Case Report

Advanced Invasive Extramammary Paget's Disease Concomitant with Cecal Cancer Possessing Rare Variant of TP53 Single Nucleotide Polymorphism

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Keywords

Cecal carcinoma · EMPD · TP53 SNP · Immunohistochemical staining · CK7 · CK20

Abstract

Patients with invasive extramammary Paget's disease have an increased risk of secondary malignancy, mostly occurring colorectal carcinoma. TP53 is a regulator of apoptosis, cell cycle arrest, and DNA damage response pathways, and has been reported as one of the genetic biomarkers for colorectal carcinoma. In this report, we describe a case of advanced invasive EMPD concomitant with cecal cancer with a rare variant of TP53 single nucleotide polymorphism (rs121912665). To our knowledge, there is no English report that presents EMPD concomitant with cecal carcinoma.

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Published by S. Karger AG, Basel

Introduction

The incidence of extramammary Paget's disease (EMPD) concomitant with colorectal carcinoma has been reported [1–3], but little is known about the genetic background. TP53 is a

regulator of apoptosis, cell cycle arrest, and DNA damage response pathways, and has been reported as one of the genetic biomarkers for colorectal carcinoma [4]. In this report, we described a case of advanced invasive EMPD concomitant with cecal cancer with a rare variant of TP53 single nucleotide polymorphism (SNP) (rs121912665). To our knowledge, there is no English report that presented EMPD concomitant with cecal carcinoma.

Case Report

A 70-year-old Japanese man visited our outpatient clinic with a 2-year history of a red nodule on the scrotum, which was resected by a private physician and suspected to be an invasive EMPD. He had also undergone resection of cecal cancer (well differentiated adenocarcinoma (tub1), T1b, N0, pStage I) endoscopically at another institute one year before. Moreover, his father, mother and sister had died from stomach cancer. On his initial visit, physical examination revealed infiltrated erythematous plaque with an operation scar, which was surrounded by vitiligo (Fig. 1). There was no tumorous lesion around the anus. In addition, we detected palpable nodules at the right inguinal lesions. The excisional biopsy specimen of the nodule revealed rounded cells that were devoid of intracellular bridges and large nucleus from the epidermis (Fig. 2a) to superficial dermis (Fig. 2b). Immunohistochemical staining revealed that these tumor cells were positive for CK7 (Fig. 2c) and BRST2 (Fig. 2d), and negative for CK20 (Fig. 2e) and CDX2 (Fig. 2f). From the above finding, our diagnosis was invasive extramammary Paget's disease concomitant with cecal cancer. We screened for a possible internal malignancy by positron emission tomography (PET)-CT, which revealed significant enlargement of the right inguinal and external iliac lymph nodes, which histologically revealed metastasis of EMPD. We resected the primary tumor with a 2 cm surgical margin. Volumetric modulated arc therapy (VMAT) after surgical treatment was performed on the pelvic and bilateral inguinal region with a total dose of 50 Gy together with oral administration of S-1 (120 mg/ day) for 6 months. Two months after the administration of this combination therapy, all swollen lymph nodes had regressed. One year after remission of the lymph nodes metastasis, invasive EMPD and cecal carcinoma was still under remission.

To exclude metastasis of the cecal metastasis of EMPD, we employed immunohistochemical (IHC) staining for the previously treated cecal carcinoma, which revealed tumor cells positive for CK20 (Fig. 3a) and CDX2 (Fig. 3b) and negative for CK7 (Fig. 3c) and BRST2 (Fig. 3d). Moreover, to further investigate the genetic background of the EMPD and cecal carcinoma, we employed next generation sequencing. We detected a rare variant of TP53 (rs121912665), which was previously reported to have been detected in a patient with multiple colorectal carcinoma [1].

Discussion

Recent reports suggested that patents with invasive EMPD have an increased risk of secondary malignancy, mostly colorectal carcinoma [1–3]. Karam and Dorigo reported that the standardized incidence ratio for secondary malignancies in patients with invasive EMPD had significantly elevated with an excessive absolute risk of 97.4 additional malignancies per 10,000 person-years [1]. In another report, Yoon et al. suggested an association between EMPD and gastrointestinal neoplasms [2]. These reports suggested that a common genetic background may correlate with the incidence of EMPD and gastrointestinal neoplasm. Indeed,

Konstantinova et al. reported the PIK3CA mutation in anogenital mammary-like gland associated malignancies, including EMPD, mammary type invasive ductal carcinoma and tubulolobular carcinoma [5].

In this report, we describe a case of advanced invasive EMPD concomitant with cecal cancer with a rare variant of TP53 SNP (rs121912665), which was previously reported to have been detected in a patient with colorectal carcinoma [1]. The TP53 gene is a tumor suppressor that is mutated or lost in more than half of human malignancies [6], and its coded protein, Tp53, is a regulator of apoptosis, cell cycle arrest, and DNA damage response pathways [6]. In addition, recently, TP53 codon 72 allele was reported to influence the early onset of colon cancer [7]. These reports suggested that TP53 SNP (rs121912665), which was detected in the present case, might correlate with the early onset of cecal carcinoma and EMPD.

To reduce the possibility of the EMPD lesion on the scrotum spreading pagetoid growth to cecal carcinoma, which skipped to a perianal lesion, we employed IHC staining focusing on CK7 and CK20, as well as BRST2 and CDX2. IHC staining in the present case revealed different profiles of IHC staining between cecal carcinoma and EMPD (positive CK7 and BRST2 for EMPD, and positive CK20 and CDX2 for cecal carcinoma). Since the standardized incidence ratio for secondary malignancies in patients with invasive EMPD has significantly elevated, a rare variant of TP53 SNP (rs121912665) might be correlated with these independently developed malignancies. Since we present only a single case, further cases are needed to gain additional insight into the genetic correlation between cecal carcinoma and invasive EMPD.

Statement of Ethics

The patient gave written informed consent.

Disclosure Statement

The authors have no conflicting interests to declare.

Funding Sources

This study was supported in part by the Japan Agency for Medical Research and Development (19cm0106434h0002).

Author Contributions

Fujimura T. designed the research study. Kambayashi Y., Fujimura T., Ohuch K., Tono H. and Asano M. treated the patients and acquired the clinical data and samples. Otsuka A. and Ishida Y. gathered and analyzed the next generation sequencing data. Fujimura T. wrote the manuscript. Fujimura T. and Aiba S. supervised the study.

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Fig. 1. Infiltrated erythematous plaque with operation scar, which is surrounded by vitiligo.

Fig. 2. An excisional biopsy specimen of the nodule: rounded cells that were devoid of intracellular bridges and large nucleus (**a**), from the epidermis to superficial dermis (**b**). Immunohistochemistry for EMPD: anti-CK7 Ab (**c**), anti-BRST2 Ab (**d**), anti-CK20 Ab (**e**), and anti-CDX2 Ab (**f**). Scale bar, 100 μ m (**a**), 200 μ m (**b–f**).

Fig. 3. Immunohistochemistry for cecal carcinoma: anti-CK20Ab (a), anti-CDX2 Ab (b), anti-CK7Ab (c), and anti-BRST2 Ab (d). Scale bar, 200 μm (a–d).