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Edema of left upper limb as the primary symptom of gastric signet-ring cell carcinoma

Chen Yang*; Miaoli Li; Ning Zhang

Department of Medical Oncology, Shanghai Minhang District Cancer Hospital, Fudan University Cancer Hospital, Minhang Branch, 106, Ruili Road, Minhang District, Shanghai, China.

***Corresponding Author: Chen Yang**
Department of Medical Oncology, Shanghai Minhang District Cancer Hospital, Fudan University Cancer Hospital, Minhang Branch, 106, Ruili Road, Minhang District, Shanghai, China.
E-mail: natoyang@126.com

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Abstract

Gastric signet-ring cell carcinoma (SRCC) is an aggressive histological subtype of gastric cancer that frequently presents with atypical symptoms. Lymphedema as the initial manifestation is exceptionally uncommon. We report a case of left upper limb edema as the primary symptom of metastatic gastric SRCC. The primary tumor and the regional lymph nodes were stable disease after 6-month of treatment with santolina and chemotherapy. But lymphedema worsened and involved the lower limbs. SRCC diagnosed at the late stage with refractory lymphedema remains a challenge with immunotherapy-based treatment.

Keywords: Gastric cancer; Signet-ring cell carcinoma; Lymphedema; Immunotherapy.

Introduction

Signet-Ring Cell Carcinoma of The Stomach (SRCC) is a distinct histological variant characterized by intracellular mucin accumulation that displaces the nucleus, creating the classic "signet-ring" appearance [1]. SRCC exhibits aggressive biological behavior with frequent peritoneal and lymphatic dissemination at diagnosis. SRCC was an independent prognostic factor associated with worse survival in gastric cancer [2]. While SRCC may share typical symptoms with gastric neoplasms, such as abdominal pain, bloating or weight loss, it may present with non-specific paraneoplastic manifestations. Lymphedema as the initial symptom is particularly uncommon. Here, we present a case of SRCC initially manifesting as unilateral upper limb edema and refractory to immunotherapy-based treatment.

Case presentation

A 75-year-old previously healthy male presented with progressive swelling of his left upper limb over four months. The edema began insidiously in the hand and gradually extended to involve the entire arm. He denied pain, trauma, or recent infections. Notably, he reported no gastrointestinal symptoms such as nausea, vomiting, or weight loss. Laboratory tests for complete blood count, liver, renal function, and electrolytes were normal. Serum tumor markers, including CEA, CA 19-9, CA 125, AFP, SCC and NSE, were within the reference range. A Doppler ultrasound excluded deep vein thrombosis. Contrast-enhanced chest CT revealed edema in the soft tissues of the left chest wall (Figure 1), multiple enlarged lymph nodes in the left axilla and moderately enlarged lymph nodes in the mediastinum and hilar regions. Left axillary lymph node biopsy was performed, and metastatic carcinoma was confirmed. Primary gastrointestinal tumor should be considered first, based on the following immunohistochemical results, ER (−), PR(−), HER2 (1+), Ki-67 (80%), AR(−), CD8 (30%), FOXC1 (20%), GATA3(−), CK20(+), TTF-1(−), TRPS1(−), CDX-2(+). 18F-Fluorodeoxyglucose Positron Emission Tomography Computed Tomography (FDG PET-CT) showed thickening of the gastric body wall with increased FDG uptake

with widespread lymph node metastases. Gastroscopy revealed malignant tumor from the lesser curvature of the gastric body to the gastric angle and posterior wall of the gastric antrum. Pathological diagnose was signet-ring cell carcinoma, with additional immunohistochemical results, HER2(−), PD ligand 1 (PD-L1) combined positive score (CPS)<1. The patient was diagnosed as stage IV gastric cancer with lymphatic metastasis causing left upper limb lymphedema, and he underwent sintilimab, a recombinant human IgG4 monoclonal antibody binding to programmed cell death 1 (PD-1), in combination with chemotherapy (mFOLFOX6 regimen) for twelve cycles. While the following CT scan at 3, 6-month of treatment showed that the primary tumor and the regional lymph nodes were stable disease, his upper limb lymphedema worsened. Moreover, he developed edema in his lower limbs (Figure 2). The patient declined further chemotherapy and received palliative diuretic therapy. The patient died nine months after diagnosis.

