Perianal Paget's disease : case report and review of the literature

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Abstract

Cutaneous Paget's disease (PD) is a rare entity, predominantly involving the breasts. Anal involvement is rather exceptional, and can be associated with underlying malignancies, among which prostate and rectal adenocarcinoma. We report the case of a 71-year-old man suffering from a long history of anal itching, associated with an erythematosquamous lesion of the right buttock extending up to the anus. The diagnosis of perianal PD (PAPD) was confirmed by histopathological demonstration of Paget's cells from a biopsy performed after ineffective topical treatment. Radiological and further clinical inspections allowed us to exclude any synchronous malignancy. A first-step surgery consisted in coelioscopic diverting sigmoid colostomy, along with multiple perianal, anal and rectal biopsies revealing an anal canal involvement. Coelioscopic abdominoperineal surgery and a wide cutaneous excision were then performed. Histopathological analysis revealed positive posterior margin, requiring further excision. No adjuvant therapy was prescribed, and to this day, after a one-year and a half follow-up, the patient remains disease-free.

Our case report and review of PAPD stress that appropriate management is required to improve the poor prognosis of this rare affection. (Acta gastroenterol. belg., **2004**, 67, **228-231**).

Key words : Paget's disease, extramammary, anus neoplasms.

Introduction

Cutaneous Paget's disease (PD) has been first described in 1874 by Sir James Paget, who reported 15 cases involving the nipple (1). Later, in 1989, Crocker *et al.* reported the first extra mammary localization, a patient with penile and scrotal involvement (2). Extra mammary disease is considerably less frequent than breast PD, and can involve the vulva, axilla, perineum, groin, thighs, eyelids, external auditory canals, umbilicus or nose. Most of those localisations are found to be in apocrine gland-bearing skin areas (4-5). Perianal PD (PAPD) is a very rare entity with only few cases described in the literature since the first one, reported by Darier and Couillaud in 1893 (6).

Since the aspect (eczematous lesion of the anal region) and the symptoms (pruritus, pain, bleeding, mucoïd discharge) are not specific, clinical diagnosis is difficult and classically requires complementary histological analysis. In this regard, mammary and PAPD are very similar morphologically, with the presence of large, anaplastic tumour cells lying separately or in small clusters within the epidermis. In contrast with nipple's PD, consistently associated with underlying breast tumour, PAPD may or not be associated with malignancy, which can be a distant one. Actually, according to the literature, 20% to 86% of the PAPD seem to be associated with neoplasia (7-9). Optimal treatment should be based upon a wide excision of the lesion, sometimes even requiring abdominoperineal surgery. Despite surgery, which is to date considered as the main curative option, recurrences are common (10).

We herein describe the case of a multidisciplinary managed PAPD, and review the scarce literature available about this rare entity.

Case report

A 71-year-old white man consulted in our institution about a sixth-month history of pruritus ani associated with an erythemato-squamous lesion of the right buttock, extending up to the anal margin (6 × 3 cm). Despite several topical treatments, there was no improvement of the lesion or the symptoms after one month. A biopsy performed afterwards showed hyperkeratosis and few large clear cells with signet ring appearance in the basal portion of the epidermis (Fig. 1 and 2), strongly positive for CAM 5.2 immunostaining (Fig. 3a and 3b), which is classical in PD. Due to the risk of associated neoplasia, breast and prostate examination, blood test for tumour marker (carcinoembryonic antigen), rectosigmoidoscopy, thoraco-abdominal computerized tomography (CT) scanning and full-body positron emission tomography scanning (PETs) were performed and all turned out to be negative. A two-step surgery was then performed. The first-step consisted in a coelioscopic diverting sigmoid colostomy to protect the future operative site, while multiple quadrant perianal biopsies were realised, along with anal and rectal ones, to rule out any anal involvement. Coelioscopic abdominoperineal excision was afterwards carried out, since the anal canal turned out being involved. The cutaneous part of the lesion, extending on the right buttock, was macroscopically completely removed at the same time. Despite this wide excision (1.5 cm outside of the lesion edge), no flap was needed to cover the defect. Later on, histopathological analysis revealed positive posterior margin, thus requiring a second large cutaneous resection (2 cm outside the surgical scar). No adjuvant treatment was prescribed. After a 18 months follow-up, the patient remains disease-free.

