

Appendix 1 Clinical specifications of each case

Case 1

A 67-year-old male with no known medication allergies or toxic habits, and a medical history that included treated arterial hypertension and peripheral vasculopathy, presented to our center with a two-month history of toxic syndrome, asthenia, and epigastralgia, along with a reported episode of upper gastrointestinal bleeding one day ago. Laboratory analysis revealed normocytic normochromic anemia.

A fibrogastroscopy was performed, revealing an ulcerated, irregular, friable, infiltrative lesion involving the prepyloric region of the antrum and deforming the pylorus. The bulb and the second portion of the duodenum were normal. A CT scan demonstrated thickening of the stomach walls in the antropyloric region, with two foci of fat infiltration and small locoregional lymph nodes on the lower aspect. Pathological findings from the fibrogastroscopy indicated infiltrating intestinal-type gastric adenocarcinoma.

The patient underwent exploratory laparoscopic surgery, during which a peritoneal implant in the falciform ligament was biopsied, testing positive for M1. The patient was diagnosed with infiltrating adenocarcinoma T3N2M1 and initiated first-line chemotherapy. A thoracoabdominal CT after three months, following three treatment cycles, revealed disease progression in the form of multiple osteoblastic bone metastases. A scintigraphy confirmed M1 at the L3 level; other blastic foci likely went unnoticed due to their subcentimeter size.

The treatment regimen was changed to second-line, but after one month, the patient experienced seizures. CT and MRI of the brain were performed, identifying leptomeningeal carcinomatosis. While considering a shift to third-line treatment, the patient passed away.

Case 2

A 67-year-old male with a history of hyperuricemia under medical treatment and a past renal lithiasis surgery presented at our center with a five-month history of abdominal pain alleviated by food intake. Laboratory data indicated mild elevation of a single tumor marker (carcinoembryonic antigen, 1.9 ng/mL; carbohydrate antigen 19-9, 2.0 U/mL; carbohydrate antigen 125, 44.5 U/mL; alpha-fetoprotein, 8.9 ng/mL) and no other significant abnormalities.

A fibrogastroscopy revealed an extensive ulcerated lesion

on the anterior aspect and greater curvature of the gastric body, with nodular protrusions friable upon endoscope passage. Endoscopic ultrasound (EUS) disclosed thickening of all layers of the gastric wall (10 mm), most pronounced in the submucosa and muscular layers, extending from the subcardial region to the distal body. Difficulty in distension with water instillation was observed. The overall findings suggested linitis plastica infiltration involving almost the entire gastric body, with the antrum remaining unaffected.

A CT scan revealed parietal thickening of the greater gastric curvature and a 7mm lymph node in the gastrohepatic ligament. PET/CT confirmed focal uptake in the gastric body and antrum, likely related to the studied process. Biopsy from the fibrogastroscopy revealed a pattern of gastric adenocarcinoma with linitis plastica features, leading to total gastrectomy with Y-Roux reconstruction. Perioperative pathology showed neoplastic cells in 11 out of 29 lymph nodes, prompting D2 lymphadenectomy. During surgery, three peritoneal implants were identified on the diaphragmatic domes. The patient was staged as diffuse gastric adenocarcinoma stage IV (T4aN3aM1).

First-line chemotherapy (cisplatin and 5FU) was initiated, and after three cycles, a thoracoabdominal CT and PET were conducted to assess evolution, revealing no macroscopic tumor activity. Subsequently, the patient underwent surgery again for peritonectomy of both diaphragmatic domes, resection of suspicious lesions in the mesentery, and instillation of hyperthermic intraperitoneal chemotherapy (HIPEC). Multiple follow-up thoracoabdominal CT scans were normal until, after 18 months from the initial diagnosis, sclerotic lesions were observed in the spine and pelvis, indicative of bone metastases (M1). Bone scintigraphy confirmed multiple M1 lesions in the skull, spine, rib cage, clavicle, left scapula, pelvis, sternum, and left femur.

