

Solitary Gastric Metastasis from a Stage IA Serous Ovarian Carcinoma: A Case Report with Literature Review

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Abstract

Gastric metastasis from ovarian cancer is exceptionally rare and generally occurs in advanced stages. A 71-year-old woman presented with a solitary gastric submucosal mass 8 years after the diagnosis of a stage IA ovarian serous adenocarcinoma. Endoscopy showed a tumor covered with normal gastric mucosa. Initially, a gastrointestinal stromal tumor was suspected, but biopsy revealed a histology of invasive micropapillary carcinoma, similar to the histological findings of the previously resected ovarian tumor. Clinicians should consider that in patients with a submucosal tumor and a history of ovarian cancer, gastric lesions may be secondary metastases from ovarian cancer.

Key words: ovarian cancer, serous carcinoma, gastric metastasis, submucosal tumor, micropapillary carcinoma, gastrointestinal stromal tumor

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Introduction

Metastatic disease involving the stomach is a rare event. The lifetime prevalence is only 0.7-1.7% in patients with known malignancies (1). Common sources are breast cancer, lung cancer, esophageal cancer, renal cell carcinoma, and malignant melanoma (1, 2). Gastric metastasis from ovarian cancer is exceptionally rare. Only 16 cases have been reported in the English literature. We herein present the 17th case of gastric metastasis from ovarian cancer, in which a serous carcinoma of the ovary, FIGO stage IA, developed a solitary intramural metastasis 8 years later. A literature review indicated that all cases of ovarian cancer that developed a metastasis to the stomach were in stages higher than IIB, except for one case of stage IA endometrioid adenocarcinoma. Gastric metastases from stage IA ovarian serous carcinoma have never been reported.

Case Report

A 71-year-old asymptomatic woman was seen for the evaluation of a gastric submucosal tumor. Eight years earlier, she had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy for ovarian cancer. Histologically, the tumor was limited to the left ovary without metastasis, and serous adenocarcinoma, grade 3 (G3), FIGO stage IA was diagnosed. Carboplatin and docetaxel were given, but she developed dyspnea, so chemotherapy was discontinued after one cycle. Afterwards, she was followed up every 6 months and remained disease-free for 8 years, when her serum CA125 and CA72-4 levels increased to 122 U/mL (reference range: <35 U/mL) and 25.2 U/mL (reference range: <8.0 U/mL), respectively. Computed tomography (CT) of the chest to the pelvis revealed a 29 × 24 mm submucosal mass in the gastric antrum and swelling of the perigastric and paraaortic lymph nodes. Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography

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(PET) combined with CT (^{18}F -FDG PET/CT) showed intense FDG uptake in the gastric mass, perigastric lymph nodes, paraaortic lymph nodes, and left supraclavicular lymph nodes (Fig. 1). Upper gastrointestinal endoscopy revealed a submucosal tumor covered with normal gastric mucosa (Fig. 2). Clinical differential diagnoses included malignant gastrointestinal stromal tumor (GIST) with metastases, malignant lymphoma, and gastric recurrence from ovarian carcinoma. She underwent gastric boring biopsy, the specimen from which revealed a poorly differentiated adenocarcinoma with a micropapillary component (Fig. 3A). Initially, invasive micropapillary carcinoma (IMPC) of the stomach was considered; however, because of her history of ovarian cancer, the specimen was compared to the previous ovarian carcinoma. The tumor was confirmed as a metastatic serous adenocarcinoma from the ovary (Fig. 3B). Immunohistochemically, both the gastric tumor and the ovarian tumor were positive for CA125, cytokeratin 7 (CK7), Wilms' tumor 1 (WT1), estrogen receptor (ER), PAX8, and p53, whereas they were negative for progesterone receptor (PR) and cytokeratin 20 (CK20). The expression of p53 was detected in >90% of cells in both tumors. The patient received 6 cycles of carboplatin and pegylated liposomal doxorubicin and is currently in complete remission 8 months after gastric biopsy.

Discussion

We herein describe the case of a solitary gastric recurrence 8 years after the initial ovarian carcinoma was diagnosed. Although several lymph nodes appeared to be involved, no obvious metastasis to other organs or the peritoneal surface was identified. There has been no previous report in which a stage IA serous ovarian carcinoma metastasized to the stomach. The reasons for this recurrence may have been insufficient initial chemotherapy due to adverse effects in this patient, and the absence of lymph node sampling at the time of ovarian surgery, because there were no findings suggestive of lymph node metastasis by imaging and intraoperative findings.

