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Case Report

T-Cell Acute Lymphoblastic Leukemia-associated Membranous Nephropathy in an Adult Patient - A Case Report

László Bitó[1]*, Szabolcs Modok[1], Alexandra Belovai[1], Dóra Bajcsi[1], Sándor Turkevi-Nagy[2], László Krenács[3] and Béla Iványi[2]

[1]Department of Medicine, University of Szeged, Hungary

[2]Department of Pathology, Albert Szent-Györgyi Health Centre, University of Szeged, Hungary

[3]Laboratory of Tumour Pathology and Molecular Diagnostics, Hungary

***Corresponding author**

László Bitó, Department of Medicine, Albert Szent-Györgyi Health Centre, University of Szeged, Szeged, Hungary, Tel: 36703876544

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Abstract

Background: Patients with membranous nephropathy (MN) may have an associated malignancy, commonly solid tumors. Here we present a case of T-cell acute lymphoblastic leukemia (T-ALL) and concurrent MN; the clinical course indicated there was a causal link between the two disorders.

Case presentation: A 58-year-old Caucasian woman was admitted because of weakness, leukocytosis, anemia, thrombocytopenia, symptoms of the nephrotic syndrome, and renal failure. The hematological workup diagnosed Philadelphia chromosome-positive T-ALL. The UKALL60+ protocol then induced the complete remission of leukemia; the renal function returned to normal, and proteinuria almost ceased. A molecular relapse of leukemia was detected in the third month of chemotherapy, followed by the recurrence of the nephrotic syndrome and renal failure. The renal biopsy workup revealed MN stage 1-2, glomerular leukocytosis, and acute tubular injury. The deposits, distributed incomplete globally, were stained brightly for polytypic IgG, IgG1, IgG4, and C3. The staining for PLA2R antigen revealed a segmental distribution and weak positivity in deposits. The IgG2, IgG3, C1q, THSD7A and NELL1 staining were negative. The leukemic lymphoblasts expressed CD10 (CALLA/NEP) immunohistochemically; no change was observed in the CD10 expression of podocytes. An indirect immunofluorescence assay for autoantibodies against PLA2R, THSD7A or NEP revealed an anti-PLA2R titer of 1:40. Despite complex therapy, she remained on hemodialysis and passed.

Conclusions: The remission of heavy proteinuria with successful treatment of leukemia followed by relapse soon after the molecular recurrence of leukemia indicated T-ALL-associated MN. The pathological phenotype was characterized by an incomplete global distribution of IgG1-IgG4 codominant deposits, segmental and weak staining for PLA2R in the deposits, and glomerular leukocytosis. Taking into consideration the low serum anti-PLAR antibody titer, MN was probably mediated by a dual autoimmune response; namely a robust one for a hidden tumor antigen, and a weak one for PLA2R.

ABBREVIATIONS

ANCA: Anti-Neutrophil Cytoplasmic Antibody; BCR-ABL: fusion of the 3' sequences from ABL1 (Abelson) gene to the 5' portion of the BCR (breakpoint cluster region) gene sequences; C3: Complement component 3; C4: Complement component 4, C1q: Complement component 1q; CD10: Cluster of Differentiation 10; dsDNA: double-stranded Deoxyribonucleic Acid; GBM: Glomerular Basement Membrane; EC: Enzyme Commission; eGFR: estimated Glomerular Filtration Rate; HER2: Human Epidermal Growth Factor Receptor 2 ; IgG: Immunoglobulin G; MN: Membranous Nephropathy; NELL1: Neural Epidermal Growth Factor-like 1; NEP: Neutral Endopeptidase; PLA2R: Phospholipase A2 Receptor; RSV: Respiratory Syncytial Virus; pT2N1: postoperative pathologic staging of cancer, the tumor (T) is larger than 20 mm but not larger than 50 mm, N1: metastasis in 1 to 3 axillary lymph nodes; T-ALL: T-cell Acute Lymphoblastic Leukemia; TdT: Terminal deoxynucleotidyl Transferase; THSD7A: Thrombospondin Type-1 Domain Containing 7A; UKALL60+: Study of Older Adults With Acute Lymphoblastic Leukemia in the United Kingdom

