A rare case of Peri-ampullary Mucosa Associated Lymphoid Tissue (MALT) Lymphoma

A Case Report

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INTRODUCTION

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma or MALToma) is a rare B-cell non-Hodgkin lymphoma (NHL) that typically runs an indolent or slow-growing clinical course. It is the third most common NHL subtype, accounting for around 6-8% of all non-Hodgkin lymphoma.[1] MALT lymphomas occur predominantly in the stomach. Involvement of the duodenum and periampullary region, on the other hand, occurs in less than 2% of lymphomas of the gastrointestinal tract and only a few cases specifically involving the ampulla of Vater have been reported.[2] Clinical data regarding MALT lymphoma solely involving the duodenum are sparse because of the relative rarity of the disease. A comprehensive literature review revealed only 17 cases reported until 2004, and only a moderate number of cases have been reported since.[3] Despite its rarity, this disease entity should be considered in the differential diagnosis of patients presenting with chronic abdominal pain, obstructive jaundice and recurrent pancreatitis. Awareness of this condition is vital to earlier diagnosis and proper management of future cases that may present similarly.

The first case of MALT lymphoma was reported by Peter Isaacson and Dennis Wright in 1983. [4] There are no available local published data on peri-ampullary MALT lymphoma in the Philippines.

CASE PRESENTATION

A 52-year-old male Filipino patient complained of recurrent upper abdominal pain for six months associated with anorexia and significant, unintentional weight loss 25% from baseline. Pain was described as vague, mild to moderate intensity, mostly localized at the epigastric and left upper quadrant areas, nonradiating, worsens on supine position and relieved with leaning forward or sleeping on prone position. There was no vomiting nor changes in bowel habits nor presence of fever or night sweats. Patient complained of a concomitant left ear pain, tinnitus and decreased hearing acuity.

Patient is a known hypertensive for 4 years and maintained on Losartan 100mg daily. His past medical history was unremarkable. Patient is a chronic smoker of tobacco leaf for 20 years and an alcoholic drinker consuming 5 bottles of beer thrice a week for 30 years. He works as a vegetable farmer and at the same time sells fertilizer and pesticides. Family history was significant for malignancy with father diagnosed of lymphoma and paternal aunt with breast cancer.

Patient was admitted at a tertiary hospital 3 months and 4 months after initial presentation due to severe attacks of abdominal pain. On the first admission, 3 months after the initial presentation, laboratory work-up revealed elevated lipase at 967 U/L and the following liver chemistry: ALT 119 U/L, alkaline phosphatase 117 IU/L, total bilirubin 1.5 mg/dl, direct bilirubin 1.3 mg/dl, indirect bilirubin 0.2 mg/dl. Tests for synthetic functions of the liver were normal (albumin 4.3, protime 12.2s, 113%

activity, INR 0.93). CBC was likewise unremarkable (hemoglobin 12.9, hematocrit 38.1, platelet 268,000 WBC 8,250, neu64, lym21, mono7). CT Scan of the abdomen showed dilated gallbladder with no lithiasis seen as well as peripancreatic fat stranding along the length of the pancreas (see Figure 1A). The pancreatic head and uncinate process appear congested and peripancreatic fluid collection measuring 3.2x5.3x3.8 cm was noted superior to the pancreatic tail in the gastrosplenic ligament. Additional findings also include mild dilation of the proximal intrahepatic bile ducts but the common bile duct was not dilated. Patient was managed as a case of pancreatitis and cholecystitis with hydrops of the gallbladder. He underwent laparoscopic cholecystectomy. During the course of hospitalization, work-up of the left ear pain was at the same time pursued. ENT referral was done and magnetic resonance imaging (MRI) of the brain was done which revealed presence of 3x3x4.9cm mass in the area of the left parapharyngeal, left carotid and left retropharyngeal spaces (see Figure 3). Biopsy done of the left parapharyngeal mass revealed squamous papilloma. The ocular globe was unremarkable. Laboratory tests repeated prior to discharge showed improvement as follows: lipase 621 U/L, ALT 47 U/L, alkaline phosphatase 115 IU/L, total bilirubin 0.5 mg/dl, direct bilirubin 0.3 mg/dl, and indirect bilirubin 0.2 mg/dl.

Patient was discharged improved but was re-admitted 1month later (4 months following initial presentation) due to recurrence of severe attack of abdominal pain. Character of the pain was the same except for the severity. There was no nausea, vomiting, nor changes in bowel habits. There was no fever, no scleral icteresia nor jaundice. At this time, repeat serum lipase was elevated at 1759 IU/L and laboratory chemistry showed the following results: slightly elevated amylase 249 IU/L, ALT 379 U/L, alkaline phosphatase 277 IU/L, total bilirubin 1.4 mg/dl, direct bilirubin 1.3 mg/dl, and indirect bilirubin 0.1 mg/dl. Repeat CT scan of the abdomen revealed a fairly delineated pancreas, with the head of the pancreas partly ill-defined. The fluid collection along the dorsal aspect of the pancreatic tail remained stable as compared in the previous scan, but this time post-contrast study showed an area of decreased enhancement at the same area representing either an inflammation or a vascular infarction (see Figure 1B). Moreover, the repeat scan showed that the intrahepatic and extrahepatic bile ducts are dilated (CBD 14mm) but no calcified stone seen within. Further imaging study with MRCP was done and confirmed the dilatation of the intrahepatic and extrahepatic ducts (CBD 14mm) with no obvious cause for obstruction revealed. No pancreatic mass lesion was demonstrated. Recurrent pancreatitis and pseudocyst formation with possible superimposed infection was entertained. Conservative management with initial bowel rest, hydration, pain relievers, and antibiotics showed slight improvement of symptoms.

