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CASE REPORT

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Lenalidomide-induced autoimmune enteropathy complicating treatment of multiple myeloma with concurrent systemic mastocytosis

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Abstract

Lenalidomide is an IMiD drug which has been associated with a variety of potential immune related complications. We describe the case of a patient with newly diagnosed multiple myeloma along with a history of systemic mastocytosis who developed evidence of an autoimmune enteropathy shortly after initiating lenalidomide based therapy.

KEYWORDS

chemotherapy, oncology, pharmacology, plasma cell neoplasms

1 | INTRODUCTION

Mastocytosis is a rare immune disease broadly categorized into cutaneous mastocytosis (CM) and systemic mastocytosis (SM).[1] The second most common subtype of SM is systemic mastocytosis with an associated hematologic neoplasm (SM-AHN).[2] The coexistence of SM and multiple myeloma (MM) is especially uncommon, representing around 3–4% of cases of SM-AHN.[3] Treatment of SM-AHN predominantly targets the concurrent hematologic malignancy.[3] In patients with newly diagnosed MM, immunomodulatory drugs (IMiDs), such as lenalidomide, are frequently used as part of an induction regimen.[4] Lenalidomide is known to stimulate helper CD4 as well as cytotoxic CD8 T-cell immunity, potentially as part of its mechanism of action against MM.[5,6] This stimulation of T-cell function may at times become pathologic in circumstances when enhanced T-cell activation may lead to increased harm, as seen in reports of increased rates of graft-versus-host disease during lenalidomide maintenance after allogeneic stem cell transplant.[7,8] There has also been increasing attention looking at the association of lenalidomide and the development of autoimmunity through disruption of immune homeostasis.[9] Lenalidomide has been shown to lead to an increased risk of development of autoimmune diseases, even when compared to other IMiDs such as thalidomide.[10] Here, we describe an unusual case of a patient with SM with associated MM who developed autoimmune enteropathy (AIE) suspected to be induced by lenalidomide therapy. This case highlights the need to keep a patient's history of immune disease into consideration during selection of treatment for MM.

2 | CASE REPORT

In July 2018, a 56-year-old man with a history of urticaria pigmentosa (diagnosed in 1992) presented after he was found to have an elevated serum total protein level of 8.9 g/dL during routine laboratory work. Further workup revealed immunoglobulin (Ig)G level of 496 mg/dL, IgA level of 3201 mg/dL, IgM level of <25 mg/dL, β-2 microglobulin level of 3.9 mg/L, lactate dehydrogenase of

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130 U/L, and a creatinine of 0.82 mg/dL. Serum protein electrophoresis showed a monoclonal band within the beta fraction, identified as IgA-κ by serum immunofixation. A bone marrow biopsy revealed 80% average cellularity with approximately 50% CD138$^+$, kappa-restricted plasma cell infiltration by immunohistochemical staining and several clusters of atypical, spindled mast cells that expressed CD117$^+$, tryptase, and aberrant CD25$^+$. Fluorescence in situ hybridization (FISH) analysis was negative for IgH rearrangements, deletions of chromosome 13q14, and deletion of chromosome 17p13.1. Karyotyping revealed a normal male chromosome complement. Skeletal survey was without lytic bone lesions. He was diagnosed with systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) of smoldering myeloma. He was then monitored expectantly for 3 months, where a rise in IgA was noted from 3201 mg/dL to 3951 mg/dL. A repeat bone marrow biopsy was performed showing normocellular marrow (approximately 50–60% average cellularity), a rise in plasmacytosis to 60–65% of nucleated marrow cells as well as 10% atypical mast cell involvement **(**See Figure 1**)**. Repeat FISH revealed hyperdiploidy of chromosome 11 and low-level gain of 1q21. On the basis of fulfilling this biomarker of disease as per the International Myeloma Working Group (IMWG), he was diagnosed with SM-AHN IgA-κ MM, Revised International Staging System (R-ISS) stage II as the associated hematologic neoplasm.

