



LOWER LIMB EDEMA CAUSED BY METASTATIC SIGNET RING CELL STOMACH CANCER

Dany Cruz, Catarina Pinto Silva, Cristina Marques, Francisca M. Pereira, Alexandra Leitão, Ana Ogando

Internal Medicine Department at Hospital Santa Maria Maior, Portugal

Corresponding author: Dany Cruz e-mail: danycamposcruz@gmail.com

Received: 04/03/2023 Accepted: 12/03/2023 Published: 07/08/2023

Conflicts of Interests: The Authors declare that there are no competing interests.

Patient Consent: Informed consent was obtained from the patient.

This article is licensed under a Commons Attribution Non-Commercial 4.0 License

How to cite this article: Cruz D, Pinto Silva C, Marques C, Pereira FM, Leitão A, Ogando A. Lower limb edema caused by metastatic signet ring cell stomach cancer. *EJCRIM* 2023;10:doi:10.12890/2023_003848.

ABSTRACT

Overall gastric cancer incidence is decreasing, but incidence of gastric signet ring cell carcinoma has been rising. The diagnosis can be challenging. It has a poorer prognosis because it tends to be diagnosed at advanced stages. Lymphedema is a rare presentation. We report a rare presentation of signet ring cell carcinoma in a 49-year old male, with no underlying medical condition. The patient presented with lymphedema of lower limbs, scrotum and abdominal wall.

KEYWORDS

Signet ring cell carcinoma, gastric cancer, paraneoplastic syndrome

LEARNING POINTS

- Signet ring cell carcinoma tends to have an infiltrative behavior. Endoscopic analysis may not lead to any macroscopic finding.
- In highly suspicious cases, endoscopic exploration should be complemented with an endoscopic ultrasound or blind random biopsies.

INTRODUCTION

Despite the decrease in overall gastric cancer incidence, signet ring cell carcinoma incidence has been slowly rising^[1]. In contrast with other gastric cancers, the incidence of signet ring cell carcinoma is higher in females and younger patients^[1,2]. Signet ring cell carcinoma may share typical symptoms with gastric neoplasms, such as abdominal pain, bloating or weight loss, or it may present with nonspecific paraneoplastic manifestations. Signet ring cell carcinoma is associated with more advanced forms of the disease at diagnosis^[1,2]. The stage at diagnosis is believed to be the main prognostic variable^[1].

CASE DESCRIPTION

The patient was a 49-year old male, nonsmoker, with an average alcohol consumption of 10 grams a week. His medical history and family history were unremarkable, without known history of cancer. He was referred by his general practitioner because of limb edema which began inexplicably two months prior to the GP consultation and progressively worsened. Deep vein thrombosis was excluded by Doppler-ultrasound. An asymmetrical indurated lymphedema of the limbs with positive Stemmer sign was identified. He did not report any gastrointestinal symptoms. Two months later, the patient's condition worsened. The lymphedema ascended to the limbs,



scrotum and abdominal wall. A nonspecific adipose and subcutaneous tissue densification of hypogastric regions and of pelvis was the only finding in his CT. Laboratory analyses were normal, except for elevated D-dimers (Table 1).

FEBRUARY 2022	
Haemoglobin (g/dL)	15
White Blood Cells	$6.9 \times 10^3/\text{mm}^3$
Neutrofiles	50.6%
Platelets	$240 \times 10^3/\text{mm}^3$
Urea (mg/dL)	42
Creatinine (mg/dL)	0.75
Electrolytes	
Sodium (mmol/L)	138
Potassium (mmol/L)	5
Chloride (mmol/L)	106
Magnesium (mmol/L)	0.9
Calcium (mg/dL)	9.7
Uric Acid (mg/dL)	5
Total proteins (g/dL)	6.1
Albumin (g/dL)	3.7
ALP (U/L)	52
AST (U/L)	15
ALT (U/L)	12
GGT (U/L)	28
Cholesterol (mg/dL)	
Total	167
HDL	59
LDL	94
Pro-BNP (pg/mL))	74.2
TSH ($\mu\text{UI/mL}$)	1.32
Free T4 (ng/dL)	0.99
Immunoglobulins (mg/dL)	
IgA	154
IgG	1087
IgM)	71
C Reative Protein (mg/dL)	0.56
Sedimentation Rate (mm)	10
Antinuclear antibodies ANCA)	Negative Negative
Prothrombin Time (seconds)	11.7
INR	1.02
aPTT (seconds))	25.5
D-dimers	2.20 $\mu\text{UI/mL}$
Homocysteine (mmol/L)	7.3
Antithrombin III function (U/mL)	0.87
Lupic inhibitor	Negative
C Protein Function (U/mL)	0.75
S Protein Function (U/mL)	1.09
Activated C Protein Resistance	2.74
Plasmatic Viscosity (25°C)	3.40 cps
Sedimentation Rate (mm)	10

Table 1. Laboratory analysis (in bold are highlighted the altered results). ALT - Alanine transaminase; ALP - Alkaline Phosphatase; ANCA - Antineutrophil Cytoplasmic Antibodies; aPTT - Activated Partial Thromboplastin Time; AST - Aspartate aminotransferase; GGT - Gamma-glutamyl transferase.

Autoimmune and prothrombotic tests were negative. He was sent to the emergency department. A CT angiography was performed and no signs of thrombotic events or compression of structures were found. Nonetheless, imaging revealed small paratracheal, aortic and perihilar adenopathies and lesser gastric curvature nonspecific adenopathies, with a dominant adenopathy of 19x15 mm. The patient was admitted for further analyses.

