

Gastric metastases from gynaecologic tumors: case reports and review of the literature

Angelo Zullo¹, Giuseppina Balsamo², Roberto Lorenzetti¹, Adriana Romiti³, Vincenzo De Francesco⁴, Cesare Hassan¹, Raffaele Manta⁵

¹Gastroenterology Unit, Nuovo Regina Margherita Hospital, Rome, Italy; ²Pathology Unit, Santo Spirito Hospital, Rome, Italy; ³Oncology Unit, Sant'Andrea University Hospital, Rome, Italy; ⁴Gastroenterology Unit, Riuniti Hospital, Foggia, Italy; ⁵Gastroenterology Unit, Nuovo Ospedale Civile Sant'Agostino-Estense, Baggiovara-Modena, Italy

Correspondence to: Dr. Angelo Zullo. Gastroenterologia ed Endoscopia Digestiva, Ospedale Nuovo Regina Margherita, Via Emilio Morosini 30, 00153 Roma, Italy. Email: angelozullo66@yahoo.it.

Abstract: The stomach is an infrequent localization of tumor metastases, and metastases originating from primary gynaecological cancers are particularly rare. We described the case of three females with ovarian, uterine, and breast metastases in the stomach, and we performed a systematic review of the literature of cases diagnosed at endoscopy. Overall, data of 18 patients with gastric metastases originating from the ovary, 11 from the uterus, and 159 from breast cancer were analyzed. Therefore, gastric metastasis mainly occurs from breast cancer, whilst both ovarian and uterine metastases are distinctly less frequent, but not impossible.

Keywords: Gastric metastasis; uterine cancer; ovarian cancer; breast cancer; endoscopy

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Introduction

The stomach is an infrequent localization of tumor metastases. In three large autopsy series an incidence rate as low as 0.54–1.7% has been found (1–3). An even lower frequency (0.2%) has been reported at clinical-endoscopic studies (4). It has been stated that gastric metastases predominantly arise from malignant melanoma, followed by lung and breast cancer (3,5). On the contrary, both ovarian and uterine metastases in the stomach are extremely infrequent. Clinical and endoscopic features of gastric metastases are nonspecific and this, together with their low frequency, contributes to a scarce knowledge among endoscopists on such a clinically relevant entity. Moreover, it has been found that even the biopsy sampling of endoscopically detected gastric lesions may be unsuccessful for an appropriate histological definition, gastric metastases no rarely sparing the mucosal layer. In addition, some metastatic tumors may mimic a primary gastric cancer, at both endoscopic and histological assessment. For instance, invasive lobular carcinoma of

the breast may resemble to gastric signet ring cell carcinoma (6). It is intuitive that a correct distinction between primary and metastatic gastric carcinoma is extremely important because of the therapeutic approach completely differs. Here, we described the case of three females with either ovarian, uterine, or breast metastases in the stomach observed in a single centre, and we performed a systematic review of the literature.

Case series

Ovarian tumor metastasis

A 49-year-old woman was diagnosed with left-side serous ovarian adenocarcinoma on 2012 when she underwent surgical hysterectomy, with bilateral salpingo-oophorectomy and pelvic lymph node dissection. In addition, adjuvant chemotherapy was administered. The patient was in good condition until July 2014 when she was admitted in Department of Oncology due to abdominal pain, persisting vomiting and weight loss. At

