Abstract

Background: The standard management of gastric cancer is complete resection if the lesion can be removed by surgery or endoscopic resection. Occasionally, some patients with gastric cancer are followed up without treatment for various reasons. However, there is little information about the natural course of gastric cancer, especially concerning the onset of symptoms. We herein report the chronological changes in a patient with asymptomatic early gastric cancer progressing to symptomatic unresectable advanced cancer.

Case Presentation: A 68-year-old man presented with epigastralgia. Esophagogastroduodenoscopy revealed a depressed lesion 35 mm in diameter at the lesser curvature of the upper gastric body (lesion 1) and a depressed lesion 40 mm in diameter at the posterior wall of the lower gastric body (lesion 2). The lesions were diagnosed as synchronous multifocal early gastric cancers, cT1bN0M, and cStage I, consisting of lesion 1 (U, Less, cT1b) and lesion 2 (M, Less, cT1a). Surgical treatment was strongly recommended, but he selected observation without any treatment. He received periodic follow-up every six months. The tumor progressed to a type 2 lesion after two years and then a type 3 lesion after two and a half years. At three years and nine months from the initial diagnosis, he requested treatment because of anorexia and weight loss of 5 kg. Gastric wall thickening and regional lymph node swelling were detected by computed tomography. Staging laparoscopy revealed massive peritoneal metastasis. The postoperative diagnosis was cT4aN+M1P1 and cStage IVB, and systemic chemotherapy was indicated.

Conclusion: Observation may be reasonable in asymptomatic patients with locally advanced gastric cancer who are expected to live for at least one year.
However, there is no detailed knowledge about the progression of symptoms when patients with early gastric cancer are followed without any treatment. We herein report a case in which we observed the progression from asymptomatic EGC to symptomatic unresectable Advanced Gastric Cancer (AGC).

Case Presentation

Patient’s History

A 68-year-old man was presenting with epigastric pain as the main complaint. He had no remarkable medical history. Physical examination revealed no palpable mass or tenderness in his abdomen with normal bowel sound. Blood tests showed no anemia or other abnormal findings. Esophagogastroduodenoscopy (EGD) revealed EGC and referred to our hospital. Two lesions were identified in the stomach. One was a superficial depressed lesion with redness 35 mm in diameter at the lesser curvature of the upper gastric body (Lesion 1, Figure 1A) and slightly central fold concentrations, where endoscopic ultrasonography showed a diffusely thickened hypoechoic region at the submucosa layer, suggesting submucosal invasion. The biopsy specimen revealed low to moderately differentiated adenocarcinoma. The second lesion was a slightly depressed lesion with erosion 40 mm in diameter at the lesser curvature of the posterior wall of the lower gastric body, suggesting mucosal lesion with ulceration (Lesion 2, Figure 1B). The biopsy specimen revealed moderately differentiated adenocarcinoma. We diagnosed the lesions as synchronous multifocal EGCs, cT1bN0M0, and cStage I, consisting of lesion 1 (U, Less, cT1b) and lesion 2 (M, Less, cT1a) according to the 15th edition of the Japanese classification of gastric carcinoma [4].

Clinical Course

His epigastric pain immediately disappeared with the administration of a proton pump inhibitor. Since neither of the lesions was indicated for endoscopic resection, total gastrectomy was recommended. The patient was informed that total gastrectomy was recommended due to possible lymph node metastasis. Additionally, he explained that endoscopic treatment could be considered although the possibility of lymph node recurrence could not be excluded. However, the patient rejected all treatment, including surgery as a primary recommendation and endoscopic treatment as a secondary recommendation, despite our repeated explanation that treatment-free could result in critical condition. We therefore decided to follow him up periodically. At six months after the initial examination, the folds of Lesion 1 had become more concentrated and conspicuous, and lesion 2 showed ulceration with elevated lesion. After 12 months, the gastric wall of lesion 1 had thickened with a clear raised margin (Figure 2A, D), and it changed to an ulcerated lesion extending to the cardia. Elevated boundaries became more obvious 24 months later, suggesting invasion to the muscularis propria (Figure 2B, E). After 36 months, lesion 1 had extended further, and the boundaries of the posterior wall were obscured with giant folds, suggesting invasion to the serosa (Figure 2C, F).
Figure 2: Chronological endoscopic changes in early gastric cancers. At 12 months from the initial examination the gastric wall of lesion 1 had thickened with a clear raised margin (A), while lesion 2 showed ulceration with elevated lesion (D). After 24 months, lesion 1 changed to an ulcerated lesion extending to the cardia, and the elevated boundaries were more obvious, indicating invasion of the muscularis propria (B,E). After 36 months, lesion 1 had extended further, and the boundaries of the posterior wall were obscured with giant folds (C). Lesion 2 also showed thickening of the gastric wall (F).

