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ABSTRACT

Glomerulonephritis associated with celiac disease (CD) is rarely reported. Here we report a rare case of nephrotic syndrome associated with C3 glomerulopathy (C3G) in a patient with CD. A 19-year-old female with bilateral leg swelling and hypoalbuminemia was referred with an initial diagnosis of nephrotic syndrome. She had also abdominal pain and diarhea. First a duodenal biopsy confirmed the diagnosis as CD. Nephrotic range proteinuria was detected so then a percutaneous renal biopsy was performed. Renal biopsy revealed membranoproliferative glomerulonephritis (MPGN) with C3 staining. Introduction of a gluten-free diet, ramipril, steroid and mycophenolic acid ameliorated clinical and laboratory parameters at three years follow up. Edema and hypoalbuminemia are common sharing clinical and laboratory parameters presented in not only patients with CD but also with glomerulonephritis. Urine analysis is very important in patients with CD to detect proteinuria. It is important to keep the possible link between CD and glomerulonephritis in mind for clinicians when working up a patient with diarhea and nephrotic syndrome.

Key Words: Celiac disease, C3 glomerulopathy, glomerulonephritis, hypoalbuminemia, nephrotic syndrome

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder characterised by malabsorption and chronic inflammation of the small intestinal mucosa, triggered by oral intake of gluten. CD is one of the most common autoimmune disorders, with a reported prevalence of %1-0.5 of the general population(1). Glomerulonephritis associated with celiac disease is rarely reported. IgA nephropathy (IgAN) is the most common glomerular abnormality in CD patients(2).

C3 glomerulopathy (C3G) is defined based on a common pathogenesis of excessive activation of the complement alternative pathway, manifesting as C3-dominant staining on renal biopsy after the exclusion of other diseases. On the basis of electron microscopy (EM), C3G is subdivided into dense deposit disease (DDD) and C3 glomerulonephritis(C3GN)(3).

We report a rare case of nephrotic syndrome associated with C3G in a patient with CD.

CASE HISTORY

A 19-year-old female patient with past medical history of hypothyroidism admitted to our hospital with bilateral leg swelling on April 2019. She had also abdominal pain and diarhea for last three years. She was referred to the Nephrology Department upon detection of proteinuria. On physical examination, her body mass index (BMI) was 20.8 kg/m^2 and her blood pressure was 120/70mmHg. She had bilateral ++ edema of the lower limbs.

Her medication: Levothyroxine, 25 µg once daily, in the morning.

Laboratory findings revealed the following: hemoglobin (Hb), 12.9 g/dL; blood urea nitrogen (BUN), 10 mg/dL; serum creatinine (SCr), 0.38 mg/dL; serum albumin, 2.9 g/L and total cholesterol, 324 mg/dL. Thyrotropin, 4.07 (normal range: 0.43–4.00) µIU/ml; Thyroperoxidase antibody, 201.8 (normal range: 0–33.9) IU/ml and Thyroglobulin antibody, 14 (normal range: <4) IU/ml. Erythrocyte sedimentation rate was 12 mm/h. Additional analysis showed as folic acid, 2.1 (normal range: 3.1-19.9) µg/L; vitamin B12, 108 (normal range: 126.5-505) ng/L; iron, 50 (60-180) ug/dL, total iron binding capacity, 236 (225-450) ug/L and ferritin, 182.8 (5.8-274) µg/L. Urinalysis showed proteinuria and sediment with 32 RBC/hpf. 24-h urine protein excretion was 6482 mg/day with a microalbuminuria of 1899 mg/day. Hepatitis B and C serologies were negative. No monoclonal protein was detected in serum electrophoresis examination. Immunological assays including antinuclear antibodies (ANA), anti-double stranded DNA (Anti-dsDNA), anti-neutrophilic cytoplasmic antibodies (ANCAs), rheumatoid factors and cryoglobulins were negative. Decreaesed C3 level was detected (0.53 g/L, normal range: 0.9-1.8 g/L) and C4 level was normal. The renal echography was normal.

