

Covert Breast Cancer Metastasis to the Gastrointestinal Tract: Is Extra Vigilance Needed?

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ABSTRACT

Breast cancer (BC) is a common cancer in females. Spread to the gastrointestinal tract is rare. This is a 61-year-old woman with history of T2N0M0 lobular BC treated 5 years earlier. She underwent endoscopic evaluation for new-onset anemia and was found to have multiple gastric ulcers, a normal-appearing duodenum, and subtle colonic nodules. Targeted and random biopsies of abnormal and normal findings, respectively, showed adenocarcinoma with diffuse immunohistochemical staining compatible with her BC history. This highlights the importance of maintaining a high suspicion index in patients with lobular BC and the utility of random biopsies in such cases.

KEYWORDS: breast cancer; metastasis; gastrointestinal tract; endoscopy; biopsy

INTRODUCTION

Breast cancer (BC) is the most common cancer in females and the second most common cause of cancer-related deaths, after cancers of the lung and bronchus.¹ Mortality is primarily related to metastasis,² with nearly 30% of women eventually developing distant spread months to years after being diagnosed with early stage cancer.³ The most common sites for BC metastasis include bones, lungs, liver, and brain.⁴ Metastasis to the gastrointestinal (GI) tract is rare and predominantly derives from lobular carcinoma, rather than other BC subtypes.^{5–7} We present the case of a patient with BC metastatic to the stomach, small intestine, and colon including areas of the stomach and duodenum with an endoscopically normal appearance.

CASE REPORT

A 61-year-old woman presented for an upper endoscopy and colonoscopy for anemia workup. She has a history of estrogen receptor (ER)-positive, progesterone receptor-negative, human epidermal growth factor-2-negative T2N0M0 grade 1 lobular BC for which she had undergone right mastectomy and sentinel lymph node biopsy 5 years before presentation followed by 5 years of adjuvant aromatase inhibitor therapy. She also has a medical history that includes hypertension for which she takes losartan and amlodipine, hyperlipidemia for which she is on atorvastatin, prediabetes mellitus for which she takes metformin, gastroesophageal reflux disease treated with omeprazole, vitamin D deficiency, osteopenia, possible fibromyalgia for which she takes duloxetine, and a history of tobacco and cocaine use in sustained remission. The patient was in her usual state of health until she developed severe muscle cramps and was subsequently admitted with a diagnosis of rhabdomyolysis, after which her statin was discontinued. Her workup revealed new-onset normocytic anemia with a hemoglobin of 10 g/dL and thrombocytopenia with a platelet count of 70 k/ μ L. At that time, the patient reported ongoing fatigue and denied significant GI symptoms including abdominal pain, nausea, vomiting, or overt GI bleeding, although she did subsequently report some decreased appetite and diarrhea. She had no history of anticoagulant or antiplatelet use but reported nonsteroidal anti-inflammatory drug use for myalgias. Her oncologist recommended endoscopic evaluation of her anemia.

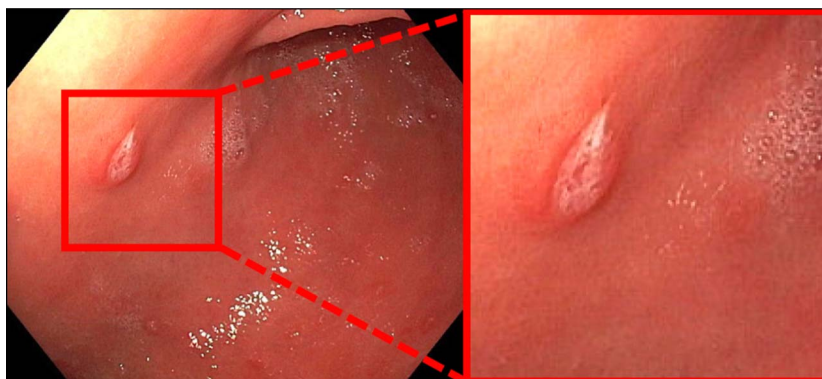


Figure 1. Ulcer in the otherwise normal gastric antrum.

