A Rare Case of Multiple Lymphomatous Polyposis With Widespread Involvement of the Gastrointestinal Tract

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• Multiple lymphomatous polyposis (MLP) is an uncommon type of primary non-Hodgkin gastrointestinal (GI) B-cell lymphoma characterized by the presence of multiple polyps along the GI tract. Malignant cells of MLP have mantle cell characteristics and thus are considered to be the counterpart of the mantle cell lymphoma (MCL) in the GI tract. Since 1961, no more than 70 well-documented cases have been published. We report the case of 53-year-old man diagnosed as having MLP. The patient presented with diffuse abdominal pain, chronic lower GI bleeding, peripheral lymphadenopathy, and weight loss. The lymphomatous polyps extended from the esophagus to the rectum, with bone marrow infiltration. Immunohistologic findings were characteristic of MCL. The patient was treated with a combined cyclophosphamide, vincristine, and prednisone chemotherapy regimen, resulting in a partial response.

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The gastrointestinal (GI) tract is the predominant appearance site of extranodal non-Hodgkin lymphomas.[1] Primary non-Hodgkin lymphomas of the GI tract are rare, accounting for only 1% to 4% of malignancies arising in the stomach, small intestine, or colon.[2] Most cases are of B-cell origin and include the mucosa-associated lymphoid tissue (MALT), mantle cell, Burkitt, and Burkitt-like lymphomas. *Multiple lymphomatous polyposis* (MLP) is a term applied to a specific lymphoma characterized by a distinctive pattern of GI involvement in which long segments of the intestine are superficially infiltrated by multiple white nodular or polypoid tumors, ranging in size from 0.2 to 2 cm.[3,4] Malignant cells in MLP originate in the mantle zone of the lymphoid follicle, so this disease is actually considered a subtype of lymphoma called *mantle cell lymphoma* (MCL).[5,6]

Since 1961,[3] no more than 70 documented cases of MLP have been reported in the literature.[6] We herein describe and discuss the clinicopathologic features of an MLP case that affected the stomach, duodenum, small intestine, and colon.

REPORT OF A CASE

A 53-year-old man presented with a 5-month history of diffuse abdominal pain, chronic lower GI tract bleeding, peripheral lymphadenopathy, and fatigue. Weight loss of 10 kg and chronic fever were also present. At admission his temperature was 38.2°C, heart rate was 112/min, respiratory rate was 28/min, and blood pressure was 100/60 mm Hg. Peripheral lymph nodes, ranging from 5 to 15 mm, were palpable in the cervical, retroauricular, neck, axilla, and inguinal regions. The abdomen was slightly distended with no tenderness. There was no hepatosplenomegaly. Soft, smooth, round, raised lesions were identified during rectal examination. The stool samples were positive for blood (Hematest), and tests revealed the following laboratory values: white blood cell count, $13.7 \times 10^3/\mu L$ (reference range, 4.0–$12.0 \times 10^3/\mu L$); hemoglobin concentration, 11.2 g/dL; hematocrit, 33.1% (reference range, 42.6%–52.6%); uric acid, 9.1 mg/dL (541.2 μmol/L; reference range, 238–530 μmol/L); albumin, 2.3 g/dL; lactate dehydrogenase, 253 U/L (reference range, 109–197 U/L); and β_2-microglobulin, 4.5 μg/mL (reference range, 1.2–2.5 μg/mL). Serological test results for human immunodeficiency virus were negative. Chest x-ray films did not show any abnormality. Computed tomographic scan revealed enlarged lymph nodes in multiple regions (submaxillar, cervical, axilla, mediastinum, retroperitoneum, and around the abdominal aorta) and wall thickening of the right colon. Small bowel follow-up examination with barium showed multiple smooth, round filling defects in the duodenum, jejunum, and ileum (Figure 1). Double-contrast barium enema showed numerous diffused barium flecks throughout the left colon and rectum. Upper endoscopy revealed multiple variable-sized, whitish, round nodules in the esophagus, antrum of the stomach, and duodenum. Colonoscopy showed multiple white polypoid tumors, ranging in size from 0.5 to 2.5 cm, some of which were ulcerated.

