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Diffuse gastric cancer with Krukenberg tumor: A case report and literature review

Manraj Khosla, Ali Imran, Panagiotis Fidias

ABSTRACT

Diffuse gastric carcinoma (DGC) is histologically characterized by increased intracellular mucin production, leading to a "signet ring cell differentiation" in tumor cells. Signet-ring tumor cells are often rapidly progressive in nature, with tumor cells diffusely infiltrating the stomach, leading to desmoplasia and thickening of the gastric wall (linitis plastica). Like intestinal gastric carcinoma (IGC), DGC can be associated with H. pylori infections, among other environmental factors such as smoking, alcohol, and socioeconomic status. DGC, however, is characterized by a higher mortality and poorer prognosis than IGC due to its rapid progression, higher metastatic potential, and delayed diagnosis. Common presentation in those with DGC include weight loss, generalized abdominal pain, nausea and vomiting. In our specific case, the rare presentation of DGC with metastasis to the peritoneum, small intestine, colon, left ovary and fallopian tube can be appreciated. A 54-year-old female presented with consistent, generalized abdominal pain, leading to an exploratory laparotomy for suspected adhesions. Examination revealed numerous tumors throughout the abdomen and pelvis, with omental and mesenteric implants. Multiple biopsies of the ovaries, mesenteric implants, and omental implants revealed well-defined glands lined by moderately atypical nuclei and focal luminal necrosis. Diagnosis of DGC with metastatic spread and Krukenberg tumors (KT) was made and treatment was initiated with palliative chemotherapy. DGC with KT is remarkably rare, as only 1% of metastatic ovarian tumors result from gastric primaries. The grim prognosis is due to rapid disease progression, advanced stage at presentation, and late diagnosis. As such, effective treatment for this subset of patients cannot be initiated.

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Keywords: Diffuse gastric carcinoma, Krukenberg tumors, Signet ring cells

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INTRODUCTION

Gastric carcinoma (GC) is one the most common malignancies in the world today. Nearly 1 million people are diagnosed worldwide annually, of which 730,000 die,

making GC the fourth most common cancerous process. In the US alone, 22,000 patients are diagnosed with GC each year, and nearly 11,000 die from the malignancy. Gastric carcinoma is more commonly present in men than their female counterparts [1]. Gastric carcinoma is divided into some different categories, of which gastric adenocarcinomas (GAC) predominate. The GAC are further divided into two subcategories; intestinal-type and diffuse-type. Risk factors for intestinal gastric carcinoma (IGC) include atrophic gastritis, *H. pylori*, and intestinal metaplasia/dysplasia secondary to environmental stimuli. For diffuse gastric carcinoma (DGC), risk factors include diet, smoking, alcohol, occupational exposures, infections (*H. pylori*) [2]. Common signs and symptoms are unintended weight loss, nausea and epigastric pain, while the most common physical examination finding is a palpable abdominal mass. DGC incorporates a poorer prognosis than IGC, with greater metastatic potential and rapid disease progression. Metastasis of DGC to the ovaries, known as Krukenberg tumors, is rarely seen and institute only 1–2% of ovarian malignancies. In this case report, we describe a unique of case DGC with peritoneal carcinomatosis and Krukenberg tumors, along with the regimen used for treatment.

CASE REPORT

A 54-year-old female was presented to the emergency department with diffuse abdominal pain. Computed tomography scan of the abdomen and pelvis depicted dilated loops of small bowel with partial obstruction and gradual tapering to the right lower quadrant. A preliminary diagnosis of small bowel obstruction was made and she was admitted to the hospital floor. Conservative measures were taken with IV fluids and pain management. Surgery consultation initially planned nasogastric tube placement, but due to improving condition, decided to continue conservative management. On the 5th day after admission, however, she was transferred to the OR for exploratory laparotomy and lysis of adhesions. Examination of the abdominal contents revealed a rigid and diffusely thickened stomach and peritoneal carcinomatosis. In addition, numerous tumors of unknown primary were present throughout the abdomen and pelvis. The tumors stretched from the small intestine to the colon and the left ovary, with multiple mesenteric tumor implants, omental tumor implants, and visceral peritoneal tumor implants in the retro-uterine cul-de-sac and pelvis. Multiple biopsies of the ovaries, mesenteric implants, omental implants, and peritoneal implants were taken for further assessment of the disease process. Histological analysis of the biopsies revealed adenocarcinoma of the left ovary with collections of signet ring cells and extensive lymphovascular invasion (Figure 1). Analysis of the mesenteric and omental implant biopsies showed well-defined glands lined by moderately atypical nuclei and focal luminal necrosis (Figure 2). Immunohistochemistry for further evaluation of malignancy demonstrated strong CDX-2, CK7 positivity, moderate CK 20 positivity and negative PAX8 and WT-1. Immunohistochemistry for HER-2 receptor was equivocal. FISH analysis for detection of genetic abnormalities revealed tumor cells to be negative for both HER-2 receptor and MET amplification. Serum levels of common tumor markers were found to be CEA of 0.08 (normal limit: 0–3 ng/ml), CA-125 of 26 (normal limit: <35 U/ml), and CA 19-9 of 18.7 (normal limit: <37). Based on the histomorphology, immunophenotypic profile, and gross examination, a diagnosis of diffuse type gastric adenocarcinoma with metastatic spread was made. Due to aggressive tumor biology, late patient presentation, and metastatic spread to distant sites, the patient was placed under hospice care. Palliative chemotherapy with the multi-drug regimen FOLFOX (folinic acid, 5-fluorouracil, and oxaliplatin) was initiated.

