Leukemia Research Reports 20 (2023) 100377

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Membranous nephropathy in chronic lymphocytic leukemia responsive to ibrutinib: A case report

Anna-Eve Turcotte [a], William F. Glass [b,c], Jamie S. Lin [a,*], Jan A. Burger [d,*]

[a] Section of Nephrology, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, United States of America
[b] Department of Pathology and Laboratory Medicine, University of Texas Health Science Center McGovern Medical School, Houston, TX, United States of America
[c] Division of Anatomic Pathology, Department of Pathology, The University of Virginia School of Medicine, Charlottesville, Virginia, United States of America
[d] Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, United States of America

ARTICLE INFO

Keywords:
Case report
Membranous nephropathy
Chronic lymphocytic leukemia
Bruton tyrosine kinase
Paraneoplastic

ABSTRACT

Membranous nephropathy (MN) is an uncommon renal presentation in patients with chronic lymphocytic leukemia (CLL), and as such, there is no standard therapy for these patients. A few cases of MN in CLL have been described with varying success in MN treatment involving alkylating agents and fludarabine. Here we report the first case of MN in a patient with CLL treated with ibrutinib with complete renal response. This presentation underlines the importance of recognizing rare glomerular diseases that may occur with CLL and offers a new therapeutic avenue to the treatment of CLL-associated MN.

1. Background

Chronic lymphocytic leukemia (CLL), the most common leukemia in adults in Western countries, is due to an expansion of monoclonal $CD5^+$ B-lymphocytes in the blood, bone marrow, and secondary lymphoid organs (lymph nodes, spleen) [1–3]. Early-stage CLL patients often are asymptomatic and extramedullary manifestations are rare [2]. Auto-immune complications in CLL patients typically target hematopoietic cells, presenting as autoimmune hemolysis or immune thrombocytopenia (ITP). While CLL infiltration can be detected in the kidneys in up to 90% of autopsy cases, an association between CLL and paraneoplastic glomerular diseases is rare. Nonetheless, approximately 2% of CLL patients can develop nephrotic syndrome [1,4]. A spectrum of CLL-associated paraneoplastic glomerular diseases have been reported, with membranoproliferative glomerulonephritis (MPGN) being the most common pathological finding [2,28]. Membranous nephropathy (MN), however, is rarely associated with CLL. MN is an autoimmune disease that classically presents with a nephrotic syndrome, i.e. proteinuria, hypoalbuminemia, and hyperlipidemia. It can develop as either a primary (idiopathic) or as a secondary condition. Secondary MN has been associated with medications, infections, autoimmune diseases, and malignancies. Between 5% to 20% of adult patients diagnosed with MN have a paraneoplastic condition associated typically with a solid tumor. In contrast, MN is infrequently associated with hematologic malignancies, such as CLL.

A few cases of MN in CLL have been described with varying success in MN treatment. Ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor, is an approved standard CLL therapy in the first-line as well as in the relapsed and refractory disease settings. Ibrutinib's efficacy in CLL-associated MN is unknown. We present the first case of MN responsive to ibrutinib therapy in a patient with CLL.

2. Case presentation

A 63-year-old male with a recent diagnosis of early stage CLL (RAI stage 0) presented to MD Anderson Cancer Center for a second opinion. Prior to his CLL diagnosis, he had complaints of fatigue, weight loss, and worsening edema of his lower extremities. Evaluation for deep venous thrombosis was negative; however, laboratory results revealed a slightly elevated white blood cell count with lymphocytosis, and flow cytometry was diagnostic for CLL, demonstrating a $CD5^+$ monoclonal B-cell population. Prognostic factor testing revealed mutated IGHV status, trisomy 12 and deletion of 13q detected by fluorescence in situ hybridization (FISH). Due to worsening edema, renal impairment, and concern for nephrotic syndrome, the patient was referred to nephrology.

