

# Natural Killer Cell Large Granular Lymphocyte Leukemia-Induced Glomerulonephritis



Pierre Isnard<sup>1,2</sup>, Charel Linster<sup>3</sup>, Julie Bruneau<sup>1,2</sup>, Eric Thervet<sup>2,3</sup>, Jean-Paul Duong Van Huyen<sup>1,2</sup>, Julien Rossignol<sup>4</sup>, Alexandre Karras<sup>2,3</sup>, Sophie Chauvet<sup>2,3</sup> and Marion Rabant<sup>1,2</sup>

<sup>1</sup>Department of Pathology, Necker-Enfants Malades Hospital, APHP, Paris, France; <sup>2</sup>Université de Paris, Paris, France; <sup>3</sup>Department of Nephrology, Européen Georges Pompidou Hospital, APHP, Paris, France; and <sup>4</sup>Department of Hematology, Gustave Roussy Cancer Campus, Paris, France

**Correspondence:** Pierre Isnard, Department of Pathology, Necker-Enfants Malades Hospital, APHP, 149 rue de Sèvres, 75015, Paris, France. E-mail: [pierre.isnard@aphp.fr](mailto:pierre.isnard@aphp.fr)

Received 28 November 2020; revised 13 January 2021; accepted 18 January 2021; published online 1 February 2021

*Kidney Int Rep* (2021) 6, 1174–1177; <https://doi.org/10.1016/j.ekir.2021.01.024>

© 2021 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

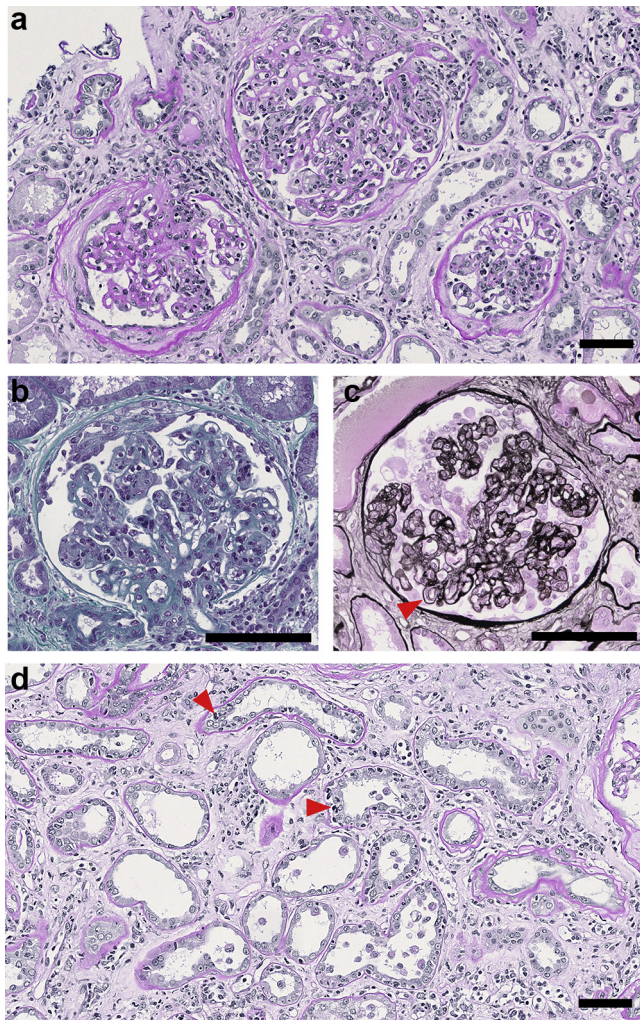
## INTRODUCTION

Large granular lymphocyte (LGL) leukemia are mature T cell and natural killer (NK) cell neoplasms that exhibit a chronic and clonal expansion of large granular lymphocytes in the peripheral blood. About one-third of patients are asymptomatic with an indolent clinical course. Clinicobiologic features are mainly characterized by cytopenias, splenomegaly, and by the frequent occurrence of various autoimmune diseases. Renal manifestations occurring in patients with LGL leukemia are rare and poorly described. They mainly involve indirect kidney damage related to dysimmune conditions, such as cryoglobulinemia-induced glomerulonephritis.<sup>1</sup> To our knowledge, this case is the first report of a glomerulonephritis directly induced by circulating LGL from a NK cell lineage.