Two months after the second admission (6 months following initial presentation), patient followed up at the clinic this time already with obstructive jaundice. There was still intermittent abdominal pain with mild to moderate severity,anorexia and noted significant weight loss 25% from baseline. The concomittant left ear pain and tinnitus persisted despite symptomatic treatment as well. Laboratory work-up showed elevated alkaline phosphatase 354 IU/L, direct hyperbilirubinemia TB 10.8

mg/dl, DB 8.8 mg/dl, slightly elevated LDH 252 U/L, elevated GGT 314 U/L, elevated ALT 91 U/L, albumin 3.1 mg/dl, protime 16.4s, 65% activity, INR 1.33, Lipase 1048 IU/L and amylase 246 IU/L. Tumor markers were normal: CA19-9 17.05 U/mL and CEA 1.53 ng/mL. Repeat CT imaging of the abdomen now revealed a hypovascular mass 2.7x3.3x2.4cm in the head of the pancreas producing extrinsic compression of the distal common bile duct (see Figure 2). There are hypovascular masses noted in the tail of the pancreas suggestive of multiple abscess versus malignancy. These findings were not seen in the prior study. There were no enlarged periaortic, interaortocaval or mesenteric lymphadenopathies. Patient was then admitted at our institution.

On physical exam, patient was normotensive with BP 110/80 mmHg, HR 80 bpm, afebrile at 36C. Scleral icteresia and generalized jaundice were noted. There was no skin lesion noted. Abdomen was soft, with normoactive bowel sounds, nontender and no masses palpated. There was an enlarged, ~5x6cm nontender mass occupying the left pre-auricular and left submandibular areas. The rest of the physical exam was unremarkable.

Diagnosis and Treatment

Patient underwent endoscopic retrograde cholangiopancreatography (ERCP) on the third hospital day. Large fungating mass measuring 2x2cm at the ampulla of Vater was visualized (see Figure 6); common bile duct was dilated with narrowing of the distal portion due to the ampullary mass, the intra and extrahepatic ducts as well as the pancreatic duct were all dilated (see Figure 5). Common bile duct decompression was done and biliary stent inserted. Biopsies of the ampullary mass were taken at this point which later revealed mucosa-associated lymphoid tumor (MALT Lymphoma). Gastric biopsy for Helicobacter pylori test was negative.

Further work-up of the left ear complaints and neck mass was pursued. CT scan of the neck was done and revealed heterogeneously enhancing lobulated mass at the left masticator space with erosion of the left pterygoid plates and left mastoid cortex as well as encasement of the left internal and external carotid arteries (see Figure 4). The salivary glands are normal in size and enhancement and there was no enlarged lymph node seen. No repeat biopsy taken as this was already done in the previous admission showing squamous papilloma.

Final diagnosis was malignant lymphoma, mucosa-associated lymphoid tumor (MALT) Stage I2E. The patient subsequently underwent first cycle of chemotherapy with CHOP regimen (Doxorubicin, Vincristine, Cyclophosphamide, Prednisone) and was discharged with instructions for subsequent chemotherapy cycles.

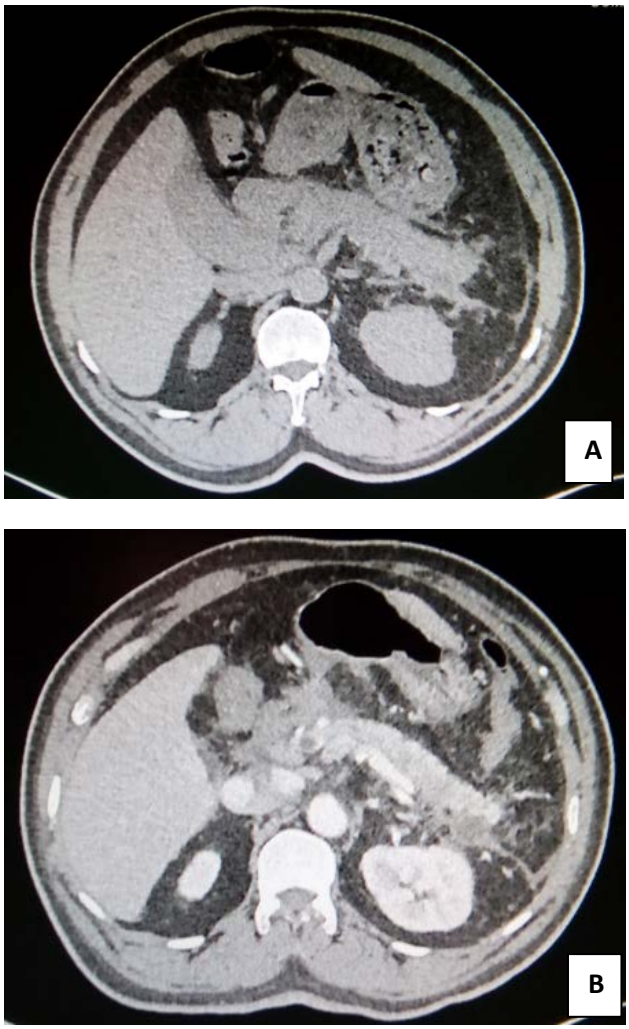

Figure 1. Serial CT scan of the abdomen done on prior hospitalizations. A. Plain CT Scan of the abdomen showing peripancreatic fat stranding along the length of the pancreas. The pancreatic head and uncinate process appear congested and peripancreatic fluid collections or pseudocysts were noted. Also noted with hydrops of the gallbladder with mild dilatation of the proximal intrahepatic duct not appreciated here. B. Repeat CT scan of the abdomen with contrast taken 1 month later showing dilated intrahepatic and extrahepatic bile ducts but no calcified CBD stone seen. Pancreatic fluid collection at the dorsal aspect of the tail of the pancreas still noted and the post-contrast study showed an area of decreased enhancement at the same area representing either an inflammation or a vascular infarction.

