

Ascites as the initial characteristic manifestation in a patient with primary gastric CD8-positive diffuse large B-cell lymphoma

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Abstract. – **CASE PRESENTATION:** Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid malignancy and the most common type of non-Hodgkin's lymphomas, the stomach is the most common extranodal site. Gastric DLBCL is often characterized by epigastric pain and vomiting. We report a case of a 78-year-old female patient with gastric diffuse large B-cell lymphoma (DLBCL) with high CD8 level which was initially manifested with ascites of unknown origin. The patient was admitted with a chief complaint of abdominal distension and scanty urine over the last twenty days, while without anorexia and fatigue until 15 March. She had no history of viral hepatitis, tuberculosis, schistosomiasis.

RESULTS: Laboratory data revealed normal aminotransferases and bilirubin levels, but serum lactate dehydrogenase, CA125, ascitic fluid lactate dehydrogenase, ascitic fluid lymphocytes increased. The ascitic fluid was yellow-colored with 98.5% lymphocytes. Stool occult blood test was positive. Upper gastrointestinal endoscopy performed a few days later revealed multiple gastric crateriform ulcers, and *Helicobacter pylori* was detected in the biopsy specimen. Peripheral blood CD8+ was increased by 51%. Pathology test showed lymphocytes with atypical hyperplasia, and immunohistochemistry test resulted CD20+, CD10-, CD79a+, κ+, bcl-6+, Ki-67+ (approximately 95%), λ-, bcl-2-, CD3-, CD43-. Immunoglobulin gene (Ig) clonal rearrangement showed IgH: FR1 (+), FR2 (+), FR3(-), Igk: VJ(+), Vkde (+) in lymphoma tissue.

CONCLUSIONS: The features of histopathology and immunohistochemistry of the tissue confirmed diffuse large B-cell lymphoma (DLBL). The patient received an uncompleted CHOP program combined with *H. pylori* eradication. However, the patient deceased due to disease development sixteen days later after the diagnosis.

Key Words:

Primary gastric diffuse large B-cell lymphoma, CD8-positive, Initial characteristic manifestation, Ascites.

Introduction

Gastric lymphoma accounts for 3%-5% of all malignant tumors of the stomach¹, which includes primary tumor and disseminated lymphoma. Approximately 10% of non-Hodgkin's lymphomas involve the gastrointestinal tract at the time of initial evaluation². Primary gastrointestinal lymphomas account for one-fourth of malignant lymphomas: the stomach and the small bowel are the most frequently involved sites. Gastric diffuse large B-cell lymphoma (DLBCL) is the most commonly high malignant type in primary gastric lymphoma, yet the etiology for most cases of gastric lymphoma is unknown, although genetic and infections agent have been implicated.

So far, CD8-positive has been previously described in very few isolated case reports. Noguchi et al³ reported the case of gastric CD8+ DLBL with HTLV-1, and Toyama et al⁴ reported the first case of primary splenic CD8-positive DLBL. Primary diffuse large B-cell lymphoma with ascites is very rare. Zenda et al⁵ reported a DLBCL case initially manifested as a form of effusion lymphoma with lymphoma cells detected in ascites but only minimum solid tumor component. Overall, CD8-positive DLBCL with ascites as the initial major characteristics is very rarely reported.

Case Presentation

A 78-year-old woman was admitted to Wuxi Traditional Chinese Medicine Hospital on 15 March 2011 with complaints of abdominal distension, scanty urine, fatigue, anorexia. She had no history of viral hepatitis, tuberculosis or schistosomiasis. On physical examination, there found no enlarged superficial lymph nodes, abdominal tenderness or rebound tenderness, a palpable liver

