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EXTRAMAMMARY PAGET'S DISEASE: A CASE REPORT

DOENÇA DE PAGET EXTRAMAMÁRIA: RELATO DE CASO

ENFERMEDAD DE PAGET EXTRAMAMARIA: REPORTE DE UN CASO

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ABSTRACT

Extramammary Paget's disease is extremely rare; it can be primary or associated with other intra-abdominal neoplasms. The most frequent sites are the vulva and scrotum; perianal presentation has a predilection for the male sex. The treatment of choice is wide resection with clear margins; non-surgical therapies are considered in patients unsuitable for surgery. This case demonstrates the use of multimodal surgical and non-surgical treatment therapy in an elderly patient with comorbidities and prior surgery, highlighting the importance of the multidisciplinary team's decision in complex scenarios. This case will help to support individualized management based on a multidisciplinary approach in cases of rare diseases in complex clinical scenarios.

Keywords: Extramammary Paget's Disease. Perianal Disease. Immunohistochemistry.

RESUMO

A doença de Paget extramamária é extremamente rara; pode ser primária ou associada a outras neoplasias intra-abdominais. Os locais mais frequentes são a vulva e o escroto; a apresentação perianal tem predileção pelo sexo masculino. O tratamento de escolha é a ressecção ampla com margens livres; terapias não cirúrgicas são consideradas em pacientes não elegíveis para cirurgia. Este caso demonstra o uso de terapia multimodal cirúrgica e não cirúrgica em uma paciente idosa com comorbidades e cirurgia prévia, destacando a importância da decisão da equipe multidisciplinar em cenários complexos. Este caso contribuirá para o manejo individualizado baseado em uma abordagem multidisciplinar em casos de doenças raras em cenários clínicos complexos.

Palavras-chave: Doença de Paget Extramamária. Doença Perianal. Imuno-Histoquímica.

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RESUMEN
La enfermedad de Paget extramamaria es extremadamente rara; puede ser primaria o estar asociada a otras neoplasias intraabdominales. Los sitios más frecuentes son la vulva y el escroto; la presentación perianal muestra una predilección por el sexo masculino. El tratamiento de elección es la resección amplia con márgenes libres; las terapias no quirúrgicas se consideran en pacientes no aptos para cirugía. Este caso demuestra el uso de un abordaje terapéutico multimodal, quirúrgico y no quirúrgico, en un paciente anciano con comorbilidades y antecedentes de cirugía previa, destacando la importancia de la toma de decisiones por parte de un equipo multidisciplinario en escenarios complejos. Este caso contribuye a respaldar un manejo individualizado basado en un enfoque multidisciplinario en enfermedades raras y situaciones clínicas complejas.

Palabras clave: Enfermedad de Paget Extramamaria. Enfermedad Perianal. Inmunohistoquímica.

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1 INTRODUCTION

Extramammary Paget's disease (EMPD) is a rare neoplasm affecting skin with a high density of apocrine glands, presenting as erythematous lesions with crusts. Its incidence is very low, estimated at 0.7 cases per million person-years (1). Clinically, two phenotypes of EMPD are recognized: primary EMPD and secondary EMPD, which develops in relation to an underlying internal malignant neoplasm, commonly from the urinary or gastrointestinal tract, which can occur synchronously or metachronously (2,3).

The diagnosis of PDEM is complex and requires histopathological analysis, which reveals Paget cells with clear, pale cytoplasm and large, hypochromatic nuclei organized in clusters, and immunohistochemical analysis to establish the diagnosis (4). The differential diagnosis for primary cutaneous erythema is broad and includes other skin diseases such as psoriasis, eczema, and dermatitis. The diagnostic approach is not limited to identifying primary erythema, since, due to its association with underlying malignancies, screening for occult malignancy is essential. The role of sentinel lymph node biopsy as a diagnostic approach for staging the disease is controversial and limited to selected cases. Wide resection remains the first-line treatment. Other non-invasive alternatives have been described with variable response rates and are reserved for cases not amenable to surgical management due to associated conditions. The role of radiotherapy has been discussed recently, both as adjuvant therapy and as primary treatment. However, management guided by associated risk factors, as well as functional status and the presence of a synchronous neoplasm, is considered the ideal approach, in which multidisciplinary management is crucial for selecting the best possible therapy (2). The present case refers to a scenario of persistence due to compromised margins in which margin expansion could be considered, although adjuvant radiotherapy is a valid option and should have been managed in a multidisciplinary manner.

2 CASE REPORT

An 86-year-old man with a history of hypertension, diabetes mellitus, and dyslipidemia presented with perianal pruritus and a perianal nodule of approximately 1 cm, treated with poor response to topical treatment, for which an excisional biopsy was performed (Figure 1), with a pathological report of a 13 x 4 mm lesion of EMPD confirmed by IHC that showed a CK7 positive, CK20 positive, CEA positive, KI-67 positive profile in 80% of intraepidermal neoplastic cells, HER2NEU negative and CDX2 positive; the

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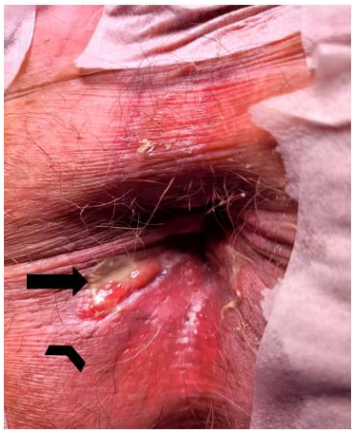
resection margin was found to be compromised, and a margin extension was required. Based on the histological and immunohistochemical findings, a primary anal intraepidermal Paget's disease was diagnosed. Due to the synchronous association of other neoplasms with the primary intraepidermal Paget's disease, staging studies were performed to search for a second primary intra-abdominal neoplasm.

