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Treatment of synchronous adenocarcinoma and lymphoma of the stomach: A case report

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Abstract. Gastric cancer is one of the leading causes of cancer-related mortality worldwide. The majority of gastric cancers are diagnosed at an advanced or metastatic stage, with a 5-year survival rate of ~5-20% and a median overall survival of <1 year. Synchronous occurrence of gastric adenocarcinoma and lymphoma is rare, and thus far there is no consensus regarding their management. We herein describe a case of synchronous gastric adenocarcinoma and diffuse large B-cell lymphoma in a patient with chronic hepatitis B and the treatment strategy. A literature review with the most up-to-date treatment options and their application in similar situations was also performed.

Introduction

Gastric cancer is the second most common cause of cancer-related mortality and the fourth most commonly diagnosed type of cancer worldwide (1,2). The majority of gastric cancers are diagnosed at an advanced or metastatic stage, with a 5-year survival rate of 5-20% and a median overall survival of <1 year (1). In countries with a high gastric cancer prevalence, such as Japan, early screening programs help to detect early-stage gastric cancer, which has a 5-year survival rate of 90%. The three most common types of gastric malignancies are gastric adenocarcinoma, gastrointestinal stromal tumor and primary gastric lymphoma. The occurrence of synchronous gastric adenocarcinoma and lymphoma is rare, and there is currently no consensus regarding their management. Thus, decision-making regarding the optimal treatment strategy may be challenging.

We herein describe the case of a patient who was diagnosed with synchronous gastric adenocarcinoma and gastric diffuse large B-cell lymphoma. Prioritizing treatment in such patients is crucial, and certain factors, such as *Helicobacter pylori* (*H. pylori*) infection, must be taken into consideration during the decision-making process.

Case report

A 51-year-old Chinese man was referred to the Taichung Veterans General Hospital from a community hospital with a history of general malaise, poor appetite, abdominal fullness and a weight loss of 10% over the past month. The patient was a chronic hepatitis B carrier, had a 30 pack-year smoking history (one pack per day for 30 years), and had suffered from epigastric discomfort for several years without seeking medical attention. There was no fever or night sweats. An abdominal contrast-enhanced computed tomography scan revealed multiple lymphadenopathies in the abdominal cavity, and the initial esophagogastroduodenoscopy revealed an irregularly elevated area in the lower-to-middle gastric body; the biopsies showed moderately differentiated adenocarcinoma and diffuse mixed small and large B-cell lymphoma. No *H. pylori* was identified on examination of Giemsa-stained specimens. As the patient refused total gastrectomy, one cycle of epirubicin, cisplatin and fluorouracil (ECF regimen) was initially administered for gastric adenocarcinoma as neoadjuvant therapy; 1 month later, a bone marrow biopsy revealed diffuse mixed small and large B-cell lymphoma negative for CD20 expression, and the patient received 8 cycles of cyclophosphamide, adriamycin, vincristine and prednisone (CHOP regimen).

Seven months later, the patient underwent distal subtotal gastrectomy and the pathological examination confirmed the diagnosis of poorly differentiated adenocarcinoma (Fig. 1) and diffuse large B-cell lymphoma (DLBCL) (Fig. 2), positive for CD20 and negative for *H. pylori*. Following surgery, the patient received 8 cycles of rituximab, cyclophosphamide, mitoxantrone, vincristine and prednisone (R-CNOP regimen) instead of CHOP to reduce cardiotoxicity, and achieved

