

Gastric metastasis of signet ring cell carcinoma of the breast

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Signet cell carcinoma is a variant of adenocarcinoma commonly seen in the gastrointestinal system. Dominance of a signet cell carcinoma component in adenocarcinoma is generally considered as a sign of poor prognosis. Primary signet cell carcinoma of the breast is not seen as a distinct histological type in the World Health Organization classification, and is generally accepted as a sub-type of mucinous and lobular carcinoma. It appears to originate from the lobular epithelium, and an intracytoplasmic mucin collection is present histologically in most of the neoplastic cells.¹⁻³ Kamiya et al⁴ divided signet cell carcinomas into 2 groups according to distribution of mucinous content within the cytoplasm, intracytoplasmic lumina type and non-intracytoplasmic lumina type. There is no agreement on the treatment and prognosis of breast carcinomas with signet cell dominance. It was suggested that the metastatic rate was higher in these tumors, and treatment should be shaped keeping in mind this important characteristic.^{1,2,5,6} Since it is a very rarely seen entity, we evaluated symptoms and signs of our case with signet cell breast carcinoma and reviewed the treatment alternatives under the light of the literature in the current paper.

Our patient was 48-year-old at the time of initial diagnosis in 1996, and admitted to Uludag University M. A. Radiotherapy Center for the palliative treatment of stomach metastasis. After the initial diagnosis in another center, modified radical mastectomy was performed. The primary tumor diameter was reported to be 7 cm. Pathology was signet cell carcinoma with lobular characteristics in most areas.

Macroscopic findings. Primary tumor size was 7 x 7 x 3 cm within the mastectomy specimen with unclear surgical margins. Breast tissue was described as hard and with fine septal appearance. Fatty tissue ratio was increased, and breast tissue ratio was decreased in other areas. Eleven lymph nodes were found in the axillary dissection with a largest size of 2 x 1 x 1 cm.

Microscopic findings. Pathology slices indicated that a sinus and terminal duct were full of small epithelial cells, and these cells infiltrated the stroma of the cells. The cells formed indices in these areas and filled the larger duct. Cells in these areas had

large nuclei, and wide cytoplasm and tumor margins were not clear. Lymphoid infiltration was minimal and epithelial proliferation obstructing ductal lumens without tumor was prominent. Three lymph nodes were found to be involved with the tumor in axillary dissection.

Immunohistochemical characteristics. Estrogen and progesterone receptors were found to be strongly positive, indicated by staining within the tumor cell nuclei using the peroxidase anti-peroxidase method (PAP method).

Patient and family history. She had her first menarche when she was 12. She had 3 births and breast-fed her children for an average of a year. Nothing else remarkable was noted in the family history.

Treatment and follow-up. Modified radical mastectomy was performed after an initial diagnosis by needle biopsy from the lump in the right breast in 1996. Pathology revealed a Stage IIIA breast cancer (AJC) that is, T3N1BiiM0. She received radiation therapy in a private center to the thoracic wall and peripheral lymphatics using a Cobalt60 machine. Total dose of radiation was 50 Gy with 2 Gy per fraction. Following radiation therapy, she was given 6 cycles of chemotherapy (CMF; 5-Flourouracil, Methotrexate and Cyclophosphamide). Hormonal therapy using tamoxifen (20 mg/day) was also initiated. Gastric burning and pain started 3 years later, and she had some symptomatic treatment. She was admitted to the Department of Gastroenterology and had an endoscopy since she did not benefit from the previous measures. An ulcerated lesion was detected in the endoscopy, and biopsy revealed signet cell carcinoma. Later, she had a laparotomy and was evaluated as unresectable due to the presence of signet cells within the omentum. Biopsy material was reevaluated by experienced pathologists at the Department of Pathology. Tumoral tissue consisting of diffusely distributed atypical cells within the lamina propria of the tissue of the antrum was reported. Cells were described as cells polygonally shaped and large vesicular nuclei. Some had the shape of signet ring and large cytoplasm (Figure 1). Immunohistochemical (IHC) stainings revealed positivity with cytokeratin (CK). Reactions were negative with leucocyte common antigene, CD20, neuron specific enolase, and synaptophysin CR-A. Cytoplasm of the tumor cells showed weak positivity with the mucin Carme stains. She was assessed as the gastric involvement of the breast cancer and received 6 cycles of chemotherapy using FEC regimen (5-Flourouracil, Epirubicin and Cyclophosphamide). After the re-assessment following chemotherapy, no other metastatic site

