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Chronic lymphocytic leukemia associated with immunotactoid glomerulopathy: a case report of successful treatment with high-dose methylprednisolone in combination with rituximab followed by alemtuzumab

Januario E. Castro^{1,3}, Julio A. Diaz-Perez¹, Juan S. Barajas-Gamboa¹, John M. Horton¹, Noel Weidner², and Thomas J. Kipps^{1,3}

¹Department of Medicine, UCSD Moores Cancer Center

²Department of Pathology, UCSD Moores Cancer Center

³CLL Research Consortium

Glomerular diseases (GD) associated with chronic lymphocytic leukemia (CLL) are unusual¹. The many causes of renal failure in CLL patients include immune-complex deposition, hyperkalemia, amyloid deposition, sepsis, hemoglobinuria in the setting of hemolysis, uric acid nephropathy caused by tumor lysis syndrome (TLS), and therapy related complications. The most common clinical manifestations of these nephropathies include proteinuria, hematuria, electrolyte abnormalities (hyperkalemia) and progressive renal failure^{2,3}. The most frequent GD associated with CLL is membranoproliferative glomerulonephritis (MPGN) (45%), followed by membranous glomerulonephritis (MGN) (20%), with occasional reports of proliferative, minimal change disease, immunotactoid glomerulopathy (ITG), as well as amyloid or focal-sclerosing glomerulonephritis⁴.

There are no controlled studies evaluating treatments for GD in CLL due to low incidence and clinical variability of this condition. Complete resolution of nephropathy associated with CLL has been observed after therapy with alkylating agents, purine analogs, steroids (prednisone) and monoclonal antibodies^{2,3}. Improvement in renal function is associated with decreased levels of monoclonal immunoglobulins (Ig) (mainly IgG), and leukemia response, suggesting a close association between CLL activity and glomerulopathy^{4,5}.

We report the case of an adult male with progressive CLL-associated nephrotic syndrome, who was diagnosed with immunotactoid glomerulopathy (ITG). He received a combination of high-dose methylprednisolone and rituximab (HDMP-R) regimen that we have previously described^{6,7}. In addition, he was treated with alemtuzumab for eradication of residual disease and with the goal to prevent early relapse.

Our patient is a 55-year-old male who was diagnosed with CLL five years before presenting with GD. Past medical history was relevant for hypertension, benign prostatic hyperplasia,

bronchitis and skin basal-cell carcinoma. HIV, hepatitis-B and hepatitis-C serologies were all negative. His initial leukemia presentation involved lymphocytosis, splenomegaly and bulky lymphadenopathy, and he was treated with HDMP-R achieving a partial response (PR) with evidence of residual disease in the bone marrow (BM). The patient was stable for 2-years until he showed signs of disease progression and received treatment under a clinical protocol with intranodal injection using an adenovirus vector expressing a CD154 homolog (Ad-ISF35). After this treatment, the patient had complete resolution of lymphadenopathy and splenomegaly, and his disease was stable for an additional year. After this remission period, the patient presented with anasarca associated to renal dysfunction, proteinuria and TLS based on Cairo-Bishop criteria⁸ (uric acid level 10.8mg/dL, blood potassium 5.4meq/L, blood calcium level 8.4mg/dL, blood phosphorus level 6.5mg/dL and urinary creatinine 2.3mg/dL, LDH 473 U/L). This required treatment with allopurinol and rasburicase. Cryoglobulins were elevated at 27mg/dl with no evidence of monoclonal-gammopathy, total proteinuria in 24 hours was 8.7gr (nephrotic syndrome). The patient had anemia and progressive lymphocytosis with a lymphocyte doubling time of one month and concomitant progression of bone marrow involvement with CLL (Table 1 and Figure 1C). The patient had lymphadenopathy with the largest lymph nodes in the abdominal region measuring up to 3 cm in diameter (lymph node biopsy to rule out Richter's transformation was not performed). He had no type-B symptoms at that time.

Renal needle core biopsy was performed. The patient's biopsy showed focal areas of glomerulosclerosis with areas of diffuse hypercellularity forming a lobular glomerulonephritis pattern with prominent subendothelial hyaline deposits mimicking wire-loop lesions (MPGN pattern type 1) (Figure 1E HE Stain, 400x), renal parenchyma showed 10% interstitial fibrosis and patchy chronic inflammation with no vasculitis (Figure 1F, Jones's silver stain, 400x). The immunofluorescent sample was insufficient for study. Electron microscopy showed glomeruli with abundant sub-endothelial electron-dense deposits organized diffusely into elongated, non-branching microfibrils/microtubules, forming tightly packed parallel arrays (Figure 1G, Uranyl acetate plus bismuth subnitrate, 400x). The microfibril/microtubule diameter was found to be in the 30 nm range (Figure 1H, Uranyl acetate plus bismuth subnitrate, 8000x). The cross-sectional appearance was of solid dot microtubules (Figure 1I and 1J, Uranyl acetate plus bismuth subnitrate, 100,000x and 400,000x). These findings were compatible with ITG.

