A Case Report of Locally Advanced Anal Cancer with Solitary Cutaneous Nodular Metastasis in the Ipsilateral Labia Majora Treated with Definitive Chemoradiotherapy

Katsuyuki Sakanaka  Yuichi Ishida  Takashi Mizowaki

Department of Radiation Oncology and Image-Applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Keywords
Anal cancer · Cutaneous metastasis · Chemoradiotherapy

Abstract
Cutaneous metastasis from anal cancer is rare at the initial diagnosis. There is a dearth of information on definitive treatment for anal cancer with cutaneous metastasis. We report the case of a 63-year-old female with locally advanced anal cancer and solitary cutaneous nodular metastasis in the right labia majora identified at the initial diagnosis that was successfully treated with definitive chemoradiotherapy. She arrived at our hospital with complaints of an enlarging perineal itching nodule. Genital and rectal examination detected an anal tumor with perineal and rectal invasion. The biopsy specimen indicated it was a squamous cell carcinoma that was accompanied by right inguinal and external iliac lymph nodal metastases and solitary cutaneous nodular metastasis in the ipsilateral labia majora. She was diagnosed with anal cancer, clinical T3N1M1, stage IV (UICC-TNM 7th). She had good performance status and effective organ function. She received definitive chemoradiotherapy with irradiation fields that included the primary tumor, pelvic lymph nodal metastases, and solitary cutaneous genital metastasis. After completing the planned treatment, all tumors vanished without recurrences at 42 months after treatment. In conclusion, patients with locally advanced anal cancer may suffer genital cutaneous metastasis that develops with lymphatic drainage from the anus to the inguinal...
lymph nodes. Anal cancer with solitary genital cutaneous nodular metastasis can be considered as a local-regional disease and can be treated with chemoradiotherapy. Chemoradiotherapy achieved a cure in our case.

Introduction

Cutaneous metastasis from visceral malignancy is rare. The rate of primary visceral malignancies with cutaneous metastasis has been reported to be 1–5% [1, 2]. Previous reports have described two characteristics of cutaneous metastasis from visceral malignancy. First, cutaneous metastasis typically presents as a nodule or mass. Approximately 80% patients with cutaneous metastasis had masses or nodules, and the remaining had an inflammatory pattern that mimicked infection [3, 4]. Second, cutaneous metastasis usually occurs in an advanced stage. A retrospective study of 7,316 cancer patients found an initial cutaneous involvement in only 59 (0.8%) patients [1]. Widespread metastases in other organs or lymph nodes already existed in 77% patients with cutaneous metastases at diagnosis [4]. Thus, the prognosis was poor. The survival rate was reported to be 6–7 months [4, 5]. Cutaneous metastasis from visceral malignancy is rare at the initial diagnosis and is usually diagnosed at an advanced stage; its clinical outcome has been shown to be poor.

Anal cancer has rarely been associated with cutaneous metastases. Information on its clinical outcome and treatment details is scarce. The types of primary malignancies associated with cutaneous metastasis have been reported as the following, listed in decreasing prevalence: breast (70%), ovary (3.3%), oral cavity (2.3%), lung (2%), and large intestine (1.3%) in woman and lung (11.8%), large intestine (11%), oral cavity (8.7%), kidney (4.7%), breast (2.4%), and esophagus (2.4%) in men [1, 6]. A retrospective study has shown that the incidence of cutaneous metastasis resulting from anal cancer was only 1 in 401 patients (0.2%) with cutaneous metastasis from all primary tumors [7]. Only one report mentioned a patient with cutaneous metastasis from anal cancer at the initial diagnosis who underwent chemoradiotherapy [8]. Here we report a case of locally advanced anal cancer associated with solitary genital cutaneous nodular metastasis at the initial diagnosis that was successfully treated with definitive chemoradiotherapy using intensity-modulated radiotherapy.

