Mantle Cell Lymphoma Presenting as a Gastric Mass & Multiple Lymphomatous Polyposis of the Duodenum: A Case Report and Review of the Literature

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Abstract

We present a case of a 61 year old man admitted for epigastric pain and fatigue. Computed tomography and endoscopy revealed the presence of a gastric mass and multiple polyps in the duodenum. The patient also had widespread lymphadenopathy, ascites and pleural effusion. Genetic and immunohistochemical testing confirmed the diagnosis of disseminated mantle cell lymphoma. To the best of our knowledge, we are the first to describe a case of simultaneous gastric and duodenal mantle cell lymphoma.

Keywords: Mantle cell lymphoma; Gastrointestinal; Gastric; mass; Polyposis; Duodenum; Endoscopy

Introduction

Mantle cell lymphoma (MCL) is a rare malignancy reported mainly through case reports [1,2]. It is a B-cell lymphoma that comprises 3-10 % of all non-Hodgkin’s lymphomas [3], and has an incidence of approximately 2 to 3 cases per 100,000 persons per year [4]. Patients typically present in their sixties [5], with a median age range of 54 to 68 years old [6]. Common symptoms include fever, heavy night sweats and weight loss [7]. MCL occurs more commonly in males, with a male to female ratio of 2- 3:1 [8]. Pathogenesis is unknown, but a susceptible genetic background, a chemotherapeutic regimen or ionized radiation could contribute to the development of MCL [9]. In up to 80% of cases of MCL, patients have involvement of extranodal sites and organs like the spleen, bone marrow, peripheral blood, gastrointestinal tract (GI), etc [10]. Furthermore, involvement of more than 2 extra-nodal sites is seen in 30 to 50% of MCL patients [11]. Peripheral blood lymphocytosis is seen in 20–40% of MCL cases [12]. The frequency of GI involvement in MCL has been previously underestimated, with previous reports citing 30% of MCL cases (by EGD and colonoscopy) [13]. But with more recent studies, GI tract infiltration has been shown in up to 92% of cases microscopically (from biopsies of lymphoid aggregates in normal and abnormal mucosae) [10]. Upper GI tract involvement is more common than colonic [6]. Major sites of GI MCL involvement are the ileocecal region (35.7%), ileum (20.3%), rectum (9.1%) and duodenum (7.7%) [14]. Gastric involvement is much rarer in MCL [15]. However, the stomach is the most commonly involved site in other B-cell lymphomas [16]. Patients also usually present with advanced disease (late stages III & IV), which includes lymphadenopathy, hepatosplenomegaly and bone marrow involvement (which alone occurs in up to 50% of presenting MCL patients) [3,17,18]. Median survival with treatment is 4 to 5 years [19]. In this case report, we present a patient with disseminated MCL that primarily involved the stomach and duodenum.

Case Report

A 61 year-old, male patient, of South-Asian ethnicity, presented to the emergency room complaining of epigastric pain, general fatigue, shortness of breath and abdominal distention of a couple of months duration. He has a past medical history significant for long-standing type 2 diabetes mellitus (complicated with diabetic nephropathy stage 3), hypertension, coronary artery disease and dyslipidemia. Review of systems indicated passing of black stool. Physical examination revealed a cachectic man, with slight tachypnea but otherwise normal vital signs. The exam was significant for bilateral pleural effusions, a palpable epigastric mass, ascites and mild sacral and pedal edema. Automated peripheral blood count uncovered leukocytosis (22.9 x 109/L, with 50.3% lymphocytes and 42.5% neutrophils), anemia (red blood cell count 3.2 x 1012/L, hemoglobin 7.1 g/dL, hematocrit 24%, MCV 73.4 fL), and increased platelets (524 x 109/L). Peripheral blood film showed severe normochromic, normocytic anemia and leukocytosis with lymphocytosis. The lymphocytes were a mixture of mature small cells and cells with clefted or irregular nuclei and single nucleoli (Figure 1).

