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Immunotherapy in combination with chemotherapy for Peutz-Jeghers syndrome with advanced cervical cancer: A case report

Hu XC *et al.* Immunotherapy combined with chemotherapy for PJS

Xiang-Cheng Hu, Chen-Xiao Gan, Hui-Min Zheng, Xue-Ping Wu, Wen-Sheng Pan

Abstract

BACKGROUND

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder, and female patients may develop gynecologic tumours. The prognosis for such patients is poor and the specific pathogenesis remains uncertain. Therefore, there are currently no uniform treatment options.

CASE SUMMARY

Herein, we introduce the case of a 45-year-old female who was diagnosed with PJS for 45 years and cervical cancer for 3 years. Postoperative pathological examination showed metastases in the right external iliac lymph nodes. The patient was initially treated with a combination of doxorubicin and carboplatin chemotherapy and pelvic magnetic resonance showed that the metastases had grown. Subsequently, we performed whole exome sequencing in this patient and identified the relevant causative gene. In addition to the chemotherapy regimen, sindilizumab was adminstered and the patient was followed up. After 4 cycles of treatment, the metastases were substantially reduced and were not enlarged after six months of follow-up. This case report suggests that patients

with PJS combined with cervical cancer may have a sustained response to immune-combination chemotherapy regimens.

CONCLUSION

Clinicians should be aware of the importance of immunotherapy in patients with PJS combined with advanced cervical cancer.

Key Words: Peutz-Jeghers syndrome; Cervical cancer; Programmed cell death protein 1; Chemotherapy; Case report

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Core Tip: Peutz-Jeghers syndrome (PJS) is a rare genetic disease with cancerous potential. In this case, the patient was diagnosed with PJS combined with progressive cervical cancer and she initially received doxorubicin and carboplatin; however, the right parietal iliac vessel metastases did not shrink. This case suggests that the use of programmed cell death protein 1 (PD-1) inhibitors was helpful in this patient and that PD-1 inhibitors combined with chemotherapy may be a good choice for treating this disease.

INTRODUCTION

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant-inherited disorder. The incidence of this syndrome ranges from 1 in 25000 to 1 in 28000 people per year[1]. Current research indicates that this disease is caused by a mutation of the *STK11* gene on chromosome 19p13.3(1). Patients with PJS are characterized by dark spots on the skin mucosa and hamartomatous polyps in the digestive tract[2]. At the same time, studies have indicated a higher incidence of malignancy in patients with PJS than in the general population. The cumulative incidence of gastrointestinal cancers is 55%, with colorectal cancer at 39%, pancreatic cancer at 36%-40%, and small bowel cancer at 13%[3,4]. The risk of cancers of the nongastrointestinal tract is also increased, with a cumulative incidence of 32%-54% for breast cancer, 21% for ovarian cancer, and 7% for lung cancer at age 60[5-8]. Cisplatin has been the standard chemotherapy for cervical cancer with distant metastases, and recent evidence supports the use of platinum-based dual therapy rather than cisplatin alone[9-11]. However, in patients with PJS combined with uterine malignancy, the pathogenesis may be more complex and unclear, and there is no standard treatment protocol. We report a patient with PJS combined with progressive cervical cancer. A regimen using a programmed cell death protein 1 (PD-1) inhibitor in combination with chemotherapy may be a good option for treating this disease.

CASE PRESENTATION

Chief complaints

A 45-year-old Chinese female was admitted to the hospital with mucous membrane black spots on the lips, intermittent abdominal pain for more than forty years and recurrent cervical cancer for three years.

History of present illness

Forty years prior, the patient visited several hospitals for lip pigmentation and abdominal pain and was finally diagnosed with PJS by gastroscopy (Figure 1A and B). The patient later underwent three "partial small bowel resections" and two "intestinal polypectomies"

for intestinal obstruction. Three years ago, the patient was diagnosed with cervical cancer and underwent "extensive hysterectomy and bilateral adnexal resection". Postoperative pathology suggested an endogenous cervical (size 5.4 cm × 3.5 cm) highly differentiated adenoma with metastasis to the right external iliac vessels (Figure 1C). The patient was treated with six cycles of chemotherapy with a carboplatin-doxorubicin (CD) (doxorubicin 30 mg/m^2 and carboplatin area under the curve = 5) regimen before admission.