The patient also admitted Gastroenterology Department because of gastrointestinal symptoms and laboratory findings including folic acid and vitamin B12 deficiencies. Antiendomysial antibody was found positive. Elevated tissue transglutaminase (TTG) IgA antibody (>200, normal range: 0-20 RU/mL), elevated antigliadin IgA antibody (44.82, normal range: 0-24 RU/mL) and elevated antigliadin IgG anibody (38.96, normal range: 0-24 RU/mL) were detected. Upper gastrointestinal endoscopy with duedonum biopsy revealed villus atrophy with intraepithelial lymphocytic infiltrates consistent with CD.

A percutaneous renal biopsy that was performed in July 2019 revealed membranoproliferative glomerulonephritis (MPGN). 20 glomeruli were observed, with global sclerosis in one glomerulus and segmental sclerosis in two glomeruli. Specifically, segmental mesangial matrix expansion, mesangial hypercellularity and thickening of the glomerular capillary loops with double contours were noted under light microscope. Lobular appearance was seen in some glomeruli. There were segmental endocapillary proliferations in five glomeruli and adhesions to bowman capsule in two glomeruli. Interstitial fibrosis was mild with

mononuclear inflammatory cell infiltrations [Figure 1A, 1B]. Kongo staining was negative. On immunofluorescence examination,C3 was present along the capillary loops and in the mesengium (+++) [Figure 1C]. IgG detected (+) along the capillary loops in a granular pattern [Figure 1D]. IgM, IgA, C1q, fibrinogen, kappa and lambda were not detected. There was no C4d deposition. EM could not be examined.

Genomic DNA extracted from blood sample of patient was used to amplify and bidirectionally sequence the coding regions and intron-exon boundary junctions of C3 (NM_000064), CFH (NM_000186), CFHR5 (NM_030787), CFB (NM_001710) and CFI (NM_0001331035). Four single nucleotide polymorphisms in CFH and C3-namely CFH c.1204C>T;p.His402Tyr (rs1061170), CFH c.184 G>A;p.Val62IIe (rs800292), C3 c.2863+7C>T (rs2287845) and C3 c.2246-8C>T (rs406514) were found.

An antibody test against C3 convertase (C3NeF) was not performed.

A gluten-free diet and ramipril 2.5 mg/day was started. After 3 months, patient was reevaluated. At this time, she had proteinuria of 5969 mg/day with SCr, 0.36 mg/d L and serum albumin, 3.1 g/L. We decided to start immunosuppressive treatment. The patient was initiated on steroids (methylprednisolone 48 mg/day) as well as an additional immunosuppressive agent (mycophenolic acid [MMF] 1500 mg/day). Over the next 38 months, the patient gained 9 kg and the oedema resolved; the proteinuria decreased to 237 mg/day, serum albumin and C3 rose to 4.4 g/L and 1.17 g/L, respectively with a normal renal function (SCr: 0.48 mg/dL). Also TTG IgA antibody decreased to < 2 RU/ml (normal range: 0-20 RU/mL).

DISCUSSION

Biopsy findings of our case presented with nephrotic syndrome and CD showed mesangial cell and matrix proliferation with C3 deposition consisted with C3G. However we could not further classify based upon ultrasuctural features observed on EM as DDD or C3 glomerulonephritis.

CD is associated with a variety of autoimmune diseases such as type 1 diabetes mellitus, autoimmune thyroid disorders, Sjogren's syndrome and IgA nephropathy[4]. The prevalence of CD in patients with autoimmune thyroid disease (Graves disease and Hashimoto disease) is around %2-7 and the risk of autoimmune thyroid disease in CD is 3 times higher than in the healthy population[5]. The coexistence of CD and autoimmune disease is thought to be partly due to a common genetic predisposition. CD and autoimmune thyroid disease are reported to be associated with the gene encoding cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), a candidate gene for conferring susceptibility to thyroid autoimmunity[6,7].

