



ONCOLOGY

# Signet ring cell gastric carcinoma with breast and leptomeningeal metastases: a case report

Tiberiu Rareș Moldovan<sup>1</sup>, Călin Căinap<sup>1,2</sup>, Zsolt Fekete<sup>1,3</sup>, Emil Pușcaș<sup>1,2</sup>, Andrei Roman<sup>1,4</sup>, Rareș Buiga<sup>1,5</sup>, Diana Olteanu<sup>1</sup>, Mădălina Bota<sup>6</sup>, Simona Căinap<sup>6</sup>, Ovidiu Bochiș<sup>1</sup>

1) “Prof. Dr. Ion Chiricuță” Oncology Institute, Cluj-Napoca, Romania

2) Oncology Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

3) Oncology - Radiotherapy Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

4) Medical Radiology Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

5) Pathology Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

6) Mother and Child Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

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Address for correspondence:  
fekete.zsolt@umfcluj.ro

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## Abstract

Gastric cancer is the 5<sup>th</sup> most common malignancy worldwide. Signet ring cell histology represents an aggressive subtype of gastric cancer, presenting at a younger age. Both breast and leptomeningeal metastases are rare locations of tumor dissemination, requiring correct and immediate diagnosis and treatment. We present a case of a 45-year old female with signet ring cell gastric carcinoma who developed both left breast and leptomeningeal metastases, requiring multiple chemotherapy lines. As far as we know, this is the first published case in literature following multiple lines of treatment for both breast and leptomeningeal metastases from signet ring cell gastric carcinoma.

**Keywords:** gastric cancer, breast metastasis, leptomeningeal carcinomatosis

## Introduction

In 2018, gastric cancer was the 5<sup>th</sup> most common malignancy worldwide [1].

Neither breast metastases from extramammary neoplasms (0.5 – 2% of all mammary malignancies [2]), nor leptomeningeal carcinomatosis (LMC) from gastric cancer (0.16 – 0.69% of patients [3]) have standard treatment protocols at present.

This pattern of metastasis (breast and leptomeningeal carcinomatosis) is extremely rarely reported. So far, a single case of breast metastasis and leptomeningeal carcinomatosis from gastric adenocarcinoma has been reported.

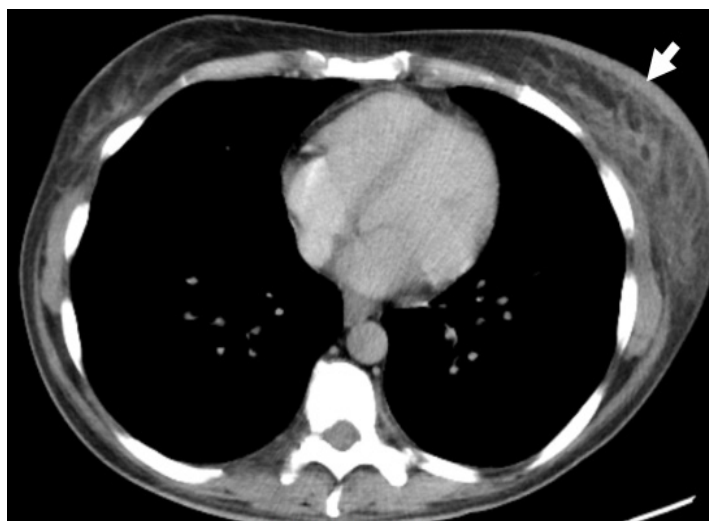
## Case presentation

A 45-year old female was admitted to our clinic after a modified Pap test during a routine health screening. Additionally, the patient presented diffuse inflammatory changes with skin thickening of the left breast, without any visible mass on mammography and ultrasonography.