and a palpable spleen. There was an exposure of varication in the abdominal wall, in combination with a distended abdomen with shifting dullness. Edema was found in the patient's lower limbs, especially the left limb. The patient was afebrile, and cardiac pulse and blood pressure were within normal range. Blood routine test showed that white blood cell (WBC) was $5.96 \times 10^9/L$ (80.4% neutrophil, 13% lymphocyte), red blood cell (RBC) $3.30 \times 10^{12}/L$, hemoglobin (Hb) 100 g/L, and platelet (PLT) $305 \times 10^9/L$. Prothrombin time was 16.5 s. Serologic studies for HIV and HCV were negative, and HBeAb and HBcAb were positive. Liver function tests were: lactate dehydrogenase 746 IU/L (normal 105-245 IU/L), cholinesterase 4215 U/L (normal 4500-13000 U/L), total protein 53.5 g/L (60-85 g/L), albumin 29.3 g/L (35-55 g/L), prealbumin 0.102 g/L (0.20-0.40 g/L). Other parameters were within normal range. Renal function and electrolytes levels were normal. Ascites was drained with abdominocentesis and tested: yellow-colored, turbid, tumor cell (-), mesothelial cell (+), lymphocytes (+), Rivalta test (+), white blood cell $18.75 \times 10^9/L$, red blood cell $3.5 \times 10^9/L$, neutrophil 1.5%, lymphocyte 98.5%, lactate dehydrogenase 4483 IU/L (normal 105-245 U/L), adenosine deaminase 64.9 U/L (normal 0-24 U/L), alpha fetal protein (AFP) (-), carcino-embryonic antigen (CEA) (-), carbohydrate antigen 19-9 (CA199) (-). Bacteria culture result of the ascites was negative. Serology tumor marker test results were: alpha fetal protein (AFP) 2.54 ng/ml (normal 0-13.4 ng/ml), carcino-embryonic antigen (CEA) 0.789 ng/ml (normal 0-10 ng/ml), carbohydrate antigen 153 (CA153) 13.41 U/ml (normal 0-25 U/ml), carbohydrate antigen 19-9 (CA199) 5.59 U/ml (normal 0-27 U/ml), and carbohydrate antigen 72-4 (CA72.4) 0.534 U/ml (normal 0-6.9 U/ml), and an increased carbohydrate antigen (CA125) 566.9 U/ml (normal 0-27 U/ml). The PPD (purified protein derivative) skin test and tubercle bacillus smear were negative, Doppler ultrasound showed that there was no thromboembolism in the limbs. Serum cellular immune function: CD16+: 27% (normal 12.5-29.2%), CD3+: 68% (normal 60.7-77.2%), CD19+: 3% (normal 5-14.7%), CD4+: 16% (normal 27.3-42.6%), Th/Ts: 0.31 (normal 0.9-2.2), CD8+: 51% (normal 19.2-30.5%).

A current-generation multislice helical computed tomography (CT) scan using intravenous contrast material called compound meglumine in chest and abdomen showed a suspicion of ascending colon cancer which maybe metastasized to

kidneys and adrenal glands, little pleural effusion in the left lower thorax, small hemangioma in the left liver, gallbladder stones, cholecystitis massive ascites, but no enlarged lymph nodes. Three stool routine tests showed that the color was yellow, shape and properties was soft, yeasts were found in the first stool sample, occult blood was negative. After taking live combined Bifidobacterium lactobacillus, and Enterococcus (420 mg, q8h) for three days, yeasts were no longer found in the second stool sample, and occult blood was slightly positive. Occult blood turned negative without acid inhibitors or hemostatic. Upper gastrointestinal endoscopy was performed on March 23, multiple gastric crateriform ulcers (fundus, body, and antrum of the stomach, about 1.5x1.5 cm multiple ulcers, surrounding with elevated crater-like mucosa) were found (Figure 1). A biopsy was taken from the border of the antrum and gastric fundus ulcers shew lymphocytes with atypical hyperplasia (Figure 2). *H. pylori* was detected from antral biopsy specimens using urease testing. Immunohistochemistry detected expression of CD20+, CD10-, CD79+, κ +, bcl-6+, Ki-67+ (approximately 95%), λ -, bcl-2-, MUM1-, CD3-, CD43- in lymphoma tissue. The results of clonal rearrangement of the immunoglobulin (Ig) gene in lymphoma tissue were IgH: FR1 (+), FR2 (+), FR3 (-), Igk: VJ (+), Vkde (+). The results of pathology, immunohistochemistry, gene rearrangements were consistent with diffusive large B-cell lymphoma. The comprehensive analysis confirmed diagnose of diffusive large B-cell lymphoma. Furthermore, capsule endoscopy did not detect tumors, or angiomas, ulcer or bleeding. Colonoscopy showed

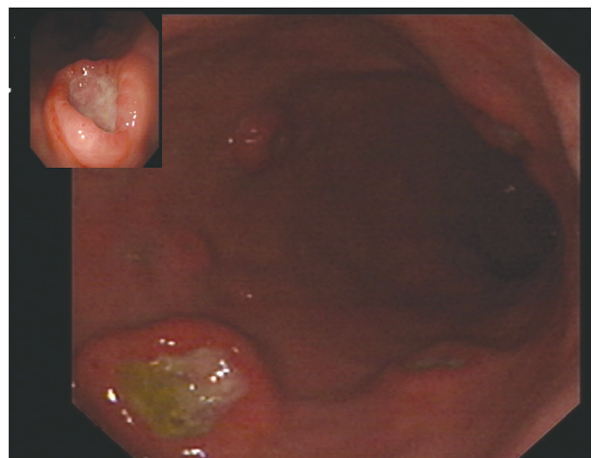


Figure 1. Panendoscopy: multiple crater-like gastric ulcers observed under upper gastrointestinal endoscopy (1.5 cm x 1.5 cm) was suspected to be malignancy.

numerous diverticula in the caecus, ulcer in the ileocecal valve, and biopsy pathology of ileocecal valve showed chronic inflammation with local dysplastic changes of local lymphocytes.

