Surg. Gastroenterol. Oncol. 2022;27(1):63-67 DOI: 10.21614/sgo-426

Perianal Extramammary Paget's Disease: A Case Report

Ana Sofia Rocha Cavadas[1*], Patrícia Cristina Fernandes Silva[1,2], Fernanda Maria da Costa Nogueira[1], Joaquim Manuel Costa Pereira[1], Sandra Fernandes Martins[1,2]

[1]Coloproctology Unit, Department of General Surgery, Hospital de Braga, Portugal
[2]Life and Health Science Research Institute, School of Health Sciences, University of Minho, Braga, Portugal

***Corresponding author:**
Ana Sofia Rocha Cavadas, MD
Coloproctology Unit
Department of General Surgery
Hospital de Braga, Portugal
Sete Fontes, 4710-243, São Victor,
Braga, Portugal
Phone number: 00351 917 709 092
E-mail: anasofiacavadas@gmail.com

ABSTRACT

Extramammary Paget's Disease is a rare cutaneous malignancy with only a few hundred cases described in the literature. Due to its rarity, diagnosis is often difficult. Here, we present a case of an 88-year-old man with a perianal lesion that persisted for two years despite treatment with multiple topical agents. A skin biopsy established the diagnosis of Perianal Extramammary Paget's Disease. After excluding an underlying adenocarcinoma, surgical treatment was proposed to the patient. Wide local excision of the lesion was performed, and a loop ileostomy was constructed for the purpose of faecal diversion. Since the superior and lateral surgical margins were positive for tumor cells, the patient was reoperated to enlarge the resection margins. Histopathological analysis did not show Paget cells in this resected specimen. Post-operative course was uneventful. We believe that our experience will contribute to the establishment of standards of care for this condition.

Key words: extramammary perianal Paget's disease, rare malignancy, surgery, reconstructive procedures

Abbreviations:
EMPD: Extramammary Paget's Disease;
CT: Computed Tomography;
MRI: Magnetic Resonance Imaging;
CEA: Carcinoembryonic Antigen;
CA 19.9: Carbohydrate Antigen.

INTRODUCTION

Extramammary Paget's Disease (EMPD) is a rare cutaneous malignancy. Its precise incidence is unknown, with only a few hundred cases reported in the literature (1). There is a female predominance (2,3), except in Asia, where males are more commonly affected than women (4,5). It is more frequent in Caucasians (2,3) and in individuals aged 50-80 years (2,5). Lesions usually appear in areas of the skin rich in apocrine glands, such as the axillae, external genitals and perianal region (2,5). Vulva is the most commonly affected site, representing approximately 65% of the cases (5,6). EMPD that occurs in non-apocrine-bearing regions is referred to as ectopic (1).

Although EMPD pathogenesis is still subject of debate, it is generally agreed that this is a heterogeneous condition that encompasses at least two entities with distinct pathological mechanisms: primary and secondary EMPD. Primary EMPD is not associated with an underlying adenocarcinoma and it is usually limited to the epidermis. Only in exceptional cases it may progress to an invasive tumor, infiltrating the dermis and spreading both to regional lymph nodes and

Received: 27.12.2021
Accepted: 24.02.2022

distant sites (1,2,7,8,9). Although neoplastic cells are thought to originate in the epidermis, it remains to clarify exactly which cells are the precursors of Paget cells in this form of the disease. Skin adnexa (eccrine or apocrine glands), ectopic mammary glands, pluripotent keratinocyte stem cells and Toker cells have all been implicated as a possible source of neoplastic cells (1,2,10). Secondary EMPD is thought to be due to epidermotropic spread of malignant cells arising either from an underlying adenocarcinoma in a dermal adnexal gland or from a contiguous epithelium neoplasm (1,2,7). It occurs less frequently than primary EMPD and it is associated with a worse prognosis (8,11). An additional theory proposes that a unique oncogenic stimulus generates (independently or simultaneously) both the intra-epidermal adenocarcinoma (EMPD) and the underlying (adnexal or visceral) one (5).

Given its rarity, there are no established staging or treatment guidelines for EMPD. In this article, we present a case of perianal Paget's Disease. It is our hope that our experience may contribute to a better management of this condition.