The patient's physical examination revealed 3+ bilateral pitting

List of abbreviations: BCR, B cell receptor; BTK, Bruton tyrosine kinase; CLL, Chronic lymphocytic leukemia; GBM, Glomerular basement membrane; ITP, Immune thrombocytopenia; MPGN, Membranoproliferative glomerulonephritis; MN, Membranous nephropathy; PLA2R, Phospholipase A2 receptor.

* Corresponding authors.
E-mail addresses: jlin8@mdanderson.org (J.S. Lin), jaburger@mdanderson.org (J.A. Burger).

https://doi.org/10.1016/j.lrr.2023.100377
Received 18 December 2022; Received in revised form 8 June 2023; Accepted 19 June 2023
Available online 20 June 2023

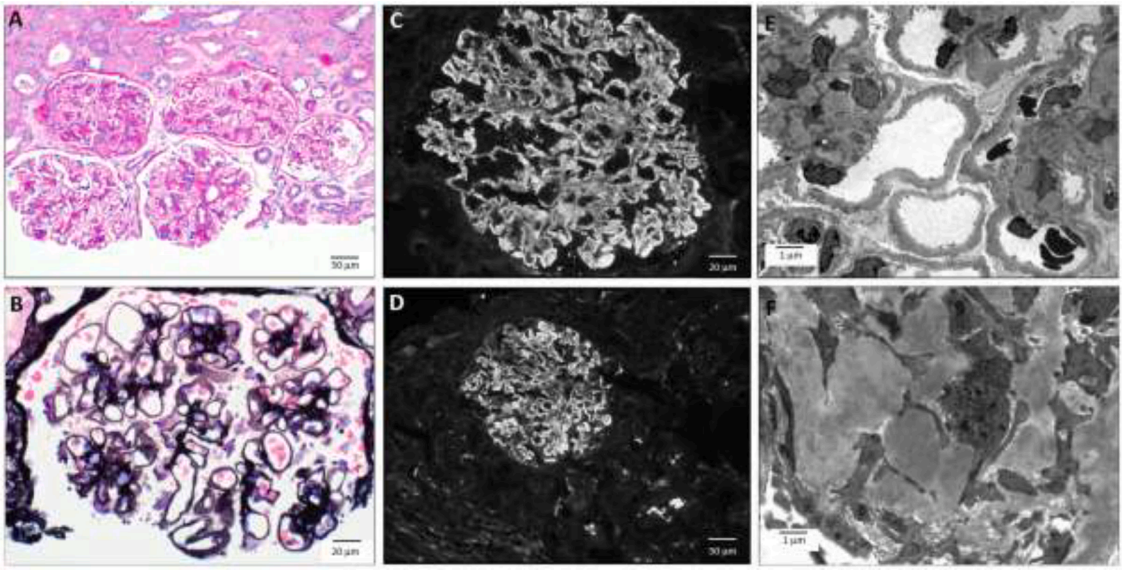

Fig. 1. Renal histology. (A) Periodic acid-Schiff (PAS) stain shows mild to moderate mesangial matrix expansion and thick glomerular basement membranes. (B) Jones silver stain demonstrating basement membrane spikes. (C) Immunofluorescence staining reveals diffuse granular immunoglobulin G (IgG) capillary wall deposits and (D) C3 capillary deposits. (E) Electron micrograph images show numerous subepithelial electron dense deposits with expansion of glomerular basement membranes and (F) expansion of mesangial matrix with abundant mesangial deposits.

lower extremity edema to mid-thigh and periorbital edema. Biochemical results were as followed: serum creatinine (Cr) 1.38 mg/dl (baseline 1.20 mg/dl), albumin 2.4 g/dl, white blood cell 13.7 K/uL with abnormal lymphocyte percent of 44, and normal platelet 169 K/uL and lactate dehydrogenase 220 U/L. Urinalysis revealed 11–25 red blood cells per high power field and 24 h urinary protein excretion was 17.9 g. No monoclonal peak was demonstrated in either serum or urine electrophoresis, or by immunofixation. The following serologies were negative: antinuclear antibody, rheumatoid factor, anti-glomerular basement membrane, myeloperoxidase and proteinase 3 antibody, hepatitis B, hepatitis C, and HIV.