DISCUSSION

Gastric carcinoma is broadly divided into a few different variants; adenocarcinoma, lymphoma, gastrointestinal stromal tumors, and neuroendocrine tumors. The most common gastric malignancy is gastric adenocarcinoma (GAC), with a further division being made into two subcategories; diffuse-type (DGC), and intestinal type (IGC). Intestinal gastric carcinoma is more common in males and older age groups, as opposed to DGC, which is more common in younger age groups with equal

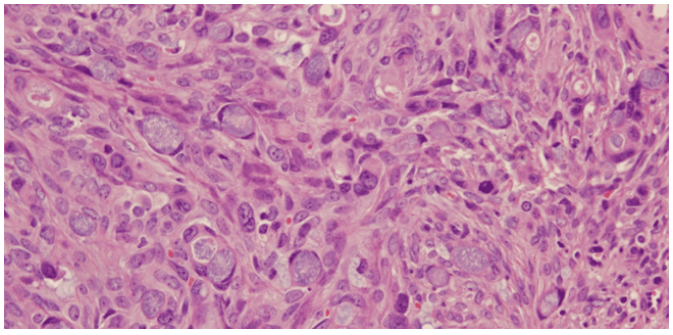

Figure 1: Ovarian metastasis with signet ring cells (H&E stain, x40).

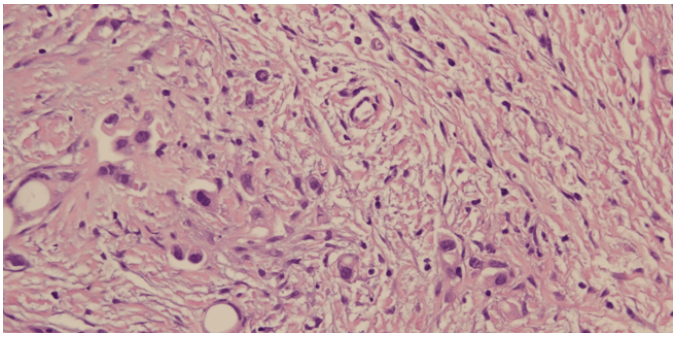

Figure 2: Omental metastasis with infiltrating tumore cells (H&E stain, x40).

sex distribution. Gastric adenocarcinoma arises from the gastric epithelium and is the most common malignancy of the stomach, instituting 90% of cases. Malignancies that arise from connective tissue and lymphatics are less common. In addition to location, GAC is also classified by histological appearance, such as tubular, signet ring cell, mucinous, papillary, or undifferentiated carcinoma. Molecularly, IGC and DGC can be differentiated based upon presence of surface-protein intercellular adhesion molecules, known as E-cadherin. IGC portrays a preservation of these adhesion molecules between cells. DGC, however, depicts a dysfunction in the E-cadherin protein. As such, DGC presents with a greater metastatic potential and rapid progression, invariably leading to a poorer prognosis [3].

The lack of specific physical findings, coupled with a later presentation and higher metastatic potential in DGC precludes a favorable prognosis. Despite the presence of signet ring cells, studies have shown that signet ring cell histology is not an independent prognostic determinant for the progression of malignancy. In a study by Kim et al. [4], the clinicopathological features and prognosis of patients with signet ring cell carcinomas (SRC) and non-signet ring cell carcinomas (NSRC) was studied. Of 2,358 patients diagnosed with GC, there were 2154 with NSRC and 204 patients with SRC. It was concluded that signet ring cell histology did not infer a worse prognosis than patients with other types of GC. However, differentiation must be made in the advancement of disease in relation to signet ring cell histology. According to a study by Yokota et al. [5] patients with early SRC had a favorable prognosis in comparison to other types of GC. This was different than patients with advanced SRC, which possessed a poorer prognosis when compared to other types of this disease.