Although most protrusions were covered by normal colonic mucosa, some were ulcerated (Figures 2 and 3). Endoscopic biopsy specimens were taken from the polypoid lesions of the esophagus, stomach, duodenum, and colorectum. Some nodules were located in the mucosa, whereas others involved the muscularis mucosa and extended to the submucosa (Figure 4). Histologically, the lesions were composed of a dense, monotonous infiltrate of small-to-intermediate cleaved cells with irregular-shaped nuclei, inconspicuous small nucleoli, and scanty cytoplasm (Figure 5). These cells resembled the mantle zone cells of secondary (reactive) follicles. Immunohistochemical studies were performed on paraffin sections using monoclonal and polyclonal antibodies with peroxidase-antioxidase and avidin-biotin complexes. The lymphoma cells were positive for CD19, CD20, CD5, and cyclin D1 and negative for CD3 and CD23 (Figure 6). The same histologic pattern was observed in all examined polypoid

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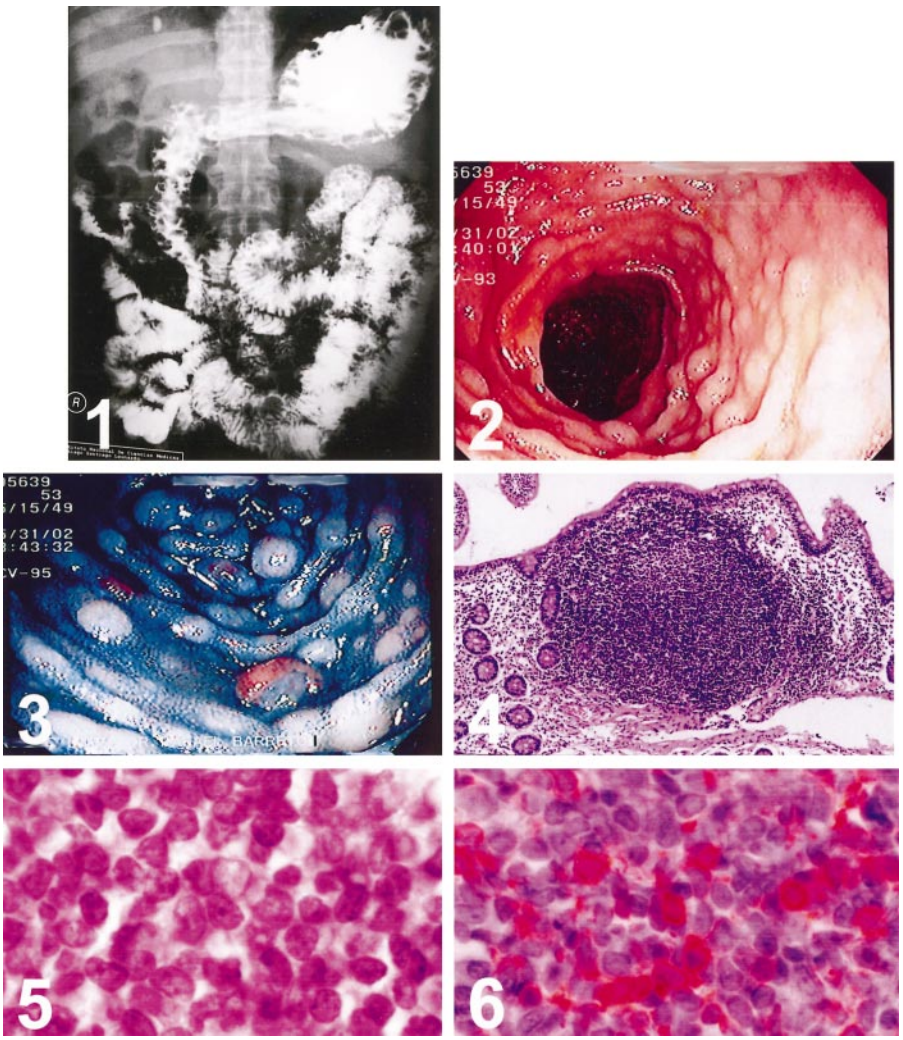

Figure 1. *Small bowel follow-up examination with barium shows multiple smooth and round filling defects in the duodenum, jejunum, and ileum.*

Figure 2. *Colonoscopy with multiple polypoid lesions ranging from 0.2 to 0.5 mm in diameter. Mucosa between polyps appears to be normal.*

Figure 3. *Colonoscopy with a sprayed dye technique (indigo carmine) showing multiple polypoid lesions of various sizes.*

Figure 4. *Colonic biopsy specimen showing a dense lymphoid infiltrate with well-defined borders (hematoxylin-eosin, original magnification ×100).*

Figure 5. *Cellular infiltrate is composed of small-to-medium cleaved lymphocytes with moderate atypia (hematoxylin-eosin, original magnification ×200).*

Figure 6. *Colonic biopsy specimen showing strong staining of lymphocytes with CD5 antibodies (hematoxylin-eosin, original magnification ×200).*

lesions. Bone marrow biopsy specimens showed infiltration by lymphoma cells.

