

Synchronous Small and Large Bowel Metastases from Lobular Carcinoma of Breast: Immunohistochemistry Is the Key to Diagnosis

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Background	Luminal gastrointestinal metastases from breast cancer are rare. Adenocarcinoma with signet ring cells can arise from all the organs of the body. It is a unique subtype of mucin producing adenocarcinoma, commonly arising from the stomach, breast, colon, prostate or lung. It can either be a primary or metastases from these sites.
Summary	A sixty-seven-year-old female with multiple comorbidities presented with complaints of abdominal pain and melena for two months. She was evaluated and found to have features of cirrhosis of the liver with splenomegaly. An upper gastrointestinal endoscopy revealed features of portal hypertension with a white patch in the duodenum, which was biopsied. Colonoscopy showed multiple diminutive polyps in the rectum, sigmoid and descending colon, and thickened ileocecal junction. Biopsies were taken from the polyps, ileum, and ileocecal junction. Histopathological examination of all the gastrointestinal biopsy specimens showed features of poorly differentiated adenocarcinoma with signet ring cells. Immunohistochemical (IHC) examination of the biopsies was carried out to identify the primary organ of origin. Other possible sites of adenocarcinoma with signet ring cells were evaluated. Clinical examination of the breast did not reveal a discrete lump. Sonomammogram showed bilateral scattered and clustered benign calcifications and a small hypoechoic lesion at one o'clock position in the right breast. Core needle biopsy taken from the breast lesion showed a focus of invasive lobular carcinoma of the breast. Immunohistochemistry of the gastrointestinal biopsies were positive for cytokeratin 7 (CK7), gross cystic disease fluid protein 15 (GCDFP-15), and estrogen receptors (ER), suggestive of primary breast adenocarcinoma. In view of the comorbid illnesses, and the presence of chronic liver disease, the patient was placed on hormonal therapy with tamoxifen.
Conclusion	Immunohistochemistry plays a crucial role in solving this diagnostic puzzle of identifying the primary adenocarcinoma. We report one such rare case of lobular carcinoma of breast with synchronous small and large bowel metastases.
Keywords	Luminal gastrointestinal metastases, metastatic carcinoma breast, immunohistochemistry

DISCLOSURE:

The authors have no conflicts of interest to disclose.

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Case Description

Distant metastases are the commonest cause of death in breast cancer patients. Common sites of breast cancer metastases, in the order of frequency are bone, lungs, soft tissue, liver, and brain.¹ Metastatic breast cancer presenting with peritoneal carcinomatosis is well described. Luminal gastrointestinal tract metastases from the breast cancer are rare.^{2,3} Biopsies from such lesions are usually reported as adenocarcinoma with signet ring cells. Adenocarcinoma with signet ring cells represent a unique subset of mucin producing carcinomas and can arise from all the organs of the body.⁴ Common sites of signet ring cell adenocarcinoma include the stomach, breast, colon, prostate, and lung. It is difficult to differentiate between primary and metastatic adenocarcinoma in these sites by histopathological examination alone. Immunohistochemistry plays a crucial role in solving this diagnostic puzzle of identifying the primary adenocarcinoma.⁵ We report one such rare case of lobular carcinoma of breast with synchronous small and large bowel metastases in which immunohistochemistry was the key to diagnosis.

A sixty-seven-year-old female with multiple comorbidities like diabetes mellitus, systemic hypertension, rheumatoid arthritis, hypothyroidism, and chronic liver disease presented with complaints of abdominal pain and melena for two months. She was evaluated elsewhere with ultrasound scan of abdomen which showed features of cirrhosis with splenomegaly and oesophagogastroduodenoscopy (OGD), which showed antral erosions, small fundal varices, and portal hypertensive gastropathy. The patient was initially treated with blood transfusions and other supportive measures. Since she continued to be symptomatic a colonoscopy was done which showed multiple polyps in the left colon, and biopsies were taken. Histopathological examination of the colonic biopsies revealed a poorly differentiated adenocarcinoma with signet ring cells. The patient was then considered for surgical management.

As a part of her diagnostic workup, a complete colonoscopy was done to rule out other lesions in colon, and an upper gastrointestinal endoscopy was done to document her present variceal and portal gastropathy changes. Colonoscopy done in our center showed multiple diminutive polyps in rectum, sigmoid and descending colon, and thickened ileocecal junction (Figure 1A). Biopsies were taken from these polyps, ileocecal junction, and ileum. Upper gastrointestinal endoscopy showed features of portal hypertension with a white patch in the duodenum which

was biopsied (Figure 1B). Computed tomography scan of the abdomen showed dysmorphic liver, mild splenomegaly without any bowel related mass lesion.

