

World Journal of *Gastrointestinal Oncology*

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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

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

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Abstract

BACKGROUND

Metastatic skin cancers 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 on 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 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 are relatively rare dermatological malignancies. They usually present as nodules, erythematous lesions, scar-like lesions or other lesion types. We report on 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.

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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 the 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 the 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 with cutaneous lymphedema as the primary symptom.

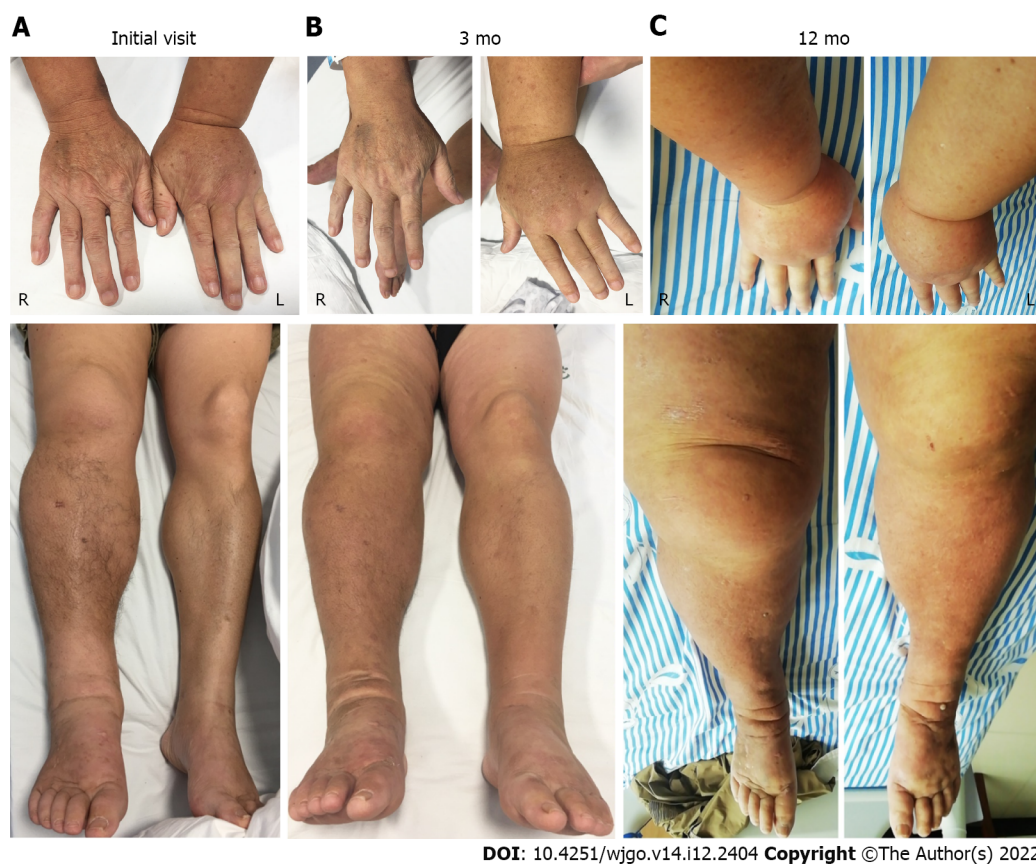
CASE PRESENTATION

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/1.73 m²). Additionally, cardiac insufficiency and hepatic insufficiency was excluded and the patient underwent magnetic resonance imaging of the lower extremity. The results showed obvious swelling of subcutaneous soft tissue in the right thigh, slight edema in the subcutaneous soft tissue of the left thigh and edema of the long and short head of the biceps femoris. One year after skin involvement, the patient presented with newly diagnosed poly-serous effusions (thoracic cavity, abdominal cavity and pericardium).



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Figure 1 The 55-year-old male patient with systemic edema. A: The images of fingers and legs of this patient at the initial visit; B: The images of fingers and legs of this patient at 3-mo visit; C: The images of fingers and legs of this patient at 12-mo visit.

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 °C, 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 sign of associated gastrointestinal symptoms such as nausea, vomiting, hematemesis or any change in bowel habits. 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, an indentation remained in the soft tissue after the pressure was removed.

