Anal canal adenocarcinoma with neuroendocrine features accompanying secondary extramammary Paget disease, successfully treated with modified FOLFOX6: a case report

Masamichi Yamaura 1, Takeshi Yamada 1*, Rei Watanabe 2, Hitomi Kawai 3, Suguru Hirose 1, Hiroki Tajima 1, Masashi Sato 1, Yuichi Uchida 1, Daisuke Suginuma 1, Yoshiyuki Yamamoto 1, Toshikazu Moriwaki 1 and Ichinosuke Hyodo 1

Abstract

Background: Anal canal cancer occasionally accompanies extramammary Paget disease. Although most of them are squamous cell carcinoma, anal canal adenocarcinoma with neuroendocrine features accompanying secondary extramammary Paget disease has never been reported.

Case presentation: Here, we report a 76-year-old man presented with pruritus in the perianal area. Investigation revealed a fist-sized perianal erythema, diffuse liver tumors, and right inguinal lymph node swelling. Pathological examination of biopsies from the erythema suggested secondary extramammary Paget disease with positive cytokeratin-7 and -20 expressions and negative GCDFP-15 expression. The anal canal tumor was confirmed by digital examination and endoscopy. Biopsies from the anal canal tumor, swollen lymph node, and Paget lesion all showed poorly differentiated adenocarcinoma with neuroendocrine features expressing synaptophysin and chromogranin A. Serum CEA and NSE levels were high, 809.4 ng/ml and 85.8 ng/ml, respectively. After chemotherapy with modified FOLFOX6 for 2 months, the Paget lesion disappeared, and the primary anal canal tumor and liver metastases shrunk remarkably. Serum CEA and NSE levels decreased promptly to within normal ranges.

Conclusions: This is a clinically significant case, as it reveals novel pathological features about anal canal cancer with secondary Paget disease and successfully treated with modified FOLFOX6. Careful pathological investigation and appropriate treatment choice are needed for this rare cancer.

Keywords: Anal canal cancer, Adenocarcinoma with neuroendocrine features, Extramammary Paget’s disease, mFOLFOX6

Background

Anal canal cancer is uncommon [1, 2], and approximately 90% of cases are associated with human papillomavirus (HPV) infection [3]. The incidence of anal canal cancer has gradually increased over the last few decades [4]. Histological findings are usually squamous cell carcinoma and the remaining including adenocarcinoma, neuroendocrine carcinoma (NEC), melanoma, lymphoma, undifferentiated carcinoma, and mesenchymal tumors [5, 6]. Anal canal adenocarcinoma is less associated with HPV infection [7] and divided into two subtypes according to the presence of mutations in EGFR signaling pathway and expression of the immune checkpoint molecules [8].

Anal canal cancer is known to occasionally accompany with secondary extramammary Paget disease (EPD) [2, 9], which is characterized histologically as the intraepidermal proliferation of unique tumor cells (Paget cells) found in classic mammary Paget disease. Although both primary...
and secondary EPD show similar erosive erythematous plaque, the prognosis is different between these two EPD and accurate differential diagnosis is important [10].

Here we present a rare case of adenocarcinoma with neuroendocrine features of the anal canal accompanying secondary EPD with diffuse liver involvements, successfully treated with an oxaliplatin-containing regimen.

Case presentation
A 76-year-old man with a history of hypertension and benign prostatic hyperplasia consulted a dermatologist with a complaint of pruritus in the perianal area. The doctor diagnosed this area as eczema, and had prescribed Corticosteroid ointment for him for 10 months. Because his symptom did not improve, he received a colonoscopy to check for colorectal malignancy. However, no anal canal lesion was noticed at that time. Two months later, multiple liver lesions were incidentally found during follow-up ultrasonography for his prostatic hyperplasia. Computed tomography (CT) scan revealed multiple liver lesions (Fig. 1a) and right inguinal lymph node swelling. Pathological examination of biopsies obtained from the perianal erythema showed infiltrating Pagetoid cells and poorly differentiated adenocarcinoma (Fig. 2a). Immunohistochemistry (IHC) demonstrated malignant cells positive for cytokeratin (CK)-7 and −20 (Fig. 2b and c) and negative for gross cystic disease fluid protein-15 (GCDFP-15) (Fig. 2d). These findings suggested secondary EPD. The lymph node was also pathologically diagnosed as a metastasis. He was referred to our hospital for further examination and treatment.

