic enzymes, biochemical analysis and urinalysis. To complete the investigation of an occult neoplasm chest radiography, colonoscopy, abdominal and urinary tract ultrason were made. Clinical assessments by a gastroenterologist and an urologist were provided. A clinical assessment by a gynecologist and mammography were performed for female patients. In none of the patients was internal neoplasm diagnosed.

Patient 1 was initially treated with radiotherapy 60 Gy in 30 fractions delivered via electrons. She had a complete response with clearing of the neoplasm (Figure 1). However, the EMPD recurred after 4 months. We then decided to excise the lesion with intraoperative frozen-section analysis of the margins. The histopathological study of the surgical sample showed compromised margins. For this reason, a complementary treatment with CO$_2$ laser therapy was administered. The laser was applied at a power of 10-12 W with a 2 mm spot, and it vaporized the area that was 1 cm beyond the visual margin of the lesion, layer-by-layer, until a depth of approximately 2 mm was reached. The patient had a complete response to the treatment, but she had a recurrence after 3 years. We then decided on surgical treatment with intraoperative frozen-section analysis of the margins. The patient was submitted to surgery in 2000 and 2001 with recurrence after 7 and 10 months, respectively. In 2002, she underwent another surgery without recurrence after 5 years of follow-up. However, due to all the treatments, the patient had important anatomic and functional impairment, even after surgical reconstruction of the vulva. She has had a colostomy and needs a permanent vesical fold.

Patient 2 was also initially treated with radiotherapy with electrons, in a similar manner to the treatment for patient 1. She also had a complete response; however, after 3 months, there was a recurrence of the neoplasm (Figure 2). She was submitted to Mohs micrographic surgery (MMS) with complete excision of the lesion with margins free from disease. After 7 years of follow-up, she had a recurrence. MMS treatment was provided again, and she has been without recurrence for 3 years now.

| Table 1 - The clinical characteristics and treatments of the patients with EMPD |
|---------------------------------|---------------|---------|-----------------|----------------|----------------|-------|
| Patient No. | Age/Sex | Location | Size (cm) | Treatment | Recurrence (months) | Response | Follow-up (years) |
| 1 | 52/f | Vulva | 17 | Radiotherapy Vulvectomy CO$_2$ laser Vulvectomy | 4 | CR | 17 |
| | | | | | 12 | CR |
| | | | | | 36 | CR |
| | | | | | 7-10 | PR |
| 2 | 71/f | Inguino-crural | 14 | Radiotherapy Mohs micrographic surgery | 3 | CR | 15 |
| | | | | | 84 | CR |
| 3 | 72/m | Penis | 7 | Surgery | 6-84 | CR | 17 |
| 4 | 68/m | Axilla | 8 | Imiquimod PDT | 0 | PR | 1 |
| 5 | 76/M | Scrotum | 5 | PDT | NA | CR | 0.5 |
| 6 | 73/F | Vulva | 10 | PDT | NA | PR | 0.5 |
| 7 | 67/F | Vulva | 20 | PDT | NA | PR | 0.5 |

CR - complete response (100% clearance); PR - partial response (50-99% clearance); MR - minimal response (< 50% clearance); NA - not applicable
Patient 3 was submitted to surgery in 1993 for a resection of a 1-cm margin. The histopathological study demonstrated that the margins were compromised. Because clinically, he did not present signs of the disease, we decided that the patient should be followed up for observation. In 2000, he had recurrence of the EMPD. Surgery with resection of a 1-cm margin was performed again. An analysis of the margin found that it was positive for neoplastic cells. He had a recurrence after 6 months. He was submitted to surgery with generous margins in 2001 and 2002; both had positive margins and led to recurrence of the EMPD after 6 and 9 months, respectively. In 2003, he was submitted to a new surgery with negative margins and has been free from disease for 4 years.

Patient 4 was first treated with topical Imiquimod (5%) cream 5 times a week for a period of 6 months. After this period, the lesion has decreased in size by approximately 50%. Then, he was started on treatment with photodynamic therapy (PDT), with 3 sections at 2 weeks intervals. The area that was treated was cleaned with saline (0.9%); then, topical aminolevulinic cream (16%, Metvix®) was applied on the lesion and extending 1 cm into the clinical disease-free margins. The area was occluded for 3 hours. Then, it was cleaned with saline (0.9%) and exposed to 37 J/cm² of visible red light. After 3 sessions were treated, a new biopsy was performed. The result was still positive for neoplastic cells. We decided that 5 more sessions were to receive PDT. This resulted in a 60% reduction of the lesion. However, the new biopsy still showed the presence of disease. The next plans are to surgically treat the patient.

Patients 5, 6 and 7 were treated with PDT using the same protocol as for patient 4. After the treatment of the first 3 sessions, they were also biopsied. Patient 5 showed no clinical or histopathological signs of the disease, with hypocromic residual macula (Figure 3). Patients 6 and 7 still had clinical and histopathological neoplasia; nevertheless, they had 40-60% reductions in their lesions and great...
improvement in the comfort level and quality of life (Figures 4 and 5). They are both undergoing the protocol for 3 more sessions of PDT.

