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Case Report
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Persistent Lymphedema in a Patient with Advanced Gastric Cancer with *ERBB3* Mutation

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Abstract

Gastric cancer remains a major global health burden with high recurrence and mortality rates, especially in countries in East Asia. Studies have shown that gastric cancer presenting with lymphedema has poor survival. Furthermore, no standard treatment has been accepted for metastatic gastric cancer with lymphedema. In this report, we present a case of advanced gastric cancer with persistent lymphedema after gastrectomy. *ERBB3* V104M mutation was identified by next-generation sequencing. The patient did not have a good response to nivolumab-based treatment with pyrotinib plus chemotherapy. Advanced gastric cancer with refractory lymphedema remains a challenge with immunotherapy based treatment.

Keywords: Gastric cancer; Lymphedema; Nivolumab; *ERBB3*; Pyrotinib

Introduction

Gastric cancer still constitutes a major global health burden, especially in countries in East Asia [1]. Metastatic gastric cancer with refractory lower extremity lymphedema has been reported to be associated with even shorter survival than gastric cancer without lymphedema [2,3]. Furthermore, there is no standard treatment for metastatic gastric cancer with lymphedema, especially for tumor with non-HER2 overexpression.

Here, we report a rare case of a patient with advanced gastric cancer presented persistent lower extremity lymphedema after gastrectomy. *ERBB3* V104M mutation was identified by next-generation sequencing. The patients received multiple lines of treatment, including chemotherapy, targeted therapy, and immunotherapy.

Case Presentation

A 71-year-old woman, diagnosed with gastric signet ring cell carcinoma by endoscopic biopsy, was referred to our hospital in May 2021. She had no family history of cancer. She complained of slight stomach ache and slow-onset, unilateral lymphedema of the lower extremity in April 2021. No causes of peripheral lymph vessel obstruction were identified by routine laboratory test and ultrasound examination. She underwent radical gastrectomy with postoperative stage IIA (pT1N3M0) in late May 2021. Immunohistochemical (IHC) analysis showed that the tumor was negative for Human Epidermal Growth Factor Receptor 2 (HER2). Programmed Death-Ligand 1 (PD-L1) expression, determined by Combined Positive Score (CPS), was <1. However, Programmed Death-1 (PD-1) expression was positive (approximately 10%). The persistent edema developed a month after the surgery. ^{18}F-Fluorodeoxyglucose Positron Emission Tomography Computed Tomography (FDG-PET/CT) did not reveal any site of malignancy. She was diagnosed of advanced gastric cancer, with lymph system micro-metastasis in the lower extremity. From July to August 2021, the patient received two cycles of FLOT regimen (fluorouracil 2400 mg/m^2 IV continuous infusion over 24 h, day 1, leucovorin 200 mg/m^2 IV, day 1, oxaliplatin 85 mg/m^2 IV, day 1, docetaxel 50 mg/m^2 IV, day 1, biweekly). She developed genital and bilateral leg edema in August 2021 (Figure 1). The patient was then administered two cycles of nivolumab (240 mg IV, day 1, biweekly) plus FLOT in September 2021. Meanwhile, the tumor tissues and matched blood samples were collected for next-generation sequencing (FoundationOne CDx, Roche). The genomic results revealed a mutation in *ERBB3* V104M, accompanied by mutation in CDH1 D400N. However, neither the tumor mutational burden nor the microsatellites status could be determined. She was treated with dose modified therapy with nivolumab, albumin-bound-paclitaxel (130 mg/m^2, IV, day1, biweekly) plus pyrotinib (240 mg PO, Qd, for 14 days, biweekly) for one cycle in

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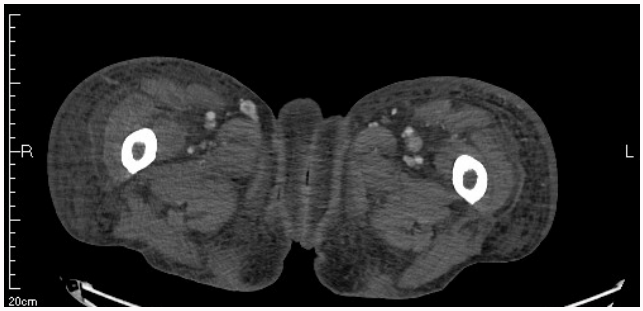

Figure 1: CT scan showing swelling of bilateral upper legs and genital area.

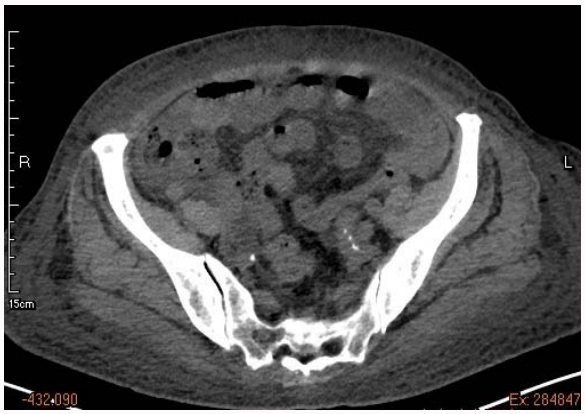

Figure 2: CT scan showing extensive swelling of abdominal wall.