Figure 1

Perianal region. 13x4 mm erythematous, friable nodule near the anal margin (black arrow). Peritumoral erythema (black arrowhead)



Sources: The authors.

Abdominal CT showed bilateral Bosniak II renal cysts and colonic diverticula without findings suggestive of a second primary or distant disease. Additional endoscopic studies and tumor markers were negative.

The histological study of the margin expansion revealed microscopically compromised edges due to neoplasia; a multidisciplinary team decided on adjuvant treatment with local radiotherapy. A regimen of 60 Gy in 30 fractions was administered; subsequently, the patient developed grade III radiodermatitis requiring conservative management, with improvement.

At the end of adjuvant therapy, the patient was placed on observation with no evidence of recurrence at 3 months.

3 DISCUSSION

Extramammary Paget's disease (EMPD) is a rare condition with few cases reported globally and an incidence that is still undetermined, although it is estimated at 0.7 cases per

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million per year. Due to its rarity, the demographic, clinical, and outcome characteristics are heterogeneous and limited to the population in which the different series are reported (1). It represents 6.5% of cutaneous Paget's disease cases; Isik et al., in one of the largest series of PDEM, reported a mean age of presentation of 67 years (5), however, a more recent review reported a mean age of diagnosis of 70 years (6), with differences between the reported series. Although there are series that report a predilection for females in PDEM, it is generally accepted that perineal and perianal PDEM has a predilection for males (6). The present case follows the trend of presentation in patients over 60 years of age, as well as being male.

The characteristic neoplastic cell is the Paget cell, which has abundant cytoplasm, pleomorphic nuclei, and frequent mitoses, often with a signet-ring appearance. In early stages, these cells are located in the basal layer of the epidermis, although they can involve its entire thickness and extend to adjacent structures. Key differential diagnoses include malignant melanoma and anogenital intraepithelial neoplasia (7). Immunohistochemistry is crucial for diagnosis, showing positivity for cytokeratin (CK) 7, CK20, p63, SOX10, and carcinoembryonic antigen (CEA). Primary Paget's disease is distinguished from secondary Paget's disease by its immunophenotypic profile (8). Although our patient's immunohistochemical profile is compatible with PDEM, the positive CEA suggests that occult neoplasia should be investigated given its association with other types of neoplasia; screening was performed in this case without evidence of demonstrable occult disease; the importance of this screening is crucial given that between 12-33% of perineal-perianal PDEMs are associated with synchronous occult neoplasia according to what was reported by Alhebshi et al., and the active search for intra-abdominal neoplasia should be carried out according to the patient's clinical profile (2). Although two classic clinical forms of PDEM have been described, primary and secondary in the case of association with an occult neoplasm, a diagnostic and prognostic approach has been proposed based on the aggressiveness determined by the degree of tissue infiltration, and they have been grouped into three categories, epidermal PDEM when it is limited to the skin, invasive when it invades soft tissues and metastatic when distant disease is evident, the latter two associated with a worse prognosis and with a greater probability of presenting occult disease (6). Our case, being a disease limited to the skin with negative staging studies and no evidence of obvious associated neoplasia, is related to primary primary epidermal necrotizing polyposis (PDNP). However, given the immunohistochemical finding of CEA, close follow-up is suggested by

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all series.

Although wide resection with adequate negative margins for local control with curative intent has traditionally been described as the gold standard treatment, Deng et al., in their series, described abdominoperineal resection for local control with negative margins in cases of PDNP associated with distal rectal adenocarcinoma (4). An evidence-based approach described and proposed by Kibbi et al. addresses management according to the clinicopathological characteristics of PDNP, in which epidermal PDNP is treated with wide resection with negative margins, and proposes non-surgical treatments such as imiquimod, photodynamic therapy, and CO2 laser as options. In invasive PDEM, wide resection with or without adjuvant treatment is proposed according to prognostic factors, in addition to the possibility of considering Mohs surgery for intraoperative control of the margins, the sentinel lymph node has had a controversial role in the management of the previous scenarios and is not currently recommended routinely; finally, systemic therapy, immunotherapy and targeted therapy are suggested in metastatic PDEM or in those patients not suitable for surgery (6).

While R1 has been described as a poor prognostic factor, in the series by Isik et al., the role of re-resecting in cases with compromised margins showed no difference in long-term follow-up, concluding that there is no clinical difference between R0 and R1 (5). Radiotherapy as adjuvant therapy has shown utility in this scenario; however, its role as primary treatment has been a subject of debate and is currently reserved for cases that are not candidates for surgery (6). Considering re-resecting in cases of positive margins is a viable option in cases of cutaneous-limited peritoneal carcinomatosis with curative intent. However, re-resecting with a report of compromised margins is a difficult decision given the intention to preserve the function of the anal sphincter, and adjuvant therapies must be considered. For this reason, this case was managed in a multidisciplinary manner and received adjuvant radiotherapy.

Close follow-up is necessary, given that metachronous neoplasms have been reported in up to 20% of patients with primary primary polycystic eruptions (PPEMs) after 5 years of follow-up, according to the review by Shah et al. Although no established interval exists, follow-up has been recommended every 3–6 months for the first 3 years, then every 6–12 months until 5 years are completed, and finally annually due to the risk of local recurrence and the development of an associated neoplasm (9). Our patient has shown no evidence of local recurrence or synchronous onset of primary neoplasm and will be

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monitored according to current recommendations.

4 CONCLUSIONS

In conclusion, extramammary Paget's disease (EMPD) is a rare condition, and due to its low incidence, the results of different therapeutic approaches are heterogeneous. Currently, there is controversy in several aspects of treatment, with multidisciplinary management being the best current approach.

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