

Case Report

Rare case of gastric extranodal marginal zone lymphoma

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ABSTRACT

True histiocytic lymphoma is considered a rare entity, and its diagnosis requires the concordance of morphological, immunophenotypic, and molecular findings. Gastric extra nodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) is a B-cell non-Hodgkin lymphoma that arises in the stomach and has a perifollicular/marginal zone growth pattern. The lymphoma is derived from marginal zone B-cells and recapitulates the architecture and organization of native MALT exemplified by the Peyer's patches in the terminal ileum. Marginal zone lymphoma of MALT (MALT lymphoma) is the most common indolent subtype and represents 7% of all non-Hodgkin lymphomas.

Keywords: True histiocytic lymphoma, MALT lymphoma, Stomach extra nodal marginal zone B cell lymphoma, Mucosa associated lymphoid tissue, Polymerase chain reaction

INTRODUCTION

The true incidence of gastric mucosa-associated lymphoid tissue (MALT) lymphoma worldwide remains unclear because presenting symptoms are nonspecific and endoscopy findings often mimic gastritis. Nonetheless, *H. pylori* prevalence can be loosely applied as a surrogate for gastric MALT lymphoma worldwide prevalence.¹

We present a case of a rare MALT-type low-grade B-cell lymphoma of the stomach, contiguous to a large tumoral mass that fulfills the morphological criteria (large cells with abundant pale cytoplasm and lobulated or kidney-shaped nuclei) and immunophenotypical features (human leukocyte antigen-DR locus, CD68, S-100, lysozyme immunoreactivity, and negative B- and T-cell markers) required for the diagnosis of histiocytic lymphoma. The patient remains in complete remission 18 months after surgery and *H. pylori* eradication, without any additional treatment.

CASE REPORT

74-year-old male presented to emergency with severe epigastric pain gradual onset of worsening constant abdominal pain for 4-5 days worse on inspiration and movement associated nausea, no vomiting given fentanyl 100 mcg with QAS, minimal improvement normal bowel movements, last opened this morning, nil blood no fevers no urinary symptoms no URTI symptoms, no chest pain, no SOB PMHx - BPH, HTN, anxiety, ETOH excess. No previous abdominal surgeries. Medicines given were Duodart and Efexor. Allergies are-Bee stings, Zoloft. He is living with wife and son and retired person. Active smoker 20 cigarettes per day, ETOH ++ half a bottle of wine every day. No previous colonoscopies or gastroscopies. No family history of bowel or upper gastrointestinal malignancies O/E afebrile sat. O₂ 92% on RA, RR 18 BP 113/79 cachectic looking-pt denies unintentional weight loss GCS 15, he was alert and orientated. In respiratory system, chest equal AE, clear and in abdominal exam, firm, increased tenderness and involuntary guarding epigastric region and RUQ. No

lower abdominal tenderness. Not peritonitic. No renal angle tenderness, appears dry, nil pedal edema, calves SNT. In bloods, Hb-157 grams per deciliter, WBC-16.4/cubic millimeter, eGFR 86 LFTs WNL Na 139 K4.4, lipase 25. Imp bowel perforation cholecystitis and gastritis. CXR: free air under diaphragm. CT abdomen: free intraperitoneal gas indicating a perforation, possibly from an anterior wall gastric ulcer.



Figure 1 (A and B): CT abdomen.

The major finding is certainly some free intraperitoneal gas most obvious anterior to the liver. Axial images suggest a defect in the anterior wall of the stomach and the may be a gastric ulcer and accounting for the year perforation. The oedema in the mesentery is explained by

the perforation as is the small amount of free intraperitoneal fluid, in the pelvis.

Patchy consolidation is seen in the basal segments of both lower lobes, more pronounced on the right than the left. No mass. No pleural fluid. No evidence of generalised lung disease.

The liver spleen and pancreas appear normal. No calcified gallstones Normal left kidney. Minor right renal scarring, probably old reflux nephropathy. No lymphadenopathy or pelvic mass. No mass or calibre change along the course of the colon. Lumbar laminectomy noted, not thought to the recent.

Patient was taken for urgent laparotomy with Billroth's II distal gastrectomy.