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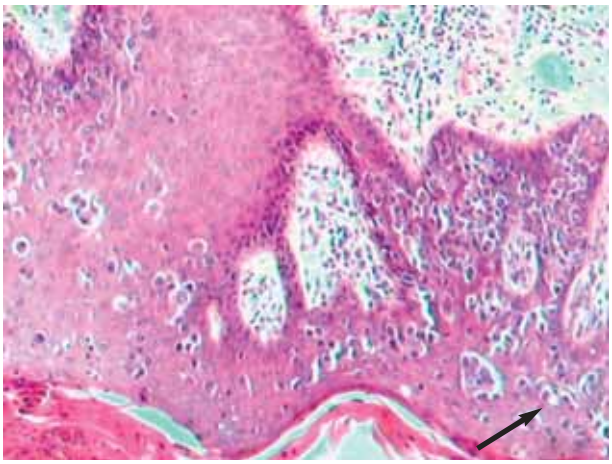


Fig. 1. — Haematoxylin and eosin staining show atypical vacuolar cells in the epidermis, suggesting Paget's disease.

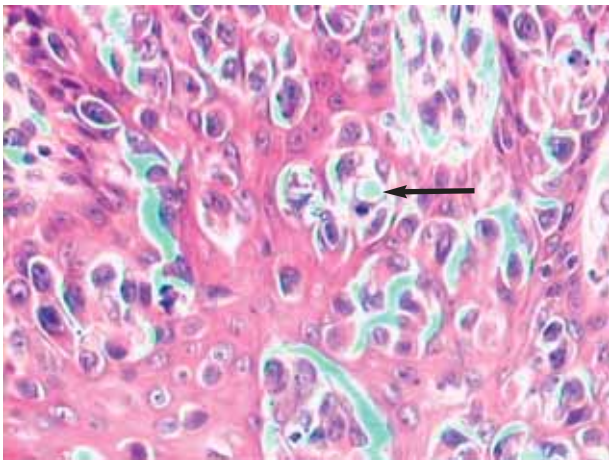
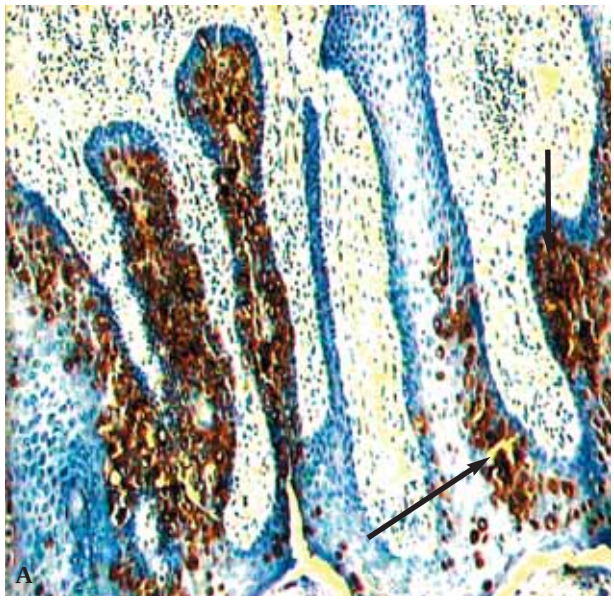


Fig. 2. — Haematoxylin-eosin coloration showing vacuolar Paget's cells in the epidermis.



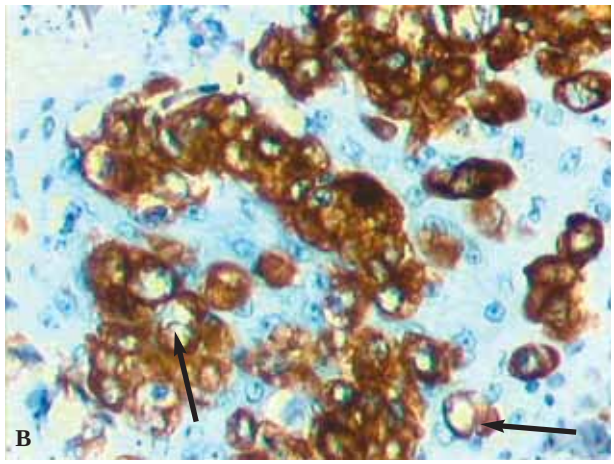


Fig. 3a and 3b. — Immunohistological staining for CAM 5.2. Paget's cells in basal layer of epidermis are strongly positive for CAM 5.2.

Discussion and review of the literature

PAPD is a very rare disorder accounting for less than 1% of all anal diseases. Since the first report of Darier and Couillaud in 1893, few cases have been described in the literature (6). It occurs more frequently in women, and usually starts in the fifth decade or thereafter, with a peak around seventy years old (10-11).

