Case Report

Primary Perianal Paget's Disease with Focal Adenocarcinoma, Signet-Ring Cell Differentiation and Unusual Immunohistochemical Expression: A Case Report

Worapop Suthiwartnarueput MD*

** Department of Pathology and Forensic Medicine, Faculty of Medicine, Thammasat University, Pathumthani, Thailand*

Perianal Paget's disease is an uncommon intraepidermal carcinoma characterized by the presence of Paget cells. It usually affects older patients and commonly presents as chronic perianal pruritus with scaly plaques. The disease is categorized into primary perianal Paget's disease of cutaneous origin and secondary perianal Paget's disease, which is due to extension of a visceral malignancy such as that of the anorectum or colon.

Cytokeratin 7 (CK7), cytokeratin 20 (CK20), and gross cystic disease fluid protein-15 (GCDFP15) expression are useful for differentiation between these two types. A tumor immunohistochemical profile of CK7+/CK20–/GCDFP15+ suggests the primary type, whereas CK7+/CK20+/GCDFP15– suggests the secondary type. The expression of caudal homeobox 2 (CDX2) suggests the secondary type from anorectal or colonic adenocarcinoma. However, approximately one-third of patients without visceral malignancy have a tumor that is CK7+/CK20+/GCDFP15–. Two percents of primary perianal Paget's disease can express CDX2.

The author reports a case of an 86-year-old man who presented with chronic perianal pruritus and a scaly plaque. A skin biopsy showed intraepidermal Paget cells with immunohistochemical profile of CK7+/CK20+/GCDFP15-/CDX2+. Initially, secondary perianal Paget's disease from colorectal adenocarcinoma was suspected. However, extensive investigations found no visceral malignancy. The patient underwent wide excision of the perianal skin. Pathological examination showed diffuse intraepidermal Paget cells with focal dermal invasion by intestinal-type adenocarcinoma and signet-ring cell differentiation. In conclusion, the final diagnosis was primary perianal Paget's disease with focal adenocarcinoma and signet-ring cell differentiation. The disease was consistent with primary perianal Paget's disease, because no visceral malignancy was found.

Keywords: *Primary perianal Paget's disease, Adenocarcinoma, Signet-ring cell, Gross cystic disease fluid protein-15, Cytokeratin 7, Cytokeratin 20, Caudal homeobox 2*

J Med Assoc Thai 2015; 94 (Suppl. 2): S162-S168
Full text. e-Journal: *http://www.jmatonline.com*

Paget's disease was first described by Sir James Paget in 1874. The disease is an intraepidermal neoplasm of the nipple and areolar skin that is usually associated with underlying mammary carcinoma. Paget's disease usually presents as an erythematous rash with scaling, oozing, and crusting and is characterized microscopically by the presence of Paget cells, which have large vacuolated cytoplasm and hyperchromatic nuclei scattered in the epidermis. However, Paget cells can be identified in the skin lesions of extramammary sites rich in apocrine glands such as the perianal region, perineum, vulva, scrotum, and penis, and in these cases, the disease is called extramammary Paget's disease[1,2].

Perianal Paget's disease is an intraepidermal carcinoma that is also characterized microscopically by the identification of Paget cells. This form of the disease accounts for approximately 20% of cases of extramammary Paget's disease, and approximately 200 cases have been reported. The disease typically occurs in the sixth and seventh decades of life, with a female preponderance[3]. The average age at diagnosis is 63 years[3]. The common manifestations are chronic perianal pruritus or plaques with scaling, crusting, or ulceration[4].

