

CASE REPORT

An unusual presentation of gastric mucosa-associated lymphoid tissue (MALT)-type lymphoma

Bikram Shrestha, MBBS, MD^{1*}, Bernard Kim, MD² and Alison Huffstetler, MD³

¹Department of Internal Medicine, Saint Agnes Hospital Center, Baltimore, MD, USA; ²Department of Critical Care and Pulmonary Medicine, Saint Agnes Hospital Center, Baltimore, MD, USA; ³Department of Family Medicine, University of Virginia Health System, Charlottesville, VA, USA

Mucosa-associated lymphoid tissue (MALT)-type lymphoma is a relatively rare disease; nevertheless, it is the third most common lymphoma type, accounting for 5–7% of all non-Hodgkin lymphomas. Case series and retrospective analysis published in the literature have suggested that extra gastrointestinal (GI) MALT-type lymphoma can occur simultaneously with MALT-type lymphoma involving the GI tract. We report the case of a healthy, 64-year-old Caucasian male who presented with progressive fatigue, non-productive cough, and worsening exertional shortness of breath for 3 months who was subsequently diagnosed with gastric extra-nodal marginal zone B-cell lymphoma or MALToma with simultaneous metastasis to the lung (bronchi) based on biopsy reports.

Case presentation: A 64-year-old Caucasian male presented to the emergency room complaining of progressive fatigue for 3 months which had progressed to the point of hindering his usual activities of daily living (ADL). He had recently visited his primary care provider for evaluation of a non-productive cough and exertional shortness of breath. A chest radiography obtained at the time showed bilateral infiltrates. He was then treated for atypical pneumonia but his symptoms unfortunately did not improve. Initial investigations in the emergency room revealed severe anemia and a positive stool guaiac test. Imaging showed bilateral pulmonary infiltrates and an irregular gastric mass. Gastric and transbronchial biopsies were suggestive of extra-nodal marginal zone B-cell lymphoma with simultaneous metastasis to the bronchi. He was treated symptomatically with transfusion of packed red blood cells (PRBC) and intravenous iron followed by radiotherapy. *Helicobacter pylori* infection was ruled out eliminating the possibility of treating him with eradication therapy.

Conclusion: Although the stomach is the most common and most extensively studied site of involvement of MALT lymphomas, they can also emerge in many other locations. MALT lymphomas have a high tendency to disseminate to other sites; therefore, extensive staging may be necessary to look for suspicious lesions.

Keywords: *extra-nodal; gastric; lungs; lymphoma; mucosa-associated lymphoid tissue*

*Correspondence to: Bikram Shrestha, Department of Internal Medicine, Saint Agnes Hospital Center, 900 S. Caton Avenue, Baltimore, MD 21229, USA, Email: Bikram.shrestha@stagnes.org

Received: 23 March 2016; Revised: 20 June 2016; Accepted: 28 June 2016; Published: 7 September 2016

Mucosa-associated lymphoid tissue lymphoma (MALT) belongs to a distinct group among non-Hodgkin lymphomas (NHL) (1). It is the third most common lymphoma type accounting for 5–7% of all non-Hodgkin lymphomas (2). This was first identified by Isaacson and Wright in 1983 (3). MALT lymphomas may be low or high grade, depending on their growth rate. MALT lymphoma usually arises in a background of chronic antigenic stimulation triggered by persistent infections and/or autoimmune processes (4). The majority of MALT lymphomas occur in the stomach, but they may affect any organ in the body including the intestines, salivary glands, thyroid, lung, ocular adnexa and less frequently skin, urinary bladder, and gonads (5).

Synchronous MALT lymphoma at different sites has been reported in the literature. Dissemination can occur without overt clinical manifestations; therefore, thorough staging is recommended to rule out multifocal involvement before initiation of therapy (6–8). We report a case of biopsy proven gastric MALT lymphoma with synchronous dissemination to the lung.

Case presentation

A 64-year-old Caucasian male presented to the emergency room complaining of progressive fatigue, lightheadedness, shortness of breath, and an intermittent cough. He reported waking up with extreme malaise and inability to ambulate on the day of presentation.

