

# Distal Ileal Ulcers as Gastrointestinal Manifestation of Waldenstrom Macroglobulinemia

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## ABSTRACT

Waldenstrom macroglobulinemia (WM) is a neoplastic disorder of the B-cell lymphoid system. A 69-year-old man with WM presented with diarrhea for 6 months. Magnetic resonance enterography showed thickening of the terminal ileum (TI). Colonoscopy with TI intubation showed a single TI ulcer, and small bowel enteroscopy revealed multiple ulcers in the TI. Biopsies from both were negative on hematoxylin and eosin staining. Immunoglobulin M immunofluorescence staining of the ulcers was positive for IgM deposits consistent with WM. After 6 cycles of chemotherapy with bendamustine and rituximab, symptoms resolved.

## INTRODUCTION

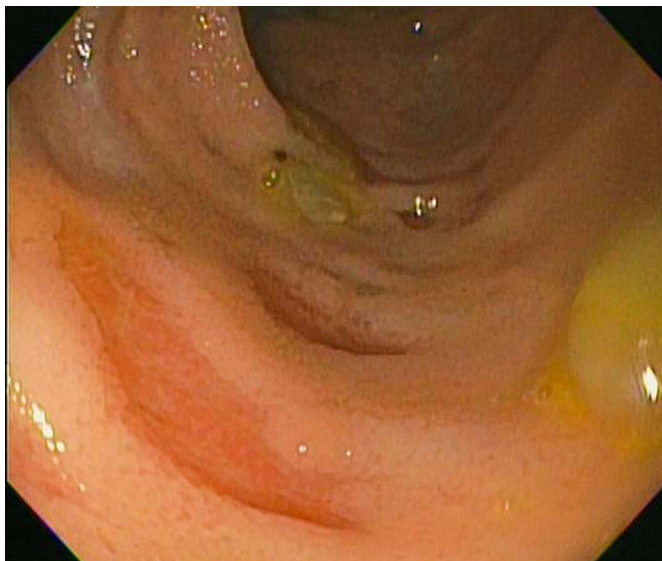
Waldenstrom macroglobulinemia (WM) is a neoplastic disorder of the B-cell lymphoid system characterized by the overproduction of large amounts of monoclonal immunoglobulin M (IgM). The disease usually presents in the sixth or seventh decade of life with symptoms such as fever, fatigue related to anemia, bleeding diathesis, weight loss, and less commonly, neurologic symptoms such as confusion, dementia, stroke, and coma due to hyperviscosity.<sup>1-6</sup> WM is a rare disease, the gastrointestinal (GI) manifestations are exceedingly rare. However, when this was initially described in 1944, 1 of the 3 cases had diarrhea as a predominant feature.<sup>2</sup> We report a rare case of WM with distal small bowel involvement causing diarrhea and weight loss, mimicking inflammatory bowel disease.

## CASE REPORT

A 69-year old man diagnosed with WM 1 year ago presented with chronic watery diarrhea for 6 months with negative infectious workup and unremarkable esophagogastroduodenoscopy and colonoscopy. He received chemotherapy (rituximab and bendamustine) for WM and budesonide for concern of Crohn's disease with which he had subsequent resolution of diarrhea. However, 2 months later, the diarrhea recurred while he was on budesonide and was associated with weight loss. A computed tomography (CT) scan of the abdomen with contrast demonstrated mucosal thickening of the terminal ileum (TI) and rectosigmoid colon. A repeat colonoscopy with TI intubation showed a solitary TI ulcer with normal biopsy on hematoxylin and eosin (H&E) staining. A magnetic resonance enterography showed distal ileal wall thickening. A retrograde small bowel enteroscopy showed multiple, shallow, irregular, nonbleeding ulcers with waxy base approximately 20 cm proximal to the ileocecal valve (Figure 1). H&E staining of the biopsies were unremarkable; however, IgM immunofluorescence staining was strongly positive in the basement membrane and lamina propria of the TI (Figures 2 and 3). The patient received a total of 6 cycles of chemotherapy (rituximab and bendamustine) and discontinuation of budesonide with resolution of diarrhea and weight gain back to his baseline. He had no recurrence of diarrhea at 1-year follow-up.