Correspondence to:
Suthiwartnarueput W, Department of Pathology and Forensic Medicine, Faculty of Medicine, Thammasat University, Klongluang, Pathumthani 12120, Thailand.
Phone: +66-2-9269366, Fax: +66-2-9269373
E-mail: worapop2526@gmail.com

Importantly, perianal Paget's disease may originate from cutaneous adnexal stem cells (primary perianal Paget's disease) or a secondary extension of an occult malignancy (secondary perianal Paget's disease) such as adenocarcinoma of the colorectum. The combination of cytokeratin (CK)7/CK20/gross cystic disease fluid protein-15 (GCDFP15) expression is useful for distinguishing between the primary and secondary types. If the immunohistochemical panel shows CK7+/CK20–/GCDFP15+, the primary type is suggested. If the panel shows CK7+/CK20+/GCDFP15–, the secondary type is suggested[5-9].

Caudal homeobox 2 (CDX2), a marker for colorectal adenocarcinoma, is also useful for discriminate primary and secondary type[16]. The expression of CDX2 suggests a secondary extension from anorectal or colonic adenocarcinoma.

Case Report

The author reports a case of an 86-year-old man who had past history of benign prostatic hyperplasia (BPH) and underwent transurethral resection of the prostate (TURP) five years ago. Serial prostate-specific antigen (PSA) levels subsequent to operation ranged from 2.3 to 4.6 ng/ml over the past 5 years and were unremarkable. He presented with chronic perianal pruritus for a duration of 1 year and perianal induration over the previous 2 months. He had no previous history of chronic perianal disease. He was treated with topical steroids by which partial response was achieved. Skin examination revealed a perianal scaly plaque without fistular tract or abscess. A perianal skin biopsy showed intraepidermal Paget cells with adnexal epithelial extension without an invasive component. The Paget cells were confirmed by positive staining for alcian blue (Fig. 1). Immunohistochemical studies showed positive expression of CK7, CK20 and CDX2 but negative expression of GCDFP15 (Fig. 2). Thus, the pre-operative diagnosis was perianal Paget's disease, suspicious for metastatic colorectal adenocarcinoma. He was subsequently transferred to the surgery clinic. Digital rectal examination, physical examination, and colonoscopy did not identify an anorectal or colonic mass. Histopathologic slides from the TURP specimen were reviewed. The diagnosis was benign prostatic hyperplasia. No malignancy was identified. An abdominal computed tomography (CT) scan revealed no evidence of distal or nodal metastasis. Thus, the pre-operative diagnosis was perianal Paget's disease that may be primary cutaneous in origin. He underwent

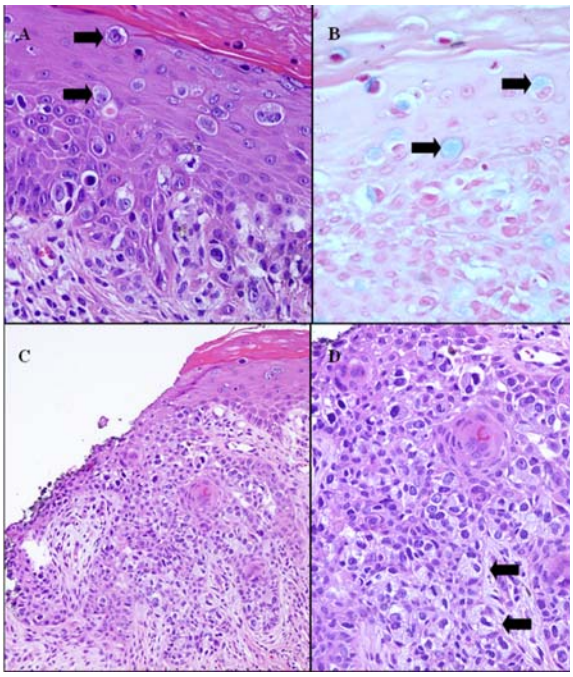

Fig. 1 Histopathology of the perianal skin biopsy. A) The epidermis was infiltrated by Paget cells with isolated large cells of a round to oval shape and granular-to-vacuolated cytoplasm, central-to-eccentric nuclei, and visible nucleoli (arrows) (H&E, x600). B) Alcian blue shows positive staining in the cytoplasm of Paget cells (arrows) (x600). C, D) Paget cells extend along the adnexal epithelium without penetrating the basement membrane (arrows in D) [H&E, x400 (C), x600 (D)].

wide excision of the perianal skin with a V-Y flap and loop sigmoid colostomy. Multiple perianal mapping biopsies were sent for frozen sectioning during surgery. All skin margins were negative for Paget cells and malignancy.