However, upon further questioning, it became evident that his symptoms had started 3 months prior and had gradually progressed in severity. He had been on a camping trip in the Rocky Mountains of Colorado and stayed in a yurt for one and half months before presentation; the trip was cut short due to his shortness of breath and decreased exercise tolerance. He had seen his primary care provider for these symptoms and a chest X-ray showed bilateral upper and lower lobe alveolar infiltrates. He was treated for atypical pneumonia with a 5-day course of azithromycin. His cough resolved but there was no improvement in the rest of his symptoms. Review of systems was significant for unintentional weight loss of 8–10 pounds over a period of 2 years; he denied nausea, vomiting, diarrhea, and/or melena.

His medical history included hypertension, glaucoma, and hyperlipidemia. He was a former smoker, having quit about 20 years prior. He drank alcohol occasionally. Family history was significant for leukemia in his father.

Physical examination was significant for pale skin and conjunctiva and a 3/6 systolic murmur best heard at the left sternal border.

Laboratory investigations showed hematocrit of 11.3% and hemoglobin of 3.7 gm/dl, and the stool guaiac test was positive. Computed tomography (CT) of the chest with intravenous contrast showed bilateral pulmonary opacities and mediastinal lymphadenopathy in the perivascular and posterior mediastinum (Fig. 1). CT of the abdomen and pelvis with contrast showed severe gastric wall thickening involving the proximal body and fundus with surrounding inflammatory changes (Fig. 2). Esophagogastroduodenoscopy with biopsy was performed. Gastric pathology showed an intense infiltrate of small, mature lymphocytes extending to the epithelium and obliteration of normal glandular architecture; immune-histochemical staining showed CD20+ and abnormal dim CD43 co-expression (Figs. 3 and 4) and BCL2+ and low to moderate Ki-67 proliferation index suggestive of extra-nodal marginal

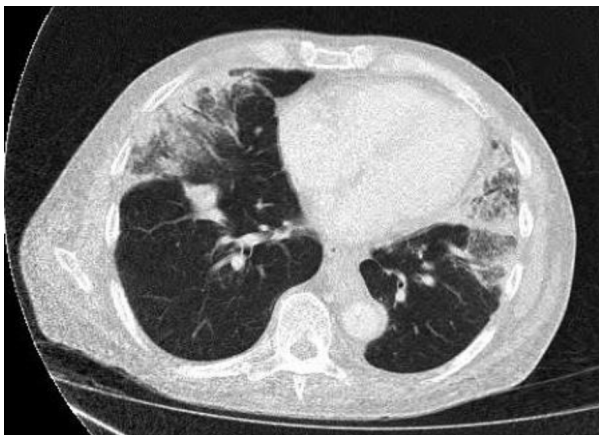


Fig. 1. CT chest with contrast showing bilateral pulmonary opacities.

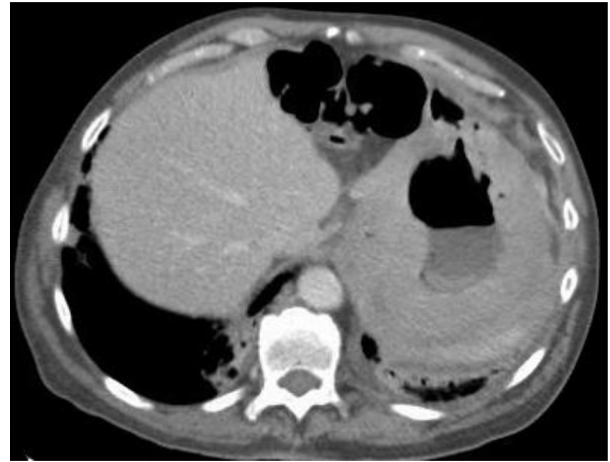


Fig. 2. CT abdomen and pelvis showing bowel wall thickening.