After she had been admitted to the hospital, she received palliative and symptomatic treatments, including salt restriction and diuretics. On the fifth day of admission, she had a moderate fever (37.8°C), with no chills, rigors, abdominal pain or cough. Blood routine test showed WBC $9.25 \times 10^9/L$ (neutrophil 88.41%, lymphocyte 7.02%), RBC $3.08 \times 10^{12}/L$, Hb 92 g/L, PLT $363.0 \times 10^9/L$, and cultures of blood were negative. Epstein-Barr virus detection was negative. The patient refused a surgical treatment and a CHOP program at first. But after being told that triple therapy might provide a better prognosis, she took esomeprazole (20 mg, q12h), amoxicillin (1 g, q12h), and clarithromycin (500 mg, q12h). The treatment only lasted one day due to severe nausea and vomiting. On March 26, the renal function tests found that urea nitrogen (BUN) increased to 11.51 mmol/L (normal 2.1-7.9 mmol/L), creatinine (Cr) increased to 425.9 $\mu\text{mol}/L$ (normal 40.0-115 $\mu\text{mol}/L$), and uric acid (UA) was 783 $\mu\text{mol}/L$ (normal 150-440 $\mu\text{mol}/L$). Then the patient decided to try CHOP program. Three days later the condition deteriorated. She decided to go home for supportive care. She died sixteen days later after being diagnosed with diffuse large B-cell lymphoma.

Discussion

Diffuse large B-cell lymphoma presenting as peritoneal carcinomatosis is rare, without definite demographic characteristics. Usually, gastric diffuse large B-cell lymphoma (DLBCL) presents with most symptoms such as epigastric pain, vomiting, melena and fever. To the best of our knowledge, ascites is rarely reported as one of the manifestations of this disease at an advanced stage. Lack of specific symptoms often delays the diagnosis. The diagnosis mainly bases on gastro-biopsy, histological, immunohistochemical and genetic examination. Gastric diffuse large B-cell lymphoma with ascites as initial characteristic feature and CD8-positive is extremely rare.

It is well known that liver cirrhosis is the underlying cause of ascites in at least 80% of patients, but other factors (e.g., heart failure, constrictive pericarditis, nephrotic syndrome, tuberculous peritonitis, peritoneal malignancy, and pancreatic duct leak) may be involved. In this case, all the

above causes were eliminated. Because of the increased serum lactate dehydrogenase, CA125, ascitic fluid lactate dehydrogenase, ascitic fluid lymphocytes and intermittent slight positive of occult blood, gastroscopy was performed. The endoscopy revealed multiple crateriform gastric ulcers measuring 1.5 cm x 1.5 cm in the fundus, body, and antrum of the stomach. *H. pylori* was also detected in antral biopsy specimens. The results of immunohistochemistry showed CD20+, CD10-, CD79 α +, κ +, bcl-6+, Ki-67+ (approximately 95%) in the biopsy tissue. And the immunoglobulin (Ig) gene clonal rearrangement demonstrated IgH: FR1 (+), FR2 (+), Igk: VJ (+), Vkde (+). So the diagnosis of gastric diffuse large B-cell lymphoma (DLBCL) was affirmed. Meanwhile, peripheral blood CD8 was highly increased. This was the first reported case of primary gastric CD8-positive DLBL with ascites, which suggested that physician may consider the possibility of gastric DLBCL in patients with similar symptoms, such as ascites. We reviewed literature reporting rare DLBCL cases and only find few hits about lymphomatosis with ascites. Weng and Wu⁶ reported one case of lymphoma presenting as peritoneal lymphomatosis with ascites, which was diagnosed with similar tests and also presented with ascites; the patients also died soon after diagnosis.

For most cases of gastric lymphoma, etiology and pathogenesis are so far poorly understood and genetic and infections factors may be implicated. *Helicobacter pylori* (*H. pylori*) plays a role in the development of most mucosa-associated lymphoid tissue (MALT) lymphoma in the stomach, which may be similarly implicated in the development of DLBCL, but DLBCL rarely complete alleviates after eradication therapy alone⁷. Chronic inflammation may enhance the probability of malignant transformation via B cell proliferation in response to *H. pylori*-mediated by tumor-infiltrating T cells. One study⁸ founds that in patients who develop gastric lymphomas in response to *H. pylori*, virulent strains expressing CagA protein are preferentially associated with diffuse large B-cell lymphoma. MALT lymphoma may transform to gastric DLBCL, but mechanisms still remains poorly understood. According to the WHO classification, low-grade MALT lymphoma with focal high-grade component constituted by “solid or sheet-like proliferations of transformed cells” were included as diffuse large B-cell lymphoma⁹. Craig et al¹⁰ elucidates a novel Myc- and FoxP1-dependent pathway of malignant transformation.