The macroscopic findings showed a circumferential scaly white plaque that was 5x4.5 cm in size (Fig. 3A). Cut surface revealed an ill-defined firm white dermal nodule of 1 cm in size at the 4-5 o'clock area (Fig. 3B). The microscopic findings of the dermal nodule showed proliferation of malignant glands lined by pleomorphic intestinal-type epithelium with focal differentiation of signet-ring cells. Paget cell spreading was prominent in the overlying skin (Fig. 4). The deep and peripheral margins were free of malignancy (not shown). No definite angiolymphatic invasion was identified. No immediate postoperative complications occurred. He underwent closure of a loop sigmoid colostomy 8 months after surgery. No evidence of tumor

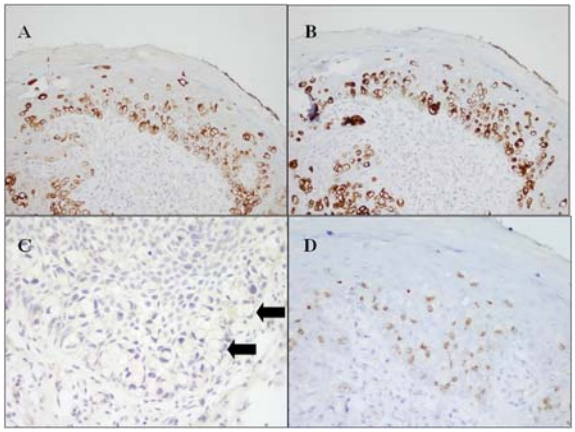

Fig. 2 Immunohistochemical study of the perianal skin biopsy. A) Paget cells were positive for CK7 (CK7, x200). B) Paget cells were positive for CK20 (CK20, x200). C) Paget cells within the adnexal epithelium were negative for GCDFP15 (arrows) (GCDFP15, x400). D) Paget cells show positive nuclear staining for CDX2, weak-to-moderate intensity (CDX2, x400).

Fig. 3 Gross pathology of the perianal skin. A) The perianal skin from the wide excision showed a circumferential plaque with white scaling that was 5x4.5 cm in size. B) Cut surface of the 4-5 o'clock region showed a dull white dermal nodule measuring 1 cm in the widest dimension (arrow).