Clinical Note

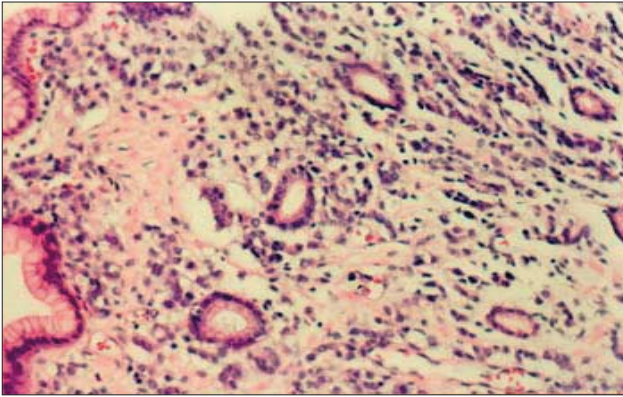


Figure 1 - Signet ring cell carcinoma (Hematoxylin & Eosin x 400)

was defined. She had radiation therapy to the gastric region in order to control the disease at this location. Radiation therapy was given using linear accelerator (Siemens MD2) and 15 MV photon beams. Total dose of radiation was 45 Gy in 5 weeks with 1.8 Gy per fraction. Symptomatic relief was achieved after radiation therapy and CT showed stable disease with no other involvement in any site. She had another exploration and assessed as unresectable disease once again. Third-line chemotherapy consisting of paclitaxel and gemcitabine was initiated. Anuria developed after the second cycle and patient died of the disease 5 years after the initial diagnosis and 14 months after the diagnosis of gastric metastasis.

Histopathology is one of the most important parameters effecting prognosis and treatment results in breast cancer. Invasive ductal carcinoma is the most commonly seen histological type (47-75%). It is followed by invasive lobular, tubular, medullary, mucinous carcinomas, and other very rarely seen histological subtypes. Signet ring cell carcinoma is a rarely seen histopathological entity in breast.⁷

Mucinous carcinoma of the breast is commonly related to invasive lobular carcinoma due to the cellular similarities, and generally considered as a variant of the invasive lobular carcinoma.^{1,3} Some other authors found this concept debatable since these tumors could also frequently be seen with ductal carcinomas.² Therefore, it was suggested that it should be considered as cellular differentiation. It was also reported that the tumors with a dominance of signet ring cell component might be more aggressive and easily metastasize to serosal surfaces.⁸ Briest et al⁶ reported a case of signet ring cell carcinoma of the stomach with a metastatic involvement of breast. In our case, primary tumor with signet ring carcinoma pathology was in the breast and it had metastatic involvement in the stomach. Defining the

primary site may generally become a clinical problem in metastatic cases. Immunohistochemical studies have shown that signet ring cell carcinoma with a gastrointestinal origin had positivity with CK20 and CK7 and negativity with estrogen receptor (ER). The CK20 positivity rate was found to be only 5% in invasive lobular carcinoma. They were stained strongly with estrogen receptors.⁹ Our case was positive for ER. Therefore, she was evaluated as breast cancer with a metastatic involvement of the stomach. Metastatic involvement within the gastric mucosa is consistent with the literature indicating that they could easily metastasize to mucosal surfaces. Pambuccian et al⁵ reported CK7, carcinoembryogenic antigenic, ER and progesterone receptors (PgR) positivity in a case with a primary tumor in the breast that they diagnosed with cervicovaginal smear initially. The breast and stomach should be considered in signet ring cell carcinoma pathology. Recently, ER and PgR have been seen in gastric cancer tissues. No correlation was found between the level of ER and that of PgR. This result suggests that the PgR in gastric cancer tissue may also be estrogen independent.¹⁰ Therefore, it should be kept in mind that the gastrointestinal tract might be a metastatic site in breast cancer cases with signet ring cell dominance and dyspeptic signs should draw attention.

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References

1. Martinez V, Azzopardi JG. Invasive lobular carcinoma of the breast. Incidence and variants. *Histopathology* 1979; 3: 467-488.
2. Merine MS, Livelsi VA. Signet ring cell carcinoma of breast. A clinicopathologic analysis of 24 cases. *Cancer* 1981; 48: 1830-1837.
3. Liu SM, Chen DR. Signet ring cell carcinoma of the breast. *Pathol Int* 2000; 50: 67-70.
4. Kamiya M, Mizuguchi K, Yoshimoto M, Tanak M, Motegi S, Matushima H, et al. Cytologic diagnosis of signet ring cell carcinoma of the breast. *Acta Cytol* 1998; 42: 650-656.
5. Pambuccian SE, Bachowski GJ, Twigg LB. Signet ring cell lobular carcinoma of the breast presenting in a cervicovaginal smear. A case report. *Acta Cytol* 2000; 44: 824-830.
6. Briest S, Horn LC, Haupt R, Schneider JP, Schneider U, Hockel M. Metastasizing signet ring cell carcinoma of the stomach-mimicking bilateral inflammatory breast cancer. *Gynecol Oncol* 1999; 74: 491-494.

7. Perez CA, Taylor M. Breast: Stage Tis, T1 and T2 tumors, Chapter 50, p. 1259-1268. Perez CA, Brady LW, editors. *Principals and practice of Radiation Oncology*. 3rd ed. Philadelphia (PA): Lippincott, Raven; 1997.
8. Kennebeck CH, Alagoz T. Signet ring breast carcinoma metastases limited to the endometrium and cervix. *Gynecol Oncol* 1998; 71: 461-464.
9. Tot T. The role of cytokeratins 20 and 7 estrogen receptor analysis in separation of metastatic lobular carcinoma of the breast and metastatic signet ring cell carcinoma of the gastrointestinal tract. *APMIS* 2000; 108: 467-472.
10. Wu CW, Chi CW, Chang TJ, Lui WY, P'eng FK. Sex hormone receptors in gastric cancer. *Cancer* 1990; 65: 1396-1400.