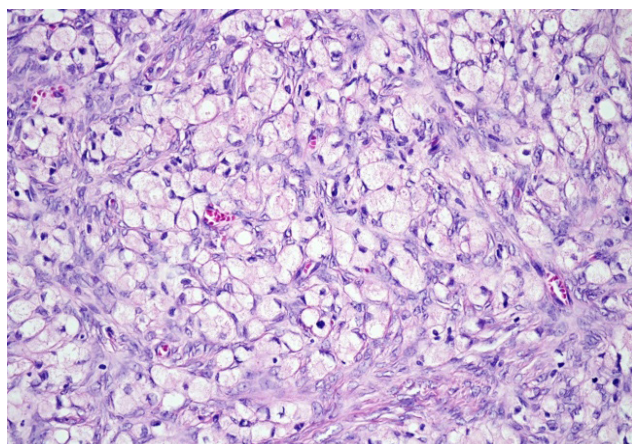
The patient had no relevant medical history. Physical examination revealed only diffuse left breast induration with uneven surface

Bilateral ovarian masses were detected during a computed tomography (CT) together with inflammatory changes in the left breast (Figure 1). An ovarian cancer suspicion was raised and total hysterectomy with bilateral oophorectomy was performed. During the surgery, an unresectable gastro-pancreatic mass, as well as peritoneal carcinomatosis were detected.

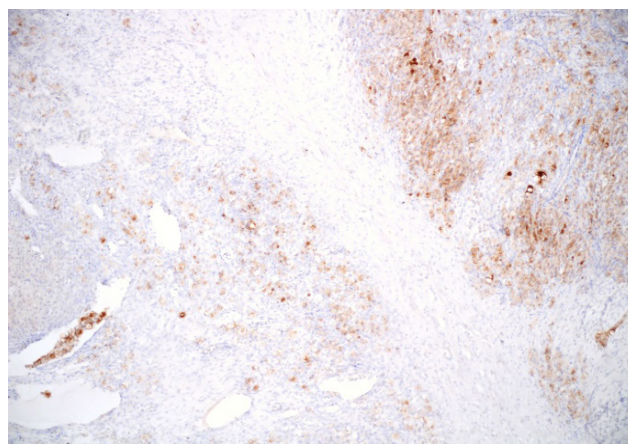
The pathological examination showed diffuse ovarian infiltration of a poorly differentiated signet ring cell carcinoma (Krukenberg tumor), most probably of gastric origin. Immunohistochemical analysis showed positive staining for cytokeratin 7 (CK7), epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA) and negative for estrogen and progesterone receptors and Wilms tumor suppressor gene (WT1) (Figure 2, A and B).



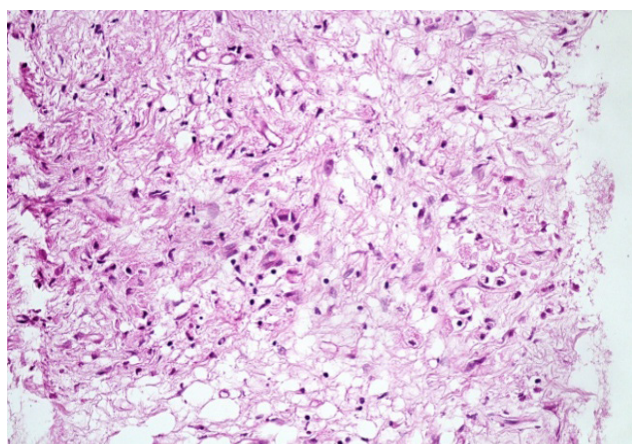
**Figure 1.** Inflammatory left breast changes detected on CT scan (indicated by the white arrow).



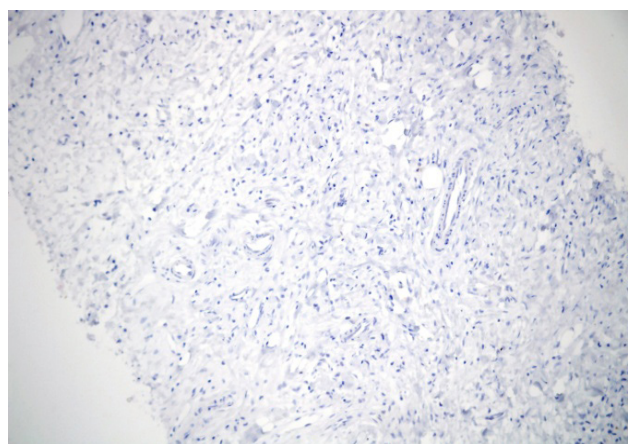
**A.** Signet ring cells in ovaries.