INTRODUCTION

Membranous nephropathy (MN), the most frequent cause of the nephrotic syndrome in adults, is characterized by the formation of subepithelial immune deposits along the glomerular basement membrane (GBM). The majority of MN are mediated by autoantibodies against a transmembrane glycoprotein, the M-type phospholipase A2 receptor (PLA2R) expressed on podocytes. IgG4 is the prevailing subclass of anti-PLA2R antibodies, and it is co-localized with the PLA2R antigen within the subepithelial deposits [1]. Other podocyte antigens, such as thrombospondin

type 1 domain-containing 7A (THSD7A) or neural epidermal growth factor-like 1 protein (NELL1) and the corresponding autoantibodies play a pathogenic role in a few cases [2-4]. The target antigen is still unknown in approximately 10% of patients. MN may be present without any underlying disease association termed primary MN, or it may be associated with autoimmune diseases, infections, drug exposure, or malignancy termed secondary MN. The classification of MN into primary and secondary will soon be replaced by a classification based on the antigen detected [5] because the presence of autoantibodies is not always in accord with the definitions of primary MN and secondary MN.

The topic of the present communication is cancer-related MN. The prevalence of cancer in patients with MN lies between 6% and 22% [6,7]. Malignancy is commonly found within a year of the diagnosis of MN, and most cases are discovered before or at the time of the diagnosis of renal disease [8]. The malignancies most frequently associated with MN are solid tumors, primarily carcinomas of the lungs, prostate, gastrointestinal tract, breast, kidney, urinary bladder, or the skin [7-9]. Pathologically, an increased number of inflammatory cells in glomerular capillaries [9] and the predominance of IgG1 and IgG2 subclasses in deposits markedly increase the chance of malignancy in patients with MN [10]. In 1999, P. Ronco proposed three criteria for diagnosing malignancy-associated, truly paraneoplastic MN: first, the treatment-induced remission of cancer is followed by the remission of the nephrotic syndrome; second, the recurrence of the neoplasia is accompanied by a renal relapse; and third, tumor antigens and antitumor antibodies are detected within the subepithelial deposits [6]. In theory, the tumor antigen may be identical to an endogenous podocyte antigen, and antibodies generated against the tumor antigen form *in situ* immune complexes along the glomerular capillaries. Alternatively, shed tumor antigens may form circulating immune complexes that become trapped in the wall of glomerular capillaries, or tumor antigens, based on size and charge, plant themselves in a subepithelial location where they react with circulating antibodies at a later stage [11]. Clinically, the tumor antigen commonly remains undiscovered during the management of the patients, and the precise pathophysiologic link between cancer and MN remains unknown.

MN is infrequently observed in hematologic malignancies. If it occurs, then in decreasing order of frequency, chronic lymphocytic leukemia, non-Hodgkin lymphoma, or Hodgkin lymphoma is in the background [9, 12, 13]. Cases of concurrent MN and acute leukemia are exceptional [14,15]. Here, we present an adult patient with T-cell acute lymphoblastic leukemia (T-ALL) and concurrent MN, in whom the clinicopathologic features indicated a causal association between the two diseases. To the best of our knowledge, no similar case has been published in the English medical literature in the past two decades.

CASE PRESENTATION

The clinical course of the disease is summarized in Figure 1. September XXX year: A 58-year-old Caucasian woman was admitted to the Emergency Department of the Albert Szent-Györgyi Health Centre, University of Szeged because of generalized weakness, myalgias, and symptoms of sinusitis. 14 months earlier, an estrogen receptor and a progesterone receptor positive, and HER2 negative invasive breast carcinoma of no special type was diagnosed. Resection of the tumor and dissection of the axillary sentinel lymph node was performed (stage pT2N1), followed by local radiotherapy and long-term administration of aromatase inhibitor anastrozole; afterwards she was on anti-estrogenic treatment until her death. The renal functional parameters checked before mammography did not indicate any alarming chronic renal disease. The oncological follow-up in the sixth month did not reveal any abnormalities in the blood picture and renal function, and in the tenth month there were no signs of any recurrence or metastatic disease.