**DISCUSSION**

Paget’s disease is a rare disease; in our ambulatory clinic, it represented only 0.01% of all registered patients over a 17-year period. In the literature, we were unable to find reports of the prevalence of PD in dermatology departments.

Patients with MPD had characteristics that were similar to what has been described: age 50 to 80 years and Caucasian.²,³,⁸,⁹

Even though the clinical and histopathological characteristics of the MPD are well established, the patients
in our study had delays in the diagnosis, with a mean of 3 years after the initial signs. This delay is detrimental to the patient because MPD is usually a sign of underlying breast cancer (invasive or in situ ductal carcinoma)\(^6,5,2\) and also because this tumor can precede the MPD by 1 to 2 years.\(^1,2,8,13\) Consequently, this delay in the diagnosis may change the staging and prognosis of the patient.

Historically, patients with MPD have been submitted to more aggressive treatments\(^8,10,13\) because the invasive cancer associated with PD is more aggressive than those not associated with PD.\(^6,7,10,13,14\) Recently, however, large randomized studies with long-term follow-up have shown that conservative surgery is equivalent to radical mastectomy in terms of overall and disease-free survival in patients with breast cancer associated with MPD.\(^5,13,14\) For that reason, breast conservation, with removal of the nipple-areolar complex, is indicated for patients without a palpable mass or mammographic abnormality.\(^5-10,13,14\) Patients with a mammographic abnormality or a palpable mass should be candidates for breast conservative surgery with negative margins and evaluation of the lymph nodes.\(^4,8\)

In agreement with those data, the conservative approach used in our patients eradicated the tumors with no recurrence after a mean of 5 years of follow-up.

Thus, breast cancer in patients with MPD should be submitted to the same treatment given to breast cancer patients without MPD. The surgical treatment plan must be chosen on the basis of careful clinical and imaging assessment for each patient.\(^4,8-10,13,14\)

There are reports of cases of MPD without breast cancer.\(^8\) In our group, one of the seven patients was not diagnosed with breast cancer in the first evaluation, but it was not possible to confirm that she did not have an associated neoplasm because she did not have a follow up exam.

MPD is rarer than MPD.\(^7,15\) In our study, however, we found the same number of patients in both groups. This identical incidence of MPD and EMPD that was found in our ambulatory was because patients with cutaneous breast lesions probably made visits to the gynecology department. Which falsely decreased the incidence of the MPD from dermatology departments.

EMPD also more frequently affects white women, with a female-to-male ratio been 4:1 and a mean age of 65.\(^5,7\) In our study, we confirmed these observations; all patients were Caucasian, and the mean age at diagnosis was 68.4 years. On the other hand, there was no statistical difference between the number of affected men and women. However, we believe that women with vulvar lesions may have visited the gynecology department directly.

The most common sites of EMPD in women are the vulva and adjacent area. Men may present cutaneous lesions in the scrotum, penis, anal, perianal region and axillae.\(^6,15\) None of the patients had any uncommon sites or clinical presentations of the disease. However, the mean time for the diagnoses of the EMPD was 5.4 years. Furthermore, six patients were treated for eczema with topical corticosteroid and dermatophytosis with topical antifungal agents, without response.

The delay in EMPD diagnosis may impair the prognosis of the patient because, even though EMPD is not typically associated with an underlying carcinoma,\(^16\) there have been reports of cases associated with urothelial, colorectal, endometrial, cervical and Bartholin’s gland cancer.\(^5,16,17\) The delay in the diagnoses will modify the staging and prognosis of the associated neoplasm. All of our patients were fully investigated for other cancers, and other cancers were not found in any of them.

Furthermore, the delay in procuring and obtaining the appropriate treatment resulted in the patients’ lesions being advanced in spread, which also impaired the response to treatment and increased the recurrence rate.\(^8,15\)

Another factor that is associated with poor prognosis in EMPD is having dermal invasion or metastasis via the lymphatic system.\(^3,5,7,17\) The invasion of the dermis is uncommon, and metastases are extremely rare. In most cases, Paget’s cells remain confined to the epidermis, and the prognosis is good.\(^3,4,18\) In particular, the prognosis is good in relation to mortality, as most of the patients will die from a pre-existing condition\(^19\) but not in relation to the disease.\(^7,19\)

There is still no effective treatment for EMPD. Traditionally, the accepted first line of treatment, for either in situ or invasive EMPD, is surgical excision with generous margins.\(^18-22\) Nevertheless, surgery is associated with a high recurrence rate, between 31 and 61%.\(^18,20\) Another problem associated with this modality of treatment is the difficulty to close or to reconstruct the defects resulting from surgery. Because the lesion is usually in the anogenital and axillary area, surgery may lead to functional and sexual problems.\(^15,21\)

With the aim to ensure a negative margin and to ensure that the skin be free from disease, we proposed surgery with intraoperative margin control,\(^6,7,15,18\) specifically, MMS.\(^18,20,22\) Nonetheless, the recurrence rate reported is still 23-27%.\(^18,21\) The high recurrence rate is attributed to the multifocal nature of the disease.\(^6,7,15\) and the high false negative margins rate of 43%.\(^23-25\) Furthermore, this surgery is also associated with the same problems of closing the wound and high morbidity.\(^7,18,22\)

Patient 1 was submitted to surgery with frozen sections in 2000, 2001 and 2002, with a great area of resection, recurrence after the first 2 surgeries, and important impairment of the vulvar area. Patient 2 was submitted to
MMS and had recurrence after living free of disease for 7 years. Patient 3 was submitted to four surgeries with 1 to 2 cm margins, with the first three surgeries having positive margins and recurrence. Our patients who were submitted to surgery, as described in the literature, presented with a high recurrence rate. Patient 1 also had an important anatomic and functional impairment.