The patient received treatment with HDMP-R monthly for a total of 4 cycles, achieving a PR with residual disease in the BM (Table and Figure 1). His WBC, LNP, proteinuria and urinary creatinine improved significantly (Table and Figure 1). His subsequent BM biopsy showed 40% residual CLL involvement, and at that time he was recommended to receive additional treatment with alemtuzumab (Campath™, Sanofi), for a total of 26 intravenous (IV) doses 30mg/each. The patient received prophylactic antibiotics (trimethoprim-sulfamethoxazole 160/800mg twice/daily, fluconazole 100 mg/day and valganciclovir 900 mg/day) during treatment and for 2 months after completion of alemtuzumab. CMV surveillance was performed weekly with PCR. HDMP-R was well tolerated without adverse events. The patient developed a mild infusion reaction to alemtuzumab IV that consisted of hives, which improved with hydrocortisone. After treatment with alemtuzumab the patient

achieved a CR, with no evidence of MRD by 4 color flow cytometry analysis (Figure 1D). He has been in CR and without recurrence of renal disease for 3 years after treatment.

The relationship between GD (including nephrotic syndrome) and malignancy was first described in 1922⁹. The nephrotic syndrome may precede, coincide with, or follow the diagnosis of malignancy^{1,3}. In a review by Seney et al.², GD associated with CLL occurred in less than 1% of cases^{2,4}.

The etiology of GD associated with CLL is unclear. Often a causal relationship between CLL and GD is difficult to prove, but typically is suspected due to evidence of monoclonal Ig glomerular deposition, parallel improvement with treatment, and worsening of GD upon CLL relapse^{2,3}. It has been suggested that GD is caused by monoclonal Ig secreted by the malignant B-lymphocyte clone. It is also hypothesized that the proliferating B-lymphocytes, arrested in their physiologic differentiation, produce abnormally organized antibody deposits within the glomerular tufts, and cause elevated levels of complement or cytokines with a resultant increase in the permeability of Bowman's capsule.^{1,10,11} Others speculate that CLL patients may have viral infections that may contribute to both hematological malignancy and glomerulonephropathy development^{5,12}. For instance, it is well known that patients with hepatitis-C are at risk of developing MPGN or MGN. Finally, splenomegaly associated with chronic leukemia (either CLL or CML) may predispose patients to various circulating infections that can induce immune complex formation and GD^{2,4,9}. The patient discussed in this case received treatment with intranodal administration of an adenovirus vector expressing a CD154 homolog (ISF35), whether or not this contributed to the development of GN is not clear. However, more than 50 patients have received treatment with CD154 / ISF35 based gene immunotherapy and we have not observed any other cases of GN (^{13,14} and unpublished data).

The patient discussed here was diagnosed with ITG, a rare subtype of GD^{12,15}. The diagnosis of ITG is established after excluding other diseases that present with glomerular immune deposits. ITG is related to the group of fibrillary glomerulonephritis (FGN), and is characterized by larger fibers arranged in parallel microtubules while cases with smaller randomly arranged fibrils are classified as FGN. It is considered that patients with ITG have worse prognosis, with poor response to steroids or cytotoxic agents and ultimately requiring hemodialysis^{12,16}.

Due to the poor prognosis that GD associated to CLL may have, and because of the presence of significant symptomatology including TLS, our patient was treated with the goal of achieving not only resolution of his nephropathy, but also a CR with eradication of residual CLL. In determining the patient's therapy we took several factors into consideration. First, we wanted to avoid additional renal insult so we avoided fludarabine-based treatments. Additionally, we wanted to control both the rapidly progressive CLL as well as GD. Based on our experience and previously published data, we considered that HDMP-R was an appropriate combination treatment that met those requirements. We have reported that treatment of CLL with HDMP-R is effective even in patients that are fludarabine refractory, with progression free survival of 54%, overall response rate of 90%, and complete responses (CR) in the 30% range^{6,7}. This non-chemotherapy regimen typically is well tolerated with

minimal side effects, does not induce BM suppression, and can be used in elderly patients as well as patients with organ dysfunction such as the case reported here.