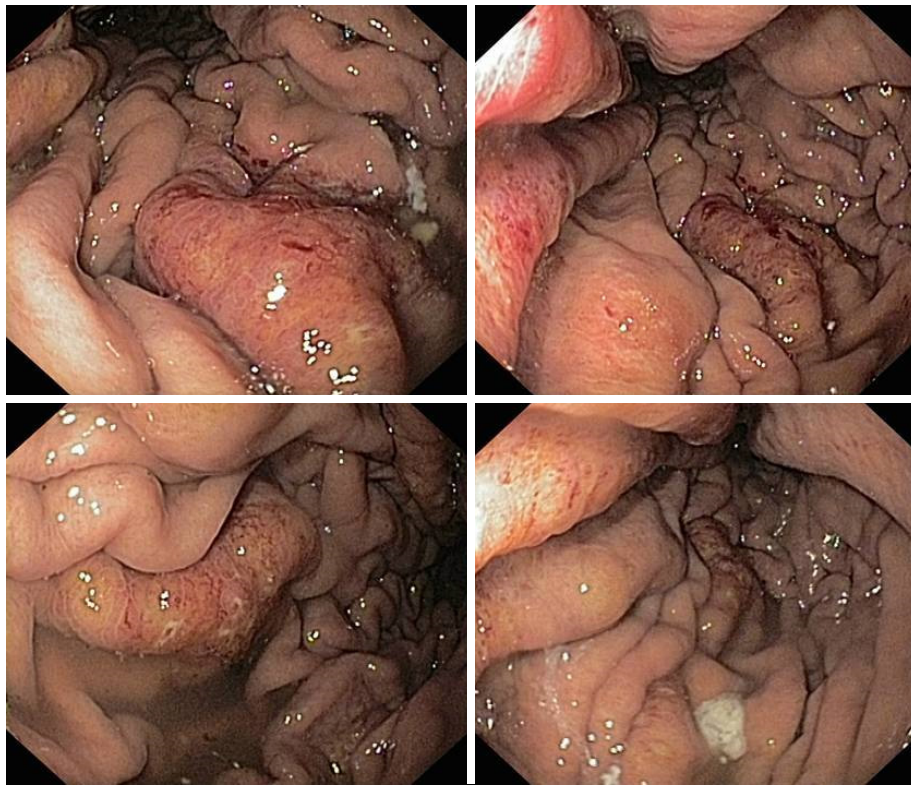


Figure 1 Endoscopic feature of gastric metastasis from ovarian cancer: presence of some irregular, hyperaemic, and enlarged folds in the gastric body mucosa.

upper endoscopy, irregular, enlarged and hyperaemic folds in the gastric body were detected (*Figure 1*), whilst the remaining mucosa was normal until to the descending duodenum. The histological examination of multiple biopsies revealed neoplastic infiltration of gastric mucosa in accordance with a metastatic ovarian cancer (*Figure 2*). At this time, peritoneal carcinosis was also detected, so that the patient received a further chemotherapy, but she died within 4 months.

Uterine tumor metastasis

An 80-year-old woman with diabetes and hypertension underwent total hysterectomy, with bilateral salpingo-oophorectomy and pelvic lymph node dissection 10 years before due to a uterine leiomyosarcoma. She revealed a total thyroidectomy and right colectomy, both for carcinoma, 7 and 5 years before the gynaecological intervention, respectively. Following the colon cancer resection, she also received adjuvant chemotherapy. The patient was referred for upper endoscopy to our Endoscopic Unit

as outpatient due to epigastric pain appeared in the last 3 months. She was receiving thyroid hormone therapy, insulin, a β -blocker, and 100 mg acetylsalicylic acid for primary cardiovascular prevention together with 30 mg lansoprazole as a gastroprotection. At upper endoscopy, multiple submucosal nodules, 7–10 mm in diameter, with apical erosion, localized in the gastric body and fundus and sparing the antral mucosa were observed (*Figure 3*). The histological examination disclosed neoplastic spindle cells infiltrating gastric mucosa with an immunohistochemical pattern compatible with metastatic leiomyosarcoma (*Figure 4*). The patient moved to another hospital so that she was lost at follow-up.

Breast tumor metastasis

A 70-year-old woman, without relevant diseases at personal clinical history, underwent radical left mastectomy with adjuvant chemotherapy. Following 2 months from chemotherapy starting, she complained with dysphagia, particularly for liquids, and epigastric pain.