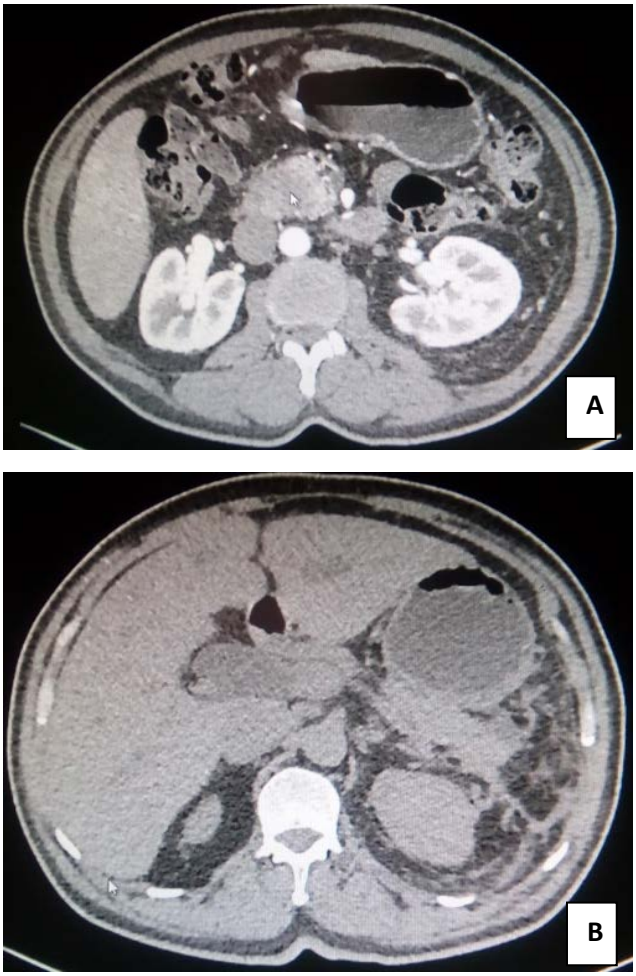

Figure 2. Repeat CT imaging of the abdomen revealing a hypovascular mass 2.7x3.3x2.4cm in the head of the pancreas (A) producing extrinsic compression of the distal common bile duct. There are hypovascular masses noted in the tail of the pancreas (B) suggestive of multiple abscess versus malignancy. There were no enlarged periaortic, interaortocaval or mesenteric lymphadenopathies.

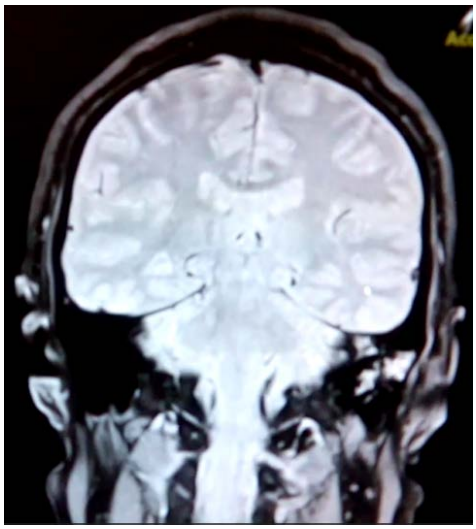

Figure 3.MRI of the Brain showing presence of 3x3x4.9cm mass in the area of the left parapharyngeal, left carotid and left retropharyngeal spaces. Ocular adnexae are normal.

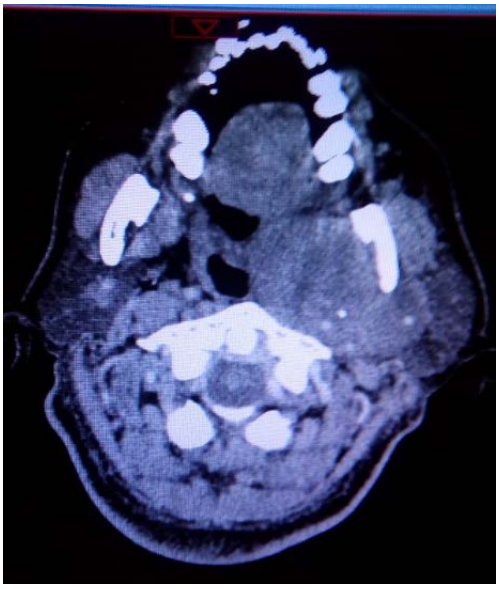

Figure 4. CT scan of the Neck showing heterogeneously enhancing lobulated mass (5.3x6.2x6cm) at the left masticator space with erosion of the left pterygoid plates and encasement of the left internal and external carotid arteries. Subcutaneous fullness at left pre-auricular region with thickening of the walls of the left external auditory canal and erosion of left mastoid cortex. Salivary glands are normal in size and enhancement. No enlarged lymph node seen.

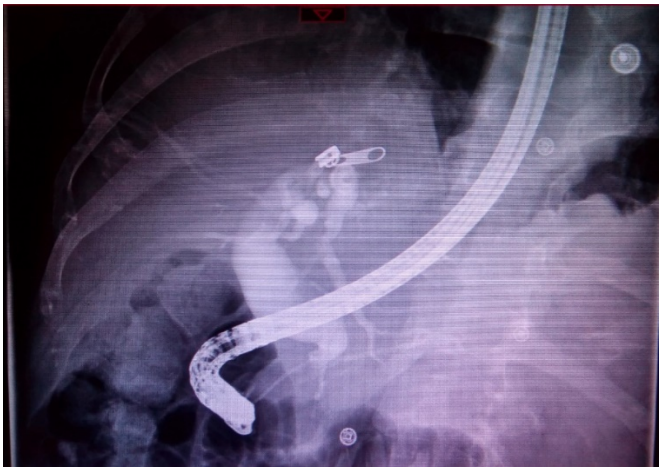

Figure 5. Xray Film taken during endoscopic retrograde cholangiopancreatography showing common bile duct up to 25mm with a 28 mm long narrowing at the distal portion. The intrahepatic ducts, left and right hepatic ducts as well as the pancreatic duct are all dilated.