Case Presentation

A 63-year-old female with a 4-month history of an enlarging perineal itching nodule was referred to our hospital. On gynecologic examination, a 4 cm-sized well circumscribed pink perineal-anal nodule with ulceration was detected (Fig. 1a). The perineal-anal nodule did not invade the urethra or vagina. Digital examination and inspection of the rectum revealed that the perineal nodule continued to the rectum via the anal canal. Biopsy specimens from the rectal mucosa and perineal nodule showed a poorly differentiated squamous cell carcinoma. Magnetic resonance imaging and 18F-fluorodeoxyglucose positron emission tomography showed a primary tumor located from the perineum to the rectum along with the anal canal (Fig. 1b, d). In addition, right inguinal and internal iliac lymph nodal metastases (Fig. 1c) and a 2 cm-sized isolated nodule in the right labia majora were observed (Fig. 1c, d). The isolated nodule in the right labia majora was clinically judged as a solitary cutaneous nodular metastasis from anal cancer via lymph channels. She was diagnosed as having anal squamous cell
carcinoma that was clinical stage IV (T3N1M1) based on the Union for International Cancer Control TNM, 7th edition.

The patient had good performance status and effective organ function. The cutaneous metastasis was a solitary lesion. The entire gross tumor, including the solitary cutaneous metastasis in the labia majora, could be encompassed by the irradiation fields. It was recommended that she undergo definitive chemoradiotherapy with curative intent rather than palliative treatment. She consented to undergo definitive treatment. Chemoradiotherapy was started with 60 Gy in 30 fractions with concurrent administration of mitomycin (10 mg/m² on day 1, 29) and 5-fluorouracil (1,000 mg/m² on days 1–4 and 29–32). Volumetric-modulated arc radiotherapy using two-coplanar arcs with a 15 megavoltage X-ray was planned. Simultaneous integrated boost method was used to deliver irradiation doses [9]. The prescribed doses were 60 Gy in 30 fractions to the gross tumors including the primary tumor and pelvic lymph nodal metastases and the solitary cutaneous nodular metastasis, and 45 Gy to the subclinical lymph nodal region including perirectal, inguinal, internal iliac, and external iliac lymph nodal regions in 30 fractions (Fig. 2). Intensity-modulated radiotherapy spared the external genitalia and intestines. She completed the chemoradiotherapy without unplanned treatment breaks of radiotherapy and dose reduction of chemotherapy. As an acute adverse event, Grade 3 leukocytopenia, thrombocytopenia, anal pain, and radiation dermatitis were observed. No adjuvant chemotherapy was performed. Colonoscopy, magnetic resonance imaging and 18F-fluorodeoxyglucose positron emission tomography showed a complete response; that is, there was no sign of residual tumor without any mucosal erosion or ulceration at seven months after the initiation of chemoradiotherapy (Fig. 1f–j). To date, i.e., 42 months after the initial day of chemoradiotherapy, she has not experienced any disease recurrences or ≥ grade 2 late toxicities, such as a rectal bleeding.

Discussion

Two important clinical observations were made in the present clinical case. First, solitary cutaneous nodular metastasis in the labia majora was present at the initial diagnosis of anal cancer. Second, anal cancer with solitary cutaneous nodular metastasis may be considered to be a local-regional disease and can be cured by chemoradiotherapy.

The patient in the present case suffered multiple inguinal and external iliac lymph nodal metastasis accompanied by an ipsilateral solitary genital cutaneous nodular metastasis. Lymph nodal metastasis was reported to develop the surrounding cutaneous metastasis [10, 11]. Metastasis in the upstream lymph nodal region blocked the downstream lymph drainage. It resulted in a mechanical tumor stasis that led to a cutaneous metastasis surrounding the lymph drainage. Genital skin located in a lymphatic channel between the anus and inguinal lymph nodes was affected. Previous studies have reported genital cutaneous metastasis accompanied by inguinal nodal metastasis of prostate cancer [10] and by inguinal nodal metastasis of cervical cancer [11]. Cutaneous metastasis may develop due to the impairment of lymphatic drainage from pelvic primary tumors to the inguinal lymph nodal region. Similar to other pelvic primary malignancies, we need to mention that the risk of genital cutaneous metastasis exists in locally advanced anal cancer with inguinal nodal metastasis.

Our patient had different points from the typical patients with cutaneous metastasis. First, the cutaneous metastasis was detected at the initial diagnosis, without diagnosis of the other distant visceral metastasis. Second, the cutaneous nodule was solitary and existed along with a lymphatic channel from the anus to inguinal nodes, which could be encompassed by
the irradiation fields. Third, the clinical application of the advanced radiotherapy technique (intensity-modulated radiotherapy) helped to spare the genital area compared with the conventional radiotherapy technique, which avoided severe toxicities without compromising efficiency [9, 12]. These positive factors probably resulted in the good clinical outcome of our patient; however, our patient was not a typical patient with cutaneous metastasis.