Laboratory examinations

The main characteristics of laboratory examinations during the initial 3-mo and 12-mo visits are listed in Table 1. Specifically, 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-mo (15.51 U/mL) and 12-mo (15.67 U/mL) visit, while serum carcinoembryonic antigen (CEA) 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-mo and 12-mo visits, respectively) were slightly elevated. Similarly, creatinine levels (126 μmol/L, 130 μmol/L, and 152 μmol/L for the initial, 3-mo and 12-mo visits, respectively) were also slightly elevated. Kidney function was evaluated as chronic kidney disease (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 χ -ray tomography of the 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

Table 1 Characteristics of laboratory examinations

Parameter	Initial visit	3 mo	12 mo	Reference value range
Full blood count				
White cell count as $\times 10^9/L$	6.4	7.55	3.58	(3.5-9.5)
Neutrophils as $\times 10^9/L$	4.51	5.56	2.25	(1.8-6.3)
Lymphocytes as $\times 10^9/L$	1.3	1.32	0.68	(1.1-3.2)
Monocytes as $\times 10^9/L$	0.36	0.5	0.23	(0.1-0.6)
Platelets as $\times 10^9/L$	218	223	208	(125-350)
Hemoglobin in g/L	144	136	157	(130-175)
Tumor markers				
Carbohydrate antigen 724 in U/mL	16.41	15.51	15.67	(< 6.9)
Carbohydrate antigen 199 in U/mL	15.88	16.84	4.43	(\leq 34)
Carcinoembryonic antigen in ng/mL)	2.81	2.86	0.78	(\leq 5)
Blood biochemical indicators				
Alanine aminotransferase in U/L	16	11	14	(\leq 41)
Aspartate aminotransferase in U/L	13	13	15	(\leq 41)
Globulin in g/L	28.9	25.5	19	(64-83)
Albumin in g/L	38.2	32.2	25	(35-52)
Creatine kinase in U/L	93	56	24	(\leq 190)
Lactic dehydrogenase in U/L	163	156	202	(135-225)
Urea nitrogen in mmol/L	8.97	12.54	12.83	(3.1-8.0)
Creatinine in $\mu\text{mol/L}$	126	130	152	(59-104)
Estimated glomerular filtration rate in mL/min/1.73 m ²	55	52.9	49.5	(> 90)
Random blood glucose in mmol/L	6.22	5.39	6.12	(< 11.1)
Serum potassium in mmol/L	4.2	3.88	3.89	(3.5-5.1)
Serum sodium in mmol/L	141.5	141	142	(136-145)
Cardiac troponin T in pg/mL	2.2	2.5	2.7	(\leq 34.2)
N terminal pro B type natriuretic peptide in pg/mL	53	45	59	(< 161)
Fibrinogen in g/L	4.31	5.03	5.88	(2-4)
D-Dimer in $\mu\text{g/mL FEU}$	1.36	1.05	7.19	(< 0.5)
Other indicators				
Antinuclear antibodies	1:100	1:100	Not available	(negative)
Immunoglobulin IgG in g/L	9.31	8.57	9.27	(7-16)
Complement C3 in g/L	1.46	1.32	1.39	(0.8-1.8)
Complement C4 in g/L	0.67	0.39	0.51	(0.1-0.4)
Erythrocyte sedimentation rate in mm/h	20	21	25	(0-15)
High sensitivity C-reactive protein in mg/L	5.52	6.43	6.83	(0-5)
Interleukin 6 in pg/mL	2.72	3.56	2.98	(0.1-2.9)
Tumor necrosis factor α in pg/mL	2.07	2.97	3.12	(0.1-23)
T lymphocyte (CD3 + CD19 -) as / μL	830	977	780	(955-2860)
B lymphocyte (CD3 + CD19 -), as / μL	62	84	52	(90-560)
Proteinuria	negative	negative	negative	(negative)
Antineutrophil cytoplasmic antibody	negative	negative	negative	(negative)

Procalcitonin	< 0.05	< 0.05	< 0.05	(< 0.05)
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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 2), 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 the lower limb revealed infiltration of the suspicious cells with a signet-ring appearance cells and gland-like structures (Figure 3A-C). Biopsy specimens of the lesions showed reactive epithelial changes [pan-cytokeratin (panCK) positive] (Figure 3C). Because the gastrointestinal tract is the most common source of SRCC, a gastrointestinal endoscopic examination (Figure 3D and E) was subsequently performed. The results showed multiple gastric ulcers without solid neoplasm (Figure 3D and E). However, biopsies of both the body and antrum gastric mucosa showed infiltrating signet ring cell type adenocarcinoma (Figure 3F and G), which were very strongly panCK positive (Figure 3H and I) 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 SRCC, 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 August 21 to September 2, 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 5 mo, he received another five cycles of chemotherapy.