CASE PRESENTATION

An 88-year-old male was referred to our hospital due to complaints of perianal pain and pruritus for more than two years, that persisted despite multiple treatments with topical agents, including corticosteroids. He had no constitutional symptoms and denied either genitourinary or gastrointestinal complaints. His medical history included arterial hypertension, depression and transurethral resection of the prostate due to benign prostate hyperplasia. There was no previous history of malignancy. At the time of the first observation, the patient was in good general condition. Upon physical examination, an erythematous plaque with approximately 8 x 10 cm, extending from the perianal region to the left gluteal region was observed (*fig. 1*). The lesion had signs of maceration, and superficial weeping ulcers could be found in its medial half. Rectal examination was unremarkable, and no regional lymphadenopathy was noted.

The patient was first evaluated by a dermatologist, who performed a skin biopsy. The histopathology analysis revealed small groups of cells within the epidermis with abundant cytoplasm, large, irregular nuclei and prominent nucleoli. Immunocytochemical analysis showed that cells were positive for the expression of CK4, CEA and GCDFP-15 and negative for CK20. These finding were compatible with Paget's disease. The patient was, then, referred to the General Surgery Department, where further investigation took place.

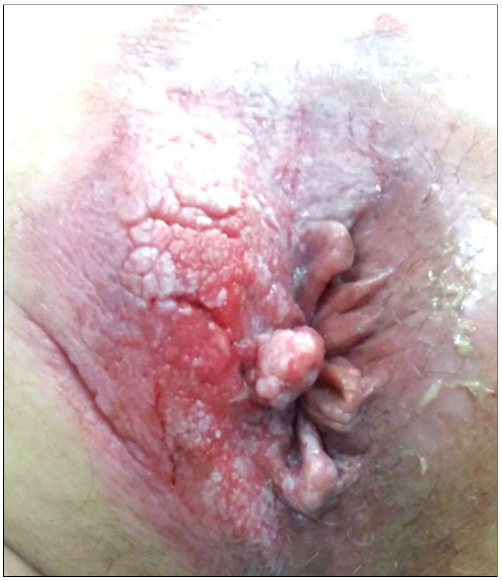

Figure 1 - Perianal lesion presented by an 88-year-old patient. A biopsy established the diagnosis of Perianal Paget's Disease

An upper endoscopy, colonoscopy and thoraco-abdominal CT scan were performed to exclude an underlying adenocarcinoma. A pelvic MRI was added to the study in order to evaluate local tumor extension. None of the examinations revealed any suggestive changes except for the MRI, which showed an area of cutaneous thickening in the perianal region, located between 3 to 7 o'clock positions. This area was about 6 mm thick and exhibited hyperintensity on T2-weighted images (*fig. 2*). There was no involvement of the anal sphincter by the above-described lesion and no

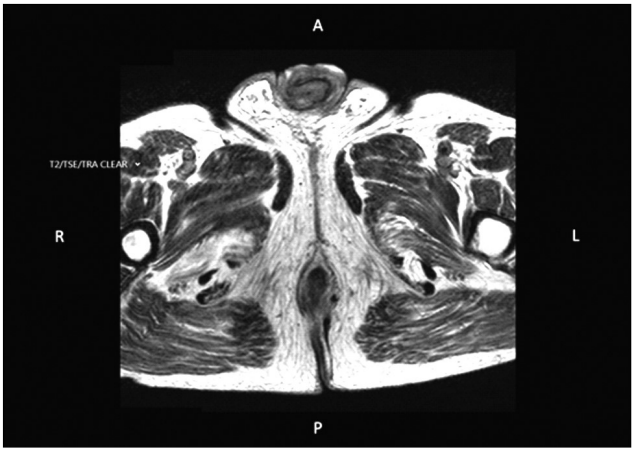

Figure 2 - Pelvic RMN of a patient with Perianal Paget's Disease, showing an area of cutaneous thickening in the perianal region, located between 3 to 7 o'clock positions. This area is about 6 mm thick and exhibits hyperintensity on T2-weighted images. A = Anterior, P = Posterior, R = Right, L = Left.

suspicious lymph nodes were found. Serum levels of both carcinoembryonic antigen (CEA) and carbohydrate antigen 19.9 (CA 19.9) were within the normal range.