Patients with celiac disease suffer from diarrhea, malabsorption, weight loss, iron deficiency, and anemia. It has been hypothesised that circulating immune complexes originating in the small intestine could be responsible for other diseases associated with CD [8,9]. In terms of renal involvement it has been reported that glomerular diseases may ensue during the course of CD [10]. Glomerulonephritis in association with enteropathy is a recognised, though rare, entity. IgA nephropathy is the most common glomerular abnormality reported in patients with CD [9]. By far the main association between CD and glomerular disease is IgA nephropathy (IgAN) with %22-77 of patients with IgAN having IgA antigliadinantibodies and %3-4 of these having CD [11,12]. A few case series described other glomerulopathies in the context of CD, such as membranous nephropathy and membranoproliferative nephropathy[13-18].

The relation of autoimmune enteropathy and glomerulonephritis is related to the elevation of gut permeability and the presence of increased intra-epithelial T lymphocytes in the duodenal mucosa of patients with primary glomerulonephritis [19,20]. It was assumed that the antigen responsible might result from increased mucosal permeability to antigens, might be a product of gluten or could be derived from damaged intestinal mucosa. Increased intestinal permeability, typically seen in inflammatory bowel disease and celiac disease, has also been reported in patients with IgA nephropathy [21-23].

Few studies have examined the possibility of complement involvement in CD pathogenesis. Untreated CD patients typically have high levels of IgG1 and IgG3 anti-gliadin antibodies in their serum both of which are capable of activating complement[24]. Sub-epithelial IgA-TG2 deposits, found in the early stages of CD might also play a role, and polymeric IgA has been shown to activate complement via the MBL pathway [25,26]. This could explain that patients with untreated celiac disease show C3 hypocomplementemia and have circulating immune complexes that disappear after gluten-free diet but reappear along with C3 split products shortly after gluten challenge along with C3 split products shortly after gluten challenge [27-30].

The alternative pathway activation in C3GN was driven by inherited or acquired defects. Complement C3 and CFH are key inhibitors of the alternative pathway. C3 c.2863+7C>T variant was associated with severe preeklampsia[31], overall survival and prognosis in patients with early stage non-small cell lung cancer after surgical resection[32].The c.1204c>T; p.His402Tyr andCFH c.184 G>A;p.Val62IIe variants in the CFH gene had significant associations with an increased risk of developing age-related macular degeneration (AMD) [33,34].

CONCLUSION

We are able to report a good renal course in the context of remission of enteropathy by the maintenance of a gluten-free diet lasting and MMF plus steroid treatment to a three years follow up. Thus it is important to keep this association in mind for primary care physicians, internists, gastroenterologists and nephrologists when working up a patient with diarhea and nephrotic syndrome.

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Declaration of Conflicting Interests

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REFERENCES

1. Therrien A, Kelly CP, Silvester JA. Celiac Disease: Extraintestinal Manifestations and Associated Conditions. J Clin Gastroenterol. 2020 Jan;54(1):8-21.

2. Collin P, Mäki M. Associated disorders in coeliac disease: clinical aspects. Scand J Gastroenterol. 1994 Sep;29(9):769-75.

3. Servais A, Noël LH, Roumenina LT, Le Quintrec M, Ngo S, Dragon-Durey MA, Macher MA, Zuber J, Karras A, Provot F, Moulin B, Grünfeld JP, Niaudet P, Lesavre P, Frémeaux-Bacchi V. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. Kidney Int. 2012 Aug;82(4):454-64.

4. Farrell RJ, Kelly CP: Celiac sprue. N Engl J Med 2002, 346:180-188.

5. Ansaldi N, Palmas T, Corrias A, Barbato M, D'Altiglia MR, Campanozzi A, et al. Autoimmune thyroid disease and celiac disease in children. J Pediatr Gastroenterol Nutr. 2003;37(July):63–6.

6. Hunt, Karen A., et al. "A common CTLA4 haplotype associated with coeliac disease." *European Journal of Human Genetics* 13.4 (2005): 440-444.

7. Chistiakov, Dimitry A., and R. I. Turakulov. "CTLA-4 and its role in autoimmune thyroid disease." *Journal of Molecular Endocrinology* 31.1 (2003): 21-36.