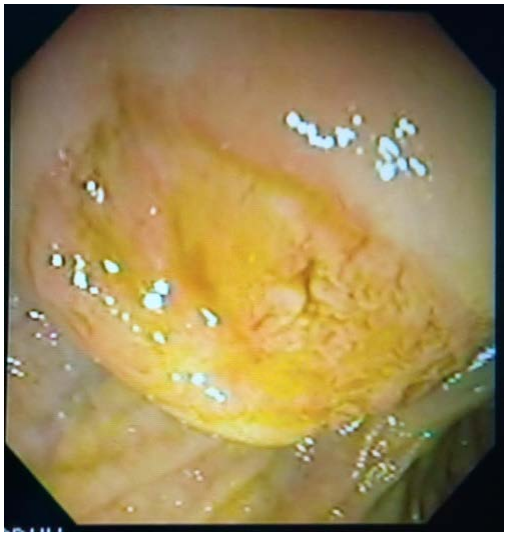

Figure 6. Endoscopic image taken during endoscopic retrograde cholangiopancreatography showing large mass 2x2cm at the ampulla of Vater

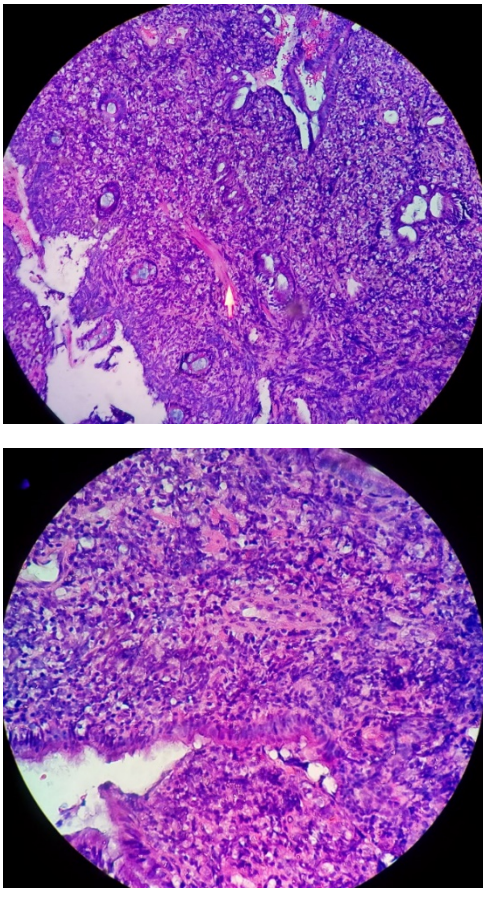

Figure 7. Histopathology images of the specimen taken from ampullary mass showing malignant neoplasm arising from the mucosa-associated lymphoid tissues composed of small to medium-sized lymphocytic cells exhibiting enlarged, mildly pleomorphic, hyperchromatic nuclei, inconscpicuous nucleoli and scant to moderate pale to clear cytoplasm. Findings are consistent with MALT lymphoma

DISCUSSION

Background

Ampullary carcinomas are uncommon and represent only 0.2% of gastrointestinal tract malignancies.[2] Lymphoma involving the duodenum and periampullary region is likewise rare with incidence rate of less than 2% of lymphomas in the gastrointestinal tract. Extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma), as defined in the World Health Organization (WHO) classification of lymphoid malignanies, is composed of morphologically heterogeneous small B-cells including marginal zone (centrocyte-like) cells, cells resembling monocytoid cells, small lymphocytes, and scattered immunoblasts and centroblast-like cells. It is a unique type of lymphoma with marked differences from other indolent B-cell lymphomas. The WHO classification of lymphoid malignancies published in 2008 defined the stomach as the most common organ of origin comprising 50-85% of cases but it has been shown that MALT lymphoma may arise in almost all organs of the human body.

Pathogenesis of MALT Lymphoma

MALT Lymphoma was initially described by pathologists Peter Isaacson and Dennis Wright in 1983[4], when they noticed that certain gastric lymphomas did not resemble lymph node architecture but strikingly recapitulated the features of Peyer patches which is a physiologic aggregate of lymphoid cells in the terminal ileum. The finding that most MALT lymphomas were diagnosed in the stomach was initially puzzling as the stomach is usually a priori devoid of lymphoid tissue. Gastric lymphoid structures develop in individuals subject to chronic antigenic stimulation and this acquired gastric MALT is more prone to the development of lymphoma. After the initial definition of MALT lymphoma, the pathogenic link between gastric MALT lymphoma and infection with the gram negative rod, *Helicobacter pylori* was soon discovered. [5] In addition to epidemiologic data showing high rate of gastric lymphoma after *H.pylori* infection, the presence of *H.pylori* was demonstrated in greater than 90% of patients with gastric MALT lymhoma.[6] *H.pylori* is believed to play a role in the pathogenesis of gastric MALT lymphomas by stimulating lymphocyte activation, proliferation, and transformation from chronic inflammation induced by *H.pylori* infection. This close association is strikingly demonstrated by complete histologic, long-term remission in 50-80% of patients with localized, early, gastric MALTomas after *H.pylori* eradication.[5]

Contrary to gastric MALT lymphoma, data regarding the pathophysiology of duodenal and peri-ampullary MALTomas are scant due to its rarity. The case reported by Gjeorgjievski et al [3] illustrates that duodenal MALTomas may be unassociated with H.pylori infection. Duodenal MALTomas appear to have different pathophysiology and therapy compared with gastric MALTomas.

