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Late Recurrence in Gastric Cancer: A Rare Case Report

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ABSTRACT

Gastric cancer (GC) is a common malignancy with a high mortality rate. Survival has improved due to advances in curative and palliative treatments. Treatment gold-standard remains complete radical surgical resection. Most recurrences happen in the first 2 years after surgery. Peritoneum is the most common site, but peritoneal late recurrences, as well bone metastases are rare. Both carry a dismal prognosis, with limited treatment options. We present a case of a GC late recurrence with peritoneal and bone metastases, 20 years after curative surgery. A 61-year-old male submitted to a total gastrectomy for a locally advanced gastric adenocarcinoma (GA) in 2002. No adjuvant treatment was accomplished, disease was considered on remission and follow-up was withdrawal after 12 years. In 2022, during workup for hematochezia and anemia, GC recurrence was suspected. Bone biopsy and exploratory laparotomy were performed, confirming GA recurrence in the form of bone metastases and bulky peritoneal mass. Patient was proposed to palliative chemotherapy. Recent treatment strategies improved GC patients' survival. Understanding recurrences' patterns and timing is essential. Certain clinicopathologic factors are associated with specific patterns, but clinically predictive models are lacking. Diffuse subtype, infiltrative growth/serosal invasion, and lymph node involvement at diagnosis favor peritoneal recurrences. Bone recurrence is more frequent at younger age, proximal tumors, advanced GC, and diffuse subtype. Systemic chemotherapy is rarely curative in these cases. Few reports exist in the literature regarding late recurrences. GC is an aggressive disease with high risk for recurrence, usually associated with poor survival. Late recurrences, especially decades after curative surgery, are exceedingly rare. Peritoneal spreading is the main cause treatment failure and death, and bone metastases are rare. Unfortunately, treatment options are limited, and survival is very poor.

Key words: gastric cancer, recurrence, peritoneal metastasis, bone metastasis, surgery, paliative treatment

Abbreviations:
CA19.9: carbohydrate antigen 19.9;
CAM5.2: cytokeratin marker 5.2;
CDX2: caudal-related homeobox transcription factor 2;
CEA: carcinoembryonic antigen;
CK7: cytokeratin 7;
CK 20: cytokeratin 20;
EBV: Epstein-Barr Virus;
HER2: human epidermal growth factor receptor 2;
MMR: mismatch repair;
PD-L1: programmed death-ligand 1;
ng/mL: nanograms per milliliter;
U/mL: units per milliliter;
GC: Gastric cancer;
GA: gastric adenocarcinoma.

INTRODUCTION

Gastric cancer (GC) is the fifth most common malignancy and the fourth leading cause of cancer-related death worldwide, with an estimated incidence of 1.08 million new cases, causing 750.000 deaths annually (1,2). Global

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incidence has been decreasing due to screening and early diagnosis, dietary changes, and Helicobacter pylori eradication, but numbers among older adults are increasing. Prevalence remains stable. The gold-standard in treatment remains complete radical surgical resection, sometimes associated with peri-operative systemic therapies. Survival has been improving, especially in the last two decades, due to advances in curative strategies, as well as palliative treatments (3). For any disease stage, 5-year survival rate is nearly 26% in Europe (4), and few stage IV disease patients live longer than 5 years after diagnosis (3). Recurrences after surgery limit survival, achieving 40-61% after curative gastrectomy (5,2) and 10-46% of patients have metachronous peritoneal recurrence (6). Most recurrences (50-80%) occur in the first 2 years after surgery (5,7), and rarely over 4 years. Recurrence-free survival ranges between 8,5-14 months, and, after its diagnosis, survival is nearly 6 months (7,8).

Not all GCs recur in the same way. Recurrences can follow a pattern of locoregional, distant or hematogenous, and peritoneal spread (2,6). Most frequent locations are peritoneum, liver, lung, bone, and brain. Different tumor biology, primary treatment , and recurrence presentation and timing need to be taken into consideration (2). Previous lymph node involvement and age have no association with recurrence pattern, and 26% of patients do not have a specific documented pattern, with two-thirds having recurrence in only one site (5). Proximal tumors, early T stage (T1-2), intestinal subtype, and male gender tend to recur in a locoregional /distant pattern, with less than 20% having peritoneal disease (5). Peritoneal recurrences, as high as 72%, occur more often in cases of distal tumors, advanced T stage (T3-4), diffuse subtype and female gender. Less than 30% of these patients have locoregional/distant disease (5). After recurrence, factors associated with earlier mortality are more advanced stage at diagnosis, initial lymph node involvement, older age, symptoms at recurrence, and recurrence in more than one site (5).