Ovarian carcinoma usually metastasizes along the peritoneal surface. About 31-38% of ovarian cancer patients develop distant metastasis during the course of the disease, of which 8-18% are synchronous metastases (3, 4). The most common metastatic sites are the pleura, liver, lung, distant lymph nodes, and, less commonly, the central nervous system, skin, pericardium, bone, spleen, and breast (3, 4). Significant risk factors for distant metastasis development are higher stage, higher histological grade, and lymph node involvement at the time of the initial diagnosis. The median interval to metastasis is 44 months, and the median survival after distant metastasis is 12-30 months (4, 5). Cormio et al. reported that, in a multivariate analysis, the time interval between the diagnosis of ovarian cancer and the documentation of distant metastasis was the only significant factor for prognosis (4). Bristow et al. reported that complete cytore-

ductive surgery for recurrent ovarian cancer was an independent prognostic factor in their meta-analysis (5).

Metastasis from an ovarian tumor to the stomach without peritoneal seeding is extremely rare. To our knowledge, including our case, only 17 such cases have been reported in the English literature (Table) (1, 6-20). These patients ranged in age from 42-73 years (mean, 58 years). Histologically, serous carcinoma accounted for 15 cases, and endometrioid adenocarcinoma accounted for 1 case. This result may indicate that serous carcinoma predominantly leads to gastric metastasis, because the reported ratio between serous and non-serous carcinoma was about 2.8:1 for all distant metastases of ovarian carcinoma (3, 4). Only five reports mentioned histological grade, and all of them were serous carcinoma G3. The stages for all cases were higher than IIB, except for one endometrioid adenocarcinoma (IA) and the present case (IA). Four cases reported the stomach as the only metastatic site; five cases, including ours, had gastric and lymph node metastases; and seven cases also had metastases to other organs. The duration to gastric recurrence from the time of ovarian cancer diagnosis, excluding synchronous metastasis, ranged from 12-144 months (median, 39 months), similar to the interval for overall distant metastases. Asymptomatic patients predominated (10 patients), and the other 7 patients had some symptoms, such as abdominal pain, discomfort, and dyspepsia (Table). Gastric tumors had ulceration in nine cases and no ulceration in seven. In 11 cases, the serum CA125 levels were checked, and all showed elevated levels. Because the information provided in the case reports is limited and varied, survival after documentation of gastric metastasis is not conclusive at this time.

Gastric metastasis without peritoneal seeding suggests metastasis through a hematogenous route or lymphatic spread. Despite the swelling of the paraaortic and perigastric lymph nodes, swelling of the pelvic lymph nodes was not observed in this patient. This finding supports the idea that gastric metastasis occurred through the paraaortic lymph node route (6).

Clinically, gastric metastases from ovarian cancer mimic GISTs (10, 11, 19). A GIST was suspected in the present case based on the imaging and endoscopic findings. Biopsy and pathological investigation are necessary to confirm gastric tumors as metastases. Histologically, the differential diagnosis from gastric adenocarcinoma, especially IMPC, is important. The present case also showed micropapillary architecture on histology. Our literature search did not reveal any IMPC cases covered with normal gastric mucosa without ulceration. Although a few intramural gastric adenocarcinomas have arisen from the diverticulum or ectopic pancreatic tissue (21, 22), the tumor cells are of the gastric or pancreaticobiliary epithelial phenotype. Clinical information and comparison with the previous ovarian cancer histology are important. In difficult cases, immunohistochemistry would further help to differentiate a metastasis from a primary gastric tumor. Specifically, a combination of PAX8, WT1, ER,

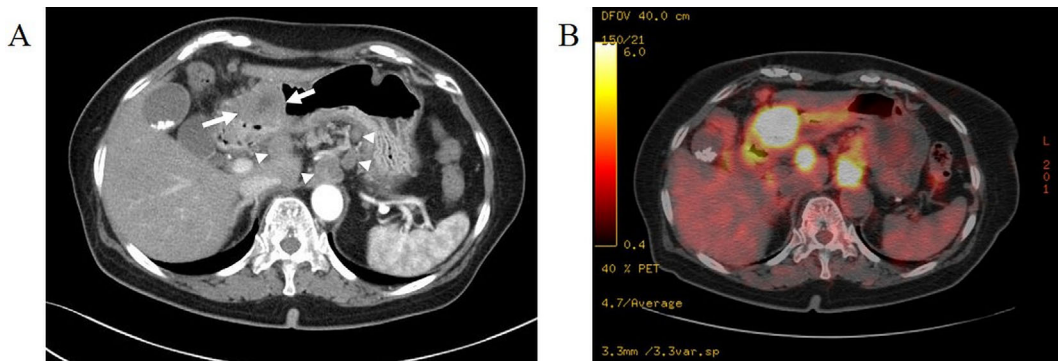


Figure 1. Computed tomography (CT) images combined with fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET/CT). (A) CT revealed a 29×24 mm mass in the gastric antrum (arrows) with perigastric and paraaortic lymph node swelling (arrow heads). (B) FDG-PET/CT showed intense FDG uptake in the corresponding mass and swellings.

