CLINCAL CASE

PAGET DISEASE OF THE BREAST – THERAPEUTIC APPROACH DEPENDING ON THE FORM OF PRESENTATION

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Abstract

The clinical description of the nipple lesion in Paget disease of the breast is of eczematous rash that may be of interest to both the nipple and areola of the same breast, accompanied, most often, by an abundant, clear, slightly yellowish exudate. The first data on Paget's disease were mentioned in 1874, by Sir James Paget, when he pointed out the malignant transformation in the case of ten women with ulceration on eczematous background of the nipple. Paget's disease is rare, accounting for 1-3% of all breast cancer diagnoses. This condition can be encountered in the population between the ages of 26 and 88, but the peak of the incidence is represented by decades 5 and 6 of life. The histopathological examination describes the adenocarcinomatous malignant intraepithelial cells, called Paget cells. The treatment as well as the prognosis in the case of Paget's disease is closely related to the existence of a palpable tumor formation and the presence of mammographic signs of breast malignancy. We present the case of a 59-year-old woman, who presents for a symptomatic, ulcerated tumor formation, with a diameter of about 6 cm, and a 6-month evolution at the level of the upper pole of the areolar complex of the left breast, after previously the nipple at the level of the involved breast underwent changes with erythematous transformation and ulceration.

Keywords*: Paget disease of the breast, Paget cells, breast surgery, total mastectomy*

Introduction

The first data on Paget's disease were mentioned in 1874, by Sir James Paget, when he pointed out the malignant transformation in the case of ten women with ulceration on eczematous background of the nipple. The median duration to malignancy in the ten patients was two years [1]. Following this description, this condition became known as Paget's disease of the breast. In the period when Sir James Paget described this condition, he considered that the mammary lesion was initially benign, but later, histopathological research showed that in fact, from the beginning there are malignant cells at the level of the epidermis, now called Paget cells [2]. The clinical description of the nipple lesion in Paget disease of the breast is of eczematous rash that may be of interest to both the nipple and areola of the same breast, accompanied, most often, by an abundant, clear, slightly yellowish exudate.

Case presentation

We present the case of a 59-year-old woman from the rural area, with grade III obesity, grade III HTA and a severe chronic lung disease, who presents for a symptomatic, ulcerated tumor formation, with a diameter of about 7.5cm, and a 6-month evolution at the level of the upper pole of the nipple-areolar complex of the left breast, after previously the nipple at the level of the involved breast underwent changes with erythematous transformation and ulceration. From the heredocollateral history, we remember the death of the father of colorectal carcinoma, and the personal pathological background emphasizes numerous spontaneous abortions until the age of 31 years, later the patient enters the menopause without being able to have a pregnancy to term. Laboratory tests showed elevated markers of inflammation (fibrinogen, C-reactive protein, and Sedimentation rate of erythrocytes), microcytic hypochromic anemia, with increased reticulocytes, mild hepatic cytolysis syndrome and mild neutrophil leukocytosis.

Examination of the skin and mucosa revealed in the left breast a cauliflower-like tumor formation, with dark-purple color, ulcerated, with signs of infection, with a diameter of about 7.5 cm, adjacent to the underlying planes, with accumulation of pus at the central level, located at the upper pole of the nipple-areolar complex. The nipple is completely eroded, eczematized, ulcerated, with retraction reaction of the areolar complex. At the palpative examination of the left axilla, there are two strong lymph nodes, immobile on the underlying planes, with a diameter of about 1.5 cm.

Due to the clinical presentation, the indication of punch biopsy at the level of the nipple was established. Histopathological examination revealed epithelial glandular malignant cells with increased pleomorphism, hyperkeratotic nuclei, with slightly prominent nucleoli, pale, clear, large cytoplasm and mucin content, being known as Paget cells. Mitotic activity and ulceration were also observed. The malignant cells were in large quantities, completely replacing the normal epidermal layer. The underlying dermal layer also has reactive changes that include a high degree of telangiectasis and chronic inflammation.

Figure 1 – Macroscopic image of the tumor formation and of the affected nipple

Thus, the diagnosis of Paget's disease was established and, due to the concomitant invasive ductal carcinoma, the total left mastectomy was recommended by the Madden technique. The patient refused the surgery, which she considered too aggressive at that time of her life, and only followed a palliative treatment with Tamoxifen. The patient's death followed 11 months after the diagnosis was established due to the appearance of pulmonary metastases.