8. Scholey J, Freeman HJ (1986) Celiac sprue-associated immune complex glomerulonephritis. J Clin Gastroenterol 8:181–183.

9. Collin P, Maki M (1994) Associated disorders in coeliac disease: clinical aspects. Scand J Gastroenterol 29:769–775.

10. Ludvigsson JF, Montgomery SM, Olen O, Ekbom A, Ludvigsson J, Fored M (2006) Coeliac disease and risk of renal disease—a general population cohort study. Nephrol Dial Transplant 21:1809–1815

11. Sategna-Guidetti C, Ferfoglia G, Bruno M, Pulitano R, Roccatello D, Coppo R: Do IgA antigliadin and IgA antiendomysium antibodies show there is latent coeliac disease in primary IgA nephropathy?. Gut. 1992, 33:476-8.

12. Almroth G, Axelsson T, Müssener E, Grodzinsky E, Midhagen G, Olcén P: Increased prevalence of antigliadin IgA-antibodies with aberrant duodenal histopathological findings in patients with IgA-nephropathy and related disorders. Ups J Med Sci. 2006, 111:339-52. 10.3109/2000-1967-060

13. Pestana N, Vida C, Vieira P, Durães J, Silva G.Celiac Disease as a Rare Cause of Membranous Nephropathy: A Case Report Cureus. 2021 Feb 12;13(2):e13312. doi: 10.7759/cureus.13312.

14. Casella G, Perego D, Baldini V et al.: A rare association between ulcerative colitis (UC), celiac disease (CD), membranous glomerulonephritis, leg venous thrombosis, and heterozygosity for factor V Leiden. J Gastroenterol 2002, 37:761-762. 3.

15. Halma C, Ubels F: Celiac sprue-associated membranous nephropathy. Clin Nephrol 2007, 68:197.

16. Prasad D, Khara HS, Gupta M, Sterman P.Celiac disease associated membranous nephropathy - a rare cause or coincidence? A case report Cases J. 2009 Jun 18;2:7018. doi: 10.4076/1757-1626-2-7018.

17. Jhaveri KD, D'Agati VD, Pursell R, Serur D.Coeliac sprue-associated membranoproliferative glomerulonephritis (MPGN) Nephrol Dial Transplant. 2009 Nov;24(11):3545-8. doi: 10.1093/ndt/gfp353.

18. Biyikli NK, Gökçe I, Cakalağoğlu F, Arbak S, Alpay H.The co-existence of membranoproliferative glomerulonephritis type 1 and coeliac disease: a case report Pediatr Nephrol. 2009 Jun;24(6):1247-50. doi: 10.1007/s00467-009-1118-9.

19. Rostoker G, Wirquin V, Terzidis H, Petit-Phar M, Chaumette MT, Delchier JC, Belghiti D, Lang P, Dubert JM, Meignan M, Lagrue G, Weil B (1993) Mucosal immunity in primary glomerulonephritis. III. Study of intestinal permeability. Nephron 63:286–290

20. Rostoker G, Delchier JC, Chaumette MT (2001) Increased intestinal intra-epithelial T lymphocytes in primary glomerulonephritis. Nephrol Dial Transplant 16:513–517

21. Davin JC, Forget P, Mahieu PR. Increased intestinal permeability to (51 Cr)EDTA is correlated with IgA immune complex-plasma levels in childrenwith IgA-associated nephropathies. Acta Paediatr Scand. (1988) 77:118–24.doi: 10.1111/j.1651-2227.1988.tb10609.x

22. Rostoker G, Terzidis H, Petit-Phar M, Meillet D, Lang P, Dubert JM,Lagrue G, Weil B. Secretory IgA are elevated in both saliva andserum of patients with various types of primary glomerulonephritis.Clin Exp Immunol. (1992) 90:305–11. doi: 10.1111/j.1365-2249.1992.tb07947.x

23. Kovács T, Kun L, Schmelczer M, Wagner L, Davin JC, Nagy J. Do intestinalhyperpermeability and the related food antigens play a role in the progressionof IgA nephropathy? I. Study of intestinal permeability. Am J Nephrol.(1996)16:500–5. doi: 10.1159/000169050

24. Gallagher RB, Cervi P, Kelly J, Dolan C, Weir DG, Feighery C. The subclass profile and complement activating potential of anti-alpha-gliadin antibodies in coeliac disease. J Clin Lab Immunol. (1989) 28:115–21.