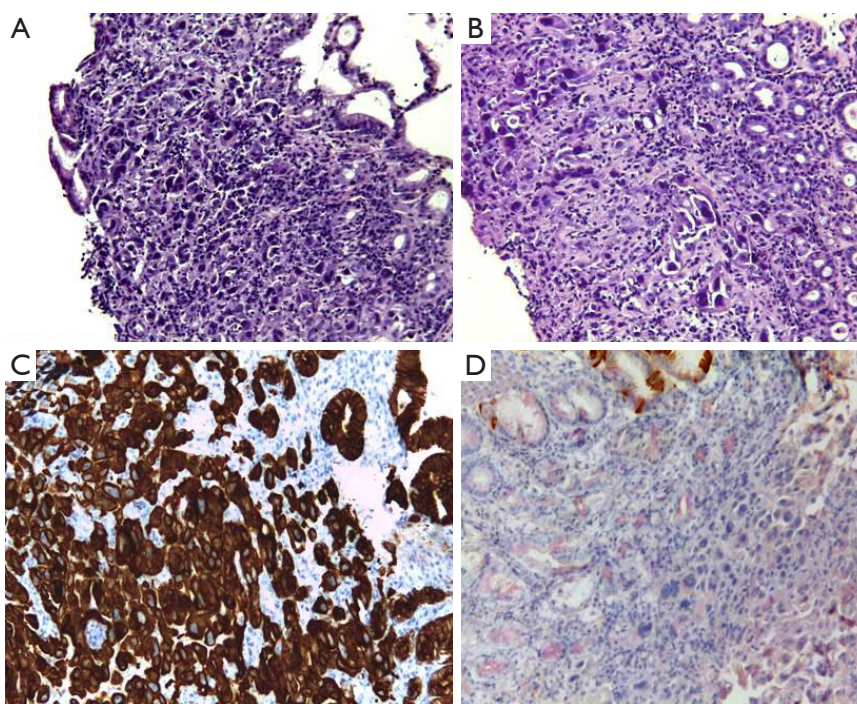


Figure 2 Histological pictures of gastric metastasis from ovarian cancer: neoplastic large cells with hyperchromic nucleus infiltrating gastric mucosa (A) (H&E, ×20) and (B) (H&E, ×40); immunohistochemistry revealed CK7 positivity (C) (×20), and negativity for CK20 (D) (×20).

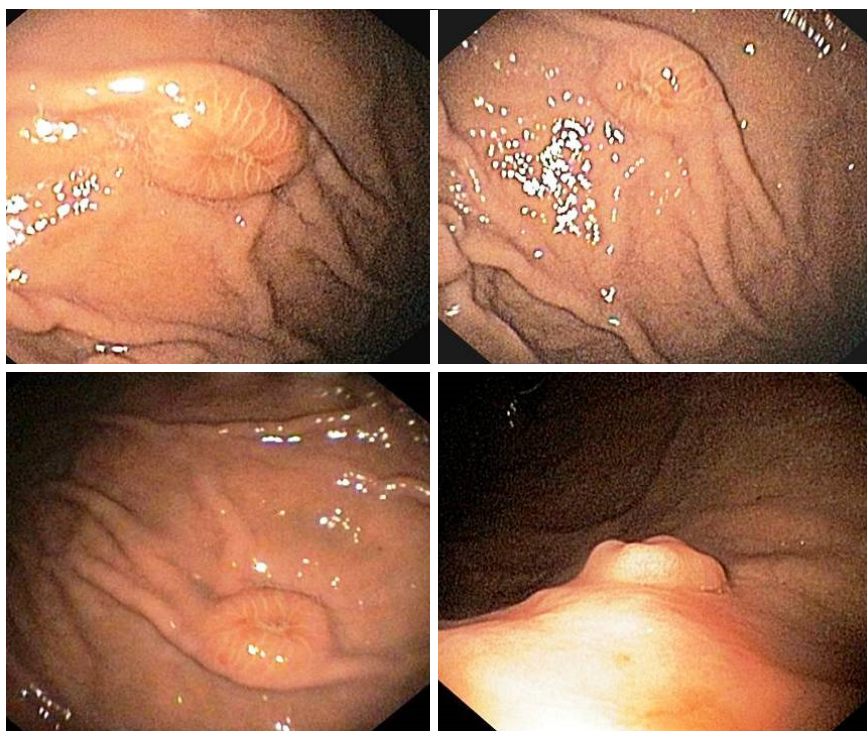


Figure 3 Endoscopic feature of gastric metastasis from uterine leiomyosarcoma. Multiple submucosal nodules with apical erosion localized in the gastric body and fundus.