Upper endoscopy revealed multiple small ulcers in the corpus and antrum, which were biopsied (Figure 1). The rest of the stomach and visualized first and second portions of the duodenum appeared normal (Figure 2). Random biopsies were taken from the normal stomach per the Sydney protocol to rule out *Helicobacter pylori* infection given the patient's anemia and from the normal duodenum to rule out celiac disease. Colonoscopy revealed subtle pale nodules scattered throughout the colon, and biopsies were obtained (Figure 3). On histological examination, both random and targeted biopsy specimens from the entire endoscopically normal and abnormal GI tract showed adenocarcinoma with diffuse immunohistochemical staining for CAM5.2, GATA3, and ER, and no staining for CDX2, compatible with metastasis from the patient's primary BC. The adenocarcinoma cells infiltrated lamina propria without disrupting the background benign epithelium or eliciting a desmoplastic stromal response. Breast biomarkers were >95% positive for ER with a moderate stain intensity and negative for progesterone receptor and for human epidermal growth factor-2 overexpression (Figure 4).

Chest, abdominal, and pelvic computed tomography did not demonstrate any GI abnormalities and showed scattered tiny

pulmonary nodules and subtle hypodense splenic foci measuring up to 1.5 cm, with follow-up recommended given the patient's known disease. A nuclear medicine bone scan did not reveal any osteoblastic metastases; however, a subsequent bone marrow biopsy revealed involvement by metastatic mammary adenocarcinoma with >90% of marrow cellularity. Her bicytopenia was hence attributed to bone marrow infiltration by metastatic cancer cells. The patient was started on fulvestrant and palbociclib with improvement in the anemia and thrombocytopenia.

DISCUSSION

Although BC metastasizing to the GI tract is rare,^{8,9} it is still one of the most frequent cancers to do so, along with melanoma and lung cancer.¹⁰ GI metastasis can be the initial presentation of BC spread, with the stomach being the most common site for metastasis.^{5,11,12} This report illustrates the unusual case of an individual with BC presumed to be in remission, who had only mild GI symptoms and who was found to have widespread metastatic disease across the GI tract, detected on random biopsies of normal gastric and duodenal mucosa, and targeted biopsies of gastric and colonic mucosal abnormalities.

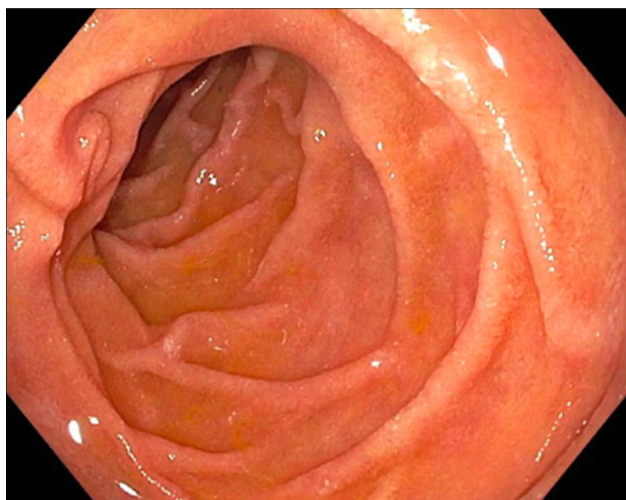


Figure 2. Normal-appearing second portion of the duodenum.

Endoscopic appearances of metastatic disease can vary significantly among patients, with most published reports describing discrete abnormalities that would warrant biopsies for diagnostic confirmation.⁵ In the stomach, metastatic BC has been reported to be a mimicker of primary gastric cancers,¹³ and its endoscopic appearances have been described in 3 patterns: (i) localized lesions (e.g., large ulcers and polypoid features), (ii) diffuse infiltration (e.g., linitis plastica, erosions, and gastritis), and (iii) local infiltration at the cardia or pylorus leading to stenosis.¹⁴ In one comprehensive review of the literature, 122 patients with BC metastatic to the stomach had their endoscopic findings documented, which included masses, linitis plastica, ulcers, polyps, nodularity, or external compression. Notably, none of them had normal mucosa reported.¹⁵ The preservation of the background benign gastric epithelium and the absence of any desmoplastic stromal response on histologic examination may explain why this patient's mucosa appeared