In cases of extragastric MALT lymphomas, association with chronic antigen stimulation including infections and autoimmune diseases have been described in various organs. Data on bacterial causes for nongastric MALT lymphoma are sparse. *Campylobacter jejuni*, for one, has been implicated in the development of a rare form of intestinal MALT lymphoma termed immunoproliferative small intestinal disease which is prevalent in the Middle East. [7] Association between *Borrelia burdorferi* and cutaneous MALT lymphoma as well as *Chlamydia psittaci* with ocular MALT lymphoma has not been uniformly accepted compared with the association between *H.pylori* and gastric MALT lymphoma. Close association with autoimmune diseases and the role of B-cell activating autoimmune diseases in the development of MALT lymphoma has also been emphasized. The close association between chronic autoimmune thyroiditis or Hashimoto disease with thyroid MALT lymphoma and Sjogren syndrome with salivary gland lymphoma has been published, and it is thought that the risk of developing lymphoma is as high as 70-fold for individuals with autoimmune diseases compared with the risk for healthy populations. The idea that chronic antigen stimulation of the target organ may give rise to acquired MALT with subsequent transformation to lymphoma is in line with the MALT lymphoma concept. [5]

Risk Factors

In our patient, significant risk factor was a family history of malignancy with father diagnosed of lymphoma and paternal aunt with breast cancer. Details as to the specific lymphoma subtype of the father was no longer determined. However, patient had no past medical history of auto-immune diseases. Patient's occupation as a farmer and seller or fertilizers and pesticides was not a predisposing factor.

The interlymph non-hodgkin lymphoma project [8] reports that apart from autoimmune conditions, additional risk factors for MALT lymphoma include hepatitis C seropositivity, self-reported peptic ulcers and a family history of a hematologic malignancy. In this pooled analysis of 1052 cases with marginal zone lymphoma MZL cases of which extranodal MZL or MALT lymphoma is a subset (633 MALT lymphomas, 140 splenic MZLs and 157 nodal MZLs), an increased risk was found for all the subtypes of MZL. Factors inversely associated with MZL included increased recreational sun exposure, consumption of any type of alcohol or wine and occupation as a teacher. No associations were observed with body mass index, physical activity, atopy/allergy other than asthma, and living or working on a farm.

Patient Profile

The median age at diagnosis is about 65 years (range, 31 –82 years) and there is a slight female preponderance (male:female ratio 1:1.2) in MALT lymphoma patients.[9] On the other hand, in the study by Radaszkiewicz et al [10] involving 307

cases of primary gastrointestinal non-Hodgkin's lymphoma (244 gastric, 63 intestinal), the average age of diagnosis was 64.5 years for gastric NHLs while mean age of diagnosis for intestinal NHLs was slightly younger at 54.4 years. There was no gender preponderance noted with male:female ratio of 0.97 and 1.1 for gastric and intestinal NHLs respectively.

In our case, the patient is 53 years old male which is about the same as the average age of diagnosis for intestinal NHLs reported by Radaszkiewicz et al.

Sites of Involvement

The gastrointestinal tract is the most frequently involved site of extranodal non-Hodgkin lymphomas (66% of all MALT lymphomas). [5] Predominant sites of extragastric involvement include ocular adnexa, salivary glands, thyroid and lungs. Gastrointestinal tract MALTomas usually occur in the stomach, sometimes the jejunum, ileum, and rarely the duodenum. In the same study by Radaszkiewicz et al involving 307 cases of primary gastrointestinal non-Hodgkin's lymphoma (NHL), 244 cases (80%) had gastric lymphoma while 63 cases (20%) had intestinal lymphoma. On the other hand, another study involving 150 GI lymphomas, 105 patients had gastric lymphoma, 27 patients had jejunal lymphoma and only 1 patient had duodenal involvement. [11]

Involvement of the ampullary region is quite unique as well in that carcinomas can arise from adjacent structures, making it difficult, if not impossible to determine in some cases whether the neoplasm originated in the periampullary duodenum, the distal common bile duct, the head of the pancreas or the ampulla itself. For these reasons, the nonspecific term peri-ampullary has been used to refer to neoplasms arising at the intersection of these four sites. In our case, the serial CT scans of the abdomen only pointed the possible location of the lesion at the head of the pancreas when patient already presented with jaundice. On ERCP, the lesion was ultimately localized at the ampulla of Vater which caused the progressive symptoms. MALT lymphoma involving the ampulla of Vater is a rare site for marginal zone lymphomas as well as lymphomas in general. The incidence rate of duodenal involvement is less than 2% of all lymphomas of the gastrointestinal tract., and only a few cases specifically involving the ampulla of Vater have been reported.[2]

Clinical presentation

The clinical presentation of MALT lymphoma is variable, mostly because of differences in signs and symptoms associated with the different location or extranodal organs involved. Ampullary carcinomas in general are often diagnosed at an early stage because of the precocity of symptoms that relate to its unique anatomic location. Patients often present with

persistent or intermittent jaundice, weight loss, abdominal pain, and less frequently, pancreatitis. “B” symptoms are exceedingly uncommon. Obstructive jaundice is the most common symptom in several cases reported. Acute recurrent pancreatitis or relapsing pancreatitis as clinical manifestation of ampullary cancer has been reported but only in very few cases reviewed.

Our patient initially presented with recurrent abdominal pain and severe attacks of pain in between which required hospitalization. On these occasions, serum lipase was consistently elevated along with CT scan findings suggestive of pancreatitis. In retrospect, these could have been clues to underlying pathology that predisposes to recurrent pancreatitis that would merit more intensive investigation. The dilatation of biliary ducts seen on serial scans also present clues to the possibility of a slowly growing lesion at the peri-ampullary region in the absence of intrinsic or extrinsic causes of obstruction in the imaging done. As the disease progressed and eventually with the development of obstructive jaundice and weight loss, diagnosis of malignancy was strongly considered. In this case, peri-ampullary MALT lymphoma with involvement of the pancreas is demonstrated. Serum tumor markers taken both CEA and CA19-9 were within normal range.

Apart from the gastrointestinal manifestations, unique to this case is the presence of concomitant squamous papilloma of the left parapharyngeal/retropharyngeal region which is considered benign and a different disease entity from the primary peri-ampullary MALT lymphoma.