Previous case reports have documented the efficacy of rituximab in CLL-associated GD, with significant reduction of proteinuria, improvement in renal function, and parallel control of the underlying CLL¹⁷. However, in those reports there is no description of the duration of response or long term follow up as we report here.

Because of the presence of significant amount of residual disease in the bone marrow, the patient was recommended to receive additional treatment with alemtuzumab (off protocol). The patient elected to proceed with this treatment with the goal to eradicate MRD and increase the duration of response to treatment, which was two years after his previous treatment with HDMP-R. In addition, we were concerned about the poor prognosis associated with ITG and the high risk of recurrence of GD and CLL.

After receiving alemtuzumab the patient achieved a CR with no evidence of MRD and complete resolution of GN. He has been followed for 3 years after treatment with no evidence of recurrence of CLL or nephropathy. In addition, he had no major adverse events related to this combination therapy. In part this could be due to the antibiotic prophylaxis and frequent monitoring for CMV reactivation that was used as well as the fact that alemtuzumab was administered after a non-chemotherapy induction regimen that could be less immunosuppressive than other standard chemotherapy combinations^{7,18}.

To our knowledge, this is the first case of ITG/GD associated to CLL that has been successfully treated with a non-chemotherapy regimen that includes HDMP-R followed by alemtuzumab. This combination offers an effective alternative for the management of challenging cases of GD associated to CLL as the one presented here. Even though our patient had no major side effects or complications, the safety of this combination treatment needs to be evaluated in larger prospective studies.

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Figure 1.

Renal function profile, is recognizes the evolution of the levels of creatinine in urine (A) and proteinuria (B); arrows indicate the initiation of treatment. Neoplastic CD19+CD5+ cells are present before treatment with HDMP+R (C), but not after (D). The histopathological analysis describes diffuse proliferative glomerulonephritis forming a lobular pattern. Note the hyaline capillary loop deposits in the upper left hand portion of the photo (HE stain, 400x) (E). A portion of a glomerulus stained with Jones silver stain shows the peripheral capillary loop double contours associated with marked subendothelial hyaline deposits (Jones silver stain, 400X) (F). Electron micrograph showing a representative peripheral capillary loop containing large amounts of subendothelial electron-dense deposits (uranyl acetate plus bismuth subnitrate, 4000X) (G). Electron micrograph showing a representative peripheral capillary loop containing large amounts of subendothelial electron-dense deposits with

apparent microtubule-like substructure (uranyl acetate plus bismuth subnitrate, 8000X) (H). The diameters (nm) of the microtubule-like structures (uranyl acetate plus bismuth subnitrate, 100,000X) (I), and a magnification to 400,000X (J).

HDMP-R: High-dose methylprednisolone and rituximab, UL: Upper left, UR: Upper right, LL: Lower left, LR: Lower right.

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Table 1

Clinical, hematology laboratory, renal function and bone marrow pathological characteristics.

Parameters	HDMP +Rituximab		Alemtuzumab	
	Pre Tx	Post Tx	Pre Tx	Post Tx
Age	52 y/o	53 y/o	54 y/o	55 y/o
WBC cells /mm ³	122,000	4,900	7,000	3,700
% Lymphocytes	98	15	13	6
ALC cells /mm ³	120,000	735	910	222
% Neutrophils	0	71	74	88
Platelets cells /mm ³	138,000	215,000	249,000	214,000
Hemoglobin	10.4	14.7	14.6	16
Largest Lymph node	1 × 1 cm	1 × 1 cm	1 × 1 cm	0
Lymph Node Product	11	13	13	0
Cytogenetic / FISH	46XY, del13q, trisomy 12, trisomy 19			
CT Scan (largest lymph node)	-	1.4 cm	-	0
Bone Marrow Bx Involvement	85%	40%	40%	< 0.1%
CLL Response Assessment *	-	CR-MRD ^{pos}	-	CR—MRD ^{neg}
Proteinuria (mg/dl)	1,526 ⁺	37	16	-
Urine Creatinine 24 hours (mg/dl)	160	81	56	ND
BUN / Cr	74 / 2.3	32 / 1.5	20 / 1.1	17 / 0.9

AdISF35: Replication defective adenovirus vector encoding a membrane-stable, re-engineered form of CD154, HDMP: High dose methyl prednisolone, WBC: white blood count, ALC: Absolute leucocyte count, FISH: Fluorescent in situ hybridization, BUN: Blood Urea Nitrogen, PD: Progressive disease, MRD: Minimal residual disease, CR: Complete response;

* IWCLL-2008 criteria.

⁺Total proteinuria in 24 hours 8.7 gr.