## DISCUSSION

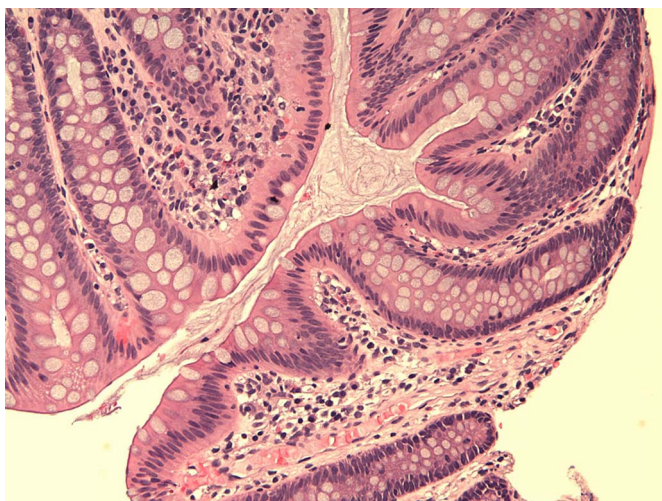
Jan Waldenstrom first described macroglobulinemia in 1944.<sup>2</sup> It is a rare condition caused by lymphoplasmacytic infiltration of the bone marrow and peripheral IgM monoclonal gammopathy. Involvement of the GI tract is rare.<sup>7-9</sup> Of interest, although WM is more



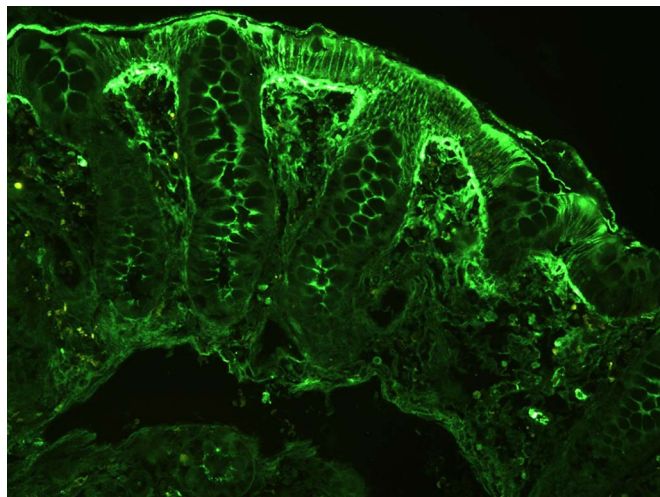
**Figure 1.** Multiple shallow ulcers in the distal ileum.

common in men, the ratio of females to males that develop small bowel disease is 2:1.<sup>10</sup> The prevalence of WM in the United States is 0.20 per 100,000 men and women, with approximately 1,400 new cases diagnosed per year.<sup>11</sup> No causative or predisposing factor has been identified.<sup>12</sup>

In rare instances, IgM paraprotein may be deposited in the lamina propria of the GI tract producing severe malabsorption with diarrhea, steatorrhea, and GI bleeding.<sup>6</sup> There are 2 different patterns of IgM tissue deposition, the cellular diffuse infiltrative pattern and the more common cellular macroglobulin deposition. Intestinal pseudo-obstruction can occur in cases with excessive tissue deposition.<sup>1,3,5,6,13</sup> Veloso et al described a patient consistent with this pattern of intestinal involvement causing intestinal pseudo-obstruction.<sup>6</sup> The patient presented



**Figure 2.** Hematoxylin and eosin (H&E) stain showing focal changes suggestive of erosion.



**Figure 3.** Immunoglobulin M immunofluorescence demonstrating positive staining of the basement membrane and lamina propria.

with severe abdominal pain suggestive of an acute abdomen and underwent an exploratory laparotomy, which ruled out mechanical obstruction. Our patient had diffuse infiltration of the cell membrane of the epithelium and in the lamina propria, seen on IgM immunofluorescence,<sup>11</sup> but it did not lead to bowel obstruction.

