Synchronous Gastric Carcinoma and Nodal Malignant Lymphoma: A Rare Case Report and Literature Review

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Key Words

Synchronous malignancies · Gastric carcinoma · Malignant lymphoma · Chemotherapy ·
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Abstract

Synchronous double malignancies of gastric carcinoma (GC) and malignant lymphoma (ML) are rare and very difficult to treat. We report a case of synchronous GC and nodal ML, regarding which clinical and pathological features and treatment are discussed. A 68-year-old woman with a history of inguinal hernia was admitted for abdominal pain and high fever and subsequently underwent herniorrhaphy, but the fever remained. Computerized tomography showed a stomach mass and multiple enlarged lymph nodes in the abdominal cavity and inguinal regions. Gastric adenocarcinoma coexistent with advanced in situ follicular lymphoma was confirmed by endoscopy, biopsy of inguinal lymph nodes and bone marrow examination. Two chemotherapy regimens, R-CHOP (rituximab, cyclophosphamide, perarubicin, vincristine and prednisone) and systemic therapy (5-fluorouracil and calcium folinate) combined with regional perfusion (oxaliplatin and etoposide) through the left gastric artery were performed at intervals against ML and GC, respectively. Partial remission in both tumors was achieved after 4 courses of treatment, but the patient finally died of heart failure. Scrupulous biopsy of non-draining lymph nodes in patients with gastrointestinal carcinomas is supposed to improve the diagnostic rate of simultaneous nodal ML. The interval chemotherapy strategy with two independent regimens is beneficial for such patients, especially for those unable to tolerate major surgery.

Introduction

Double primary tumors including synchronous and metachronous ones are uncommon, but have been reported relatively more frequently in recent years. The coexistence of gastric carcinoma (GC) with gastric malignant lymphoma (ML) or gastric mucosa-associated lymphoid tissue (MALT) lymphoma is uncommon; therefore, careful endoscopy, sampling and pathological detection may improve the diagnostic accuracy [1, 2]. Herein we present a very rare case of coexistent GC and nodal ML, the subtype of in situ follicular lymphoma (FL), which was effectively treated with interval chemotherapies including two different regimens.

Case Report

A 68-year-old woman with a 20-year history of a reducible right inguinal hernia was admitted to a basic hospital with complaints of abdominal pain for 40 hours and high intermittent fever for 1 month. The patient underwent herniorrhaphy but fatigue, high fever, abdominal distension, food reflux and loss of appetite remained. Computerized tomography of the abdomen indicated a mass in the lesser curvature of the stomach and multiple swollen lymph nodes in the peritoneal and retroperitoneal cavities. Then, the patient was transferred to our hospital.

A physical examination showed splenomegaly, ascites, and many enlarged lymph nodes which were hard, not painful and of poor motion in bilateral inguinal areas. Laboratory tests revealed anemia (hemoglobin 68 g/l), thrombocytopenia (platelet count $67 \times 10^9/l$), and elevated serum levels of lactate dehydrogenase (LDH) (440 U/l; normal range 60–240 U/l), cancer antigens 125 (110.7 IU/ml; normal range <35.0 IU/ml) and 19-9 (49.6 IU/ml; normal range <37.0 IU/ml). Ascites were detected as reddish exudates with increased LDH (359 U/l) but normal cancer antigen levels, and some lymphoma cells and many monocytes confirmed by exfoliative cytologic examinations. Sputum and blood cultures were negative. On gastroscopy, a 4×3 cm mucosal zone of erosion and contact bleeding was observed below the cardia on the lesser curvature. Histopathological examination demonstrated that the lesion was a moderately differentiated adenocarcinoma accompanied by chronic gastritis (fig. 1), with positive detection of *Helicobacter pylori* using rapid urease test and Warthin-Starry stain. The specimen of the swollen inguinal lymph nodes histologically displayed an atypical hyperplasia of lymphoid follicles, being strongly diffusely positive for CD20, Bcl-2 and Pax-5 and scattered positive for CD3, CD5 and Ki67, but negative for CD10 and Bcl-6 by immunohistochemistry (fig. 2). Microscopical examination of bone marrow revealed lymphoid hyperplasia with about 13.5% of infiltrated lymphoma cells (fig. 3). The chromosome analysis exhibited an abnormal karyotype, 50,XX, +1, +3, +8, +18, del(22)(q?)[1]/46,XX[14]. Epstein-Barr virus (EBV) and EBV-encoded RNA were negative in both specimens of lymph nodes and gastric tissue by immunohistochemistry and in situ hybridization, respectively. As regards serum EBV-specific antibodies, anti-capsid antigen (CA) IgM was negative and anti-nuclear antigen-1 IgG was weakly positive, but anti-CA IgA, anti-CA IgG and anti-early antigen IgG were significantly positive and had dynamic changes within 6 months. EBV copy numbers were twice negatively determined in the serum by real-time polymerase chain reaction.