In January 2019, the patient started clarithromycin, lenalidomide, and dexamethasone (BiRd) induction therapy as previously published.[11] IgA decreased from 3951 mg/dL on January 8, 2019, to 2280 mg/dL on February 6, 2019. At the end of February 2019 during cycle 2 of BiRd therapy, he developed severe non-bloody diarrhea (>10 stools per day) associated with diffuse abdominal cramps necessitating hospitalization for intravenous hydration and eventually total parenteral nutrition due to oral food intolerance. Initial trial of therapy with a bile acid sequestrant did not lead to symptom improvement. Computed tomography (CT) imaging of the abdomen and pelvis without contrast demonstrated multifocal small bowel wall thickening with associated adjacent fat stranding. Extensive infectious workup was negative. He underwent upper and lower endoscopy with multiple biopsies during his hospitalization which tested negative for amyloidosis and revealed a variable degree of epithelial cell atrophy, marked paucity of goblet cells and Paneth cells without associated inflammatory cell infiltrates with a pattern of injury described as reminiscent of that seen

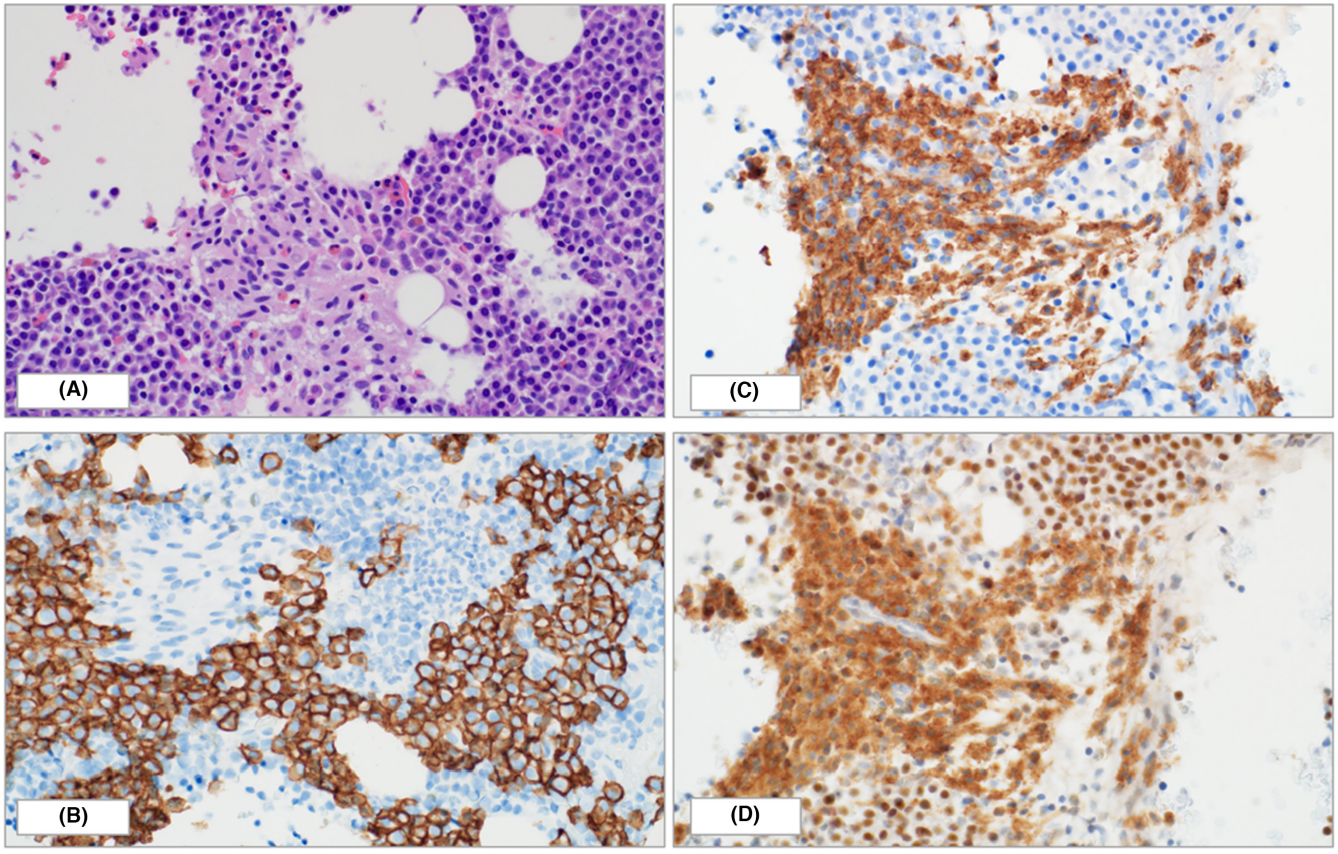

FIGURE 1 Bone marrow biopsy from December 21, 2018. (A): Hematoxylin & eosin (H&E) stain ×20 demonstrating 50–60% average bone marrow cellularity; (B): CD138 stain demonstrating 60–65% plasma cell infiltration; (C): Cluster of CD117$^+$ mast cells; (D): CD25 stain for mast cells and plasma cells

in graft-versus-host disease, autoimmune enteropathy, or immunotherapy type drug-related injury (See Figure 2). Mast cells were found in increased density within the lamina propria, but no confluent infiltrates suspicious for systemic mastocytosis directly involving the GI tract were present. Bile acid malabsorption is a common cause of diarrhea associated with lenalidomide. However, the patient's severe and sudden onset of diarrhea, lack of response to bile acid sequestrant, imaging findings suggestive of enteritis, and biopsy findings all supported the diagnosis of an inflammatory/immune-mediated enteropathy. He was diagnosed with immune-mediated gastroenteropathy likely related to lenalidomide and started on 1 mg/kg methylprednisolone with improvement in diarrhea. He was discharged from the hospital approximately 1 week after admission on an oral prednisone taper.