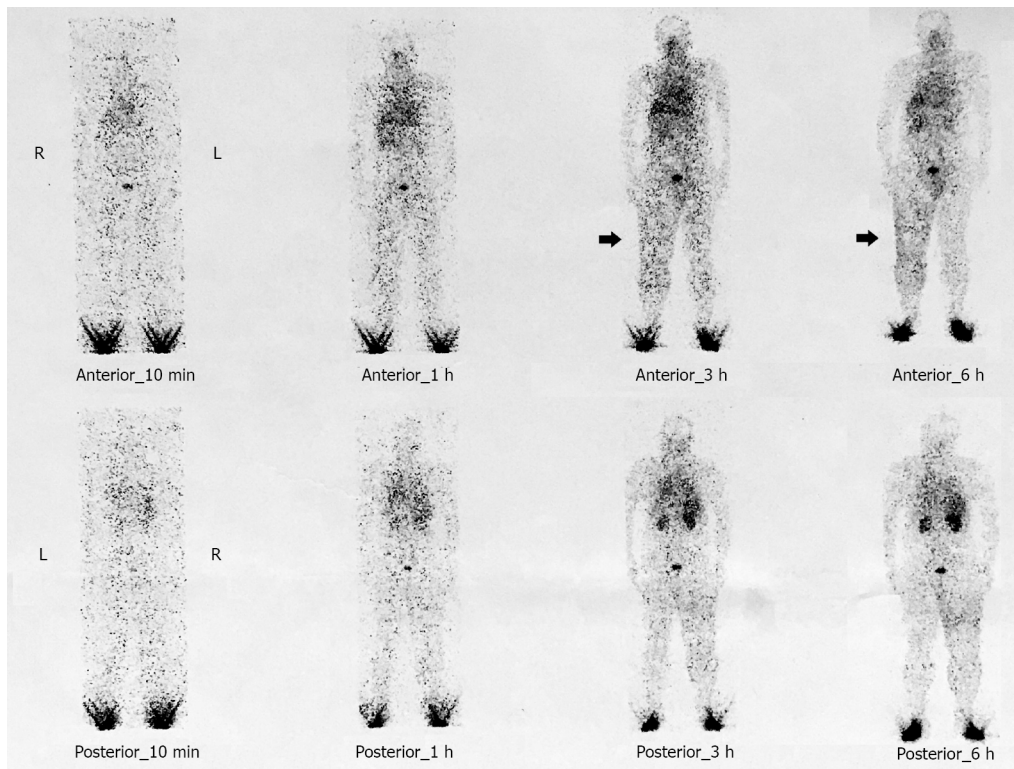
OUTCOME AND FOLLOW-UP

At the 3-mo visit, his limb edema had worsened. By the 12-mo visit, edema had spread from the lower limbs to the entire body (Figure 1), and the patient presented with newly diagnosed polyserous effusions (thoracic cavity, abdominal cavity and pericardium). After 6 mo 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 SRCC. 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 SRCC 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



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Figure 2 99mTc-DX lymphoscintigraphy. Images were recorded 10 min, 1 h, 3 h, and 6 h after infusion with the 99mTc-DX indicators at both feet. Lymphoscintigraphy showed an obvious accumulation of the radiotracer both the anterior and posterior sides of the right leg.

publication of small series or case reports. The first thorough review of a 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 SRCC and cutaneous metastases”. The data of publication ranged from 1989 to 2022. There were a total of 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 and 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).

