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Case Report

Metachronous Multiple Primary Malignant Neoplasms of the Stomach and the Breast: Report of Two Cases With Review of Literature

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Multiple primary malignant neoplasm is the occurrence of a second primary malignancy in the same patient within 6 months of the detection of first primary (synchronous), or 6 months or more after primary detection (metachronous). Multiple primary malignant neoplasms are not very frequently encountered in clinical practice. The relative risk for a second primary malignancy increases by 1.111-fold every month from the detection of the first primary malignancy in any individual. We present 2 patients treated for carcinoma of the breast who developed a metachronous primary malignancy in the stomach to highlight the rare occurrence of multiple primary malignant neoplasms. These tumors were histologically dissimilar, with distinct immunohistochemical parameters. The importance lies in carefully identifying the second primary malignancies, not dismissing them as metastases, and treating them accordingly.

Key words: Breast neoplasms – Stomach neoplasms – Neoplasms – Second primary

Breast cancer is the most common malignancy among women worldwide. With proper screening, earlier detection, and improved treatment, survival has greatly increased, with the result that there is now a large population of women with a present or past history of breast cancer. This has led to an increased detection of second primary malignancies among these women. The relative risk for a second primary malignancy increases by 1.111-fold every month from the detection of the first primary malignancy in any individual.[1] Several authors have reported on a lesion in the stomach being labeled as a second

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primary malignancy and subsequently found to be metastasis. When the primary breast tumor is positive for estrogen and progesterone receptors (ER/PRs) and the stomach tumor is ER/PR negative, the diagnosis is established easily.[2] However, studies have shown that some primary gastric cancers can have ER/PR positivity. Further, if the primary breast lesion is ER/PR negative, the same cannot be used as a marker. Here, we present 2 breast cancer patients who developed second primary malignancies in the stomach and the final diagnosis was established based on histopathology and immunohistochemistry.

Case Summaries

Patient 1

A 35-year-old premenopausal woman—a follow-up patient for metastatic carcinoma of the breast—presented with dyspeptic symptoms for 3 months. An esophagogastroduodenoscopy showed a growth at the cardia that on biopsy was reported as mucin-secreting adenocarcinoma. During admission the patient developed partial intestinal obstruction, probably due to peritoneal carcinomatosis. Because her general condition was poor, she was deemed unfit for any surgery and was given supportive care. The patient died due to advanced malignancy. One year previously, she had had a tumor in the right breast with bilateral ovarian metastasis, confirmed by laparotomy and bilateral salpingo-oophorectomy, and had received 6 cycles of palliative chemotherapy with 5-fluorouracil, epirubicin, and cyclophosphamide. The slides and immunohistochemistry patterns of the breast, stomach, and ovarian lesions were compared, showing similarities between the stomach [mucin-secreting adenocarcinoma; positive for cytokeratin 8 (CK8), CK20, and carcinoembryonic antigen; negative for estrogen receptor (ER), progesterone receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2/neu), and CK7] and ovarian (Krukenberg tumor; negative for ER, PR, HER2/neu, and CK 7) tumors, whereas the breast lesion (infiltrating ductal carcinoma, not otherwise specified; ER and PR 10% positive; HER2/neu^{+}; CK7 positive; negative for CK8 and CK20) was dissimilar (Fig. 1). Hence, it was concluded that the patient had 2 separate primary malignancies in the stomach and breast, with Krukenberg tumor from the stomach.

Patient 2

A 45-year-old premenopausal woman, treated for metastatic carcinoma of the right breast 5 years previously with toilet mastectomy and 6 cycles of chemotherapy (cyclophosphamide, Adriamycin, 5-fluorouracil) and currently on letrozole, presented with symptoms of early satiety, loss of appetite, and loss of weight for 3 months. Esophagogastroduodenoscopy revealed a large friable growth in the distal stomach, and biopsy showed adenocarcinoma with signet ring cell morphology. She had no evidence of locoregional or distant recurrence of the breast tumor (infiltrating ductal carcinoma, scirrhous; positive for HER2/neu, CK7, and CK8; negative for ER, PR, and mucicarmine). Computed tomography of the abdomen showed a lesser curve and antral growth extending up to the cardia. She was considered for surgery because the stomach tumor (signet ring cell adenocarcinoma; negative for ER, PR, and CK8; positive for CK7 and mucicarmine) was thought to be a distinct malignancy based on the differential immunohistochemistry characteristics. Intraoperatively, she was found to have extensive metastasis, and resection was abandoned. The patient has subsequently received palliative chemotherapy with 3 cycles of epirubicin, 5-fluorouracil and cisplatin.