After completing the steroid taper, in May 2019, he began second-line therapy for his MM with ixazomib and dexamethasone. Although kappa-free light chains began to decrease from 17.1 mg/dL on June 4, 2019, to 5.2 mg/dL on June 25, 2019, IgA levels began to increase from 1098 mg/dL to 1232 mg/dL during the same time period. Daratumumab was added to the regimen in August 2019 to augment therapy, and he reached a very good partial response (VGPR). As of March 2021, he remained on daratumumab, ixazomib, and dexamethasone with a stable VGPR and no evidence of recurrence of his autoimmune gastroenteropathy.

3 | DISCUSSION

Mastocytosis is a rare disorder of the immune system defined by excessive proliferation of mast cells in one or more organs.[1] Broadly, mastocytosis is classified into cutaneous mastocytosis (CM) when limited to the skin and systemic mastocytosis (SM) when involving extracutaneous organs, most often the bone marrow.[2] Urticaria pigmentosa (UP) is a type of cutaneous mastocytosis most frequently occurring in childhood.[12] In children, the prognosis for UP tends to be very good with most cases resolving by puberty; whereas adult-onset CM tends to persist lifelong and is highly indicative of underlying systemic mastocytosis.[12–14] There are multiple subtypes of SM with the second most common being systemic mastocytosis with an associated hematologic neoplasm (SM-AHN).[15] Patients with SM-AHN must satisfy the World Health Organization (WHO) criteria for both SM and the associated hematological neoplasm. In most cases, the associated hematologic malignancy involves a myeloid cell line malignancy, and associated plasma cell disorders, as seen in our patient, are less common.[3,16] In a series of 138 patients diagnosed with SM-AHN, Pardanani et al. found 5 patients (3.6%) with coexistent SM and MM[3]. It is unknown how long our patient's UP may have overlapped with the existence of an asymptomatic plasma cell disorder precursor, such as monoclonal gammopathy of undetermined significance (MGUS) or smoldering myeloma, during the interval prior to his diagnosis of MM.