It was postulated that IgM is locally sourced from the intestinal plasma cells in the wall of the GI tract and bears no direct correlation with the serum IgM levels, likely due to its pentameric configuration and its restriction to the intravascular compartment.<sup>14-17</sup> Pratz et al validated this theory when they found that patients with a near normal serum IgM levels were presenting with signs and symptoms of intestinal obstruction, whereas the same was not always the case with high serum IgM levels. This is due to the locally produced IgM in the GI tract, overwhelming the lymphatic drainage system, thereby leading to deposition and increasing the risk of intestinal pseudo-obstruction.<sup>14-17</sup>

Patients with WM may not necessarily present with the common symptoms such as weakness, fatigue, weight loss, or the less common signs such as hepatosplenomegaly or lymphadenopathy. As with our patient, they may present with symptomatology exclusive to the small intestine secondary to WM.<sup>6</sup> Our patient did have bone marrow involvement and was diagnosed with WM around the time when his GI symptoms initially began. The colonic and duodenal biopsies were normal. A retrograde small bowel enteroscopy and TI ulcers were identified and biopsied. The TI ulcer biopsies were initially sent for H&E staining and it was reported as focal changes suggestive of erosion. It was only after a high index of suspicion, we obtained IgM immunofluorescence, confirming the diagnosis.

GI bleeding is another unusual presentation reported by Venkateshan et al.<sup>18</sup> Initially, the patient presented with GI

bleeding because of compression of the porta hepatis by the bulky lymph nodes, causing portal hypertension with esophageal varices, hemorrhoids, and splenomegaly. The unusual feature of this case was extensive extracellular deposition of immunoglobulin in the abdominal lymph nodes, spleen, and liver. The diagnosis of WM was made on autopsy.

Imaging could aid in the diagnosis of GI disease by demonstrating an inflammatory or infective or ischemic process affecting the intestines. Radiologic abnormalities due to infiltrative processes from lymphocytic or eosinophilic deposition in the bowel wall could include thickened mucosal folds, diffuse bowel wall thickening, and luminal dilation in cases of partial or complete bowel obstruction.<sup>7</sup> Lymph node involvement and splenomegaly are detected in 20%–40% of patients undergoing CT and magnetic resonance imaging of the abdomen. It is interesting to note that in all cases of WM with intestinal involvement, there was no evidence of the disease in other parts of the GI tract.<sup>4</sup> Our patient had a CT abdomen and a magnetic resonance enterography with findings of distal ileal thickening and hyperemia suggestive of infective or inflammatory process.

As in this case, imaging evidence of distal ileal wall thickening may be an important indicator of a local or a systemic disease. Differential diagnoses for a presentation like this include cancer, various infections such as *Cytomegalovirus* and *Clostridium difficile*, inflammatory bowel disease (Crohn's disease), infiltrative disease process such as amyloidosis, and graft-vs-host disease. In addition, one should consider WM.

This case adds to the many different ways WM can present involving the GI tract and points to the need for considering this diagnosis along with other common causes of chronic diarrhea and TI ulceration. When clinical suspicion is high for WM, we recommend that IgM immunofluorescence should be tested because H&E stain alone is not sufficient for the diagnosis. Our case also demonstrates that the GI symptoms of WM respond well to therapy.

## DISCLOSURES

Author contributions: K. Gurram, R. Khehra, and A. Kulkarni planned the study. V. Kantamaneni wrote the manuscript, and is the article guarantor. G. Koneru reviewed the literature.

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Informed consent was obtained for this case report.

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