

# Extramammary Paget's Disease of Anal Canal Associated With Rectal Adenoma Without Invasive Carcinoma

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## Abstract

Extramammary Paget's disease (EMPD) is a rare disease which is found in apocrine-rich locations such as anogenital region, axilla and rarely in other sites. Perianal EMPD is often reported as the involvement of perianal skin, but involvement of anal mucosa is very rare. Based on pathogenesis and association with either synchronous or metachronous malignancy, EMPD can be divided into primary and secondary types. Treatment approach for these two types of Paget's disease and their prognosis is different, thus it is important to make the distinction. Secondary type of Paget's disease is almost always described in association with invasive malignancy. While secondary Paget's disease arising in association with ductal carcinoma *in situ* of the breast is common, secondary EMPD associated with precursor lesion of the rectum without invasion is exceedingly rare. We report a very rare case of secondary Paget's disease of the anal canal in association with rectal tubular adenoma (precursor lesion) without malignancy.

**Keywords:** Paget's disease; Adenoma; Anorectal; Anus; Secondary; Perianal

## Introduction

Paget's disease of breast was described in late 19th century by Sir James Paget [1] and extramammary Paget's disease (EMPD) involving the scrotum and penis [2] was described shortly later. While EMPD has been recognized for many years, very few cases are reported, thus it is considered a rare disease. The most commonly affected demography comprises females and Caucasians between ages 50 and 80 [3]. The most

common site is vulva, followed by perineal, perianal, scrotal and penile skin. Other rarer sites are axilla, buttocks, thigh, eyelids and external auditory canal [4]. EMPD manifests as an erythematous or eczema like skin lesion that is long standing and refractory to conservative local treatment based on the assumption that it is a benign condition [5]. Histologically, Paget's disease is characterized by the presence of atypical large vacuolated cells within the epidermis. Based on suggested pathogenesis and histochemical markers, two types of EMPD - primary and secondary - are described [6-8]. Primary EMPD is mostly local and a relatively benign disease [9-11]. Secondary EMPD has a relatively poor prognosis and is almost always associated with synchronous or metachronous malignancy [6, 12-14]. Based on our review, EMPD is extremely rarely reported in association with tubular adenoma without evidence of underlying invasive carcinoma [15]. Herein we report such a case.

## Case Report

A 68-year-old gentleman with past history of renal cell carcinoma, prostatic adenocarcinoma and metastatic thyroid cancer but with no history of colorectal carcinoma underwent hemorrhoidectomy for recurrent internal hemorrhoids. On histological examination of the hemorrhoidectomy specimen in addition to a hemorrhoidal lesion, large atypical cells with pale and vacuolated cytoplasm were noted infiltrating the squamous epithelium of the anal mucosa. The atypical cells were positive for mucicarmine, CK20, CEA and CK7 (focally) and negative for melan A and GCDFP15 (Fig. 1). CDX2 immunohistochemistry was not performed. A diagnosis of anal EMPD was rendered. In addition to this, a detached portion of colonic mucosa involved by adenoma was noted. There was no evidence of invasive malignancy in the specimen.

Given the strong association between EMPD and underlying malignancy, unsampled colorectal adenocarcinoma was suspected. To evaluate the possibility of underlying malignancy, a follow-up colonoscopy was performed within a month, which revealed a localized area of moderately congested and nodular mucosa in the distal rectum. The biopsy of this nodular mucosa revealed hyperplastic polyp.

The patient was referred for consultation to our institute at this time. Flexible sigmoidoscopy was performed under