A blood chemistry test uncovered low albumin (33 g/L) and high lactate dehydrogenase (302 IU/L). A chest X Ray showed a left hemithorax effusion and consolidation. COMPUTED TOMOGRAPHY (CT) of the chest with IV contrast confirmed bilateral pleural effusions instead and a compression-collapsed left lung. A diagnostic pleural tap was then done, and it showed hemorrhagic fluid, with lymphocytosis (92% of cells) and an LDH of 485 IU/L (an exudate). A therapeutic ascitic tap was also performed, and it in turn showed a hemorrhagic fluid as well, with lymphocytosis of 87%, and a Serum-Ascites Albumin Gradient (SAAG) of 1.5 g/dL. In addition, fecal occult blood test was positive. CT of the abdomen and pelvis disclosed a large epigastric mass with diffuse lymphadenopathy. There was a moderate amount of ascites. A subsequent Esophagogastroduodenoscopy (EGD) revealed a large fungating lesion on the greater curvature of the stomach, likely surrounding an ulcer. There was also a diffuse process involving the antrum and pylorus, with complete absence of peristalsis.

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The duodenum had multiple polyoid lesions with surrounding inflammation involving the first and second part of the duodenum (Figure 2). Biopsy of the gastric mass (Figure 3) revealed that the lamina propria and sub-mucosa were expanded by a population of small to medium lymphocytes that replaced the normal glandular architecture of the gastric body and extended into the sub-mucosa. The infiltration was diffuse rather than nodular. IHC stains showed the malignant population of lymphocytes to be positive for CD20, CD79, CD5, CD43, cyclin D1 (100%), BCL-2 & PAX5; and negative for the markers CD10, BCL-6, CD56, CD7 and CK. Additionally, these cells were IgM and IgD positive and they were also kappa light chain positive and lambda light chain restricted. Biopsy of the duodenal polyoid lesions uncovered a similar picture to the stomach biopsy, where the duodenal mucosa was expanded by a population of small to medium-sized lymphocytes that were CD5, CD79, CD20 and PAX5 positive. Unfortunately, a biopsy of any of the involved lymph nodes was not performed. Nonetheless, a bone marrow aspirate and biopsy later confirmed the involvement of the marrow. The smear revealed marrow infiltration with many small to medium sized lymphoid cells; some of them appeared small & mature-looking, with condensed nuclear chromatin, while others appeared larger with more primitive, diffuse nuclear chromatin, prominent nucleoli and high N/C ratio. Nuclei in many lymphocytes showed pronounced nuclear clefting, indentation, with a few binucleated forms as well. Erythropoeisis appeared markedly depressed; but with no significant dyserythropoietic changes. Granulopoiesis appeared adequate with a markedly increased M/E ratio (29:1), a normal maturation pattern and some with toxic granulation. IHC stain of the biopsy showed scattered cells in small aggregates positive for the markers BCL2, CD3, CD5, CD20, CD79a and PAX-5. Flow cytometry (FCM) on the bone marrow aspirate showed a monotypic, kappa-restricted B-cell population; expressing CD5, CD19, CD79b, CD20 & FMC7 with kappa light chain restriction. There was also partial expression of CD38. However, there was no significant expression of CD10, CD23, CD25, CD11c or CD103. Similar results were seen in the FCM of the ascitic fluid and pleural fluid, but instead both had a small population (3-6%) expressing CD10.

Fluorescence in situ hybridization (FISH) evaluation showed an abnormal fusion hybridization signal pattern consistent with the presence of a t(11;14) rearrangement in 40% of interphase nuclei cells (from the bone marrow) analyzed. With respect to the patient’s clinical course, he deteriorated very quickly and did not get a chance to receive any chemotherapy. Unfortunately the patient’s general condition rapidly worsened and within a month, he succumbed to septic shock, with blood and ascitic fluid cultures growing the yeast Candida glabrata.

