



Concomitant Nephrotic Syndrome with Diffuse Large B-cell Lymphoma: A Case Report

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Membranous nephropathy (MN) is a common glomerular disease that is characterized by diffuse thickening of the glomerular basement membrane, and a common cause of nephrotic syndrome (NS). MN is often accompanied with malignant disease; The solid tumors are commonly associated with MN, whereas hematological malignancies are rarely found in patients with MN. A 68-year-old man with a history of diabetes mellitus visited a hospital with a chief complaint of general fatigue. He was previously not diagnosed with any complications of diabetes. Computed tomography revealed a pancreatic tumor, and the pathological findings of the biopsied tumor revealed the tumor was diffuse large B-cell lymphoma (DLBCL). Concurrently, he developed severe proteinuria, hypoalbuminemia, systemic edema and hyperlipidemia, consistent with the diagnosis of NS. The biopsied renal specimen revealed minute spike lesions of glomerular basement membrane, and abnormal lymphocytes infiltrated in the kidney interstitially. Anti-glomerular basement membrane antibody, proteinase-3-/myeloperoxidase antineutrophil cytoplasmic antibody and hepatitis B antigenemia, are absent in the patient. Serum anti-phospholipase A2 receptor (PLA2R) antibody (marker for primary MN) was not detected. A diagnosis of secondary MN induced by DLBCL was made. He received rituximab containing chemotherapy for DLBCL, resulting in amelioration of both DLBCL and MN. We report the rare case of a patient co-existing NS and DLBCL. DLBCL might be pathogenesis of NS; the findings are supported by the presence of MN, an underlying malignancy (DLBCL), and the lack of anti-PLA2R antibodies. Although further investigation is warranted, our case suggests that DLBCL is a possible cause of secondary MN.

Keywords: anti-PLA2R antibody; autoantibodies; diffuse large B-cell lymphoma; membranous nephropathy; nephrotic syndrome

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Introduction

Nephrotic syndrome (NS) is a common glomerular disease prevalent among adult-onset proteinuria (Hull and Goldsmith 2008). Membranous nephropathy (MN) is a major cause of NS, which is often accompanied with malig-

nant diseases (Glassock 2003). Solid tumors are major involved malignancies, meanwhile, hematological malignancies are rarely found in the patients with MN (Kim et al. 2012). Diffuse B-cell lymphoma (DLBCL) is a common aggressive lymphoma which consists about 30% of malignant lymphoma (Gascoyne et al. 2017), often complicated

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with renal failure (Li et al. 2014; Corlu et al. 2019). Although direct infiltration to kidneys by DLBCL is a well-known cause of renal failure, concomitant NS is rarely reported in patients with DLBCL. Here, we report a case of a patient with concomitant NS complicated with DLBCL.

Case Presentation

A 68-year-old man with type 2 diabetes mellitus (DM) and dyslipidemia visited a hospital due to a one-month history of gradual exacerbated edema, general fatigue, and appetite loss. The patient was regularly treated with metformin and linagliptin for DM 20 years without histories of diabetic neuropathy, retinopathy or nephropathy. He was a never smoker and he was not prescribed non-steroidal anti-inflammatory drugs (NSAIDs). On physical examination, abdominal shifting dullness and bilateral fast pitting edema on both legs were prominent otherwise unremarkable. The results of patient's laboratory test were as follows: white blood cell count, 5,130/ μ L without abnormal lymphocytes; creatinine (Cr), 1.87 mg/dL; total protein, 5.2 g/dL; albumin, 1.7 g/dL; total cholesterol, 313 mg/dL; lactate dehydrogenase, 233 U/mL; IgG, 1,185 mg/dL (range, 861-1,747); IgA, 183 mg/dL (range, 93-393); IgM, 80 mg/dL (range, 33-183); C3, 110 mg/dL (range, 73-138); C4, 49 mg/dL (range, 11-31); soluble interleukin-2 receptor, 1,702 U/mL (range, 121-613); C-reactive protein (CRP), 0.54 mg/dL (range, 0.00-0.14); interleukin 6 (IL-6), 4.3 pg/mL

(range, 0-4.0); and tumor necrosis factor (TNF- α) 3.3 pg/mL (range, 0.75-1.66). Anti-glomerular basement membrane antibody, proteinase-3, myeloperoxidase antineutrophil cytoplasmic antibody, rheumatoid factor, antinuclear antibody, anti-phospholipase A2 receptor (PLA2R) antibody, hepatitis B antigen (HBsAg) and antibodies (anti-HBs and anti-HBc) were not detected. Serum and urine electrophoresis did not reveal monoclonal protein and thyroid function was normal. Urinary test revealed severe proteinuria: total protein 852 mg/dL, albumin 475 mg/dL, protein/creatinine ratio 18.52 g/gCr (estimated 24-hour urinary protein excretion). An initial diagnosis of nephrotic syndrome (NS) was made.