On admission, the laboratory evaluation found alterations suggestive of acute leukemia, *i.e.,* leukocytosis (62.26 G/L), anemia (hemoglobin 92 g/L, hematocrit 30%), and thrombocytopenia (129 G/L). Her renal function was markedly impaired (serum creatinine 339 μmol/L, eGFR 12 ml/min/body surface area), and severe proteinuria, mild hematuria, and hypoalbuminemia (26 g/L) were detected. Abdominal ultrasonography disclosed normal-sized kidneys, normal echogenicity of renal parenchyma, and mild splenomegaly. An evaluation of the needle biopsy of the iliac crest bone demonstrated 100% infiltration of the bone marrow spaces by CD3-positive and TdT-positive leukemic blasts. The results of the flow cytometry immunophenotyping and cytogenetic analysis classified the disease as Philadelphia chromosome-positive T-ALL. Computed tomography scans excluded the extramedullary leukemic infiltration of organs, and leukemic blasts were not detected in the cerebrospinal fluid sample obtained by a lumbar puncture.

The induction phase 1 of UKALL60+ protocol (dexamethasone, idarubicin, vincristine, intrathecal methotrexate, and 400 mg/day imatinib) decreased the leukocyte count to 1.6 G/L. Days after the initiation of the protocol, the eGFR value had risen to 72 ml/min/body surface area, and the serum creatinine value had decreased to 90 μmol/L. The follow-up biopsy of the bone marrow disclosed complete remission of leukemia. Soon after the administration of induction phase 2, the renal function returned to normal. A biopsy evaluation of the bone marrow did not detect any residual disease.

January: Before the second course of high-dose methotrexate infusion, there was a slight worsening of some of the renal functional parameters (creatinine clearance 55 ml/min, proteinuria 2+, 6-8 red blood cells in the urinary sediment). A bone marrow biopsy revealed a regeneration-induced moderate degree of panhyperplasia; but leukemic residual disease was not detected immunomorphologically. The interphase fluorescence in situ hybridization for the BCR-ABL translocation on peripheral blood white cells was also negative. However, an investigation of bone marrow-derived total RNA with real-time quantitative RT-PCR of BCR-ABL1 RNA revealed a 3.8% BCR-ABL1 fusion gene expression relative to ABL gene expression, indicating molecular

