C3 glomerulonephritis accompanied with lupus nephritis

Lomerulonefritis C3 acompañada de nefritis lúpica

Dear Editor:

Complement 3 (C3) glomerulopathy is diagnosed when C3 dominant glomerulonephritis is seen in kidney biopsy with C3 only deposition without immunoglobulin (Ig), or dominant C3 with up to 1 + IgM, or dominant C3 of +2 orders of magnitude of intensity by immunoflourescent (IF) greater than any other immune reactant (using a scale of 0 to 3, including 0, trace, 1+, 2+, 3+).[1] Systemic lupus erythematosus (SLE) lead to renal damage through immune deposition such as IgG, IgA, IgM, C3, and C1q, with IgG dominance or codominance in a specific pattern known as full-house.[2]

A 49 year old male patient applied to our clinic due to high serum creatinine levels noticed at dermatology department during examination for discoid rash. He was well until his skin eruptions have erosen one month ago. Hydroxychloroquine and topical corticosteroid were prescribed to him for cutaneous lupus erythematosus diagnosed by skin biopsy. His blood pressure was 120/80 mmHg. Trace pretibial edema and hypopigmented lesions on forearms were detected. Biochemically, his serum creatinine (Cr) level was 1.28 mg/dL, estimated glomerular filtration rate (eGFR) Chronic Kidney Disease Epidemiology Collaboration equation (CKD–EPI-cre based): 66 mL/min/1.73 m^2, serum albumin level was 3.6 g/dL, proteinuria was 660 mg/day, his urine sediment was inactive at admission. Kidneys were ultrasonographically normal in size and echogenicity. Double-checked result of proteinuria level was 1.87 g/day, complement 3 (C3) and complement 4 (C4) levels were normal (104 mg/dL, normal range = 90–180; and 16 mg/dL, normal range = 10–40 respectively), antinuclear antibody (ANA) was detected positive at 1/1000–1/3200 titration by IFA (immunofluorescence assay), anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibody level was found as 176.2 IU/mL (negative titration = <100 IU/mL) by IFA, presence of perinuclear (myeloperoxidase) anti-neutrophil cytoplasmic antibodies (ANCA) was observed by IFA with a serum titration between 1/32 and 1/100 together with positive anti-SS-A, anti-Smith (anti-Sm), anti-histone, and anti-nucleosome antibodies tested by immunoblot analysis.

Renal biopsy revealed membranoproliferative glomerulonephritis with diffuse glomerular basal membrane thickening and global mesangial matrix expansion by light microscopy (Fig. 1). Six of the 17 glomeruli were globally sclerotic. No cellular/fibrous crescent and necrosis was noticed. Direct immunofluorescence microscopy displayed granular full-house staining with predominant intense C3 staining (severity degree of +3) (Fig. 2), followed by C1q (mild staining), and IgG (mild staining), in addition to lambda (moderate staining), kappa (mild staining) and fibrin (severe staining). C4d staining showed presence of C4d deposition. Autoantibody test results and findings of skin biopsy made us thought lupus nephritis at first. However kidney biopsy revealed findings associated with both lupus nephritis class IV-G (A/C) and C3 dominant glomerulopathy. The dominant C3 deposition made it necessary to research molecular genetic

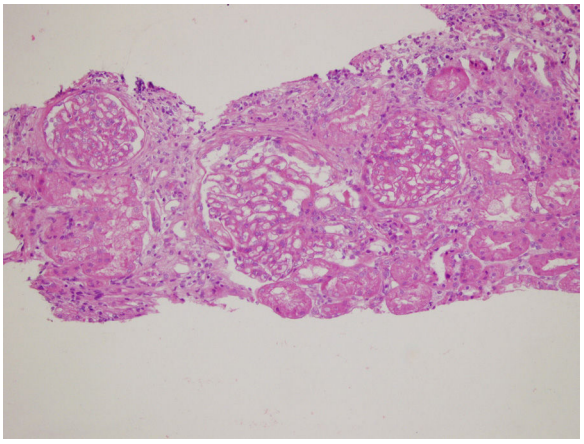

Fig. 1 – Renal biopsy which shows diffuse global basal membrane thickening, lymphocyte dominant tubulointerstitial inflammation, increased fibrosis, and tubular atrophy by light microscopy, H.E. 400×.

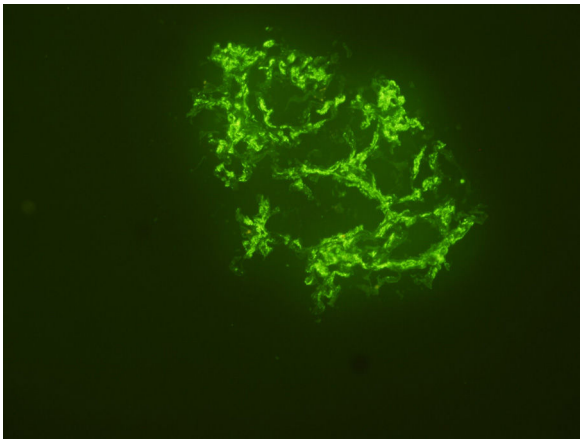

Fig. 2 – Renal biopsy which shows peripheral and mesangial granular pattern severe (+3) C3 deposition in glomerulus by immunoflourescence microscopy, 400×.