Computed tomography (CT) showed a solitary tumor on dorsal head of pancreas (27 mm in diameter) and systemic lymphadenopathy. Subsequently endoscopic fine needle aspiration of the pancreatic tumor was performed, and histopathological findings of the biopsied tumor revealed diffusely proliferated medium to large sized lymphocytes with oval to round, vesicular nuclei containing fine chromatin. On immunohistochemistry, these abnormal lymphocytes were positive for CD20, Bcl-2, and Bcl-6, while CD3, CD10, and MUM1 (not shown) were negative (Fig. 1). The anti-CD20 antibody and anti-CD3 antibody were purchased from Nichirei bioscience (Tokyo, Japan), and antibodies against Bcl-2, Bcl-6, and CD10 were purchased from Roche (Basel, Switzerland). Epstein-Barr

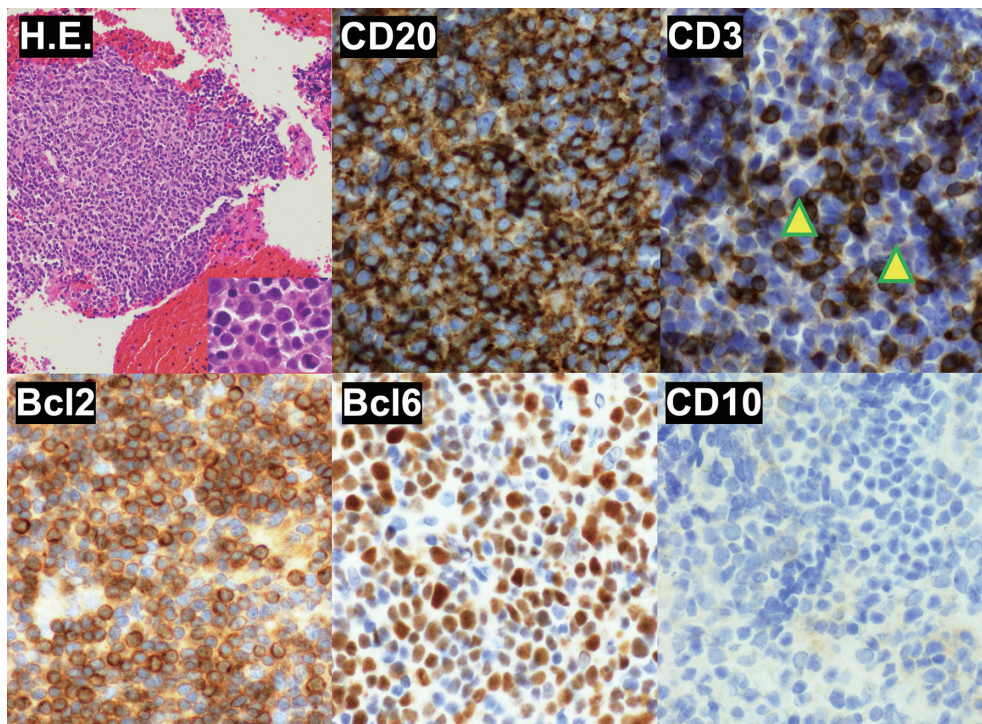


Fig. 1. Pathological features of pancreatic tumor.

Consecutive tissue sections: Hematoxylin Eosin (H.E.) stain showed diffusely proliferated medium to large sized lymphocytes which contains fine chromatin (original magnification, $\times 100$ and $\times 400$; inset). On immunohistochemistry, these lymphocytes are positive for CD20, Bcl2, and Bcl6. CD3 (arrowhead) and CD10 are negative ($\times 400$). CD3-positive cells are reactive T cells.