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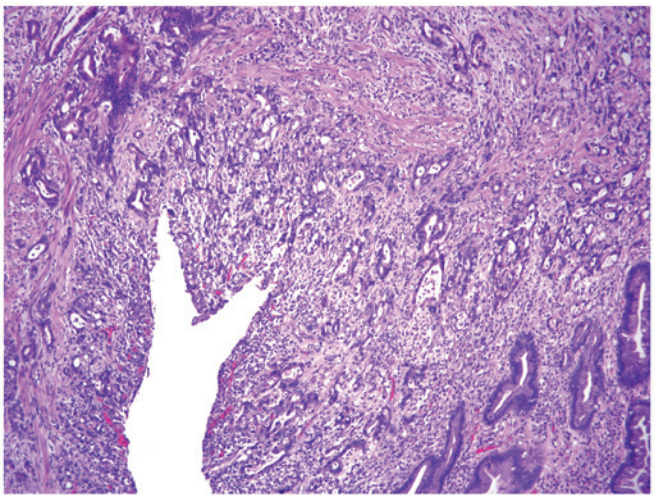

Figure 1. Gastric adenocarcinoma invading through the muscularis mucosa, with abortive glandular structure and infiltrative growth pattern. Hematoxylin and eosin staining; magnification, x100.

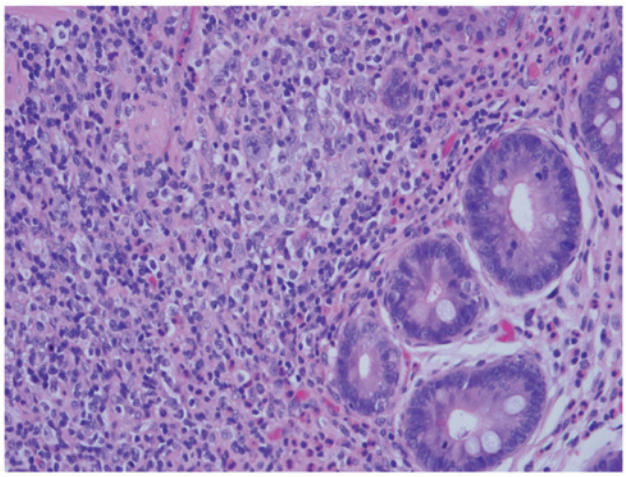

Figure 2. Large atypical lymphocytes infiltrating the lamina propria with sheet-like aggregations. Hematoxylin and eosin staining; magnification, x400.

complete remission of the DLBCL. The patient declined further chemotherapy for the gastric adenocarcinoma due to the deterioration of his liver function.

Three years later, the patient presented with obstructive jaundice. Laparoscopic biopsy at the porta hepatis showed moderately to poorly differentiated metastatic adenocarcinoma (Fig. 3). Immunohistochemical staining revealed 2+ human epidermal growth factor-2 (HER-2) expression. Four cycles of capecitabine plus oxaliplatin were administered and trastuzumab treatment was recommended. However, trastuzumab was not initiated due to the patient's financial difficulties. After 6 months, the patient achieved near complete remission radiographically and was followed up for another 6 months at the oncology clinic; however, he succumbed to metastatic disease after ~1 year.

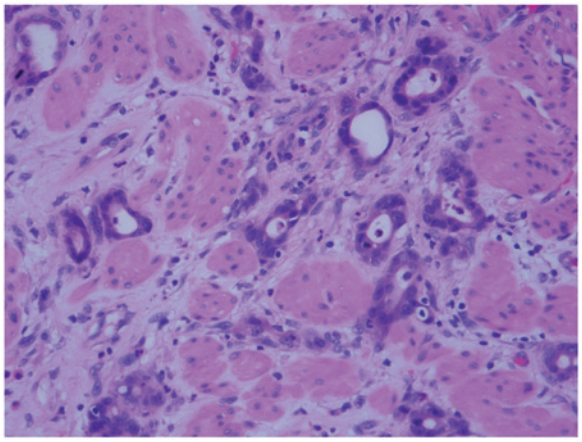

Figure 3. Abortive glandular structures invading the muscularis propria. Hematoxylin and eosin staining; magnification, x400.

