

A Rare Case of Double Acquired Hemophilia in Association With CLL: A Case Report

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Abstract

Chronic lymphocytic leukemia/small cell leukemia makes up the significant bulk of adult hematological malignancies. Autoimmunity is a well-documented complication affecting about 25 % of the CLL/SCL patient population. We report a case of a 77-year-old Caucasian female who presented with increasing shortness of breath and was found to have acute exacerbation of CHF associated with NSTEMI. A pre-op workup for cardiac catheterization revealed a severely abnormal coagulation profile, leukocytosis, predominant lymphocytosis, and the presence of smudge cells. No risk factors for coagulopathy like a history of liver disease or use of Coumadin were noted. Mixing studies showed that inhibiting antibodies for factors VIII and IX in very high concentrations led to acquired hemophilia A and B. Peripheral blood flow cytometry showed two separate, clonally related monoclonal B cell populations. A new diagnosis of CLL was made. Due to persistent coagulopathy, cardiac Cath was post ponded, and an NM cardiac stress test showed evidence of cardiac ischemia. Guideline-directed medical therapy for cardiac ischemia started along with diuretics resulting in improvement of symptoms. The patient was started on high-dose steroids at 1mg/kg, and a dose of Rituximab was given during the hospital stay with an improved coagulation profile. Although autoimmune phenomena are common in CLL /SLL, hemophilia is rarely described, and our report is probably the only documented case of dual acquired hemophilia A and B associated with CLL. **Keywords:** Chronic lymphocytic leukemia (CLL); Small Lymphocytic leukemia (SLL); Acquired hemophilia A; Acquired hemophilia B; Autoimmune hemolytic anemia (AIHA)

Introduction

CLL/SCL is the most common adult hematological malignancy characterized by runaway production of morphologically mature but immunologically dysfunctional Lymphocytes. These dysregulated lymphocytes are non-functional and often produce an excess of monoclonal antibodies without antigen trigger. CLL/SCL is a slowly progressing and undulating disease that affects both Cellular and

humoral immunity. Autoimmunity is a well-documented complication in CLL/SCL that can manifest as hematological and non-hematological complications. Autoimmune hemolytic anemia and thrombocytopenia are often described as hematological complications with sporadic cases of acquired hemophilia due to clotting factor inhibitor formation.

Case Presentation

77-year-old Caucasian female with a past medical history of essential hypertension and Type 2 diabetes mellites presented with intermittent substernal chest pains and worsening shortness of breath for 1-2 weeks; SOB was both exertional and orthopneic and associated with bilateral lower extremity swelling.

The patient had a temperature of 98.8° F, a pulse of 110 bpm, BP of 130/75 mmHg, and oxygen saturation of 94 % on physical examination. Chest auscultation revealed normal heart sounds and bilateral basilar fine crepitations. Gastrointestinal and neurological tests were routine.

Her initial EKG showed atrial fibrillation with RVR and marked ST-segment abnormalities in inferior and anterolateral leads. High sensitivity troponins were elevated but minimally trending at 110,

115, and 116 at baseline, 1 hour, and 3 hours, respectively. CXR was consistent with cardiomegaly and pulmonary vascular congestion. Pt was admitted with a diagnosis of NSTEMI and new-onset atrial fibrillation with RVR, leading to acute CHF.

Lab investigations showed WBC 29, haemoglobin 11.1, MCV 84, RDW 16, platelets 199, segmented neutrophils 21, lymphocyte 78 %, monocyte 1 %, eosinophils 0 %, basophils 0 %, slight anisocytosis, and smudge cells noted, Creatinine and electrolytes within normal limits, INR 2.3, PT 25.5, APTT 170. Due to coagulopathy, she was not started on anticoagulation. Pt was started on Lasix, ASA, and beta-blockers with spontaneous conversion to normal sinus rhythm. The patient's shortness of breath improved significantly with diuresis.

2-D Echocardiogram showed a newly decreased LV EF of 30-35%, dilated LV cavity, and moderate MR. Left heart catheterization was planned to rule out and possibly treat any fixable coronary artery disease after correction of the coagulation profile. The patient was empirically given Vitamin K and two units of FFPs without improving PT/INR. The patient denied any use of warfarin, history of hemophilia or liver disease, LFTs were normal; Hematology service was consulted. Also, the patient denied any fever, cough, nausea, vomiting, diarrhoea, urinary symptoms, or other signs of infection to explain leukocytosis.

Further lab investigations revealed uncorrected APTT with mixing study, Activity levels normal for Factor II, V, and VII. Factor VIII activity required a dilution of 1:80 to correct, and Factor XI required a dilution of 1:160 with only a partial correction revealing the presence of both FVIII and FIX inhibitors in high concentration. Peripheral blood Flow cytometry revealed two separate, clonally related, monoclonal B-cell populations. A larger population (61 % of Total lymphocyte count]) co-expressing CD23, but negative for CD5 with strong expression of CD20, A Smaller population (26 % of

TLC)) co-expressing CD5 and CD23 and dim co-expression of CD20.

The patient was also DAT positive for both anti- IGG and anti-C3 antibodies, warm type. LDH 337, Haptoglobin normal, Retic count 3.4 % with absolute 150 (20-80 K/mm³). Serum IgM 1036 (range: 48 to 271), IgG 812 (range: 694 to 1618), IgA 76 (range: 81 to 463) and markedly elevated beta-2 microglobulin of 10.30 (normal < 2.51).