Following a multidisciplinary discussion involving General Surgery, Oncology, Radiology and Plastic Surgery, surgical treatment was proposed to the patient. After obtaining patient's consent, a wide local excision of the lesion was performed. A loop ileostomy was constructed for the purpose of fecal diversion. Surgical wound was left open to heal by secondary intention. The histopathological analysis of the surgical specimen confirmed Paget's disease; there was no dermal invasion. The superior and lateral surgical margins were positive for tumor cells. Given this finding, the patient was reoperated to enlarge the resection margins. Histopathological analysis did not show Paget cells in this resected specimen.

Postoperative course was uneventful. Currently, the surgical wound is healing by secondary intention, and there are no signs of complications. The patient is being followed by a plastic surgeon. The necessity and timing for a reconstructive procedure are being evaluated. Closure of the ileostomy should be considered once perianal region is completely healed.

DISCUSSION

Since EMPD is a rare condition, a delay in the diagnosis is common. A median delay of two years has been reported (12). Patients are frequently though to have anal eczema and treated with topical agents, namely corticosteroids (13). Definitive diagnosis can only be achieved by cutaneous biopsy.

Once the diagnosis has been made, management of these patients is not standardized, as was previously stated. Nevertheless, it is of paramount importance to exclude the existence of an underlying adenocarcinoma (8,9). Most authors suggest a complete medical history and physical examination, including a complete cutaneous examination and evaluation of lymph nodes, liver and spleen. Breast and gynaecological examination are also recommended for female patients (1). Given the fact that perianal EMPD tends to be associated with gastrointestinal neoplasms (6), an upper endoscopy and colonoscopy are usually required in these cases. Additionally, a cystoscopy may be valuable in order to exclude an urothelial carcinoma of the bladder (1). Measurement of CEA levels has also been previously endorsed by some authors (1).

The presented case reflects the delay frequently present in the diagnosis of EMPD. Since the clinical investigations described above did not encounter an underlying adenocarcinoma, we may assume that this is a case of primary EMPD. Although primary EMPD has the potential to become disseminated, patients with this form of the disease usually have a better prognosis than the ones with secondary EMPD. Several factors may portend a greater risk of death, namely: i) presence of dermal invasion; ii) elevated CEA levels; iii) presence of regional lymphadenopathy and iv) bilateral lymph node metastases. Presence of dermal invasion is probably the most significant factor affecting survival (12). As none of the factors known to negatively affect survival are present in this case, the clinical course is expected to be positive.

Although there are no established guidelines for treatment of EMPD, surgery is considered the mainstay of treatment (1,5). In an effort to reduce the morbidity frequently associated with the surgical treatments performed, many other therapeutic approaches have been attempted on patients with EMPD. Therapeutic regimens other than surgery include radiotherapy (15-21), topical chemotherapy with 5-fluorouracil (22,23) and imiquimod (24-30), CO2 laser therapy (31) and photodynamic therapy (32-37). Since EMPD is a rare and heterogeneous condition, studies reviewing or proposing different treatment strategies are often retrospective and include a small number of patients. Therefore, regimens like radiotherapy and topical chemotherapy, despite being associated with promising results in some studies, are usually reserved for patients unfit for surgery (1,5).

In the reported case, the patient was considered fit for surgery. Although a wide local resection was performed, surgical margins were positive, which led to a reoperation. No Paget cells were found in the resected specimen after the second procedure. Several methods for intraoperative assessment of margin involvement were previously described in literature, including the use of frozen sections and fluorescein (38-41), but are still of unproven value.

Complete post-operative recovery will require several months and at least one more surgical procedure. Meanwhile, patient is back to his usual activities.

CONCLUSIONS

EMPD is a rare cutaneous neoplasm that can affect the perianal region and that may be misdiagnosed as chronic intertrigo, eczematous dermatitis or tinea cruris. Therefore, considering this pathological entity in the differential diagnosis of perianal skin lesions is of paramount importance to avoid a delay in the diagnosis and to achieve an optimal management. Definitive

diagnosis can only be made by cutaneous biopsy.

EMPD may be primary or secondary in its etiology. Primary EMPD is thought to arise as a primary intra-epithelial adenocarcinoma in most cases, while secondary EMPD represents extension of an underlying adnexal adenocarcinoma or visceral malignancy. Investigations should be made in order to exclude an underlying malignancy.

This reported case of EMPD was successfully treated with surgery, the mainstay of treatment.

Conflicts of interest

All authors declare that they have no conflicts of interest.

Funding

This case report received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical statement

Informed consent was obtained from the patient for the publication of this case report and any accompanying figures.