In conclusion, genital cutaneous metastasis may occur along the lymphatic drainage channels from the anal primary cancer to the inguinal lymph nodal region at the initial diagnosis. Locally advanced anal cancer with solitary genital cutaneous nodular metastasis could be treated with chemoradiotherapy as a local-regional disease. Chemoradiotherapy yielded a cure for this case.

Acknowledgement

The authors would like to thank Enago (http://www.enago.jp) for the English language review.

Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subject in Japan. General written consent for the use of clinical data for research purposes was obtained from the patient before starting radiotherapy.

Disclosure Statement

Authors have no conflicts of interest.

Funding Sources

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan under Grant number (17 K16434).

Author Contributions

Katsuyuki Sakanaka participated in the study design, contributed to the radiotherapy planning and drafted the manuscript. Yuichi Ishida contributed to the radiotherapy planning. Yuichi Ishida and Takashi Mizowaki provided writing assistance of the manuscript. All authors read and approved the final manuscript.
References

1. Lookingbill DP, Spangler N, Sexton FM. Skin involvement as the presenting sign of internal carcinoma. J Am Acad Dermatol. 1990 Jan;22(1):19–26.

2. Hu SC, Chen GS, Wu CS, Chai CY, Chen WT, Lan CC. Rates of cutaneous metastases from different internal malignancies: experience from a Taiwanese medical center. J Am Acad Dermatol. 2009 Mar;60(3):379–87.

3. Lookingbill DP, Spangler N, Helm KP. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. J Am Acad Dermatol. 1993 Aug;29(2 Pt 1):228–36.

4. Saeed S, Keehn CA, Morgan MB. Cutaneous metastasis: a clinical, pathological, and immunohistochemical appraisal. J Cutan Pathol. 2004 Jul;31(6):419–30.

5. Schoenlaub P, Sarraux A, Grosshans E, Heid E, Cribier B. Survival after cutaneous metastases: a study of 200 cases. Ann Dermatol Venereol. 2001 Dec;128(12):1310–5.

6. Brownstein MH, Helwig EB. Metastatic tumors of the skin. Cancer. 1972 May;29(5):1298–307.

7. Wong CY, Helm MA, Helm TN, Zeitouni N. Patterns of skin metastases: a review of 25 years’ experience at a single cancer center. Int J Dermatol. 2014 Jan;53(1):56–60.

8. Koeck J, Lohr F, Buerger D, Busing K, Trunk MJ, Wenz F, et al. Genital invasion or perigenital spread may pose a risk of marginal misses for Intensity Modulated Radiotherapy (IMRT) in anal cancer. Radiat Oncol. 2016 Apr;11(1):53.

9. Sakanaka K, Itasaka S, Ishida Y, Fujii K, Horimoto T, Mizowaki T, et al. Dosimetric advantages and clinical outcomes of simultaneous integrated boost intensity-modulated radiotherapy for anal squamous cell carcinoma. Radiat Oncol. 2017 Dec;35(4):368–79.

10. Rattanasirivilai A, Kurban A, Lenzy YM, Yaar R. Cutaneous metastasis of prostatic adenocarcinoma: a cautionary tale. J Cutan Pathol. 2011 Jun;38(6):521–4.

11. Palaia I, Angioli R, Cutillo G, Mand N, Panici PB. Skin relapse from cervical cancer. Gynecol Oncol. 2002 Oct;87(1):155–6.

12. Kachnic LA, Winter K, Myerson RJ, Goodyear MD, Willins J, Esthappan J, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys. 2013 May;86(1):27–33.
Fig. 1. (a) A pink ulcerative nodule in the perineum; (b) sagittal magnetic resonance imaging: primary tumor located from the perineum to the rectum; (c) and (d) 18F-fluorodeoxyglucose positron emission tomography: an abnormal accumulation existed in the right labia majora, in addition to those in the ipsilateral inguinal and external iliac nodes. The red and blue arrows indicate primary anal cancer, and genital cutaneous nodular metastasis, respectively.
**Fig. 2.** The abnormal accumulation of 18F-fluorodeoxyglucose positron emission tomography before chemoradiotherapy (a–e) and no abnormal accumulation after chemoradiotherapy (f–j). Dose distribution of radiotherapy: (k) sagittal image; (l–n) axial images.