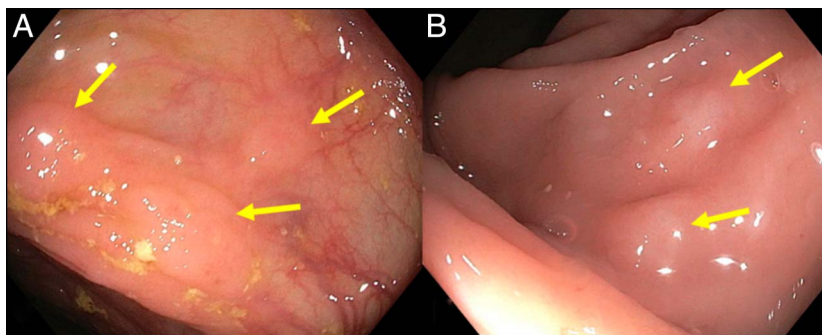


Figure 3. Subtle and pale nodules were identified during colonoscopy at the splenic flexure (A) and sigmoid colon (B) (yellow arrows).

endoscopically normal. Although metastatic BC involving endoscopically normal GI tract mucosa has not been previously reported in the literature, early stage gastric signet ring cell carcinoma can show a similar growth pattern and also be endoscopically invisible like this case.¹⁶ Our case highlights the

fact that normal gastric mucosa can still harbor metastatic cancer cells and that extra vigilance is needed.

Endoscopic findings of intestinal metastasis also vary widely and can include ulcers, mucosal thickening, friability, linitis

