Hepatic Metastasis from Perianal Paget's Disease Without Identified Underlying Carcinoma: A Case Report

Yi-Sheng Cao (✉ iloveurandy163@hotmail.com)

HwaMei Hospital, University of Chinese Academy of Sciences <https://orcid.org/0000-0002-8195-6826>

Shu-Yan Wang

Ningbo Pathological Diagnosis Center

Case report

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Abstract

Background: Perianal Paget's disease (PPD) is a rare malignancy, often associated with an underlying adenocarcinoma and a poor prognosis.

Case presentation: A 69-year-old female was presented with a history of perianal pruritus for 6 months and enlarged inguinal lymph nodes in the left side. Paget cells were confirmed by pathology after a wide excision of perianal skin. Radiotherapy was performed covering the bilateral inguinal lymphatic drainage area. Hepatic metastasis was found 8 months after surgery. Hepatic artery embolization (HAE) and high intensity focused ultrasound therapy (HIFU) were performed successively. However, hepatic metastasis happened again 3 months later. Ultrasound guided percutaneous radiofrequency ablation (PRFA) was carried out and various means of inspection could not identify the primary tumor. In the case of rapid progression of the tumor, we gave the patient chemotherapy regimens of XELOX. After four cycles' chemotherapy, the tumor marker went down continuously and the hepatic metastasis stayed stable.

Conclusions: Hepatic metastasis from perianal Paget's disease without identified underlying carcinoma may benefit from XELOX on the basis of adenocarcinoma.

Background

Paget's disease was an uncommon intraepithelial adenocarcinoma named by Sir James Paget describing breast cancer patients with characteristic lesions around the nipples in 1874[1]. While perianal Paget's disease (PPD) was firstly reported in 1893, which accounted for 20% of extramammary Paget's disease cases that usually happened in vulva, perineum, penis, scrotum and axilla[2]. Those patients may have a high incidence of underlying primary carcinoma, which often refers to a poor prognosis. We report a rare case of hepatic metastasis from PPD without underlying carcinoma detected and discuss the possibly effective therapy.

Case Presentation

A 69-year-old female was presented to the hospital in April 2019 with a history of perianal pruritus for 6 months. Physical examination showed a raised and raw hyperaemic area 8cm in diameter surround the anal (Fig. 1) and enlarged inguinal lymph nodes in the left side. The patient had neither weight loss nor gastrointestinal symptoms, and had no other history of surgery except local resection for benign breast lobular hyperplasia 30 years ago. The patient's tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 199 (CA199), were normal. Abdominal enhanced computerized tomography (CT) showed multiple intrahepatic cysts and perianal skin thickening, with lymph nodes as large as 35*19mm in the left inguinal region. Chest high resolution CT (HRCT) reveals a 5mm ground glass nodule with a clear boundary in the posterior segment of the upper lobe tip of the left lung (LUNG-RADs 3). Both of the gastroscopy and colonoscopy had no positive findings. Ultrasound exam and mammography of the breast were also normal. Local biopsy conformed with the diagnosis of Paget's

disease. A wide excision of perianal skin and loop stoma of the transverse colon was performed. Post-operation pathology confirmed the diagnosis of Paget's disease with negative surgical margin (Fig. 2A), and the tumor was as large as 7.5cm×5.0cm×0.2cm, without any infiltration or vessel invasion. Immunohistochemical analysis was positive in caudal type homeobox 2 (CDX-2) (Fig. 2B) and cytokeratin 20 (CK20) (Fig. 2C), and negative in GCDFP-15 and Her-2. From July 2019, the patient began to receive radiotherapy covering the bilateral inguinal lymphatic drainage area. In December 2019, the abdominal enhanced CT showed a nodule in slightly low density in Ⅷ-Ⅸ segment of the liver, 21×21mm in size under regular follow-up (Fig. 3A). Magnetic resonance imaging (MRI) revealed the nodule in Ⅷ segment of the liver to be the long T1 and T2 signal one, as well as nodules in segment Ⅷ and Ⅸ, 4-5mm in diam. Ultrasound-guided puncture was used to confirm the nodule to be poorly differentiated adenocarcinoma (Fig. 2D), positive in cell keratin 7 (CK7) CK20 and CDX-2, and negative in Hepatocyte and CgA. Hepatic artery embolization (HAE) and high intensity focused ultrasound therapy (HIFU) were performed successively. After those therapies, the patient's tumor marker went down a bit but soon rose again. In March 2020, the abdominal CT scan showed the nodule in segment Ⅷ was 12×15mm in size, bigger than it was three months ago (Fig. 3B). One and a half months later, MRI found these nodules grew rapidly accompanied with some new ones, and the biggest one was as large as 41×33mm (Fig. 3C). Ultrasound guided percutaneous radiofrequency ablation (PRFA) was carried out on May 5th. Colonoscopy, chest CT scan and breast ultrasound were performed again to identify the primary tumor as well as PET-CT. Though there was still no positive finding, we gave the patient chemotherapy regimens of XELOX (Oxaliplatin 130mg/m², ivgtt D1, Xeloda 1000mg/m², po bid, D1-14, repeat every three weeks) since May 22nd. After four cycles' chemotherapy, the patient tolerated it well, the tumor marker went down continuously (Chart 1) and MRI on July 29th found the patient in the status of partial response (PR) (Fig. 3D).