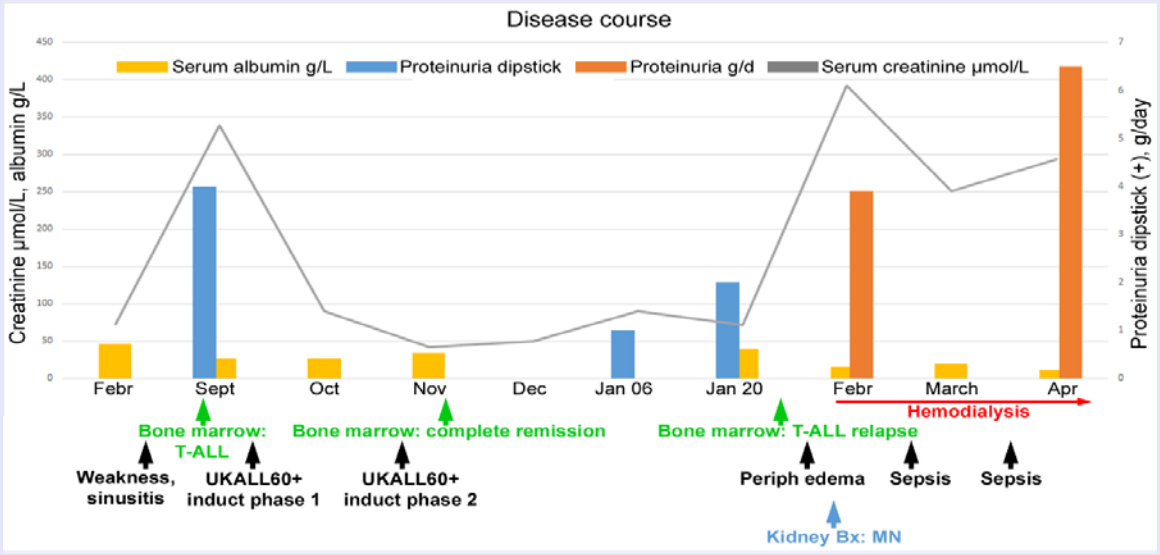

Figure 1 The tight chronological correlation between the bone marrow alterations of T-ALL and renal symptoms.
Abbreviations: Bx: biopsy, MN: membranous nephropathy, Periph edema: peripheral edema, UKALL60+ induct phase 1: induction phase 1 of the chemotherapeutic protocol to treat older adults with acute lymphoblastic leukemia in the United Kingdom, UKALL60+ induct phase 2: induction phase 2 of the chemotherapeutic protocol to treat older adults with acute lymphoblastic leukemia in the United Kingdom, T-ALL: T-cell acute lymphoblastic leukemia.

minimal residual disease. The imatinib was due to be replaced with dasatinib, but the intake of drug was arbitrarily stopped by the patient.

February: Flow cytometry did not reveal any immunologic residual disease. In the third week of the month, fully blown nephrotic syndrome, hematuria, and acute renal failure evolved (eGFR 10 ml/min/body surface area, 100-150 ml of daily urine), necessitating hemodialysis 3 times per week.

Abdominal ultrasonography revealed a 132x48 mm-sized right kidney, and a 137x58-sized left kidney, and the renal parenchyma was hyperechogenic. An ultrasound-guided percutaneous renal biopsy and extended evaluation of the patient's serum were performed, including serum protein and immunofixation electrophoresis, an investigation of the complement system, and search for antibodies to nuclear components (ANA), dsDNA, ANCA, and to podocyte antigens PLA2R and THSD7A. Here, monoclonal immunoglobulin component was not detected. A decreased level of total complement activity, classical pathway (33 CH50/ml, ref: 48-103); total complement activity, alternative pathway (35%, ref: 70-125%); complement C3 (0.33 g/L, ref: 0.9-1.8); complement C4 (0 g/L, ref: 0.15-0.55), and markedly activated terminal complement complex (SC5b-9: 1381 ng/mL, ref: 110-252) were found. The level of factor H antigen was low (62 mg/L, ref: 250-880). The level of C3-nephritic factor, and the ADAMTS13 metalloprotease activity were normal. The autoimmune panel was negative. The anti-PLA2R titer was mildly elevated (indirect immunofluorescence assay, 1:40); and the anti-THSD7A antibody evaluation was negative.

March and April: A couple of days after the biopsy procedure, bronchopneumonia and sepsis appeared. Microbiological tests confirmed RSV and Klebsiella pneumoniae infection. The targeted antibiotic treatment eliminated the sepsis, and she was discharged. Regular hemodialysis treatment was continued from home. After two and a half weeks of being at home, she was readmitted because of recurrent sepsis. After a short observation, she died due to multiple organ failure. An autopsy was not performed (Figure 2 a-k).

The biopsy sample was evaluated with light microscopy of the formalin-fixed and paraffin-embedded sample and the frozen sample (hematoxylin-eosin, periodic acid-Schiff, methenamine silver, trichrome, and Oil Red O), direct immunofluorescence (IgG, IgG1-4, IgA, IgM, kappa, lambda, PLA2R, C3, C1q, and fibrinogen), and electron microscopy. The intensity of immune reactivity was assessed at low-power magnification (objective lens 10x), expressed semiquantitatively with a score of 0 to 3+. THSD7A and CD10 immunostaining were performed on paraffin-embedded tissue sections. One case of THSD7A-associated MN, four cases of membranous lupus nephritis, four cases of PLA2R-associated primary MN, and two cases of minimal change nephropathy served as controls.