Histology

Distal gastrectomy: Extranodal marginal zone (MALT) lymphoma. The sections show a perforated ulcer within the gastric antrum with adjacent acute serositis admixed with gastric contents. The gastric wall adjacent to the ulcer and extending more proximally into the gastric body is thickened by a transmural lymphoid infiltrate exhibiting vague nodularity. The infiltrate is composed of relatively small lymphocytes with mild nuclear membrane irregularities and coarse chromatin. In some areas the lymphocytes have retracted clear cytoplasm giving them a monocytoid appearance. No plasmacytoid features are seen. Lymphoepithelial lesions are identified within the involved gastric mucosa. There is no evidence of high-grade transformation within multiple sections examined. The lymphoid infiltrate stains diffusely for CD20 and bcl2. There is some staining of the B cells for CD43. CD3 and CD5 stain background small T cells. CD23 stains background follicular dendritic meshworks. There is no staining for CD10, bcl6 or Cyclin-D1. The Ki67 proliferative index is variable but no more than 10%.

The morphology and immunoprofile are consistent with extranodal marginal zone (MALT) lymphoma. The lymphoma is clear from the gastric resection margins. The uninvolved gastric body and antral mucosa shows no significant pathologic features. There is no significant inflammation, no *Helicobacter* can be seen and there is no evidence of intestinal metaplasia or epithelial dysplasia. The perigastric lymph nodes exhibit reactive follicular hyperplasia but there is no definite evidence of involvement by nodal marginal zone lymphoma.

Liver biopsy: Features suggestive of a hemangioma.

Patient was discussed our multidisciplinary meeting with need for *H. pylori* eradication.

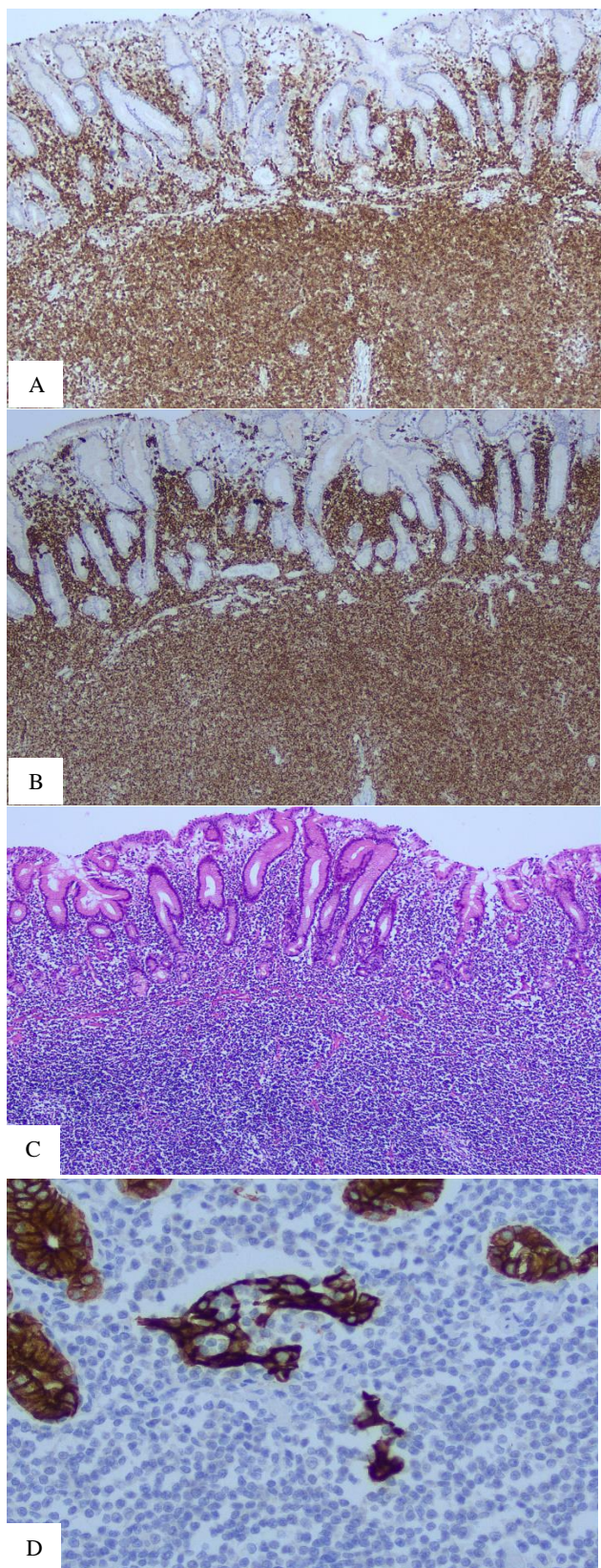


Figure 2 (A-D): Histology.