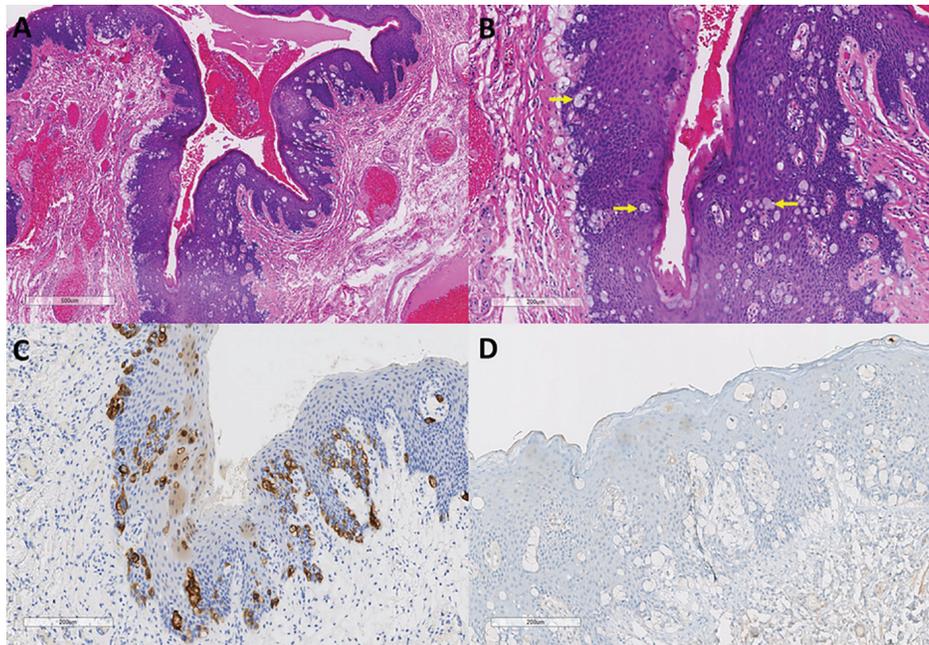
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**Figure 1.** Paget's disease of anal canal. (A, B) Anal mucosa from first resection specimen showing infiltration of large atypical vacuolated cells (Paget's cells, arrows) with cytoplasmic mucin (hematoxylin and eosin stain, original magnification  $\times 40$  (A);  $\times 100$  (B)). (C, D) These cells are CK20 positive and GCDFP15 negative (immunoperoxidase stain, CK20, original magnification  $\times 100$  (C); GCDFP15, original magnification  $\times 100$  (D)).

anesthesia at the time of wide excision of the lesion, which revealed old hemorrhoidectomy site and two small benign appearing nodules close to the anorectal junction in the rectum. Transanal wide excision of the mucosa to include the previous hemorrhoidectomy site and the additional rectal nodules was performed.

This transanal excision specimen consisted of two tan fragments of anorectal mucosa measuring 1.5 and 1.7 cm. The specimen was entirely submitted for microscopic examination.

Upon microscopic examination, the larger tissue fragment - previous hemorrhoidectomy site - showed residual Paget's disease adjacent to residual adenomatous lesion. No high grade dysplasia or invasive malignancy was identified. The Paget cells stained positive for CK7 and CDX2 and were minimally positive for CK20 (Fig. 2). The Paget's disease was noted close to the distal anal margin, but the margin was negative for the disease. The smaller tissue fragment revealed a small adenomatous lesion (Fig. 2D) without high grade dysplasia or invasion. No Paget's disease was noted in this smaller tissue fragment.

The patient is being followed till submission of this manuscript (11 months after excision) by physical examination and anoscopy and there is no recurrence of the disease.

## Discussion

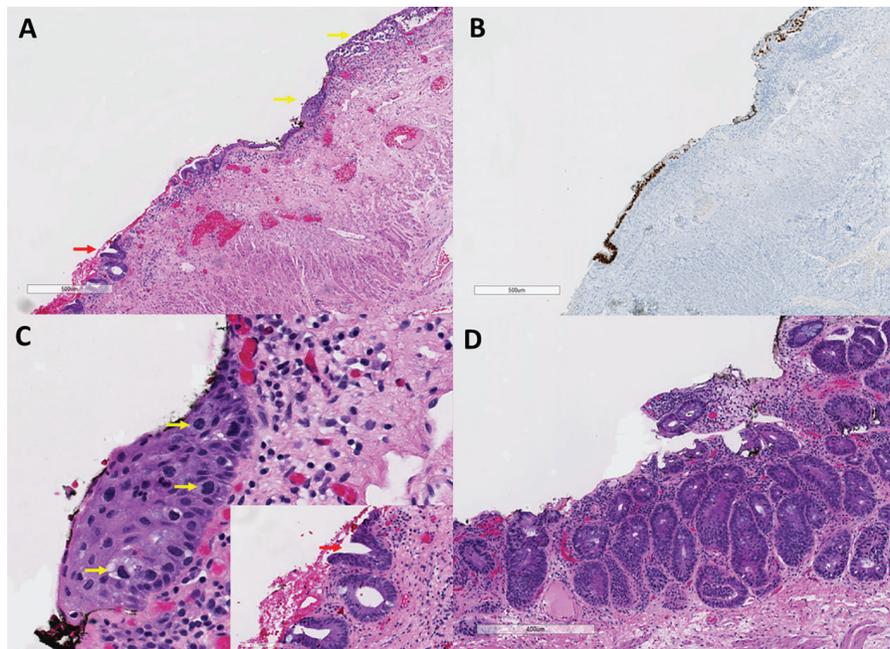
Paget's disease of anal canal is an extremely rare condition based on rare reports [16]. Some reports in the literature which discuss Paget's disease of the anus indeed describe perianal Paget's disease [13]. Given the anatomic continuity of the anal

canal and perianal skin and the extreme rarity of anal canal lesions, these two entities can be discussed together.