Light microscopically, fifteen patent and two globally sclerosed glomeruli were observed in the paraffin sections, and six patent and one globally sclerosed glomeruli in the frozen sections. The GBM appeared normal. The cytoplasm of podocytes frequently contained proteinaceous droplets. Leukocytes had accumulated intracapillary (Figure 2a); and their median number per glomerulus was 4 (range: 1-15). 8 and 15 leukocytes (monocytes, neutrophils, and lymphocytes) were noted in

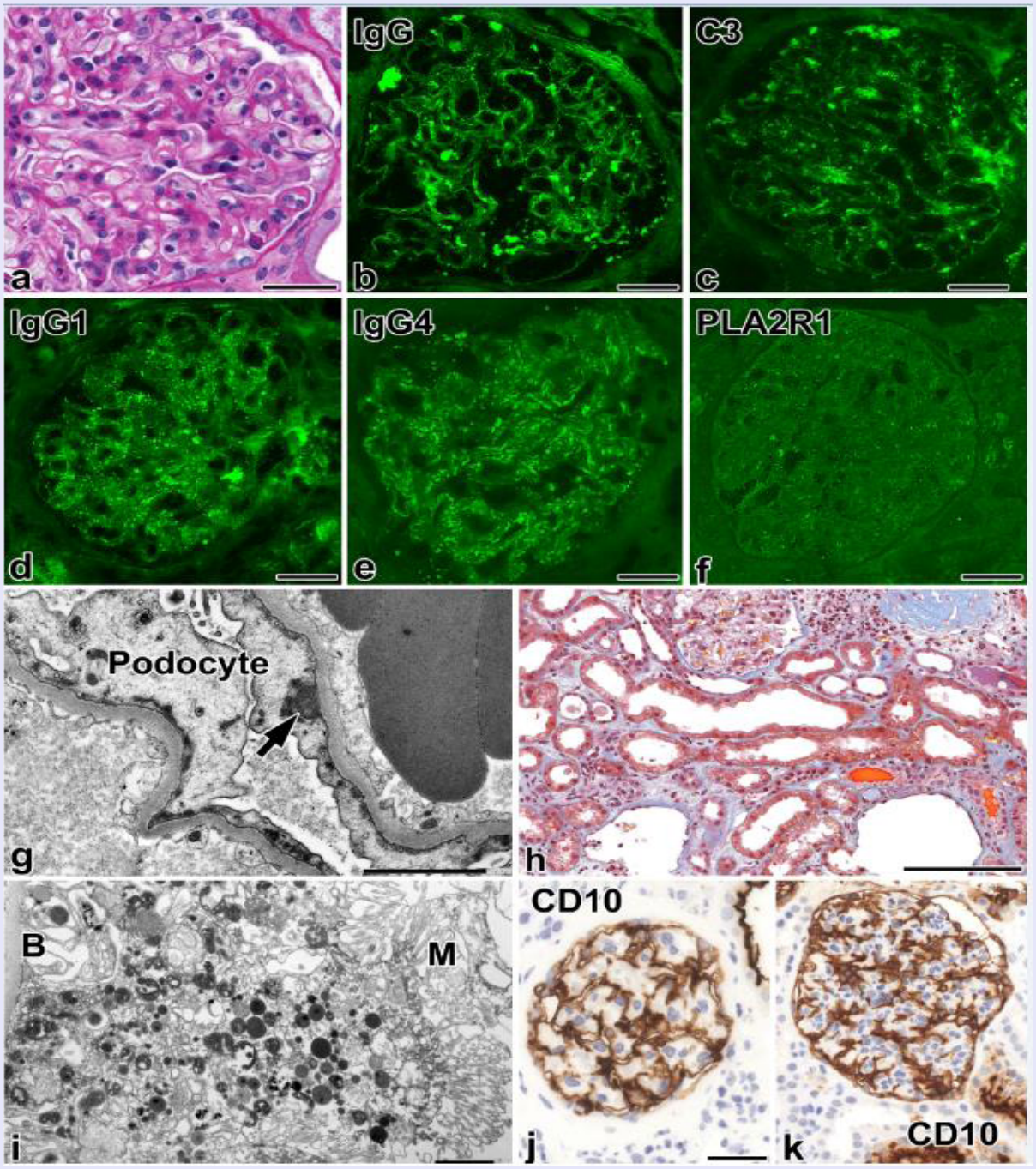

Figure 2 Light microscopical, immunofluorescent and electron microscopical features of T-ALL-associated membranous nephropathy. The bar represents 50 μm in histological and immunofluorescence micrographs, and 2 μm in electron microscopical micrographs.

a. Glomerular leukocytosis. At least eight intracapillary leukocytes in one of the glomerular profiles. Periodic acid-Schiff, x40.

b. Incomplete global immune deposits along the glomerular capillary loops. Several loops are devoid of deposits. IgG, x40.

c. The deposits were C3-positive. C3, x40.

d to f. The staining intensity and distribution of immune deposits: IgG1 (2+, incomplete global), IgG4 (2+, incomplete global), and PLA2R (1+, segmental). x40.

g. Just one subepithelial electron dense deposit (arrow) can be seen in the two capillary profiles. Spikes of the glomerular basement membrane are not present in this visual field. The foot processes are diffusely effaced. x8000.

h. Features of acute tubular injury in proximal tubules: the lumina are dilated, the walls are thinned, and the brush border is thinned or focally absent. Trichrome, x20

i. Ultrastructural features of proximal tubular cell injury: the cytoplasm is vacuolated, the mitochondria display electron dense configuration, and there is a focal loss of microvilli (M). B: the tubular basement membrane. X8000.

j and k. No difference in the expression of CD10 by podocytes in the index case (j) and the case of minimal change nephropathy (k). x40.