Review of the Literature

In MCL, B-cells in the antigen-naïve pre-germinal center of primary follicles or the mantle zone of secondary follicles undergo a malignant transformation [15]. Histologically, MCL is usually composed of monomorphic small to medium sized lymphocytes with irregular nuclear contours (may be cleaved), a scanty, faintly-stained cytoplasm, moderately dispersed chromatin but inconspicuous nucleoli [20-23] – as was seen in the GI biopsies of our patient. Cyclin D1, a nuclear protein, is normally not expressed in B lymphocytes. It has a critical role in cell cycle regulation and promotes cellular proliferation [15,24,25]. It is over-expressed in MCL due to a specific genetic translocation, t(11;14)(q13;q32), which juxtaposes immunoglobulin heavy chain (IgH) gene sequences (on chromosome 14) with the BCL-1 locus (on chromosome 11) and leads to CCND1 gene up-regulation and cyclin D1 over-expression [5,20,24]. This translocation is seen in most of the MCL patients (up to 73% of cases [26]), although some cases of t(11;14)(q13;q32) negative MCL have also been reported [27-30]. Cyclin D1 is almost always over-expressed though, making it the most important and useful finding for diagnosing MCL [3,11,31]. Nonetheless, very rare MCL cases may also lack cyclin D1 expression [29]. FISH has been shown to be the most sensitive technique to detect the BCL-1/IgH translocation [32]. It is found in 90% to 1000% of MCL patients by FISH, in 50% to 70% by conventional cytogenetic analysis, but in just 30% to 50% by Polymerase Chain Reaction (PCR) [33-41]. The neoplastic cells in MCL are usually positive for pan-B lymphocyte markers, such as CD19, CD20, CD79a and Pax5, and show a strong expression of surface IgM/IgD. They often also express CD5, FMC-7, CD22, CD43, BCL-2, but lack CD23 and germinal center markers of CD10 and BCL-6 [20,42].

In about 11% of MCL cases, lymphoma cells do not express CD5 [43]. CD5 is expressed by T cells and a small population of B cells in the mantle zone of normal lymph nodes [44]. It is involved in the survival of lymphocytes...
B-cells through stimulation of autocrine production of the cytokine IL-10 [45]. MCL not expressing CD5 have genetic modifications that do not depend on CD5 stimulation [45]. Other markers like CD23 and CD10 are negative in MCL in contrast to chronic lymphocytic leukemia and follicular lymphoma respectively [44]. Almost all MCL cases express cyclin D1 though, including the cases lacking CD5 (5% of the cases) or expressing CD23 (10% of the cases) [46]. GI tract involvement occurs frequently in MCL, typically in the form of multiple lymphomatous polyposis (MLP) [13]; and many consider MLP as the GI counterpart of MCL [47]. It is characterized by the presence of numerous polyloid lesions of malignant lymphoma, and is often accompanied by extra-abdominal dissemination (especially to peripheral lymph nodes) [48]. The polyps range in size from a few millimeters to centimeters [49], and may occur at any location between the esophagus and the rectum [50]. The most common location of MLP is in the ileocecal region [51,52], and they involve the stomach or duodenum in 50% of cases, and the small and large intestines in 80 – 90% of cases [49]. In addition, one third of cases may present as a mass [51,52]. Not all MLP in the GI tract result from MCL [53]. Less commonly, MLP may be due to mucosa-associated lymphoid tissue lymphoma [50]. In our case, the polyloid lesions in the duodenum were most probably MLP. Recent reports have endoscopically revealed that 46%-49% of MCL patients had esophago-gastroduodenal involvement, and that 38%-62% had colorectal involvement [10,13]. Endoscopic findings of the upper and lower GI tract in MCL have included inflammation, nodules, polyps, ulcers, thickened walls, and masses [13]. Masses have been usually found in the upper GI tract (4.2% of the upper GI tract findings vs. 0% of the lower GI tract findings) [13]. Generally speaking, GI lymphomas, in decreasing order of frequency, involve the stomach, ileum, jejunum, and duodenum, a pattern that reflects the relative amount of normal lymphoid cells in these organs [9]. However, gastric involvement is much rarer in MCL. It is unknown why extra-nodal MCL preferentially arises in the intestine [16].

