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Case Report

Autoimmune Hemolytic Anemia: A Rare Presentation of Mantle Cell Lymphoma

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ABSTRACT

Autoimmune hemolytic anemia (AIHA) is a well-recognized phenomenon of non-Hodgkin lymphoma, albeit with only few cases described with mantle cell lymphoma (MCL). The characteristics of such cases can improve understanding and management of AIHA in this type of lymphoma. To that end, we describe herein two cases of patients with MCL who presented with AIHA, with comparison to nine previously described cases in literature.

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is caused by autoantibodies that react with self-red blood cells (RBCs) resulting in destruction of RBCs. Warm AIHA, related to IgG autoantibodies that are active at 37 °C or body temperature, is the most common type of AIHA. Cold-induced hemolysis is comprised of cold agglutinin disease (CAD) and paroxysmal cold hemoglobinuria (PCH). CAD is a form of AIHA in which cold agglutinins cause clinical symptoms related to RBC agglutination in cooler parts of the body and hemolytic anemia. Cold agglutinins are IgM autoantibodies against RBC antigens with an optimum temperature of 3 to 4 °C. With warm AIHA and CAD, the Coombs test is often employed to identify autoantibodies and complement. The IgG autoantibody directed at P antigen on erythrocytes is associated with PCH and can be identified using indirect anti-IgG Donath–Landsteiner test.

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Warm AIHA constitutes approximately 70 to 80% of AIHA, with the remainder due to cold-induced hemolysis.[1] Associated diseases with AIHA vary between immune and lymphoproliferative disorders, with non-Hodgkin lymphoma among them. Approximately 2-3% of warm AIHA and 9% of CAD have been associated with non-Hodgkin lymphoma (NHL).[2-4] As such, only few studies have reported AIHA/NHL subtypes and clinical characteristics.

Representing a lesser-identified subtype of AIHA/NHL, mantle cell lymphoma (MCL) with AIHA has only been reported in nine patients at present time. Two of these patients are found within a retrospective analysis of 20 AIHA/NHL patients, which also identified a predominance of bone marrow involvement in these patients. Although number of cases are yet limited, important clinically implications can be initiated from comparison of the AIHA/NHL subtypes. Thus, two cases of mantle cell lymphoma and AIHA will be compared to already reported cases of MCL presenting with AIHA to reveal unique associations and to aid in the management of these patients.

CASE DESCRIPTION

Case 1: A 73-year-old female who was referred to the hematology clinic for symptomatic anemia. She developed progressive fatigue over the course of two months. Laboratory studies were significant for white blood cell count 3.8 x 10^3/L (normal 4.5 to 11.0 × 109/L), hemoglobin 5.9 g/dL (normal 12-16 g/dL), LDH 342 U/L (normal 140-280 U/L), total bilirubin 5.0 mg/dL (normal <1.3 mg/dL), undetectable haptoglobin, and absolute reticulocyte count 16 x 10^3/L (normal 5-10 x 10^3/L). Antibody screen was positive for IgG warm antibody and direct Coombs test positive for anti-C3.

Bone marrow biopsy was obtained for diagnosis and demonstrated involvement by B-cell lymphoma with immunohistochemistry positive for CD5 and cyclin D1 meeting criteria for mantle cell lymphoma. Pro-

liferative index with Ki-67 was low. CD34-positive blasts were not increased. Flow cytometry was positive for CD5, FMC7, CD19, CD20, and negative for CD200 and CD23. Gene expression was positive for SOX11. PET-CT imaging revealed diffuse mildly FDG avid lymphadenopathy above and below the diaphragm with splenic involvement. Hemoglobin improved to 8.5 g/dL after a two-week prednisone taper. With the diagnosis of mantle cell lymphoma, patient was started on chemoimmunotherapy with bendamustine and rituximab. Patient had resolution of hemolytic anemia and has been transfusion-independent after two cycles of bendamustine-rituximab induction therapy. Patient has completed five cycles and will have repeat PET-CT imaging after the sixth cycle.

