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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.

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.

Keywords

CLL; MPGN; Obinutuzumab; Renal failure

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Conflicts of interest

None.

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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/organo-megaly 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 ⩾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 under-went 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.

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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 review of her outside renal biopsy reconfirmed the presence of a type 1 acute MPGN on electron microscopy (Fig. 1A–E). Immunofluorescence studies showed diffuse granular deposits of C3, immunoglobulin-G, and kappa light chains. We considered MPGN as a paraneoplastic renal manifestation of CLL, and initiated her on obinutuzumab monotherapy on March 11, 2015. She tolerated obinutuzumab well with no infusion reactions and within a month her creatinine improved from 3.2 mg/dL to 1.0 mg/dL (Fig. 2). She received a total of six cycles of obinutuzumab as per the approved dosing schedule. There was significant improvement in all hematological parameters with normalization of white blood cell count, absolute lymphocyte count, and hemoglobin. At her last follow up on September 28, 2015, she had a normal renal function, and was in complete remission with a positive minimal residual disease status using FCM.

Discussion

MPGN is a rare manifestation in patients with CLL and it is quite heterogeneous in presentation [5,6]. Its clinical profile may vary from an asymptomatic hematuria or proteinuria, a classical acute nephritic or a nephrotic syndrome, acute renal failure, or even with features of chronic kidney disease [7]. The pathogenesis of MPGN could result from an immune-complex mediated phenomenon or a C3 mediated complement activation [7,8]. CLL is known to cause an immune-mediated MPGN as a result of localization of the antigen–antibody complex in the glomeruli which reflects as granular deposits on electron

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microscopy of the renal biopsy [9]. These antibodies are usually polyclonal and stain for both kappa and lambda light chain, as seen in the present case. Steroids and cyclophosphamide have shown responses in patients with idiopathic MPGN [8,9]. Rituximab, a type I CD20-monoclonal antibody has also been shown to be effective in patients with MPGN [5,9]. In an open label trial of six patients with MPGN (six idiopathic, two with cryoglobulinemic MPGN), use of rituximab caused a significant improvement in the proteinuria along with a suppression in the peripheral B cells, though the creatinine clearance did not change significantly [10]. In a retrospective study by Guiard et al. [11] on 26 patients with noncryoglobulinemic glomerulonephritis and monoclonal immunoglobulin-deposits [MPGN ($n = 5$) and membranous glomerulopathy ($n = 2$)], rituximab was administered as 4-weekly doses of 375 mg/m^2 in seven patients [MPGN ($n = 5$) and membranous glomerulopathy ($n = 2$)] [11]. One patient received two maintenance doses, 8 months and 14 months after the initial treatment. A complete response (CR) of the nephrotic syndrome ($n = 22$) was seen in five patients receiving rituximab ($n = 7$) after a mean delay of 9 months (range, 4–24 months). Two patients showed a partial response with a significant reduction of proteinuria, serum albumin, and stabilization of the renal functions. Only one patient relapsed after 44 months of therapy. Due to severe renal dysfunction, rituximab was not administered again in that patient.

Obinutuzumab is a novel type II glycoenginered anti-CD20 monoclonal antibody inducing higher antibody dependent cellular cytotoxicity than type I antibodies such as rituximab [12–14]. Obinutuzumab–chlorambucil combination in patients with CLL have shown higher rates of CR (20.7% vs. 7.0%) and a superior progression-free survival (hazard ratio, 0.39; $p < .001$) in comparison with rituximab–chlorambucil (CLL11 trial) [15]. Although the obinutuzumab–chlorambucil combination arm did have a higher incidence of infusion-related reactions and neutropenia in comparison with the rituximab–chlorambucil arm, the overall risk of infection was not increased [15]. Additionally, dose modifications for obinutuzumab are not considered necessary even in patients with extreme renal function, although the data are limited [14–16]. As our patient had a high-risk CLL due to the presence of a *TP53* mutation, we considered treating her with obinutuzumab. She received six cycles of obinutuzumab, and achieved a minimal residual disease-positive CR. To our knowledge, this is the first report of a patient with CLL and renal failure due to MPGN treated successfully with obinutuzumab. Use of obinutuzumab led to a rapid recovery of the underlying renal dysfunction in our patient. Notably, there were no infusion reactions or prolonged cytopenia secondary to obinutuzumab.