Discussion

The incidence of multiple primary tumors has been investigated for a long time. The first description was given by Theodore Billroth. In 1932 Warren and Gates established criteria for multiplicity of malignancies: *each tumor must present a definite picture of malignancy, each must be distinct, and the probability of one being a metastasis of the other must be excluded*.[3] The tumors may be called synchronous when a second tumor develops within 6 months of detection of the first, and metachronous when the second tumor develops more than 6 months after detection of the first.

Survivors of breast cancer have been shown to develop metastases in the stomach, which is otherwise rarely involved by metastases from other organs. The differentiation of a second primary malignancy in the stomach from a metastatic involvement clearly assumes significance owing to potentially curative management being possible in the former. Various reports show that second primary tumors are less frequent than metastatic gastric involvement.[4] There have been numerous other case reports and series of second primary malignancy in the stomach among breast cancer patients. In all of the reports, the cornerstone of management has been differentiation between a second primary malignancy

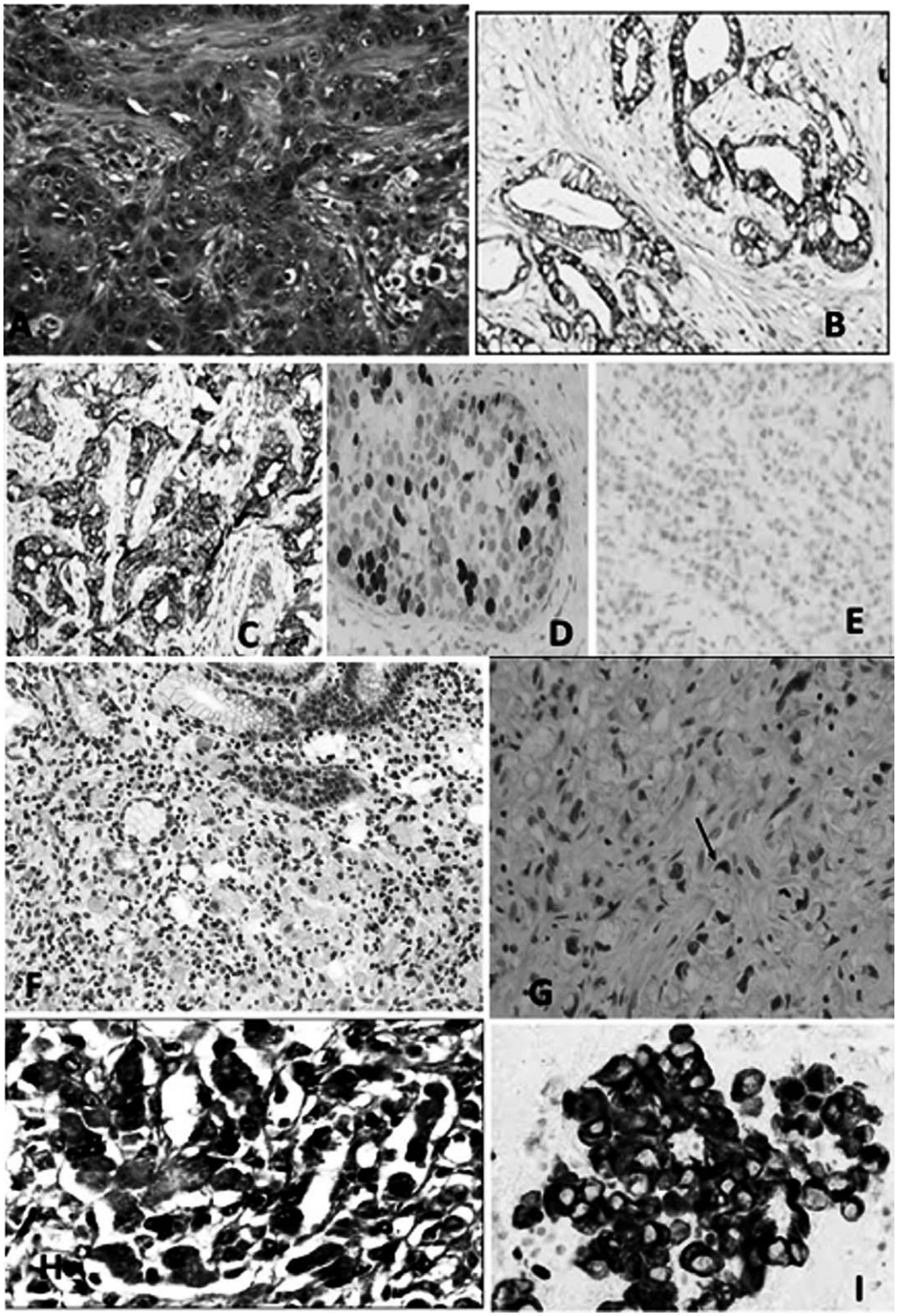

Fig. 1 Patient 1: histopathology and immunohistochemistry of (A–E) infiltrating ductal carcinoma of the breast and (F–I) signet ring cell adenocarcinoma of the stomach with ovarian metastasis (400X). (A) Infiltrating ductal carcinoma of the breast. (B) CK7 positive. (C) HER2/neu positive. (D) ER around 10% positive. (E) CK8 negative. (F) Signet ring cell carcinoma stomach. (G) Signet ring cell in ovarian tumor (arrow). (H) Mucicarmine positive. (I) CK8 positive.

and metastasis from the original breast tumor. In the cancer registry–based retrospective study by the Karolinska Institute over a period of 40 years, the incidence of second primary malignancy in noncardia stomach was 41% higher compared with the general population.[5] Ellis *et al*[6] reported an incidence of 0.15% for the development of second primary malignancy in the stomach. Several authors have reported on a lesion in the stomach being labeled as a second primary malignancy and then subsequently found to be metastasis. Schwarz *et al*[7] have recommended making a histopathologic and immunohistochemical comparison between the