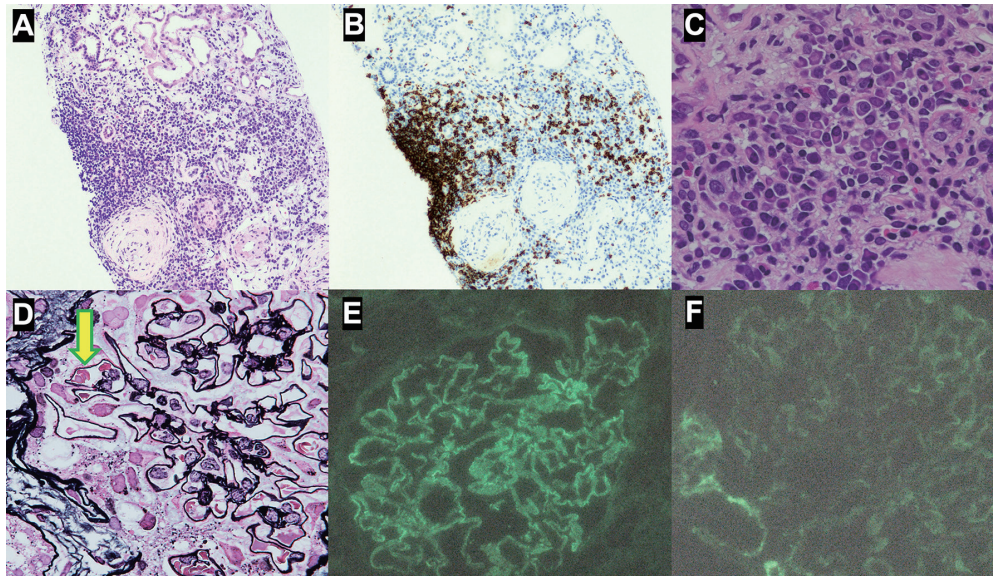


Fig. 2. Pathological features of renal biopsy.

Consecutive tissue sections: Top panels; (A), (B), and (C). On H.E. stain, small to medium sized lymphocytes are infiltrating to renal tubular interstitium (A) ($\times 100$). These lymphocytes showed positive for CD20 on immunohistochemistry (B) ($\times 100$). Abundant plasma cells are surrounding around the infiltrated part of renal tubular interstitium (C) ($\times 400$). A selected region of a tissue is enlarged at bottom panels; (D), (E), and (F). Minute spike lesions of glomerular basement membrane on periodic acid-methenamine silver (PAM) stain (arrow) (D) (original magnification, $\times 400$). Immunoglobulin G (IgG) is strongly positive with granular pattern (E) ($\times 400$). C3 antibodies showed positive alongside the basement membrane of glomeruli (F) ($\times 400$).

virus (EBV)-encoded small RNA in situ hybridization (EBER-ISH) was not investigated. The diagnosis of diffuse large B-cell lymphoma (DLBCL), not otherwise specified (Ann Arbor staging IV) in patient complicated with NS was made.

The patient was referred to our hospital for the treatment of DLBCL. Renal failure was deteriorated within a few days (serum creatinine level was increased to 2.73 mg/dL) and developed oliguria (400 mL/day) regardless of diuretics administration. Abdominal ultrasonography showed a large volume of ascites without hydronephrosis or urinary tract obstruction, indicating the NS developed. Renal biopsy was performed. Among the interstitial space between tubules, small to medium sized lymphocytes infiltrated with abundant plasma cells (Fig. 2A-C). Over 40% of the plasma cells were positive for IgG4 staining (not shown). Results of light chain staining (kappa or lambda chain) were not obtained from the renal sample. Membranous thickening of glomerular basement or proliferation of mesangial cells and mesangial matrix were not observed. Focal sclerotic glomerulus was not observed and the hyalinosis of arterioles was also slightly observed. Histopathological findings of biopsied renal tissue revealed minute spike lesions of glomerular basement membrane on periodic acid-methenamine silver (PAM) stain (Fig. 2D). Immunofluorescent staining revealed granular capillary wall deposit with polyclonal immunoglobulin G (IgG) and C3 antibodies (Fig. 2E, F), which is a characteristic pathological feature of membranous nephropathy (MN). The final diagnosis of MN (Stage II) with concomitant DLBCL

infiltration in kidney was made.