two glomeruli. One to two small intracapillary thrombi were observed in two glomeruli. Segmental mesangial hypercellularity (3 nuclei/area) was present in two glomeruli. Lipid droplets had accumulated in podocytes and tubular cells. The proximal tubules displayed focal dilation, thinning or focal loss of microvilli; necrobiotic cells were seen occasionally in the lumina of distal tubules (Figure 2h). Interstitial infiltrates not exceeding 15% of the cortical interstitial area were seen mainly along the proximal straight tubules. The infiltrates were composed of mononuclears, lymphocytes, and a smaller number of plasma cells, and on occasion, eosinophilic granulocytes. Mild mononuclear tubulitis (3 to 5 cells/tubular profile) accompanied the infiltrates. Viral inclusions in tubules or monotonous leukemic lymphoblastic interstitial infiltrates were not observed. Interstitial fibrosis and tubular atrophy affecting 15% of the cortex completed the renal changes. The small arteries and arterioles appeared to be normal. A calculation of the total renal chronicity score [16] gave a value of 3.

Immunofluorescence microscopy (Figure 2b-f), revealed incomplete global fine granular staining along the glomerular capillaries with IgG, kappa, lambda, IgG1, IgG4, and C3 (intensity: 2+, respectively), and segmental and weak (1+) staining of PLA2R antigen in the deposits. The staining for IgG2, IgG3, C1q, and THSD7A was negative. There was a fibrinogen-positive thrombus in one glomerular capillary.

One glomerulus was evaluated electron microscopically. The podocyte foot processes were diffusely effaced. Subepithelial, homogeneously dense deposits of varying size and distribution were observed in some capillary loops; and several loops were devoid of deposits (Figure g). Fine GBM projections ("spikes") noted next to the deposits on occasion and the case was classified as MN, stage 1-2. Subendothelial or mesangial deposits were not encountered. The proximal tubular cells focally showed a varying degree of injury, including loss of the microvilli, cytoplasmic vacuolation, and dense widening of the mitochondrial cristae (Figure 2i). The swelling of mitochondria with amorphous flocculent densities and ruptures of mitochondrial membrane were noted focally.