Based on these findings, a diagnosis of MCL compatible with stage IV of the Ann Arbor staging system was made. Combined chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was initiated. Although peripheral lymphadenopathy and fever improved significantly, the patient was regarded as being in partial remission, because additional endoscopic studies after 3 chemotherapy courses identified polypoid lesions in the entire GI tract. The patient is still alive 6 months after initial treatment.

COMMENT

Although there has been controversy about whether MLP is a clinical manifestation of lymphoma with heterogeneous histologic features or a distinctive clinicopathologic disorder, multiple studies[6–8] have concluded that this disorder is a single distinct disease. Malignant cells have morphologic, cytologic, and immunophenotypical characteristics of mantle cells, so this entity is in fact considered the counterpart of MCL in the GI tract.[5] Multiple lymphomatous polyposis was first described and reviewed by Cornes in 1961.[3] Since then, most cases in the literature have been presented in small series or case reports.[9–11] In the largest series (31 cases), reported by Ruskoné-Fourmestraux et al,[6] MLP accounted for only 9% of primary GI lymphomas. The disease occurs more commonly in men 55 to 64 years old. Patients usually have symptoms related to GI involvement, which may include abdominal pain, diarrhea, obstruction, or hematochezia. Occasionally, lymphomatous polyposis can be present as protein-losing enteropathy, intestinal malabsorption, chylous ascites, or acute abdomen due to perforation. The polyps usually appear in the ileocecal region, but any other area of the GI tract might be involved, from the esophagus to the rectum. Complete GI involvement is rare, which makes the case presented herein remarkable. Locoregional mesenteric lymphadenopathy is often present at the time of diagnosis, and involvement of peripheral nodes, liver, spleen, and bone marrow may be evident early in the disease.[6,7]

Radiographic and endoscopic images of MLP patients show characteristic smooth and sessile polyps from 2 mm to several centimeters in diameter, affecting one or more segments of the intestine. The larger polyps are usually seen in the ileocecal region and occasionally may be ulcerated.[12] MALT lymphomas, follicular lymphomas, B-cell chronic lymphocytic leukemia, UCHL-1–positive lymphoma, α-heavy chain disease, adult T-cell lymphoma, and angioimmunoblastic lymphadenopathy are conditions with similar macroscopic findings and should be considered in the differential diagnosis.[13] Histologic characteristics of MLP (MCL) include a monomorphic neoplastic infiltration that consists of a uniform population of small

to medium cells with irregular nuclei and scanty cytoplasm. Cell proliferation may be nodular or diffuse with a mixed nodular pattern.[4,14] Histologic similarities can be found in MCL and MALT lymphoma, especially when diffuse cell proliferation is found; therefore, immunohistochemical studies are necessary. The tumor cells in MCL express pan-B-cell markers (such as CD19, CD20, and CD22) and the T-cell marker CD5. This antigen is normally expressed by a minor subpopulation of B cells in the adult follicular mantle zone of lymph nodes. The lack of T-cell markers such as CD3 is common in MLP. These morphologic and immunohistochemical properties indicate that MLP originates from the mantle cell zone.[6] Interestingly, in this case, we found cyclin D1 (a cell cycle regulatory protein) antibodies in tissue samples; this finding is the result of a chromosomal translocation, t(11; 14)(q13;q32), and rearrangement of the *Bcl-1* locus on chromosome 11.[15] The overexpression of cyclin D1 antigen has been proposed as another marker for MCL.

The prognosis of MLP is poor due to its accelerated proliferation. Most of the patients had advanced diseases at the time of diagnosis. Patients with obstructive tumor masses require surgical resection. Chemotherapy is the treatment of choice, including regimens with (1) CHOP; (2) cyclophosphamide, vincristine, and prednisone (COP); and (3) doxorubicin, teniposide, cyclophosphamide, and prednisolone (AVmCP). In a French study using the AVmCP regimen, the response rate was 80%, with a 5-year survival rate of 59%. Less aggressive regimens, such as COP, appear to be less effective, with a response rate of 30% and a mortality rate of 100% 3 years after treatment.[6] The same study suggested that total body irradiation and autologous stem cell transplantation may benefit younger patients who responded to first-line therapy. Most of the patients with MCL show a initial good response to chemotherapy; however, eventually patients become refractory. The mean survival time is 20 to 30 months after diagnosis.

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