Attenuated R-CHOP chemoimmunotherapy (rituximab 375 mg/m² on day14, cyclophosphamide 325 mg/m² on day1, doxorubicin 25 mg/m² on day1, vincristine 1.4 mg/m² on day1, and prednisolone 60 mg/body on day 1 to 5) was initiated. The dose of chemotherapy was reduced 50% from the designated R-CHOP protocol on the first cycle, concerning development of adverse effects due to renal failure and severe hypoalbuminemia. Moreover, rituximab was postponed after CHOP therapy to avoid possible tumor lysis syndrome. After the commencement of chemoimmunotherapy, his body weight decreased 5 kg within 1 month and increased urine output was observed (over 1,000 mL/day) with minimum maintenance diuretics administration (furosemide 20 mg/day and trichlormethiazide 1 mg/day). Peripheral edema was also ameliorated, nevertheless his serum albumin level was under 1.0 g/dL yet. After 2 courses of R-CHOP chemoimmunotherapy (80% dose), abdominal ultrasonography showed the ascites was diminished and abdominal CT revealed the pancreatic tumor was shrunk and obscured. The inflammatory cytokine data was not measured after R-CHOP therapy. He discharged from our hospital with gradual ameliorated renal function and proteinuria (serum Cr, 1.26 mg/dL and urine protein/creatinine ratio 2.54 g/gCr; Fig. 3).

Informed consent

The patient provided informed consent on March 20th, 2020.

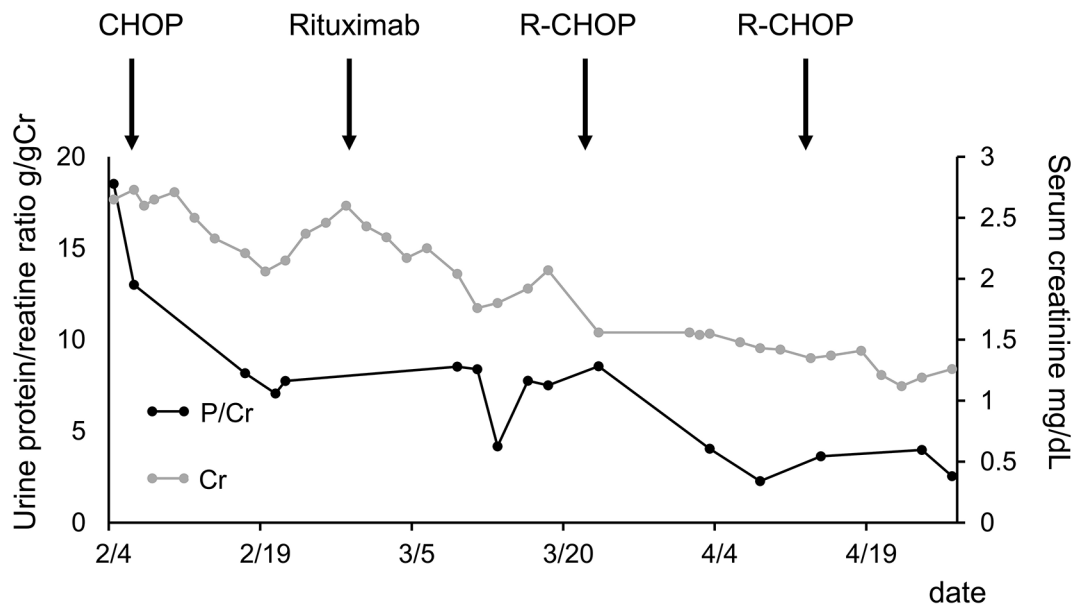


Fig. 3. Clinical course of the patient.

Repeated R-CHOP chemoimmunotherapy decreased both proteinuria and serum creatinine level.

Cr, serum creatinine; P/Cr, urine protein/creatinine ratio; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

Discussion

NS is a common renal disease characterized by severe proteinuria (> 3.5 g/day), hypoalbuminemia (< 2.5 g/dL), systemic edema and hyperlipidemia (Orth and Ritz 1998). Common primary causes of NS in adult include glomerular diseases such as MN or focal glomerulosclerosis, whereas, secondary causes include DM, or autoimmune diseases. Specific treatment for NS depends on its cause, thus differential diagnosis is important. DM is the most common cause of NS in elderly adults. In the present patient, the histopathological specimen of biopsied renal tissue revealed the features of MN with slight hyalinosis of arterioles consistent with diabetic nephropathy, indicating diabetic nephropathy could not be denied the involvement of the patient's NS.