At 45 months after the initial diagnosis, the patient complained anorexia and developed 5 kg weight loss. He finally requested surgical resection. Endoscopically, lesion 1 involved lesion 2 and had formed giant folds (Figures 3A, B). Abdominal Computed Tomography (CT) showed circumferential wall thickening from the esophagus to the lower part of the body and enlarged lesser curvature lymph nodes (Figures 3C, D). Staging laparoscopy revealed that the tumor was extensively exposed on the serosa, mainly located in the cardia, and the lesser omentum was thickened by Peritoneal Metastasis (PM) (Figure 3E). Disseminated nodules were also found on the left diaphragmatic surface and rectovesical fossa (Figure 3F). Peritoneal lavage cytology was positive for cancer cells. The postoperative diagnosis was unresectable AGC, cT4aN+M1P1, and cStage IVB. He agreed to undergo systemic chemotherapy.
Figure 3: Clinical findings 45 months after the initial diagnosis when the patient requested surgical resection, complaining of anorexia and weight loss. Endoscopically, lesion 1 involved lesion 2, forming giant folds (A,B). Abdominal CT showed circumferential wall thickening from the esophagus to the lower part of the gastric body and enlarged lesser curvature lymph nodes (C, D). Staging laparoscopy revealed that the tumor was extensively exposed on the serosa, mainly located in the cardia, and the lesser omentum was thickened by peritoneal dissemination (E). Disseminated nodules were also found on the left diaphragmatic surface (F).

Discussion

The present case showed the natural history of EGC observed without any treatment. The lesion in the upper third of the stomach was a mixed-type adenocarcinoma with submucosal invasion, and the other lesion in the middle body was an intestinal-type intramucosal adenocarcinoma with ulceration. Despite our strong recommendation for surgery as standard treatment, the patient rejected surgery and requested observation [5]. At three years and nine months from the initial examination, he complained of anorexia and required initiation of treatment. However, unfortunately, staging laparoscopy revealed the disease had progressed to an unresectable AGC with PM, resulting in a missed opportunity for curative treatment and the need to undergo systemic chemotherapy instead. Among endoscopic findings, the lesion at the upper body changed from a slightly depressed lesion (type 0-IIc lesion) to an ulcerated lesion (type 2 lesion), involving the other lesion at the lower body, and the two lesions formed one large type 3-like lesion with giant folds. Several previous reports have described the morphological changes of EGC, mainly including single lesions. Similar changes were observed in synchronous multiple EGCs, except that the lesions were involved and transformed into a single-like lesion [1,2,6].

The type 0-IIc lesion at the upper body appeared to be limited to submucosal invasion for one year after the diagnosis but morphologically changed to a type 2 AGC after another year in this case. Two previous case reports showed that the progression time from T1a to T1b was approximately three years, and that from T1b to T2 was two years.[1,2] Another study reported that it took 34-44 months for gastric cancer to progress from EGC to AGC. [3,7] Considering that the present lesion was EGC with the deep submucosal invasion at the initial examination, the chronological course was consistent with previous reports. After the initiation of a proton pump inhibitor, the patient’s epigastric pain disappeared, and he subsequently had no subjective symptoms for one year and nine months, even after the type 0-IIc EGC progressed to type 2 AGC. Symptoms of upper gastrointestinal bleeding with or without anemia and epigastric pain tend to appear in EGCs and benign ulcers, while anorexia and weight loss often occur in AGCs, which
are known as alarm symptoms.[8,9] Although previous studies reported on the association of the duration of the symptoms with the outcome of GC or cancer stage, when the tumor-related symptoms develop following cancer progression has been unclear.[8] Iwai et al. reported the natural history of EGC of a very elderly patient in their 80s with severe comorbidities.[2] Anemia appeared six months after the tumor invaded the intramuscular layer, and then anorexia developed after another year. The symptoms appeared in a shorter interval than in the present case, possibly because the tumor was morphologically prone to bleeding. The location of the tumor may also affect the duration of the asymptomatic period. In cases of AGCs at the cardia or antrum, which can lead to stenosis, tumor-related symptoms are expected to manifest at an earlier point.

In the present case, the tumor had already spread to the peritoneum diffusely when the symptoms related to the tumor developed, indicating that surgical tumor removal was impossible. In the study of Bowrey et al., approximately 50% of patients with alarm symptoms had stage IV disease.[9] Furthermore, Kobayashi et al. reported that the non-curative resection rate in AGCs exposed beyond the serosa with tumor-related symptoms was 35%, and the non-curative factor was PM in 61% of cases.[10] While we cannot precisely pinpoint how long curative resection was possible, it is unlikely that PM had already occurred when the patient developed type 2 AGC 24 months later, as the PM rate is low in patients with type 2 AGC, and patients with PM would not survive for one year and nine months without treatment.[11,12] For asymptomatic patients with AGC and an elderly age or severe systemic disease, treatment-free observation may be selected as the clinical management occasionally. However, it should be noted that the window of time for symptoms to appear is at most one to two years, during which the curative potential might be lost.

**Conclusion**

The present case showed the chronological change of EGC progressing to a large, unresectable type 3 AGC with PM. Patients with early gastric cancer are expected to be asymptomatic for at least one year with no treatment but to progress to unresectable diseases in a few years. This may be helpful in selecting treatment for patients with a short or frail prognosis.

**References**