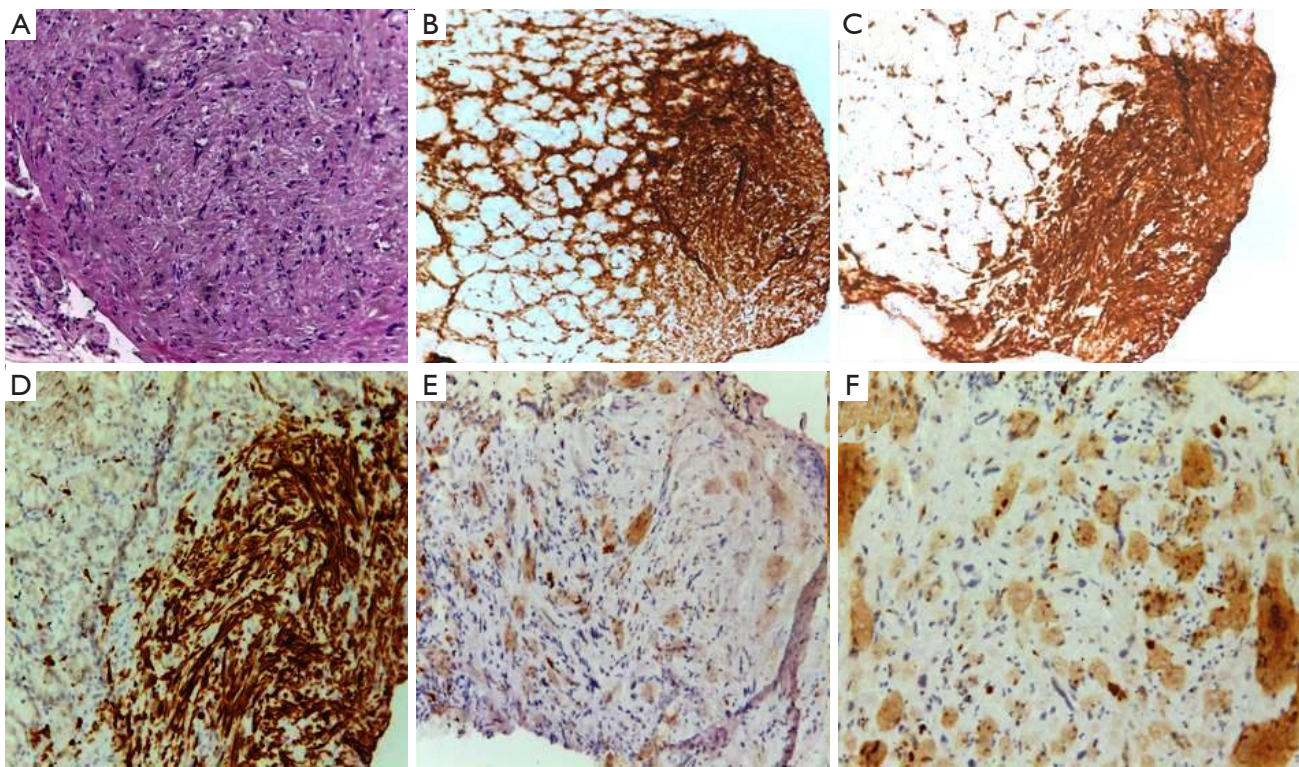


Figure 4 Histological pictures of gastric metastasis from uterine leiomyosarcoma. Neoplastic spindle cells infiltrating gastric mucosa (A) (H&E, $\times 20$); immunohistochemistry found positivity for vimentin (B) ($\times 10$); actin (C) ($\times 10$); and desmin (D) ($\times 10$); with CD117 negativity (E) ($10\times$) and low proliferative index (F) (Ki67, $\times 10$).

Therefore, the patient undergo to upper endoscopy in another Endoscopic Unit, which showed irregular folds in the upper third of the stomach, but the histological examination of biopsies showed only inflammatory infiltration in the gastric mucosa. One month later, she was referred to our Endoscopic Unit for repeating upper endoscopy. We noted a regular oesophageal mucosa, including the cardia, which appeared easily surmountable with the standard endoscope, and we confirmed the presence of irregular fold in the gastric body mimicking linitis plastica (*Figure 5*). Despite several biopsies were taken, the histological examination failed to demonstrate the neoplastic nature of the lesion, revealing only reactive gastritis. Five months later, at the end of six chemotherapy cycles, a further upper endoscopy was performed due persistent epigastric pain without dysphagia. The endoscopic examination was substantially unchanged, and the histological feature eventually showed a metastatic breast cancer in the stomach (*Figure 6*). The patient is on ongoing chemotherapy.

Literature review

Cases of gastric metastasis from primary gynaecologic tumors—including ovarian, uterine and breast cancers—diagnosed at endoscopy and published on PubMed in English language were reviewed. All relevant articles were retrieved, and a manual search of reference lists was performed to identify any additional study that might have been missed.