Discussion

The PPD is rare and accounts for 5.4–20% of extramammary paget's disease (EMPD) cases [2, 3, 4], often associated with internal malignancies and a poor prognosis [5]. The number of recorded cases is small, most of which describe the disease manifestations, and a variety of treatment modalities. The most important diagnostic criteria for PPD is Paget's cells, which are characterized by round cells with a pale vacuolated cytoplasm and a large reticular nucleus [6]. A biopsy of the lesion should be implemented to confirm the diagnosis before surgery. The differential diagnosis should include leukoplakia, Bowen's disease, squamous-cell cancer, eczema, and so on. In a review by Grow, PPD can be divided into three different patterns on the basis of origins, 50% of cases associated with an apocrine or eccrine carcinoma, called "original paget's disease (PD)", 25% with an underlying anal/rectal adenocarcinoma or squamous cell carcinoma, called "pagetoid extension", and 25% with no underlying malignant lesion [7]. These lesions might locate within the anal canal, perianal area or around the anus, and involve one quadrant to the whole circle. In our case, the patient suffered from PPD around the anal without underlying carcinoma according to CT scans, gastroenteroscopy, PET-CT and any other

examination methods. The enlarged inguinal lymph nodes in the left side indicated a high degree of malignancy.

Treatment for PPD varies depending on the different origins and staging of the disease. It is commonly accepted that wide excision could direct toward achieving local control, especially for the “original PD”, and it can be performed repeatedly if recurrence happens. If the skin defect is huge after resection, local rotation flaps, or skin grafting might preserve patients’ anal function. For patients with downward spread of anal/rectal malignant, more aggressive surgery should be considered to cure the disease, including the possibility of an abdominoperineal resection (APR) [8]. For PPD patients with no underlying carcinoma, there is no widely accepted recommendation yet because of the small number of the cases. Wide excision is the first choice just like the one we performed, and a negative margin should be guaranteed. Patients must be closely followed up, to detect not only a possible recurrence, but also delayed underlying malignant tumor. Besides surgery, radiation therapy is an alternative treatment in some circumstances. Though there are no randomized controlled trials to compare surgery with radiation therapy for EMPD, radiation therapy for EMPD may be indicated in patients medically unfit for surgery, for recurrence following surgery, in any patient who wishes to preserve the functional or as an adjuvant to surgery in patients with an underlying adenocarcinoma [9]. However, some literature contained a view that radiotherapy had no place in the management of the condition because of high recurrence rates [10, 11]. We gave the patient radiotherapy covering the bilateral inguinal lymphatic drainage area because of the enlarged inguinal lymph nodes to prevent possible lymph node metastasis. Chemotherapy is another way of adjuvant treatment often combined with radiation, but there is no guideline for the deployment of chemotherapy drugs. Topical chemotherapeutic agents include 5-fluorouracil (5-FU) and mitomycin C, though no survival data has been recorded due to sporadic cases. In general, this is in the setting of invasive or more aggressive recurrent disease, because the response to chemotherapy has been poor. 5-FU may be useful for symptomatic relief, preoperative delineation of disease extent, cytoreduction prior to surgery and postoperative detection of early disease recurrence [12]. Although some authors have reported successful treatment of Paget’s disease with chemo-radiotherapy, the use of adjuvant therapy has not been associated with improved local control or survival [13]. Based on our experience, the patient was treated with XELOX regimen according to pathological findings of adenocarcinoma from hepatic metastasis without any identified underlying carcinoma, and it worked, to a certain extent, from the descending tumor marker and the steady state of metastases.