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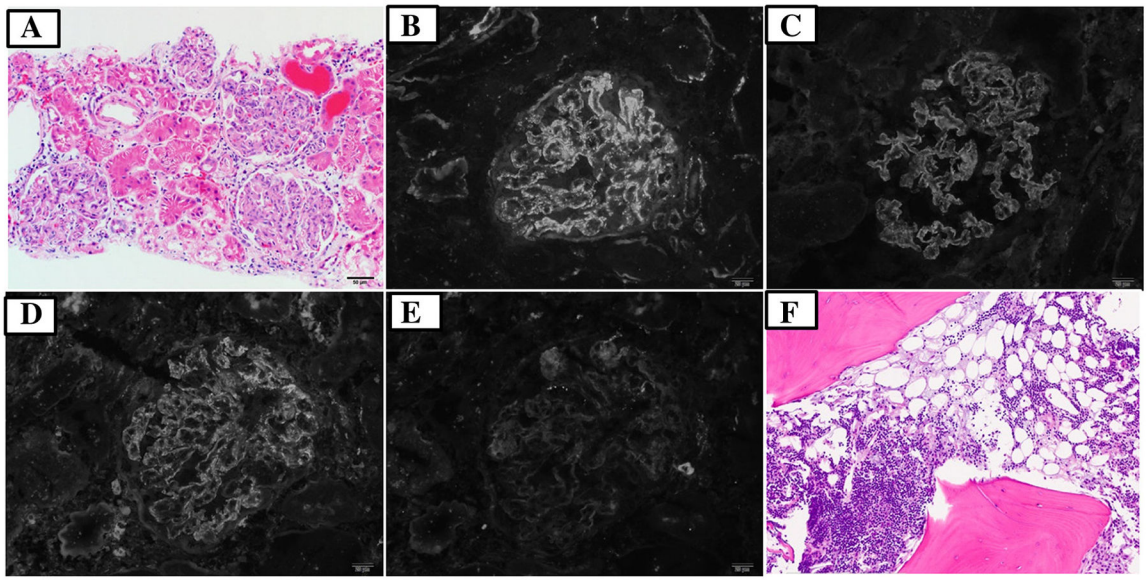

Fig. 1.

(A) Hematoxylin and eosin showing diffuse endocapillary and mesangial hypercellularity, focal red blood cell casts and increased small round lymphocytes; (B–E) showing diffuse capillary granular deposits of complement 3, immunoglobulin-G, kappa, and lambda, respectively; (F) bone marrow biopsy showing nodular and interstitial small lymphocytic infiltrates.

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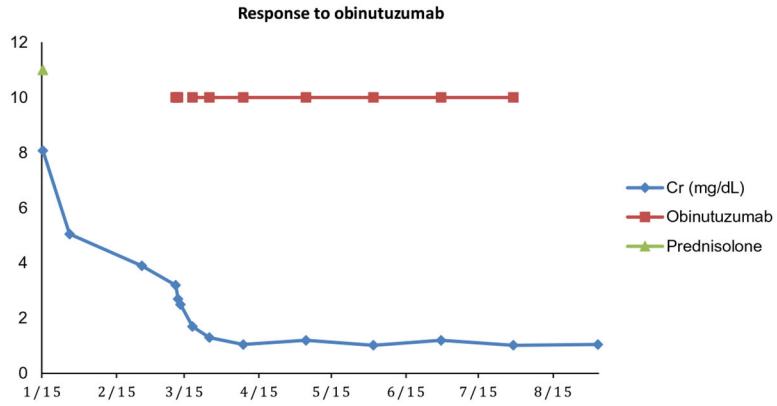

Fig. 2.

Improvement in creatinine (Cr) levels with obinutuzumab.