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complement disorders.[3,4] In our patient, further examinations in order to enlighten C3 glomerulopathy, yielded homozygous p.His402Tyr mutation due to c.1204C>T change in the complement factor H (CFH) gene and homozygous p.Val306fs mutation due to c.914_915insA insertion in the complement 3 (C3) gene and heterozygous p.Lys565Glu mutation due to c.1693A<G change in the complement factor B (CFB) gene by new generation DNA sequencing analysis. In the meantime, proteinuria level of the patient was increased to 5.7 g/day. Methylprednisolone and mycophenolate mofetil were given to the patient because he developed hypersensitivity to cyclophosphamide. Proteinuria level decreased to 2.56 g/day, serum creatinine level decreased to 1 mg/dL, and serum albumin level increased to 3.9 g/dL after 1 year of follow-up.

Our patient was diagnosed as SLE by fulfillment of either the 1997 American Collage of Rheumatology (ACR) criteria and by the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria.[5] The signature of lupus nephritis in renal pathology is polyclonal staining of IgG, IgA, IgM, C3 and C1q with dominant or codominant IgG.[2] There was no dominant IgG deposits, even no uniform involvement of IgG and C3 deposits in our case.[6] Instead, C3 dominance fulfilled the criterion necessary to diagnose C3 glomerulopathy defined by consensus report of International Society of Nephrology.[1] Dysregulation of complement system due to mutations or antibodies lead to C3 glomerulopathy. Only ≅25% of cases diagnosed as C3 glomerulopathy were reported to have genetic mutations in genes of C3 (encoding complement factor 3), CFB (encoding complement factor B), CFH (encoding complement factor H, the regulatory protein of compleman activation), CFI (encoding complement factor I, inactivator of C3b), and CFHR5 (encoding complement factor H-related protein 5, enhancer of complement activation).[7] The c.1204c>T; p.His402Tyr variant in the CFH gene has been reported to be highly associated with dense deposit disease and favorable outcomes in age-related macular degeneration.[8,9] This variant of CFH put our patient at an increased risk for liability to complement-mediated diseases which emerge in adulthood. The second variant in genetic sequence of complement factor B gene was probably pathogenic for complement mediated disorders like thrombotic microangiopathy as reported previously.[10] It remains to be determined whether the third genetical variant in complement 3 gene is capable of causing complement mediated disease. The data about mutation in the complement factor B gene of our patient and its clinical importance for enhanced formation and delay in inactivation of C3bBb convertase needs to be searched.

In conclusion, as far as we know this is the first case showing the togetherness of C3 glomerulopathy and lupus nephritis. After one year of treatment with methylprednisolone and mycophenolate mofetil, renal improvement was achieved. Further studies will enlighten the best therapeutic approach for this new entity in the future.

Authorship contributions

Concept: Kubra Kaynar. *Design*: Kubra Kaynar, Beyhan Güvercin. *Control*: Kubra Kaynar, Beyhan Güvercin, Sahile Safarlı, Sevdegül Mungan, Mustafa Şahin. *Data Collection*: Sahile Safarlı, Sevdegül Mungan, Mustafa Şahin. *Literature review*: Kubra Kaynar. *Writing the manuscript*: Kubra Kaynar.

Compliance with ethical standards

All authors declare that there are no conflicts of interests related to the study and no fund was taken. Informed consent was obtained from patient.