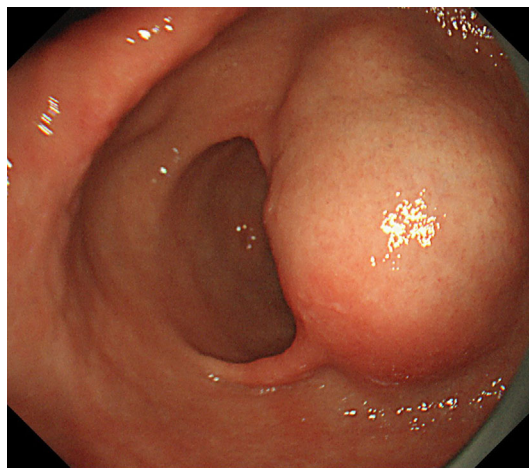


Figure 2. Upper gastrointestinal endoscopy revealed a submucosal tumor covered with smooth mucosa in the gastric antrum.

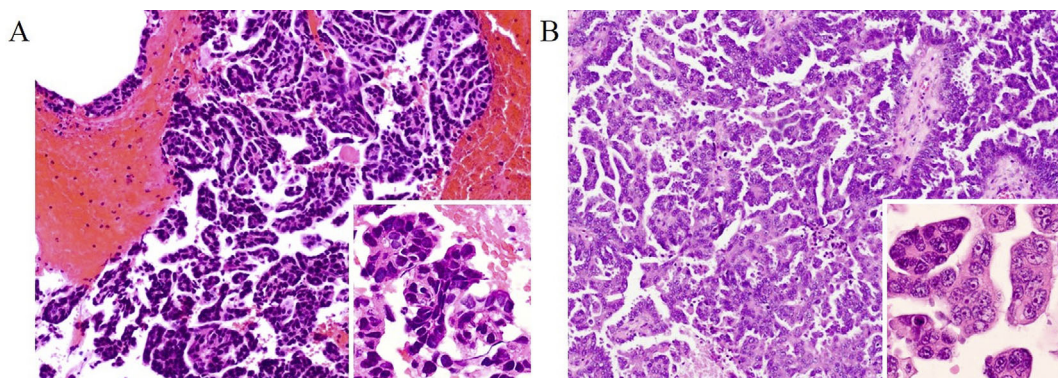


Figure 3. Light microscopy of gastric biopsy and ovarian tumor specimens. (A) Gastric biopsy revealed an adenocarcinoma with papillary and micropapillary growth patterns (Hematoxylin and Eosin (H&E) staining, original magnification ×20). With higher magnification, the tumor cells showed high nuclear grades with high nuclear/cytoplasmic ratios (inset, H&E staining, original magnification ×40). (B) Histology of the previous ovarian tumor showed a similar growth pattern to that of the gastric tumor (H&E staining, original magnification ×20, inset ×40).

Table. Summary of Clinicopathological Findings of Gastric Metastases from Ovarian Carcinomas.