Discussions

Paget's disease is rare, accounting for 1-3% of all breast cancer diagnoses [3]. In the medical literature, cases of Paget's disease have been described in men also, but in an extremely small number [4]. This condition can be encountered in the population between the ages of 26 and 88 years of age, but the peak of the incidence is represented by decades 5 and 6 of life, an interval in which is included the case of our patient [5,6].

According to a study from 1979 [7], based on the histopathological examination of 3000 biopsy specimens from mastectomy, only 0.7% had the disease clinically manifest, while histopathological up to 4.9% had a diagnosis of the Paget disease, concluding that subclinical disease (which can be histopathologically proven) is much more common. According to the latest studies, Paget's disease has a decreasing tendency in terms of epidemiology, while the spread of breast cancers has an increasing tendency [8].

The clinical presentation of Paget's disease is represented by a vesicular, erythematous or ulcerated lesion, sometimes with bleeding, which starts at the nipple, and then spreads to the areola. A less common form is bilateral Paget's disease. Also, retractions of the nipple have been described in a more limited number of cases [9]. The symptoms most commonly described by patients are burn feeling, pain or itching, and in most cases, they are noticed before the clinical signs appear. This is why patients with such symptoms. even if they do not have obvious lesions, they should be carefully monitored to determine if these manifestations persist. Because the clinical presentation of this disease is nonspecific, there is an average duration of 6-8 months between the first signs of the disease and a histopathological diagnosis of certainty, with a diagnostic delay that may deteriorate the subsequent prognosis [10,11].

The signs and symptoms that lead to the suspicion of Paget's disease lead to the establishment of a diagnosis and treatment plan, which is based both on establishing the diagnosis of certainty and on revealing an underlying cancer of the same breast. A concomitant neoplasm is present in up to 80% of the cases, either in the form of invasive or “in situ” cancer, and in a large number of these cases there are no signs of palpable mammary formation or mammographic signs of a malignant mammary tumor [8].

Thus, if there are no clinical or mammographic signs of a breast tumor, there is a high chance that an "in situ" cancer will be present, but if any of these signs are found, there is a higher chance of invasive breast cancer [12].

The differential diagnosis in the case of Paget's disease includes both benign and malignant diseases. Among the benign conditions that need to be considered in the case of differential diagnosis, are: eczema, adenoma of the nipple, contact dermatitis, post-radiation dermatitis, and from the list of malignancies to be considered in the differential diagnosis we note: Bowen's disease-which is a squamocellular carcinoma of the epidermis, basal cell carcinoma, extensive malignant melanoma on the surface [13]-[17].

As a diagnosis of eczema is often suspected, it is a massive tendency to prescribe topical corticosteroids, an attitude that most often leads to delayed diagnosis, because even if the underlying condition is Paget's disease, it is observed both by the patient and by the doctor an improvement of the moment after this therapy. Therefore, the correct attitude that can optimize the prognosis is to perform a biopsy on any suspected modification of the nipple [18,19].

The histopathological examination describes the adenocarcinomatous malignant intraepithelial cells, called Paget cells, which can be observed both alone and in groups of several cells in the epidermis. These cells are large in size with clear cytoplasm, with giant nuclei and containing prominent nucleoli. This condition can mimic malignant melanoma when it incorporates melanic pigment from the underlying epidermis. Immunohistochemical examination is recommended in cases difficult to interpret only histopathologically. The differentiation between Paget disease and malignant melanoma is made by the positivity for carcinoembryonic antigen (CEA) and negativity for S-100 protein in Paget's disease [20]. Another immunohistochemical sign of great help in diagnosing this condition is the positivity of estrogen or progesterone receptors, but this sign is found in only half of the cases. The situation of negative receptors is common in the case of many invasive ductal carcinomas with negative hormonal receptors. Paget cells are usually positive for low-weight cytokines, a sign that distinguishes this disease from Bowen's disease, which has positive cells for high-weight cytokines. The most commonly used marker is CK7, but this marker can also be found in benign diseases such as Toker cell hyperplasia [21,22]. There are also situations of Paget's disease that do not express the CK7 marker at all, so it is not an absolute sign [23]. Between 84% and 94% of the biopsies that reveal Paget's disease,

overexpress HER2 at the immunohistochemical examination, which is a negative prognostic factor [24].