October 2021. Her performance status deteriorated, and suffered from severe diarrhea, an intolerable adverse event of pyrotinib. Additionally, she complained of abdominal distension and difficulty breathing. CT scan showed a large amount of ascites, bilateral pleural effusion, extensive swelling in connective tissue of abdominal wall and right breast, indicating disease progression (Figure 2). Repetitive abdominocentesis and thoracentesis were preformed. The effusion from both the pleural and abdominal cavities was chylous; however, metastatic cells were not confirmed by the repetitive cytological exams. She finally agreed to receive nivolumab plus apatinib (500 mg PO, Qd, for 14 days, biweekly) for another cycle in November 2021. However, the pleural effusion and ascites were not controlled. She died seven months after initial diagnosis of gastric cancer.

Discussion

We presented the history and treatment of a patient who had refractory lymphedema caused by advanced gastric cancer with a shorter-than-average survival. Her performance status was worsening gradually due to the presence of uncontrolled pleural and abdominal effusion and intolerable severe side effects of drugs she had.

Lymphedema may be a common consequence of lymph system micro-metastasis in patients with gastric signet-ring cell cancer. Abdominal, pelvic or inguinal lymph node destruction by metastases may not be prerequisite for acquired lymphedema of the lower extremity in malignancy [4]. Tumor infiltration into the small lymphatic vessels of the lymphedema lesion was pathologically proven in a case of advanced gastric cancer-- this may explain the subsequent development of ascites and pleural effusion after the development of peripheral lymphedema [5]. In few cases with lymphedema caused by advanced gastric cancer, chylothorax has been shown to be closely associated with the presence of lymphedema [2,3]. Therefore, despite a lack of direct pathologically or cytologically malignancy evidence in this patient, it was highly likely that the tumor invasion into the lymphatic circulatory system may have caused lymphedema as well as chylous effusion in both the abdominal and the pleural cavities. Distant site metastasis of signet-ring cell gastric cancer should be included in the differential diagnosis of unexplainable acquired peripheral lymphedema [4].

After the surgery, the patient showed no evidence of any target lesion in the follow-up chest/abdominal/pelvic CT and FDG-PET/CT scans. Progressive lymphedema without measurable target lesion, spreading from lower extremity to abdominal soft tissue, was confirmed in the later imaging evaluation. After the patient was diagnosed with metastatic gastric cancer post-surgery, FLOT regimen was administered as first line treatment, given that FLOT is shown to prolong Overall Survival (OS) compared with ECF regimen (epirubicin, cisplatin and fluorouracil) [6].

In the Checkmate-649 study, nivolumab plus chemotherapy resulted in a significant improvement in OS and Progress-Free Survival (PFS) versus chemotherapy in PD-L1 CPS>=5 gastric cancer patients. Additionally, this study also showed that nivolumab plus chemotherapy provided significant improvement in OS, along with PFS benefit, versus chemotherapy in all-randomized patients [7]. Based on the results from this study, nivolumab was approved by FDA, in combination with chemotherapy for the first-line treatment in patients with advanced or metastatic gastric cancer. Nivolumab was administered in combination with FLOT after this patient developed bilateral lymphedema of the lower extremity.

Considering the higher objective response observed with nivolumab plus chemotherapy across PD-L1 CPS cutoffs, including CPS<1, and the potential delayed treatment effect seen with immuno-oncology therapy [7], we did not discontinue nivolumab-based regimen even her symptom deteriorated.

ERBB3, encoded by the *ERBB3* gene, a member of the Epidermal Growth Factor Receptor (EGFR) family, can form active heterodimers with other EGFR members and activate the downstream signal pathways [8,9]. *ERBB3* mutations have been identified in some cancers, however, effective targeted therapy are still under investigation. In a few case reports, clinical benefits have been observed with trastuzumab, lapatinib, and afatinib [10,11]. A metastatic urothelial cancer with *ERBB3* V104M mutation achieved 6.3 months of PFS after treated with afatinib [12].

Pyrotinib is an oral, irreversible pan-ERBB inhibitor that blocks EGFR, HER2, and HER4 pathways. In the randomized, double-blind, placebo-controlled phase III PHENIX study, pyrotinib plus capecitabine provided a significant improved PFS for HER2-positive metastatic breast cancer with prior trastuzumab and taxanes treatment [13]. The PHOEBE study demonstrated that pyrotinib plus capecitabine had prolonged PFS compared with lapatinib and capecitabine in trastuzumab-treated TKI-untreated patients [14]. In this patient with HER2-negative gastric cancer harboring *ERBB3* V104M mutation, pyrotinib plus albumin-bound-paclitaxel in combination with nivolumab was administered as a third-line treatment. The dose of pyrotinib was reduced from the standard dose of 320 mg Qd to 240 mg Qd due to poor performance status and consideration for potential toxicity of the combined treatment. Since the most common grade 3-4 adverse events of pyrotinib is diarrhea [13,14], we did not administer pyrotinib and irinotecan concurrently.

Oral pill of the target drugs was selected. Excessive introvenous fluid was avoided for potential development of lymphedema. However, the patient discontinued pyrotinib-containing treatment after one cycle due to severe diarrhea and refused to receive further dose reduced pyrotinib. Therefore, the therapeutic effect was not evaluable for the third-line regimen combined with chemotherapy, targeted therapy, and immunotherapy. In these patients, the persistence of lymphedema followed by a large volume of ascites and pleural effusion deteriorated the performance status of the patient and contributed to the short OS.

Ethics Approval

This study was approved by the ethics committee of Ruijin Hospital affiliated to Shanghai Jiatong University School of Medicine. Written informed consent was obtained from the patient for the publication of the study.

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