PET scan

Diffuse mild FDG avidity seen associated with the surgical clips within the distal gastrectomy, equivocal for

ongoing post-surgical changes versus residual FDG avid disease. Noted no staging FDG PET performed to assess the FDG avidity of the primary tumour. No definite evidence of FDG avid nodal or distant metastatic disease involvement. However, the sensitivity for the detection of nodal or distant metastatic disease is reduced as avidity of the primary disease not known. Follow-up scopes in 6 months.

Gastroscopy

Patients had normal oropharynx and LA grade B reflux oesophagitis, patent Billroth II gastrojejunostomy was found, characterized by erythema, biopsied and erythematous mucosa in the gastric body.

Colonoscopy

Preparation of the colon was fair. Diverticulosis in the sigmoid colon and in the descending colon, nine 4 to 9 mm polyps in the rectum, in the sigmoid colon, in the descending colon, in the transverse colon, at the hepatic flexure and in the ascending colon, removed with a cold snare. Resected and retrieved. The examined portion of the ileum was normal and the distal rectum and anal verge are normal on retroflexion view.

Patient had benign condition. Patient has an ongoing follow-up at hematology and surgical clinic. Surgically, he has recovered well and is recuperating at home.

Repeat colonoscopy and gastroscopy performed 6 months post-surgery showed a tubular adenoma only but no tumour recurrence.

DISCUSSION

Marginal zone lymphoma of MALT is acquired secondary to persistent antigenic stimulation with either chronic infectious conditions or autoimmune processes, such as *H. pylori* gastritis, Hashimoto thyroiditis, and Sjögren syndrome.² Extra nodal marginal zone lymphomas occur outside lymph nodes (e. g., in the gastrointestinal tract, thyroid, orbit, leptomeninges, spinal cord, or skin). MALT (mucosa-associated lymphoid tissue) lymphoma (MALToma) is the term traditionally used for extra-nodal marginal zone lymphoma of MALT.

Nearly all patients with gastric MALT lymphoma are infected with *Helicobacter pylori*. Further, histological and endoscopic improvement commonly follows *H pylori* eradication.³ Lymphoid follicles are a ubiquitous finding in MALT lymphoma. The neoplastic cells infiltrate and may overrun these follicles. Sometimes specific colonization of the germinal centers may occur.

The neoplastic cells have variable morphology including mature round lymphocyte cells resembling germinal center centrocytes with irregular nuclei, cells with monocytoid/marginal zone B-cell appearance and cells

with lymphoplasmacytic appearances. Plasma cell differentiation is a frequent finding, and in some cases may be very prominent.

Features that help to distinguish MALT lymphoma from reactive infiltrates include the presence of a dense infiltrate of monotonous B-cells (identified by staining for CD20 or another B-cell marker) extending away from lymphoid follicles with a poorly demarcated border, the presence of cytological atypia and the finding of Dutcher bodies. Immunohistochemistry is used to distinguish MALT lymphoma from other non-Hodgkin lymphomas. Staining for CD20 or another pan B-cell antigen confirms the B-cell nature of the infiltrate. Although a few gastric MALT lymphomas stain for CD5, positive staining is more characteristic for B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, which also express CD23, and mantle cell lymphoma which co-expresses cyclin D1. A stain for cytokeratin may help to identify lymphoepithelial lesions and a stain for follicular dendritic cells (e.g., anti-CD21) will identify indistinct lymphoid follicles.

Where large cells are present, immunohistochemistry to distinguish neoplastic cells from residual germinal center centro-blasts should be used (antibodies to CD10 and bcl-6). Staining for bcl-2 protein is helpful as reactive germinal center cells are negative and neoplastic blasts are usually positive. Staining for Ki67 may help in identifying large cell components.

Immunohistochemistry

Wide-spectrum keratin immunostaining such as AE1/AE3 or low-molecular-weight cytokeratin CK8 or Cam 5.2 can highlight the presence of destructive lymphoepithelial lesions.