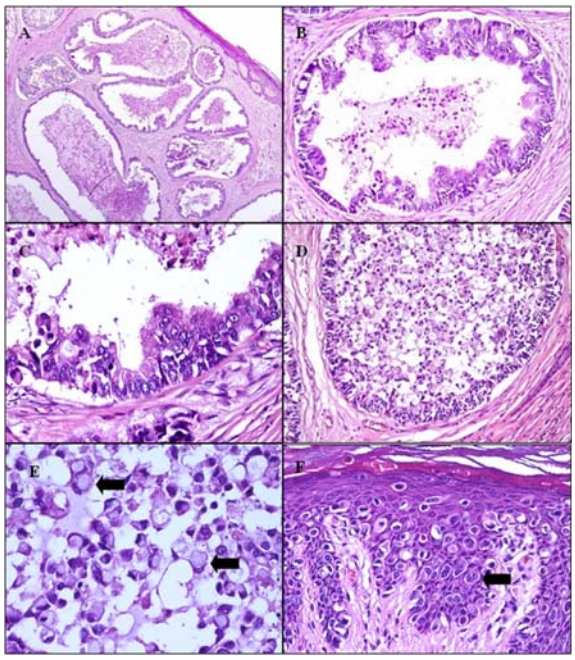

Fig. 4 Histopathology of the perianal mass (wide excision). A) Low magnification of an intradermal mass with glandular proliferation that was variable in size and shape (H&E, x40). B, C) The neoplastic glands were lined with intestinal-type epithelium with stratification, nuclear atypia and containing mucous material, inflammatory cells, and karyorrhectic debris (intraluminal dirty necrosis) [H&E, x200 (B), x600 (C)]. D, E) Some glands contained signet ring cells showing intracytoplasmic vacuoles and nuclei that were pushed aside (arrows in E). [H & E, x200 (D), x600 (E)]. F) The epidermis was infiltrated with Paget cells (mainly type A), with large round-to-oval cells, granular amphophilic-to-clear vacuolated cytoplasm, hyperchromatic nuclei, and occasional distinct nucleoli in the lower epidermis (H & E, x400).

recurrence or nodal metastasis was found 1 year after surgery. A follow-up abdominal CT scan did not show evidence of recurrence or nodal or distant metastasis.

In conclusion, the diagnosis was consistent with primary perianal Paget's disease with focal invasive adenocarcinoma and signet-ring cell differentiation. Although the immunohistochemical study suggested secondary spreading from a colorectal adenocarcinoma, no internal malignancy was identified.

Discussion

Perianal Paget's disease is defined as an intraepidermal carcinoma characterized by the presence of Paget cells in the epidermis. The disease typically occurs in the sixth to the seventh decades of life, predominantly in females. The common presenting symptoms are perianal itching or a rash that is unresponsive to local treatment[4]. The skin lesions usually manifest as a slowly growing erythematous plaque with scaling, crusting, or ulceration[2].

Perianal Paget cells can originate from stem cells of the skin adnexae (primary perianal Paget's disease) or by spreading from carcinoma of the visceral organs such as the rectum, penis, scrotum, or vulva (secondary Paget's disease)[10,11]. Adnexal involvement and invasive component can be found in either type.

The invasive component is found in 44% of cases and is related to poor prognosis[1,4].

Goldblum and Hart characterized two types of perianal Paget cells, the classic type (type A) and the signet-ring type (type B). Type A Paget cells are characterized by abundant clear or amphophilic cytoplasm with vesicular nuclei and prominent nucleoli. This type is predominant in primary perianal Paget's disease. Type B Paget cells are characterized by eccentrically displaced nuclei that result from large cytoplasmic mucin droplets. This type is predominant in secondary perianal Paget's disease[5].

Goldblum and Hart also proposed two histological patterns of perianal Paget's disease. The first pattern mainly consists of gastrointestinal-type glands containing intraluminal dirty necrosis, numerous signet-ring cells, CK20 positivity, and GCDFP15 negativity. This pattern is associated with rectal adenocarcinoma. The second pattern lacks gastrointestinal-type glands and intraluminal dirty necrosis but shows CK20 negativity and GCDFP15 positivity. This type is predominantly found in primary perianal Paget's disease. Four out of six patients with perianal Paget's disease without rectal adenocarcinoma showed CK7+/CK20–/GCDFP15+, and the other two without rectal adenocarcinoma were CK7+/CK20+/GCDFP15– [5].

Subsequent studies support the idea that combinations of positivity for CK7, CK20, and GCDFP15 are useful for distinguishing primary and secondary perianal Paget's disease. They concluded that tumors that are CK7+/CK20+/GCDFP15– with predominant signet ring–type Paget cells are suggestive of secondary perianal Paget's disease. In addition, CK7+/CK20–/GCDFP15+ is suggestive of primary perianal Paget's disease, based on immunoreactivity of GCDFP15, an apocrine gland marker[6,7,12].

Perrotto et al studied CDX2 expression in six cases of perianal Paget's disease secondary to anorectal adenocarcinoma. Five of six cases (83%) show CDX2 expression whereas one of six cases (17%) shows negative study for CDX2. Hence, CDX2 may be a useful marker for perianal Paget's disease secondary to the extension of anorectal adenocarcinoma. Nevertheless, approximately 2% (1 of 45 cases) of primary perianal Paget's disease express CDX2[16].