Peritoneum is the most frequent recurrence site. Spreading occurs through lymphatics and seeding is due to serosal invasion. Peritoneal metastases usually are the cause of death. At diagnosis, 53-60% of stage II-IV GC have peritoneal metastases, but peritoneal late recurrences are extremely rare. Peritoneal carcinomatosis symptoms can be unspecific, delaying diagnosis. Disease usually progresses under chemotherapy, and bulky tumoral growth in the mesenteric root can cause abdominal pain and distention, ascites, and intestinal obstruction. Response to palliative treatments is poor and patients have a dismal prognosis, with a median survival of 4–7 months. Regimens like triplet FLOT, XELOX and FOLFOX can be employed (9).

Bone metastases are rare, occurring in 0,9-13,4% of GC patients (10,11), more frequently in individual younger than 65 years-old, with proximal tumors (cardia/gastric body versus antrum/pylorus), and in stage IV, poorly differentiated GC, and diffuse subtype gastric adenocarcinoma (GA)(12). Nearly 80% of patients have metastases in multiple sites, most frequently in the axial skeleton (spine, pelvis, ribs, and sternum). Prognosis is also dismal, with a mean survival of 8 months (3-14 months)(12). Treatment options are limited. Traditional chemotherapy regimens, targeted drugs, and immunotherapy can relieve symptoms. First-line chemotherapy drugs are platinum-derivatives and 5-fluouracil. Few first-line agents are approved in metastatic HER2-positive GC (12).

We present a case of a patient with a late recurrence of GC in the form of peritoneal and bone metastases, 20 years after curative surgical resection.

CASE REPORT

A 61 years-old Caucasian male with a past medical history of a GA submitted to an open total gastrectomy with D1-lymphadenectomy with Roux-en-Y reconstruction 20 years earlier, in 2002. Patient remained otherwise healthy, no alcohol consuming or smoking habits. He had no family history of gastrointestinal or hereditary malignant tumors. Primary GC was in the small curvature of the gastric body, had 3 centimeters in length, with no evidence of metastatic disease at diagnosis. Histopathologic examination of surgical specimen revealed an ulcerated GA, with signet ring cells, diffuse subtype, serosal invasion, and positive lymph nodes. Tumor had perineural invasion, but no signs of vascular invasion were evident. Pathological staging was pT3N1M0. No adjuvant treatment was accomplished. A computed tomography (CT)-scan and upper endoscopy performed in 2014 had no evidence of recurrence, and tumor serum markers were normal (CEA 2 ng/mL (0-3); CA19.9 4 U/mL (0-37); alpha-fetoprotein 5,3 ng/mL (1-8)). Patient was followed in our institution for 12 years and disease was considered on remission.

In 2022, due to hematochezia and anemia over a few months course, patient underwent a colonoscopy, showing a plan ulcerated lesion at splenic colonic flexure. Endoscopic biopsy revealed an adenocarcinoma (no further information provided). Only CA19.9 was elevated (131 U/mL), other tumor serum markers were normal.