The patient was finally diagnosed as GC coexisting with stage IVB nodal ML (in situ FL) and chronic gastritis, accompanied by present *H. pylori* infection and recent EBV infection. Stomach operation and biopsy of abdominal lymph nodes were not made because the patient had just undergone herniorrhaphy and could not tolerate them. The eradication therapy against *H. pylori* infection was made with rabeprazole (20 mg) daily and bismuth citrate (220 mg), tinidazole (500 mg), and clarithromycin (250 mg) twice daily for 1 week. Furthermore, an R-CHOP regimen with rituximab (375 mg/m², day 1), cyclophosphamide (750 mg/m², day 2), perarubicin (40 mg/m², day 2), vincristine (1.4 mg/m², day 2), and prednisone (60 mg, days 2–6) was used to treat the ML. The intravenous therapy with 5-fluorouracil (750 mg, days 1–5) and calcium folinate (200 mg, days 1–5), combining perfusion chemotherapy with oxaliplatin (150 mg, day 6) and etoposide (100 mg, day 6) through the left gastric artery, was performed against GC during intervals of R-CHOP. The patient reached partial remission in the two tumors after 4 courses of each regimen. However, severe thrombocytopenia delayed subsequent chemotherapies and she finally died of heart failure after discharge.

Discussion

Synchronous malignancies of GC and nodal ML are very rare. One possible reason is that the enlargement of lymph nodes in a GC patient usually indicates lymphatic metastasis, which easily causes omission of further biopsy in order to reduce injury and discomfort. But in this case of GC, the unexplainable continuous high fever besides enlargement of non-draining lymph nodes was a key clue for successful diagnosis of simultaneous nodal ML, the second primary tumor. It is notable that the ML subtype in the present patient is considered very rare for in situ FL. The diagnosis was based on reliable evidence, including atypical hyperplasia of lymphoid follicles, strongly positive immunostains of CD20 and Bcl-2, and a relatively low level of Ki67 expression, although the immunophenotype is not common, with CD10 and Bcl-6 being negative [3, 4]. We presumed that this in situ FL patient might just have been in a specific transition stage from atypical hyperplasia to classical FL while being diagnosed, and therefore, typical phenotypes in biopsied lymph nodes were missing.