Anal itching and soreness are the most common manifestations. Others symptoms frequently encountered are bleeding, mucoid discharge and change in defecation rhythm (10,12-13). The lesion is typically erythematous, raised, scaly and excoriated, but may also be ulcerated, crusty, lichenified, leukoplakia-like, or papillary. It may also weep clear serous fluid. The edge of the lesion is usually well delimited, with irregular borders (10-14). Clinical differential diagnosis should include eczema, psoriasis, intertrigo, erythrasma, Crohn's disease, hydradenitis suppurativa, leukoplakia, superficial achromic melanoma, Bowen's disease, human papilloma virus intra-epithelial neoplasia, squamous cancer of the anus and adenocarcinoma of the rectum (5,10-14).

Because of the wide variety of cutaneous aspects, PAPD is not easy to diagnose. Therefore, any peri-anal erythematous lesion that has failed to improve after a one-month topical therapy should undergo biopsy to rule out histologically the possibility of PAPD (5,10-12,14).

Typically, Paget's cell is a large rounded cell characterised by a pale and foamy cytoplasm, with a hyperchromatic large nucleus often displaced to its periphery (Fig. 2). They have been described as signet-ring cells (4,15). Simple staining with haematoxylin and eosin might be sufficient to see Paget's cells (Fig. 1 and 2). However, cytochemical (Periodic Acid Schiff, mucicarmine, colloidal iron) and/or immunohistochemical (cytokeratin antibodies AE1/AE3 and CAM 5.2, epithelial membrane antigen, immunoperoxydase, carcinoembryonic antigen, Brst-2, S100) stains may be required

Table 1. — **Perianal Paget's disease staging classification (adapted from Schutze *et al.* (20))**

Stage	Description	Recommended therapy
I	Paget's cells in perianal epidermis without adnexal primary carcinoma.	Wide local excision
IIA	Paget's disease with associated adnexal primary carcinoma.	Wide local excision
IIB	Paget's disease with associated anorectal carcinoma.	Abdominoperineal resection
III	Paget's disease in which associated carcinoma has spread to regional nodes.	Inguinal node dissection included with resection
IV	Paget's disease with distant metastases of associated adenocarcinoma.	Chemotherapy ± radiotherapy : local palliative management

to confirm final diagnosis. Careful histological examination is indeed necessary to differentiate PD from Bowen's disease (AE1/AE3 positive) or malignant melanoma (S100 positive), since pagetoid cells can be found in both of them (10). In our case, immunostaining with CAM 5.2 (Fig. 3a and 3b) clearly identifies Paget's cells. Paget's cells appear to be quite epidermotropic. They spread laterally within the epidermis, without breaching the basal lamina, and are usually found in clusters among the keratinocytes, to whom they are not linked. They tend towards the annexial structures (hairs, eccrine canals). Hyperkeratosis of epidermal cells can also be seen, as well as in late stages, some signs of erosions or atrophy (3,11,14).

The pathogenesis of extramammary PD is unclear. However, for several reasons, an apocrine origin has been suggested as its histogenesis. Indeed, most of the extramammary Paget's cells are found to be in apocrine gland-bearing skin areas (4-5,10). It has also been suggested that they are arising from extensions or metastasis from an underlying carcinoma (16-17). Another supposition considers there might be a common neoplastic milieu that stimulates a multicentric reaction in adjacent apocrine structures, anal derma and rectal mucosa, causing simultaneous cancers. A fourth hypothesis suggests that Paget's cells correspond to an in situ adenocarcinoma coming from pluripotential ectodermic basal cells (3).

In contrast with nipple's PD, consistently associated with underlying breast neoplasia, PAPD may or not be associated with a malignancy. The rate of PAPD associated malignancy ranges from 20 to 86% according to available literature (7-8,11,18-19). Locoregional (rectum, anus, prostate, urethra, cervix, uterus, bladder), as well as distant neoplasia (breast, bile duct cancer, colon cancer), have been described (9-11). Those associated cancers can be anterior, synchronous or future ones.

Few, if any guidelines about pre-therapeutic neoplasia screening are available in the literature (14). However, due to the significant risk of associated neoplasia, we would recommend breast, prostate and anorectal examination, along with abdominal computerized tomography (CT) scanner, since most associated tumours are found in the abdomen. The helpfulness of PETs for PAPD is unknown yet. We decided to perform a PETs to assess the presence of possible tumour and /or metastases. In our case, PAPD lesion itself did not fix PETs fluorodeoxyglucose, nor did any other part of the patient's body.