The treatment of SM-AHN is primarily directed at the AHN.[3] In this case, our patient with concurrent MM was treated with upfront clarithromycin, lenalidomide, and dexamethasone (BiRd). In patients with newly diagnosed MM, BiRd therapy was shown to have an overall response rate of 90%.[17] In a case-matched study, compared with lenalidomide and dexamethasone alone (Rd), patients with untreated MM who received BiRd therapy had improved complete response (45.8% vs. 13.9%, $p < 0.001$) and progression-free survival (PFS) (median 48.3 vs 27.5 months, $p = 0.044$).[18] The increased myeloma treatment response associated with the addition of clarithromycin to lenalidomide and dexamethasone may be in part related to increased glucocorticoid exposure through inhibition of dexamethasone metabolism via CYP3A4.[19] This hypothesis is supported by the results of a study of BiRd vs Rd as initial therapy in upfront non-transplant eligible MM treatment.[20] In this study, BiRd did induce deeper responses than Rd, however, was also associated with more treatment toxicity likely due to greater steroid exposure.[20]

Immunomodulatory drugs (IMiDs), such as lenalidomide are widely used in the treatment of both newly diagnosed MM and relapsed/refractory MM.[4] Lenalidomide is a thalidomide analog that acts through the binding of cereblon by inducing the selective ubiquitination of cellular proteins leading to proteasomal degradation and ultimately the death of MM cells.[4] Furthermore, lenalidomide also has been shown to alter cytokine production which is part of the immunomodulatory effect.[21] Lenalidomide down-regulates pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 and leads to increased secretion of IL-2 and IFN-γ which stimulates both T cell and natural killer cell activity.[21]

The major adverse effects of lenalidomide therapy includes myelosuppression, increased risk of thromboembolic events when combined with corticosteroids, and a risk of secondary primary malignancies.[22,23] However, over several years, there has been an accumulation of evidence regarding the relationship between lenalidomide and a variety of autoimmune diseases.[9] In 2009, Dasanu and Alexandrescu published a case report of a patient with MM treated with lenalidomide who developed severe aplastic anemia that spontaneously recovered after lenalidomide discontinuation.[10,24] Montefusco et al. conducted a study evaluating the occurrence of autoimmune diseases among patients with MM treated with IMiDs.[9,10] The absolute risk of autoimmune diseases with lenalidomide