On 2012, a systematic review of gastric metastasis from ovarian carcinoma was published (7), including a total of 11 case reports. However, 1 out of these case reports was erroneously included, since it was dealing with an ovarian metastasis from primary gastric cancer (8). A successive systematic review of data published between 1970 and 2013, reported a total of 9 cases (4). By selecting only different patients from the first review (10 cases) (8), the second review (3 cases) (4), and by adding further case reports published thereafter we retrieved (4 cases) (9-12), and our case report, a total of 18 patients with gastric metastases from ovarian cancer have been published. Further 3 cases were included

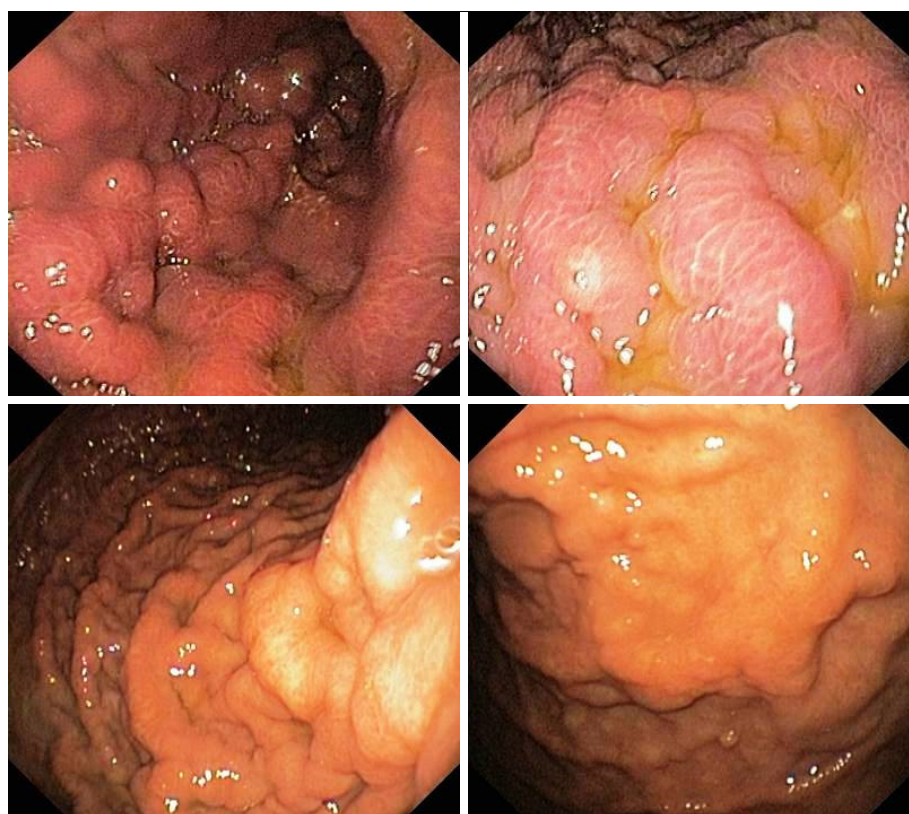


Figure 5 Endoscopic feature of gastric metastasis from breast cancer: irregular and enlarged folds in the upper stomach mimicking linitis plastica.

in a study of metastases in the stomach arising from different primary tumors, but no details were specifically provided for those patients with gynaecologic metastases (3).

Overall, the mean age at metastasis diagnosis was 58.8 years (range, 41–73 years), and the median interval between the primary tumor and the diagnosis of the metastatic tumor in the stomach was 32 months (range, 14–84 months), whilst 2 patients had synchronous gastric metastases. The metastases were localized in the antrum in 13 (72%) cases and in upper two third of the stomach in remaining 5 cases. At endoscopy, the metastasis presented as submucosal mass (with or without apical erosion) in 11 (61%) cases, ulcer in 2 cases, and enlarged folds in 1 patient. The main presenting symptoms were anaemia/haemorrhage (4 cases), vomiting (2 cases), perforation (1 case), and dyspeptic symptoms (6 cases), whilst in 5 asymptomatic patients the metastasis was suspected due to either PET finding or CA-125 elevation at follow-up.

Overall, 5 studies reported cases of gastric metastasis from uterine tumors, including a case series of 4 patients,

2 series with 2 patients, and 2 single case reports (3,13–16). Therefore, by adding our case, a total of 11 patients were described. However, no specific details were provided for the 6 patients included in a retrospective study on gastric metastases of different origin (3,15), and we were unable to retrieve a publication (16). The scanty data available are summarized in *Table 1*.