Infections of *H. pylori* and EBV are possibly related with synchronous tumors, especially when both occur in the stomach. Nakamura et al. [1] described 10 patients with synchronous GC and gastric ML, in two of whom a simultaneous double infection with *H. pylori* and EBV was histopathologically confirmed in the stomach. As for *H. pylori*, it has been detected in over 50% of GC patients and in about 90% of gastric MALT lymphoma patients [5, 6]. Sakai et al. [7] even reported a 100% positivity rate for *H. pylori* in their 13 reviewed cases of synchronous adenocarcinoma and MALT lymphoma of the stomach. The tumor genesis processes of most GC and ML were postulated to be associated with chronic *H. pylori* gastritis, which was also found in our patient. Potential carcinogenic mechanisms of *H. pylori* are related with both host factors mainly meaning DNA damage, inadequate genetic repair and inflammatory reactions, and bacterial factors including cellular incorporation of *H. pylori* DNA and toxic effects of bacterial products, such as vacuolating toxin A, cytotoxin-associated gene A and ulcer-associated gene restriction endonuclease [8]. In addition, there was evidence that low-grade MALT lymphoma cells proliferated specifically dependent on T cell activation by *H. pylori*, which indicated key roles of *H. pylori* infection in the progression of lymphoid nodules to lymphoma [9]. Also, the gastric epithelium present inside a MALT lymphoma is susceptible to malignant transformation, owing to the presence of oncogenic factors, suppression of host immune functions, and the induction of autoimmune responses towards mimic *H. pylori* antigens, which may cause a further tissue injury and lead to simultaneous GC and lymphoma [10]. However, no reports, including our own, have confirmed a definite role of *H. pylori* in the pathogenesis of nodal FL. As for EBV, only a recent systemic infection was indicated but could not be linked to the double tumors in this case, although EBV is likewise thought to be involved in the development of the mentioned double malignancies [11–13]. Furthermore, the chromosome analysis in our patient suggested that gains in chromosomes 1, 3, 8, and 18 and the loss in 22q should be related with synchronous malignancies of GC and nodal ML, which needs confirmation in more cases.

There are still no standard treatments for synchronous malignancies because of the rare occurrence. As for double tumors occurring in the stomach, the presence of adenocarcinoma usually determines the treatment modalities, which mainly include distal or total gastrectomy depending on the tumor localization, preoperative or postoperative chemotherapy, and radiotherapy [2]. If simultaneous lymphoma and carcinoma are correctly diagnosed, the gastrectomy will be the first-line choice referring to GC surgery principles. However, radical surgery for gastrointestinal lymphoma is now not often

suggested due to an increased additional morbidity for those with localized or residual disease or with certain complications [14–16]. Recently, Hamaloglu et al. [2] reviewed 25 cases of synchronous gastric adenocarcinoma and lymphoma published with therapy information. There are 6 advanced-stage and 19 early-stage GC cases in the mentioned series, with median age being 68 (range 47–79) years and the majority of lymphoma types being MALT lymphoma. Twenty-four patients were treated with total or subtotal gastrectomy, 10 of whom were also subjected to radiotherapy and/or chemotherapy. Only 1 case of synchronous early-stage adenocarcinoma and diffuse large-cell lymphoma was treated with chemotherapy and endoscopic mucosectomy. It is a pity that the data about the tumor size and survival time of these patients are not complete. As for synchronous GC and non-gastric ML (such as nodal FL in this case), reports are rare and no consensus on management principles exists. Surgery and systemic chemotherapy are basic treatments for GC and nodal ML, respectively [2]. Nevertheless, in this special patient with poor performance status, any aggressive surgery may increase risk of death even compared with best supportive care. Interval chemotherapies with two regimens containing systemic plus regional use of 5-fluorouracil, oxaliplatin and etoposide against GC and classical R-CHOP against CD20-positive ML were therefore chosen to treat the coexisting malignancies and actually brought about a survival gain.

To our knowledge, this is the first case of synchronous primary GC and nodal ML encountered in the English literature. Our case suggested that a scrupulous biopsy of the non-draining lymph nodes in patients with gastrointestinal carcinomas, with or without B symptoms of ML, is supposed to improve the diagnostic rate of related double primary tumors. The interval chemotherapy strategy with double regimens targeting different tumors that we adopted may be one of the prospective choices for some patients, especially those with poor performance status.

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Fig. 1. Moderately differentiated adenocarcinoma of the stomach, accompanied by chronic gastritis (HE, ×20).

Fig. 2. Inguinal lymph node sections showing a rare in situ follicular lymphoma (**a** HE, $\times 40$; **b** HE, $\times 200$) with the special immunophenotype containing positive Bcl-2 (**c** $\times 40$, **d** $\times 200$), Pax-5 (**e** $\times 40$, **f** $\times 400$), CD20 (**g** $\times 400$) and Ki67 (**h** $\times 200$), but negative CD10 (**i** $\times 100$) and Bcl-6 (**j** $\times 400$).

Fig. 3. Bone marrow examination showing lymphoid hyperplasia with infiltrated lymphoma cells (Giemsa staining, $\times 1,000$).

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