According to Schutze *et al.*, extramammary PD can be divided in four stages, each with therapeutic recommendation, based upon the anatomopathology and the potential existence of an underlying neoplasia (Table 1) (20). Most authors consider surgery as the gold standard in PAPD (10,15,18-20). The key for successful therapy is therefore based upon total resection of the lesion 18. To assess local extension, some authors recommend multiple quadrant biopsies (18), while others prefer intra-operative frozen section checking (10). In the eventuality of multiple quadrant biopsies, it is important to perform some around the lesion, in healthy looking skin, since it could contain Paget's cells, stressing the need of wide margins when performing excision. Invasive tumour with anal involvement should also undergo surgery, meaning usually, as in our case, an abdominoperineal resection (10-11,21). Most operative defects require skin coverage, and several techniques are available, some also allowing to preserve anorectal function, if needed (split-thickness skin graft, rotational or island flaps and myocutaneous flaps) (22,29).

To our knowledge, since PAPD is such a rare affection, there is no consensus about the importance of non-surgical therapy. Radiotherapy has probably a place in the management of PAPD in some carefully selected cases. Radiotherapy is indeed used by some authors as primary treatment, for instance for people not eligible for surgery, keeping however in mind that subsequent perianal necrosis can happen (23). It is also sometimes used, still in selected cases, as adjuvant therapy, combined or not with chemotherapy (23-24). Radiotherapy might also be suitable after surgery failure, as a salvage treatment, or be used as palliation for disease related symptoms (11, 25). The use of chemotherapy, on the other hand, is not as well documented. Most of the time, it is combined with radiotherapy, in locally advanced or metastatic disease (5,26-27), and consists in an association of 5-fluorouracil and mitomycin C (5,27), which is the recommended therapy for anal squamous cell carcinoma.

PAPD has a high rate of local recurrence. In their study, Sarmiento *et al.* described a cumulative recurrence at five years rising up to 61% after surgery alone (10). Furthermore, Jensen *et al.* insisted on the fact that recurrences can occur even years after initial resection (28). With cutaneous involvement only, the long-term prognosis of PAPD is quite good. However, since these patients are at high risk of developing subsequent invasive cancer as well as associated tumours (locoregional

or distant), long term follow-up is required (11) and could consist of physical examination, procto-sigmoidoscopy (colonoscopy at 2 to 3-year intervals), combined with biopsies of any new lesions and random biopsies at the edge of the skin graft, if relevant (29-30).

In conclusion, PAPD is a rare disease that may be associated with local or distant malignancies. It presents as chronic eczematous perineal lesion and biopsies are required to confirm any clinical suspicion. Local excision is the treatment of choice if the disease is not invasive, while abdominoperineal resection is proposed for locally advanced stages. To date, there is no consensus about other therapies. Despite wide excision, the prognosis is rather poor in case of invasive disease, and recurrences are frequent. For those reasons, and because possible associated malignancy can occur after years, long-term follow-up is mandatory.