Due to the broad differential diagnosis including MPGN, minimal change disease, MN, focal segmental glomerulosclerosis, amongst other glomerular pathologies, a percutaneous renal biopsy was performed revealing a diagnosis of membranous nephropathy. Light microscopy revealed thickened glomerular capillaries with pathognomonic pits and spikes on Jones methenamine silver stain (Fig. 1A and B). Monotypic CLL cell infiltration was not seen in the renal interstitium. By electron microscopy, glomerular basement membranes (GBM) measured over 1000 nm (normal adult male average = 230–430 nm) with subepithelial immune complex-type electron-dense deposits and mesangial deposits (Fig. 1C and D). Indirect immunofluorescence staining for phospholipase A2 receptor (PLA2R), a marker of primary or idiopathic MN, was negative. The presence of mesangial deposits and negative PLA2R stain favored secondary membranous glomerulopathy.

Due to the concern that his MN was a paraneoplastic complication associated with his recent diagnosis of CLL, treatment with prednisone and ibrutinib was discussed and agreed on. He was also started on low-dose furosemide and an angiotensin converting enzyme inhibitor. Labs the following week revealed an improved serum Cr of 1.25 mg/dl (Cr peak 1.38 mg/dl and Cr baseline 1.20 mg/dl) decreased urinary protein excretion to 5.7 g on a spot urine protein/creatinine ratio (from 17.9 g from initial 24 h urine protein collection). A month later, the prednisone was completely tapered and the BTK inhibitor was stopped due to gastrointestinal side effects. The spot urine protein/creatinine ratio temporarily increased to 6.6 g and the creatinine rose to 1.40 mg/dL, but the complete blood count remained normal. The proteinuria subsequently decreased progressively and the creatinine improved to 1.10 mg/dl. After 10 months of follow-up, the serum creatinine recovered to baseline, the serum albumin level improved to 3.2 g/dL from 2.4 g/dL with a spot urine protein/creatinine ratio of 0.66 g (Table 1). The CLL was also noted to be inactive.

Table 1
Pre-treatment and post-treatment laboratory values.

	Initial work-up	10 months post-treatment
Creatinine (mg/dl)	1.38	1.10
24 h urinary protein excretion (g/24 h)	17.9	—-
Spot urine protein/creatinine ratio (g)	—-	0.66
White blood cell (K/ul)	13.7	8.8
Lymphocyte percentage	44.0	27.3
Albumin (g/dl)	2.4	3.2

3. Discussion

CLL is recognized as the most common leukemia in adults [3], paraneoplastic glomerular kidney pathologies associated with CLL are rare. We report the first case of suspected paraneoplastic MN in a patient with CLL that responded to ibrutinib therapy. Consensus guidelines of the International Workshop on Chronic Lymphocytic Leukemia suggest that CLL should be treated when it is progressive or symptomatic. Kidney involvement is among the criteria used to define active disease and justifies to initiate treatment [5]. Although our patient had early stage CLL he had active kidney disease, presumably CLL-related, necessitating CLL therapy. A diverse spectrum of glomerular renal lesions have been described in patients with CLL and nephrotic syndrome including MPGN, minimal change disease, and MN [6,7]. Other more rare paraneoplastic pathologies described with CLL include: amyloidosis, immunotactoid glomerulopathy, proliferative glomerulonephritis with cryoglobulinemia, light chain deposition disease, C3 glomerulonephritis, fibrillary glomerulonephritis, focal segmental glomerulosclerosis, focal crescentic pauci-immune glomerulonephritis and light chain cast nephropathy [2,7-12]. A renal biopsy was obtained for definitive diagnosis which assisted in his clinical treatment plan and expectations of renal response.

