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Case Report

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Sequential Occurrence of Eosinophilic Gastrointestinal Disease in a Case of Waldenström's Macroglobulinemia in Remission: An Unusual Report with Review

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ABSTRACT

Waldenström macroglobulinemia (WM) is a rare lymphoproliferative malignancy presenting with para-proteinemia. The symptoms are attributable to both lymphoproliferation and IgM flare. Gastrointestinal manifestations are not uncommon. It is an indolent disease with good response to chemoimmunotherapy but with possible persistence of asymptomatic paraproteinemia. Resurgence of gastrointestinal symptoms in a patient of WM maintaining reasonable response warrant a thorough search for alternate pathology. Herein we describe a rare case of sequential occurrence of WM with Eosinophilic Gastrointestinal Disease posing a diagnostic and therapeutic challenge.

Keywords: Waldenström's macroglobulinemia; Eosinophilic gastrointestinal disease (EGID); Eosinophilia

INTRODUCTION

Waldenström Macroglobulinemia (WM) is a rare lymphoproliferative malignancy classified as lymphoplasmacytic lymphoma (LPL), characterized by the hypersecretion of immunoglobulin M (IgM)[1]. This indolent disorder responds well to therapy, with median survival ranging from 6 to 11 years[2]. Eosinophilic gastrointestinal disease (EGID) is an inflammatory disorder marked by eosinophilic infiltration in gastrointestinal mucosa without a known cause for eosinophilia. Although current literature on the association between WM and EGID is limited, this report discusses a patient with WM who, after achieving and maintaining a good partial response for two years post-therapy, developed refractory EGID. This condition presented both a diagnostic dilemma and a therapeutic challenge.

Case presentation

A 70-year-old female was diagnosed with IgM monoclonal gammopathy of unknown significance (MGUS) in 2004 during an annual health check-up, with a serum IgM level of 1.3 gm/dL. She remained asymptomatic for the next 10 years under consistent and close observation. During this period, she developed acute cholecystitis, underwent cholecystectomy, and subsequently experienced episodic diarrhea, attributed to irritable bowel syndrome. She also had a history of primary hypertension and type II diabetes mellitus, both managed with oral medication. There was a gradual increase in serum IgM during follow-up, but she remained asymptomatic. Moreover, a bone marrow evaluation revealed normocellular marrow with the

presence of lymphoplasmacytoid cells (10%). Immunophenotyping indicated lymphoplasmacytic lymphoma, defined by CD19+, CD20+, CD79a+, PAX5+, sIgM+, CD5–, CD10–, and CD23–markers. The karyotype was normal (46, XX), and there were no signs of hyperviscosity. After 15 years of follow-up, she developed easy fatigability and recurrent viral infections. Clinically the patient exhibited no pallor, bleeding manifestations, lymphadenopathy, or hepatosplenomegaly, and there was no evidence of peripheral neuropathy. Fundoscopy results were normal. Investigations revealed anemia (Hemoglobin of 90 g/L) with normal white blood cell and platelet counts. Liver function, renal function, serum lactate dehydrogenase, and uric acid results were unremarkable. Immunoparesis was present (IgA 0.3 g/dL, IgG 4.46 g/dL, IgM 4.03 g/dL), with a rising paraprotein level (M-band of 3.64 g/dL). Molecular studies identified wild-type MYD88 and a missense mutation in CXCR4 (CXCR4:c.28G>A; p.D10N) .

Imaging did not show lymphadenopathy or hepatosplenomegaly. The patient was then diagnosed with Waldenström's macroglobulinemia, classified as intermediate international prognostic stage (IPS). Considering the presence of symptomatic disease, she was scheduled for chemoimmunotherapy. She underwent six cycles of bendamustine and rituximab chemoimmunotherapy. Plasmapheresis was not performed due to the absence of symptomatic hyperviscosity, and rituximab was avoided in cycle one. After completion of therapy, she achieved a good partial response (80% reduction in M-band) with complete resolution of disease-related symptoms. However, a month after completing chemoimmunotherapy, the patient developed persistent low-grade fever and extreme weakness. She was extensively evaluated for all possible infective, inflammatory, autoimmune, and neoplastic etiology but all the results were unremarkable. Her WM remained in partial response (PR). The fever subsided with empirical treatment but was followed by intractable watery, non-foul-smelling diarrhea (15 – 20 episodes per day), requiring recurrent hospital admissions. She also developed extreme fatigue and significant weight loss. Differential diagnoses considered were WM recurrence, amyloidosis, tuberculosis (considering the immunosuppression and regional prevalence), localized gastrointestinal tumor infiltration, inflammatory bowel disease, celiac disease, etc. Despite these concerns, the paraprotein level continued to indicate PR, and tests for serum calprotectin, anti-endomysial antibody, and tissue transglutaminase were unremarkable.