**B.** Positive CK7 staining on IHC.

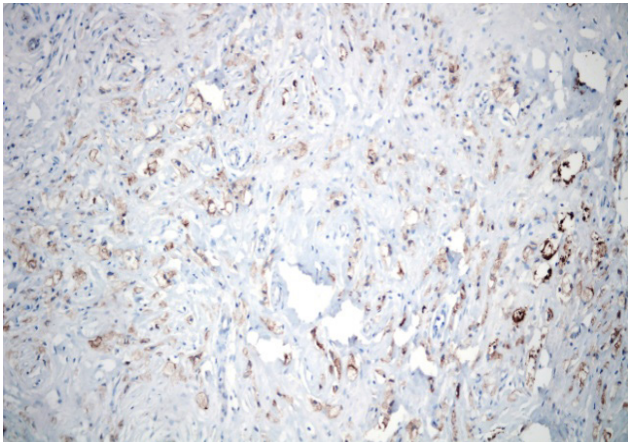


**C.** Signet ring cells in breast biopsy.

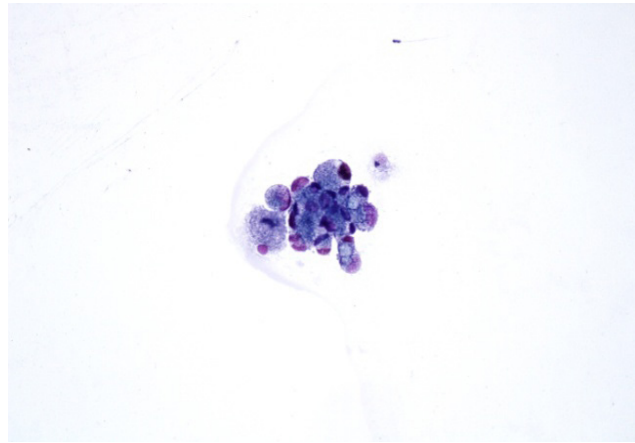


**D.** Negative estrogen receptors on IHC.

**Figure 2 A-D.** Histological examinations of ovaries (A, B) and breast (C, D, E).



E. Positive CK staining on IHC.



F. Signet ring cells in cerebrospinal fluid.

**Figure 2 E-F.** Histological examinations of breast (C, D, E) and cerebrospinal fluid (F).

An upper gastrointestinal endoscopy was performed in order to identify the primary site and detected a circumferential cardia tumor. Biopsies were taken, revealing the same histology as before, namely poorly differentiated signet ring cell gastric carcinoma.

Based on these findings, we established a diagnosis of a gastric signet ring cell carcinoma with peritoneal carcinomatosis, metastasized to the ovaries and bones and first metastatic line of chemotherapy with epirubicin 50 mg/m<sup>2</sup>, oxaliplatin 130 mg/m<sup>2</sup> and capecitabine 1250 mg/m<sup>2</sup> q21d was initiated. After 6 cycles of chemotherapy and clinical stable disease, the patient continued with oxaliplatin 130 mg/m<sup>2</sup> and capecitabine 2000 mg/m<sup>2</sup>.

Progressively, the left breast inflammation worsened and a biopsy was performed which established signet ring cell infiltration (Figure 2 C,D,E). Also, the disease progressed with left pleurisy with pulmonary atelectasis and second metastatic line of chemotherapy with paclitaxel 80 mg/m<sup>2</sup>, q7d, in association with ramucirumab 8 mg/kg, q14d was started.

Third metastatic line with irinotecan 180 mg/m<sup>2</sup>, q14d was started due to anaphylaxis to paclitaxel and persistent inferior digestive bleeding caused by ramucirumab. After a couple of months, persistent headaches and diplopia developed, without any signs or cerebral CT and magnetic resonance imaging (MRI). A spinal tap was performed with normal cerebrospinal fluid (CSF) pressure and appearance. Only the lactate dehydrogenase (LDH) level was elevated (21 IU/l), raising the suspicion of a cerebrospinal dissemination. CSF cytology revealed 4 nucleated cells/mm<sup>3</sup> with signet ring aspect, confirming the diagnosis of LMC (Figure 2F).