Table 2
Case reports of CLL and membranous nephropathy.

Case no	Ref	Age/ sex	Cr (mg/ dL)	Proteinuria (g/24 h)	Monoclonal protein	C3/C4	LM	IF	EM	Treatment	Renal outcome	CLL outcome
1	[25]	64/ M	NA	NA	NA	NA	MN	NA	NA	CBL	PR	NA
2	[14]	61/ M	NA	NA	None	NA	MN	IgG, C3, C1q	NA	CBL	Improve	Improve
3	[26]	64/ M	Normal	8.5	None	N	MN	IgG, C3	NA	NA	NA	NA
4	[10]	57/F	NA	NA	None	C3/C4 N CH50↓	Atypical MN	IgG, K, C	Deposits	CBL + Pred	Improve	Improve
5	[10]	75/ M	NA	NA	IgM K, free kappa urine	C1q, C3, C4 ↓	Atypical MN	IgG, IgM, K, L, C	Deposits	CBL	Improve	Improve
6	[12]	55/ M	1.7	NA	None	CH50↓	Atypical MN	IgG, C3, K	Fibrillary deposits	CHOP + CBL	PR	NA
7	[27]	82/F	NA	NA	None	N	MN	NA	Fibrillary deposits	CBL + Pred, CP + Pred, CsA	NR	NR
8	[17]	NA/F	N	6.7	None	NA	MN	NA	Deposits	Flu	Improve	Improve
9	[7]	56/F	3.8	19.2	None	NA	MN	NA	NA	Flu	Improve	Improve
10	[4]	66/F	1.18	5–8	None	N	MN	C3, IgG	Fibrillary deposits	CP + Pred	Temporary improve	Improve
11	[11]	72/ M	0.8	5	None	NA	MN	NA	Deposits	CBL + Pred	PR	Stable
12	[1]	73/ M	3.2	4.3	None	N	Atypical MN	IgG, C3, C1q, K, L	NA	CHOP	Improve	Improve
13	[1]	56/ M	2.4	13	NA	NA	MN + FSGS	IgG, C3, K, L	Deposits	NA	NA	NA
14	[19]	74/ M	1.7	7	None	N	MN	IgG, IgM, C3, C1q, L	NA	Flu	Improve	Improve
15	[11]	59/ M	1.14	NA	None	N	MN	IgG, K	FP effacement, subepithelial deposits	Flu + CP + Ritux	Improve	NA
16	[16]	67/F	1	9.6	None	NA	Atypical MN	IgG, C3, K	Deposits	NA	NA	NA
17	[16]	67/F	2.3	NA	None	NA	Atypical MN	IgG, C3, K	Deposits	NA	NA	NA
18	[16]	64/F	1.4	7.4	Free L urine	NA	MN	IgG, C3, L	Deposits	NA	NA	NA
19	[16]	64/ M	1	5.9	None	NA	MN	IgG, C3, C1q, K	Deposits	NA	NA	NA
20	[16]	63/ M	NA	8	None	NA	Atypical MN	IgG, C3, C1q, L	Deposits	NA	NA	NA
21	[29]	49/F	1.1	2.2	Free K urine	NA	MN + FSGS	NA	Deposits	CBL	Improve	Improve
22	[18]	NA	NA	NA	NA	NA	MN	IgG, K	Deposits	None	NA	NA
23	[18]	NA	NA	NA	NA	NA	MN	IgG, K	Deposits	CP + Flu	CR	NA
24	[18]	NA	NA	NA	IgG, K	NA	MN	K	Deposits	CHOP + CBL	NR	NA
25	[18]	NA	NA	NA	NA	NA	MN	IgG, L	Deposits	CHOP + Flu	CR	NA
	This case	63/ M	1.3	17.9	None	N	MN	IgG, C3	Mesangial deposits	Ibrutinib	CR	Improve

Abbreviations: C, complement; CBL, chlorambucil; Pred, Prednisone; CP, cyclophosphamide, CsA, cyclosporine; FP, foot process; FSGS focal segmental glomerulosclerosis; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; flu fludarabine; ritux, rituximab; L, lambda; K, kappa; CR, complete response; PR, partial response; NR, no response.