## CASE PRESENTATION

A 78-year-old man was referred to our nephrology department for renal impairment and proteinuria. His medical history consisted of non-insulin-dependent type 2 diabetes with mild retinopathy and nephropathy associating microalbuminuria and normal kidney function, controlled hypertension, and dyslipidemia. He had no family history of hematologic, immune, or kidney disorders. The patient was diagnosed with an expanded clonal NK cell LGL population 3 years earlier, with a lymphocyte count of 16,000 cells/mm<sup>3</sup>, the presence of large lymphocytes containing typical azurophilic granules on blood smear, and flow

cytometry analysis showing a CD2<sup>+</sup>/CD3<sup>-</sup>/CD4<sup>-</sup>/CD8<sup>-</sup>/CD56<sup>+</sup>/CD16<sup>+</sup> phenotype. Because of the indolent evolution of this NK cell lymphoproliferation, therapeutic abstention was decided with a biologic follow-up every 6 months. Upon admission, the results of the physical examination were unremarkable, but laboratory investigations revealed rapidly progressive renal failure with increased serum creatinine (220 μmol/l vs. 170 μmol/l 6 months earlier and 80 μmol/l 1 year before the current admission to the renal unit). The urinary protein-to-creatinine ratio was 2 g/g and urinalysis revealed microscopic hematuria at 420 cells/mm<sup>3</sup> together with sterile leukocyturia at 100 cells/mm<sup>3</sup>. Antinuclear antibodies, antineutrophilic cytoplasmic antibodies, and cryoglobulinemia were negative. Complement level and serum proteins electrophoresis were normal. Tests for HIV and hepatitis B and C viruses were negative. A hematologic analysis revealed persistent leukocytosis at 16,400 cells/mm<sup>3</sup> with mild anemia at 10.5 g/dl, and normal neutrophil and platelet counts. Renal ultrasound and a computed tomography scan were performed upon admission and showed kidneys of preserved size and shape with a kidney length pole to pole of 110 mm on both the right and left kidneys. A kidney biopsy specimen was obtained for light microscopy and immunofluorescence analysis. The histologic analysis revealed diffuse glomerular lesions with mainly global endocapillary proliferation with marked predominance of mononuclear circulating cells (Figures 1a and 1b). The mesangial axes were discreetly thickened without