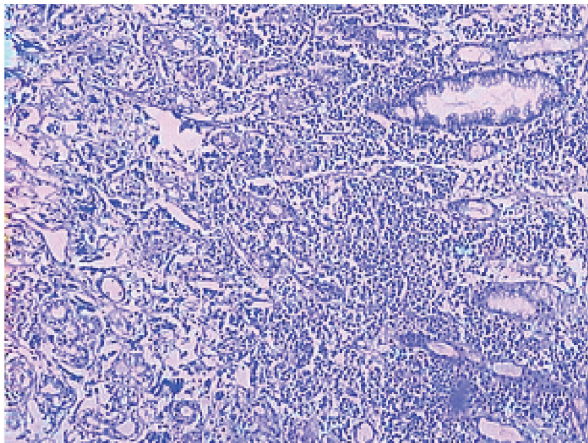


Figure 2. Histological examination of ulcers (HE staining).

The genetic susceptibility to develop primary gastric B-cell lymphoma in patients with chronic *H. pylori* infection is still unknown. Sun et al¹¹ have investigated polymorphisms of MALT1 as genetic risk factors in the development of primary gastric lymphoma. The clonal rearrangements of the IGH and IGK genes can serve for long-term monitoring of the disease activity as molecular markers^{12,13}. In this case, we also detected these genes and found they presented a relationship with the severity of the disease. The extremely rapidly progress without specific gastric symptoms in the early stage may also be involved with *H. pylori* virulence and host gene polymorphism, which indicated that virulent strains culturing and gene expression profiling may be helpful to its diagnosis and treatment.

Treatment strategies for gastric lymphoma have dramatically improved over the last two decades but the efficiency is still controversial. Primary gastric large B-cell MALT is a transformed, antigen-independent and autonomous lymphoma, which is unlikely to respond to eradication therapy of the *H. pylori* infection. However, we do find some anecdotal studies reported primary gastric large B-cell lymphoma responded to antibiotic therapy effectively. Chen et al¹⁴ reported in a prospective study the disappearance of primary gastric large B-cell lymphoma at gastroscopy examination in 14 of 22 patients (64%) after HP eradication therapy. Currently, surgery is only reserved for those with significant solid tumor and complications such as perforation, hemorrhage or obstruction that cannot be treated with alternative therapies. The most widely recommended strategy for DLBCL is CHOP

(cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy regimen. Some new treatments are built on the CHOP backbone: R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone) which prolonged survival among patients with DLBCL¹⁵, and R-miniCHOP (rituximab combined with low-dose CHOP), which was proposed as a potential standard treatment in elderly patients¹⁶. Micallef et al¹⁷ suggested that ER-CHOP (Epratuzumab with R-CHOP) is a well-tolerated schedule with improved event-free survival and overall survival. Similarly, Craig et al¹⁰ also suggested that miR-34a replacement therapy was a promising strategy in lymphoma treatment. In this case, the patient received CHOP chemotherapy and *H. pylori* eradication therapy, but received little effect.

The International Prognostic Index, which has become the most widely used means to evaluate prognosis for DLBCL, incorporates five factors (age, performance status, lactate dehydrogenase level, number of extranodal sites of disease, and stage). Gene expression profiles could be considered as better predictors of prognosis than currently-used clinical prognostic factors. In most studies, the proliferation rate in diffuse large B-cell lymphoma was estimated by Ki-67, which could be used as a potential predictor of poor prognosis and help to identify a high-risk subgroup of newly diagnosed DLBCL^{18,19}. High LDH and CD79 expression were also associated with poor prognosis that high LDH levels and poor performance status at diagnosis are associated with shorter overall and disease-free survival²⁰. In this case, besides the above five factors (high LDH in both ascites and serum of this case), expressions of ki67, CD79 α , κ , CD8+, and ascites may also indicate a poor prognosis.

Conclusions

This case illustrates that cytology and imaging are an effective method for making diagnosing DLBCL. Disseminated peritoneal involvement of extranodal and gastrointestinal lymphoma is unusual and needs further attention. The ascitic fluid analysis was characteristic for such patient. Management such as gene expression profiling would be tried with a patient with gastric DLBCL in the future, but first of all the most significant issue in managing gastric lymphoma is to establish an accurate diagnosis as early as possible.

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