The findings led to the biopsy diagnosis of MN, and acute tubular injury. The mild mononuclear tubulointerstitial nephritis present predominantly in medullary rays was probably related to the massive proteinuria.

Investigations after the renal biopsy procedure

Leukemic lymphoblasts in T-ALL occasionally express CD10 antigen (also called common lymphoblastic leukemia antigen). CD10 is the enzymatically active form of neutral endopeptidase (NEP, EC 3.4.24.11) and it is naturally expressed at the sole of podocyte foot processes [2]. We assumed that if the leukemic cells had expressed the CD10 molecule, autoantibodies to NEP could have been generated, and it could have led to MN. On the CD10 immunostaining performed retrospectively, a significant number of leukemic lymphoblasts did indeed display strong positivity. Regarding the expression of CD10 in podocytes, it was strong and global, and did not differ in the index case (Figure 2j), control cases of MN and minimal change nephropathy (Figure 2k). P. Ronco's lab (Paris, France) kindly evaluated the stored serum sample of our patient for autoantibodies to NEP by indirect immunofluorescence (substrate: mouse kidney) and stained the formol-fixed biopsy sample for NELL-1 antigen. Both evaluations gave negative results.

DISCUSSION

The remission of heavy proteinuria with treatment of T-ALL with the UKALL60+ protocol, and then the relapse of heavy proteinuria soon after the molecular recurrence of T-ALL fulfilled the proposed clinical criteria of malignancy-associated MN [6]. The pathologic phenotype of T-ALL-associated MN was incomplete global distribution of deposits staining brightly with IgG1 and IgG4 molecule, segmental and weak staining of PLA2R antigen in the deposits, glomerular leukocytosis, and focal-segmental mesangial cell proliferation. Electron microscopically, the deposits were subepithelially located and they were distributed unevenly, sparing complete capillary loops. Segmental GBM spikes classified the case as early (stage 1-2) MN. The glomerular leukocytosis, albeit mild, was distinct. The number of inflammatory cells per glomerulus focally reached or exceeded 8, the proposed threshold of glomerulitis suggesting cancer-related MN [9].

Patients with NELL1-associated MN or THSD7A-associated MN quite frequently have a coexisting malignancy, and in some of these cases, the tumor cells expressed the relevant podocyte antigen, and anti-NELL1 or anti-THSD7A antibodies were detected in the sera of patients, indicating a causal relationship between the cancer and the glomerulopathy. The predominant IgG subclass in deposits was IgG4 in THSD7A-associated MN [17], and IgG1 in NELL1-associated MN [4]. In our patient, the negative assay for autoantibodies to THSD7A, along with the negativity of THSD7A immunostaining in the deposits excluded THSD7A-associated MN. The negativity of staining for NELL1 antigen in immune deposits did not support NELL1-associated MN.

Malignancy-associated MN is generally regarded as PLA2R-negative. However, there are publications on MN patients who had cancer and serological positivity for anti-PLA2R antibodies. In a study from Italy, investigating the diagnostic specificity of PLA2R antibodies in differentiating primary MN from secondary MN, 7 patients with MN and anti-PLA2R positivity had a solid cancer [18]. In a study from China investigating the presence of antibodies against PLA2R or THSD7A in 692 MN patients, anti-PLA2R antibodies were detected in 18 MN patients with cancer [19]. The problem with interpreting publications on malignancy-associated MN retrospectively is the lack of a generally agreed definition of the entity. The selection criteria for enrolling patients into cohorts labelled as "MN associated with cancer" or "MN in patients with cancer" are sometimes not mentioned, and prior to assigning patients to the study group of "malignancy-associated MN", it is not always checked whether the patient had primary PLA2R-associated MN with coincidental malignancy, or

the malignancy induced the formation of PLA2R autoantibodies that resulted in MN [20]. A recent study on the clinical phenotype of patients with MN according to the target antigen [5] addressed this issue. Accordingly, solid cancer was diagnosed in 22 of 270 patients, with 11 being PLA2R-positive. No patient with PLA2R-associated MN went into remission with malignancy treatment alone, suggesting a coincidence rather a causal relation.