A CT scan of the abdomen revealed thickening of the ileocecal junction. Additionally, she underwent esophagogastroduodenoscopy and colonoscopy, revealing pangastritis (H. pylori positive) and hypertrophic ileocecal and colonic mucosa. Biopsy findings suggested eosinophilic enteritis (Figures 1 & 2) and colitis (> 20 eosinophils/hpf). Serum antibody tests for autoimmune disease, vasculitis, and celiac disease were negative, and there was no evidence of any other infection, tumor, or amyloidosis.

Serum IgE levels were marginally high (203 IU/mL) but there was no peripheral blood eosinophilia. She was diagnosed with EGID and started on prednisolone (0.5mg/kg/day) followed by oral budesonide (9 mg/day). This led to a marginal improvement in the frequency of diarrhea, however, the frequency increased when prednisolone was tapered after two weeks. Montelukast, ketotifen, sodium cromoglycate, chlordiazepoxide, and clidinium bromide were subsequently administered, but there was no improvement. She remained extremely weak with severe hypoproteinemia, severe dyselectrolytemia, and pancytopenia (Hb 8 g/dL, WBC count 2600/cu mm, and platelet 79,000/cu mm).

She was started on parenteral methylprednisolone (MPS) 1 mg/kg/day, alongside aggressive fluid, electrolyte, and nutritional replacement. After MPS administration, her stool frequency reduced, consistency improved, and she began gaining weight. After two weeks, the MPS dose was tapered to 0.5 mg/kg/day, followed by a gradual 20% reduction every week. When the MPS dose reached 0.2 mg/kg/day, oral budesonide (9 mg/day) was reintroduced, and a week later, MPS was reduced to 0.1 mg/kg/day and maintained at that dose. She continued to improve clinically with normal stool frequency and consistency, became ambulatory, and

further gained weight. Paraprotein tests conducted after 24 months of WM therapy continued to sustain a PR, with an 80% reduction in M-band compared to baseline.

DISCUSSION

The primary risk factor for developing WM is a preexisting diagnosis of IgM-type monoclonal gammopathy of undetermined significance (MGUS), which progresses into WM at a rate of 1.5% per year[3]. Around 1 in 4 of these patients remain asymptomatic, while the remainder develop symptoms within 3 to 10 years. Common presenting symptoms include fatigue, fever, and weight loss. Lymphadenopathy and hepatosplenomegaly are less common, and anemia occurs frequently, attributable to multiple etiology.

IgM forms pentamers that contribute to hyperviscosity symptoms and may function as an autoantibody, causing peripheral neuropathy. Precipitation of IgM may also lead to cryoglobulinemia. Diarrhea is a rare presenting feature, occurring in only 5% of cases[4,5]. Additionally, the patient may experience recurrent infections due to immunoparesis. The two rare presenting features in this case study suggest the progression from IgM MGUS to WM.

MYD88 L265P mutation is found in approximately 67-100% of WM cases. CXCR4 frameshift and nonsense mutations in the C-terminal occur in 30 to 40% of cases, co-occurring with MYD88 L265P, and correlate with inferior survival outcomes. This mutation resembles those documented in autosomal dominant congenital disorder WHIM (Warts, Hypogammaglobulinemia, Infection, and Myelokathexis) syndrome[6]. This patient was MYD88 wild type but exhibited a previously unreported, pathogenic missense mutation in CXCR4. Although CXCR4 mutations typically co-occur with MYD88 L265P, the clinical significance of the CXCR4 mutation in this case remains unknown.