MN is one of the most prevalent cause of primary NS in adult (Couser 2017) and is also divided into primary MN (approximately 75 to 80% of cases) or secondary (20 to 25% of cases). The pathogenesis of primary MN is explained that immune complexes are formed circulating autoantibodies binding to podocyte antigens; Three major antigens have been reported [M-type phospholipase A2 receptor (PLA2R), thrombospondin type-1 domain-containing 7A (THSD7A), and neural epidermal growth factor-like 1 protein (NELL-1)] (Sethi et al. 2020). Recently, these autoantibodies are used for diagnostic marker for primary MN, especially anti-PLA2R antibody is detected in majority of patients (approximately 70%) with primary MN (Beck et al. 2009). Hepatitis B antigenemia, autoimmune diseases, thyroiditis, malignancies, and the drug use such as NSAIDs are major causes of secondary MN. Differential

diagnosis between primary and secondary MN is challenging because approximately 30% in primary MN are lack of anti-PLA2R (Beck et al. 2009) and rituximab is effective for the disease (Fervenza et al. 2019). On the other hand, secondary MN accounts for about 10% of nephrotic syndrome associated with non-Hodgkin's lymphoma (Ronco 1999). The patient suffered malignancy such as DLBCL without detected anti-PLA2R autoantibody, hepatitis B antigenemia, other autoantibodies, thyroiditis, and use of NSAIDs, indicating DLBCL may be possible cause of the patient's secondary MN.

The prevalence of malignancies in patients with MN in adults is estimated in 6%-22% (Cambier and Ronco 2012). Solid tumors, such as lung, bronchus, and gastric cancers, renal cell carcinoma, prostate cancer, and thymoma, are major involved malignancies in MN. Meanwhile, hematological malignancies, including non-Hodgkin lymphoma, chronic lymphocytic leukemia, acute myeloid leukemia and chronic myeloid leukemia, are rarely found in the patients with MN (Bacchetta et al. 2009). A systematic review and meta-analysis revealed that the majority of tumors associated with MN are solid tumors (73 cases, 86%), otherwise hematologic malignancies consist 14% in Europe and the United States (Leeaphorn et al. 2014). On the contrary, in Japanese cohort, the complication rate of malignant neoplasm in Japanese patients with MN is reported 1% (Yokoyama et al. 2012). Six out of 8 patients diagnosed as secondary MN with cancer were related to hematological diseases (post bone-marrow transplantation: 3, IgG4-related disease: 2, and monoclonal gammopathy of undetermined significance: 1). The hematological diseases might relatively common in Japanese patient of

secondary MN compared to Caucasians.

The pathogenesis of MN associated with malignancies were explained by infiltrated immune complexes that are formed circulating paraneoplastic autoantibodies or *in situ* immune complexes in the glomerular subepithelial. Furthermore, MN causes increased proinflammatory cytokines such as, interleukin 1 β , IL-6 and TNF-alpha. In the present patient, infiltrated DLBCL in the kidney was observed, and could directly induce renal impairment and work autoantigen (Kayataş et al. 2011; Silva et al. 2018). Pathological findings confirmed existing immune complexes consistent with MN. Increased serum CRP, IL-6, and TNF-alpha was also observed, indicating proinflammatory cytokine activation associated with non-Hodgkin's lymphoma could occur (Pedersen and Sørensen 2003). Interstitial abundant inflammatory cells including lymphocytes, plasma cells indicate that the membranous change was accompanied with renal inflammation. Both inflammatory cytokines and direct infiltration of lymphoma cells to kidney are possible cause of the membranous change. Rituximab is efficacious for treating primary MN because B-cell anomalies play a critical role in the pathogenesis of MN (Fervenza et al. 2019). Rituximab might also have therapeutic effect in cases of secondary MN. R-CHOP immunotherapy ameliorated both DLBCL and NS. Hence, the infiltrated DLBCL in the kidney may be highly associated with the pathogenesis of MN in the patient.

In conclusion, we report the rare case of a patient with concomitant NS possibly induced by DLBCL; the findings are supported by the presence of MN, an underlying malignancy (DLBCL), and lack of anti-PLA2R antibodies. Further investigation is warranted to clarify the relationship between DLBCL and MN.

Conflict of Interest

The authors declare no conflict of interest.