25. SalmiTT,HervonenK,LaurilaK,CollinP,MäkiM,KoskinenO,etal.Small bowel transglutaminase 2-specific IgA deposits in dermatitis herpetiformis. Acta Derm Venereol. (2014) 94:393–7. doi: 10.2340/00015555-1764 157.

26. Roos A, Bouwman LH, van Gijlswijk-Janssen DJ, Faber-Krol MC, Stahl GL, Daha MR. Human IgA activates the complement system via the mannan-binding lectin pathway. J Immunol. (2001) 167:2861– 8. doi: 10.4049/jimmunol.167.5.2861

27. Mohammed I, Holborow EJ, Fry L, Thomsen BR, HoffbrandAV, Stewart JS. Multiple immune complexes and hypocomplementaemiain dermatitis herpetiformis and coeliac disease.Lancet 1976;2:487-490.

28. Doe WF, Booth CC, Brown DL. Evidence for complementbindingimmune complexes in adult coeliac disease, Crohn'sdisease and ulcerative colitis. Lancet 1973;1:402-403.

29. Doe WF, Henry K, Booth CC. Complement in coeliac disease. In: Hekkens WTHJM, Pena AS, eds. Coeliac disease. Proceed-ings of the Second International Coeliac Symposium. Leiden,Belgium: Stenfert Kroese, 1974;189-196.

30. Mcneish AS, Rolles CJ, Thompson RA. Complement and itsdegradation products after challenge with gluten in childrenwith coeliac disease. In: Hekkens WTHJM, Pena AS, eds. Coeliacdisease. Proceedings of the Second International CoeliacSymposium. Leiden, Belgium: Stenfert Kroese, 1974:197-202.

31. Lokki AI, Kaartokallio T, Holmberg V, Onkamo P, Koskinen LLE, Saavalainen P, et al. Analysis of Complement *C3* Gene Reveals Susceptibility to Severe Preeclampsia. Front Immunol. 2017 May 29;8:589. doi: 10.3389/fimmu.2017.00589. eCollection 2017.

32. Lee SY, Choi JE, Jeon HS, Choi YY, Lee WK, Lee EB, et al. A panel of genetic polymorphism for the prediction of prognosis in patients with early stage non- small cell lung cancer after surgical resection. *PLoS One* (2015) 10:e0140216. doi:10.1371/journal.pone.0140216

33. Ulańczyk Z, Grabowicz A, Mozolewska-Piotrowska K, Safranow K, Kawa MP, Pałucha A, Krawczyk M, Sikora P, Matczyńska E, Machaliński B, Machalińska A. Genetic factors associated with age-related macular degeneration: identification of a novel PRPH2 single nucleotide polymorphism associated with increased risk of the disease. Acta Ophthalmol. 2021 Nov;99(7):739-749. doi: 10.1111/aos.14721.

34. García M, Álvarez L, Nogacka AM, González-Iglesias H, Escribano J, Fernández-Vega B, Fernández-Vega Á, Fernández-Vega L, Coca-Prados M. CFH polymorphisms in a Northern Spanish population with neovascular and dry forms of age-related macular degeneration. Acta Ophthalmol. 2015 Dec;93(8):e658-66. doi: 10.1111/aos.12790

LEGENDS OF THE FIGURES

Figure 1. Renal histopathological findings

[A,B] Mesangial hypercellularity and thickening of the glomerular capillary wall with double contour formation, giving the glomeruli a lobular appearance (Periodic acid staining, 100X and Hematoxylin Eosin staining, 200X)

[C] Granular C3 deposition (+++) along the capillary wall and in the mesangium (indirect immunofluorescence staining on frozen tissue, 200X)

[D]Segmental IgG deposition (+) along the capillary wall and in the mesangium (indirect immunofluorescence staining on frozen tissue, 200X)