Nephrologic, liver and thyroid diseases were excluded. Heart failure was also excluded and a transthoracic echocardiogram was normal. Doppler examination of limbs and CT angiography of major vessels found no obstruction or thrombus. Because of the dominant perigastric adenopathy he underwent an abdominal MRI and upper gastrointestinal endoscopy that were both normal. To this time, all analyses were negative, except for persistent elevated D-dimers (Table 2) and elevated blood viscosity. Prophylactic anticoagulation with enoxaparin was initiated and maintained during his stay. The treatment was discontinued on discharge.

	1st APPOINTMENT	ER	DISCHARGE
D-Dimers ($\mu\text{UI/mL}$)	2.20	3.23	1.21

Table 2. Evolution of D-dimers through the first appointment, the first admission in the Emergency Room (ER) and the first time he was discharge, all before the first thrombotic event.

One week later, he underwent further examination in an ambulatory setting, and again a clinical worsening was evident. The lymphedema had worsened and a new painful left cervical tumefaction was evident. A CT angiogram revealed left jugular vein thrombosis and bilateral segmental pulmonary thromboembolism. A pre-carinal adenopathy of 15mm and a discreet and irregular parietal thickening of gastric fundus were evident in the venous phase of contrast injection - elements which were not evident in previous scans (Figure 1). Anticoagulation with enoxaparin was restarted, but in therapeutic dose. The persistent elevation of D-dimers and evidence of thrombotic events were interpreted in the context of a paraneoplastic syndrome. Because of gastric fundus thickening, even though the endoscopy was normal, an endoscopic ultrasound was made, that revealed an infiltrative lesion of 5 mm in depth in the small curvature of the stomach with mucosal, submucosal and muscularis propria involvement (Figure 2), and multiple perigastric adenopathies. These elements are suggestive of gastric neoplasia with ganglion involvement. Multiple tissue samples were taken and biopsies revealed poorly cohesive signet ring cell carcinoma. The PET-scan with F18-FDG did not show any hypermetabolic intensification suggestive of high metabolic neoplastic lesion in activity. The carinal adenopathy was biopsied via endobronchial ultrasonography. The cytologic examination was consistent with signet ring cell carcinoma. A diagnosis of advanced signet ring cell carcinoma was made. The patient was referred to Oncology and General Surgery.

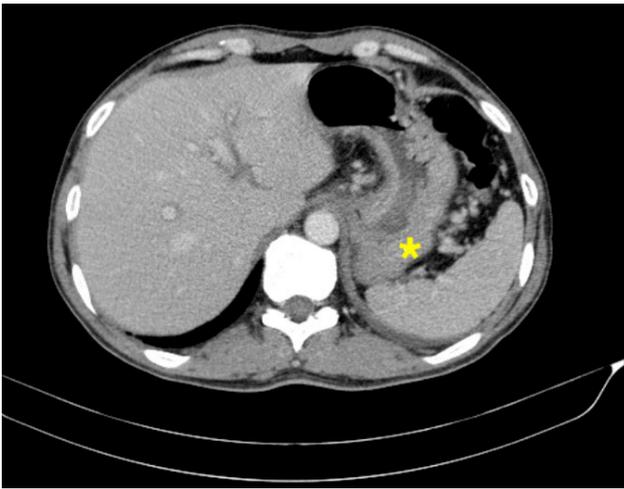


Figure 1. Gastric wall thickening (*) evident in the venous phase of the CT contrast injection.



Figure 2. Hypoechoic thickening on endoscopic ultrasound suggestive of an infiltrative lesion.

DISCUSSION

Signet ring cell carcinoma is a specific adenocarcinoma of the stomach^[2]. It has a higher rate of regional and disseminated invasion at diagnosis than other gastric cancers^[3].

In patients with cancer, lymphedema is usually a complication of treatment such as lymphadenectomy or radiotherapy, or a result of carcinomatous lymphangitis. In this case, there was no mechanical cause nor history of previous treatment, which made cancer the most probable hypothesis. Cutaneous biopsies would be of interest to confirm lymphogenic dissemination.

Because the first endoscopic study showed no macroscopic abnormalities, no biopsy was made at the time of first admission. Signet ring cell carcinoma tends to have an infiltrative behavior, in contrast to other gastric cancers that usually evolve to present ulcerations. In highly suspicious cases it may be of interest to complement observations with an endoscopic ultrasound or, if not available, with blind random biopsies. Additionally, PET-scans are usually associated with lower FDG uptake, which compromises their overall sensitivity and increases the rate of false negatives. This increases the complexity in analyzing findings and hinders the diagnosis approach.

The first time the patient was discharged he had persistently

elevated D-dimers and increased blood viscosity, but no documented vascular thromboembolic events. There is no consensus about the timing to start prophylactic anticoagulation in patients with paraneoplastic syndromes and without thromboembolic events while the primary cause is still occult. The authors defend that anticoagulation could be initiated at that moment, but an individual decision must be made for each patient.

While writing this report, we only found two similar cases in which a clinical association between lymphedema and gastric signet ring carcinoma has been made^[4].

REFERENCES

1. Pernet S. Signet-ring cell carcinoma of the stomach: Impact on prognosis and specific therapeutic challenge. *World Journal of Gastroenterology*. 2015;21:11428.
2. Taghavi S, Jayarajan SN, Davey A, Willis AI. Prognostic significance of Signet Ring Gastric Cancer. *Journal of Clinical Oncology*. 2012;30:3493–8.
3. Raval N, Shmuylovich L, Strickley J, Chen TY, Rosman IS, Musiek A. Signet-ring cutaneous metastasis presenting with massive anasarca. *JAAD Case Reports*. 2021;10:123–5.
4. da Souza B, Bonamigo RR, Viapiana GL, Cartell A. Signet ring cells in carcinomatous lymphangitis due to gastric adenocarcinoma. *Anais Brasileiros de Dermatologia*. 2020;95:490–2. doi:10.1016/j.abd.2019.12.004