References

- Bacchetta, J., Juillard, L., Cochat, P. & Droz, J.P. (2009) Paraneoplastic glomerular diseases and malignancies. *Crit. Rev. Oncol. Hematol.*, **70**, 39-58.
- Beck, L.H. Jr., Bonegio, R.G., Lambeau, G., Beck, D.M., Powell, D.W., Cummins, T.D., Klein, J.B. & Salant, D.J. (2009) M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N. Engl. J. Med.*, **361**, 11-21.
- Cambier, J.F. & Ronco, P. (2012) Onco-nephrology: glomerular diseases with cancer. *Clin. J. Am. Soc. Nephrol.*, **7**, 1701-1712.
- Corlu, L., Rioux-Leclercq, N., Ganard, M., Decaux, O., Houot, R. & Vigneau, C. (2019) Renal dysfunction in patients with direct infiltration by B-cell lymphoma. *Kidney. Int. Rep.*, **4**, 688-697.
- Couser, W.G. (2017) Primary membranous nephropathy. *Clin. J. Am. Soc. Nephrol.*, **12**, 983-997.
- Fervenza, F.C., Appel, G.B., Barbour, S.J., Rovin, B.H., Lafayette, R.A., Aslam, N., Jefferson, J.A., Gipson, P.E., Rizk, D.V., Sedor, J.R., Simon, J.F., McCarthy, E.T., Brenchley, P., Sethi, S., Avila-Casado, C., et al. (2019) Rituximab or cyclosporine in the treatment of membranous nephropathy. *N. Engl. J. Med.*, **381**, 36-46.
- Gascoyne, R.D., Campo, E., Jaffe, E.S., Chan, W.C., Chan, J.K.C., Rosenwald, A., Stein, H., & Swerdlow, S.H. (2017) Diffuse large B-cell lymphoma, NOS. In *WHO classification of tumors of haematopoietic and lymphoid tissues*, Revised 4th ed., edited by Swerdlow, S.H., Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H. & Thiele, J., IRAC Press, Lyon, France, pp. 291-297.
- Glasscock, R.J. (2003) Diagnosis and natural course of membranous nephropathy. *Semin. Nephrol.*, **23**, 324-332.
- Hull, R.P. & Goldsmith, D.J. (2008) Nephrotic syndrome in adults. *BMJ*, **336**, 1185-1189.
- Kayataş, M., Yildiz, G., Timuçin, M., Candan, F., Yildiz, E. & Sencan, M. (2011) A case of acute renal failure caused by Hodgkin's lymphoma: concurrent membranous glomerulonephritis and interstitial HL-CD 20 lymphoid infiltration. *Ren. Fail.*, **33**, 363-366.
- Kim, C.S., Choi, Y.D., Choi, J.S., Bae, E.H., Ma, S.K. & Kim, S.W. (2012) EBV-positive diffuse large B-cell lymphoma in a patient with primary Sjögren's syndrome and membranous glomerulonephritis. *BMC Nephrol.*, **13**, 149.
- Leeaphorn, N., Kue, A.P.P., Thamcharoen, N., Ungprasert, P., Stokes, M.B. & Knight, E.L. (2014) Prevalence of cancer in membranous nephropathy: a systematic review and meta-analysis of observational studies. *Am. J. Nephrol.*, **40**, 29-35.
- Li, S.J., Chen, H.P., Chen, Y.H., Zhang, L.H., Tu, Y.M. & Liu, Z.H. (2014) Renal involvement in non-Hodgkin lymphoma: proven by renal biopsy. *PLoS One*, **9**, e95190.
- Orth, S.R. & Ritz, E. (1998) The nephrotic syndrome. *N. Engl. J. Med.*, **338**, 1202-1211.
- Pedersen, L.M. & Sørensen, P.G. (2003) Mediators of inflammation correlate with microalbuminuria in patients with non-Hodgkin's lymphoma. *Br. J. Haematol.*, **121**, 275-279.
- Ronco, P.M. (1999) Paraneoplastic glomerulopathies: new insights into an old entity. *Kidney Int.*, **56**, 355-377.
- Sethi, S., Debiec, H., Madden, B., Charlesworth, M.C., Morelle, J., Gross, L., Ravindran, A., Buob, D., Jadoul, M., Fervenza, F.C. & Ronco, P. (2020) Neural epidermal growth factor-like 1 protein (NELL-1) associated membranous nephropathy. *Kidney Int.*, **97**, 163-174.
- Silva, W.F.D. Jr., Pinho, L.L.F., Farias, C.L.G., Torres, V., Costalonga, E.C., Filho, G.C., Testagrossa, L.A., Rocha, V. & Buccheri, V. (2018) Renal infiltration presenting as acute kidney injury in Hodgkin lymphoma: a case report and review of the literature. *Leuk. Res. Rep.*, **10**, 41-43.
- Yokoyama, H., Taguchi, T., Sugiyama, H. & Sato, H.; Committee for the Standardization of Renal Pathological Diagnosis and for Renal Biopsy and Disease Registry in the Japanese Society of Nephrology (2012) Membranous nephropathy in Japan: analysis of the Japan Renal Biopsy Registry (J-RBR). *Clin. Exp. Nephrol.*, **16**, 557-563.