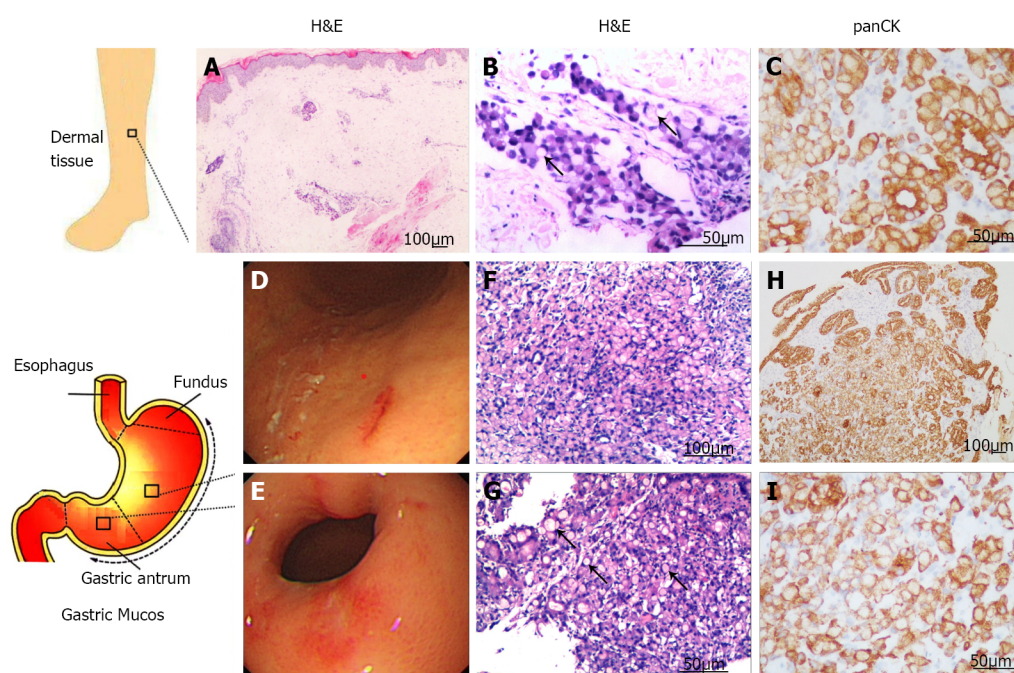
In the review by Cesaretti *et al*[13] in 2014, 80% of the patients received a management approach ranging from local excision to chemotherapy or chemoradiation therapy to treat their cutaneous metastases. In our review, 16 patients were treated with chemotherapy (11/16), chemoradiation therapy (1/16), 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.