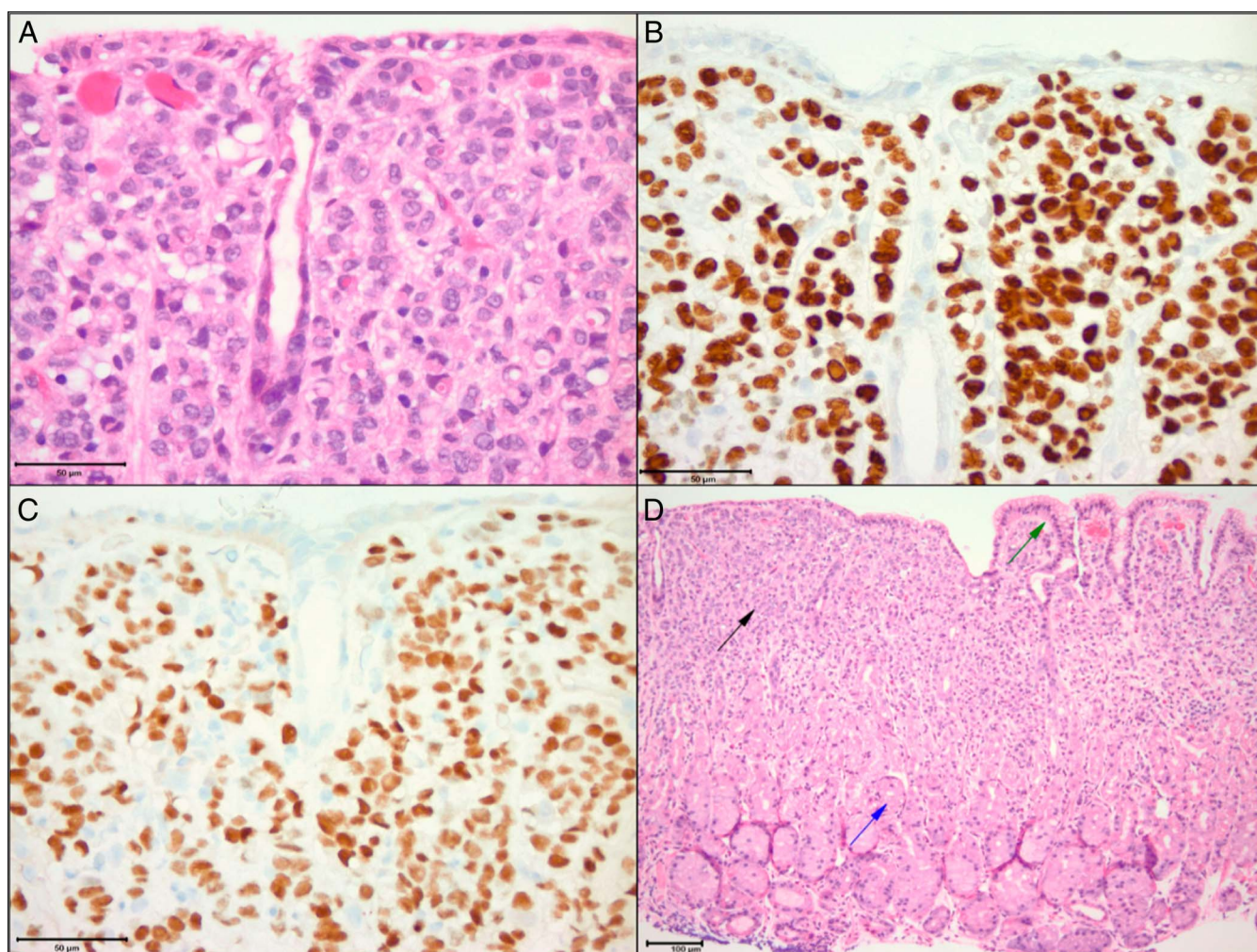


Figure 4. Histologic examination biopsies acquired from endoscopically normal-appearing gastric body mucosa. (A) Hematoxylin and eosin–stained slide showing surface epithelium, benign gastric gland, and numerous adenocarcinoma cells (40×); (B) tumor cells show positive staining with a GATA3 immunohistochemical stain supporting metastasis from the patient's primary breast cancer (40×); (C) tumor cells show positive staining for an estrogen receptor immunohistochemical stain supporting metastasis from the patient's primary breast cancer (40×); and (D) relatively lower-magnification hematoxylin and eosin–stained slide (10×) showing adenocarcinoma cells infiltrating gastric lamina propria (black arrow) without disruption of normal surface epithelium (green arrow) or oxyntic glands (blue arrow).

plastica–like inflammation, stenosis, polyps, and obstructing masses.¹⁷ Other more subtle signs may include edema and pallor.¹² To the best of our knowledge, this case is the second reported case of an endoscopically normal duodenum involved with metastatic lobular BC.⁸ Instances of normal mucosa with biopsy-proven metastasis are rare and have been described in specific sites, such as the esophagus and colon.^{15,18} Therefore, it is essential to maintain a high level of clinical suspicion when performing endoscopic examinations on patients with known primary BC, even those in remission.

In addition, patients with BC metastatic to the GI tract typically have GI symptoms, with a minority being diagnosed incidentally.¹⁷ Presentations include abdominal pain, dyspepsia, weight loss, change in bowel habits, and bleeding.⁵ Our patient did not report significant GI symptoms before her diagnosis, adding another case to the literature. She did have anemia; however, in her case, the anemia was most likely a result of bone marrow infiltration as opposed to GI blood loss secondary to metastasis.

This case highlights a relatively asymptomatic patient who was found to have widespread metastatic BC throughout the stomach, small intestine, and colon, with metastasis found in both normal- and abnormal-appearing GI mucosa. This underscores the importance of maintaining a high index of suspicion in patients with a history of a malignancy known to metastasize to the GI tract and the potential utility of taking random biopsies in patients with a history of lobular BC.

DISCLOSURES

Author contributions: S. Wehbe, SA Firkins, JR Sweeney, HCF Moore, and C. Roupheal have equally contributed to the conception and design of the work, drafting and critically revising the work for important intellectual content, approved the final version of the manuscript, and agreed to be accountable for the work. C. Roupheal is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received August 20, 2024; Accepted December 3, 2024

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