The renal biopsy revealed MN which was presumed to be associated with his recent diagnosis of CLL. The characteristic mesangial deposits that are only seen in secondary MN cases strengthened the association [13]. Currently the pathogenesis of MN in CLL remains incompletely understood. Several hypothesis have been proposed to explain the development of immune complex deposition in relation to what is known about CLL and immune dysregulation [1,4,7,8,11,14-20]. One proposed mechanism is directly attributed to leukemic cells acting as effector cells producing autoantibodies that can recognize podocytes expressed proteins, resulting in complement activation and formation of immune complexes [21,1,14]. Another proposed mechanism is associated with the production of nephrotoxic monoclonal immunoglobulins by malignant B lymphocytes triggering complement activation and immune complex formation [7,9,11,18]. Although monoclonal immunoglobulin in serum or urine electrophoresis is generally absent, it is possible that a concentration of immunoglobulin could be below the

lower limit of detection but still induce renal induced toxicity [16]. Less well-understood proposed mechanisms include antibody recognition of oncogenic virus antigens leading to the formation of antigen-antibody complexes(14, 15, 19, 20) and malignancy associated re-expression of fetal antigens triggering immune complex disease [15,20]. Due to the paucity of MN cases in CLL (Table 2), further mechanistic investigation is unlikely; however, dysregulation of the humoral and cellular immune processes caused by leukemic cells is central to the development of MN.

Treatment for CLL has rapidly evolved over the past decade with the development of targeted therapies [22,23]. These novel targeted agents include oral inhibitors of BTK, an enzyme important for B cell receptor (BCR) signaling. Its enzymatic activity is necessary for B cell development and function, including the survival and proliferation of normal and malignant B cells, such as CLL cells. Specifically, BTK signaling inhibition in CLL disrupts CLL cell migration and tissue homing, leukemia cell survival, and proliferation of the CLL cells [23,24]. Based on a series of Phase 3 trials demonstrating improved survival outcomes when compared to chemotherapy-based CLL treatment, ibrutinib became approved for CLL therapy and is increasingly replacing chemotherapy-based CLL treatment. The RESONATE-2 trial, for example, showed superior overall response rate, progression-free survival and overall survival in ibrutinib compared to chlorambucil-treated patients [24].

We assumed our patient was presenting with CLL-associated paraneoplastic MN due to the timing of his presentation with newly diagnosed CLL, and the histopathologic findings suggesting secondary MN on the kidney biopsy. Treatment with ibrutinib likely inhibited the activity of the CLL cell clone, consequently inhibiting the production of any antibody production by CLL cells. Remission of paraneoplastic MN in CLL has been reported with older types of CLL therapy involving alkylating agents and fludarabine, a purine analog [18]. However, to our knowledge, this is the first report of a patient with MN associated CLL with complete renal response to BTK inhibitor therapy. The response to ibrutinib of both, the patient's MN glomerular disease and his leukemia suggests that ibrutinib can function as active therapy in secondary MN in CLL.

Ethics approval and consent to participate

This study was approved by the institutional review board in accordance with the principles of the Declaration of Helsinki. The patient provided written informed consent.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Funding

J.S.L. is supported by National Institutes of Health (K08DK119466 and L30CA274749). This research is also supported by the Division of Internal Medicine Immuno-Oncology Toxicity Award Program of the University of Texas MD Anderson Cancer Center (PI: J.S.L.) and the University Cancer Foundation via the Institutional Research Grant program at the University of Texas MD Anderson Cancer Center (PI: J.S.L.). The University of Texas MD Anderson Cancer Center is supported in part by the National Institutes of Health through Cancer Center Support Grant P30CA016672.