initial primary breast cancer and the gastrointestinal (GI) tumor to make the differentiation between second primary malignancy and metastasis. In most series of GI metastasis from breast cancer, the histology of the breast tumor has almost always been lobular. The histology of breast tumor where a second primary gastric cancer develops is more frequently infiltrating ductal carcinoma, and concordantly both of our patients had a ductal tumor in the breast. Among immunohistochemical markers, the most frequently used have been ER and PR. Where the primary breast tumor is ER/PR positive and the stomach tumor is ER/PR negative, the diagnosis is established easily. However, studies have shown that some primary gastric cancers can have ER/PR positivity.[2] Further, if the primary breast lesion is ER/PR negative, it cannot be used as a marker. Other immunohistochemistry markers that have been used include HER2/neu; gross cystic disease fluid protein (GCDFP-15); CK7, CK8, and CK20; mucin glycoprotein antigens (MUC2), MUC5AC, and MUK6; and caudal-type homeobox transcription factor CDX2.[8] The interval between the diagnosis of the breast lesion and the second primary malignancy in the stomach has ranged from 0 months to 30 years.[6]

A second primary malignancy in the form of noncardia gastric malignancy was more often observed in survivors of breast cancer on antiestrogen therapy. Also, the risk of noncardia gastric cancer was 50% lower in patients receiving hormonal therapy. Further, a trend of decreased survival was observed among gastric cancer patients on tamoxifen and those gastric cancers positive for ER in a randomized trial. Thus, a harmful effect of antiestrogen therapy is the risk of developing gastric noncardia adenocarcinoma.[5]

The importance of the differentiation between second primary malignancy and metastasis cannot be overstressed, because the treatment radically differs between the two. Although a second primary malignancy has to be offered surgery as first-line treatment with curative intent, the treatment of metastatic tumor is by systemic chemotherapy with a uniformly poor prognosis.[9] Prompt and aggressive investigation of GI symptoms among breast cancer patients has been recommended in order to pick up a second primary malignancy or metastasis as early as possible so as to offer the best possible treatment and improve survival.[9]

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