In response to oncologic progression, chemotherapy with CBDCA and 5FU, along with zoledronate for bone-related events, was restarted. After three months, a thoracoabdominal CT to assess response showed an increase in the size and number of multiple bone metastases. Consequently, second-line chemotherapy with docetaxel was initiated. The patient experienced an episode of subocclusion in the splenic angle, likely due to peritoneal carcinomatosis. Emergency CT scans revealed a further increase in the size and number of bone metastases. Palliative care services were activated, and one month later,

the patient succumbed to the disease.

Case 3

A 68-year-old male with a medical history notable for pulmonary tuberculosis at the age of 23 and Dupuytren's disease presented with a one-year history of sporadic vomiting, postprandial regurgitation, and weight loss, prompting the performance of a fibrogastroscopy.

The fibrogastroscopy revealed a protruding lesion measuring 3 cm in maximum diameter on the posterior aspect and lesser curvature of the distal antrum, resulting in a circular stenotic retraction without obstructing the endoscope's passage. Pathological examination confirmed the presence of signet-ring cell carcinoma.

A thoracoabdominal CT scan demonstrated significant distension of the fundus and body of the stomach with stenosis attributed to thickening of the wall at the antrum from the known neoproliferative process. The lesion contacted the pancreatic head, prompting concerns about infiltration. Locoregional lymphadenopathies were observed in the hepatic hilum, measuring less than a centimeter, and a 12 mm node in the lesser gastric curvature adjacent to the left crus.

Endoscopic ultrasound (EUS) revealed marked hypoechoic thickening of all layers of the antral wall, indicative of the known neoproliferative process. The lesion made contact with the pancreas and the left hepatic lobe, but clear infiltration was not observed. Two metastatic-appearing lymph nodes, up to 15 mm in diameter, were identified in the gastrohepatic ligament. Staging classified the patient as T2N2M0, leading to the decision for a total gastrectomy with esophagojejunostomy and D2 lymphadenectomy. Adjuvant chemotherapy with the Mitomycin + Utefo regimen was initiated, and regular monitoring with thoracoabdominal CT scans showed no evidence of disease progression.

After 3 years and 3 months, the patient developed symptoms of postprandial fullness and abdominal pain. Elevated CEA levels prompted fibrogastroscopy and colonoscopy. While the former yielded normal results, the latter revealed two flat-elevated polyps in the sigmoid and up to ten depressed lesions in the right colon, transverse colon, and sigmoid. Biopsy results confirmed gastric

metastases of adenocarcinoma with signet-ring cells.

Given the disease-free interval and the atypical pattern of dissemination, exploratory laparoscopy was ruled out to assess for peritoneal carcinomatosis, which was not detected, enabling the patient to undergo total colectomy. Subsequent evaluations, including thoracoabdominal CT and bone scintigraphy, were performed to assess disease progression before initiating chemotherapy, revealing disseminated bone metastases. First-line chemotherapy with Carboplatin and Capecitabine was initiated.

After a year, disease progression manifested as an increase in the size and number of bone metastases and the development of leptomeningeal carcinomatosis involving the central nervous system. Ultimately, the patient succumbed to the disease.

Case 4

An 87-year-old male, currently under anticoagulation with warfarin (INR of 8) and presenting with melena, was admitted for an upper gastrointestinal endoscopy. The examination revealed a deep ulcer on the greater curvature at the mid-body level, characterized by irregular edges and retraction. Due to the patient's anticoagulation status, no biopsy was performed during the initial procedure. Subsequent to reevaluation a few days later, samples were obtained, indicating cohesive (diffuse) type gastric adenocarcinoma with the presence of signet ring cells, indicative of an invasive nature.

A thoracoabdominal CT scan was conducted, revealing no signs of local or distant extension. Given the patient's advanced age, a comprehensive assessment, in concordance with the family, concluded that aggressive maneuvers such as radical surgical intervention and lymphadenectomy combined with chemotherapy were not suitable. Consequently, the decision was made to optimize symptomatic medical treatment.

Over the course of 2 years, progressive monitoring through thoracoabdominal CT scans unveiled the emergence of bone metastases in the pelvis, vertebrae, ribs, sternum, and scapulae. Confirmation through bone scintigraphy indicated a pattern suggestive of medullary dissemination. Palliative support treatment was initiated, and the patient eventually succumbed to the disease.