Diagnosis

A.Duodenoscopy/ERCP

Our patient underwent ERCP and findings include a large mass at the ampulla of Vater measuring 2x2cm. According to Isomoto et al, endoscopy may reveal a mass, slight enlargement of the papilla, or only granularity of the mucosa. [2] In one series of 149 cases, the mean greatest diameter of ampullary carcinoma was 2.7cm, significantly smaller than carcinomas of the pancreatic head (3.5cm).[12]

B.CT scanning and image evaluation

Our patient had serial abdominal CT scans taken in the course of the disease presentation. The first CT scan was done due to the severe attack of abdominal pain on a background of recurrent upper abdominal pain. This revealed findings of dilated gallbladder with mild dilatation of the proximal intrahepatic ducts as well as peripancreatic fat stranding along the length of the pancreas consistent with acute pancreatitis. The second CT scan was taken one month apart due to persistence of abdominal pain this time already showing dilated intrahepatic and extrahepatic bile ducts but no calcified CBD stone.

Pancreatic fluid collection at the tail of the pancreas likely represented pseudocysts following episode of pancreatitis although areas of infarction have been entertained. The third CT scan taken at 4months following initial presentation and now with the development of jaundice revealed a hypovascular mass 2.7x3.3x2.4cm in the head of the pancreas producing extrinsic compression of the distal common bile duct along with hypovascular masses noted in the tail of the pancreas suggestive of multiple abscess versus malignancy.

The CT scan and over-all radiologic appearance of ampullary carcinoma may mimic pancreatic carcinoma as what is evident in our case. CT scan often demonstrates a mass but is not helpful in differentiating ampullary carcinoma from tumors of the head of the pancreas or periampullary region. If the lesion is smaller than 2 cm, pancreatic or bile duct dilation might be the only abnormalities noted on CT scan. Such findings are highly suggestive of pancreatic malignancy and require further evaluation, usually with endoscopic retrograde cholangiopancreatography (ERCP). This is consistent with the findings on serial CT scan done in the initial presentation of this case.

Imaging evaluation in this case also included the CT scan of the neck and MRI of the brain which in this case were done due to concomitant presentation of left ear pain and enlarging pre-auricular mass. The findings of both imaging points to a different lesion further confirmed by biopsy as benign squamous papilloma. Chest Xray was taken to complete the work-up with unremarkable findings. 18F-FDG-PET/CT imaging was not done in this case and is not recommended in routine clinical practice.

C.Histopathology

In our patient, tissue biopsy was done during endoscopic retrograde cholangiopancreatography and findings showed malignant neoplasm from mucosa-associated lymphoid tissues composed of small to medium-sized lymphocytic cells exhibiting enlarged, mildly pleomorphic, hyperchromatic nuclei, inconspicuous nucleoli and scant to moderate pale to clear cytoplasm consistent with MALT lymhoma.

The diagnosis of MALT lymphoma is established by histopathologic assessment of tissue samples according to standardized criteria. MALT lymphoma arising at different anatomical sites nevertheless share common morphological features. MALT lymphoma is characterized by cellular heterogeneity of neoplastic cells, including centrocyte-like cells, monocytoid B-cells, small lymphocytes, and plasma cells.[5] The biopsy in our case exhibited features of centrocyte-like cells. The neoplastic cells infiltrate around secondary lymphoid follicles in a marginal zone distribution and spread to form diffuse interfollicular sheets or, in some cases, a vaguely nodular pattern. [1] Although diagnostically helpful, identification of reactive follicles is not required for diagnosis as they may not be present in the small biopsy specimens often submitted for assessment as in our case.

According to Bacon et al, an important diagnostic feature of MALT lymphoma at many sites is the presence of lymphoepithelial lesions, defined by the infiltration and distortion of epithelial structures by aggregates of usually three or more neoplastic lymphoid cells. [1]The affected epithelium often shows degenerative changes such as cellular swelling and eosinophilia, and, if infiltration is extensive, may disintegrate, leaving only clusters of degenerate cells among the lymphoid infiltrate. It is also important to note that lymphoepithelial lesions may be formed by lymphomas other than MALT lymphomas and that, although highly suggestive of MALT lymphoma if present in the context of a small lymphocytic proliferation, lymphoepithelial lesions can be seen occasionally in inflammatory states including florid gastritis and reactive pulmonary infiltrates.[1]

The immunophenotype of the neoplastic cells of MALT lymphoma is virtually identical to that of non-neoplastic marginal-zone B cells: CD20+, IgD−, IgM (>IgA>IgG)+, CD5−, CD10−, Bcl6−, cyclin D1−. No specific immunohistochemical marker has yet been identified for MALT lymphoma, but evaluation of a panel of immunostains is necessary for assessment of the architecture of the lymphoid infiltrate, lineage assignment, identification of an aberrant phenotype or immunoglobulin light-chain restriction, and for the exclusion of other lymphomas. [1]

Immunohistochemical staining was not done in our patient because malignant cells were already identified on biopsy with presence of characteristic mucosa-associated lymphoid tissue cells.

Due to the presence of concomitant left parapharyngeal mass and to complete the work-up for lymphoma, tissue biopsy was done. On review, it showed surfaces lined by stratified squamous epithelium that demonstrated mild papillomatosis with the underlying stroma that is fibrotic and collagenized. No evidence of malignancy was seen.

Once definitive diagnosis of MALT lymphoma has been established by histopathology, the next step is sufficient staging work-up prior to initiating therapy.

Staging

A.Staging Procedures

Various recommendations have been published in recent guidelines, especially for patients with gastric lymphoma. In the review article by Raderer et al, recommended staging procedures for nongastric MALT lymphoma include the following: (1) CT scan of the thorax/abdomen/pelvis, (2) imaging of salivary glands and ocular adenexa (MRI or sonography), (3) Endoscopy with multiple biopsies in cases of clinical symptoms or suspicion, (4) colonoscopy (mandatory in case of clinical symptoms or suspicion), (5) dermatologic assessment for ocular adnexal/mammary MALT lymphomas, (6) bone marrow

biopsy (not mandatory). [5] In our patient, all these procedures were met except for colonoscopy and bone marrow biopsy which were not warranted in this case.