REFERENCES

1. Lam C, Funaro D. Extramammary Paget's disease: Summary of current knowledge. Dermatol Clin. 2010;28(4):807-26.
2. Shepherd V, Davidson EJ, Davies-Humphreys J. Extramammary Paget's disease. BJOG. 2005;112(3):273-9.
3. Pierie JP, Choudry U, Muzikansky A, Finkelstein DM, Ott MJ. Prognosis and management of extramammary Paget's disease and the association with secondary malignancies. J Am Coll Surg. 2003; 196(1):45-50.
4. Curtin JP, Rubin SC, Jones WB, Hoskins WJ, Lewis JL Jr. Paget's disease of the vulva. Gynecol Oncol. 1990;39(3):374-7.
5. Kanitakis J. Mammary and extramammary Paget's disease. J Eur Acad Dermatol Venereol. 2007;21(5):581-90.
6. Chanda JJ. Extramammary Paget's disease: prognosis and relationship to internal malignancy. J Am Acad Dermatol. 1985; 13(6):1009-14.
7. Lloyd J, Flanagan AM. Mammary and extramammary Paget's disease. J Clin Pathol. 2000;53(10):742-9.
8. Feuer GA, Shevchuk M, Calanog A. Vulvar Paget's disease: the need to exclude an invasive lesion. Gynecol Oncol. 1990;38(1):81-9.
9. Goldblum JR, Hart WR. Vulvar Paget's disease: a clinicopathologic and immunohistochemical study of 19 cases. Am J Surg Pathol. 1997;21(10):1178-87.
10. Willman JH, Golitz LE, Fitzpatrick JE. Vulvar clear cells of Toker: precursors of extramammary Paget's disease. Am J Dermatopathol. 2005;27(3):185-8.
11. Kodama S, Kaneko T, Saito M, Yoshiya N, Honma S, Tanaka K. A clinicopathologic study of 30 patients with Paget's disease of the vulva. Gynecol Oncol. 1995;56(1):63-70.
12. Hatta N, Yamada M, Hirano T, Fujimoto A, Morita R. Extramammary Paget's disease: treatment, prognostic factors and outcome in 76 patients. Br J Dermatol. 2008;158(2):313-8.
13. Ibrahim SF, Grekin RC, Neuhaus IM. Chapter 121. Mammary and Extramammary Paget's Disease. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, editors. Fitzpatrick's Dermatology in General Medicine, 8th edition. New York: McGraw Hill; 2012.
14. Brierley JD, Stockdale AD. Radiotherapy: an effective treatment for extramammary Paget's disease. Clin Oncol (R Coll Radiol). 1991; 3(1):3-5.
15. Moreno-Arias GA, Conill C, Castells-Mas A, Arenas M, Grimalt R. Radiotherapy for genital extramammary Paget's disease in situ. 2001;27(6):587-90.
16. Guerrieri M, Back MF. Extramammary Paget's disease: role of radiation therapy. Australas Radiol. 2002;46(2):204-8.
17. Burrows NP, Jones DH, Hudson PM, Pye RJ. Treatment of extra-mammary Paget's disease by radiotherapy. Br J Dermatol. 1995; 132(6):970-2.
18. Luk NM, Yu KH, Yeung WK, Choi CL, Teo ML. Extramammary Paget's disease: outcome of radiotherapy with curative intent. Clin Exp Dermatol. 2003;28(4):360-3.
19. Besa P, Rich TA, Delclos L, Edwards CL, Ota DM, Wharton JT. Extramammary Paget's disease of the perineal skin: role of radio-therapy. Int J Radiat Oncol Biol Phys. 1992;24(1):73-8.
20. Yanagi T, Kato N, Yamane N, Osawa R. Radiotherapy for extra-mammary Paget's disease: histopathological findings after radio-therapy. Clin Exp Dermatol. 2007 Sep;32(5):506-8.
21. Kwan WH, Teo PM, Ngar YK, Yu KH, Choi PH. Perineal Paget's disease: effective treatment with fractionated high dose rate brachytherapy. Clin Oncol (R Coll Radiol). 1995;7(6):400-1.
22. Del Castillo LF, Garcia C, Schoendorff C, Garcia JF, Torres LM, Almagro DG. Spontaneous apparent clinical resolution with histo-logic persistence of a case of extramammary Paget's disease: response to topical 5-FU. Cutis. 2000;65(5):331-3.
23. Eliezri YD, Silvers DN, Horan DB. Role of preoperative topical 5-FU in preparation for Mohs micrographic surgery of extramammary Paget's disease. J Am Acad Dermatol. 1987;17(3):497-505.
24. Qian ZQ, Zeitoun NC, Shieh S, Helm T, Oseroff AR. Successful treatment of extramammary Paget's disease with imiquimod. J Drugs Dermatol. 2003;2(1):73-6.
25. Wang LC, Blanchard A, Judge DE, Lorincz AA, Medenica MM, Busbey S. Successful treatment of recurrent extramammary Paget's disease of the vulva with topical imiquimod 5% cream. J Am Acad Dermatol. 2003;49(4):769-72.
26. Mirer E, El Sayed F, Ammoury A, Lamant L, Messer L, Bazex J. Treatment of mammary and extramammary Paget's skin disease with topical imiquimod. J Dermatolog Treat. 2006;17(3):167-71.
27. Badgwell C, Rosen T. Treatment of limited extent extramammary Paget's disease with 5 percent imiquimod cream. Dermatol Online J. 2006;12(1):22.
28. Ye JN, Rhew DC, Yip F, Edelstein L. Extramammary Paget's disease resistant to surgery and imiquimod monotherapy but responsive to imiquimod combination topical chemotherapy with 5-FU and retinoic acid: a case report. Cutis. 2006;77(4):245-50.
29. Vereecken P, Awada A, Ghanem G, Marques da Costa C, Larsimont D, Simoens C, et al. A therapeutic approach to perianal extramammary Paget's disease: topical imiquimod can be useful to prevent or defer surgery. Med Sci Monit. 2007;13(6):CS75-7.
30. Hatch KD, Davis JR. Complete resolution of Paget disease of the vulva with imiquimod cream. J Low Genit Tract Dis. 2008; 12(2):90-4.
31. Becker-Wegerich PM, Fritsch C, Schulte KW, Megahed M, Neuse W, Goerz G, et al. Carbon dioxide laser treatment of extramammary Paget's disease guided by photodynamic diagnosis. Br J Dermatol. 1998;138(1):169-72.
32. Fukui T, Watanabe D, Tamada Y, Matsumoto Y. Photodynamic therapy following carbon dioxide laser enhances efficacy in the treatment of extramammary Paget's disease. Acta Derm Venereol. 2009;89(2):150-4.
33. Shieh S, Dee AS, Cheney RT, Frawley NP, Zeitouni NC, Oseroff AR. Photodynamic therapy for the treatment of extramammary Paget's disease. Br J Dermatol. 2002;146(6):1000-5.
34. Henta T, Itoh Y, Kobayashi M, Ninomiya Y, Ishibashi A.