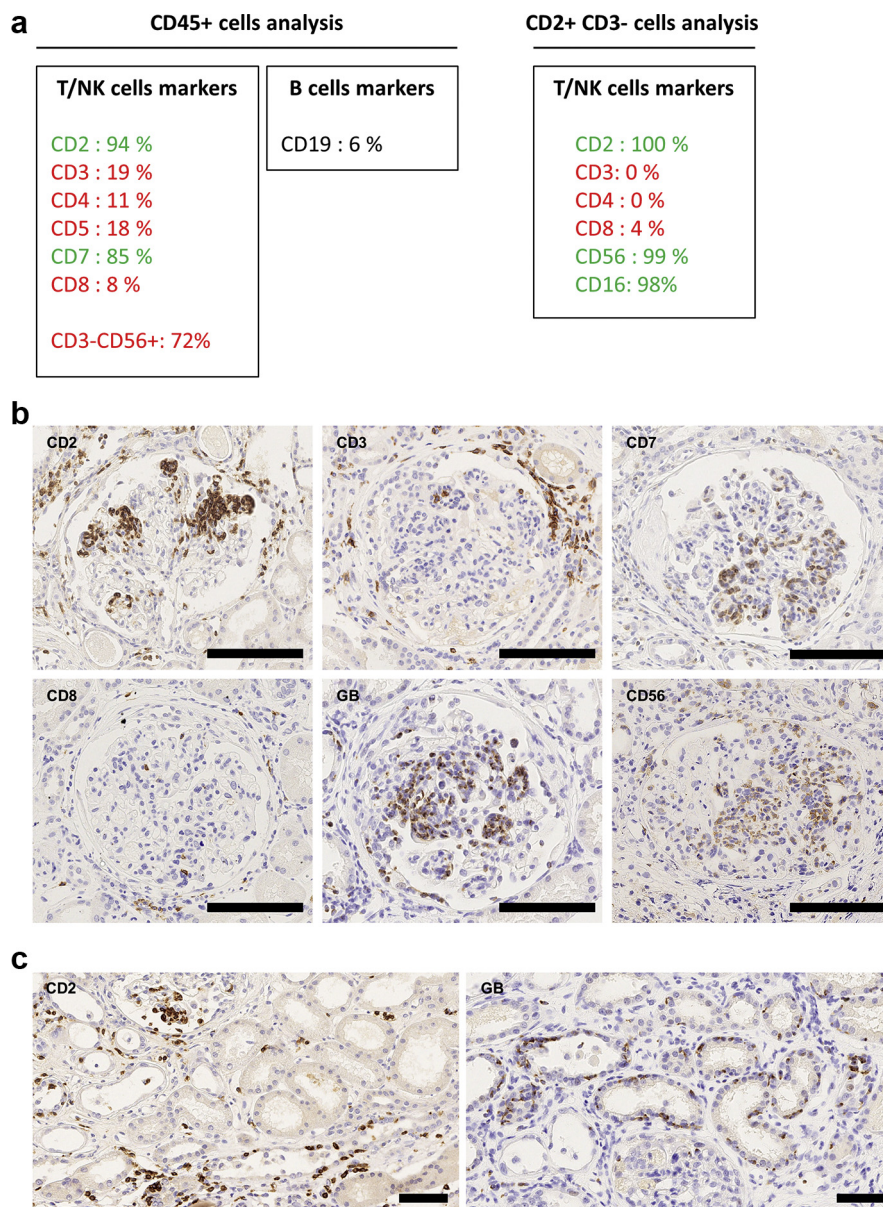
**Figure 1.** Light microscopy and immunofluorescence analysis. (a) Light microscopy using periodic acid–Schiff staining showing diffuse glomerular lesions with mainly global endocapillary proliferation composed of mononuclear circulating cells and interstitial edema with acute tubular necrosis lesions within the tubulointerstitial compartment (original magnification  $\times 200$ ). (b) Light microscopy using Masson Trichrome staining showing global endocapillary proliferation composed of mononuclear circulating cells (original magnification  $\times 400$ ). (c) Light microscopy using silver staining showing rare glomerular basement membrane double contours (red arrow; original magnification  $\times 400$ ). (d) Light microscopy using periodic acid–Schiff staining showing acute tubular necrosis with numerous tubulitis lesions (red arrow; original magnification  $\times 200$ ). Scale bar = 100  $\mu\text{m}$ .

cell proliferation and the glomerular basement membranes rarely showed a duplication appearance on silver staining without clear subendothelial deposits (Figure 1c). The tubulointerstitial compartment revealed interstitial edema with mononuclear cells infiltration, together with acute tubular necrosis lesions (Figures 1a and 1d). Moreover, numerous tubulitis lesions were seen (Figure 1d). Immunofluorescence analysis on glomeruli was negative for immunoglobulin A, immunoglobulin G, C1q, and fibrin staining. However, segmental and parietal immunoglobulin M (IgM),

kappa, lambda, and C3 deposits were found on segmental glomerulosclerotic lesions. No renal amyloidosis was observed. According to the flow cytometry immunophenotyping of the patient's NK cell lymphocytosis, immunohistochemistry (IHC) targeting CD2, CD3, CD4, CD7, CD8, granzyme B, and CD56 was performed on the kidney biopsy specimen (Figures 2a and 2b). Strikingly, IHC confirmed that the glomerular endocapillary infiltrating cells shared the same phenotype as the LGL NK cells (Figure 2b), suggesting that the circulating tumor cells were directly responsible for the endocapillary glomerulonephritis lesions. In addition, IHC also revealed that the inflammatory cells in the tubular wall responsible of tubulitis lesions also derived from the LGL NK cells (Figure 2c).