The treatment as well as the prognosis in the case of Paget's disease is closely related to the existence of a palpable tumor formation and the presence of mammographic signs of breast malignancy. In patients suffering from Paget's disease, accompanied by an underlying neoplastic tumor, excision is required, which is most often performed by total mastectomy. There is also the possibility of performing a conservative breast resection operation, when there is the possibility of excision of the affected nipple and of the underlying tumor with a satisfactory cosmetic result and with negative margins, the procedure followed by radiotherapy of the entire affected breast. There is a possibility, if the patient has sufficiently large breasts, at the same operator time, a combination of the excision of the areolar complex together with the tumor formation and the reconstruction of the nipple with the reduction of the contralateral breast, followed by the radiotherapy of the breast, the procedure that has both satisfactory oncological behavior and good aesthetic result with the symmetry of the breasts [25]. However, most cases have multicentric tumor formations or diffuse mammographic signs, or too large distance between the tumor and the areolar complex, so the therapeutic conduct involves a total mastectomy with evidence of the axillary lymph nodes. Also, if the cosmetic result is not satisfactorily or the margins remain positive, conservative breast surgery should be replaced by a total mastectomy.

In patients without a palpable tumor formation or mammographic signs of mammary neoplasia, is an underlying "in situ" cancer, in most cases. There is, however, a 25% chance of invasive ductal carcinoma, so standard treatment includes mastectomy or conservative breast surgery followed by irradiation of the breast involved, with the same indications described above [25,26]. The most commonly used option is simple mastectomy. Research has shown that recurrences occur in a small percentage after simple mastectomy, only 5% at follow-ups for an average period of 40 months [27]. Alternative therapies for this class of patients have been tried and less aggressive approaches such as total irradiation of the involved breast, followed only by biopsy of the affected nipple [28]-[31] or conservative surgery of the affected breast without being followed by total irradiation of the breast [32,33]. However, these procedures have been studied in a limited number of cases, and are not introduced into Paget's disease protocol without a palpable tumor formation or mammographic signs of neoplasia.

The use of adjuvant therapy with tamoxifen, aromatic inhibitors, trastuzumab or chemotherapies is recommended only in cases of invasive ductal cancer or "in situ" carcinoma of the breast involved [34].

Prognostic factors imply the presence or absence of metastases in the axillary lymph nodes and invasive ductal cancer. Thus, the 5-year survival is 20% -60% in Paget's disease cases accompanied by a palpable tumor formation or mammographic signs of mammary neoplasia and 75% -100% in Paget's disease cases without being accompanied by a formation palpable tumor or mammary signs of mammary neoplasia [35].

Conclusion

Paget's disease is rare, accounting for 1-3% of all breast cancer diagnoses and cases of this disease have been described in men also, but in an extremely small number. Subclinical disease, which can be only histopathologically proven, is much more common. Paget's disease has a decreasing tendency in terms of epidemiology, while the spread of breast cancers has an increasing tendency.

The clinical presentation of Paget's disease is represented by a vesicular, erythematous or ulcerated lesion, sometimes with bleeding, which starts at the nipple, and then spreads to the areola. The symptoms most commonly described by patients are burn feeling, pain or itching, and in most cases, they are noticed before the clinical signs appear. This is why patients with such symptoms. even if they do not have obvious lesions, they should be carefully monitored to determine if these manifestations persist. A concomitant neoplasm is present in up to 80% of the cases, either in the form of invasive or “in situ” cancer.

As a diagnosis of eczema is often suspected, it is a tendency to prescribe topical

corticosteroids, that often delays the diagnosis, because even if the underlying condition is Paget's disease, it is observed an improvement of the moment after this therapy. Therefore, the correct attitude is to perform a biopsy on any suspected modification of the nipple.

Although Paget's disease is much rarer than other types of breast cancer, it is a decisive step in the differential diagnosis for any anomaly of the nipple and of the areolar area.

The treatment as well as the prognosis in the case of Paget's disease is closely related to the existence of a palpable tumor formation and the presence of mammographic signs of breast malignancy. In the cases accompanied by an underlying neoplastic tumor, excision is required, which is most often performed by total mastectomy. There is also the possibility of performing a conservative breast resection operation, when there is the possibility of excision of the affected nipple and of the underlying tumor with a satisfactory cosmetic result and with negative margins, the procedure followed by radiotherapy of the entire affected breast. In patients without a palpable tumor formation or mammographic signs of mammary neoplasia, is an underlying "in situ" cancer, in most cases and, a 25% chance of invasive ductal carcinoma, so standard treatment includes mastectomy or conservative breast surgery followed by irradiation of the breast involved. The use of adjuvant is recommended only in cases of invasive ductal cancer or "in situ" carcinoma of the breast. Prognostic factors imply the presence or absence of metastases in the axillary lymph nodes and invasive ductal cancer.

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