Case 2: A 56-year-old male who presented with progressive fatigue. He was found to have pancytopenia with white blood cell count 1.4 x 103/L and 1% peripheral blasts, hemoglobin 6.4 g/dL, and platelets 55,000/L (normal 150-450,000). Hemolysis labs were notable for LDH 520 U/L, total bilirubin 2 mg/dL, undetectable haptoglobin, and absolute reticulocyte count 11 x 103/L. Antibody screen was positive with direct Coombs test was positive for C3-positive, IgG antibody-negative. Cold agglutinins and Donath Landsteiner antibody tests were not performed at diagnosis. Urinalysis did not reveal blood on dipstick.

Bone marrow biopsy was performed for diagnosis and demonstrated a hypercellular bone marrow of 95% involved by CD5-positive B-cell lymphoma, most consistent with mantle cell lymphoma. Immunohistochemistry was positive for Cyclin-D1 and t(11;14) was detected on FISH. The Ki-67 proliferation index was moderate but could not be reliably interpreted because of background hematopoiesis. CD34-positive blasts were not increased. Flow cytometry was positive for CD5, FMC7, CD19, CD20, and CD23, and negative for CD200. Gene expression did express SOX11. Staging CT scan of chest, abdomen, and pelvis demonstrated mild mediastinal lymphadenopathy, numerous mildly enlarged mesenteric and retroperitoneal abdominal lymph nodes, and marked splenomegaly measuring 24 x 14 x 20 cm, compatible with hematologic malignancy. The patient was initiated on combined R-CHOP/R-DHAP induction with the plan for consolidation with high dose therapy and autologous stem cell transplant. After 1 cycle of R-CHOP, his Coombs test was negative. At that time, cold agglutinins and Donath Landsteiner antibody tests were performed and were both negative. He will have a repeat CT imaging after 3 cycles for response assessment.

DISCUSSION

AIHA is an extremely rare and life-threatening presentation of MCL with few cases described in the literature on our review at the present time. The two cases of AIHA secondary to MCL described herein share nodal and bone marrow involvement presentations with SOX11-positive gene expression. Also, findings of mild FDG-avid lymphadenopathy and low proliferative index on bone marrow biopsy suggest more indolent MCL in these cases. These are important distinctions as comparisons are drawn against previously reported cases to better understand when AIHA can present with MCL. The review of these characteristics within the cases are summarized in Table 1.

In looking at the biologic features of the underlying lymphoma, SOX11 transcription factor overexpression is more common to MCL than other B-cell lymphomas. In transgenic mice models, SOX11 has been shown to act as an oncogene for B-cells to develop an MCL phenotype.[6] SOX11 status has not independently shown to be of prognostic significance, however some clinical and histologic features appear to be more common depending on SOX11-positive or SOX11-negative MCL. SOX11-negative MCL patients have been more commonly noted to have the leukemic non-nodal disease phenotype than when SOX11- positive: 21% compared to 4% in one study.[7] In our review, SOX11-positive gene expression is described in four of the six cases that had gene expression profiling (*Table 1*). Of the cases with available nodal status, six of the nine cases had nodal disease and three had leukemic phase only. Overall, most of the reported cases of AIHA secondary to MCL had SOX11-positive gene expression and nodal disease.

The five cases of AIHA secondary to MCL described by Doni et al suggest predominance for indolent MCL or the indolent leukemic non-nodal clinical subtype, as four of their five cases presented with leukemic phase and three were without nodal involvement.[8] This represents an important distinction of the MCL with associated AIHA, as only a small subset of MCL patients tend to have an indolent course. Although our two patients did not have leukemic disease, the mildly FDG avid lymphadenopathy and low proliferative index on bone marrow biopsy suggest an indolent course. Therefore, AIHA may represent a complication of more clinically indolent MCL, however there is a need for more well-described cases to better assert this hypothesis.

The second patient described here represents an even lesser seen presentation of mantle cell lymphoma with AIHA, with findings suggestive of CAD. He

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Table 1. Review and comparisons of various characteristics between cases of AIHA secondary to MCL.