Metastasis in DGC is commonly seen due to a predilection of DGC to invade the gastric wall. Metastasis can occur in a variety of organs such as lungs, bone, or liver. Metastasis of DGC to the ovaries, however, known as Krukenberg tumors (KT), is rare, and make up only 1–2% of all ovarian tumors. In a study by Ummugul et al. [6], patients diagnosed with KT of GC origin were retrospectively analyzed. Of 1,755 patients, eight patients (0.45%) were diagnosed with KT. It was concluded that KT from a GC primary was rare, and patients with KT were frequently younger, usually during the premenopausal period. In our case, however, the unique presentation of KT in a postmenopausal female can be appreciated. Pathological evaluation exhibited signet ring cell differentiation of the gastric malignancy with metastasis to the omentum, mesentery, small intestine, colon, left ovary, and fallopian tube. The presence of KT, along with metastasis to other abdominal and pelvic organ indicated a late-stage malignancy and precluded a favorable prognosis or five-year survival rate.

In addition to clinical and histological findings, immunohistochemistry plays a vital role in determining malignant primary in metastatic gastric cancer. According to a study Park et al. [7], 314 primary adenocarcinomas of colorectal, gastric, lung, pancreatic, bile duct, breast, and ovaries were studied using the tissue array method. Results of the study confirmed that organ-specific immunostaining markers provided higher sensitivities and specificities, along with greater positive predictive values in detecting primary adenocarcinomas. In our specific case, the immunostaining method was used, along with clinical and histological evaluation, for confirmation of the diagnosis. Immunohistochemical markers were positive for CDX2 (gastrointestinal marker), CK7 and CK20 (glandular epithelial markers), and negative for PAX8 (gynecological, renal, thyroid markers), and WT-1 (ovarian marker) (Figures 3–7). Additional testing for HER-2 immunostaining was equivocal, FISH analysis for HER-2 was negative, and MET amplification was negative. Thus, a diffuse gastric malignancy was established in conjunction with histopathological findings.

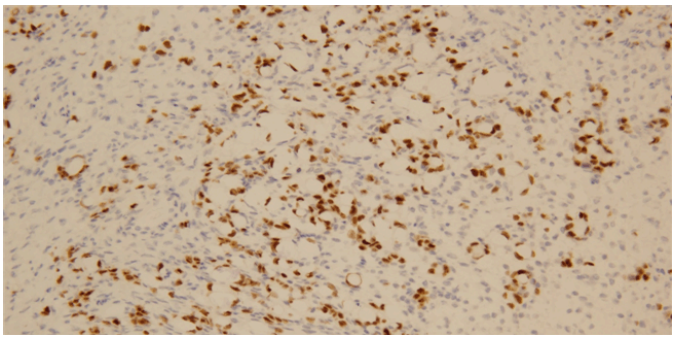

Figure 3: Ovarian metastasis, 20x, CDX2 immunostain - tumor cells strongly positive.

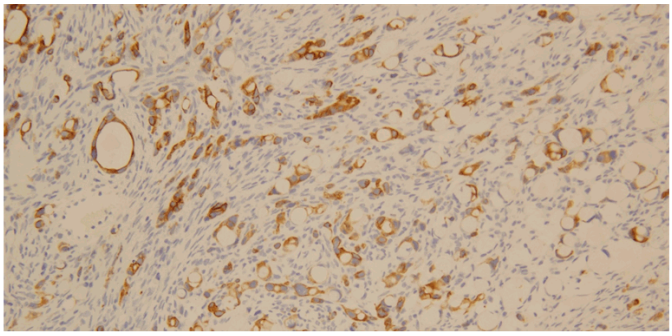

Figure 4: Ovarian metastasis, 20x, CK7 immunostain - tumor cells strongly positive.

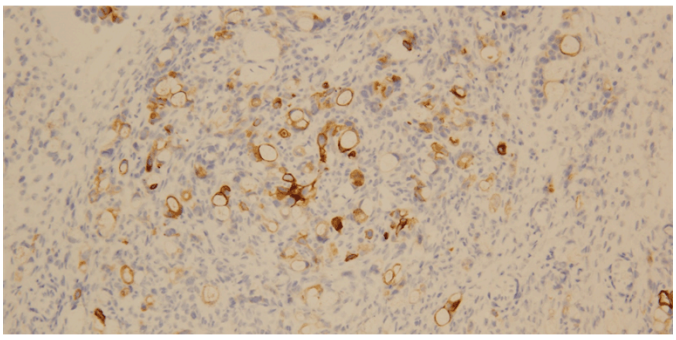

Figure 5: Ovarian metastasis, 20x, CK20 immunostain - tumor cells positive.