Discussion

Gastric cancer is the second most common cause of cancer-related mortality worldwide (1-3). Approximately 70% of gastric cancer cases are associated with *H. pylori* infection, and 5.5% of all cancer cases globally are *H. pylori*-associated gastric cancer (2,4,5). *H. pylori* infection is very common in several parts of the world; its prevalence may be ≥50% in certain areas, particularly in developing countries (4). Among individuals infected by *H. pylori*, ~1-2% may develop gastric cancer, including adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma (3,6,7). Risk factors include the strain of *H. pylori*, the duration of the infection, host genetic polymorphisms, and diet or other environmental factors (8-13). In cases with synchronous adenocarcinoma and lymphoma, *H. pylori* infection was present in 92% of the cases in Eastern countries and 68% of the cases in Western countries (14), although it remains rare for synchronous tumors. Among all histological types of gastric lymphoma, DLBCL and MALT lymphoma are the types most significantly associated with *H. pylori* infection (15,16). The possible mechanism underlying *H. pylori* as a causative factor for gastric lymphoma is that chronic infection with *H. pylori* causes hormonal and cellular changes and damages the gastric cells. The damaged gastric cells then induce clonal expansion of B cells (17,18). Thus, the current concept suggests *H. pylori* eradication as an effective method in treating low-grade gastric lymphoma (18,19). In high-grade gastric lymphoma or DLBCL, due to a higher number of genetic mutations, the response to *H. pylori* eradication appears to be more limited (15,20).

The positive correlations between Epstein-Barr virus (EBV) infection, gastric carcinoma and DLBCL have been investigated and confirmed (21,22). Approximately 10% of gastric carcinomas are EBV-positive, as are 9% of DLBCLs (21,22). The positivity of EBV infection in patients with DLBCL is associated with poorer response to treatment and survival (22). Chronic HBV infection may increase the risk of non-Hodgkin lymphoma (NHL) by 3 times, particularly in DLBCL (23,24).

Our patient was diagnosed with synchronous gastric adenocarcinoma and diffuse large B-cell lymphoma, whereas *H. pylori* infection was not identified. Since the patient initially refused gastrectomy and was later found to have co-existing DLBCL with bone marrow involvement, the CHOP regimen was recommended prior to receiving subtotal gastrectomy, as DLBCL is an aggressive NHL and bone marrow involve-

ment indicates a more aggressive condition with a worse outcome. Patients with chronic hepatitis B infection may have compromised liver function and may not be able to tolerate the stronger hepatotoxicity associated with standard chemotherapy for gastric adenocarcinoma. Our patient presented with metastasis of residual adenocarcinoma 3 years after the gastrectomy. Although the patient responded well to standard chemotherapy, from 2010 onwards there is another option for patients with synchronous tumors and HER-2 positivity.

Studies suggest that the use of trastuzumab in patients with HER2-positive advanced gastric or gastro-oesophageal junction cancer significantly improved overall survival, with a 26% reduction in mortality and prolongation of the median overall survival (13.8 vs. 11.1 months) (1). The addition of trastuzumab to chemotherapy does not increase the toxicity associated with standard fluoropyrimidine-based (5-fluorouracil) and platinum-based chemotherapy (1). Treatment with trastuzumab and platinum may be a suitable and effective option for patients with HER-2-positive gastric adenocarcinoma who cannot tolerate strong hepatotoxicity. In the current 2016 NCCN guidelines for gastric cancer treatment, the addition of trastuzumab to standard chemotherapy is recommended as a first-line treatment option for HER-2-positive patients (25). For cases similar to our patient, trastuzumab may be added regardless of the status of HER-2 expression, since the biopsy result may not represent the expression status in all malignant tissues and tumor cells exhibit a high mutation rate.

In conclusion, for patients diagnosed with synchronous gastric adenocarcinoma and lymphoma, a number of factors must be taken into consideration during decision-making in terms of which cancer to treat first and which is the optimal regimen. EBV and HBV play important roles in adenocarcinoma as well as lymphoma. HER-2-positive patients with poor liver function may be treated with trastuzumab in addition to platinum-based chemotherapy. Surgical resection and subsequent pathological examination of the tumor may offer more precise information regarding the tumor types and optimal treatment.

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