Discussion

The findings of our case are thus consistent with a CD5-positive mature B-cell neoplasm, and the overall histopathologic pattern is that of a mantle cell lymphoma of the GI tract. The differential diagnosis may also include chronic lymphocytic lymphoma (CLL), but lack of expression of CD23 and the FISH findings of (11;14) favor mantle cell lymphoma. Our case is unique amongst previous case reports on gastrointestinal MCL in that it describes a case with a gastric mass and MLP simultaneously. The pathogenesis of MCL is unknown. Unlike Mucosa-Associated Lymphoid Tissue (MAL T) lymphoma, there are no studies to determine the relationship between MCL and Helicobacter pylori. On the other hand, gastric MALT lymphoma is associated with H. pylori infection, and tumor regression is related to the eradication of these bacteria [54-56]. However, the relationship between Helicobacter pylori (H. pylori) infection and duodenal MALT lymphoma is unclear [57]. It has been shown that its eradication can be either effective [58-60] or ineffective [54, 61-63]. In MALT lymphoma, the pathogenesis is explained by Helicobacter pylori chronically stimulating the immune system of the GI tract to maintain an extended and prolonged proliferative state, thereby increasing the likelihood of lymphoid transformation [64]. Whether or not H. pylori have any role in MCL pathogenesis is yet to be determined. A recently published population-based study [65] revealed that almost 91% of MCL cases found were ethnically white, almost 4% were black and almost 4% were Asian/Pacific Islander. In addition, Asian/Pacific islander patients had significantly more common involvement of extra-nodal primary sites than white or black patients. These ethnic differences may be a result of genetic or other environmental and lifestyle factors [65-70], and future exploration of them may help in elucidating the etiology of MCL. Both pleural effusions and ascites were seen in this case. Pleural effusions are seen in approximately 20 to 30% of patients with lymphoma [71]. The involvement of the peritoneal cavity in lymphomas; however, is infrequent [71-73]. Serosal involvement is caused by either direct infiltration or vascular leakage (due to increased production of VEGF in malignancy) [74]. Malignant cells were found by FCM in our patient’s ascitic fluid (and pleural fluid too). Our patient; however, had a SAAG of 1.5 g/dL (≥ 1.1) which indicates a portal-hypertension cause of his ascites rather than a non-portal hypertension related cause such as peritoneal carcinomatosis or TB. Infiltration of the reticuloendothelial system (including sinusoids of the liver) due to extensive malignancy can lead to portal hypertension, and this may explain this additional finding.

In the study by Ambinder et al. [65] mentioned earlier, almost 80% of MCL patients were found to have the primary site of disease in the lymph nodes. Of extra-nodal primary sites, the GI tract was the most common (almost 40%). Of note, patients with primary GI tract disease presented less frequently (56.9%) with advanced stage disease (Stage III/IV) compared with patients with primary lymph node disease (86.8%) [65]. Because the patient presented with multiple foci and disseminated MCL – it is difficult to speculate on where the primary location was. There was involvement of the bone marrow and most probably the lymph nodes too (CT scan revealed extensive and widespread lymphadenopathy). We have three hypotheses that may explain this presentation: 1. The MCL originated in a lymph node, and then metastasized to the blood, bone marrow, GI tract, peritoneal and pleural cavities. 2. Tumor formation started within the GI tract (either the gastric mass or the duodenal polyps, whether concurrently or separately), and then disseminated elsewhere. 3. Tumor formation started somewhere else (e.g. the bone marrow or reticuloendothelial system), and then disseminated elsewhere. Our patient presented with disseminated disease with involvement of the bone marrow and widespread lymphadenopathy (stage IV - modified Ann Arbor staging [12]). The prognosis of MCL patients at this stage is very poor with an overall survival ranging from 36 to 52 months, and fewer than 8% of patients alive at 10 years [3,26]. Our patient died within a month of presentation due to complications of the widespread metastasis and his previous medical conditions.

References