Table 2 Gastric signet ring cell adenocarcinoma

Patients	Sex/age	Sites of skin involvement	Initial present symptoms	Stage	Follow-up	Management	Ref.
1	Male/67	Nodular lesions on his eyelid, cheeks, scalp, and back	Weight loss of 8 kg within 1 mo	Not available	DOD 3 mo after skin	XELOX chemotherapy (oxaliplatin and capecitabine)	[23]
2	Male/69	On forehead, back, neck, and arms	Dysphagia from eating and multiple cutaneous nodules	Not available	DOD 1 mo after skin	Surgery	[24]
3	Female/53	On abdomen and thighs	Livedo reticularis	Not available	DOD 7 mo after skin	Chemoradiation	[25]
4	Female/72	Skin infiltration in the lower limbs, abdomen, and root of the upper limbs	Lymphangitis	Stage IIIa	DOD 5 mo after skin	Adjuvant chemotherapy with capecitabine + oxaliplatin	[26]
5	Female/75	On the abdomen	Indurated scarlike lesions on the epigastric area	Stage IIIa (T4aN1M0)	DOD 3 mo after skin	Chemotherapy (5-fluorouracil, infusional folinic acid, and oxaliplatin)	[27]
6	Female/57	On the abdomen	With growing lesions on skin	Stage IIIa (T3N2M0)	Not available	Adjuvant chemotherapy [infusional folinic acid + 5-fluorouracil] and radiotherapy, a second round of chemotherapy	[20]
7	Female/45	On head and the back	The cutaneous metastases disappeared		Survival	Chemotherapy with S-1 (Tegafur) plus cisplatin	[28]
8	Male/52	Armpits, axillae, groin, and neck folds	Progressive dermal, mucosal, and perianal lesions, weight loss	T3N2M1	Not available	N/A	[18]
9	Male/21	Cutaneous nodule on his chest	Cutaneous nodule	Stage IV	Survival	Chemotherapy with oxaliplatin (day 1) and S-1	[29]
10	Male/85	A lesion of the right occipital scalp	Abdominal pain, malaise	T4N1M0	DOD 5 mo after skin	Not available	[30]
11	Male/35	Cutaneous nodules on the upper chest, abdomen and left scapular region	Without any local or general clinical symptoms	Not available	Not available	Not available	[15]
12	Male/76	Skin ulcer on right hypochondrium	Hematemesis, weight loss and loss of appetite	T4N2M0	DOD 1 mo after skin	Chemotherapy with irinotecan and oxaliplatin	[16]
13	Female/50	Large erythematous plaque on the left side of the neck; and an erythematous lesion in the perineal region	Bowel habit and weight loss	Not available	DOD 0.5 mo after skin	Not available	[31]
14	Male/59	Painless nodule of the left flank	Painless nodule of the left flank	Not available	DOD 0.5 mo after skin	Metastatic infiltration of a 32-yr-old surgical scar	[32]
15	Male/50	The umbilical area	With a single asymptomatic skin lesion	Not available	Not available	Not available	[19]
16	Male/69	Asymptomatic indurated scar-like lesion	Asymptomatic indurated scar-like lesion	Stage IV	DOD 10 mo after skin	Chemotherapy with cisplatin, Taxotere, and xeloda	[33]
17	Female/71	Limited cyan erythema on the right side of the middle and lower abdomen	Abdominal skin	Not available	DOD 12 mo after skin	Chemotherapy (unknown medication)	[34]
18	Male/48	Bracelet bracelet ("tripe palm"); and hyperkeratosis of fingers	Skin edema with pigmentation	Not available	DOD 36 mo after skin	Chemotherapy with cisplatin, 5-fluorouracil and folic acid	[35]
19	Male/44	Multiple cutaneous eruptions on face and neck	Vomiting and weight loss	Not available	N/A	Not available	[17]
20	Male/51	Abdominal and back	Without any symptom	Not available	DOD 2 mo after skin	Surgery	[36]
21	Male/67	Diffuse erythematous and warm induration over his right cheek	Dyspepsia	Stage IV	DOD 0.75 mo after	Radiotherapy	[37]

		and neck			skin		
22	Male/55	Lower part of face and neck	With multiple itchy nodules	Not available	DOD 7~8 mo after skin	Not available	[21]
23	Female/58	Right inguinal erythema with itching	With chylothorax	Not available	DOD 4 mo after skin	Not available	[38]
24	Male/44	On the face, trunk, and upper extremities	Multiple cutaneous nodules	Stage IV	Survival	Chemotherapy with an oxaliplatin-based regimen and denosumab	[39]
25	Male/68	Right chin region and on the left forehead	Erythematous skin lesion, nodular skin lesion	T4N0M0	Not available	Surgical treatment	[40]

DOD: Dead of disease; N/A: Not applicable.



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Figure 3 The immunohistochemistry and gastric endoscopy. A: H&E histological samples of the skin tissue on the right lower limb, 10 ×; B: H&E histological samples of the skin tissue on the right lower limb, 20 ×; C: Histological samples of the skin tissue on the right lower limb stained for panCK, 20 ×; D: Images of gastric endoscopy: Gastric body; E: Images of gastric endoscopy: Gastric antrum; F: H&E histological samples of the mucosa in gastric body, 10 ×; G: Gastric antrum, 20 ×; H: Histological samples of the mucosa in gastric body stained for panCK, 20 ×; I: Gastric antrum, 20 ×. Note the abundant signet-ring cells (black arrows) (B) and (G). H&E: Hematoxylin and eosin; panCK: Pan-cytokeratin.

Because carcinomas generally spread preferentially *via* the lymphatic route and gastrointestinal tumors are known to spread to lymph nodes or lymph-vessels, in this case, it is hypothesized that an aggressive clone of signet cell gastric carcinoma metastasized to the lymph-vessels and then, by making a blockage of lymph-vessels, 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 calculating 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 on a case of skin metastases from gastric SRCC 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.

FOOTNOTES

Author contributions: Wang B wrote the manuscript; Chen J and Wang Y diagnosed and treated the patient; Dong LL collected associated references; Shen GF commented on the manuscript and all authors discussed the results, read and approved the manuscript.

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