CRediT authorship contribution statement

Conceptualization: JAB. Data curation: AT and JSL. Formal analysis: AT, WFG, and JSL. Methodology: AT, WFG, JSL, and JAB. Project administration: JSL and JAB. Supervision: JSL and JAB. Writing original draft: AT and JSL. Writing review & editing: AT, WFG, JSL, and JAB.

Declaration of Competing Interest

The authors have declared that no conflict of interest exists.

Acknowledgements

We thank the patient for providing permission to report adverse events and for their participation and contribution to research.

References

[1] P.D. Ziakas, S. Giannouli, E. Psimenou, L. Nakopoulou, M. Voulgarelis, Membranous glomerulonephritis in chronic lymphocytic leukemia, Am. J. Hematol. 76 (3) (2004) 271–274.
[2] P. Strati, S.H. Nasr, N. Leung, C.A. Hanson, K.G. Chaffee, S.M. Schwager, et al., Renal complications in chronic lymphocytic leukemia and monoclonal B-cell lymphocytosis: the mayo clinic experience, Haematologica 100 (9) (2015) 1180–1188.
[3] J.A. Burger, Treatment of chronic lymphocytic leukemia, N. Engl. J. Med. 383 (5) (2020) 460–473.
[4] N. Yahata, Y. Kawanishi, S. Okabe, Y. Kimura, T. Okada, M. Otani, et al., Membranous glomerulonephritis with nephrotic syndrome associated with chronic lymphocytic leukemia, Am. J. Nephrol. 20 (5) (2000) 402–407.
[5] M. Hallek, B.D. Cheson, D. Catovsky, F. Caligaris-Cappio, G. Dighiero, H. Döhner, et al., iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL, Blood 131 (25) (2018) 2745–2760.
[6] M.M. Abdel-Raheem, M.G. Jamil, A. Potti, G.G Gross, Fludarabine therapy in chronic lymphocytic leukemia-associated severe nephrotic syndrome, Haematologica 85 (11) (2000) 1224–1225.
[7] F.D. Seney, W.R. Federgreen, H. Stein, M. Kashgarian, A review of nephrotic syndrome associated with chronic lymphocytic leukemia, Arch. Intern. Med. 146 (1) (1986) 137–141.
[8] J. Kowalewska, R.F. Nicosia, K.D. Smith, A. Kats, Alpers CE. Patterns of glomerular injury in kidneys infiltrated by lymphoplasmacytic neoplasms, Hum. Pathol. 42 (6) (2011) 896–903.
[9] G. Touchard, J.L. Preud'homme, P. Aucouturier, C. Giraud, D. Gouet, L. Yver, et al., Nephrotic syndrome associated with chronic lymphocytic leukemia: an immunological and pathological study, Clin. Nephrol. 31 (2) (1989) 107–116.
[10] S. Ahmed, P. Blanco, D.A. MacDonald, Hundemer GL. The case | Nephrotic syndrome in a patient with chronic lymphocytic leukemia, Kidney Int. 99 (3) (2021) 777–778.
[11] B. Moulin, P.M. Ronco, B. Mougenot, A. Francois, J.P. Fillastre, F Mignon, Glomerulonephritis in chronic lymphocytic leukemia and related B-cell lymphomas, Kidney Int. 42 (1) (1992) 127–135.
[12] R. Wanchoo, C. Bernabe Ramirez, J. Barrientos, K.D Jhaveri, Renal involvement in chronic lymphocytic leukemia, Clin. Kidney J. 11 (5) (2018) 670–680.
[13] W. Liu, C. Gao, H. Dai, Y. Zheng, Z. Dong, Y. Gao, et al., Immunological pathogenesis of membranous nephropathy: focus on PLA2R1 and its role, Front. Immunol. 10 (2019) 1809.