zone B-cell lymphoma of mucosal-associated lymphoid tissue. *Helicobacter pylori* was not identified on immunohistochemical staining and a serological analysis of IgG antibodies was negative ruling out previous exposure. A HLA-DQ pattern analysis for celiac disease was inconclusive. Serological analysis to rule out chronic infective etiology for immune stimulation from blastomyces, coccidioides, histoplasma, legionella, mycoplasma, aspergillus, and hepatitis B or C was negative. Subsequently, he also underwent bronchoscopy with transbronchial biopsy of the right upper and middle lobes, which showed atypical lymphoid infiltrate consistent with involvement from known MALT lymphoma with CD20+ and dim CD43 co-expression (Figs. 5 and 6). He was treated symptomatically for anemia with blood transfusion and intravenous iron administration. He underwent radiation therapy for MALT lymphoma of the stomach due to gastric bleeding and severe anemia requiring multiple transfusions. Radiation treatment was given with 15 MV photons with an AP/PA treatment technique using MLC shaping with CT based three-dimensional treatment and planning.

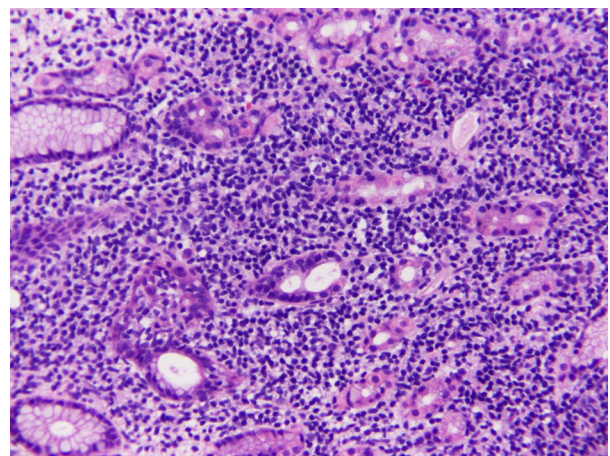


Fig. 3. Gastric biopsy showing small lymphocytic infiltration with glandular involvement in the H&E stain.

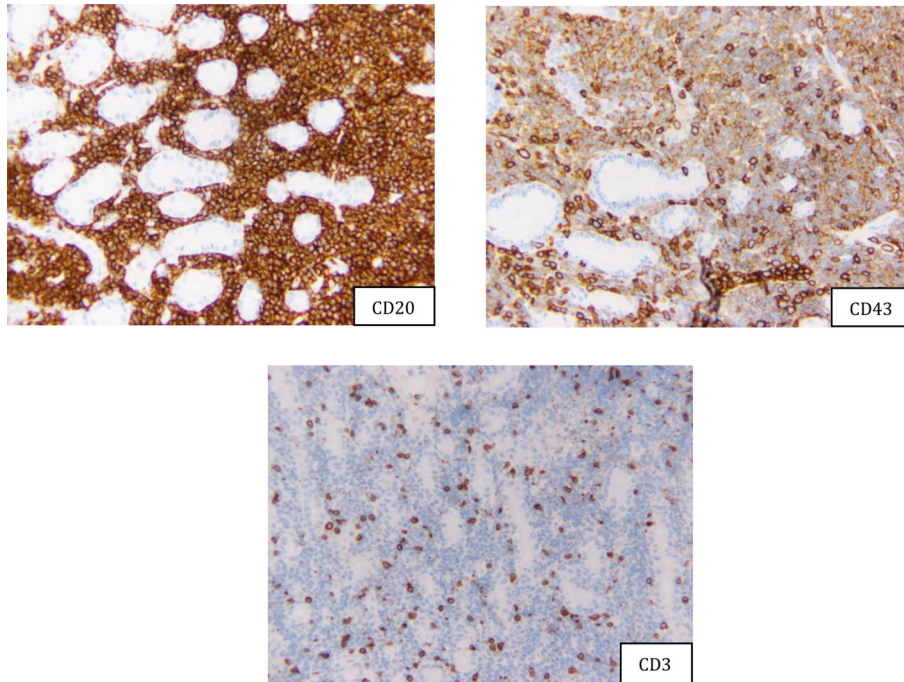


Fig. 4. Positive immunohistochemistry stains in the gastric biopsy.