EMPD is a very rare condition with variable histology amongst different cases. In some cases, Paget's cells are predominant in basal layer while in others Paget's cells are spread throughout the epidermis. Moreover, the appearance of Paget's cell is different and is described as type A (classical) and type B (signet ring like) [7, 15, 17]. Two different hypotheses are proposed for the development of EMPD. According to the first hypothesis, it is a neoplasm of apocrine cells occurring within skin epidermis [18], while the other hypothesis suggests a "pagetoid" migration of malignant cells from an underlying malignancy such as anorectal adenocarcinoma [9].

Based on these hypotheses, two different types of perianal EMPD are described. Primary perianal EMPD is classically described as cutaneous adenocarcinoma commonly seen in apocrine rich zones with typical Paget cells [19]. In contrast, secondary EMPD will exhibit intraepidermal invasion of an underlying anorectal adenocarcinoma wherein the neoplastic cells demonstrate signet ring morphology or endodermal differentiation similar to colonic type mucosa [5]. Clinical presentation may be similar for both types. Even upon histological evaluation, these two types cannot always be distinguished. Distinguishing primary from secondary type is important as primary Paget's disease has better prognosis and is treated differently than a secondary Paget's disease. In addition, if secondary Paget's disease is identified, a thorough effort should be made to identify associated malignant lesion [20, 21].

Immunohistochemical study can help in differentiating these two types [6, 21, 22]. CK7 is a sensitive marker for Paget cells, but not very specific [6]. Paget cells also stain positive for



**Figure 2.** Residual Paget's disease and rectal adenoma. (A) Anal mucosa from second resection specimen showing residual Paget's disease (yellow arrows) adjacent to flat adenoma (red arrow) (hematoxylin and eosin stain, original magnification,  $\times 40$ ). (B) The Paget's cells and adenomatous cells are CDX2 positive (immunoperoxidase stain, CDX2, original magnification,  $\times 40$ ). (C) Higher magnification view of residual Paget's disease (yellow arrows) and adenomatous crypts (inset with red arrow) (hematoxylin and eosin stain, original magnification,  $\times 200$ ). (D) Adenoma in the smaller tissue fragment (hematoxylin and eosin, original magnification,  $\times 62$ ).

GCDFP15, which is a marker of apocrine cells and is used to identify primary EMPD [20]. CK20 is more typical for anorectal cancer and hence its positivity suggests secondary EMPD [6]. Similarly, CDX2, which is sensitive and specific marker for gastrointestinal mucosa, can be used to identify secondary type EMPD [22]. Overall, primary EMPD exhibits positivity for CK7 and GCDFP15 consistent with apocrine origin, while secondary EMPD is positive for CK20, CDX2 and variably positive for CK7 consistent with lower gastrointestinal origin. The staining pattern in our case is consistent with secondary EMPD.

Paget's disease needs to be differentiated from other lesions with similar morphological features. Certain reactive changes such as pagetoid dyskeratosis are seen with hemorrhoidal disease [23]. Also, human papilloma virus (HPV) induced lesion with or without anal intraepithelial neoplasm, Bowen's disease, and melanocytic lesions can mimic Paget's disease [21]. Histochemical markers such as mucicarmine, periodic acid-Schiff and immunohistochemical markers such as CK7, CK20, GCDFP15, CDX2, S-100, p16, melan A, and CEA can be employed to establish the diagnosis among these differentials.

Till now, almost all the cases of secondary EMPD described in the literature showed invasive adenocarcinoma associated with it. The current case is a very rare instance in which precursor lesion - tubular adenoma - is present in association with EMPD. We found only two reports in the literature describing perianal Paget's disease in association with adenoma of colon with no obvious invasive lesion [15, 24].

This may represent a phenomenon similar to Paget's disease of breast where its association with ductal carcinoma *in*

*situ* is relatively common [25]. One of the leading hypotheses for the pathogenesis of Paget's disease of breast is secretion by keratinocytes of epidermal heregulin- $\alpha$  (neuregulin I) which induces chemotaxis of Her-2 positive malignant cells to epidermis [26]. Overexpression of Her-2 is noted on the membrane and in the cytoplasm of approximately 25% and 66% of colorectal cancer cases, respectively [27] and is also reported on colorectal adenomas [28]. Similar to breast, Her-2 positive malignant cells of colorectal adenocarcinoma or tubular adenoma may migrate toward the anal mucosa or perianal epidermis due to chemotaxis in perianal EMPD.

## Conclusion

We report an exceedingly rare case of anal Paget's disease associated with adjacent precursor lesion (tubular adenoma) with no overt invasive lesion. Awareness of this association may alert endoscopists and pathologists of the need to pay close attention to adjacent anal mucosa when an adenomatous lesion of the rectum is encountered. Immunohistochemistry can aid in rendering a correct diagnosis and in distinguishing primary from secondary EMPD, a distinction of important therapeutic and prognostic significance.

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