BR (bendamustine and rituximab) chemoimmunotherapy is a well-tolerated and effective treatment option, typically administered for 4 to 6 cycles. However, patients with hyperviscosity symptoms require plasmapheresis prior to chemoimmunotherapy. Rituximab is generally avoided in initial cycles to prevent IgM flare (≥25% increase in IgM from baseline) which can be seen in up to 50% of cases[7,8].

WM is an indolent disease, and a low level of disease burden may persist after chemotherapy. However, as seen in this case, the patient developed post-treatment symptoms resembling those in WM at presentation, despite reasonably good disease control as indicated by paraprotein evaluation. Recurrence of symptoms requires detailed evaluation, especially in a post-chemotherapy setting, to rule out infective etiology such as tuberculosis, or other conditions such as localized disease recurrence, amyloidosis, inflammatory or irritable bowel disease, and celiac disease. Early esophagogastroduodenoscopy and colonoscopy are essential for diagnosis. In this case, while serum biomarkers were non-contributory, gastrointestinal endoscopy established the diagnosis of EGID involving both small and large intestines.

Treatment modalities for EGID include dietary and medical therapy. Pharmacologic options include corticosteroids, mast cell inhibitors, H2 antagonists, leukotriene receptor antagonists, and immunomodulators, with 76% of patients requiring more than one line of therapy. Biological therapies, such as anti-IL5 and anti-IgE, have shown limited efficacy in some cases[9,10].

Managing steroid therapy in these patients is critical. A very gradual taper of systemic steroids is essential to prevent breakthrough symptoms, as seen in this case. Strict management of steroid toxicity is necessary to prevent infective episodes, especially in the immunocompromised state associated with WM. Oral budesonide, used in this patient, was effective in tapering systemic steroids and avoiding the toxicity of long-term systemic steroids. Although there is no established link between WM with EGID, one similar case has been reported in the literature[11].

CONCLUSION

Considering the rarity of both diseases, it is reasonable to propose that persistent gastrointestinal symptoms in a WM patient with well-controlled serum paraprotein warrant a detailed gastrointestinal evaluation. EGID should be

kept in the differential diagnosis, and efforts to obtain tissue samples from different parts of the intestine should be attempted to confirm the diagnosis and establish the extent of involvement. Early diagnosis can prevent significant morbidity and potential mortality.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

1. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: Consensus Panel Recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol. 2003;30(2):110–5.
2. Morel P, Duhamel A, Gobbi P, et al. International prognostic scoring system for Waldenstrom macroglobulinemia. Blood. 2009;113(18):4163–70.
3. McMaster ML, Kristinsson SY, Turesson I, et al. Novel Aspects Pertaining to the Relationship of Waldenström's Macroglobulinemia, IgM Monoclonal Gammopathy of Undetermined Significance, Polyclonal Gammopathy, and Hypoglobulinemia. Clin Lymphoma Myeloma. 2009;9(1):19–22.
4. Waldenström J. Incipient myelomatosis or «essential« hyperglobulinemia with fibrinogenopenia — a new syndrome? Acta Med Scand. 1944;117(3-4):216–47.
5. Dimopoulos MA, Panayiotidis P, Moulopoulos LA, et al. Waldenström's macroglobulinemia: clinical features, complications, and management. J Clin Oncol. 2000;18(1):214–26.
6. Vinarkar S, Arora N, Chowdhury SS, et al. MYD88 and CXCR4 Mutation Profiling in Lymphoplasmacytic Lymphoma/Waldenstrom's Macroglobulinaemia. Indian J Hematol Blood Transfus. 2019;35(1):57–65.
7. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381(9873):1203–10.
8. Treon SP, Branagan AR, Hunter Z, et al. Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenstrom's macroglobulinemia. Ann Oncol. 2004;15(10):1481–3.
9. Reed C, Woosley JT, Dellon ES. Clinical characteristics, treatment outcomes, and resource utilization in children and adults with eosinophilic gastroenteritis. Dig Liver Dis. 2015;47(3):197-201
10. Gonsalves N. Eosinophilic Gastrointestinal Disorders. Clin Rev Allergy Immunol. 2019;57(2):272-285.
11. Ibis M, Beyazit Y, Sayilir A, et al. Successful treatment of eosinophilic colitis by montelukast sodium plus budesonide in a patient with Waldenstrom macroglobulinemia. J Crohns Colitis. 2011;5(3):277-8.