On admission, his European Cooperative Oncology Group performance status was 0. Physical examination revealed hepatomegaly and erythematous perianal skin lesion (Fig. 3a). Elastic hard tumor in the anal canal was palpable by digital examination. Serum carcinoembryonic antigen (CEA), neuron specific γ-enolase (NSE), and lactate dehydrogenase (LDH) levels were high, with 809.4 ng/mL (normal range, 0 to 5 ng/mL), 85.8 ng/mL (normal range, 0 to 16.3 ng/mL), and 1176 U/L (normal range, 115 to 245 U/L), respectively. Carbohydrate antigen 19–9 level was normal. Endoscopy showed an elevated tumor of the anal canal like a submucosal tumor (Fig. 4a and b). Pathological examination revealed poorly differentiated adenocarcinoma (Fig. 2e) with neuroendocrine features of positive synaptophysin and chromogranin-A expressions (Fig. 2f and g). Ki-67 showed a high proliferation index of 60% (Fig. 2h). A KRAS mutation at codon 12 was detected in the primary anal canal lesion. The previously diagnosed perianal skin lesion and lymph node tumor showed the same pathological features. Finally, the patient was diagnosed with metastatic anal canal adenocarcinoma with neuroendocrine features, accompanying secondary EPD.

He received chemotherapy with mFOLFOX6 (oxaliplatin 85 mg/m², bolus 5-FU 400 mg/m², and folinic acid 200 mg/m² on day 1 with 46-h infusional 5-FU 2400 mg/m², every 2 weeks). Soon after treatment, his hepatomegaly improved day by day. CT scan after 4 courses of mFOLFOX6 showed remarkable tumor shrinkage and morphological changes to homogenous nonenhanced lesions (Fig. 1b), and the EPD disappeared (Fig. 3b). Serum levels of LDH, CEA, and NSE decreased promptly to within normal range (Fig. 5). The primary anal canal lesion also responded to the treatment (Fig. 4c and d). The treatment regimen of mFOLFOX6 was switched to CAPOX (capecitabine 2000 mg/m²/day for 14 days and oxaliplatin 130 mg/m² on day 1, every 3 weeks) due to thrombus formation around the central venous catheter. Currently, he is receiving capecitabine plus bevacizumab together with edoxaban to prevent secondary deep venous thrombosis after removal of central venous catheter as a maintenance therapy, and a good partial response with normal serum tumor markers has been maintained for more than 11 months after the initial treatment.

Discussion
Anal canal cancer is occasionally associated with secondary EPD. Goldman et al. reported the frequency of secondary EPD accompanied with anal canal cancer as 33% [11]. The most common histological findings with secondary EPD

Fig. 1 CT scan showed diffuse liver metastases before treatment (a); cystic morphologically changed after 4 courses of mFOLFOX6 (b)
are adenocarcinoma and squamous cell carcinoma [12]. Other histological types with secondary EPD are rare and there are only a few case reports including NEC [13], signet ring cell carcinoma [14], and mucinous carcinoma [15, 16]. The present case was extremely rare in terms of the particular histological type accompanied with secondary EPD.

It is not easy to distinguish between secondary and primary EPD by the clinical and histological findings, especially if primary EPD invades the epidermis or if an underlying visceral carcinoma is not apparent. IHC with CK-7, CK-20, and GCDFP-15 may be useful to distinguish them. In secondary EPD, the tumor cells are positive for CK7 and CK20, but negative for GCDFP-15, whereas primary EPD is commonly positive for GCDFP-15 and CK-7, but negative for CK-20 [17–21]. A detailed examination to detect primary tumors should be performed especially in anorectal lesions such as the present case [10].

In this case, anal canal lesion was missed by previous colonoscopy. We think the reason for difficulty in detection is based on the feature that the anal lesion developed like submucosal tumor. We could detect the lesion because we had information about secondary Paget disease and strongly suspected the anal cancer by digital examination. Most anal canal squamous cell carcinoma is caused by high risk HPV, anal canal adenocarcinoma is less related with HPV [7]. This patient did not have certain sexual history and had KRAS-mutant tumor. Although we did not evaluate HPV infection in this case,
the carcinogenesis of this patient seemed to be less associated with HPV infection [8].

There is no report of mixed adenoneuroendocrine carcinoma of anal canal cancer, and only one case, involving an elderly female patient, of NEC with squamous intraepithelial neoplasm of the anal canal has been reported [22]. The present case was a rare anal canal adenocarcinoma with neuroendocrine features, in which prognosis seemed poor with metastases like those reported in intestinal NEC [23, 24].

