ISSN-e 1984-8773



Surgical & Cosmetic Dermatology

www.surgicalcosmetic.org.br/

Recurrent extramammary Paget's disease successfully treated with peripheric Mohs micrographic surgery associated with rapid immunohistochemistry

Doença de Paget extramamária recidivada tratada com sucesso com cirurgia micrográfica de Mohs periférica associada à imuno-histoquímica rápida

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.2024160280

ABSTRACT

Extramammary Paget's disease is a slow-progressing, cutaneous adenocarcinoma of the apocrine glands with an uncertain etiology. The standard treatment is surgical removal of the tumor. However, the usual surgical methods – wide local excision and Mohs micrographic surgery – pose challenges and high recurrence rates. Often, these are extensive lesions with poorly defined boundaries located in critical anatomical regions. Additionally, they exhibit unpredictable subclinical intraepithelial spread. We present a case of a recurrent extramammary Paget's disease successfully treated with peripheric Mohs micrographic surgery associated with rapid immunohistochemistry for CK8/18.

Keywords: Paget Disease, Extramammary; Mohs Surgery; Immunohistochemistry

RESUMO

A doença de Paget extramamária é um adenocarcinoma cutâneo das glândulas apócrinas, de progressão lenta e etiologia incerta. O tratamento padrão é a remoção cirúrgica do tumor. No entanto, os métodos cirúrgicos usuais - excisão local ampla e cirurgia micrográfica de Mohs - apresentam dificuldades e elevadas taxas de recorrência.

Frequentemente, trata-se de lesões extensas, de limites mal-definidos, e localizadas em regiões anatômicas críticas. Além disso, apresentam disseminação subclínica intraepitelial imprevisível. Apresentamos o caso de um paciente com doença de Paget extramamária recorrente, tratado com sucesso com cirurgia micrográfica de Mohs periférica associada à imuno-histoquímica rápida para CK8/18.

Palavras-chave: Doença de Paget Extramamária; Cirurgia de Mohs; Imuno-Histoquímica

How do I do it?

Authors:

José Antonio Jabur¹ Selma Schuartz Cernea² Bianca Spina Papaleo¹ Rute Facchini Lellis³

- ¹ Irmandade da Santa Casa de Misericórdia de São Paulo, Dermatology, São Paulo (SP), Brazil.
- ² Hospital do Servidor Público Municipal, Dermatology, São Paulo (SP), Brazil.
- ³ Irmandade da Santa Casa de Misericórdia de São Paulo, Department of Pathology, São Paulo (SP), Brazil.

Correspondence:

José Antonio Jabur E-mail: jaburcunha@hotmail.com

Financial support: None. Conflicts of interest: None.

Submitted on: 07/19/2023 **Approved on:** 11/01/2023

How to cite this article:

Jabur JA, Cernea SS, Papeleo BS, Lellis RF, Rêgo LC. Recurrent extramammary Paget's disease successfully treated with peripheral Mohs micrographic surgery associated with rapid immunohistochemistry. Surg Cosmet Dermatol. 2024;16:e20240280.



INTRODUCTION

Extramammary Paget's disease (EMPD) is a rare, slow-progressing cutaneous adenocarcinoma of the apocrine glands with an unclear etiology.¹ Raising awareness of this disease is crucial, since diagnosis is often late, and recurrence rates tend to be high.²

Desquamative and erythematous plaques affect older people and are common on the vulva, perianal region, pubis, penis, scrotum, and inguinal region.³ Dermatologists should suspect EMPD in unilateral, chronic lesions located in typical areas, in older patients, and refractory to treatment. Diagnosis is based on pathological examination, with the presence of Paget's cells, associated with positive immunohistochemistry (IHC) for cytokeratin 7 (CK7) or cytokeratin 8/18 (CK8/18).^{1,3}

The standard treatment for EMPD is to remove the tumor surgically. This can basically be a wide local excision (WLE) with a predetermined margin or through techniques that evaluate 100% of the operative margins, such as staged surgeries or Mohs micrographic surgery (MMS).