In contrast, the heavy proteinuria in our patient displayed a close relationship with the presence, chemotherapy-induced remission, and then molecular relapse of T-ALL, hence the glomerular disorder was a paraneoplastic phenomenon. The PLA2R-positivity of deposits was segmentally distributed, and the intensity of PLA2R-staining was weak. Since a low titer of autoantibodies to PLA2R was detected serologically, the glomerulopathy appeared to be PLA2R-associated to some degree. The striking difference between the extent of distribution and staining intensity of IgG1 and IgG4 compared to that of PLA2R suggests that the glomerulopathy was mediated by a dual autoimmune response, namely an intense one for an antigen that remained undetected, and a weak one for PLA2R. A dual production of PLA2R and THSD7A autoantibodies has been demonstrated in some rare instances of primary MN [19,21]. The evaluation of serum complement components revealed deficient C4, low C3, low classic and alternative pathway activity, a markedly activated terminal pathway, and a critically low level of factor H antigen (regulator of the alternative pathway), indicating the activation and consumption of the complement system. Since the IgG1-IgG4 codominant deposits were associated only with C3 positivity (the C1q-staining was negative), the immunopathological findings did not entirely mirror the changes in the complement system in the blood. In most cases of primary MN, the complement activity occurs *via* the activation of the mannose-binding lectin pathway or through the dysregulation of the alternative pathway [22, 23].

The CD10 expression of leukemic lymphoblasts led us to think that the glomerulopathy was mediated somehow by autoantibodies to NEP, even though classic NEP-associated MN has a different pathophysiologic background. With this entity, infants with MN are born to mothers genetically deficient in NEP. Circulating maternal anti-NEP IgG1 antibodies cross the placenta, bind to epitopes of NEP of fetal glomeruli, and induce alloimmune antenatal MN in the fetus [2]. In our patient, the staining characteristics of CD10 in podocytes was essentially the same as in the controls, and identical to that seen in non-diseased mature glomeruli [24]. The expression pattern did not suggest the participation of NEP in the evolution of MN. And the serological evaluation excluded the presence of circulating anti-NEP autoantibodies, so our idea about the mechanism of CD10-positive leukemia-induced MN had to be discarded.

In summary, we presented the unique case of a 58-year-old woman with Philadelphia chromosome-positive and CD10-positive T-ALL and concurrent MN. The temporary relationship between the hematologic disorder and the nephrotic syndrome indicated malignancy-associated MN. The paraneoplastic MN was not driven by NELL1, THSD7A, or NEP antigens/autoantibodies. It was most likely mediated by a dual autoimmune response, a vigorous one for an antigen that remained undetected, and a weak one for PLA2R.

DECLARATIONS

Ethics approval and consent to participate

All investigations and procedures were carried out in accordance with the ethical standards of the Institutional committee and the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for all investigative procedures detailed in the text. No ethics approval was required for this case presentation.

Consent for publication

Since the patient is deceased, written consent was obtained from the patient's family for the publication of this case report and the accompanying images. The consent form from the patient's family can be made available to the Editor if needed.

Availability of data and materials

The data referred to from previous publications are cited in the text.

Competing interest

The authors declare that there is no conflict of interest.

Authors' contributions

LB wrote the draft version of the manuscript. LB (nephrologist) and SzM (hematologist) managed the clinical evaluation and the treatment of the patient. AB retrieved and summarized the data of medical records of the patient. The evaluation of the bone marrow biopsy samples and CD10 immunostaining of leukemic cells were performed by LK. DB (senior nephrologist) gave advice on the clinical evaluation and management of the kidney disease. The photodocumentation of the renal biopsy sample was performed by ST-N (junior pathologist). BI (senior pathologist) diagnosed the case, conducted collaborative studies, and critically reviewed the manuscript. All authors read and approved the final manuscript.

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