REFERENCES

1. Pickering MC, D'Agati VD, Nester CM, Smith RJ, Haas M, Appel GB, et al. C3 glomerulopathy: consensus report. Kidney Int. 2013;84:1079–89, http://dx.doi.org/10.1038/ki.2013.377.
2. Fogo AB, Lusco MA, Najafian B, Alpers CE. AJKD atlas of renal pathology: focal and diffuse lupus nephritis (ISN/RPS class III and IV). Am J Kidney Dis. 2017;70:e9–11, http://dx.doi.org/10.1053/j.ajkd.2017.06.001.
3. Bajema IM, Wilhelmus S, Alpers CE, Bruijn JA, Colvin RB, Cook HT, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Kidney Int. 2018;93:789–96.
4. Fervenza FC, Sethi S. Membranoproliferative glomerulonephritis: classification, clinical features, and diagnosis; 2020 March. UpToDate.com.
5. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the systemic lupur international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64:2677–86, http://dx.doi.org/10.1002/art.34473.
6. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. American College of Rheumatology guidelines for screening, treatment and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64:797–808, http://dx.doi.org/10.1002/acr.21664.
7. Smith RJH, Appel GB, Blom AM, Cook T, D'Agati VD, Fakhouri F, et al. C3 glomerulopathy-understanding a rare complement-driven renal disease. Nat Rev Nephrol. 2019;15:129–43, http://dx.doi.org/10.1038/s41581-018-0107-2.
8. Servais A, Noel LH, Roumenina LT, Le Quintrec M, Ngo S, Dragon-Durey MA, et al. Acguired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. Kidney Int. 2012;82:454–64, http://dx.doi.org/10.1038/ki.2012.63.
9. Menghini M, Kloeckener-Gruissem B, Fleischhauer J, Kurz-Levin MM, Sutter FK, Berger W, et al. Impact of loading phase, initial response and CFH genotype on the long term outcome of treatment for neovascular age-related macular degeneration. PLoS ONE. 2012;7:e42014, http://dx.doi.org/10.1371/journal.pone.0042014.
10. Bernards J, Doubel P, Meeus G, Lerut E, Corveleyn A, Van Den Heuvel LP, et al. Hyperhomocysteinemia: a trigger for complement-mediated TMA? Acta Clin Belg. 2019;111:1–5, http://dx.doi.org/10.1080/17843286.2019.1649039.

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Severe hypernatremia after hypertonic saline use as treatment of hepatic hydatidosis surgery☆

Hipernatremia grave tras el empleo de cloruro sódico hipertónico en cirugía de hidatidosis hepática

Dear Editor,

Hypernatremia secondary to the use of hypertonic saline solution (HSS) as a scolicidal agent in hydatid cyst surgery is a complication that is very uncommon but extremely serious as it can cause irreversible neurological complications.[1]

We report a case of severe acute hypernatremia following hydatid cyst surgery. The patient was a 60-year-old woman who had no prior medical history and lived in an urban setting. She sought care for abdominal discomfort in the right hypochondrium during the past year. Abdominal ultrasound imaging revealed a cyst consistent with a hydatid cyst measuring 20 cm in diameter, category CE1–CE2 according to the World Health Organization classification;[2] in addition, *Echinococcus granulosus* serology was positive. She was diagnosed with hepatic hydatid disease. A decision was made to administer treatment with albendazole for four weeks and perform a partial cystectomy/pericystectomy.

A laparotomy was done with local opening of the cyst, as well as protection of the abdominal wall and peritoneum with plastic material; a total of 2500 cc of cyst contents were aspirated. During cyst puncture, the patient presented sudden arterial hypotension and bradycardia that responded to epinephrine, methylprednisolone and dexchlorpheniramine. Thereafter, 3% HSS was twice instilled in the cyst cavity up to full repletion; each time, the HSS was left in place for 15 min and then a total of 5 l of contents were aspirated. An estimated 1000 cc of bleeding occurred. During surgery, a total of 1000 cc of 0.9% normal saline and 600 cc of packed red blood cells were administered. After that, the patient showed a tendency towards arterial hypotension, requiring norepinephrine as a continuous infusion. When the procedure was complete, marked hypernatremia was seen with Na^+ 182 mmol/l (plasma osmolarity 378 mOsm/kg).

In the first 24 h, 2000 cc of 5% glucose in saline were administered. The patient also presented acute liver failure, development of anaemia, hyperfibrinolysis and disseminated intravascular coagulation with a blood deficit due to drainage of 1500 cc, requiring transfusion of red blood cells, platelets and fresh frozen plasma, for a total volume of 1650 cc. She presented diuresis of 680 cc. A CT scan of the head showed no acute abnormalities.

After 24 h, her sodium level dropped to 171 mOsm/l (plasma osmolarity 361 mOsm/kg), her blood glucose level was 445 mg/dl and acute kidney failure (AKF) was seen with a creatinine level of 2.22 mg/dl and diuresis of 180 cc. The patient was administered 1800 cc of 5% glucose in saline, furosemide infusion was started at a rate of 20 mg/h for 24 h and insulin infusion was initiated.

After 72 h, her hypernatremia had been corrected, so infusion of 5% glucose in saline was suspended and parenteral nutrition was started. The patient's haemodynamic status remained poor. She was dependent on invasive mechanical ventilation and norepinephrine infusion. In addition, she had oligoanuria with a creatinine level of 4.45 mg/dl. She required continuous venovenous hemodiafiltration (CVVHDF) for two weeks; subsequently, negative balances were achieved with a diuretic, and after that spontaneous diuresis was achieved and full kidney function was recovered. On hospital discharge, she exhibited no neurological or other sequelae. Table 1 shows the patient's laboratory values of note.

Total open or partial cystectomy/pericystectomy requires the use of scolicidal agents intended to kill the parasite and impede its intraperitoneal spread. Various scolicidal agents have been used, including: silver nitrate, formaldehyde, oxy-

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