## DISCUSSION

LGL leukemia are rare mature T cell and NK cell neoplasms. According to the 2016 World Health Organization classification, there are 3 subtypes of LGL leukemia: chronic T cell leukemia (85%), NK cell lymphocytosis ( $<10\%$ ), and aggressive NK cell leukemia ( $<5\%$ ).<sup>2</sup> The first 2 entities are chronic and indolent diseases characterized by cytopenias and autoimmune conditions; the latter is a more aggressive neoplasm with a poor outcome. LGL leukemia principally affects elderly people with a median age of 60 years and clinical manifestations are mainly related to neutropenia-induced recurrent infections. Among autoimmune diseases associated with LGL leukemia, rheumatoid arthritis is the most common, occurring in  $\leq 20\%$  of patients.<sup>1</sup> In our patient, the combination of lymphocytosis (16,000 cells/ $\text{mm}^3$ ), the presence of large lymphocytes containing typical azurophilic granules on blood smear, and flow cytometry analysis showing a  $\text{CD3}^-/\text{CD8}^-/\text{CD16}^+/\text{CD56}^+$  phenotype led to the diagnosis of NK LGL leukemia. Renal manifestations occurring in LGL leukemia are rare and poorly described and mainly involve indirect kidney damage related to dysimmune conditions, such as renal amyloidosis.<sup>3</sup> Of interest, Audemard *et al.*<sup>4</sup> reported a series of 11 patients displaying LGL leukemia associated with vasculitis with 3 T cell LGL leukemia (28%) showing histopathologic evidence of membranoproliferative/endocapillary glomerulonephritis related to mixed type 2 cryoglobulinemia and the presence of a monoclonal IgM kappa.<sup>4</sup> Unfortunately, no specific kidney histopathologic findings nor immunophenotyping results were reported. In our patient, the detection of IgM and C3 deposition by immunofluorescence analysis may suggest a diagnosis of cryoglobulinemia. However, no mesangial cell proliferation nor subendothelial deposits were seen and



**Figure 2.** Flow cytometry and immunohistochemistry analysis. (a) Flow cytometry analysis on a blood sample with CD45<sup>+</sup> cells gate analysis and CD2<sup>+</sup>/CD3<sup>-</sup> gate analysis showing a CD2<sup>+</sup>/CD3<sup>-</sup>/CD4<sup>-</sup>/CD5<sup>+</sup>/CD7<sup>+</sup>/CD8<sup>-</sup>/CD56<sup>+</sup> phenotype. Green: positive marker; red: negative marker. (b) Immunohistochemistry analysis on a kidney biopsy specimen targeting CD2, CD3, CD7, CD8, granzyme B, and CD56 showing a CD2<sup>+</sup>/CD3<sup>-</sup>/CD7<sup>+</sup>/CD8<sup>-</sup>/CD56<sup>+</sup>/granzyme B<sup>+</sup> phenotype of the infiltrating endocapillary glomerular cells (original magnification  $\times 400$ ). (c) Immunohistochemistry analysis on tubulointerstitial compartment targeting CD2 and granzyme B showing CD2<sup>+</sup>/granzyme B<sup>+</sup> cells within tubular epithelium (original magnification  $\times 200$ ). Scale bar = 100  $\mu$ m.

we failed to detect any cryoglobulin in patient's blood samples. Moreover, the IgM and C3 immunofluorescent deposits were segmental and focal, more probably reflecting the fibrous segmental lesions. On the other hand, IHC staining confirmed in our patient that the glomerular endocapillary infiltrating cells shared the same phenotype as LGL NK cells (CD2<sup>+</sup>/CD3<sup>-</sup>/CD7<sup>+</sup>/CD8<sup>-</sup>/CD56<sup>+</sup>/granzyme B<sup>+</sup>). In the absence of electronic microscopy, we were not able to formally exclude early diabetic kidney lesions regarding the patient's medical history of type 2 diabetes with microalbuminuria. Moreover, we could not exclude