Reference	Age (years)	Histology	Stage	Therapy for primary tumor	Recurrent organs	Duration to gastric recurrence (months)	Symptoms at gastric recurrence	Ulcer	Serum CA125 at gastric recurrence	Immuno-histochemistry	Follow-up after gastric metastasis
1	1	Serous	≥ IIIB	Tumor reduction +chemotherapy	Stomach, pelvic mass	20	Asymptomatic	-	NA	NA	NA
2	6	Endometrioid	IA	TAH+BSO+LN +omentectomy +chemotherapy	Stomach, paraaortic LNs	12	Asymptomatic	-	high	NA	NA
3	7	Serous, G3	IIIC	Surgery +chemotherapy	Stomach, lung, liver	15	Abdominal discomfort	+	high	NA	6 months, DOD
4	8	Poorly differentiated carcinoma	NA	Surgery +chemotherapy	Stomach	84	Belching, reflux, discomfort	+	high	CA125+, CK-AE1/AE3+, CK7+, CK20-, vimentin-, CD117-, CEA-	NA
5	9	Serous, G3	IIIC	TAH+BSO +omentectomy +bowel nodule resection +chemotherapy	Stomach, perigastric LNs	13	Asymptomatic	NA	high	NA	12 months, NED
6	10	Serous	IV	TAH+BSO +omentectomy +chemotherapy	Stomach, right adrenal gland, suprarenic mass	0	Epigastric pain, fullness	+	high	CK-AE1/AE3+, CK7+, WT1+, CK20-, ER-, PR-	12 months, NED
7	11	Serous	≥ IIB	TAH+BSO +LNs +resection of colon metastasis +chemotherapy	Stomach	42	Asymptomatic	-	high	NA	18 months, NED
8	12	Serous	IV	NA	NA	0	Dyspepsia	+	NA	NA	NA
9	13	Serous, G3	NA	Surgery +chemotherapy	Stomach	144	Asymptomatic	+	high	CA125+, CK7+, WT1+, ER+, CK20-, PR-, CDX2-	5 months, NED
10	14	Serous	IIIB	TAH+BSO +omentectomy +chemotherapy	Stomach, spleen, peritoneum	60	Fatigue, melena	-	NA	ER+, PR+, p53+	NA
11	15	Serous, G3	IV	TAH+BSO +LNs +omentectomy +chemotherapy	Stomach, hepatoduodenal LN	0	Pain, perforation	+	high	CA125+, WT1+, CK20-	NA
12	16	Serous	IIIB	TAH+BSO +LNs +omentectomy +chemotherapy	Stomach, peritoneum, omentum, pelvis, iliac perigastric LNs	36	Asymptomatic	+	NA	WT1+, GCDFP-15-, CD117-	NA
13	17	Serous	NA	TAH+BSO +LNs +chemotherapy	Stomach	72	Asymptomatic	+	NA	CA125+, ER+, PR+	9 months, DOD
14	18	Serous	NA	Tumor reduction +chemotherapy	Stomach, rectum, lymph nodes (paraortic, perihepatic, perigastric, cecum)	84	Epigastric pain, dyspepsia	+	NA	NA	94 months, DOD
15	19	Serous	III	TAH+BSO +LNs +omentectomy +chemotherapy	Stomach, perigastric LNs	20	Asymptomatic	-	high	WT1+, ER+, PR+, CK20-	NA
16	20	Serous	NA	Surgery	Stomach, pancreas	25	Asymptomatic	-	high	CA125+, CK7+, ER+, PR+, CD56+, CK20-, CDX2-	NA
17	Present case	Serous, G3	I A	TAH+BSO +omentectomy +chemotherapy	Stomach, lymph nodes (paraaorta, perigastric, left supraclavicle)	96	Asymptomatic	-	high	CA125+, CK7+, WT1+, ER+, p53 +, PR-, CK20-	8 months, NED

BSO: bilateral salpingo-oophorectomy, CK: cytokeratin, DOD: died of disease, ER: estrogen receptor, LN: lymphadenectomy, LNs: lymph nodes, NA: not available, NED: no evidence of disease, PR: progesterone receptor, TAH: total abdominal hysterectomy, WT1: Wilms' tumor 1

CEA, and CDX2 generally resolves this issue, since PAX8, WT1, and ER are highly sensitive to ovarian adenocarcinoma, whereas CEA and CDX2 are sensitive to gastric adenocarcinoma (23-25).

In conclusion, although gastric metastasis from ovarian carcinoma is exceptionally rare, clinicians should nevertheless be aware that, in patients with a submucosal tumor and a history of ovarian cancer, gastric lesions may be secondary metastases from the ovarian cancer. For gastric metastatic lesions, complete cytoreductive surgery is recommended when possible; however, at present, it is not clear which factors most influence survival after gastric metastasis.

The authors state that they have no Conflict of Interest (COI).

