A case report of anal canal cancer with pagetoid spread requiring differential diagnosis

Ryohei Yukimoto a, Shiki Fujino a,*, Norikatsu Miyoshi a, Takayuki Ogino a, Hidekazu Takahashi a, Mamoru Uemura a, Atsushi Tanemura b, Chu Matsuda a, Hirofumi Yamamoto a, Tsunekazu Mizushima a, Yuichiro Doki b, Hidetoshi Eguchi a

a Osaka University, Graduate School of Medicine, Department of Gastroenterological Surgery, Osaka, Japan
b Department of Dermatology, Osaka University Graduate School of Medicine, Osaka, Japan

ARTICLE INFO

Article history:
Received 21 July 2020
Received in revised form 16 August 2020
Accepted 5 September 2020
Available online 10 September 2020

Keywords:
Paget’s disease
Diagnosis
Anorectal cancer
Case report

ABSTRACT

INTRODUCTION: Paget’s disease is an intraepithelial invasion by a malignant tumour and is characterised by erythema and inflammation. It can manifest as mammary or extramammary Paget’s disease (EMPD), with the latter often developing in the perianal area. Anorectal cancer can cause transepithelial invasion into the epidermis, resulting in an appearance similar to that of EMPD. This is called pagetoid spread (PS), which is completely different from EMPD. These two conditions are difficult to differentiate because of the nature of intricacy and requirements of histopathology.

PRESENTATION OF CASE: We present a case in which differential diagnosis between these two conditions was not possible during the preoperative examination, resulting in difficulties in treatment. The patient was a 70-year-old woman who experienced pain in the anus since the previous month and presented with red, flat and elevated lesions.

DISCUSSION: Treatment for dermatitis was ineffective, and endoscopic examination did not indicate rectal or anal cancer. However, immunohistochemical examination of the biopsy specimen suggested PS. Thus, two-stage operation was planned. Transanal surgery was performed to confirm the diagnosis of PS and intersphincteric resection was allowed as a radical surgery.

CONCLUSION: Thus, when differentiation between EMPD and PS is intricacy, two-stage operation is useful in selecting an appropriate radical surgery method, leading to preservation of anal function.

© 2020 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Perianal Paget’s disease and pagetoid spread (PS) associated with anorectal cancer both present with anal inflammation and erythema. Although these two diseases are clinically similar, the treatment method and prognoses are notably different [1]. To differentiate between these two diseases, colorectal endoscopy, computed tomography (CT), magnetic resonance imaging (MRI) or immunohistochemical examination are often used. However, definitive diagnosis and treatment can be difficult to achieve [2]. Here, we report a planned two-stage operation case in which transanal surgery was used to achieve a definitive diagnosis and select an appropriate treatment method to conserve anal function. The work has been reported in line with the SCARE criteria [3].

2. Presentation of case

The patient was a 70-year-old woman who had developed red and flat elevated lesions, with surrounding inflammation on the left side of the anus that persisted for one year before treatment (Fig. 1a). She began experiencing pain in the anus a month prior to treatment, and subsequent treatment for dermatitis was ineffective.

Colorectal endoscopy confirmed an elevated lesion continuing from the anal skin lesion in the 3 o’clock direction toward, but not reaching, the pectinate line (Fig. 1b). There was no abnormality in the rectal mucous membrane. We could not find any visible indications of primary colorectal cancer and lymph node metastasis through a preoperative CT scan, MRI and 18F-FDG PET/CT scans (Fig. 1c). Moreover, there was no metastasis in groin lymph node on preoperative examinations.

Pathological examination of the skin biopsy specimen confirmed multiple Paget cells. On immunohistochemical testing, the samples stained positive for cytokeratin-7 (CK7) and cytokeratin-20 (CK20), but not for gross cystic disease fluid protein-15 (GCDFP15; Fig. 2). These results strongly suggested PS. However,
Fig. 1. Preoperative examination.
a. Visual inspection revealed flat, elevated lesions and surrounding inflammation on the left side of the anus.
b. Colonoscopy revealed an elevated lesion continuing from the anal skin lesion in the 3 o’clock direction of the anal canal, going toward, but not reaching, the pectinate line.
c. There was not any abnormal accumulation in the anus or rectum through a CT scan and 18F-FDG PET/CT scans.