On 2014, a systematic review on gastric metastases of different origin has been performed, including data of 4 case series and 2 case reports on breast cancer metastases in the stomach, accounting for a total of 95 patients (4). Our literature search found further 13 publications, including 5 case series and 8 case reports, with a total of 63 patients (17–29). Therefore, by adding our case, data of 159 patients with gastric metastasis from breast cancer are available. Overall, the mean age at metastasis diagnosis extrapolated from 136 patients was 47.4 years (range, 35–90 years), and the median interval between the primary tumor and the diagnosis of the metastatic tumor in the stomach was 78 months (range, 33–96 months), whilst 8 patients had

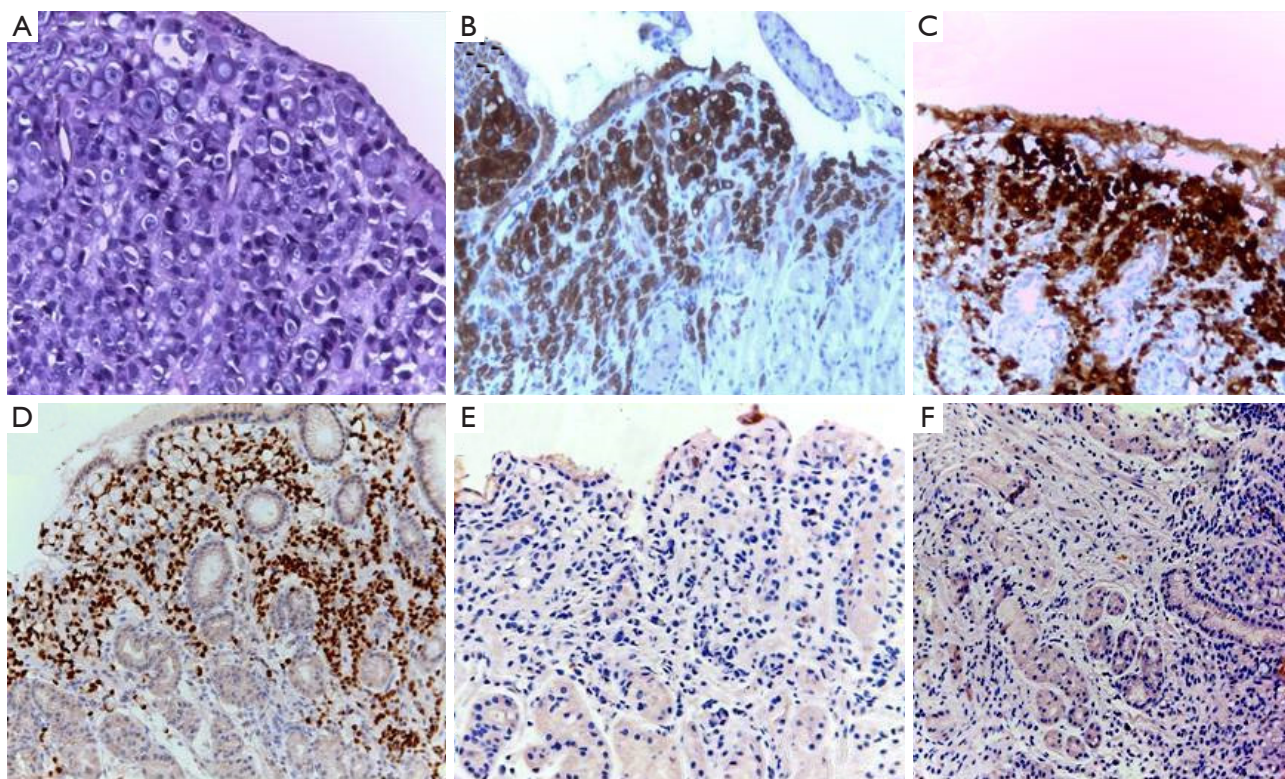


Figure 6 Histological pictures of gastric metastasis from breast cancer. Neoplastic large cells with enlarged nucleolus infiltrating gastric mucosa (A) (H&E, $\times 40$); immunohistochemistry showed positivity for CK7 (B) ($\times 20$); gross cystic disease fluid protein (GCDFP-15) (C) ($\times 20$); and oestrogen receptors (D) ($\times 20$); with both CK20 (E) ($\times 20$) and CDX2 (F) ($\times 10$) negativity.