Alternatively, some patients can also be treated with topical application of imiquimod, with good results.⁴

Advanced age, tumor extension, poorly defined boundaries, and an affected anatomical region often hinder the use of wide margins. Although the margin to be applied in these patients is unclear in the literature, some authors agree on 2 to 3cm.² In addition, WLE has high recurrence rates, which vary from 22% to 60%, depending on the study and characteristics of the tumor.^{5,6}

The typical subclinical spread and high recurrence rates favor the use of MMS or staged surgeries.⁵ In the case of MMS, however, it is difficult to identify subtle intraepithelial neoplastic proliferations using hematoxylin & eosin (HE) stain for fresh frozen sections.⁵

On the other hand, this can be overcome in staged surgeries, in which the margins are analyzed in paraffin, possibly using IHC, at the cost of several surgical times until the lesion has been cleared up.

Therefore, rapid IHC techniques have been described to aid the intraoperative assessment of the margins of intraepithelial tumors with extensive subclinical spread.⁷ This report describes the case of a patient with recurrent EMPD, successfully treated with MMS associated with rapid IHC for CK8/18.

CASE REPORT

A 73-year-old male patient presented with recurrent EMPD located in the inguinal region and pubis (Figure 1) for years. The patient had coronary insufficiency and was taking warfarin. He was initially treated with imiquimod, administered five times a week for 15 weeks. He was treated once again with imiquimod with no success. He then underwent two surgical resections with a 10mm margin at an interval of 1 year, with a persistent local recurrence. There was no evidence of invasion or involvement of internal organs at any time.



FIGURE 1: EMPD in the pubic region of a male patient. Desquamative, erythematous lesion with irregular borders and poorly defined boundaries, surrounded by a hypochromic area

The patient was then submitted to peripheral MMS associated with rapid IHC for CK8/18 (Novodiax ihdDirect[®]). For debulking, the tumor was marked and excised in the superficial subcutaneous plane. We decided to include the perilesional hypochromic area in this stage of the surgery (Figure 2). Debulking was assessed using vertical HE sections, in which Paget's cells were observed between the keratinocytes in all layers of the epidermis (Figure 3). The first phase of MMS was then marked with a 5 to 8mm margin (Figure 4).

The peripheral margin was incised at 90°, processed using en face sections, initially stained with HE, and the slides were examined by an experienced dermatopathologist. Margins that were negative or doubtful on HE were submitted to rapid IHC for CK8/18. In this case, no HE-negative margins were positive on IHC. However, in the margins suspected of being positive,



FIGURE 2: Marking the tumor for debulking. We decided to include the surrounding hypochromic area at this stage

FIGURE 3: HE-stained histological section obtained during intraoperative examination (frozen). Presence of atypical Paget's cells isolated (arrows) or in clusters (circles) in the epidermis

Paget's cells were stained brown on the IHC, confirming their presence in the keratinocytes (Figure 5).

The lesion required two phases and 14 fragments to clear, creating a surgical defect measuring 90 x 75mm. Reconstruction by approximation of the edges, associated with second intention, was then performed after the margins had been cleared. The patient was followed up in the outpatient clinic for 9 months with no recurrence (Figures 6 and 7). Due to the Covid-19 pandemic, medical interviews were conducted by telephone, the last of which took place 35 months after surgery, when no recurrence

was reported. The patient died of other causes 36 months after surgery.

DISCUSSION

The case studied illustrates a frequent situation in EMPD. An older patient with an extensive lesion in the perigenital region and a history of multiple recurrences to treatment. Due to associated comorbidities, treatment was initially attempted with topical treatment with imiquimod. Non-invasive therapies, such as imiquimod, may be indicated for patients in whom surgical morbidity may be considered high. A recent review identified



FIGURE 4: Surgical defect after debulking the tumor and marking the first phase of MMS



FIGURE 5: Histological section (100x magnification) subjected to rapid IHC reaction during intraoperative examination (frozen) with CK8/18

276 patients treated with imiquimod, in which a complete response was observed in 30% of cases and a recurrence rate of 35.4%.⁸ In our experience, in addition to recurrence rates, prolonged exposure time to the drug and intense local inflammatory reaction also add morbidity and should be considered when choosing a therapy.