References

- De Wilde V, Voet D, Dhont M, De Roose J, Vallaey J, Afschrift M. Ultrasound diagnosis of a solitary gastric metastasis. *J Clin Ultrasound* **17**: 678-681, 1989.
- Namikawa T, Hanazaki K. Clinicopathological features and treatment outcomes of metastatic tumors in the stomach. *Surg Today* **44**: 1392-1399, 2014.
- Dauplat J, Hacker NF, Nieberg RK, Berek JS, Rose TP, Sagae S. Distant metastases in epithelial ovarian carcinoma. *Cancer* **60**: 1561-1566, 1987.
- Cormio G, Rossi C, Cazzolla A, et al. Distant metastases in ovarian carcinoma. *Int J Gynecol Cancer* **13**: 125-129, 2003.
- Bristow RE, Puri I, Chi DS. Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. *Gynecol Oncol* **112**: 265-274, 2009.
- Mibu R, Anbe K, Nakahara S, Torisu M. Pyloric stenosis caused by metastases from ovarian carcinoma. *J Clin Gastroenterol* **16**: 269-270, 1993.
- Taylor RR, Phillips WS, O'Connor DM, Harrison CR. Unusual intramural gastric metastasis of recurrent epithelial ovarian carcinoma. *Gynecol Oncol* **55**: 152-155, 1994.
- Sangha S, Gergeos F, Freter R, Paiva LL, Jacobson BC. Diagnosis of ovarian cancer metastatic to the stomach by EUS-guided FNA. *Gastrointest Endosc* **58**: 933-935, 2003.
- Pernice M, Mancini N, Marchetti C, et al. Solitary gastric recurrence from ovarian carcinoma: a case report and literature review. *Surg Oncol* **15**: 267-270, 2006.
- Kang WD, Kim CH, Cho MK, et al. Primary epithelial ovarian carcinoma with gastric metastasis mimic gastrointestinal stromal tumor. *Cancer Res Treat* **40**: 93-96, 2008.
- Jung HJ, Lee HY, Kim BW, et al. Gastric metastasis from ovarian adenocarcinoma presenting as a submucosal tumor without ulceration. *Gut Liver* **3**: 211-214, 2009.
- Carrara S, Doglioni C, Arcidiacono PG, Testoni PA. Gastric metastasis from ovarian carcinoma diagnosed by EUS-FNA biopsy and elastography. *Gastrointest Endosc* **74**: 223-225, 2011.
- Zhou JJ, Miao XY. Gastric metastasis from ovarian carcinoma: a case report and literature review. *World J Gastroenterol* **18**: 6341-6344, 2012.
- Akce M, Bihlmeyer S, Catanzaro A. Multiple gastric metastases from ovarian carcinoma diagnosed by endoscopic ultrasound with fine needle aspiration. *Case Rep Gastrointest Med* **2012**: 610527, 2012.
- Obeidat F, Mismar A, Shomaf M, Yousef M, Fram K. Gastric perforation secondary to metastasis from ovarian cancer: case report. *Int J Surg Case Rep* **4**: 541-543, 2013.
- Kim EY, Park CH, Jung ES, Song KY. Gastric metastasis from ovarian cancer presenting as a submucosal tumor: a case report. *J Gastric Cancer* **14**: 138-141, 2014.
- Namikawa T, Kobayashi M, Hanazaki K. Metastatic gastric tumor arising from ovarian cancer. *Gastrointest Endosc* **79**: 332-333, 2014.
- Hwangbo S, Kwon OK, Chung HY, Yu W. Improved survival of a patient with gastric and other multiple metastases from ovarian cancer by multimodal treatment: a case report. *J Gastric Cancer* **15**: 218-221, 2015.
- Liu Q, Yu QQ, Wu H, Zhang ZH, Guo RH. Isolated gastric recurrence from ovarian carcinoma: a case report. *Oncol Lett* **9**: 1173-1176, 2015.
- Yamao K, Kitano M, Kudo M, Maenishi O. Synchronous pancreatic and gastric metastasis from an ovarian adenocarcinoma diagnosed by endoscopic ultrasound-guided fine-needle aspiration. *Endoscopy* **47** Suppl 1 UCTN: E596-E597, 2015.
- Chapple CR, Muller S, Newman J. Gastric adenocarcinoma associated with adenomyoma of the stomach. *Postgrad Med J* **64**: 801-803, 1988.
- Oya M, Akahoshi K, Toyomasu T. Adenocarcinoma arising in an intramural diverticulum presenting as a long-standing submucosal tumor. *Gastric Cancer* **15**: 216-220, 2012.
- Park SY, Kim BH, Kim JH, Lee S, Kang GH. Panels of immunohistochemical markers help determine primary sites of metastatic adenocarcinoma. *Arch Pathol Lab Med* **131**: 1561-1567, 2007.
- Yaziji H, Battifora H, Barry TS, et al. Evaluation of 12 antibodies for distinguishing epithelioid mesothelioma from adenocarcinoma: identification of a three-antibody immunohistochemical panel with maximal sensitivity and specificity. *Mod Pathol* **19**: 514-523, 2006.
- Tacha D, Qi W, Zhou D, Bremer R, Cheng L. PAX8 mouse monoclonal antibody [BC12] recognizes a restricted epitope and is highly sensitive in renal cell and ovarian cancers but does not cross-react with B cells and tumors of pancreatic origin. *Appl Immunohistochem Mol Morphol* **21**: 59-63, 2013.

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