Fig. 2. The schema showed resection line and lymph node metastasis (*). Photomicrograph of resected specimen showed lymph node metastasis. Blue line transanal resection line, and red line is resection line of ISR.
since the Colonoscopy and CT did not confirm a primary neoplastic lesion, we could not confirm the diagnosis. For procedure, we performed a transanal resection with local excision of the skin and full-thickness skin grafting.

Our strategy was to precede transanal local resection with local excision of the skin and full-thickness skin grafting for diagnostic purpose and to determine the need for radical surgery with a pathological diagnosis.

During surgery, concordant with the endoscopy result, we observed that the mucosal lesion continued for approximately 3 cm in the 3 o’clock direction from the skin lesion up the anal canal but did not reach the pectinate line. Therefore, we made en-bloc resection of perianal lesion of the cutaneous disease to secure a margin of approximately 1 cm from the mucosal lesion. Thus, the external anal sphincter was preserved (Fig. 3). Pathological examination of resected specimens revealed anal adenocarcinoma with lymph node metastasis. Immunostaining of the tumor showed positive signals for CK7 and CK20. Hence, additional surgical resection was deemed necessary, and laparoscopic total intersphincteric resection (ISR) and a temporary ileostomy were performed. Pathological examination of the additional resection specimen did not reveal any malignancy. The patient was discharged thirteen days post-operatively without complication. During the final postoperative pathological examination, the tumour was categorised as P, Type 2, 20 × 13 mm, tub2, pT2, INFb, ly1, v1, Pn1a, pN1.

The patient is currently undergoing a postoperative adjuvant chemotherapy regimen (FOLFOX), with no recurrence for 17 months.

3. Discussion

For perianal inflammation and erythema that do not respond to typical dermatitis treatment, EMPD and PS should be considered strong candidates for the differential diagnosis, for which diagnostic imaging and immunohistochemical examinations should be used [4]. Specifically, if PS is suspected, it is essential to examine for malignancy in adjacent organs by conducting a lower endoscopic examination. However, as observed in this case, if malignancy is not confirmed despite the spread of the lesion to the anal mucous membrane and PS is suspected based on the immunohistochemical examination, the treatment modality can be difficult to determine. In such scenarios, with respect to an anal function, procedure such as transanal surgery can be performed for the mucosal lesion. The specimen should subsequently be analysed to make a definitive diagnosis and develop a treatment strategy.

It has been reported that approximately 20% of perianal skin lesions are malignant [4]. Both primary Paget’s disease of the skin and PS are clinically characterised by inflammation and erythema. In the latter case, cancer in an organ adjacent to the skin spreads and develops conditions similar to those of intra-epidermal carcinoma. However, both diseases have their own unique primary lesions, and their treatment methods and prognoses are completely different. We summarised 10 cases of PS (Table 1), and our case was the case to perform ISR for anal adenocarcinoma with PS. Eight patients with PS who had associated anorectal cancer underwent abdominoperineal resection (APR). Additionally, rectal excision often results in decreased postoperative quality of life (micturition problems, gastrointestinal tract symptoms, defecation problems, stoma-related problems and male and female sexual problems) [5]. In order to avoid overtreatments, it is vital to clearly differentiate between Paget’s disease and PS.

