Case Report: SLL/CLL Associated With Paraneoplastic Hyperimmunoglobulinemia and Vasculitic Skin Lesions

Neil Nagovski, MD; Amanda Brahim, PharmD; Alina Khan, PharmD; and Marco Ruiz, MD

Abstract
There are a limited number of reports describing high immunoglobulin (Ig) E levels in association with B-cell malignancies. We report our experience with a patient with small lymphocytic lymphoma/chronic lymphocytic leukemia who presented with bilateral symmetric lower extremity hyperpigmented lesions and a rise in polyclonal immunoglobulins. The patient was treated with obinutuzumab and we observed a marked clinical improvement as well as decline in polyclonal immunoglobulins (serum IgE, IgD, and IgG levels) as a response.

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Introduction
Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are different manifestations of the same disease and are generally managed in the same way. In SLL, the bulk of disease is in the lymph nodes, bone marrow, and other lymphoid tissues, with few, if any, abnormal lymphocytes found in the blood. In contrast, in CLL, a significant number of the abnormal lymphocytes are also found in the blood. The diagnostic workup in patients with suspected CLL/SLL includes review of complete blood count (CBC) with differential, chemistry panel, imaging studies, and bone marrow biopsy. Quantitative immunoglobulin (Ig) types (IgG, IgA, IgM) are checked in certain circumstances; however, serum IgE level is not routinely measured. Incidental findings of high IgE levels require additional investigation.

The differential diagnosis for elevated serum level of IgE includes inflammatory, infectious, immunologic, idiopathic, hematologic, and drug-reaction etiologies. Very high IgE levels may be found in association with hematologic malignancies, such as non-Hodgkin and Hodgkin lymphomas. There are a limited number of reports describing high IgE levels in association with B-cell malignancies.

Case Presentation
A 64-year-old African American woman, a nonsmoker, with a history of diabetes, transient ischemic attack, hypertension, and hypothyroidism was diagnosed with SLL/CLL in March 2011 upon presenting with bilateral axillary lymphadenopathy on a routine screening mammogram. The largest lymph node was 6 cm × 2 cm in size. Physical examination at the time of initial presentation was notable for diffuse palpable lymphadenopathy, but was otherwise unremarkable. There were no signs of hepatosplenomegaly or skin lesions.

Ultrasound-guided core needle lymph node biopsy demonstrated the presence of a small SLL/CLL. Flow cytometry showed a lambda clonal population of B cells with the following immunophenotype: CD19-positive, CD22-positive, CD20-negative, dim, CD5-negative, CD23-negative, CD43-negative. By immunohistochemistry, the neoplastic lymphoid infiltrates were positive for CD20, CD5, CD23, BCL2, and CD43; they were negative for CD3, CD10, cyclin D1, and BCL6. The diagnosis was confirmed by a bone marrow aspiration, with reported diffuse involvement by CLL cells. Karyotype was normal; fluorescence in situ hybridization (FISH) didn’t detect any specific abnormalities.

CT scan of the neck, chest, abdomen, and pelvis with contrast showed extensive lymphadenopathy in the lower neck, supraclavicular region (largest on the left 2.7 cm × 2.2 cm), bilateral axillary regions (largest on the right 7.4 cm × 3.5 cm; largest on the left 5.1 cm × 3.7 cm), retroperitoneal (iliac/obturator regions, 6.2 cm × 2.3 cm on the right, 6.6 cm × 2.1 cm on the left) pelvic, iliac, and inguinal regions. CBC revealed white blood cell (WBC) count of 24.2 × 1000/μL, hemoglobin 11 g/dL, and normal platelet count. Differential was unremarkable with normal eosinophil count.

Beta-2 microglobulin was elevated to 4.6 mg/L; chemistry panel was notable for mild elevation in blood urea nitrogen (BUN) to 22 mg/dL and creatinine of 1.12 mg/dL; and electrolytes were normal. There was no evidence of hemolysis. HIV and hepatitis B serologies were nonreactive.

The patient received six 4-week cycles of bendamustine (90 mg/m²) and rituximab (375 mg/m²), leading to interval decrease in lymphadenopathy within the chest, abdomen, and pelvis as demonstrated on CT scans performed in October 2011. CBC was normalized.

Fifteen months later, the patient presented with bilateral
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symmetric lower extremity hyperpigmented lesions (Figure 1). CBC demonstrated a rise in WBC to 17.5 × 1000/µL, with predominantly neutrophils up to 17,000/µL; absolute lymphocyte count and differential were otherwise normal (absolute eosinophil count 0.3 × 10³/µL). Hemoglobin was 10.5 g/dL. Chemistry panel revealed elevated BUN to 22 mg/dL, creatinine 1.72 mg/dL, uric acid of 9.3 mg/dL, and no other electrolyte abnormalities. The patient was started on allopurinol. Comprehensive metabolic panel showed elevation in total serum protein to 9.1 g/dL, creatinine 1.09 mg/dL, and anemia. She underwent a workup for monoclonal gammopathy, and no evidence of monoclonal protein was demonstrated on serum immunofixation or urine protein electrophoresis.

Progressive elevations in serum BUN and creatinine were evaluated by kidney biopsy, revealing membranous glomerulonephritis with focal fibrocellular crescent formation, features of diabetic nephropathy, and secondary focal segmental glomerulosclerosis. The findings were most likely representing a secondary membranous nephritis due to the patient’s underlying lymphoproliferative disorder.