Table 1 Data on patients with gastric metastasis from uterine tumors

N	Age	Onset	Gastric site	Tumor type	Main symptom	Ref.
1	49	2 years	Antrum	Submucosal	Vomiting	(13)
2	63	ND	Antrum	Linitis plastica	Dysphagia	(14)
3	52	ND	Gastric body	Submucosal	Anaemia	(14)
4	80	10 years	Gastric body	Erosions	Epigastric pain	Our case

synchronous gastric metastases. The metastasis site was available in 100 cases, and the lesions were localized in the upper two third of the stomach in 58 (58%) cases, diffuse lesions in 28 (28%), whilst 14 (14%) patients had the main lesions confined in the antrum. The endoscopic description was available in 58 patients, and the metastasis presented as linitis plastica in 27 (47%), ulceration in 12 (21%) submucosal mass in 8 (14%), multiple erosions in 5 (9%), gastritis in 4 (7%), and as polyps in the remaining 2 patients. The main presenting symptom, extrapolated

from 133 patients, was vomiting (43 cases; 32%), dyspeptic symptoms (42 cases; 31%), dysphagia (28 cases; 21%), anaemia/bleeding (19 cases; 15%), and perforation (1 case).

Discussion

It is known that the stomach represents an infrequent site of tumor metastases (30). In particular, metastases originating from primary gynaecological cancers are particularly rare, although those from the breast appear to be less uncommon (6).

Indeed, the incidence of gastric metastases was 3.6% on 694 patients with breast cancer (7). In addition, the breast cancer was the most prevalent cause of gastric metastases (27%), followed by lung cancer (23%), renal cell cancer (7.6%) and malignant melanoma (7%) in a recent review (4). On the other hand, metastases from gastric cancer to either breast or uterus are exceptional (31,32), whilst, ovarian metastases secondary to gastric cancer—the so called Krukenberg tumor—has been extensively described in the literature (33). Synchronous or metachronous presence of primary gastric cancer and primary gynaecological tumor (ovary, uterus, and breast) has been described in 15 (0.6%) cases out of 2,668 patients with gastric cancer (34). Of note, it has been also found that patients with a personal history of uterine cancer are at 1.38-fold (95% CI: 1.09–1.72) increased risk of developing primary gastric cancer (35). Finally, women with hereditary inactivating mutations in the E-cadherin gene *CDH1* are at increased risk for both gastric cancer and breast carcinoma (6). All these observations would indicate an intriguing link between gastric and gynaecologic organs carcinogenesis.

The present study described 3 new cases of gastric metastases and we reviewed data of literature on such a topic. Overall, we analyzed data 18 patients with gastric metastases from the ovary, 11 from the uterus, and 159 from breast cancer. Gastric metastases from uterine tumors appear to be less frequent. However, an autopsy series on 414 females with primary uterine tumors found a prevalence of 4.6%, a rate comparable with the 4.1% found on 101 patients with ovarian cancer (3). In the same study, the breast metastasis rate was found to be 11.6%.

Based on the detailed data we collected, a reliable comparison is possible only between ovarian and breast metastasis pattern. We found that the mean age at metastasis diagnosis was distinctly lower in breast than in ovarian cancer females (47 *vs.* 59 years), the mean interval for metastasis onset was longer (78 *vs.* 32 months), the gastric lesions were localized more frequently in the upper stomach (58% *vs.* 28%), and the most frequent endoscopic feature was linitis plastica (47%) for breast metastases and submucosal lesions for ovarian metastases (61%). Moreover, the most prevalent symptoms were vomiting (32%) in breast cancer metastasis and dyspeptic symptoms/asymptomatic in the ovarian cancer (61%). Overall, a synchronous gastric lesion was detected in only few cases, whilst in the majority of patients a metachronous metastasis developed, with an onset as long as 33 years in a breast cancer case (27). Of note, a metastatic breast cancer was diagnosed

in patients with an endoscopic feature of “gastritis” (4 cases) or simple “erosions” (4 cases) (21), suggesting the need of adequate biopsy sampling in these patients. In our case, the histological diagnosis of breast cancer metastasis in the stomach was achieved only at third endoscopic sampling, despite the macroscopic suspect of neoplastic lesion. Such a finding is not uncommon, the failure of histological diagnosis on endoscopic biopsies being reported in 8–9% of cases (3,15). Finally, we found that the main lesions of gastric metastases are localized in either gastric body or fundus more frequently than in the antrum.

In conclusion, gastric metastasis mainly occurs from breast cancer. Both ovarian and uterine metastases are distinctly less frequent, but not impossible.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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