Local surgical excision was unsuccessfully attempted after imiquimod proved unsuccessful. In this technique, the vertical processing of the surgical specimen limits the assessment of the margins to less than 0.1%,⁵ which is reckless in lesions with poorly defined boundaries, an irregular growth pattern and extensive subclinical dissemination.⁷

In a meta-analysis evaluating the efficacy of MMS in the treatment of EMPD, the recurrence rate observed was 12.2% over a mean follow-up of 27.5 months.⁹ This rate is considered high when compared to other skin tumors routinely treated with MMS. Part of these recurrences are believed to be due to the difficulty in visualizing intraepithelial malignant cells in HE

FIGURE 6: Immediate post-operative procedure with edge approximation associated with second intention

FIGURE 7: Postoperative appearance 6 months from surgery

frozen sections.⁵ In these cases, rapid IHC is useful, as it highlights the malignant cells and can facilitate adequate control of the margins.⁷

In this case, IHC did not change the interpretation of the margins. However, it was performed by an experienced dermatopathologist, which does not reflect the Mohs surgeon's routine. Damavandy et al. in their 2018 study evaluated the use of IHC to interpret margins in EMPD treated with MMS. In this study, the authors reported a recurrence rate of 5.6% in recurrent tumors treated with staged surgery associated with IHC for CK7, compared to a 50% recurrence rate in patients in whom IHC was not used. However, surgical treatment required up to 5 days to complete.⁸

In our experience, peripheral MMS associated with rapid IHC provided prolonged remission of a recurrent tumor; it was performed in an outpatient setting and in a single surgical procedure. It also avoided the use of extensive margins, which reduced the morbidity of the surgery. However, the high cost and low availability of reagents in our setting are still an obstacle to the diffusion of this technique. Future studies will be useful in proving the real value of rapid IHC in the surgical treatment of EMPD.

REFERENCES:

- 1. Extramammary Paget's disease [Internet]. Available from: www.blackwellpublishing.com/bjog
- Wollina U, Goldman A, Bieneck A, Abdel-Naser MB, Petersen S. Surgical treatment for Extramammary Paget's disease. Curr Treat Options Oncol. 2018;19(6).
- Kanitakis J. Mammary and extramammary Paget's disease. J Eur Acad Dermatology Venereol. 2007;21(5):581–90.
- Dogan A, Hilal Z, Krentel H, Cetin C, Hefler LA, Grimm C, et al. Paget's disease of the vulva treated with imiquimod: case report and systematic review of the literature. Gynecol Obstet Invest. 2017;82(1):1–7.
- Hendi A, Brodland DG, Zitelli JA. Extramammary Paget's disease: surgical treatment with Mohs micrographic surgery. J Am Acad Dermatol. 2004;51(5):767–73.
- Damavandy AA, Terushkin V, Zitelli JA, Brodland DG, Miller CJ, Etzkorn JR, et al. Intraoperative immunostaining for cytokeratin-7 during Mohs micrographic surgery demonstrates low local recurrence rates in extramammary Paget's disease. Dermatol Surg. 2018;44(3):354–64.
- 7. Trimble JS, Cherpelis BS. Rapid immunostaining in Mohs: current applications and attitudes. Dermatol Surg. 2013;39(1 Pt 1):56–63.
- Kibbi N, Owen JL, Worley B, Wang JX, Harikumar V, Downing MB, et al. Evidence-based clinical practice guidelines for Extramammary Paget disease. JAMA Oncol. 2022;8(4):618–28.
- Bae JM, Choi YY, Kim H, Oh BH, Roh MR, Nam K, et al. Mohs micrographic surgery for Extramammary Paget disease: a pooled analysis of individual patient data. J Am Acad Dermatol. 2013;68(4):632–7.

AUTHOR'S CONTRIBUTION:

José Antonio Jabur D ORCID 0000-0002-5780-0653 Study design and planning; writing of the manuscript; critical review of the manuscript.

Selma Schuartz Cernea D ORCID 0000-0002-0710-5935 Approval of the final version of the manuscript.

Bianca Spina Papaleo DCCD 0000-0002-8380-9088 Preparation and writing of the manuscript; data collection, analysis, and interpretation.

Rute Facchini Lellis DCCID 0000-0001-7690-0513 Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases.