Severe upper gastrointestinal bleeding determined by a gastric lymphoma associated with *Helicobacter pylori*-positive atrophic gastritis

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**Abstract**

The pathogenesis of gastric cancer regardless of histological structure is a classic example of gene–environment interaction, and an important epidemiological aspect was the recognized association with *Helicobacter pylori* infection. This paper describes a case of gastric mucosa-associated lymphoid tissue (MALT) lymphoma in a young patient whose first sign of the disease was upper gastrointestinal bleeding and associated hemorrhagic shock. The patient is a 31-year-old man, diagnosed by endoscopy 10 years ago with *H. pylori*-positive chronic atrophic gastritis, who refused treatment to eradicate the bacterium and presents currently in the emergency room for serious upper gastrointestinal bleeding. Emergency upper gastrointestinal tract endoscopy highlights the presence of bleeding gastric tumors. It was a surgical emergency and intra-operatively the presence of invasive gastric cancer into the left hepatic lobe was noted which required total gastrectomy with the purpose of hemostasis. Immediate and remote postoperative evolution was favorable and post-operative follow-up at six months, 12 months, and 24 months showed no signs of local or distance occurrence.

**Keywords**: *Helicobacter pylori*, upper gastrointestinal bleeding, MALT lymphoma hemorrhagic, centrocytic-like cells.

**Introduction**

Acute lesions of the upper gastrointestinal tract have multifactorial etiology, but whatever the cause, they are grounded on the destruction of the mucosal barrier. Because *Helicobacter pylori* induces chronic superficial gastritis with infiltration of neutrophils in the mucosa, it was speculated that *H. pylori* infection may be the underlying cause of bleeding lesions. The diagnosis of *H. pylori* infection, effective treatment, and revaluation can be effective prophylaxis of serious sequel such as peptic ulcers, gastric lymphoma of mucosa-associated lymphoid tissue (MALT), and gastric cancer, diseases that endanger the patient’s life [1]. MALT lymphoma is an extra-nodal lymphoma developed from mucosa-associated lymphoid tissue. MALT lymphoma represents 7–8% of non-Hodgkin’s B-cell lymphoma (NHL), and 50% of primitive gastric lymphomas as reported in medical literature [2]. Gastric mucosa does not normally contain lymphoid tissue, but MALT can occur in response to *H. pylori* colonization. In rare cases, a monoclonal B-cell population may arise from this tissue proliferation and begin to form a MALT lymphoma [3]. Of the total MALT lymphomas, 50% are developed from the gastrointestinal tract, while 85% affects the stomach. Most cases are found in adults, the gender ratio being slightly elevated in women (men/women = 1/1.2) [4]. Regarding the etiology, it seems that infection with *H. pylori* in the patient’s history plays an important role in the disease development [2].

**Case presentation**

Male, aged 31, presents in the emergency room for impaired general condition, low blood pressure, and hematemesis. Family history was positive for a family member diagnosed via endoscopy with erosive chronic gastritis with positive *H. pylori* with fully remission after specific treatment. Patient personal history revealed chronic gastritis and infection with *H. pylori* diagnosed by endoscopy 10 years ago, for which the patient refused to pursue any treatment. The onset of the patient’s current symptoms was about five hours ago with hematemesis. Immediate and remote postoperative evolution was favorable and post-operative follow-up at six months, 12 months, and 24 months showed no signs of local or distance occurrence.
120 beats/min. Nasogastric tube was placed and bright-red blood was evacuated. Under treatment with hemostatic agents and transfusions of whole blood and plasma, we were able to temporarily stop the bleeding, which allowed additional biological and imagistic exploration. The biological analysis picture at admission was hemoglobin (Hb) 7 g/dL, hematocrit (Ht) 17%, white blood cells (WBC) 27 120/mm³, total proteins 4 g/dL, and albumin level at 20 g/L. Upper endoscopy revealed ulcero-vegetative tumors in the gastric body, circumferentially disposed, with areas of necrosis and spontaneously bleeding. The tumors were extended from the pylorus up to 3 cm from the cardia. Thorax and abdominal computed tomography (CT) showed a “cauliflower-like” gastric tumor along the lesser curvature of the stomach (Figure 1), with irregular borders which seems to elude the gastric wall and with intense fat infiltration in the neighborhood of about 40×60 cm in diameter, normal looking liver without any visible tumors, without any other intra-abdominal lesions, and normal lung parenchyma.

The resuming of the bleeding forced the surgical intervention that was performed two hours after admission. Exploratory laparotomy revealed voluminous tumor along the lesser curvature of the stomach extending from the pylorus to the cardia, which penetrated the gastric serosa and infiltrated the left lobe of the liver, without infiltration of the posterior transverse mesocolon and pancreatic capsule. There was no secondary liver, peritoneal, or other abdominal viscera involvement. We performed a total gastrectomy with T-L esophagojejunal anastomosis with Roux-en-Y and left hepatic segmentectomy (Figure 2). A lateral duodenostomy was also performed for an early postoperative feeding. Due to the poor condition of the patient under general anesthesia with evident tendency of shock, the lymphadenectomy in the splenic hilum and hepatic pedicle was abandoned. Immediately post-operatively, the patient’s evolution was slowly favorable being released at two weeks.

The gastrectomy specimen was processed by standard techniques with paraffin embedding using the following steps: fixation in 10% buffered formalin, washing with water or alcohol, dehydration via successive washing with alcohol, clarification via washing with benzene, toluene, xylene and paraffination. Hematoxylin–Eosin (HE) staining was used. Histopathological standard examination showed ulcerated malignant lymphoid proliferation of the stomach, diffuse form, with medium and large cells, with total infiltration of the gastric wall. The microscopic structure of the resected hepatic parenchyma showed lymphoid infiltrates in the portal space and subcapsular lymphoid tumor proliferation. A histological criterion for the diagnosis of MALT lymphomas as for differentiation in terms of reactive polyclonal infiltrates remains controversial. In particular, the diagnosis is based on histological appearance during routine microscopic examinations, and on the demonstration of clonality with immunohistochemistry (IHC) or molecular techniques such as polymerase chain reaction (PCR).

Microscopic evaluation of HE-stained blades showed a monomorphic cellular proliferation with diffuse pattern, consisting predominantly of small and medium lymphocytes with abundant cytoplasm and cleaved nuclei. These cells are similar to centrocytes and are called centrocyte-like cells (CCLs) (Figures 3 and 4). In the tumoral infiltration, we observed cells of large size with exocentric nucleoli attached to the nuclear membrane (centroblast) or with central nucleoli (immunoblasts) and rare karyorrhexis (Figure 5). The neoplastic infiltration surrounded the reactive lymphoid follicles like a cuff (Figures 6 and 7). Cellular proliferation infiltrated the gastric walls in totality. The lymphoepithelial lesions were extended in the entire glandular mucosa determining large areas of ulceration (Figure 8). For a correct and accurate diagnosis, we decided to proceed to immunohistochemical (IHC) study. We used the LSAB–HRP (labeled Streptavidin–Biotin–Horseradish peroxidase) method with following antibodies: cyclin D1, Ki-67, CD20, CD10, CD79a, CD5, bcl-2, bcl-6. The election of the antibodies was made based on the algorithm for the positive and differential diagnosis in gastric MALT lymphoma, as described in World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues [2] and highlighted in Table 1.
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Figure 3 – Gastric MALT lymphoma: cells with unequal nuclei and abundant cytoplasm. HE staining, ×400.

Figure 4 – Gastric MALT lymphoma: tumor cells with nuclei with irregular contour, incised (centrocyte-like cells) or karyorrhexis, rare immunoblasts and centroblasts. HE staining, ×200.

Figure 5 – Gastric MALT lymphoma: centrocyte-like cells, rare immunoblasts and centroblasts. HE staining, ×400.

Figure 6 – Gastric MALT lymphoma: neoplastic cells infiltrate surrounding reactive lymphoid follicles as a sleeve. HE staining, ×40.

Figure 7 – Gastric MALT lymphoma: diffuse neoplastic infiltrate represented by small lymphocytes surrounding lymphoid follicles. HE staining, ×100.

Figure 8 – Gastric MALT lymphoma: neoplastic infiltration in the muscular layer. HE staining, ×100.

CD20 is membrane marker of mature B-lymphocytes. In our case, we discovered that the tumor cells diffusely and intensely expressed this marker (Figures 9 and 10).