He received a total dose of 36.0Gy in 20 fractions over 27 elapsed days. Immunotherapy with rituximab was considered. However, since the only symptomatic manifestations were related to his severe anemia secondary to the gastric involvement of his lymphoma, he was treated as localized disease. He is being closely followed by his oncologist and has been undergoing surveillance CT-scan of his chest/abdomen every 6 months and yearly PET scan. He has not required any chemotherapy or further radiation therapy and his lymphoma has remained stable.

Discussion

MALT-type lymphoma, also known as extra-nodal marginal type B-cell lymphoma, is an extra-nodal lymphoma

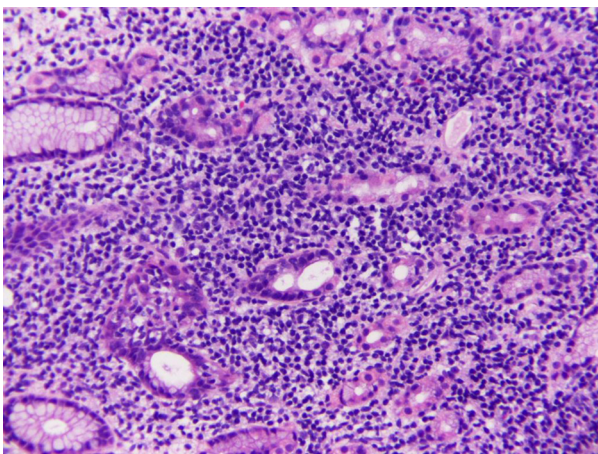


Fig. 5. Transbronchial biopsy specimen showing lymphocytic infiltration on H&E staining.

arising in a number of epithelial tissues including stomach, lung, salivary glands, skin, etc. (9). Previously it was also known as 'pseudo-lymphoma' due to its tendency to remain localized to the tissue of origin for a prolonged period of time; however, it is now recognized as a clonal B-cell neoplasm that frequently recurs locally and has potential for systemic spread and transformation to a high grade B-cell lymphoma. Extra-nodal marginal zone lymphoma of the lung is sometimes referred to as bronchial-associated lymphoid tissue lymphoma (BALT lymphoma). It has been suggested that these lymphomas are the result of chronic immune stimulation, often due to bacterial, viral, or autoimmune antigens; a good example is the well-known association between chronic gastritis due to *Helicobacter pylori* and the development of gastric MALT lymphoma (10). It is postulated that these lymphomas arise from post-germinal center memory B cells with the potential to differentiate into marginal zone cells or plasma cells. At least four different chromosomal translocations have been identified in these lymphomas, namely t(14, 18), t(11, 18), t(1, 14), and t(3, 14) (11). Chronic immune stimulation has been thought to trigger an interaction between antigens and receptors on the cell surface; this causes the B-cell lymphoma (BCL-10) protein to bind to the MALT lymphoma-associated translocation (MALT1) protein which in turn activates a set of genes that promote survival of extra-nodal marginal zone lymphoma cells (12).

Although the stomach is the most commonly involved site, the evidence shows that MALT lymphomas can involve a variety of organs like the lungs, breasts, thyroid,