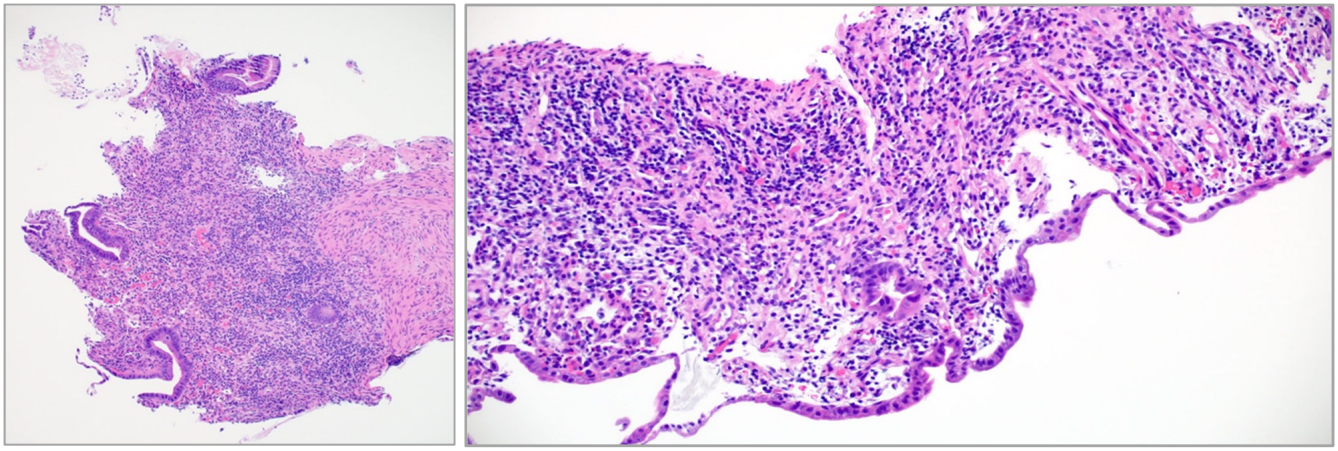

FIGURE 2 Distal duodenum biopsy with hematoxylin & eosin (H&E) stain ×10 (left panel) and ×100 (right panel) demonstrating a variable degree of epithelial cell atrophy and loss; there is no associated marked inflammatory cell infiltrate. There is a marked paucity of goblet cells and Paneth cells. There is no intraepithelial lymphocytosis or prominence of epithelial cell apoptotic bodies. The pattern of injury is reminiscent of that seen in graft-versus-host disease, autoimmune enteropathy, and some medication related injury (e.g., immunotherapy). There is no monotypic plasma cell population (confirmed with kappa and lambda in situ hybridization tests). Mast cells are increased in density within lamina propria but no confluent infiltrate of mast cells suspicious for systemic mastocytosis are present (confirmed with CD117 immunohistochemical stains on both biopsy sites). No pathogenic microorganisms are identified

was 4.3% compared with a 0.4% absolute risk with thalidomide.[10] This retrospective study also found the most commonly manifested autoimmune diseases included not only autoimmune cytopenias, but also optic neuritis, cutaneous vasculitis, thyroiditis, and polymyositis.[9,10] Most autoimmune diseases developed within the first 6 months of therapy with lenalidomide.[9]

In our case, we report a 56-year-old man who developed autoimmune enteropathy approximately 1 month after starting BiRd therapy for his newly diagnosed MM. To our knowledge, this is the first reported case of suspected lenalidomide-induced autoimmune enteropathy. Autoimmune enteropathy (AIE) is a rare disease most commonly affecting children within the first 6 months of life.[25] Symptoms typically include refractory diarrhea, often requiring treatment with total parenteral nutrition and immunosuppression. Histology of the small bowel in AIE demonstrates atrophy or blunting of the villous structures, infiltration of the lamina propria with lymphocytes and macrophages, and a lack of surface lymphocytes.[25,26] Furthermore, Paneth and goblet cells may be absent.[25] Our patient had gradual complete resolution of his diarrhea with discontinuation of lenalidomide therapy and treatment with corticosteroids. Notably, he developed AIE despite his exposure to dexamethasone as part of his regimen with a potentially enhanced glucocorticoid exposure due to co-administration with clarithromycin. He was started on second-line treatment with ixazomib, a proteasome inhibitor, and dexamethasone without recurrence of his autoimmune enteropathy.

In patients with a history of autoimmunity, there is a known increased risk of malignancy, including MM and MGUS compared with the general population.[27] Conversely, a 2016 literature review consisting of case reports and case series suggests a higher prevalence of autoimmune conditions in those with MM[9]. Although the mechanism of the association between MM and autoimmunity is not fully understood, there are multiple hypotheses for this relationship. There is an increased risk of development of both MM and autoimmunity in patients with a first-degree relative with those conditions, respectively, suggesting genetic factors may play a role in the development of autoimmune conditions and MM. Furthermore, dysregulation and chronic activation of the immune system may be the underlying pathogenesis of both myeloma and autoimmune conditions.[28] Lenalidomide's strong immunostimulatory effects, especially on CD4 and CD8 T cells, may lead to an imbalance and relative decrease of T regulatory cells that prevent autoimmunity.[9,21] Compared with thalidomide, lenalidomide has exhibited greater potency and an enhanced ability to promote T-cell activation.[29] This may explain why the association between lenalidomide and autoimmune diseases has not been seen with thalidomide.[21]

4 | CONCLUSION

This case illustrates lenalidomide-induced autoimmune enteropathy likely due to excess T-cell stimulation in a patient with MM and underlying immune disease. To our knowledge, this is the first case of autoimmune enteropathy that developed as a result of lenalidomide therapy. Autoimmunity is an increasingly recognized

adverse effect of lenalidomide with diverse manifestations. Patients treated with lenalidomide, especially those with concurrent immune disorders, should be closely monitored for the development of immune disease flare or other complications. After the development of autoimmune-related complications of this therapy, lenalidomide should be discontinued and caution should be exercised before restarting lenalidomide or another IMiD. Alternative classes of anti-myeloma therapy may be preferred in patients at highest risk of autoimmunity. Further research analyzing the underlying mechanisms linking lenalidomide, multiple myeloma, and autoimmune diseases could continue to help identify patients at increased risk of development of autoimmune complications. This further emphasizes the importance of personalized medicine in the treatment of multiple myeloma.