In this case, the patient presented with chronic perianal pruritus and a scaly plaque, which are classic symptoms of perianal Paget's disease. No visceral malignancy was identified after thorough investigations. Histopathology of the perianal skin revealed diffuse intraepidermal Paget cells, predominantly of type A, with focal adnexal involvement (Fig. 1). Focal dermal invasion 1 cm in size was identified and was mainly composed of intestinal-type glands with signet ring cells and intraluminal dirty necrosis (Fig. 4). Although the histopathology of the invasive component showed intestinal-type adenocarcinoma and a tumor that was CK7+/CK20+/GCDFP15–/CDX2+, suggestive of secondary extension from the colorectum, no internal malignancy was identified. Moreover, the non-invasive component was predominantly composed of type A Paget cells, supporting a diagnosis of primary perianal Paget's disease. The clinical observations and histopathology were correlated and consistent with primary perianal Paget's disease with focal invasive adenocarcinoma. The author's conclusions are supported by the study of Goldblum and Hart, who reported that about one-third of patients with perianal Paget's disease without rectal adenocarcinoma have tumors that are CK7+/CK20+/GCDFP15– [5,8]. In addition, approximately 50% of patients with primary perianal Paget's disease are GCDFP15 negative[8]. Moreover, CDX2 expression can be found in 2% of patients with primary perianal Paget's disease[16].

The principle of management of perianal Paget's disease depends on the extent of involvement including an association with anorectal carcinoma, dermal invasion, and nodal or distant metastasis. Recently, staging classification and recommended treatment were proposed (Table 1)[3]. Our current case was consistent with stage II, based on invasive disease without internal malignancy. Wide excision is the treatment of choice[3]. Abdominoperineal resection is recommended if synchronous anorectal carcinoma or extensive lesions are present[1,4]. Inguinal node dissection is recommended if nodal metastasis is suspected[4]. Chemoradiation is controversial but recommended in cases with distant metastasis[4,13,14].

The prognosis of patients with invasive disease is worse than of patients with non-invasive disease. McCarter et al found that the overall disease-free 5-year survival rates of patients with invasive and non-invasive disease were 59% and 64%, respectively[15]. The recurrence rate is higher in patients with invasive disease (67%) compared with those with non-invasive disease (35%)[3]. Annual follow-ups with random perianal skin biopsies are recommended. Fiberoptic endoscopy is recommended every 2 to 3 years because of the possibility of underlying gastrointestinal malignancy. Wolfgang et al recommend a CT scan every 1 to 2 years after surgery[4].

Table 1. The proposed classification and management of perianal Paget's disease (adapted from Kyriazanos et al[3])

Stage	Description	Management
I	Non-invasive disease: Paget cells confined to the epidermis and skin adnexa without primary carcinoma	Wide excision
II	Invasive cutaneous disease: Paget cells penetrating the basement membrane into the stroma and/or synchronous localized malignancies:	
IIA	Perianal Paget's disease with associated adnexal carcinoma	Wide excision
IIB	Perianal Paget's disease with associated anorectal carcinoma	Abdominoperineal resection
III	Presence of regional lymph node metastasis	Abdominoperineal resection or wide excision with inguinal lymph node dissection
IV	Presence of distant metastasis	Chemotherapy, radiotherapy, and palliative treatment

Conclusion

Although the combinations of CK7, CK20, GCDFP15 and CDX2 expression are useful for differentiation between primary and secondary perianal Paget's disease, the correct diagnosis depends on additional consideration of clinical presentation, colonoscopic findings, and radiologic studies. Approximately one-third of patients without identifiable visceral malignancies have tumors that are CK7+/CK20+/GCDFP15–. Two percent of patients with primary perianal Paget's disease express CDX2. The treatment of choice is surgery with/without adjuvant therapy depending on the extent of the disease. Many differential diagnoses of perianal Paget's disease exist that require clinicopathological correlation including superficial spreading melanoma, Bowen's disease, psoriasis, and superficial fungal infection[3].