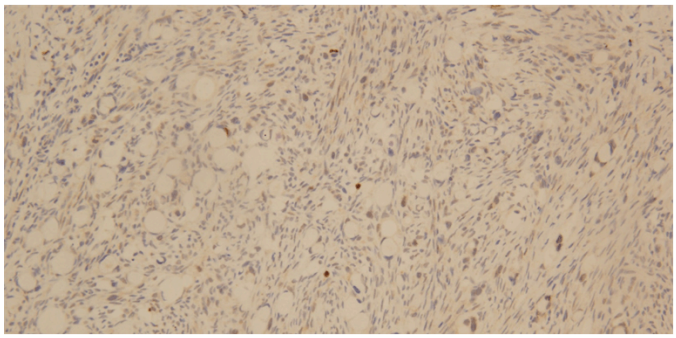

Figure 6: Ovarian metastasis, 20x, PAX-8 immunostain - tumor cells negative.

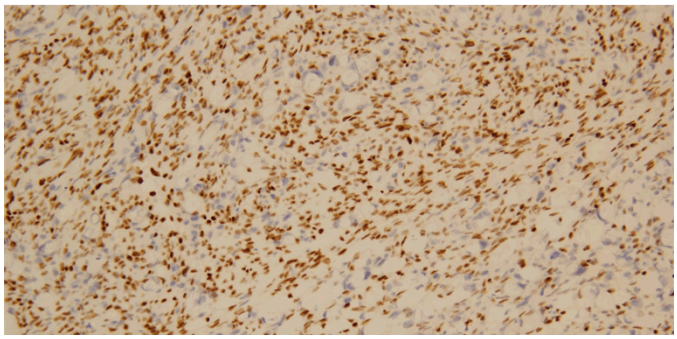

Figure 7: Ovarian metastasis, 20x, WT-1 immunostain - tumor nuclei negative.

The majority of patients with DGC present with advanced stage disease due to gastric muscle invasion and metastasis to distant sites. In this subpopulation of patients with metastatic, unresectable DGC, multi-agent therapy provides some benefit. In a study by Bhumsuk et al. [8], 73 patients with advanced gastric cancer (AGC) were treated with oxaliplatin, folinic acid, and 5-fluoruracil (modified FOLFOX). Results showed overall survival to be increased to 12.6 months with tolerable chemotherapy toxicity. It was concluded that the modified FOLFOX chemotherapy appeared to be a well-tolerated, adequate first line chemotherapy choice in AGC. EOX (epirubicin, oxaliplatin, capecitabine) is another chemotherapy regimen used. But despite being more efficacious than FOLFOX, it is less well tolerated [9, 10]. In our patient, DGC with metastasis to distant sites could be appreciated. Signet ring cells on histology with demonstration of lymphovascular involvement of the left ovary (Krukenberg tumors) and fallopian tube suggested lymphatic and/or hematogenous spread. Due to the malignant spread from the stomach diffusely throughout the abdomen and pelvis, curative treatment with resection was unobtainable. As a result of poor prognosis and low five-year survival rate, she opted to spend her final days in hospice care, where palliative chemotherapy was initiated with FOLFOX therapy.

CONCLUSION

Diffuse gastric carcinoma (DGC) with metastasis and Krukenberg tumors is a rare cause of gastric carcinoma, with a prognosis that is unfavorable. The prognostic factors leading to a low five-year survival rate is due to advanced malignancy stage at presentation, metastasis, and rapid disease progression. Due to this poor presentation, effective treatment cannot be initiated. In the case of our patient, DGC with diffuse metastatic spread was made after histological and immunohistochemical evaluation of tumor biopsies. Due to the overwhelming spread of the malignancy, treatment in our patient with resection could not be done. Instead, she was started on FOLFOX chemotherapy as a palliative measure. DGC with widespread metastasis carries a poor prognosis that is rapidly progressive in nature. Due to the dismal outlook for patients, importance is placed upon palliation and psychological support.

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Author Contributions

Manraj Khosla – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Ali Imran – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Panagiotis Fidias – Analysis and interpretation of data, Drafting the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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