AUTHOR CONTRIBUTIONS

Contribution: SL collected and interpreted data; all authors wrote and provided final approval for the manuscript.

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CONFLICTS OF INTEREST

TMM: consultancy: Bristol Myers Squibb Inc, Adaptive Inc, Karyopharm Inc., Takeda Inc., Amgen Inc. PF: honoraria for speakers bureau activities: Bristol Myers Squibb Inc. The remaining authors have stated that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

Ethical approval was not mandatory for publication of case reports as per the institutional policy.

CONSENT

Published with written consent of the patient.

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REFERENCES

1. Abid A, Malone MA, Curci K. Mastocytosis. *Primary Care*. 2016;43(3):505-518. doi:10.1016/j.pop.2016.04.007
2. Ibrahim FA, Abdulla MAJ, Soliman D, et al. A rare case of systemic Mastocytosis with associated hematologic neoplasm (SM-AHN) involving chronic myeloid leukemia: A case report and literature review. *Am J Case Rep*. 2020;21:e923354-1-e923354-9. doi:10.12659/ajcr.923354
3. Pardanani A. Systemic mastocytosis in adults: 2019 update on diagnosis, risk stratification and management. *Am J Hematol*. 2019;94:363-377. doi:10.1002/ajh.25371
4. Fink EC, Ebert BL. The novel mechanism of lenalidomide activity. *Blood*. 2015;126(21):2366-2369. doi:10.1182/blood-2015-07-567958
5. Krämer I, Engelhardt M, Fichtner S, et al. Lenalidomide enhances myeloma-specific T-cell responses in vivo and in vitro. *Onco Targets Ther*. 2016;5(5):e1139662. doi:10.1080/2162402X.2016.1139662
6. D'Souza C, Prince HM, Neeson PJ. Understanding the role of T-cells in the Antimyeloma effect of immunomodulatory drugs. *Front Immunol*. 2021;12:632399. doi:10.3389/fimmu.2021.632399
7. Alsina M, Becker PS, Zhong X, et al. Lenalidomide maintenance for high-risk multiple myeloma after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2014;20(8):1183-1189. doi:10.1016/j.bbmt.2014.04.014
8. Kneppers E, van der Holt B, Kersten MJ, et al. Lenalidomide maintenance after nonmyeloablative allogeneic stem cell transplantation in multiple myeloma is not feasible: results of the HOVON 76 trial. *Blood*. 2011;118:2413-2419.
9. Shimanovsky A, Alvarez AJ, Murali S, Dasanu CA. Autoimmune manifestations in patients with multiple myeloma and monoclonal gammopathy of undetermined significance. *BBA Clinical*. 2016;6:12-18. doi:10.1016/j.bbacli.2016.05.004
10. Montefusco V, Galli M, Spina F, et al. Autoimmune diseases during treatment with immunomodulatory drugs in multiple myeloma: selective occurrence after lenalidomide. *Leuk Lymphoma*. 2014;55(9):2032-2037. doi:10.3109/10428194.2014.914203
11. Niesvizky R, Jayabalan DS, Christos PJ, et al. BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naive symptomatic multiple myeloma. *Blood*. 2008;111(3):1101-1109. doi:10.1182/blood-2007-05-090258
12. Castells M, Metcalfe DD, Escribano L. Diagnosis and treatment of cutaneous Mastocytosis in children. *Am J Clin Dermatol*. 2011;12(4):259-270. doi:10.2165/11588890-000000000-00000
13. Oakley A. Maculopapular cutaneous mastocytosis | DermNet NZ. 1997. https://www.dermnetnz.org/topics/maculopapular-cutaneous-mastocytosis/. Accessed March 11, 2021.
14. Berezowska S, Flaig MJ, Ruëff F, et al. Adult-onset mastocytosis in the skin is highly suggestive of systemic mastocytosis. *Mod Pathol*. 2013;27(1):19-29. doi:10.1038/modpathol.2013.117
15. Coltoff A, Mascarenhas J. Relevant updates in systemic mastocytosis. *Leuk Res*. 2019;81:10-18. doi:10.1016/j.leukres.2019.04.001
16. Ghanem S, Garcia G, Ying L, Hurford M, Odaimi M. Systemic Mastocytosis with smoldering multiple myeloma: report of a case. *Case Rep Oncol Med*. 2016;2016:1-6. doi:10.1155/2016/3161768
17. Rossi A, Mark T, Jayabalan D, et al. BiRd (clarithromycin, lenalidomide, dexamethasone): an update on long-term lenalidomide therapy in previously untreated patients with