Fortunately, the patient was successfully treated with mFOLFOX6, which is a standard treatment for colorectal adenocarcinoma. CT scan after 4 courses of mFOLFOX6 showed remarkable tumor shrinkage and morphological changes to homogenous nonenhanced lesions. CT-based morphological changes correlate with pathologic response.
and overall survival among patients with colorectal liver metastases treated with bevacizumab-containing chemotherapy [25]. NEC is commonly treated with a platinum-based doublet, such as etoposide plus cisplatin, following the treatment guideline for small-cell lung cancer. We selected mFOLFOX6 regimen for the patient because the lesion included both components of adenocarcinoma and NEC. Baba, et al. reported a case of anal canal NEC successfully treated with mFOLFOX6 [26]. Further studies are needed to develop the optimal treatment for these particular types of cancer.

Conclusions
We reported here the rare case of anal canal adenocarcinoma with neuroendocrine features accompanying secondary EPD, and found mFOLFOX6 to be a very effective treatment. Careful evaluation is necessary for perianal skin lesion as anal canal cancer with EPD might be hidden.

Abbreviations
CEA: Carcinoembryonic antigen; CK-20: Cytokeratine-20; CK-7: Cytokeratine-7; CT: Computed tomography; EPD: Extramammary Paget disease; FDG PET: 18F-fluorodeoxy glucose positron emission tomography; GCCFP-15: Gross cystic disease fluid protein-15; HPV: Human papillomavirus; LDH: Lactate dehydrogenase; mFOLFOX6: modified FOLFOX6 regimen; NEC: Neuroendocrine carcinoma; NSE: Neuron specific γ-enolase

Acknowledgements
The authors would like to acknowledge the medical staff who took care of this patient and the patient and his wife for their courage to fight this disease. We also thank Thomas Mayers (Medical English Communications Center, University of Tsukuba) for critical editing this manuscript.

Funding
English editing and submission fees were funded from Non-profit organization, Tsukuba Cancer Clinical Trial Group.

Availability of data and materials
The data showed in the report is available from the corresponding author upon reasonable request.

Authors’ contributions
M.Y and T.Y mainly took care of the patient and S.H, H.T, M.S., Y.U and D.S supported the care conducting endoscopy and administering chemotherapy; Y.Y ad T.M discussed the chemotherapy regimen with T.Y.; RW and H.X made diagnosis for secondary extramammary Paget disease; M.Y, TY, TM and I.H wrote the manuscript on behalf of all authors; all authors approved the final version of the manuscript and agreed for publication. The corresponding author (T.Y) has final responsibility to submit for publication.

Ethics approval and consent to participate
Ethical approval is not applicable for this manuscript. The authors obtained the patient’s written consent to the major procedures for diagnosis and treatment.

Consent for publication
The authors obtained written informed consent from the patient to publish information on his disease and clinical course.

Competing interests
The authors declare that they have no competing interests.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details
1Department of Gastroenterology, University of Tsukuba Hospital, 1-1-1 Tennomachi, Tsukuba, Ibaraki 305-8575, Japan. 2Division of Dermatology, University of Tsukuba Hospital, Ibaraki, Japan. 3Division of Pathology, University of Tsukuba Hospital, Ibaraki, Japan.

Received: 13 December 2017 Accepted: 12 November 2018 Published online: 20 November 2018

References
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30.
2. Salati SA, Al Kadi A. Anal cancer - a review. Int J Health Sci. 2012;6(2):206–30.
3. Centers for Disease Control and Prevention (CDC). Human papillomavirus-associated cancers - United States, 2004–2008. MMWR Morb Mortal Wkly Rep. 2012;61:258–61.
4. Shields MS, Kreimer AR, Coughill AE, Darragh TM, Devesa SS. Anal Cancer incidence in the United States, 1977-2011: distinct patterns by histology and behavior. Cancer Epidemiol Biomarkers Prev. 2015;24(10):1548–56.
5. Hoff PM, Coudry R, Moniz CM. Pathology of anal Cancer. Surg Oncol Clin N Am. 2017;26(1):57–71.
6. Lee RT, Ferreira J, Friedman K, Moss SF. A rare cause of constipation: obstructing small cell neuroendocrine carcinoma of the anal canal. Int J Color Dis. 2015;30(9):1291–2.