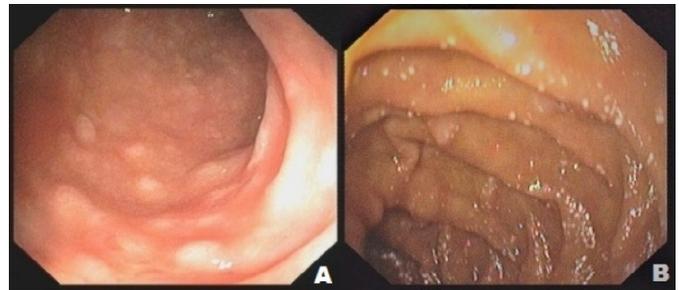


Figure 1. A: Colonoscopy showing multiple small sessile polyps. **B:** OGD showing multiple small white patches in duodenum.

Histopathological examination of all the biopsies showed infiltrating neoplastic cells in sheets interspersed with cells of signet ring morphology suggestive of poorly differentiated adenocarcinoma with signet ring cells (Figure 2A and Figure 2B). Immunohistochemical (IHC) examination of the biopsies was carried out to identify the primary organ of origin. Other possible sites of adenocarcinoma with signet ring cells were evaluated. Clinical examination of the breast did not reveal a discrete lump, but some areas of induration with discrete axillary lymphadenopathy were seen. Sonomammogram showed bilateral scattered and clustered benign calcifications and a small hypoechoic lesion at one o'clock position in the right breast. Core needle biopsy taken from the breast showed foci of neoplastic cells arranged in a single file suggestive of invasive lobular carcinoma of breast (Figure 2C). Similarly, core biopsy from the axillary nodes on histopathological examination showed similar neoplastic cells with signet ring cells.

Immunohistochemistry of the gastrointestinal biopsies were positive for Cytokeratin 7 (CK 7), gross cystic disease fluid protein (GCDFP-15), and estrogen receptors (ER), while cytokeratin 20 (CK 20), E-cadherin and progesterone receptor (PR) was negative, suggestive of primary breast adenocarcinoma (Figure 2D and Figure 2E). IHC of the breast lesion was positive for estrogen receptors, while progesterone and human epidermal growth factor receptor 2 (HER2/neu) were negative.