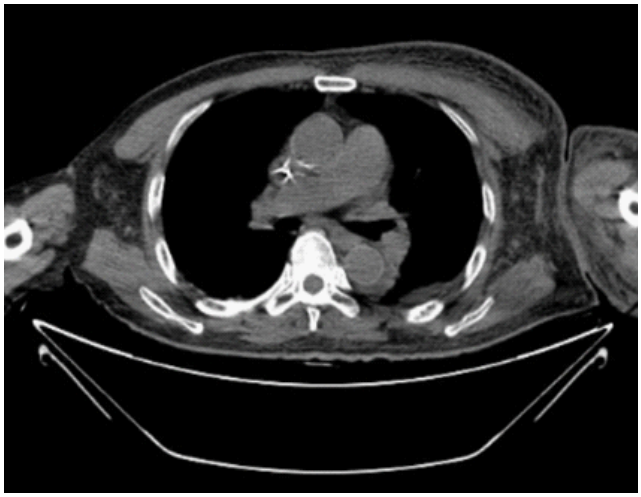

Figure 1: CT scan showing edema in the soft tissues of the left chest wall.

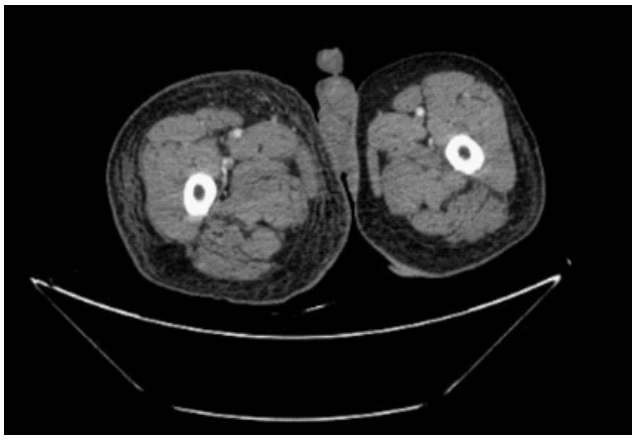

Figure 2: CT scan showing edema in the lower limbs.

Discussion

This case highlights an unusual presentation of gastric Signet-Ring Cell Carcinoma (SRCC), where lymphedema of the unilateral upper limb served as the initial clinical manifestation, preceding the detection of the primary gastric malignancy. Typically, gastric SRCC metastasizes to the liver, peritoneum, or regional lymph nodes, while cutaneous involvement is rare, occurring in less than 2% of cases. When skin metastases do occur, they often present as nodules or erythematous plaques, whereas lymphedema as a primary symptom is exceptionally uncommon [3]. The pathogenesis of lymphedema in this context likely involves tumor cell infiltration into lymphatic vessels, leading to obstruction and impaired drainage—a condition termed carcinomatous lymphangitis. Tumor infiltration into the small lymphatic vessels of the skin was pathologically proven in one case [4]. Cutaneous biopsy would be of interest to confirm lymphogenic dissemination in our case. Additional lymphoscintigraphy could be performed to demonstrate impaired lymphatic flow. Notably, the absence of typical gastrointestinal symptoms in this case underscores the diagnostic challenge posed by SRCC, which can progress silently before manifesting with paraneoplastic or metastatic features. Our patient's presentation-progressing from unilateral limb edema to systemic involvement—aligns with the aggressive behavior of SRCC, which often evades early detection due to its infiltrative growth pattern. A dozen cases of advanced gastric cancer with lymphedema were reported to accompanied by refractory chylothorax as initial symptom [5]. PET-CT scans are usually associated with lower FDG uptake, which compromises their overall sensitivity and increases the rate of false negatives [6]. This increases the complexity in analyzing findings and hinders the diagnosis approach. Therapeutic options for metastatic SRCC remain limited. While chemotherapy (eg, fluoropyrimidine, oxaliplatin, S-1) is the mainstay, response rates are modest, and lymphedema often proves refractory to treatment. Among patients with unresectable locally advanced or metastatic gastric and gastroesophageal junction adenocarcinoma treated with first-line chemotherapy, sintilimab significantly improved overall survival for all patients and for patients with a CPS≥5 compared with chemotherapy (XELOX regimen) alone [7]. Next-generation sequencing is increasingly being used to identify microsatellite instable, genomically stable and chromosomal instable gastric cancers, and to search for druggable targets in advanced settings [8].

Conclusion

This case emphasizes the importance of considering gastric SRCC in unexplained lymphedema. Early endoscopic evaluation with biopsies is critical for timely diagnosis. Further research is warranted to elucidate the mechanisms of lymphatic invasion in SRCC and to develop more effective treatments for this aggressive variant of gastric cancer.

Ethics approval: This study was approved by the ethics committee of Shanghai Minhang District Cancer Hospital/Fudan University Cancer Hospital Minhang Branch. Written informed consent was obtained from the patient for the publication of the study.

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