History of past illness

The patient reported no remarkable history of past illness.

Personal and family history

The patient's mother, brother, sister and daughter all had PJS. Her mother died of colon cancer at the age of forty. Genetic mapping was recorded (Figure 2).

Physical examination

A surgical scar of approximately 5 cm was visible below the umbilicus. Other physical examinations showed no important abnormalities.

Laboratory examinations

The leukocytes, bilirubin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, infectious disease screening and serum tumour markers were within normal limits, but the carbohydrate antigen-199 (CA199) level was elevated (71.2).

Imaging examinations

After admission, 18F-fluorodeoxyglucose positron emission tomography (PET)/computed tomography (CT) indicated multiple small metastases next to the right iliac vessels [the largest was approximately 0.5 cm × 0.5 cm; the regular scan maximum standardized uptake value (SUVmax) = 1.4; delayed scan SUVmax = 3.2].

FINAL DIAGNOSIS

Based on the patient's transoral single-balloon enteroscopy findings and the patient's surgical report, we diagnosed her with PJS combined with advanced cervical cancer.

TREATMENT

The patient was hospitalized to complete PET-CT and transoral single-balloon enteroscopy and did not continue chemotherapy due to financial reasons. In September 2021, pelvic magnetic resonance (MR) suggested a substantially larger right iliac metastasis than before, with CA199 = 146.8 U/mL. The patient then underwent a four-cycle CD chemotherapy protocol. In January 2022, pelvic MR suggested that the metastases continued to increase in size and CA199 was 160.8 U/mL. The patient's platelet count was 42×10^9/L, suggesting a risk of bleeding, so the patient was not directly punctured to test the expression of PD-L1 on the surface of the tumour cells. In addition, considering that the patient had both PJS and cervical cancer, whole exome sequencing (WES) was performed on the patient's blood and showed a mild correlation between Janus kinase-2 (JAK2) and the development of the disease (Figure 3). The patient was then treated for the first time with a PD-1 inhibitor (sindilizumab 200 mg, 21 d per cycle) in combination with the CD chemotherapy regimen[12]. In April 2022, pelvic MR suggested that the lesion had decreased greatly and CA199 was 29.8 U/mL, so the treatment was continued with the above regimen. In September 2022, pelvic MR showed no progression of metastases and CA199 was 27.1 U/mL. The whole treatment process was documented (Figure 4), and the overall health parameters during treatments were recorded (Table 1).

OUTCOME AND FOLLOW-UP

Studies have found that sindilizumab-treated patients often suffer from adverse effects such as fever (38%), anaemia (74.1%) and elevated aspartate aminotransferase (41%) and alanine aminotransferase (40.6%)[13,14]. At the same time, carcinoma embryonic antigen

(CEA), CA199 and cancer antigen-125 (CA125) are useful markers for detecting cervical cancer and monitoring the clinical course. In particular, CA199 and CA125 have been shown to be particularly useful in patients with adenocarcinoma[15]. In our case, after two months of follow-up, the patient's temperature, heart rate, respiratory rate, blood pressure, white blood cell, haemoglobin concentration, liver function and tumour markers (including CA199, CA125 and CEA) were within the normal ranges (Table 2).

DISCUSSION

We introduced a case of PJS combined with advanced cervical cancer. After the use of a PD-1 inhibitor combined with a CD chemotherapy regimen, the patient's right iliac metastases were markedly reduced in volume to a stable state, and a more satisfactory result was achieved.