7. Tachezy R, Jarosek T, Salakova M, Ludvikova V, Kubecova M, Horak L, Mandys V, Hansikova E. Human papillomavirus infection and tumours of the anal canal: correlation of histology, PCR detection in paraffin sections and serology. APMIS. 2007;115(1):195–203.

8. Herfs M, Roncarati P, Koopmansch B, Peulien O, Breyne D, Lebeau A, Hendrick E, Hubert P, Poncin A, Penny W et al. A dualistic model of primary anal canal adenocarcinoma with distinct cellular origins, etiologies, inflammatory microenvironments and mutational signatures: implications for personalised medicine. Br J Cancer. 2018;118(10):1302–12.

9. Chanda J. Extramammary Paget’s disease: prognosis and relationship to internal malignancy. J Am Acad Dermatol. 1985;13(6):1009–14.

10. Shepherd V, Davidson EJ, Davies-Humphreys J. Extramammary Paget’s disease. Bjog. 2005;112(3):273–9.

11. Goldman S, Ihre T, Lagerstedt U, Svensson C. Perianal Paget’s disease: report of five cases. Int J Color Dis. 1992;7(3):167–9.

12. Isik D, Aytaç B, Brainard J, Valente MA, Abbas MA, Gorgun E. Perianal Paget’s disease: three decades experience of a single institution. Int J Color Dis. 2016;31(1):29–34.

13. Guo L, Kuroda N, Miyazaki E, Jin Y, Toi M, Hamaizu T, Hiroi M, Inoue T, Inoue A, Enzan H. Anal canal neuroendocrine carcinoma with Pagetoid extension. Pathol Int. 2004;54(8):630–5.

14. Kim NR, Cho HY, Baek JH, Jeong J, Ha SY, Seok JY, Park SW, Sym SJ, Lee KC, Chung DH. Rare case of Anal Canal signet ring cell carcinoma associated with perianal and vulvar Pagetoid spread. J Pathol Transl Med. 2016;50(3):231–7.

15. Wong AY, Rahilly MA, Adams W, Lee CS. Mucinous anal gland carcinoma with perianal Pagetoid spread. Pathology. 1998;30(1):1–3.

16. Selvaggi F, Guadagni I, Pellino G, De Rosa M, Ippolito G, Sciudone G. Perianal Paget’s disease happening with mucinous adenocarcinoma of the anal canal: managing rarities. J Cutan Pathol. 2010;37(11):1182–3.

17. Ordonez NG, Awalt H, Mackay B. Mammary and extramammary Paget’s disease. An immunocytochemical and ultrastructural study. Cancer. 1987;59(6):1173–83.

18. Goldblum JR, Hart WR. Vulvar Paget’s disease: a clinicopathologic and immunohistochemical study of 19 cases. Am J Surg Pathol. 1997;21(10):1178–87.

19. 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(2):170–9.

20. Novak MA, Guerriero-Kovach F, 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(12):1077–81.

21. Ohnishi T, Watanabe S. The use of cytokeratins 7 and 20 in the diagnosis of primary and secondary extramammary Paget’s disease. Br J Dermatol. 2000;142(2):243–7.

22. Onomura R, Sekine S, Taniguchi H, Tsuda H, Moriya Y, Kushima R. Anal canal neuroendocrine carcinoma associated with squamous intraepithelial neoplasia: a human papillomavirus 18-related lesion. Pathol Int. 2012;62(5):356–9.

23. Bernick PE, Klimenta DS, Shia J, Minsky B, Saltz L, Shi W, Thaler H, Guillen J, Paty P, Cohen AM, et al. Neuroendocrine carcinomas of the colon and rectum. Dis Colon Rectum. 2004;47(2):163–9.

24. Aytaç B, Ozdemir Y, Oztunay G. Long term outcomes of neuroendocrine carcinomas (high-grade neuroendocrine tumors) of the colon, rectum, and anal canal. J Visc Surg. 2014;151(1):3–7.

25. Chun YS, Vauthey JN, Boonsrirakhamai P, Maru DM, Kopeck S, Palavecino M, Curley SA, Abdalla EK, Kaur H, Chamsangavej C, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. JAMA. 2009;302(21):2338–44.

26. Baba H, Ishikawa T, Iwata N, Takahashi H, Masuda T, Okazaki S, Matsuyama T, Ishiguro M, Kobayashi H, Iida S, et al. A case of neuroendocrine carcinoma of the anal canal with multiple bone metastases successfully treated with combined modality therapy. Gan To Kagaku Ryoho. 2013;40(12):2017–9.