[14] P.G. Row, J.S. Cameron, D.R. Turner, D.J. Evans, R.H. White, C.S. Ogg, et al., Membranous nephropathy. Long-term follow-up and association with neoplasia, Q. J. Med. 44 (174) (1975) 207–239.
[15] R.G. Gagliano, J.J. Costanzi, G.A. Beathard, H.E. Sarles, J.D. Bell, The nephrotic syndrome associated with neoplasia: an unusual paraneoplastic syndrome. Report of a case and review of the literature, Am. J. Med. 60 (7) (1976) 1026–1031.
[16] A. Best Rocha, C.P. Larsen, Membranous glomerulopathy with light chain-restricted deposits: a clinicopathological analysis of 28 cases, Kidney Int. Rep. 2 (6) (2017) 1141–1148.
[17] H. Butty, J. Asfoura, F. Cortese, M. Doyle, G Rutecki, Chronic lymphocytic leukemia-associated membranous glomerulopathy: remission with fludarabine, Am. J. Kidney Dis. 33 (2) (1999) E8.
[18] E. Guiard, A. Karras, E. Plaisier, J.P. Duong Van Huyen, F. Fakhouri, J.P. Rougier, et al., Patterns of noncryoglobulinemic glomerulonephritis with monoclonal Ig deposits: correlation with IgG subclass and response to rituximab, Clin. J. Am. Soc. Nephrol. 6 (7) (2011) 1609–1616.
[19] A.R. Rocca, C. Giannakakis, I. Serriello, G. Guido, G. Mosillo, C. Salviani, Fludarabine in chronic lymphocytic leukemia with membranous nephropathy, Ren Fail 35 (2) (2013) 282–285.
[20] J.W. Eagen, Glomerulopathies of neoplasia, Kidney Int 11 (5) (1977) 297–303.
[21] K. Hodgson, G. Ferrer, E. Montserrat, C. Moreno, Chronic lymphocytic leukemia and autoimmunity: a systematic review, Haematologica 96 (5) (2011) 752–761.
[22] C.S. Tam, J.N. Allan, T. Siddiqi, T.J. Kipps, R. Jacobs, S. Opat, et al., Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort, Blood 139 (22) (2022) 3278–3289.
[23] T.D. Shanafelt, X.V. Wang, C.A. Hanson, E.M. Paietta, S. O'Brien, J. Barrientos, et al., Long-term outcomes for ibrutinib-rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial, Blood 140 (2) (2022) 112–120.
[24] M. Bewarder, S. Stilgenbauer, L. Thurner, D. Kaddu-Mulindwa, Current treatment options in CLL, Cancers (Basel). 13 (10) (2021).
[25] S. Cameron, C.S. Ogg, Letter: nephrotic syndrome in chronic lymphatic leukaemia, Br. Med. J. 4 (5937) (1974) 164.

[26] C.A. White, R.O. Dillman, I. Royston, Membranous nephropathy associated with an unusual phenotype of chronic lymphocytic leukemia, Cancer 52 (12) (1983) 2253–2255.
[27] W. Eisterer, U. Neyer, W. Hilbe, G. Diem, C. Ohlschlegel, C. Ludescher, et al., Effect of cyclosporin A in a patient with refractory nephrotic syndrome associated with B chronic lymphocytic leukemia, Nephron 72 (3) (1996) 468–471.
[28] N. Da'as, A. Polliack, Y. Cohen, G. Amir, D. Darmon, Y. Kleinman, et al., Kidney involvement and renal manifestations in non-Hodgkin's lymphoma and lymphocytic leukemia: a retrospective study in 700 patients, Eur. J. Haematol. 67 (3) (2001) 158–164.
[29] H.S. Brodovsky, M.L. Samuels, P.J. Migliore, C.D. Howe, Chronic lymphocytic leukemia, Hodgkin's disease, and the nephrotic syndrome, Arch. Intern. Med. 121 (1) (1968) 71–75.