CD79a is a membrane marker of pre-B-cells. MALT lymphoma diffusely and intensely expresses this marker (Figure 11). Bcl-2 is cytoplasmic marker and particularly interfollicular lymphocytes. In our case, the tumor cells were diffusely and intensely positive for bcl-2 (Figure 12).

Cyclin D1 is a cell cycle regulatory proto-oncogene and expresses membrane marker. In our case, it was negative (Figure 13). Lymphocyte membrane marker CD5 is expressed in T-cells, and is a subclass of B-lymphocytes.
In our case, it was intensely positive but only in isolated tumor cells (Figure 14).

CD10 is a marker for membrane and cytoplasmic B-lymphocytes, neutrophils, and for tubular epithelium, glomerular bile ducts and myoepithelial cells. In our case, this marker was negative in the tumor cells (Figure 15).

Ki-67 is a nuclear marker expressed in the G1, S, G2 and M phases of the cell cycle but negative in the G0 phase. In our case, around 30% of the tumoral cells strongly expressed this marker (Figure 16).

Bcl-6 is a nuclear marker and usually is positive in germinating centers. In our case, this marker had variable positive intensity focused in tumoral cells (Figure 17).

Based on IHC study results, the patient was subjected to oncological treatment with the definitive diagnosis of gastric MALT lymphoma, Ann Arbor stage IIE. After oncological treatment, the patient presented for clinical assessment at 12 months with general good condition, asymptomatic, without any clinical or imagistic signs of relapse.

<table>
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<tr>
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<th>Dilution</th>
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<td>Leica</td>
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<td>Nuclear lymphocytes germinal centers</td>
<td>Leica</td>
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IHC: Immunohistochemistry; MALT: Mucosa-associated lymphoid tissue; EDTA: Ethylenediaminetetraacetic acid.

Figure 9 – Gastric MALT lymphoma: diffuse and intensely positive CD20 reaction in the tumoral cells. CD20 immunostaining, ×100.

Figure 10 – Gastric MALT lymphoma: diffuse and intensely positive CD20 reaction in the tumoral cells – detail. CD20 immunostaining, ×200.

Figure 11 – Gastric MALT lymphoma: diffuse and intensely positive CD79a reaction in the tumoral cells – detail. CD79a immunostaining, ×200.

Figure 12 – Gastric MALT lymphoma: diffuse and intensely positive bcl-2 reaction in the tumoral cells – detail. Bcl-2 immunostaining, ×200.
Discussion

The most common symptoms of gastric MALT lymphoma are non-specific upper gastrointestinal tract symptoms, which frequently call for endoscopy that highlights gastritis or peptic ulcer, while tumoral aspect of the lesions is uncommon [5]. In our case report, the clinical appearance was dominated by upper gastrointestinal hemorrhage, outwardly shown through massive hematemesis associated with hemorrhagic shock, in a young patient with a history of untreated chronic gastritis and *H. pylori* infection. This presentation of symptoms is exceptional being that it is very rare for upper gastrointestinal hemorrhage with hypovolemic shock to be the first sign of a gastric MALT lymphoma. Current treatment of gastric MALT lymphoma is oncological—chemotherapy/radiotherapy [6], and in case of *H. pylori*-positive MALT lymphoma, the eradication of the bacteria is an imperative goal [7, 8]. The indication for surgery is nowadays very rare and limited to cases of perforation, bleeding or obstruction due to the tumor [9], complications that were reported between 0 and 25%, but with a very high mortality [10]. In our case, the choice treatment was total gastrectomy performed in emergency settings to reduce the risk of death from a severe uncontrolled gastric bleeding from a tumor with unknown etiology.