In a few cases out of the 10 that we summarised, when differentiating between EMPD and PS, either endoscopic examination or diagnostic imaging revealed the possibility of anal/rectal cancer, which in turn led to preoperative pathological diagnosis. Eight out of 10 cases had preoperative malignant findings (Table 1). There were two cases with no malignant finding in the preoperative examination, such as our case, and APR has also been selected for
Table 1
Summary of reports on pagetoid spread (PS) cases, preoperative diagnoses and treatment methods.

| Author                          | Year of report | Chief complaint | Preoperative endoscopic examination | Preoperative endoscopic examination biopsy | Treatment                  |
|--------------------------------|----------------|-----------------|-------------------------------------|--------------------------------------------|-----------------------------|
| Tjandra et al. [9]             | 1988           | Pruritus        | Rectal lesion                       | Adenocarcinoma                             | APR                         |
| Lertprasertsuke et al. [10]    | 1991           | None            | Tumour                              | Adenocarcinoma                             | APR                         |
| Goldman et al. [11]            | 1992           | Pruritus        | Hard mass in the upper anal canal    | Adenocarcinoma                             | APR                         |
| Goldman et al. [11]            | 1992           | Pruritus        | Tumour                              | Adenocarcinoma                             | Radiation + APR             |
| Kubota et al. [12]             | 1998           | Anal bleeding   | Tumour                              | Adenoma                                   | APR                         |
| Suenaga et al. [13]            | 2006           | None            | Tumour                              | Adenocarcinoma                             | Wide local excision         |
| Ishida et al. [14]             | 2013           | Anal fistula    | Tumour                              | Adenocarcinoma                             | APR                         |
| Shimizu et al. [15]            | 2017           | Anal pain       | No significant finding              | No                                         | APR                         |
| Matsubara et al. [16]          | 2017           | Warts           | No significant finding              | No                                         | APR                         |
| Yamamuro et al. [2]            | 2018           | None            | Tumour                              | Adenocarcinoma                             | Chemotherapy                |
| This case                      | 2019           | Anal pain       | No significant finding              | No                                         | ISR                         |

ISR: intersphincteric resection; APR: abdominoperineal resection.

Table 2
Summary of the results of immunohistochemical staining for CK20 and GCDFP-15 in pagetoid spread (PS) cases.

| Case                | Year of report | Sex  | Age | CK7 | CK20 | GCDFP-15 |
|---------------------|----------------|------|-----|-----|------|----------|
| Goldblum et al. [7] | 1988           | Male | 66  | +   | +    | –        |
| Goldblum et al. [7] | 1988           | Female | 74 | +   | +    | –        |
| Goldblum et al. [7] | 1988           | Female | 81 | +   | +    | –        |
| Goldblum et al. [7] | 1988           | Female | 89 | +   | +    | –        |
| Luo et al. [11]     | 2014           | Male | 78  | +   | +    | –        |
| Shimizu et al. [15] | 2017           | Male | 81  | N.A.| +    | –        |
| Matsubara et al. [16]| 2017           | Female | 81 | +   | +    | –        |
| Yamamuro et al. [2] | 2018           | Male | 76  | +   | +    | –        |

4. Conclusion

The treatment methods and prognoses for Paget’s disease and PS are notably different, making it extremely important to clearly differentiate between the two conditions. We reported a two-stage operation case in which a transanal resection was performed for diagnosis followed by a radical ISR in a case which was difficult to diagnose EMPD or PS.

Funding

The authors declare that there are no sources.

Ethical approval

IRB number: 15144-6 Osaka university.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

S.F. and N.M. conceptualized the project, designed and performed the experiments, interpreted the results, and co-wrote the manuscript. N.M. supervised the experimental design and interpreted the results. N.M., M.O., and M.Y. performed the surgeries and prepared the culture samples. N.M., T.M., Y.D., and M.M. analysed data or participated in discussions of the results.
Registration of research studies
1. Name of the registry: Research registry.
2. Unique identifying number or registration ID: Researchregistry5806.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/5f0e8bf136e4900154e8811/.

Guarantor
Shiki Fujino is guarantors for this article.
Shiki Fujino: sfujino@gesurg.med.osaka-u.ac.jp.

Provenance and peer review
Not commissioned, externally peer-reviewed.

Declaration of Competing Interest
The authors report no declarations of interest.

Acknowledgment
None.