Acknowledgement

The author thanks Drs. Panlop Chakkavittumrong and Amornpol Gunlerd for providing the biopsy and wide excision specimens, respectively.

Potential conflicts of interest

None.

References

1. Leonard D, Beddy D, Dozois EJ. Neoplasms of anal canal and perianal skin. Clin Colon Rectal Surg 2011; 24: 54-63.
2. Mengjun B, Zheng-Qiang W, Tasleem MM. Extramammary Paget's disease of the perianal region: a review of the literature emphasizing management. Dermatol Surg 2013; 39: 69-75.
3. Kyriazanos ID, Stamos NP, Miliadis L, Noussis G, Stoidis CN. Extra-mammary Paget's disease of the perianal region: a review of the literature emphasizing the operative management technique. Surg Oncol 2011; 20: e61-71.
4. Wietfeldt ED, Thiele J. Malignancies of the anal margin and perianal skin. Clin Colon Rectal Surg 2009; 22: 127-35.
5. Goldblum JR, Hart WR. Perianal Paget's disease: a histologic and immunohistochemical study of 11 cases with and without associated rectal adenocarcinoma. Am J Surg Pathol 1998; 22: 170-9.
6. Nowak MA, Guerriere-Kovach P, Pathan A, Campbell TE, Deppisch LM. Perianal Paget's disease: distinguishing primary and secondary lesions using immunohistochemical studies including gross cystic disease fluid protein-15 and cytokeratin 20 expression. Arch Pathol Lab Med 1998; 122: 1077-81.
7. Liu CF, Wang Q, Kong YY, Tu XY, Wang J, Zhu XZ. A clinicopathological study of perianal Paget's disease associated with internal rectal adenocarcinoma. Zhonghua Bing Li Xue Za Zhi 2004; 33: 11-5.
8. Selvaggi F, Guadagni I, Pellino G, De Rosa M, Imbrogno G, Sciaudone G. Perianal Paget's disease happening with mucinous adenocarcinoma of the anal canal: managing rarities. J Cutan Pathol 2010; 37: 1182-3.
9. Tulchinsky H, Zmora O, Brazowski E, Goldman G, Rabau M. Extramammary Paget's disease of the perianal region. Colorectal Dis 2004; 6: 206-9.
10. Welton ML, Lambert R, Bosman FT. Tumours of the anal canal. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of

tumours of the digestive system. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2010: 191-2.
11. Regauer S. Extramammary Paget's disease-a proliferation of adnexal origin? Histopathology 2006; 48: 723-9.
12. Amano K, Kumamoto K, Ohsawa T, Okada N, Ishibashi K, Inokuma S, et al. The prognosis and immunohistochemical evaluation of five perianal Paget's disease cases. Gan To Kagaku Ryoho 2010; 37: 2653-5.
13. Leal RF, Ayrizono ML, Coy CS, Fagundes JJ, Goes JR. Mucinous adenocarcinoma derived from chronic perianal fistulas: report of a case and review of the literature. Tech Coloproctol 2007; 11: 155-7.
14. Ong J, Jit-Fong L, Ming-Hian K, Boon-Swee O, Kok-Sun H, Eu KW. Perianal mucinous adenocarcinoma arising from chronic anorectal fistulae: a review from a single institution. Tech Coloproctol 2007; 11: 34-8.
15. McCarter MD, Quan SH, Busam K, Paty PP, Wong D, Guillem JG. Long-term outcome of perianal Paget's disease. Dis Colon Rectum 2003; 46: 612-6.
16. Perrotto J, Abbott JJ, Ceilley RI, Ahmed I. The role of immunohistochemistry in discriminating primary from secondary extramammary Paget disease. Am J Dermatopathol 2010; 32: 137-43.