A new diagnosis of CLL, its presenting complications, and treatment options was discussed with the patient. She was started on prednisone at 1mg/kg and given a dose of Rituximab during the hospital stay. Due to persistent coagulopathy, cardiac catheterization was postponed, and a nuclear medicine cardiac stress test showed Moderate-sized inferolateral wall scar without reversible defect. Pt refused to wear a life vest for primary prevention of life-threatening arrhythmias in the setting of ischemic cardiomyopathy. Early follow-up with cardiology and hematology was set up. The patient was discharged on goal-directed cardiac therapy and oral prednisone (1 mg/kg) with a plan of slow outpatient taper off over the following weeks to months.

Discussion

CLL/SLL is a chronic lymphoproliferative disorder characterized by dysregulated monoclonal B cell proliferation; CLL is the most common leukemia in the western world, comprising 25-30 % of all leukemias in the adult population in the United States. Western countries have a similar incidence as the US, but CLL is rarely seen in

Asian countries like China or Japan. The incidence of CLL is slightly higher in the male population than in females, but it tends to be more aggressive in females than in males. The incidence is higher in Caucasians than African Americans and the least in Asian descent. Some CLL also tends to run in families, called familial CLL. The median age of diagnosis is 64 to 70 years, and 5-year survival is above 80 % for those younger than 65 years old and 68 % for those 65 years old. [1]

Autoimmunity is a well-known complication of CLL, affecting up to 25 % of patients during the disease process. Hematological manifestations of autoimmunity are the most common, including Autoimmune hemolytic anemia (AIHA), followed by immune thrombocytopenic purpura (ITP) and pure red cell aplasia (PRCA). [2]

Non-hematological autoimmune manifestations are not very common, but various autoimmune conditions have been reported in the literature. It is worth mentioning that most of the autoantibodies in the CLL are polyclonal produced from non-malignant B cells. Pathological high-affinity polyclonal IgG antibodies created by non-malignant B cells are responsible for AIHA/ITP in 90 % of cases. Usually, monoclonal antibodies by malignant cells cause cold hemagglutinin hemolytic disease (10 %). Along with B cell, T cell

dysregulations are also seen in CLL. The exact mechanism of T cell dysregulation is still not fully understood, but it appears to be a loss of functional capability, especially of regulatory T-cells resulting in T cells' auto reactivation, contributing to the loss of self-tolerance.

Warm autoimmune hemolytic anemia (AIHA) is due to autoantibodies against Rh proteins. However, the direct antiglobulin test (DAT) is helpful but does not always detect autoantibodies. DAT negative AIHA can be due to low levels or affinity of anti-RBC antibodies. [4]. Furthermore, DAT positivity does not always mean a clinical disease; some studies show that only 1/3 cases of DAT positive have clinically significant AIHA. Steroids are considered first-line therapy for warm AIHA. IVIg is usually reserved with or without steroids for severe disease or slow response to steroid therapy. Cold hemagglutinin hemolytic disease is generally mild to moderate in severity, and observation is needed. In the case of advanced disease, high-dose steroids are used with Rituximab; Rituximab is considered first-line therapy for cold agglutinin hemolytic disease. [5]

Immune thrombocytopenic purpura (ITP) is challenging to diagnose as anti-platelet antibodies are neither sensitive nor specific for the disease. A rapid decline with no other signs of bone marrow failure or hypersplenism suggests the presence of ITP, and it usually responds to steroids and IVIg therapy. ITP needs treatment only in severe thrombocytopenia (platelets < 30 × 10⁹/L) or bleeding. Steroids are the first line; IVIg and Rituximab are used in refractory or resistant diseases. Splenectomy is usually discouraged due to the increased risk of infections but should be considered for disease refractory to medical treatment. [5]

Pure red cell aplasia (PRCA) is characterized by severe normochromic normocytic anemia and absolute reticulocytopenia; a bone marrow biopsy must assess the hemopoietic precursor cells.

Angioedema
Bullous pemphigoid/paraneoplastic pemphigus
Churg-Strauss syndrome
Immune thyroiditis
Nephrotic syndrome (glomerulonephritis)
Polyneuropathy
Sjögren's syndrome
Systemic lupus erythematosus
Raynaud's syndrome
Rheumatoid arthritis
Ulcerative colitis
Vasculitis

Non-hematological autoimmune complication associated with CLL [3,6]

Conclusion

Autoimmune complications of CLL can be wide-spreading and should promptly be identified and treated. To our knowledge, this case report is the only one in the literature with the simultaneous presence of FVIII and FIX inhibitors in association with CLL. CLL-associated inhibiting antibodies should be suspected in CLL patients with deranged coagulation profile, uncorrected with vitamin K or

Viral infections, including CMV, Parvovirus, EBV, etc., must be ruled out before diagnosis.

Following is the list of non-hematological autoimmune diseases described in the literature in association with CLL.

FFPs administration. A prompt diagnosis and treatment result in an improvement of the coagulation profile.

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References

1. Mukkamalla SKR, Taneja A, Malipeddi D, Master SR. Chronic Lymphocytic Leukemia. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing.
2. Hamblin TJ (2006) Autoimmune Complications of Chronic Lymphocytic Leukemia. *Seminars in Oncology*. 33(2): 230-9.
3. Vitale C, Montalbano MC, Salvetti C, Boccellato E, Griggio V, et al. (2020) Autoimmune Complications in Chronic Lymphocytic Leukemia in the Era of Targeted Drugs. *Cancers*. 12(2): 282.
4. Takahashi T (2018) Direct Antiglobulin Test-Negative Autoimmune Hemolytic Anemia. *Acta Haematologica*. 140(1): 18-19.
5. Fattizzo B, Barcellini W (2020) Autoimmune Cytopenias in Chronic Lymphocytic Leukemia: Focus on Molecular Aspects. *Front Oncol*. 9: 1435.
6. Dearden C (2008) Disease-Specific Complications of Chronic Lymphocytic Leukemia. *Hematology, ASH Education Program*. American Society of Hematology.