Case	Age/Sex	AIHA	Nodal/Bone marrow/Spleen involvement	Gene expression	Treatment	Outcome since diagnosis
1	73/F	W, C3	Yes/Yes/Yes	SOX11+	Steroids, BR	Alive 10 months later
2	56/M	C, C3	Yes/Yes/No	SOX11+	Steroids, R-CHOP/R-DHAP + ASCT	Alive 4 months later
Eve et al	66/F	W, IgG&C3	Yes/Yes/Yes	NA	Steroids, MCP	Alive 13 months later
Zhou et al	61/M	C, C3	NA/Yes/NA	NA	Steroids, EPOCH	Alive 38.6 months later
	39/M	W, IgG&C3	NA/Yes/NA	NA	Steroids, R-EPOCH	Alive 1.5 months later
Doni et al	73/M	W, IgG	No/Yes/No	IGHV mutated	Steroids, R-CVP, BR	Died 3 months later with uncontrolled hemolysis
	62/M	W, IgG	No/Yes/Yes	NA	Steroids, R-chemo + ASCT	Alive 6 months later
	73/M	W, IgG	No/Yes/No	SOX11-	Steroids, R-BAC	Died of disease progression 4 months later
	75/M	W, IgG	Yes/Yes/Yes	SOX11+	Steroids, BR	Alive 5 months later
	57/M	W, IgG	Yes/No/No	SOX11+, IGHV unmutated	Steroids, R-chemo + ASCT, R-BAC	Alive 12 months later, but with disease progression
Keramati et al	28/F	C, cold agglutinin titer positive	Yes/NA/No	NA	NA	NA

NA, not available; IgG, immunoglobulin G; SOX11, SRY-box transcription factor 11; IGHV, immunoglobulin heavy chain, R-CHOP, rituximab, cyclophosphamide, doxorubicin, prednisone; DHAP, dexamethasone, cytarabine, cisplatin; ASCT, autologous stem cell transplant; MCP, mitoxantrone, chlorambucil, and prednisolone; EPOCH, etoposide, prednisone vincristine, cyclophosphamide, doxorubicin; BAC, bendamustine, cytarabine

presented with a cold autoantibody that fixed complement (C3 positive, IgG negative), however cold agglutinins nor Donath Landsteiner antibody were checked initially. However, these were negative after one cycle of Bendamustine-rituximab chemoimmunotherapy. Review of admission testing with urinalysis did not reveal urobilinogen, which does not support hemoglobinuria or intravascular hemolysis which is typically seen with PCH. Only two other cases of cold-reactive autoantibody related hemolysis with MCL have been described at the time of this report.[3,9]

In both of our cases, immunochemotherapy directed at MCL was able to achieve rapid remission of the AIHA, while our first case also had notable improvement in anemia after corticosteroids alone. Response to corticosteroids alone has been described in three reported cases of AIHA with MCL, while failure to respond to corticosteroids alone have been described by two reported cases.[3,8,10] In general, treatment of AIHA due to MCL appears to be in keeping with data available for secondary AIHA due to other lymphomas, where in one analysis of 108 patients there was higher rate of complete remission of the AIHA following anti-lymphoma treatment (69%) than with corticosteroids or immunoglobulin (23%).[11] Notably, rituximab alone or in combination with chemotherapy represents an active treatment for secondary AIHA as it carries the dual benefit of targeting the malignant clone and the B cell-mediated immune destruction of erythrocytes. Splenectomy has also achieved high response rates (75%), and while performed mostly in patients with marginal zone lymphoma, may offer another treatment option for refractory cases in of AIHA with MCL as well.[11,12] Four of the nine AIHA secondary to MCL cases described splenomegaly or presumed spleen involvement.

MCL can be a challenging lymphoma to treat with frequent relapses and currently not curable with our treatments. The median overall survival is 3 to 5 years.[7] The prognostic significance of AIHA in this context is still unclear. While most of the patients (8 of 10) were still alive at the time of their case description, longer term prospective reviews are necessary to elucidate the prognostic significance.

CONCLUSION

With only few cases described in the current literature, AIHA with underlying MCL is an uncommon and perhaps underreported entity. There appears to be a prevalence of this complication with indolent MCL, often with the leukemic non-nodal phenotype. However, most cases had SOX11 gene expression which is typically not associated with the leukemic non-nodal phenotype. Due to the uncommon occurrence of AIHA with MCL, more cases and longitudinal follow up of the existing cases will be needed to better understand the prognostic significance of MCL presenting with AIHA.

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