As marginal zone lymphomas arise from B cells, B-cell markers (e.g., CD20, CD79a, CD10, CD23, and bcl-2) are expressed. Frequently, a co-expression of T-cell marker CD43 suggests a neoplastic proliferation. In some cases, light-chain restriction can be demonstrated with kappa and lambda light-chain antibodies. In neoplastic proliferations, there is an excess of kappa-positive, exceeding 10:1 of lambda-positive, cells.⁴

The translocation is specifically associated with the MALT lymphoma entity, but occurs at remarkably variable incidences in different anatomical sites. Translocation t (11;18) (q21;q21) API2-MALT1 is found in around 30% of MALT lymphomas. Two other known genetic alterations include translocation t (14;18) (q32;q21)/IGH-MALT1 found in roughly 10% of MALT lymphomas and t (1;14)(p22;q32)/BCL10-IGH. There is also a prominent population of T cells, predominantly CD4 positive. Importantly, the neoplastic cells of MALT lymphoma show immunoglobulin light chain restriction, and its demonstration is helpful in the differential diagnosis with reactive hyperplasia.

Translocation t (11;18) (q21;q21) can be detected fairly simply by interphase fluorescence in situ hybridization (FISH) with a commercial MALT1 dual-colour break-apart probe and a API2- MALT1 dual-colour dual-fusion probe, or reverse transcription PCR (RTePCR) of the AP.

There is now overwhelming evidence that *H. pylori* infection causes gastric MALT lymphoma, and a systematic review of published series has shown *H. pylori* infection in 88.8% of 2000 patients with gastric MALT lymphoma.⁵ A minority of gastric MALT lymphomas are caused by a different *Helicobacter* species named '*H. heilmannii*'. This is not a validated species and corresponds to a group of different microorganisms which are very fastidious to grow and, consequently, difficult to differentiate. There is evidence that *H. pylori* eradication cures gastric MALT lymphoma only in stage IE and, to a much lesser percentage, in stage IIIIE. Nevertheless, it is preferable to eradicate *H. pylori* in all cases as it is a trigger of the immune response. *H. pylori* eradication therapy with antibiotics can cure about 70% of gastric MALT lymphomas.⁶

In the case of positive histology, culture is recommended as the second diagnostic test, if another endoscopy is needed for diagnosis or gastric mapping. In gastric MALT lymphoma, culture has a lower sensitivity than histology even if performed under good conditions.

Mucosa-associated lymphoid tissue (MALT) lymphomas remain localized to their site of origin for long periods, during which locally directed therapy is effective. Several systems are available for staging gastric marginal zone lymphomas. The classic Ann Arbor staging system as modified for extra nodal disease 7-8 and the Luagano staging system have been in wide use over the past two decades. *H. pylori* eradication therapy with antibiotics can cure about 70% of gastric MALT lymphomas.

Different types of chemotherapy and immunotherapy are effective in the treatment of gastric (and non-gastric) MALT lymphoma with both limited and advanced stages of disease. Relatively short duration of follow-up. Radiation is effective for patients with localized gastric MALT lymphoma of stage IEeIIIIE (T1e4, N0/1M0B0) that failed to respond to *H. pylori* eradication. Chemotherapy and immunotherapy are effective in patients with gastric MALT lymphoma of all stages.

Differential diagnosis

Not surprising, the most common differential diagnosis is distinguishing between florid lymphoid hyperplasia associated with *H. pylori* gastritis and incipient marginal zone lymphoma. Morphologic features that favor mucosa-associated lymphoid tissue (MALT) lymphoma include extensive infiltrates, B-cell lymphocytic infiltrates (rather than plasma cells) found between glands, destructive lymphoepithelial lesions (LELs) in which intraepithelial lymphocytes express CD20 (B

cells), the presence of Dutcher bodies, and moderate cytologic atypia.

CONCLUSION

In this case we described a case of gastric extra nodal marginal zone B-cell lymphoma of MALT. Upon the review of the literature, this is quite a rare occurrence and an incidental finding. It has a tendency to occur in elderly people, but has no distinctive clinical features, including radiological features. Currently, there are no standard therapeutic protocols or guidelines for the treatment of primary hepatic MALT lymphoma. surgery, chemotherapy, or radiotherapy alone, or in combination had been commonly used. Since it was usually misdiagnosed before histological confirmation, surgery resection may be a good choice and most patient don't require additional treatment post-surgery.

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