Paget's disease รอบทวารหนักชนิดปฐมภูมิร่วมกับมะเร็งชนิดต่อมเฉพาะจุด การแปรเปลี่ยนเป็น signet-ring cell และการแสดงออกทางอิมมูโนฮิสโตเคมิสทรีซึ่งไม่เป็นไปตามที่ควร: รายงานผู้ป่วย

วรภพ สุทธิวาทนฤพุฒิ

Paget's disease รอบทวารหนักคือมะเร็งของหนังกำพร้าซึ่งพบได้น้อยอันมี Paget cells เป็นลักษณะสำคัญ ส่วนมากพบในผู้สูงอายุ อาการที่พบบ่อยคือคันรอบทวารหนักเรื้อรังร่วมกับผื่นนูนแบบมีขุย แบ่งออกเป็น 2 ชนิด คือ ชนิดปฐมภูมิซึ่งมีต้นกำเนิดจากผิวหนังรอบทวารหนักและชนิดทุติยภูมิซึ่งมีต้นกำเนิดจากมะเร็งของอวัยวะภายใน และแพร่กระจายมายังผิวหนังรอบทวารหนัก ตัวอย่างเช่น มะเร็งจากลำไส้ใหญ่หรือไส้ตรง

การแสดงออกของ cytokeratin 7 (CK7), cytokeratin 20 (CK20) และ gross cystic disease fluid protein-15 (GCDFP15) มีประโยชน์ในการแยกระหว่างสองชนิดดังกล่าว เนื้องอกที่มีการแสดงออกแบบ CK7+/CK20-/GCDFP15+ บ่งชี้ถึงชนิดปฐมภูมิและ CK7+/CK20+/GCDFP15- บ่งชี้ถึงชนิดทุติยภูมิ นอกจากนี้การแสดงออกของ caudal homeobox 2 (CDX2) บ่งชี้ถึงชนิดทุติยภูมิจากการแพร่กระจายของมะเร็งจากลำไส้ใหญ่หรือไส้ตรง ทว่าประมาณหนึ่งในสามของผู้ป่วยซึ่งตรวจไม่พบมะเร็งของอวัยวะภายในนั้นมีการแสดงออกแบบ CK7+/CK20+/GCDFP15- ได้ และ 2% ของผู้ป่วยชนิดปฐมภูมิสามารถพบการแสดงออกของ CDX2 ได้

ผู้นิพนธ์รายงานผู้ป่วยชายอายุ 86 ปี ซึ่งมาพบแพทย์ด้วยอาการคันเรื้อรังรอบทวารหนักและตรวจพบผื่นนูนแบบมีขุย เมื่อตัดผิวหนังมาวิเคราะห์พบ Paget cells ในหนังกำพร้าซึ่งมีการแสดงออกแบบ CK7+/CK20+/GCDFP15-/CDX2+ ในเบื้องต้นผู้ป่วยได้รับการสงสัย Paget's disease รอบทวารหนักชนิดทุติยภูมิอันเนื่องจากการแพร่กระจายของมะเร็งชนิดต่อมจากลำไส้ใหญ่หรือไส้ตรง ทว่าหลังการสืบค้นอย่างละเอียดกลับไม่พบมะเร็งของอวัยวะภายใน ต่อมาผู้ป่วยจึงได้รับการผ่าตัดผิวหนังรอบทวารหนักแบบ wide excision การตรวจทางพยาธิวิทยาพบ Paget cells แพร่กระจายในหนังกำพร้าร่วมกับมีการลุกลามเข้าสู่หนังแท้เฉพาะจุดโดยมะเร็งชนิดต่อมแบบลำไส้ร่วมกับการแปรเปลี่ยนเป็น signet-ring cell โดยสรุปการวินิจฉัยขั้นสุดคือ Paget's disease รอบทวารหนักชนิดปฐมภูมิร่วมกับมะเร็งชนิดต่อมเฉพาะจุดและมีการผันแปรเป็น signet-ring cell ในผู้ป่วยรายนี้สอดคล้องกับ Paget's disease รอบทวารหนักชนิดปฐมภูมิเนื่องจากตรวจไม่พบมะเร็งของอวัยวะภายใน