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# Edema of limbs as the primary symptom of gastric signet-ring cell carcinoma: A rare case report and literature review

Gastric cancer and lymphedema

**Abstract**

BACKGROUND

Metastatic skin cancers (MSCs) are relatively rare dermatological malignancies. They usually present as nodules, erythematous lesions, scar-like lesions or other lesion types. Signet-ring cell carcinoma (SRCC) is an uncommon histological type of gastric cancer that usually behaves aggressively and has a poor prognosis. Skin metastasis may be the first sign of clinically silent visceral cancer or recurrence of an internal malignancy.

CASE SUMMARY

Herein we report the case of a 55-year-old man with edema of a lower extremity as the primary symptom, which progressed from local to generalized pitting edema in the year following skin involvement. Pathological evidence from gastroscopic specimens and subcutaneous tissue biopsy showed typical signet-ring cells and gland-like structures. Consistently, immunohistochemical analysis revealed positive pan-cytokeratin (panCK) expression in tumor cells. A diagnosis of gastric SRCC with skin metastasis was established. Moreover, lymphoscintigraphy showed an obvious accumulation of radiotracer on the anterior and posterior sides of the right leg, which indicated lymphedema. We reviewed the relevant literature on subcutaneous metastases of gastric SRCC.

CONCLUSION

This rare case emphasizes the importance of physical examination as it may help elucidate the etiology of edema.

**Key Words:** Gastric cancer; Signet-ring cell carcinoma; Skin metastasis; Lymphedema; Prognosis; Case report.

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**Core Tip:** Metastatic skin cancers (MSCs) are relatively rare dermatological malignancies. They usually present as nodules, erythematous lesions, scar-like lesions or other lesion types. We report a case of skin metastases from gastric signet-ring cell carcinoma, in which lymphedema of the limbs presented as an initial symptom. This rare case emphasizes the importance of physical examination as it may help elucidate the etiology of edema.

## INTRODUCTION

Metastatic skin cancers (MSCs) are relatively rare dermatological malignancies. They constitute 2% of all skin tumors, and the reported incidence rates range from 0.7% to 9.0%[1]. MSCs originate most commonly from breast, lung and gastrointestinal tissues and are recognized as having a poor prognosis[1,2]. Furthermore, cutaneous metastases from gastric signet-ring cell carcinoma (SRCC) are uncommon[3]. The clinical presentation of cutaneous metastases from gastric adenocarcinoma is usually single or multiple nodules or erythematous lesions; only 6.4 % to 7.8 % of these cutaneous metastases are the first clinical manifestation[4,5]. Moreover, to the best of our knowledge, there is no report describing edema of limbs as the primary symptom of MSCs originating from signet-ring cell gastric carcinoma .

The causes of edema vary. Most causes of edema are due to increased capillary filtration overwhelming normal lymphatic system[6]. Under some conditions, lymphedema occurs when lymph transport capacity is impaired. Lymphedema can be classified into primary and secondary categories[7]. Both primary and secondary forms of lymphedema are often chronic and insidious in nature. Infections such as lymphatic filariasis are a frequent cause of secondary lymphedema in developing countries, whereas in developed countries, a common cause of secondary lymphedema is cancer treatment. Of note, the metastasis or, rarely, direct invasion of active tumor into the lymphatic network can also produce a severe form of lymphedema[8].

In this study, we present a case of atypical gastric adenocarcinoma with signet-ring cell morphology, which presented cutaneous lymphedema as the primary symptom.

## CASE PRESENTATION

### *Chief complaints*

A 55-year-old Chinese male first presented with cutaneous edema of the right lower limb, which developed as systemic edema of all limbs over the course of a year (Figure 1).

### *History of present illness*

In April 2019, the patient developed edema of the right lower limb with an unknown cause . The edema began to spread from the end of the lower extremity to the groin and trunk area. At a local hospital, he was diagnosed with slight renal insufficiency (estimated glomerular filtration rate: 59 mL/min/1.73m$^2$). Additionally, cardiac insufficiency and hepatic insufficiency was excluded and the patient underwent magnetic resonance imaging (MRI) of the lower extremity. The results showed obvious swelling of subcutaneous soft tissue in right thigh, slight edema in subcutaneous soft tissue of left thigh, and edema of long and short head of biceps femoris. One year after skin involvement, the patient presented with newly diagnosed poly-serous effusions (thoracic cavity, abdominal cavity and pericardium).

***History of past illness***

None.

***Personal and family history***

The patient had no significant personal history and denied any health issues or genetic problems in his family. There was no obvious weight loss or significant family history.

***Physical examination***

On admission, the patient's temperature was 36.0 ℃, heart rate was 91 beats/min, respiratory rate was 20 breaths/min, and blood pressure was 143/92 mmHg. No abnormality was found in the heart and the lungs were clear to bilateral auscultation, without any wheezes, rales, or rhonchi. Furthermore, there was no tenderness or rebound pain in the abdomen. Additionally, there is no signs of associated gastro-intestinal symptoms, such as nausea, vomiting, hematemesis, or any change in bowel habit. However, he had obvious pitting edema in the right lower limb but not in the left limb. When pressure was applied to the right lower limb, indentation remained in the soft tissue after the pressure was removed.