References
[1] X. Liao, W. Mao, Perianal Paget's disease co-associated with anorectal adenocarcinoma: primary or secondary disease, Case Rep. Gastroenterol. 8 (2014) 186–192.
[2] M. Yamamura, T. Yamada, R. Watanabe, H. Kawai, S. Hirose, H. Tajima, et al., Anal canal adenocarcinoma with neuroendocrine features accompanying secondary extramammary Paget disease, successfully treated with modified FOLFOX6: a case report, BMC Cancer 18 (2018) 1142.
[3] R.A. Agha, M.R. Borrelli, R. Farwana, K. Koshiy, A. Fowler, D.P. Orgill. For the SCARE Group, The SCARE 2018 statement: updating consensus Surgical Case Report (SCARE) guidelines, Int. J. Surg. 60 (2018) 132–136.
[4] V. Shepherd, E.J. Davidson, J. Davies-Humphreys, Extramammary Paget’s disease, BJOG 112 (2005) 273–279.
[5] M.M. Russel, P.A. Ganz, S. Lopa, G. Yothers, C.Y. Ko, A. Arora, et al., Comparative effectiveness of sphincter-sparing surgery versus abdominoperineal resection in rectal cancer: patient-reported outcomes in National Surgical Adjuvant Breast and Bowel Project randomized trial R-04, Ann. Surg. 261 (2015) 144–148.
[6] V. Chumbalkar, T.A. Jennings, S. Ainechi, E.C. Lee, H. Lee, Extramammary Paget's disease of anal canal associated with rectal adenoma without invasive carcinoma, Gastroenterol. Res. 9 (2016) 99–102.
[7] J.R. Goldblum, W.R. Hart, Perianal Paget’s disease: a histologic and immunohistochemical study of 11 cases with and without associated rectal adenocarcinoma, Am. J. Surg. Pathol. 22 (1998) 170–179.
[8] J. Perrotto, J.J. Abbott, R.J. Ceilley, I. Ahmed, The role of immunohistochemistry in discriminating primary from secondary extramammary Paget disease, Am. J. Dermatopathol. 32 (2010) 137–143.
[9] J. Tjandra, Perianal Paget’s disease: report of three cases, Dis. Colon Rectum 31 (1988) 462–466.
[10] N. Lertrprasertsuke, Y. Tsutsumi, Latent perianal Paget’s disease associated with mucin-producing rectal adenocarcinoma: report of two cases, Acta Pathol. Jpn. 41 (1991) 386–393.
[11] S. Goldman, T. Itoe, U. Lagerstedt, C. Svensson, Perianal Paget’s disease: report of five cases, Int. J. Colorectal Dis. 7 (1992) 167–169.
[12] K. Kubota, T. Akasu, Y. Nakamishi, K. Sugihara, S. Fujita, Y. Moriya, Perianal Paget’s disease associated with rectal carcinoma: a case report, Jpn. J. Clin. Oncol. 28 (1998) 347–350.
[13] M. Suenga, M. Oya, M. Ueno, J. Yamamoto, T. Yamaguchi, N. Mizunuma, et al., Anal canal carcinoma with Pagetoid spread: report of a case, Surg. Today 36 (2006) 666–669.
[14] M. Ishida, M. Iwai, K. Ushida, A. Kagotani, H. Okabe, Pigmented porocarcinoma: a case report with review of the literature, Int. J. Clin. Exp. Pathol. 6 (2013) 3033–3035.
[15] T. Shimizu, T. Inouzume, M. Takaki, T. Ohnuma, S. Sano, T. Kawamura, et al., Case of anal adenocarcinoma in situ with pagetoid spread but without microscopic abnormality in anal mucosa, J. Dermatol. 44 (2017) 1076–1077.
[16] T. Matsubara, Y. Kasagi, K. Ogaki, Y. Nakaji, R. Nakamichi, Y. Nakashima, et al., Recurrence with pagetoid spread arising 17 years after surgery for intramucosal rectal cancer: a case report, Surg. Case Rep. 3 (2017) 85.

Open Access
This article is published Open Access at sciencedirect.com. It is distributed under the IJSCR Supplemental terms and conditions, which permits unrestricted non commercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.