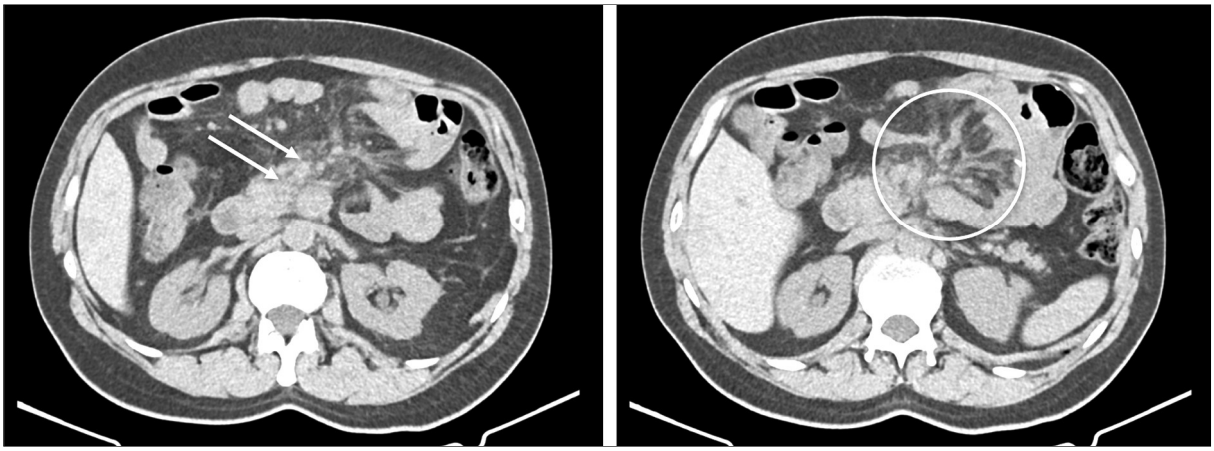

Figure 1 - Axial reconstructed CT-scan images revealing a bulky mass was present in the mesenteric root (white arrows) with mesocolon and mesenteric retraction (white circle), with apparent colonic wall invasion

Thoraco-abdominopelvic CT-scan (*fig. 1* and *2*) showed wall thickening of transverse colon with mesocolon and mesenteric retraction, and apparent invasion of the colonic wall at the splenic flexure. A bulky volumous mass was present in the mesenteric root and several mesenteric and lumbo-aortic adenopathy were found. Common bile duct and intrahepatic biliary tree were slightly dilated, and pancreatic head was heterogenous. Esophago-jejunal anastomosis was otherwise normal, with no sign of tumor recurrence at this level. Multiple sclerosing lesions, diffusely distributed, were found in the spine, ribs, sternum, and hip bone. No evidence of thoracic metastasis. Bone scintigraphy with tecnesium-99m revealed multifocal/disseminated bone lesions, and its biopsy confirmed the presence of a poorly cohesive adenocarcinoma metastasis, from gastrointestinal origin.

Case was discussed in multidisciplinary meeting and patient was proposed to exploratory laparotomy. Intraoperatively, we found a bulky infiltration of the mesenteric root of jejunum, including biliopancreatic and alimentary loops, enrolling transverse mesocolon with multiple adhesions and colonic wall invasion at splenic flexure. Esophago-jejunal anastomosis was normal. Mesenteric peritoneal mass was biopsied, and histopathologic exam confirmed GA recurrence.

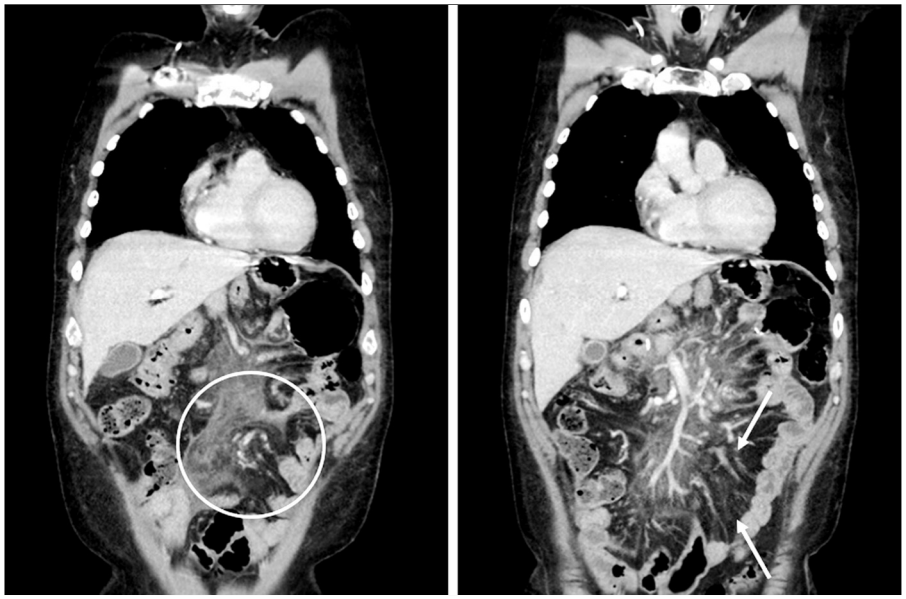

Figure 2 - Coronal reconstructed CT-scan images showing a volumous mass extending along the mesenteric root (white circle), with several mesenteric and lumbo-aortic adenopathy (white arrows)

Immunohistochemistry studies revealed CAM5.2, CK7 and CDX2 expression, but no expression of cytokeratin 20. Testing for microsatellite instability and HER2 were negative, and PD-L1 was expressed in 60% of clone tumoral cells.

Post-operative period was uneventful, and patient was discharged home at day 7 after surgery. Patient was proposed to palliative chemotherapy. He is currently in the 6th month follow-up after recurrence diagnosis, under FOLFOX chemotherapy regimen.