***Laboratory examinations***

The main characteristics of laboratory examinations during the initial-, 3-month, and 12-month visits are listed in Table 1. Specially, the results showed that the patient's carbohydrate antigen 724 Levels were slightly elevated during the initial (16.41 U/mL, reference value range < 6.9 U/mL), 3-month (15.51 U/mL) and 12-month (15.67 U/mL) visit, while serum carcinoembryonic antigen and carbohydrate antigen 19-9 Levels were within the normal range. The levels of urea nitrogen (8.97 mmol/L, 12.54 mmol/L, and 12.83 mmol/L for the initial, 3-month and 12-month visits, respectively) were slightly elevated. Similarly, creatinine levels (126 μmol/L, 130 μmol/L, and 152 μmol/L for the initial, 3-month and 12-month visits, respectively) were also slightly elevated. Kidney

function was evaluated as CKD G3a by calculating the estimated glomerular filtration rate[9]. However, the results were normal for the patient's kidney, ureter, and bladder on color Doppler ultrasound. Routine urine tests indicated no proteinuria or hematuria. Thyroid function test results were normal.

***Imaging examinations***

No obvious abnormality was found on computed X-ray tomography of chest and abdomen. The 18F-fluorodeoxyglucose (FDG) positron emission tomography was performed. No pathological FDG uptake was detected in the liver, spleen, kidneys, gastrointestinal system, or in either the abdominal or pelvic lymph node groups. Moreover, lymphoscintigraphy labeled with $^{99m}$Tc-DX showed an obvious accumulation of radiotracer in the right leg on both the anterior and posterior sides after 3 and 6 h diffusion (Figure 3), indicating lymph angiodysplasia and lymphedema. Color Doppler ultrasound of the heart and blood vessels of both lower limbs showed no abnormality.

***PATHOLOGICAL AND GASTROINTESTINAL ENDOSCOPIC EXAMINATION***

First, the biopsy of the skin on lower limb revealed infiltration of the suspicious cells with a signet-ring appearance cells and gland-like structures (Figure 2G-I). Biopsy specimens of the lesions showed reactive epithelial changes (pan-cytokeratin [panCK] positive) (Figure 2I). Because gastrointestinal tract is the most common source of SRCC, a gastrointestinal endoscopic examination was subsequently performed. The results showed multiple gastric ulcers without solid neoplasm (Figure 2D and E). However, biopsies of both the body and antrum gastric mucosa showed infiltrating signet ring cell type adenocarcinoma (Figure 2B, and 2E), which were very strongly panCK positive (Figure 2C, and 2F) and CEA positive. Additionally, histopathology showed a less differentiated signet cell ring carcinoma with approximately 20% ki-67 positivity. Taken together, gastrointestinal metastasis was confirmed as the source of the signet-ring cells

in skin biopsies. Thus, a diagnosis of metastatic signet-ring cell carcinoma, most likely from the stomach, was made.

## FINAL DIAGNOSIS

Gastric SRCC with skin metastases.

## TREATMENT

Surgical intervention is not possible for advanced or metastatic gastric cancer. First-line systemic therapy regimens with 2 cytotoxic drugs are preferred for these patients[10]. The preferred regimens for first-line systemic therapy includes fluoropyrimidine (fluorouracil or capecitabine) combined with either oxaliplatin or cisplatin (category 2B)[10]. Given the renal insufficiency in this patient, oxaliplatin or cisplatin was not suitable[11]. Thus, from 21 August 2019, to 2 September 2019, the patient received a combination of chemotherapy with tegafur (a prodrug of 5-fluorouracil, 60 mg PO bid), and paclitaxel (second-line systemic therapy; 100 mg iv QW). Over the next five months, he received another five cycles of chemotherapy.

## OUTCOME AND FOLLOW-UP

At the 3-month visit, his limb edema worsened. By the 12-month visit, edema had spread from the lower limbs to the entire body (Figure 1C), and the patient presented with newly diagnosed polyserous effusions (thoracic cavity, abdominal cavity and pericardium). After six months of treatment, the patient declined further chemotherapy and received palliative diuretic therapy.

## DISCUSSION

This report describes a rare case in which cutaneous metastasis led to the detection of gastric signet-ring cell carcinoma. Additionally, this gastric SRCC primarily presented as lymphedema of the limbs after the subcutaneous metastases. The typical sites for metastasis of gastric cancer are the liver, peritoneal cavity, and regional lymph

nodes[12]. The incidence rate of cutaneous metastasis from gastric signet-ring cell carcinoma is less than 2%; however, when present, the median survival time is 6.5 mo. Common cutaneous manifestations of gastric SRCC include single or multiple red, violet, or hyperpigmented asymptomatic nodules, or more rarely, as cellulitis-like or erysipelas-like erythematous plaques[12]. However, our report presents a case of a patient with gastric SRCC who developed carcinomatous lymphangitis, which is very rare in clinical practice.