PJS is a rare autosomal dominant disorder characterized by gastrointestinal malformations and skin pigmentation. Mutations in the *STK11* gene can be detected in 50% to 80% of patients. Other related causative genes include the possible gene in the 19q13.4 region, the *Brg1* gene and the *IFTTM1* gene[16]. Patients with PJS are more prone to various malignancies, among which gastrointestinal and reproductive tract and endocrine tumours are the most common. Cervical adenocarcinoma is a common malignancy among patients with PJS (46.8%)[17]. Patients with PJS combined with cervical cancer often present with symptoms such as menstrual irregularities, endocrine disorders and abnormal vaginal bleeding, but there is no uniform treatment protocol. In 2008, Li *et al*[18] first reported a case of PJS complicated by cervical adenocarcinoma and small bowel malignancy in which the patient underwent total hysterectomy after neoadjuvant chemotherapy (paclitaxel 120 mg/dL and carboplatin 350 mg/dL 1 d per week for 6 wk, and the tumour markers returned to normal after three months. However, the patient was not followed up. In 2008, Kilic-Okman *et al*[19] reported a case of PJS combined with stage IIIB cervical cancer in which the patient received six cycles of combination chemotherapy (5-fluorouracil, adriamycin, and cyclophosphamide) and radiotherapy. That patient died of cervical adenocarcinoma progression within one month after the

completion of radiotherapy. In 2019, Kim *et al*[20] reported a case of PJS combined with gastric-type mucinous cervical adenocarcinoma. As the mass was confined to the cervix and no peripheral lymph node metastasis was present in this patient, the patient achieved recovery after radical cervical surgery followed by adjuvant radiotherapy. In 2021, Vu Dinh *et al*[21] reported a case of PJS combined with stage IIIC gastric cervical mucinous adenocarcinoma. After adjuvant radiotherapy, the disease was stable with no recurrence at one year of follow-up.

PD-1 (also known as CD279) is a coreceptor expressed on the surface of antigen-stimulated T cells. PD-1 and its ligand (PD-L1) belong to the immune checkpoint pathway. Cervical cancer patients can exhibit PD-L1 expression. In 2018, Feng *et al*[22] reported that 59.1% of cervical cancer patients exhibited PD-L1 expression. Additionally, increased incidents of abortion and childbearing can also enhance PD-L1 expression in tumour cells. The study confirmed that PD-1 in tumour-invasive lymphocytes (TILs) and PD-L1 and TILs in cancer cells together constitute the PD-1/PD-L1 pathway, and the imbalance of this pathway is one of the mechanisms of tumour development and cellular immune escape. In addition, Meng *et al*[23] revealed that 60.82% of patients had PD-L1 expression, and PD-L1 overexpression was associated with vascular invasion and lymph node metastasis in cervical cancer.

JAK2 is a nonreceptor tyrosine kinase that plays key roles as the intracellular signalling effector of the cytokine receptor[24]. JAK2 was also found to regulate the expression of PD-L1. In 2016, Ikeda *et al*[25] found that the PD-L1 protein is upregulated by the simultaneous amplification of the PD-L1 and JAK2 genes through JAK-STAT signalling in non-small cell lung cancer. In 2017, Garcia-Diaz *et al*[12] discovered that interferon-γ could induce PD-L1 expression *via* the interferon-γ-JAK1/JAK2-STAT1/STAT2/STAT3-IRF1 axis in tumour cells, leading to immune escape and cancer induction.

Based on the above studies and the WES in this case, JAK2 was mildly associated with the development of the disease, and we used sindilizumab in combination with carboplatin and doxorubicin for the treatment of PJS combined with advanced cervical

carcinoma[12,22-25]. A more satisfactory result was achieved based on the comparison of the right parietal iliac metastases on pelvic MR before and after drug administration, which showed a substantial reduction.

The unique feature of this case is that PJS is a rare disease about which there are only a few international reports, and there is no uniform treatment protocol. We performed WES, identified the relevant causative genes, and treated the patient with sindilizumab in combination with chemotherapy for the first time. The metastases were substantially reduced and the CA199 was greatly decreased after the treatment, which may suggest that immune-combination chemotherapy may be one of the future treatment directions for PJS combined with progressive cervical cancer.

CONCLUSION

We reported a case of PJS combined with advanced cervical cancer. Protein 1 inhibitor combined with a CD chemotherapy regimen substantially decreased the size of the patient's metastases showing that the aforementioned protocol could be a good choice for such patients.

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