membranoproliferative glomerulonephritis with masked monotypic immunoglobulin deposits. However, in this rare condition, most patients (14/16) have paraprotein on serum immunofixation, which was not present in our patient.<sup>5</sup> Of interest, renal B cell lymphoma involvement could also rarely present as an endocapillary glomerulonephritis with glomerular capillaries being occluded by intravascular lymphoma cells.<sup>6</sup> Nevertheless, interstitial topography is observed in most of the kidney biopsy specimens.<sup>7</sup> Of note, Christopoulos *et al.*<sup>8</sup> reported a 65-year-old patient with acute renal failure the presence of T cell large

granular lymphocytes (CD3<sup>+</sup>/CD8<sup>+</sup>/CD56<sup>-</sup>/CD57<sup>+</sup>) within the renal interstitium without glomerular involvement nor tubular involvement. In our case, IHC analysis also revealed that the tubulitis lesions were related to the leukemic NK cells.

## CONCLUSION

To our knowledge, this current case is the first report of a direct glomerular detection by IHC of tumor lymphoid cells from LGL leukemia in a clinical and biologic context of glomerulonephritis. This report could also alert clinicians of this rare connection between LGL leukemia and endocapillary glomerulonephritis, which should prompt discussion of extensive lymphocyte immunophenotyping by IHC. Despite the indolent course of most cases of LGL leukemia that do not require a specific treatment, clinicians should be aware of this rare association that could lead to a clone-directed therapy that may improve renal outcome (Table 1).

**Table 1.** Teaching points

Renal manifestations occurring in large granular lymphocyte leukemia are rare and mainly involve indirect kidney damage, such as cryoglobulinemia.
First report of a direct glomerular detection by immunohistochemistry of tumor lymphoid cells from large granular lymphocyte leukemia in a clinical and biological context of glomerulonephritis.
Immunohistochemistry analysis also revealed that the leukemic natural killer cells were responsible for the tubulitis lesions observed on the kidney biopsy specimen.
This rare connection between large granular lymphocyte leukemia and endocapillary glomerulonephritis, should prompt discussion of extensive lymphocyte immunophenotyping by immunohistochemistry.
Despite the indolent course of most of the large granular lymphocyte leukemia that do not require a specific treatment, clinicians should be aware of this rare association that could lead to a clone-directed therapy that may improve renal outcome.

## DISCLOSURE

All the authors declared no competing interests.

## ACKNOWLEDGMENTS

Reporting of this case was approved by the local ethics review committees at Necker Hospital, Paris, France, and the patient provided written informed consent.

## REFERENCES

1. Lamy T, Moignet A, Loughran TP. LGL leukemia: from pathogenesis to treatment. *Blood*. 2017;129:1082–1094.
2. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375–2391.
3. Fu J, Lee L, Zhou P, Fogaren T, Comenzo R. A case report—renal heavy chain amyloidosis and T-cell large granular lymphocytic leukaemia. *Amyloid*. 2019;26(suppl 1):130–131.
4. Audemard A, Lamy T, Bareau B, et al. Vasculitis associated with large granular lymphocyte (LGL) leukemia: presentation and treatment outcomes of 11 cases. *Semin Arthritis Rheum*. 2013;43:362–366.
5. Larsen CP, Messias NC, Walker PD, et al. Membranoproliferative glomerulonephritis with masked monotypic immunoglobulin deposits. *Kidney Int*. 2015;88:867–873.
6. Törnroth T, Heiro M, Marcussen N, Franssila K. Lymphomas diagnosed by percutaneous kidney biopsy. *Am J Kidney Dis*. 2003;42:960–971.
7. Kohn M, Karras A, Zaidan M, et al. Lymphomas with kidney involvement: the French multicenter retrospective LyKID study. *Leuk Lymphoma*. 2020;61:887–895.
8. Christopoulos PD, Katsoudas S, Androulaki A, Nakopoulou L, Economopoulos T, Vlahakos DV. T-cell large granular lymphocyte leukemia presenting as end-stage renal disease: the diagnostic role of flow-cytometric and clonality analysis of the urine sediment. *Clin Nephrol*. 2009;71:198–202.