Intrathecal methotrexate (12 mg, q2d) and fourth line of chemotherapy with docetaxel 60 mg/m<sup>2</sup>, q21d were started with a visible improvement of neurological

symptoms. After 6 doses of methotrexate (MTX) q2d we continued the administration on a weekly basis.

For 7 months, a clinically stable disease was maintained, with a total of 21 MTX cycles. We repeated a CSF cytology every month, with varying number of signet ring cells (from 0 to 5).

Neurological symptoms reappeared, with grade 4 thrombocytopenia. Despite palliative treatment, the patient's status progressively declined and the patient ultimately deceased, 20 months after the diagnosis of signet ring cell gastric cancer, 13 months after breast metastasis and 7 months after the diagnosis of LMC.

### Discussion

In 2018, gastric cancer was the 5<sup>th</sup> most common type of cancer worldwide. In the same year, gastric cancer had the 3rd highest mortality [1]. In recent decades, despite a decrease in the overall incidence of gastric cancer, signet ring cell gastric carcinoma (SRCC) has had a constantly increasing incidence, accounting for 35% to 45% in recent studies [4]. SRCC usually occurs in younger patients, with a mean age of onset between 55 and 61 years.

The breast is an uncommon site of metastasis from an extramammary neoplasm (including gastrointestinal malignancies), representing 0.5 – 2% of all mammary malignancies [2].

Median age of diagnosis is 46 years [5]. Our patient was diagnosed at 45 years, which confirms the younger age of occurrence for breast metastasis from gastric carcinoma.

Breast biopsy should be performed even in the presence of an extramammary neoplasm. Histologic similarities between the primary and breast lesion need to exist for a definitive diagnosis [6].

A breast lumpectomy is currently the recommended treatment in case of nodular breast metastases [7]. In our case, breast metastasis mimicking mastitis delayed our diagnosis until the primary disease disseminated, warranting only systemic chemotherapy, with no local treatment.

Breast metastasis from gastric carcinoma has a poor overall prognosis, more than 80% of patients dying within one year [8]. Our patient had an overall survival of 13 months.

LMC represents a very rare complication of gastric cancer, occurring in 0.16 – 0.69% of patients. The time from gastric cancer to LMC diagnosis is approximately 12 months [3]. Our patient was diagnosed with LMC 12 months after the signet ring cell carcinoma diagnosis.

Due to the fact that tumor cells gain access to every level of the neuraxis, patients with LMC may present with a variety of signs and symptoms (nausea, vomiting, headaches, diplopia).

The diagnosis of LMC is usually established by clinical presentation, imaging techniques and CSF cytology. The presence of malignant cells in CSF is mandatory for the positive diagnosis of CSF. In our case, a positive diagnosis of LMC was made after the first CSF cytology detected signet ring cells.

If untreated, the median survival of patients is 4 – 6 weeks, and 2 – 4 months with therapy [10]. Our patient's overall survival was 7 months after the diagnosis of LMC.

The benefit achieved by IT chemotherapy in LMC is debatable. Despite limited success and serious adverse effects, the most commonly utilized drug for IT therapy remains MTX [10].

In our case, we opted for a dose dense IT MTX due to the fact that the patient had no other comorbidities, with a good performance status and in accordance with her wishes, in association with fourth line of metastatic chemotherapy.

The presence of both breast metastases and LMC in signet ring cell gastric carcinoma is extremely rare. A single case [5] has been reported in literature of this specific polymetastatic context. In that case, the patient developed LMC after 10 months from the diagnosis of breast metastasis and died, without being able to start any treatment.

### Conclusions

Signet ring gastric cancer may present uncommon and rare metastases (breast, leptomeningeal), prompting the immediate recognition of signs and symptoms and requiring urgent biopsies in order to establish a positive diagnosis.

There is no current standard treatment protocol for breast metastasis from gastric cancer. Primary tumor treatment is essential in case of breast metastases.

At present there are no established guidelines for the diagnosis and treatment of signet ring cell gastric carcinoma with leptomeningeal carcinomatosis. IT chemotherapy remains the mainstay of treatment.

To our knowledge, this is the first published case of a signet ring cell gastric carcinoma patient treated for breast metastases and leptomeningeal carcinomatosis.

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