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CASE REPORT

Membranoproliferative glomerulonephritis and acute renal failure in a patient with chronic lymphocytic leukemia: Response to obinutuzumab

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Abstract
Objective/background: Membranoproliferative glomerulonephritis (MPGN) is a common extramedullary renal presentation in chronic lymphocytic leukemia (CLL) and can present with either a frank renal failure or proteinuria. One of its etiologies has been attributed to a paraneoplastic, immune complex phenomenon occurring in CLL. Although there is no standard of care in such patients, use of anti-CD20 monoclonal antibodies like rituximab have been used before in such patients with variable responses. Obinutuzumab is a novel, type II, immunoglobulin-G1 monoclonal antibody with a higher efficacy than rituximab and has an established safely profile in patients with comorbidities and poor renal functions. There are no such reported cases of MPGN in CLL being treated with obinutuzumab.
Methods: We used the standard doses of obinutuzumab in our elderly patient (78-year-old woman) with high-risk CLL due to an underlying *TP53* mutation, along with a MPGN-related acute renal failure.
Results: The patient achieved complete remission after six cycles of obinutuzumab; however, she remained positive for minimal residual disease on flow cytometry. Her renal function improved completely, suggesting a complete response of her underlying MPGN.

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Conclusion: Obinutuzumab has an established safety profile in patients with CLL, but our case is the first reported case of a paraneoplastic, immune complex-mediated MPGN in CLL being treated with obinutuzumab. Obinutuzumab should be explored as a potential option in patients with CLL and MPGN.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the United States [1,2]. Most patients are asymptomatic at the time of diagnosis, and do not require CLL-directed treatment. Progressive adenopathy/organomegaly and cytopenias are common reasons to initiate treatment for CLL. The incidence of extramedullary/extranodal organ involvement is low [3]. Ratterman et al. [3] identified 192 extramedullary/extranodal cases of CLL reported between 1975 and 2012 in literature. Skin (33%) and the central nervous system (27%) were the most commonly involved sites. Involvement of genitourinary and gynecological sites was rare, constituting less than 10% of the total reported cases. A recent study from the group at the Mayo Clinic reported renal insufficiency (serum creatinine $\geqslant$1.5 mg/dL) in 153 (7.5%) patients of CLL, with patients presenting with either a nephrotic syndrome or with an acute renal failure [4]. Membranoproliferative glomerulonephritis (MPGN), interstitial infiltration by CLL cells, minimal change disease, and thrombotic microangiopathy constitute the most commonly reported renal pathologies in patients with CLL and renal involvement [5,6]. Here, we report a patient with CLL with extramedullary involvement of the kidneys in the form of MPGN and presenting with acute renal failure. The patient received six cycles of obinutuzumab (type II CD20-monoclonal antibody) with normalization of her renal function. To our knowledge, this is the first case of CLL with MPGN that was treated with obinutuzumab.

Patient profile

A healthy 78-year-old woman was noted to have leukocytosis on a routine annual medical evaluation in 2002. Her white blood cell count was 18.6 K/μL with lymphocytosis. Hemoglobin and platelet count were normal. She was advised clinical observation given her early stage CLL. She remained asymptomatic until December 2014 when she started to develop fatigue. She also started to have dark-colored urine along with a decreasing urine output over a period of 2 weeks. She was evaluated at an outside hospital on January 15, 2015, and was found to have an oliguric renal failure with a creatinine level of 8.1 mg/dL. Her white blood cell count was 9.2 K/μL, hemoglobin 8.9 g/dL, and her platelet count was 154 K/μL. She was found to have proteinuria (1980 mg/24 h) with low levels of complement 3 and 4. Antinuclear antibody levels were normal. Ultrasonography of the kidneys excluded an obstructive uropathy. She underwent multiple sessions of hemodialysis. A renal biopsy revealed features of monoclonal gammopathy with membranous glomerulonephritis (Fig. 1A–E). A bone marrow biopsy showed a mildly hypercellular bone marrow with 50% cellularity with trilineage hematopoiesis and CLL/small lymphocytic lymphoma involving 40% of the cellularity. Flow cytometry (FCM) revealed a clonal population of small cells with CD19+, CD20dim+, CD5+, CD10-,CD38-, CD23+, FMC7-, kappa-, and lambda-immunophenotype. Positron emission tomography–computed tomography scan showed mildly prominent lymph nodes in the cervical, axillary, and inguinal areas. She received high-dose steroids for 4 weeks to treat her MPGN. Her renal function stabilized with a creatinine level of around 3.5–4 mg/dL, and she was able to cease dialysis. She was then referred to our center for further management.

Clinical findings

At presentation to our hospital, the patient complained of extreme fatigue and was wheelchair bound. She had no other comorbidities. Physical examination was significant for <1-cm lymph nodes in the cervical and axillary area. Peripheral smear showed a normocytic normochromic anemia with mild anisopoikilocytosis, leukocytosis with mainly atypical lymphocytes, and numerous smudge cells. Her white blood cell count was 19.4 K/μL, with an absolute lymphocyte count of 17.6 K/μL, hemoglobin 9.2 g/dL, and platelet count of 308 K/μL. Other parameters at presentation included a lactate dehydrogenase level of 668 IU/L, blood urea nitrogen of 47 mg/dL, and a creatinine level of 3.94 mg/dL.

Diagnosis

Considering her unusual presentation, we repeated the bone marrow examination. Bone marrow (Fig. 1F) and FCM done on February 02, 2015, were confirmatory of CLL. Cytogenetics showed a normal female karyotype. CLL fluorescence *in situ* hybridization panel was positive for deletion 13q. Additional prognostic markers included a β2-microglobulin of 13.5 mg/L and a mutated *IGVH* gene. CD38 was not expressed. Next-generation sequencing performed for the detection of somatic mutations revealed two *TP53* mutations. The first *TP53* was a missense mutation (c.641 A>G p.H214R) in exon 6 and the second *TP53* mutation was a previously unknown, splice mutation (c.672+1G>A). Serum immunoglobulin levels were normal. A urine analysis showed multiple red blood cells, white blood cells, and hyaline casts, suggestive of a nephritic syndrome. Serum protein electrophoresis and immunofixation studies excluded multiple myeloma. Hepatitis B and C viral serology was also negative. There was no evidence of cryoglobulinemia. A

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