Bibliography

1. PAGET J. On disease of the mammary areola preceding cancer of the mammary gland. *St Bartholomew's hospital Report*, 1874, **10** : 87-89.
2. CROCKER H.R. Paget's disease affecting the scrotum and penis. *Trans. Pathol. Soc. London*, 1889, **40** : 187-191.
3. HEYMANN W.R. Extramammary Paget's disease. *Clin. Dermatol.*, 1993, **11** : 83-87.
4. JONES R.E. Jr, AUSTIN C., ACKERMAN A.B. Extramammary Paget's disease : a critical reexamination. *Am. J. Dermato-pathol.*, 1979, **1** : 101-132.
5. THIRLBY R.C., HAMMER C.J. Jr, GALAGAN K.A., TRAVAGLINI J.J., PICOZZI V.J. Jr. Perianal Paget's disease : successful treatment with combined chemoradiotherapy. Report of a case. *Dis. Colon Rectum*, 1990, **33** : 150-152.
6. DARIER J., COUILLAUD P. Sur un cas de maladie de Paget de la région périnéo-anale et scrotale. *Ann. Dermatol. Syphiligr. (Paris)*, 1893, **4** : 25-31.
7. LERTPRASERTSUKE N., TSUTSUMI Y. Latent perianal Paget's disease associated with mucing-producing rectal adenocarcinoma : report of two cases. *Acta Pathol. Jpn.*, 1991, **41** : 386-393.
8. HELWIG E.G., GRAHAM J.H. Anogenital (extramammary) Paget's disease : a clinicopathological study. *Cancer*, 1963, **16** : 387-403.
9. SKOGA F., GOTOH S., SUZUKI S. A case of invasive bladder cancer with Pagetoid skin lesion of the vulva and anogenital Paget's disease. *Nippon Hinyokika Gakkai Zasshi*, 1997, **88** : 503-506.
10. SARMIENTO J.M., WOLFF B.G., BURGART L.J., FRIZELLE F.A., ILSTRUP D.M. Paget's disease of the Perianal Region- An Aggressive Disease ? *Dis. Colon Rectum*, 1997, **40** : 1187-1194.
11. AMIN R. Perianal Paget's disease. *Br. J. Radiol.*, 1999, **72** : 610-612.
12. JABBAR A.S.A. Perianal extramammary Paget's disease. *Eur. J. Surg. Oncol.*, 2000, **26** : 612-614.
13. HERZOG U., von FLUE M., de ROCHE R., CURSCHELLAS E. Perianal extramammary Paget's disease : Report of two cases. *Eur. J. Surg. Oncol.*, 1993, **19** : 469-473.
14. FITZPATRICK T.B., JONHSON R.A., POLANO M.K., SUURMOND D., WOLFF K. Dermatologie clinique, atlas commenté en couleur : seconde édition : 748-751.
15. GOLDMAN S., IHRE T., LAGERSTEDT U., SVENSSON C. Perianal Paget's disease : report of five cases. *Int. J. Colorectal. Dis.*, 1992, **7** : 167-169.
16. ORDONEZ N.G., AWALT H., MACKAY B. Mammary and extramammary Paget's disease : an immunocytochemical and ultra structural study. *Cancer*, 1987, **59** : 1173-1183.
17. WOOD W.S., CULLING C.F. Perianal Paget's disease : histochemical differentiation utilizing the borohydride-KOH-PAS reaction. *Arch. Pathol.*, 1975, **99** : 442-445.
18. BECK D.E., FAZIO V.W. Perianal Paget's disease. *Dis. Colon Rectum*, 1987, **30** : 263-266.
19. TJANDRA J. Perianal Paget's disease. Report of three cases. *Dis. Colon Rectum*, 1988, **31** : 462-466.
20. SHUTZE W.P., GLEYSTEEN J.J. Perianal Paget's disease. Classification and review of management : report of two cases. *Dis. Colon Rectum*, 1990, **33** : 502-507.
21. PITTMAN G.H., McCARTHY J.G., PERZIN K.H., HERTER F.P. Extramammary Paget's disease. *Plast. Reconstr. Surg.*, 1982, **69** : 238-244.
22. LAM D.T.Y., BATISTA O., WEISS E.G., NOGUERAS J.J., WEXNER S.D. Staged and split-thickness skin graft for circumferential perianal Paget's disease. *Dis. Colon Rectum*, 2001, **44** : 868-870.
23. BESA P., RICH T.A., DELCLOS L., EDWARDS C.L., OTA D.M., WHARTON J.T. Extramammary Paget's disease of the perianal skin : role of radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.*, 1992, **24** : 73-78.
24. BROWN R.S.D., LANKESTER K.J., MC CORMACK M., POWER D.A., SPITTLE M.F. Radiotherapy for Perianal Paget's disease. *Clin. Oncol. (R. Coll. Radiol.)*, 2002, **14** : 272-284.
25. WILLIAMS S.L., ROGER L.W., QUAN S.H. Perianal Paget's disease : report of seven cases. *Dis. Colon Rectum*, 1976, **19** : 30-40.
26. BALDUCCI L., ATTAR M., SMITH G.F., KHANSUR T., MC KENZIE D., CRAWFORD E.D. Metastatic extramammary Paget's disease : dramatic response to combined modality treatment. *J. Surg. Oncol.*, 1988, **38** : 38-44
27. SECCO G.B., LAPERTOSA G., SERTOLI M.R., SCARPATI D., RIBOLI E.B. Perianal Paget's disease : case report of an elderly patient treated with polychemotherapy and radiotherapy. *Tumori*, 1984, **70** : 381-383.
28. JENSEN S.L., SJOLIN K.E., SHOKOUH-AMIRI M., HAGEN K., HARLING H. Paget's disease of the anal margin. *Br. J. Surg.*, 1988, **75** : 1089-1092.
29. CORMAN M.L., ALLISON S.T., KUEHNE J.P. Handbook of colon and rectal surgery, 2002 : 365-368.
30. STRAUSS R.J., LEVON R.R., TENENBAUM N. Bowen's disease and Paget's disease. *In* : FAZIO V.W. ed. Current therapy in colon and rectal surgery. Toronto : Decker, 1990 : 59-62.