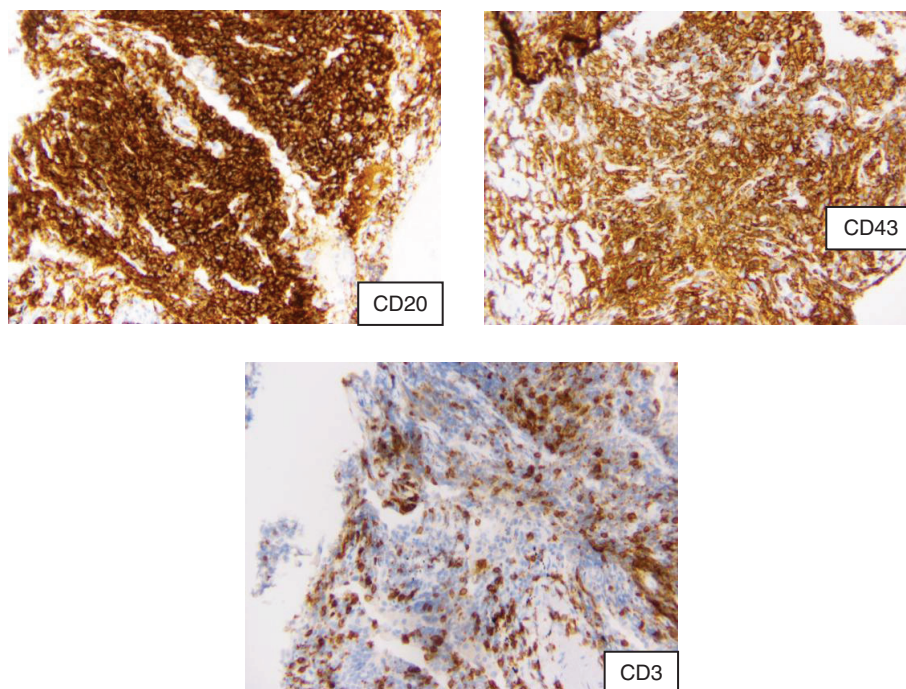


Fig. 6. Positive immunohistochemistry stains in the transbronchial biopsy specimen.

salivary glands, lacrimal glands, soft tissues, skin, etc. In a retrospective study of 35 patients with MALT lymphoma, 2 out of 24 patients were found to have multifocal disease with involvement of lung and colon, whereas 6 out of 11 patients with extra-gastric primary MALT lymphoma were found to have synchronous involvement of different anatomic sites (13). Another case series of 140 patients with MALT lymphoma demonstrated multi-organ involvement in 25% of patients with gastric MALT and in 46% of patients in non-gastric MALT (14). Due to these observations, it is recommended that patients newly diagnosed with MALT lymphoma undergo extensive diagnostic staging prior to initiation of any therapy. Some of the routine investigation modalities outlined for staging include ophthalmologic examination, otolaryngologic evaluation including sonogram of salivary glands or MRI if indicated. CT of the thorax and abdomen, endoscopy with sonography of upper gastrointestinal (GI) tract and biopsies, and colonoscopy and bone marrow biopsy as indicated should also be considered for staging purposes (13).

A retrospective study conducted on 21 patients diagnosed with BALT lymphoma to identify common imaging findings concluded that a single nodular or consolidative pattern was observed in 33%, multiple nodules or multiple areas of consolidation was observed in 43%, bronchiectasis/bronchiolitis in 14%, and diffuse interstitial lung disease (DILD) was seen in 10% of the patient population (15).

This is a case of gastric MALT lymphoma with either synchronous or disseminated MALT lymphoma with

involvement of lung or BALT lymphoma; this patient had bilateral opacities seen on CT chest. These findings are consistent with those seen in previous studies (16, 17).

Conclusion

MALT lymphomas are not very common malignancies. Presentation varies widely depending on the involved organ(s), a potential source of chronic immune stimulation may not always be apparent as evident in this case. Non-invasive *Helicobacter pylori* testing as stool antigen or blood antibody test should be tested if *Helicobacter pylori* is negative by histopathology. MALT lymphomas were once thought to be localized to one organ, but this concept has since been disproved; multiple case reports and case series have demonstrated its multi-organ involvement at presentation or on subsequent staging. Therefore, thorough staging and diagnostic work up should be completed on all newly diagnosed MALT lymphoma cases before initiation of any treatment.

Ethics/consent

Written consent obtained from the patient and can be submitted on request.

Authors' contributions

BS, the principal author, and BK conceived the idea and critically reviewed the manuscript, whereas BS and AH drafted the manuscript.