The differential diagnosis demonstrated a CBC with moderate anemia, hemoglobin of 9.8 g/dL, differential with mild elevation in absolute lymphocyte count, atypical lymphocytes, and a rouleaux formation; no other abnormalities on differential were noted. Total serum protein rose to 10 g/dL. The patient underwent additional testing with reported serum IgG level of 6999 mg/dL, IgE of 12,022 IU/mL, IgA of 585 mg/dL, and normal serum IgM. Her serum protein electrophoresis pattern was characterized by decreased albumin and increased polyclonal gamma globulins; serum immunofixation showed no monoclonal immunoglobulins (IgG, IgA, IgE, IgD, and IgM); however, both free serum kappa and lambda were markedly elevated, with normal kappa to lambda ratio. Serum viscosity was 2.6 relative to water, and lactate dehydrogenase and haptoglobin remained normal. Peripheral blood flow cytometry revealed low-level light chain–restricted B-cell population and granulocytopenia. Skeletal survey/x-ray indicated no skeletal lesions. Stool test for parasites was nondiagnostic.

Bone marrow biopsy demonstrated a small lambda clonal population of B cells (approximately 1% of nonerythroid cells) with coexpression of CD5 and CD23; 15% to 20% polyclonal plasma cells were present. The FISH panel was negative and karyotype was normal. Skin lesions were present on examination (see Figure 1).

Progressive anemia in the absence of other explanation was attributed to SLL/CLL progression, and the patient was started on obinutuzumab in November 2015. A 100-mg initial dose was administered intravenously on day 1, then 1000-mg doses were infused on days 8 and 15 of the first treatment cycle. Upon initiation of therapy, hemoglobin began improving, serum IgE and IgG levels declined through the course of therapy (Table), and skin lesions have resolved (Figure 2).
Discussion
SLL/CLL is a lymphoproliferative disorder characterized by accumulation of mature monoclonal lymphocytes. This leads to generalized lymphadenopathy, peripheral lymphocytosis, and the development of symptoms including fever, weight loss, drenching sweats, fatigue, and immune-mediated cytopenias.9 Treatment options for patients with symptomatic SLL/CLL have very rapidly evolved over the last decade, notably with the introduction of immunomodulatory agents, Bruton’s tyrosine kinase inhibitors, PI3K inhibitors and a few generation CD-20 monoclonal antibodies (mABs).4,8

Significant elevation of IgE as an initial manifestation of a lymphoproliferative disorder is infrequently seen. Clonal IgE elevations are reported in IgE-producing plasmacytomas, which account for approximately 0.01% of cases.9 Although rare, nonclonal elevated IgE levels have been reported in a very few cases of B- and T-cell non-Hodgkin lymphomas (NHL) and Hodgkin lymphomas. In a single case report of a 73-year-old female with elevated IgE and no underlying allergic or other conditions associated with elevated IgE, a diagnosis of B-cell lymphoma was made due to an abnormal lymphocyte profile.10 T-cell lymphoma was diagnosed in an 8-year-old female with significantly elevated serum IgE.11 In another case, a 60-year-old male with NHL demonstrated pulmonary nodules mirroring miliary tuberculosis in conjunction with apparent eosinophilia and excessive IgE.12 Furthermore, a 22-year-old female was diagnosed with Hodgkin lymphoma after presenting with remarkably increased IgE serum levels,12 while 2 patients with Hodgkin lymphoma presented with moderate elevations in IgE levels.13 There are also single case reports of B-cell CLL14 and B-cell SLL15 that presented with extremely high IgE levels.

Obinutuzumab is a humanized type II anti-CD20 mAB approved for use in CLL and relapsed follicular lymphoma.9 It was specifically engineered to induce greater antibody-dependent cellular cytotoxicity and direct cell death as compared with rituximab. Once bound to CD20, obinutuzumab mediates B-cell lysis through binding and activation of immune effector cells, direct cell death, and activation of the complement cascade.14,15

In this patient, we observed a marked clinical improvement as well as decline in polyclonal immunoglobulins (serum IgE, IgD, and IgG levels) as a response to mAB. The treatment was continued as maintenance and, to date, the patient has been enjoying the symptomatic improvement without recurrence of the skin lesions or SLL/CLL relapse for 2 years. The utility of maintenance in SLL/CLL has been addressed and demonstrated a promising efficacy.16

Conclusions
Skin lesions in the setting of an elevated IgE level have been described in association with multiple nonmalignant disorders, such as Wegener granulomatosis.17 Hypersensitivity skin reactions to mosquito bites have also been described in patients with hematologic malignancies.18,19 In our case, in the setting of symptomatic SLL/CLL, skin lesions presented de novo in a paraneoplastic fashion. While the treatment using a single-agent, monoclonal antibody has led to a clinical response, it also resulted in immunoglobulin decline; hence improvement in immunoglobulin-related nephropathy, and resolution in vasculitis. Although a very high serum IgE level may, as a secondary effect, lead to development of skin lesions,20 paraneoplastic SLL/CLL-associated etiology cannot be ruled out. Patients who develop such lesions are often referred to various specialists (eg, dermatologists, infectious disease experts, and allergists/immunologists) who may prescribe symptom-directed therapy. Although paraneoplastic skin changes do not indicate the poor risk21 that other malignancies may, clinicians should remain alert for unusual presentations beyond the classical symptoms of underlying or newly diagnosed hematologic disorders, and should maintain a high level of suspicion for potential disease progression.

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IgE indicates immunoglobulin E; IgG, immunoglobulin G; N/A, not available.

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References