B.Staging System

The optimal staging system in MALT lymphomas is a matter of debate and various staging systems have been applied for diverse situations. The Ann Arbor staging which is based on the presence and localization of additional nonnodal lesions and the extent of lymph node involvement, is the most widely used system for extragastric MALT lymphomas, and several staging systems have been proposed for GI MALT lymphomas to take into account the nature of GI MALT lymphoma.[5] Table 1 presents the comparison between staging systems.

Table1. Comparison between Ann Arbor, Paris, and Lugano Staging Systems

LYMPHOMA EXTENT	ANN ARBOR STAGE	PARIS STAGING[a]	LUGANO STAGING
Mucosa and submucosal layer	I1E	T1N0M0	I
Muscularis propria, serosal layer	I2E	T2N0M0	I
Penetration beyond serosa	I2E	T3N0M0	I
Direct infiltration of adjacent organs	I2E	T4N0M0	IIE
Locoregional lymph nodes	II1E	T1-T4N1M0	II1
Abdominal lymph nodes (beyond local)	II2E	T1-T4N2M0	II2
Extra-abdominal lymph node spread	IIIE	T1-T4N3M0	IV
Dissemination to distant/non-GI organs	IV	T1-T4N0-N3M1	IV

GI indicates gastrointestinal. [a]Bone marrow involvement is rated "B1" in the Paris staging system.

taken from Raderer M, Kiesewetter B, Ferreri A. Clinicopathologic characteristics and treatment of marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT Lymphoma). Cancer J Clin 2016; 66:152-171.

In our case, there were no regional lymph nodes involved as well as extra-abdominal lymph node spread or dissemination to other distant/non-GI organs. The depth of involvement however was not determined. Owing to the unique anatomic location of the tumor at the ampullary region, direct infiltration to adjacent organs especially the pancreas was very likely. CT scan done prior to ERCP revealed mass at the pancreatic head. In light of the available data for work-up of staging the case, disease stage at diagnosis is Ann Arbor I2E.

Treatment

Therapeutic management of MALT lymphomas is extremely heterogeneous, and universally accepted therapeutic guidelines do not exist. Therapeutic choice depends on two main aspects: the primary involved organ and the extension of disease. Stage of disease is important because patients with limited-stage MALT lymphoma can achieve long-term complete

remission, and probably a cure, with local treatments. On the other hand, patients with advanced disease require systemic treatments. Due to its rarity, no consensus exists regarding peri-ampullary MALToma therapy.

A.Treatment of Limited Disease (Stage I-II)

Patients with limited-stage disease constitute the vast majority of cases of MALT lymphoma.[5] Patients can be managed with local treatments, which include surgical resection or radiotherapy, with a curative intent or systemic therapies, which could be ethiopathogenic, using a microorganism as the therapeutic target or conventional chemotherapy or immunotherapy.

Local Treatments

Surgery is often recommended to eradicate and achieve a nearly 100% cure for localized gastrointestinal lymphoma, as demonstrated in a study which included 15 patients with duodenal lymphoma. [13] However, the use of this strategy in patients with MALT lymphoma is progressively decreasing due to the fact that postsurgical sequels and organ dysfunction are more injurious than the lymphoma itself. The role of surgery is mostly limited to diagnostic procedures for histopathologic diagnosis, management of therapeutic complications, or treatment of relapsing disease in patients who are not candidates for other treatments.

Radiotherapy is the most extensively studied treatment in patients with MALT lymphoma. It is the standard primary treatment in many cases of extragastric MALT lymphoma and is used as salvage therapy in patients with gastric MALT lymphoma who do not respond or who relapse after HP eradication. The best disease control is attained in lymphomas arising in the thyroid gland, whereas up to 40% of patients with ocular adnexal MALT lymphoma experience contralateral or distant relapse. MALT lymphomas of the lung and salivary glands exhibit intermediate survival rates. [5] Most irradiated patients with stage I MALT lymphoma achieve an objective response that is slow and gradual.

Ethiopathogenetic Therapies

Some MALT lymphoma entities are associated with chronic persistent infections. These microorganisms can be used as therapeutic targets. *H.pylori* and gastric MALT lymphoma, *Chlamydia psitacci* and ocular adnexal MALT lymphoma, and Borrelia strains and cutaneous MALT lymphoma are the best-studied bacteria-lymphoma associations. *Helicobacter pylori* eradication with specific antibiotics is the standard treatment for patients with gastric MALT lymphoma.

In our patient, gastric biopsy for H.pylori test was negative. Peri-ampullary MALT lymphoma is not associated with *H.pylori* infection among cases reviewed.

Systemic Treatments

Chemotherapeutic and immunomodulatory agents were rarely used as part of first-line treatment for patients with limited-stage MALT lymphoma. This was based on the assumption that local therapies can lead to long-term local control in these patients. However, there has been a philosophical shift, at least in certain oncologic communities, also integrating systemic approaches into the front-line management of localized disease based on the clinicopathologic properties of the disease. [5] Previously, the indications for use of systemic agents included the following: (1) selected patients who, because of disease site or extension of disease, could not be managed with local treatments and were affected by MALT lymphomas unrelated to a known ethiopathogenic microorganism, (2)unresectable, symptomatic, pulmonary MALT lymphoma and (3) symptomatic, HP-negative, gastric MALT lymphoma. The recent European Gastro-Intestinal Lymphoma Study consensus[14] has stated that there is equally curative potential for systemic therapies and for radiation in localized gastric MALT lymphoma, and recent data obtained in 185 patients with extragastric MALT lymphoma who were followed for a median of 49 months have also shown no difference in outcome between various therapeutic approaches in localized nongastric lymphomas in terms of response rates and progression-free survival (PFS).