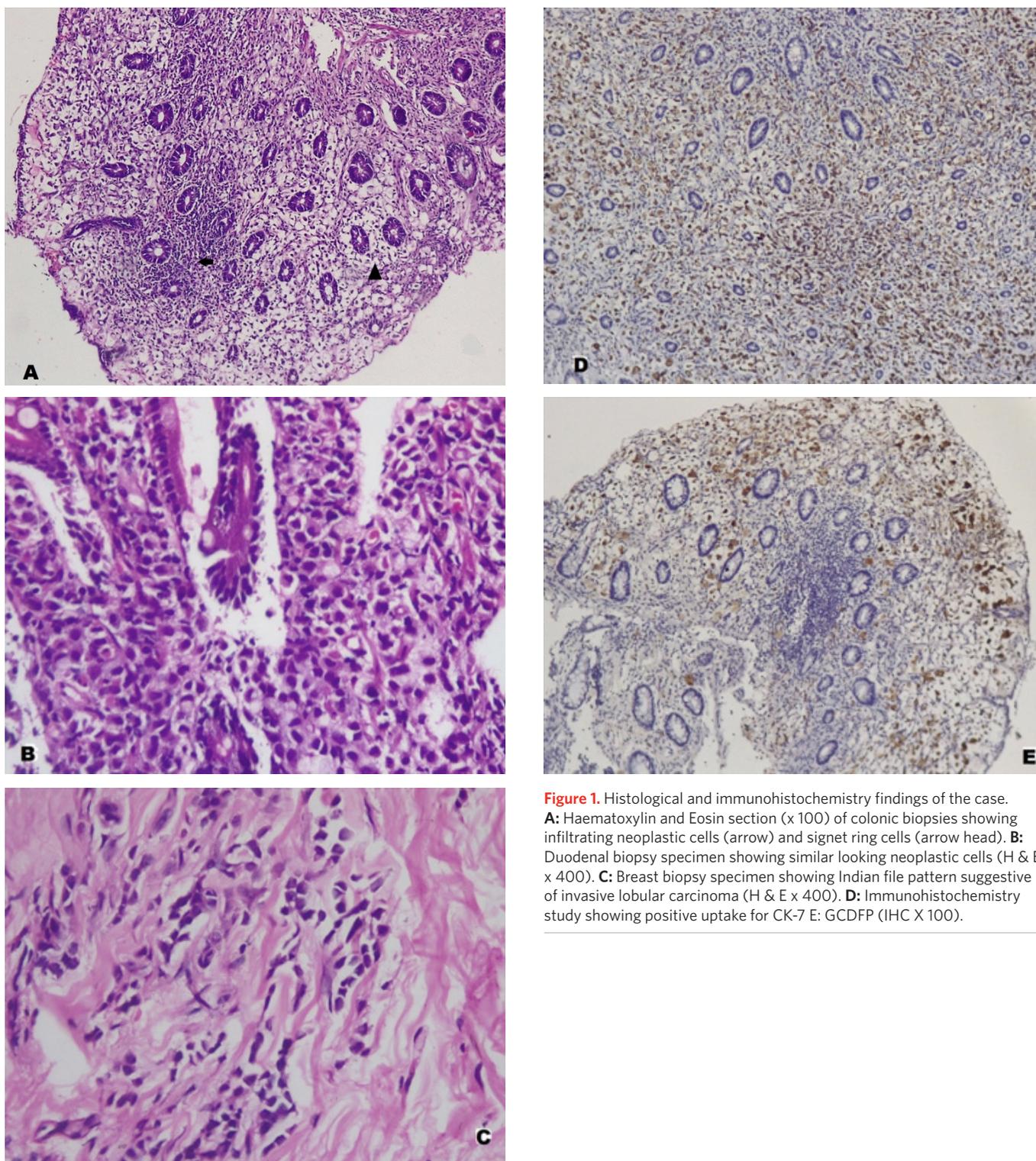


Figure 1. Histological and immunohistochemistry findings of the case. **A:** Haematoxylin and Eosin section (x 100) of colonic biopsies showing infiltrating neoplastic cells (arrow) and signet ring cells (arrow head). **B:** Duodenal biopsy specimen showing similar looking neoplastic cells (H & E x 400). **C:** Breast biopsy specimen showing Indian file pattern suggestive of invasive lobular carcinoma (H & E x 400). **D:** Immunohistochemistry study showing positive uptake for CK-7. **E:** GCDFP (IHC X 100).

In view of the comorbid illnesses, and the presence of chronic liver disease, the patient was placed on hormonal therapy with tamoxifen.

Discussion

Isolated luminal gastrointestinal metastases from breast carcinoma are rare. Gastrointestinal metastases from breast cancer range from 8 to 35 percent in an autopsy survey. The most common site of gastrointestinal metastases is the stomach (60 percent), followed by the esophagus (12 percent), and colon (11 percent).^{3,6} Small bowel metastases are still rarer. Multiple-site gastrointestinal metastases, as in our case, have also been reported, but are extremely rare.⁷

Invasive lobular carcinoma of breast is the most common histological type of breast cancer causing gastrointestinal metastases.⁸ In one series, 1 in 20 patients with invasive lobular carcinoma were found to have gastrointestinal metastases.⁷ Gastrointestinal metastases usually occur late following the treatment of primary breast cancer. The median interval from diagnosis of primary tumour to gastrointestinal metastases is about six years (range 0 to 22 years) in literature.^{3,9} Synchronous metastases as in our case are still rarer.

Primary signet-ring cell carcinoma (SRCC) of the breast is a rare disease, constituting 2 to 4.5 percent of all breast cancers.⁴ Primary SRCC of the breast and signet-ring cell variant of lobular carcinoma of the breast can be differentiated from the metastatic SRCC by immunohistochemical markers. IHC uses monoclonal as well as polyclonal antibodies to determine tissue distribution of specific antigens of interest. IHC revolutionized the approach to diagnosing tumors of uncertain origin by using a panel of antibodies based on clinical history, morphological findings, and other investigations.¹⁰ IHC markers, importantly GCD-FP-15, are positive in primary lesions of breast and negative in gastrointestinal SRCC. CK 7 and ER are positive in primary carcinoma from breast, while CK 20 and CDX2 are usually negative.^{4,9,11}

Treatment of gastrointestinal metastases from breast cancer is usually endocrine therapy and chemotherapy, depending upon the hormonal receptor status of the metastases. Surgical management of the metastatic lesion is usually reserved for complications like obstruction, bleeding, and perforation. Survival of these patients with gastrointestinal metastases from the available data is similar to metastatic breast cancer to other sites; five-year survival is around 29 percent.

Conclusion

Synchronous, multiple-site luminal gastrointestinal metastases from primary breast cancer do occur. Biopsy from the luminal gastrointestinal metastases is likely to show features of signet ring cell carcinoma. Given the high prevalence of breast cancer, it should be considered in any female presenting with new gastrointestinal symptoms and signet-ring cell histological pattern. Immunohistochemistry is the key to solving this diagnostic puzzle and may prevent an unnecessary surgery.

Lessons Learned

Biopsies from the gastrointestinal tract that yield an appearance of a poorly differentiated carcinoma should preferably undergo immunohistochemistry.

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