Shutze et al. gave classification to PPD based on the disease pathology from the cases reported in the literature and correlated with surgical treatment [14]. The survival data varied dramatically from diseases in different stages. Wide local excision was recommended for patients with Paget’s cells found in perianal epidermis and adnexae without primary carcinoma (Stage I) and cutaneous Paget’s disease with associated adnexal carcinoma (Stage IIA), though the most common morbidity after surgery was local recurrence with the rates of 44–60% [15, 16]. Repeated resection is an effective way when it happens and often obtains a good survival outcome. But tumor stages are not fixed and sometimes require restaging as the disease progresses or the underlying carcinoma is identified. For patients with PPD of more aggressive staging, the prognosis is extremely poor. Distance metastases often occur months after the

first treatment, usually involving the liver, the lung, and the bone, and may lead to rapid progress. Among three different patterns of PPD, the pagetoid extension has worse prognosis than original PD [17], while PPD without underlying malignant lesion has the most uncertain outcome. Immunohistochemical stains are helpful in identifying the origins of the disease from raising the suspicion of underlying malignancy with positive CK20 and CEA [18]. Brown et al. found that survival was significantly worse for cases of primary PPD treated with radiotherapy compared to cases treated upon recurrence [19], but this might be because those patients were likely to have poorer general condition or more extensive metastasis so that they could receive radiotherapy at primary stage. This patient had non-invasive PPD at first surgery except enlarged inguinal lymph nodes in the left side, but only seven months since surgery, she was found to have hepatic metastasis, which recurred after HAE and HIFU. When distant metastasis happens, local treatment alone cannot obtain satisfactory effect. So we gave her chemotherapy regimens of XELOX based on the pathologic findings of adenocarcinoma, and fortunately, the patient got a declining tumor marker value and stable metastases.

Conclusions

When PPD is diagnosed, a careful screening should be done to detect the underlying primary malignancy to identify the origin, which often brings different outcomes. Besides, post operation pathology and immunohistochemical stains are also helpful. Local resection with clear negative margins is recommended for the primary cases, and can be repeated when recurrence happens. For PPD with underlying primary adenocarcinoma, APR may achieve better survival, but for those without underlying malignant lesion, close follow-up is important to find the potential malignancy and metastasis. The primary PPD has a high rate of recurrence and the latter two patterns have poor prognosis. Although the role of chemotherapy and radiotherapy in the management of PPD has not been fully assessed, combination chemotherapy may be a choice for patients in intolerant condition or with advanced unresectable metastasis.

Abbreviations

PPD—Perianal Paget's disease

HAE—Hepatic artery embolization

HIFU—High intensity focused ultrasound therapy

PRFA—Percutaneous radiofrequency ablation

CEA—Carcinoembryonic antigen

CA199—Carbohydrate antigen 199

CT—Computerized tomography

CDX-2—Caudal type homeobox 2

CK20— Cytokeratin 20

MRI— Magnetic resonance imaging

CK7— Cell keratin 7

EMPD—Extramammary paget's disease

PD— Paget's disease

APR—Abdominoperineal resection

5-FU—5-fluorouracil

Declarations

- Ethics approval and consent to participate

The study has been approved by the institutional review board of Ethics Committee of HwaMei Hospital, University of Chinese Academy of Sciences. Informed consent was assigned in Chinese format and the patient was willing to share her experience provided that her name and portrait would not be exposed.

- Consent for publication

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 Editors-in-Chief of this journal.

- Availability of data and materials

The authors confirm the data and materials are availability.

- Competing interests

The authors declare that they have no conflict of interest.

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- Authors' Contributions

YS C: Drafting of the manuscript; disease treatment

SY W: Acquisition of data; analysis and interpretation of pathology

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Figures

Figure 1

A raised and raw hyperaemic area 8cm in diameter surround the anal.

Figure 2

The paget's cell is characterized by large volume, rich and transparent cytoplasm, and the round, large hyperchromatic nuclei, with mitotic figures (2A). Immunohistochemical analysis was positive in CDX-2 (2B) and CK20 (2C), which strongly suggested the possible origin of adenocarcinoma. Heteromorphous solid cell nests were observed in the hepatic penetrating tissues. Liver biopsy showed large cell body, little cytoplasm, hyperchromatic nuclei with distinct atypia, and the mitotic figures were visible, as well as intracellular mucous (2D).

Figure 3

The size change of hepatic metastasis judging by images from 2019-12-29 (3A), 2020-03-05 (3B), 2020-04-28 (3C), and 2020-07-29 (3D).

Figure 4

Trend of the tumor markers