Acknowledgements

Maria del Pilar Morales, M.D., F.A.C.P., Associate Program Director, Department of Internal Medicine, Saint Agnes Hospital Center, Baltimore, MD, USA.

Conflict of interest and funding

All authors declare no conflicts of interest and funding relationships.

References

- Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. *Blood* 1994; 84: 1361–92.
- The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood* 1997; 89: 3909–18.
- Isaacson P, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue: A distinctive type of B-cell lymphoma. *Cancer* 1983; 52: 1410–16.
- Berlin C, Berg EL, Briskin MJ, Andrew DP, Kilshaw PJ, Holzmann B, et al. Alpha 4 beta 7 integrin mediates lymphocyte binding to the mucosal vascular addressin MAdCAM-1. *Cell* 1993; 74: 185–95.
- Papaxoinis G, Fountzilias G, Rontogianni D, Dimopoulos MA, Pavlidis N, Tsatalas C, et al. Low-grade mucosa-associated lymphoid tissue lymphoma: A retrospective analysis of 97 patients by the Hellenic Cooperative Oncology Group (HeCOG). *Ann Oncol* 2008; 19: 780–6.
- Kawamata N, Miki T, Fukuda T, Suzuki K, Sumi Y, Ohdama S, et al. Determination of a common clonal origin of gastric and pulmonary mucosa-associated lymphoid tissue lymphomas presenting five years apart. *Intern Med* 1995; 34: 220–23.
- Graziadei G, Pruneri G, Carboni N, Luminari S, Targia ML, Neri A, et al. Low-grade MALT-lymphoma involving multiple mucosal sites and bone marrow. *Ann Hematol* 1998; 76: 81–3.
- Stephen MR, Farquharson MA, Sharp RA, Jackson R. Sequential MALT lymphomas of the stomach, small intestine and gall bladder. *J Clin Pathol* 1998; 51: 77–9.
- Zucca E, Roggera E, Bertoni F, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part I: Gastrointestinal, cutaneous and genitourinary lymphomas. *Ann Oncol* 1997; 8: 727–37.
- Hussell T, Isaacson PG, Crabtree JE, Spencer J. The response of cells from low-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue to *Helicobacter pylori*. *Lancet* 1993; 342(8871): 571–4.
- Sagaert X, De Wolf-Peeters C, Noels H, Baens M. The pathogenesis of MALT lymphomas: Where do we stand? *Leukemia* 2007; 21(3): 389.
- Willis TG, Jadayel DM, Du MQ, Peng H, Perry AR, Abdul-Rauf M, et al. Bcl10 is involved in t(1;14)(p22;q32) of MALT B cell lymphoma and mutated in multiple tumor types. *Cell* 1999; 96(1): 35–45.
- Raderer M, Vorbeck F, Formanek M, Osterreicher C, Valencak J, Penz M, et al. Importance of extensive staging in patients with mucosa-associated lymphoid tissue (MALT)-type lymphoma. *Br J Cancer* 2000; 83(4): 454–7.
- Raderer M, Wöhrer S, Streubel B, Troch M, Turetschek K, Jäger U, et al. Assessment of disease dissemination in gastric compared with extragastric mucosa-associated lymphoid tissue lymphoma using extensive staging: A single-center experience. *J Clin Oncol* 2006; 24(19): 3136–41.
- Bae YA, Lee KS, Han J, Ko YH, Kim BT, Chung MJ, et al. Marginal zone B-cell lymphoma of bronchus associated lymphoid tissue: Imaging findings in 21 patients. *Chest* 2008; 133: 433–40.
- Knisely BL, Mastey LA, Mergo PJ, Voytovich MC, Zander D, Almasri NM, et al. Pulmonary mucosa-associated lymphoid tissue lymphoma: CT and pathologic findings. *AJR Am J Roentgenol* 1999; 172: 1321–6.
- Lee DK, Im JG, Lee KS, Lee JS, Seo JB, Goo JM, et al. B-cell lymphoma of bronchus-associated lymphoid tissue (BALT): CT features in 10 patients. *J Comput Assist Tomogr* 2000; 24: 30–4.