For these reasons, conservative approaches to EMPD have been studied, including radiotherapy, CO₂ laser, topical Imiquimod 5% and, more recently, PDT.²³⁻⁴²

The role of radiotherapy is still not clear. Studies show good local control of the disease with minimal side effects. On the other hand, it also showed a recurrence rate greater than 80%.²² For these reasons, radiotherapy is usually used for patients who are unfit for surgery, for recurrence after excision, and for adjuvant treatment for surgery.²⁶ Radiotherapy with megavoltage photons, superficial x-rays, brachytherapy and electrons have better rates of local long-term control.²²⁻²⁴

Because of the location and extent of the lesions, we proposed to treat patients 1 and 2 with radiotherapy with electrons. These patients showed a full response. However, both had recurrence of EMPD only 3-4 months after the treatment. Based on the literature, we expected a longer time free from disease after radiotherapy with electrons.

Another alternative treatment studied was the CO₂ laser. PD is an intraepidermal neoplasm, the laser radiation vaporizes the epidermal layer, therefore the laser was to eliminate the neoplasm with preservation of the anatomy and function of the area.²⁶⁻²⁷ However, with a recurrence rate ranging from 31-67%, most of the patients complained about the pain both after the vaporization and for a long period afterwards.²⁷ For this reason, the use of CO₂ laser should be evaluated carefully for the suitability to each patient.

In patient 1, conservative treatment was associated with surgery, which included radiotherapy and CO₂ laser, with the aim to preserve the function of the vulva area. The patient had recurrence after treatment. Thus, she was submitted to vulvectomy, but she had recurrence of the disease, and the new resections resulted in great impairment.

More recently, a treatment with topical Imiquimod cream was reported.²⁸⁻³² The Imiquimod (5%) cream is a topical imidazoquinoline immunomodulator that is a proinflammatory Toll-like receptor agonist that boosts the innate and acquired immune response.²⁸ The patients were treated from 3 to 7 times each week for 6 to 17 weeks. Initial improvement was noted after 6 to 9 weeks. A 78% complete response to treatment without recurrence after 2 to 12 months of follow-up was demonstrated.²⁸⁻³²

Although those are promising reports of successful treatment with Imiquimod (5%), the use of this agent must be viewed with guarded optimism because the number of cases and the follow-up time are still small. Therefore, randomized controlled trials with long-term follow-up to determine the true safety and efficacy of Imiquimod compared with other therapy modalities for EMPD would be useful.²⁸⁻³² In our experience with Imiquimod in patient 4, the lesion decreased by 50% after Imiquimod (5%) treatment five times a week for 24 weeks. However, this treatment was not satisfactory as it did not clear the neoplasm 6 month of treatment.

PDT is the most recent modality of therapy, and the reports to date have used 5-aminolevulinic acid 20% (ALA). The topical application of ALA leads to the biosynthesis and transient accumulation of the endogenous photosensitizer protoporphyrin IX (PpIX). ALA can diffuse in the skin and be preferentially accumulated in neoplastic cells. When a specific light wavelength is applied to the site, the light will be absorbed, and the energy will be transferred to molecular oxygen producing reactive singlet oxygen capable of causing direct cellular killing.⁴⁰⁻⁴²

There is still no consensus about the treatment with ALA-PDT in Paget’s disease. In previous reports, a topical application of ALA followed by occlusion, which varied from 3 to 18 hours, was proposed. Then ALA was removed, and the lesion was exposed to red light at 630 nm, with a light dose ranging from 37 to 200 J cm⁻². The number of sections also varied from 3 to 10 sections.³⁴⁻³⁹ Complete remission was obtained in approximately 50%, and the recurrence was 37% in 10 months.³⁴ In some cases, ALA-PDT was associated with surgery.³⁸

Patient 4 had a partial response with 8 sessions of PDT, and the treatment complemented with surgery. Patient 5 had a complete response, has been free from disease after 3 sessions and has been in remission for 3 months. Patients 6 and 7 had partial responses to 3 sessions and are scheduled for 3 more sessions.

Photodynamic therapy is a promising treatment or adjuvant treatment that also needs further study with a randomized, well-controlled, long-term study for determining its function in the treatment of EMPD.

In conclusion, EMPD is an uncommon neoplasm without any effective treatment. The traditional surgical excision has a high recurrence rate and may result in aesthetic, anatomic and functional impairment. For this reason, conservative treatments such as topical Imiquimod cream and PDT have been studied recently. However, both treatments need further randomized, long-term studies to evaluate their effectiveness.
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