According to the notion that MALT lymphoma was just another type of indolent lymphoma, patients with advanced MALT lymphoma had been and still are included in trials mostly encompassing follicular lymphomas. The first paper to single out MALT lymphoma patients treated with the oral alkylating agents chlorambucil and cyclophosphamide was published in 1995, showing a 75% complete response rate (CRR) after a median duration of therapy of 12 months. Since then, several mostly small, uncontrolled trials using various agents and combinations in MALT lymphoma have been published, although few randomized data currently exist. [5] To date, the randomized, multicenter IELSG-19 trial[15] is the largest prospectively randomized trial in MALT lymphoma, including a total of 231 patients, comparing chlorambucil versus rituximab-chlorambucil. The response rate was 87% for the chlorambucil arm and 94% for the combination arm, whereas both the CRR and the 5-year event-free survival rate were significantly higher with the combination (78% vs 65% and 68% vs 50%, respectively) in both gastric and extragastric MALT lymphoma.

Following the publication of a randomized phase 3 trial of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) versus rituximab plus bendamustine (RBenda), [16] the latter regimen has become the standard for treatment of various types of indolent lymphoma.

In keeping with the initial phase 2 study of the same regimen, which included 6 patients with MZL (without further specification of MALT vs non-MALT), such patients were also treated within the phase 3 Study Group Indolent Lymphomas study. In total, 37 patients with MZL were included in the R-Benda arm, and 30 were included in the R-CHOP arm, but the

PFS was not significantly different for the subgroup of patients with MZL (57.2 vs 47.2 months, respectively; P 5 .32). However, the missing information on the exact nature of the MZL subtypes makes extrapolation of the findings to MALT lymphoma generally difficult.

In our patient, no surgery and radiotherapy were done. Since patient already had obstructive jaundice, insertion of biliary stent for bile duct decompression was completed during ERCP. Several cases reported surgery with Whipples procedure for limited stage ampullary carcinomas. However, the use of this strategy in patients with MALT lymphoma is progressively decreasing due to the fact that postsurgical sequelae and organ dysfunction are more injurious than the lymphoma as what has been observed in some cases. Our patient was started on chemotherapy with R-CHOP regimen as previously described. Conventional chemotherapy and its associated high remission rates is one of the options for first line treatment even in limited stage disease.

B. Treatment of Relapsed or Refractory Disease

Late recurrences and distant relapses have repeatedly been reported in patients with MALT lymphoma even after a prolonged follow-up time. In the case of dissemination or refractory disease, systemic treatment options with chemoimmunotherapy are seen as the treatment of choice.[5] In the past, several cytostatic substances and regimens mostly adapted from other indolent lymphoma entities have been successfully tested in this setting, achieving CRRs of 80% to 100%; regimens that include anthracyclines, alkylating agents, and purine analogues, combined or not with rituximab, have been associated with high response rates. However, many of these combinations are quite toxic. Thus, anthracycline-containing regimens in particular should be restricted to patients in need of rapid response or to those with transformation to diffuse large B-cell lymphoma.

Prognosis

MALT lymphoma is an indolent malignancy that often presents with limited stage of disease. Both GI and non-GI MALT lymphomas have an excellent prognosis, with 5-year overall survival rates higher than 90% and a 10-year survival rate of 75% to 80%. Recurrences can occur several years after treatment, with a median of 5 years, involving the same organ (60% of cases) or other extranodal sites.[17]

Transformation to large-cell aggressive lymphomas can occur in the first or later relapses.[5] The precise frequency and related mechanisms of histologic transformation are unclear. Several genetic alterations have been associated with histologic transformation, including p53 allelic loss and mutation, hypermethylation of p15 and p16, and p16 deletions.

Commonly reported indicators of a poorer outcome in MALT lymphoma are advanced age, impaired performance status, systemic symptoms, splenomegaly, elevated lactate dehydrogenase serum levels and/or b2-microglobulin levels, stage of disease, and, for primary gastric MALT lymphoma, the depth of infiltration of the gastric wall. Chromosomal translocations are related to lower responsivity to different therapies. [5]

Future Directions

Because of the indolent clinical course of MALT lymphoma and the high remission rates achieved by conventional chemotherapy, modern treatment strategies concentrate on “chemo-free” approaches to minimize toxicities, maintaining efficacy.[5] Among the therapeutic options being studied are Bortezomib, a protaeasome inhibitor, Thalidomide monotherapy, and Lenalidomide combination with Rituximab. The macrolide antibiotic Clarithromycin which apparently has additional immunomodulatory and antitumoral effects in addition to antimicrobial properties has also been studied. Moreover, with increasing use of targeted therapies, MALT lymphoma also might become a focus of interest for such agents such as idelalsisib. The pivotal study leading to the approval of idelalsisib in follicular lymphoma has also included 15 patients with MZL,[18] showing a promising response rate in this small subset of patients.

CONCLUSION AND RECOMMENDATION

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma or MALToma) involving duodenum and periampullary region occurs in less than 2% of lymphomas of the gastrointestinal tract. Despite their rarity, primary lymphomas of the gastrointestinal tract are important since their evaluation, diagnosis, management and prognosis are distinct from that of lymphoma at other sites and other cancers of the gastrointestinal tract. MALT lymphoma of the ampulla of Vater should still be considered in patients presenting with chronic abdominal pain, recurrent pancreatitis and obstructive jaundice. Over-all, MALT Lymphoma is an indolent malignancy that often presents with limited stage of disease. The management strategies are diverse and no treatment consensus exists. The possibility of transformation to large-cell aggressive lymphoma in the first or later relapses likewise needs consensus guidelines on follow-up. It is advised that further studies are needed to document the survival advantage and safety profile in the management approaches in patients with peri-ampullary MALT lymphoma as well as long-term or lifelong follow-up of these patients. Furthermore, targeted therapies show promise in the management of gastrointestinal MALT lymphoma in the near future and should be further studied.

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