Photodynamic therapy for inoperable vulval Paget's disease using delta-aminolaevulinic acid: successful management of a large skin lesion. Br J Dermatol. 1999;141(2):347-9.
35. Mikasa K, Watanabe D, Kondo C, Kobayashi M, Nakaseko H, Yokoo K, et al. 5-Aminolevulinic acid-based photodynamic therapy for the treatment of two patients with extramammary Paget's disease. J Dermatol. 2005;32(2):97-101.
36. Runfola MA, Weber TK, Rodriguez-Bigas MA, Dougherty TJ, Petrelli NJ. Photodynamic therapy for residual neoplasms of the perianal skin. Dis Colon Rectum. 2000;43(4):499-502
37. Li L, Deng Y, Zhang L, Liao W, Luo R, Huang Z. Treatment of perianal Paget's disease using photodynamic therapy with assistance of fluorescence examination: case report. Lasers Med Sci. 2009;24(6): 981-4.
38. Mohs FE, Blanchard L. Microscopically controlled surgery for extramammary Paget's disease. Arch Dermatol. 1979;115(6):706-8.
39. Stacy D, Burrell MO, Franklin EW. Extramammary Paget's disease of the vulva and anus: use of intra-operative frozen-section margins. Am J Obstet Gynecol. 1986;155(3):519-23.
40. Murata Y, Kumano K. Extramammary Paget's disease of the genitalia with clinically clear margins can be adequately resected with 1 cm margin. Eur J Dermatol. 2005;15(3):168-70.
41. Misas JE, Cold CJ, Hall FW. Vulvar Paget disease: fluorescein-aided visualization of margins. Obstet Gynecol. 1991;77(1):156-9.