Skin metastases from internal tumors are uncommon in clinical practice. In women, the most common origin of skin metastases is adenocarcinoma of the breast, whereas squamous cell carcinoma of the lung is the most common in men. Skin metastases in patients with gastric SRCC are extremely rare. The largest series of patients with skin metastases came from a study by Lookingbill *et al*[3] with a total of 4020 patients. Current information about skin metastases from cancer of the stomach comes from the publication of small series or case reports. The first thorough review of cutaneous metastases from gastric cancer was performed in 2014 by Cesaretti *et al*[13] and included 72 reported patients with cutaneous lesions at various locations on the body surface. However, to the best of our knowledge, skin metastases from gastric SRCC as the first manifestation have not yet been reviewed.

An electronic literature search was conducted using Medline (PubMed) and Google Scholar databases in August 2022 with the terms"(gastric signet-ring cell carcinoma) AND (cutaneous metastases)." The data of publication ranged from 1989 to 2022. There were a total 30 studies, of which 5 Lacked main information; thus, we present a review of 25 studies on cutaneous metastases from gastric signet-ring cell adenocarcinoma (Table 2). The 25 studies included 17 male and 8 female patients with an average age of approximately 58.0 years old. Although reliable allocation of a skin metastasis to the original tumor is not possible, some preferential associations are obvious. Previous data showed that gastrointestinal and colorectal tumors mainly develop distant skin metastases in the abdomen[14]. In our review, the locations of skin metastases from gastric signet-ring cell adenocarcinoma included the abdomen (10/26, 40.0%), face

(7/25, 28.0%), head (5/25, 20.0%), neck (6/25, 24.0%), back (8/25, 32.0%), chest (3/25, 12.0%), armpits (1/25, 4.0%), groin (2/25, 8.0%), arms (3/25, 12.0%) and limbs (3/25, 12.0%). Only one patient presented with initial symptoms, without any local or general clinical symptoms[15]. In all cases, only seven patients presented with weight loss and gastrointestinal symptoms (such as vomiting, loss of appetite, dyspepsia, or abdominal pain)[16,17] as the first manifestation. For the cutaneous manifestations, seven patients presented with skin lesions[18-20] (scar-like or other types of lesions), nine patients with nodules[21] and five with erythema. Ours is a rare case, not only due to dramatic skin metastasis as the first presenting sign but also because the patient presented with obvious edema of the lower limbs. In addition, the prognosis of skin metastases from gastric signet cell carcinoma is poor. In all 25 cases reviewed, only 4 patients survived. Most patients died a few weeks (mean 6.1 wk) later after skin involvement[16]. Currently, the patient in our case is alive, but also has advanced symptoms (systemic edema in all limbs) (Figure 1).

In the review by Cesaretti *et al* in 2014, 80% of the patients received a management approach ranging from local excision to chemotherapy or chemoradiation therapy to treat their cutaneous metastases[13]. In our review, 16 patients were treated with chemotherapy (11/16), chemoradiation therapy (1/16), surgery (3/16), or radiotherapy (1/16). Chemotherapy is the first choice for the treatment of advanced gastric signet-ring cell adenocarcinoma. In particular, chemotherapy regimens 5-fu/fa/oxaliplatin (5-fluorouracil, folinic acid, and oxaliplatin) and S-1 (tegafur plus cisplatin) were preferred in our review of cutaneous metastases after gastric signet-ring cell adenocarcinoma.

Because carcinomas generally spread preferentially *via* the lymphatic route and gastrointestinal tumors are known to spread to lymph nodes or lymph-vessel, in this case, it is hypothesized that an aggressive clone of signet cell gastric carcinoma metastasized to lymph-vessel and then, by making a blockage of lymph-vessel, appeared in the dermis of the skin as an apparently primary skin edema or lymphedema. Lymphedema is a clinical condition characterized by an increased volume of subcutaneous soft tissues due to impairment of the lymphatic system. Lower

limb edema is a very common symptom; the most common underlying mechanisms include venous and lymphatic disease, volume overload, increased capillary permeability, and decreased oncotic pressure. The most commonly associated diseases are deep vein thrombosis and chronic venous insufficiency, heart failure, hepatic or renal failure hypoproteinemia, idiopathic cyclic edema, and drug-induced edema. Lymphedema induced by gastric SRCC is rare and has not been previously reported.

Additionally, the patient's kidney function was evaluated as CKD G3a by calculated the estimated glomerular filtration rate. Renal dysfunction is classified into nonuremic and uremic stages. Patients with non-uremic renal failure (NURF) are defined as having impaired renal function, but are dependent on their own kidneys. The reason is currently unknown. Recently, owing to the increase in the aged population and the incidence of diabetes mellitus, the number of patients with gastric cancer associated with NURF have been increasing[22]. Whether gastric cancer itself or other factors led to the NURF in this patient remains unclear.

## CONCLUSION

We report a case of skin metastases from gastric signet-ring cell carcinoma, in which lymphedema of the limbs presented as an initial symptom. This case emphasizes the importance of excluding malignancy from the differential diagnosis of edema. Thus, a careful clinical physical examination must be performed on patients with edema to ensure that no information is missing and to obtain further clinical data, which could pave the way for further studies.

## ACKNOWLEDGEMENTS

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