DISCUSSION

Recent treatment strategies improved GC patients' survival, especially in the long-term (8,13). Complete radical surgical resection of the primary tumor, with appropriate lymphadenectomy, remains the cornerstone of curative treatment (14,7). Patients with locally advanced disease (cT3 and/or positive lymph nodes) at diagnosis require multimodal treatment. Accurate staging is critical to define appropriate strategy, but more effective adjuvant therapies are needed. If diagnosed today, our patient would have been submitted to diagnostic laparoscopy and proposed to neoadjuvant chemotherapy if lymph node involvement was confirmed and/or peritoneal cytology was positive. Due to pathological staging (pT3N1M0), he would also be proposed for adjuvant chemotherapy, which was not advocated back then.

Understanding the pattern, timing, common sites, and impact of recurrences is essential. Differences in those patterns are multifactorial and may correlate with tumor biology, operative technique, and perioperative therapies (7). Certain clinicopathologic factors are associated with specific patterns, but clinically relevant predictive models for adjuvant therapy planning, that could also help defining a more reliable follow-up strategy, improving treatment outcomes and survival, are lacking (8).

In our case, T3 stage at diagnosis and diffuse GA subtype favor peritoneal recurrence. However, male gender and a proximal tumor would rather predict locoregional/distant recurrence. Patient accomplished 12 years of follow-up after surgery and recurrence was diagnosed another 10 years after.

Peritoneal recurrence is often perceived as unsurprising and somewhat unavoidable. Systemic (neo)-adjuvant therapies seem to be ineffective in preventing it, especially in initially advanced GC (8,15). Diffuse subtype, infiltrative growth/serosal invasion, and lymph node involvement appear to favor peritoneal recurrences. Bone recurrence is rarer, and more frequent in younger age, proximal tumors, advanced GC, and diffuse subtype. Our patient had a late recurrence, 20 years after primary GC surgery, in the form of peritoneal and bone metastases. Some characteristics made him more susceptible to peritoneal (advanced stage at diagnosis and serosal invasion) and bone metastases (61 years-old at primary surgery, advanced stage, gastric body tumor and diffuse subtype).

Several studies demonstrate systemic chemotherapy superiority over best supportive care in recurrences (6). Unfortunately, it is rarely curative. Further treatment options are needed. Molecular GA subclassifications have been developed and might offer an opportunity to treat recurrent GC (5). Guidelines recommend molecular tumor testing for MMR genes, HER2, EBV, and PD-L1. Some agents like trastuzumab, pembrolizumab, bevacizumab, and apatinib have all been approved in selected GA patients (12). None proved to be curative, which may be explained by mutational diversity and a high degree of primary-metastasis and intratumor heterogeneity (12).

There are very few reports in literature regarding late GA recurrences. Some describe peritoneal disease as a solitary metastasis (16) or a volumous colonic metastasis (17) in alpha-fetoprotein-producing GC occurring few time after primary resection. Aihara, R. et al. described a case of a 46 years-old man with peritoneal recurrence as a pelvic mass diagnosed 12 years after curative surgery for advanced antral GC(18). Miyatani, K.et al. reported a case of a 65 years-old man, with peritoneal recurrence 13 months after total gastrectomy followed by adjuvant chemotherapy in an advanced GC(19). A study in Japan, published in 2022, reported 30 cases of GC recurrences 10 years after initial surgery. 60% of those cases occurred in female patients, with a mean age of 50-years-old at the time of surgery, and 82% of tumors were poorly differentiated /signet ring cell GC(20). As to our knowledge, there are no published reports of late recurrences with such a long time elapsed between primary resection and recurrence diagnosis in locally advanced GA.

CONCLUSIONS

Gastric cancer is an aggressive disease. Advanced tumor stage at initial diagnosis increases recurrence risk (2,21). Peritoneal spreading is the main cause treatment failure and death in GC (21). Bone metastases are rare but carry a dismal prognosis (12). Late recurrences, especially decades after initial curative surgery, are exceedingly rare. Multidisciplinary team discussion is

central to treatment strategy and multimodal therapy is essential to improve survival. Treatment options are still very limited in GC recurrences, and survival is very poor. Research is necessary to understand recurrence patterns and new treatment strategies need to be developed for those patients.

Authors' contribution

All listed contributors designed the study and did the collection and assembly of data as well as data analysis and interpretation. All authors wrote the manuscript and did its final approval.

Conflict of interest and source of funding

The authors have no conflict of interest to declare. No financial support and technical or other assistance were received.

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