multiple myeloma. *Blood*. 2013;121(11):1982-1985. doi:10.1182/blood-2012-08-448563

18. Gay F, Rajkumar SV, Coleman M, et al. Clarithromycin (Biaxin)-lenalidomide-low-dose dexamethasone (BiRd) versus lenalidomide-low-dose dexamethasone (Rd) for newly diagnosed myeloma. *Am J Hematol*. 2010;85(9):664-669. doi:10.1002/ajh.21777
19. Fost D, Leung D, Martin R, et al. Inhibition of methylprednisolone elimination in the presence of clarithromycin therapy. *J Allergy Clin Immunol*. 1999;103(6):1031-1035.
20. Puig N, Hernández MT, Dachs LR, et al. Randomized trial of Lenalidomide and dexamethasone versus Clarythromycin, Lenalidomide and dexamethasone as first line treatment in patients with multiple myeloma not candidates for autologous stem cell transplantation: results of the GEM-Claridex clinical trial. *Blood*. 2019;134(Suppl_1):694. doi:10.1182/blood-2019-123997
21. Kotla V, Goel S, Nischal S, et al. Mechanism of action of lenalidomide in hematological malignancies. *J Hematol Oncol*. 2009;2(1):36. doi:10.1186/1756-8722-2-36
22. Kotchetkov R, Masih-Khan E, Chu C-M, et al. Secondary primary malignancies during the lenalidomide-dexamethasone regimen in relapsed/refractory multiple myeloma patients. *Cancer Med*. 2016;6(1):3-11. doi:10.1002/cam4.799
23. Palumbo A, Miguel JS, Sonneveld P, et al. Lenalidomide: a new therapy for multiple myeloma. *Cancer Treat Rev*. 2008;34(3):283-291. doi:10.1016/j.ctrv.2007.12.005
24. Dasanu CA, Alexandrescu DT. A case of severe aplastic anemia secondary to treatment with lenalidomide for multiple myeloma. *Eur J Haematol*. 2009;82(3):231-234. doi:10.1111/j.1600-0609.2008.01176.x
25. Gentile NM, Murray JA, Pardi DS. Autoimmune enteropathy: a review and update of clinical management. *Curr Gastroenterol Rep*. 2012;14(5):380-385. doi:10.1007/s11894-012-0276-2
26. Akram S, Murray JA, Pardi DS, et al. Adult autoimmune enteropathy: mayo clinic Rochester experience. *Clin Gastroenterol Hepatol*. 2007;5(11):1245. doi:10.1016/j.cgh.2007.08.027
27. Lindqvist EK, Landgren O, Lund SH, et al. History of autoimmune disease is associated with impaired survival in multiple myeloma and monoclonal gammopathy of undetermined significance: a population-based study. *Ann Hematol*. 2017;96(2):261-269. doi:10.1007/s00277-016-2859-8
28. Reske T, Fulciniti M, Munshi NC. Mechanism of action of immunomodulatory agents in multiple myeloma. *Med Oncol*. 2010;27(S1):7-13. doi:10.1007/s12032-010-9527-y
29. Chanan-Khan AA, Cheson BD. Lenalidomide for the treatment of B-cell malignancies. *J Clin Oncol*. 2008;26(9):1544-1552. doi:10.1200/jco.2007.14.5367

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