The decision to perform a duodenostomy for early enteral nutrition was taken because of the risk of dehiscence of the esophagojejunal anastomosis considering that major surgery was performed. The anastomotic fistula, local abscess or postoperative diffuse peritonitis resulting
from anastomosis dehiscence are severe postoperative complications with very high mortality. Malnutrition, vitamin deficiencies, and anemia are systemic factors involved in inducing hypoxia and microcirculation alteration along the anastomosis site [11]. Akiyama [12] demonstrated the role of hypoalbuminemia in the etiology of anastomotic dehiscence, and Patil et al. [13] found a positive correlation between esophageal-digestive anastomosis dehiscence and serum albumin levels less than 30 g/L. The need for intraoperative transfusions according to some authors correlates with the incidence of fistulas; on the one hand as a result of existing postoperative anemia and on the other hand due to hypotension induced by intraoperative blood loss [11, 14]. All of those conditions favoring anastomotic dehiscence were present in our patient. Also, long term use of parenteral nutrition can boost septic and metabolic risk, immunosuppression and the possibility of developing serious fungal infections, even if a well trained medical stuff can reduce the complication rate [15]. By performing a duodenostomy, the patient can benefit of rapid resumption of enteral nutrition as soon as first bowel movements appear.

We underline here the association between untreated chronic H. pylori (HP) infection and gastric MALT type lymphoma that was present in our case. We can also mention that in our case another member of patient’s family diagnosed with HP-positive erosive gastritis had a simple evolution after correct therapy of the infection. Since 1991, it is a very well documented fact that H. pylori can be a major risk factor in gastric MALT development [16]. Moreover, H. pylori eradication treatment proved to be very effective in low malignity gastric MALT resulting in complete remission, as single treatment or in association with oncological regimens. The US National Comprehensive Cancer Network recommends the eradication of H. pylori as the first line of treatment for positive H. pylori lymphoma, followed by oncological treatment [17] in advanced stages, and surgical resection in complicated cases. Regarding prognosis, despite a complete remission of the disease, recurrence in conservative treated gastric MALT is possible even after several years [18]. The need for adding chemotherapy in HP-positive gastric MALT treated with anti-Helicobacter regimens is evaluated through endoscopic surveillance with multiple biopsies. Both, in primary diagnosis, but also in the surveillance, the immunohistochemical diagnosis plays a central role. In some cases, endoscopic biopsy samples examined only in HE staining can be a source of diagnostic error since the appearance of centrocyte-like cells can be mistaken for adenocarcinoma [19] or signet ring cell carcinoma. The IHC studies are thus useful in positive lymphoma diagnostic but also in differentiating lymphoma type – mantle cell lymphoma (cyclin D1+), diffuse large B-cell lymphoma (bcl-2+ and bcl-6+), follicular lymphoma (bcl-2+, bcl-6+ and CD10+), etc.

Data from the literature [2] shows that the immunohistochemical profile of MALT lymphoma is positive for B-lymphocytes origin of tumoral cells (CD20+, CD79a+) and also for bcl-2 (Figures 10–12). Cyclin D1, CD5 and CD10 are usually negative, but there are rare cases with positive CD5 [2], as was the case with our patient (Figure 14). Ki-67 proliferative index was positive in about 30% of the tumor cells (Figure 14). Tumor cells expressed bcl-6 with variable focal intensity (Figure 17). Based on this expression, we can speculate a possible lesion evolution to a diffuse large B-cell lymphoma as Thieblemont et al. reports in an exhaustive study [20].

## Conclusions

The presence of H. pylori is correlated with the occurrence of chronic gastritis and gastric malignancy (either epithelial cancers or lymphoma), demonstrated also by this presented case. Clinical symptoms of gastric lymphomas are non-specific, usually occurring in a patient with a long history of upper gastrointestinal tract distress. Bratal onset of the illness with an acute complication like perforation or massive bleeding is uncommon. Moreover, in our case, the diagnosis of gastric tumor in a young patient represented another surprise upon presentation in emergency room. Both of these conditions – massive bleeding and gastric tumor – dictated the therapeutic attitude, total gastrectomy, the diagnosis of MALT lymphoma being a retrospective one. In fact, nowadays, surgery for gastric lymphomas is rare and restricted to complications – perforation, hemorrhage or obstruction. Otherwise, the first therapeutic option is for H. pylori eradication therapy (when infection is present) and chemotherapy in advanced aggressive stages. Outside the emergency settings, endoscopy with biopsy and immunohistochemical studies have a central role in gastric lymphomas positive and differential diagnostic as well as for follow-up and treatment response evaluation.

## Conflict of interests

The authors declare that they have no conflict of interests.

## Author contributions

Cosmin Vasile Obleaga and Costin Teodor Streba contributed equally to preparing the manuscript and share main authorship.

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## References


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