Original Article

Identification of celiac disease associated IgA nephropathy by IgA anti-tissue transglutaminase2 antibody deposits in archived formalin-fixed tissues

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Abstract

Background: The causal association between IgA nephropathy (IgAN) and celiac disease (CeD) is based on their clinical coexistence. In this prospective study, we screened patients with IgAN for CeD and explored the utility of analysis of IgA anti-TG2 antibody deposits, for establishing a causal association.

Methods: Biopsy-proven patients of IgAN were screened for serum IgA anti-tissue transglutaminase antibody (IgA anti-tTG Ab) titer and thereafter were invited to undergo endoscopic duodenal biopsy. Corresponding duodenal and kidney biopsies were subjected to IgA anti-TG2 antibody colocalization study using dual-color immunohistochemistry and immunofluorescence techniques. Additionally, kidney biopsies from 105 patients with IgAN who did not give consent for serology analysis, 30 non-IgA nephropathies, and 10 normal controls were also included. Dual-color-stained slides were interpreted based on stain distribution and intensity scores, and Pearson's index >0.3–1 on confocal imaging was considered significant.

Results: Of a cohort of 151 patients with IgAN, 32 consented to undergo sero-screening and 5 of them had high serum anti-tTG Ab titer. Two out of the latter consented to endoscopic duodenal biopsies, in whom modified Marsh grade 3b changes were identified. Strong IgA anti-TG2 antibody deposits were noted in the kidney and duodenal biopsies of these patients. One patient out of non-consenting 105 patients with IgAN and 3 out of 30 patients with other non-IgA nephropathies also showed IgA anti-TG2 deposits. None of the healthy kidney tissues showed IgA anti-TG2 Ab deposits.

Conclusions: Co-localized IgA anti-TG2 deposits in the kidney biopsies in patients with IgAN help to establish a pathogenic link with CeD. A small proportion of patients with IgAN have associated CeD.

Keywords: Anti-tissue transglutaminase 2, celiac disease, duodenal biopsy, IgA nephropathy, IgA, nephropathy, pathogenesis

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INTRODUCTION

Until recently, an aberrant immune reaction to immunogenic gluten peptides in patients with celiac disease (CeD) was thought to be limited to the intestinal mucosa only, and other extra-intestinal manifestations were considered secondary to enteropathy and malabsorption. However, gradually extra-intestinal manifestations were implicated in CeD pathogenesis.[1] IgA nephropathy (IgAN) is one of the most common glomerulonephritis reported worldwide.[2] The diagnostic hallmark of IgAN is the dominant deposition of under galactosylated polymeric IgA1 antibodies in the glomerular mesangium.[3] Many studies have described the co-occurrence of IgAN with CeD; however, it is still not known whether this association is casual or causal.[4-11] Till now, CeD is identified by the presence of celiac-specific serological tests and other gluten-specific T-cells in the tissue or peripheral circulation. The tissue injury caused by this aberrant immune reaction in them is generally non-specific and there are no characteristic histological features. Demonstration of IgA anti-TG2 Ab deposits in tissue biopsies has been proposed to be a tissue-specific marker of association with CeD.[1,12,13] IgA anti-TG2 Ab deposits have been shown in the duodenal biopsies of patients with CeD,[1,12] and in liver biopsies of patients suspected to develop celiac-associated liver disease.[12] Animal studies have evinced the essentiality of transglutaminase in the development of IgAN, as polymeric IgA1-soluble CD89 mesangial deposits have not yet been identified in IgAN models in absence of transglutaminase2.[7] Since tissue transglutaminase enzyme is involved in the repair of most tissues, a mere immunocytochemical positivity for IgG anti tTG Ab is not indicative of involvement by CeD.[14] Hence, to establish a link between IgAN and CeD, we explored the utility of identifying IgA anti-TG2 Ab deposits in kidney biopsies and corresponding duodenal biopsies of patients with celiac-associated IgAN.

PATIENTS AND METHODS

Ethics

The study design was ambispective (both prospective and retrospective) and ethical clearance (IESC/T-446/30.11.2012) was obtained from the Institute's Ethics Committee.

Patients

From the department of nephrology database, patients with biopsy proven IgAN were identified. These patients were invited for screening for CeD using serum anti-tTG antibody testing, and those who gave informed consent and had raised anti-tTG titers were invited to undergo upper gastrointestinal endoscopic duodenal biopsy. The severity of villous atrophy was assessed using the modified Marsh grading system.[15] The study was done according to the ethical standards of human experimentation in accordance with the Helsinki Declaration (www.cirp.org/library/ethics/helsinki).

Kidney biopsies

The formalin-fixed paraffin-embedded (FFPE) tissue blocks of kidney biopsies and corresponding duodenal biopsies of IgAN patients with high anti-tTG Ab sero titer, and kidney biopsies of non-consenting patients with IgAN (serology screening could not be done) (n = 105), kidney biopsies from patients with non-IgA nephropathies (n 30) including membranous nephropathy (n = 7), membranoproliferative glomerulonephritis (n = 2), and minimal change disease (n = 21), were processed for IgA anti-TG2 antibody

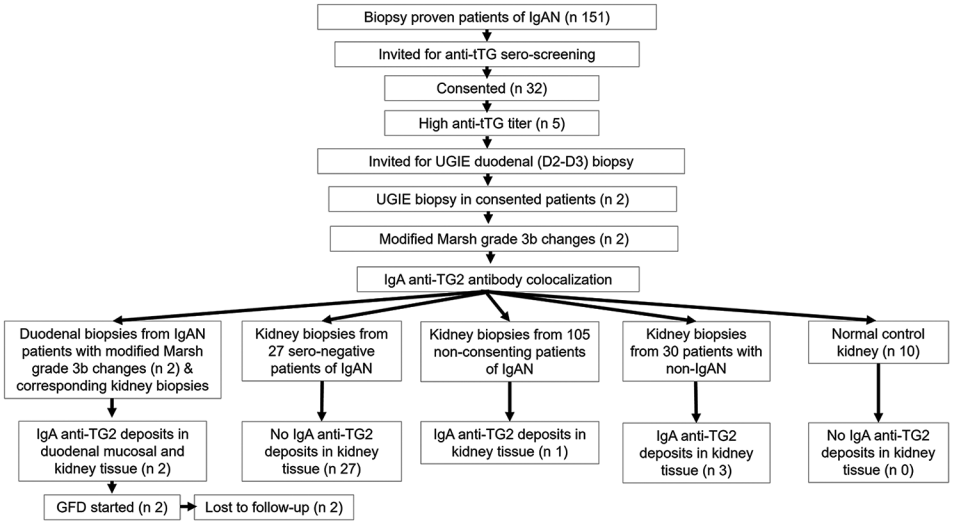

Figure 1: The flow chart shows the work protocol followed in this study

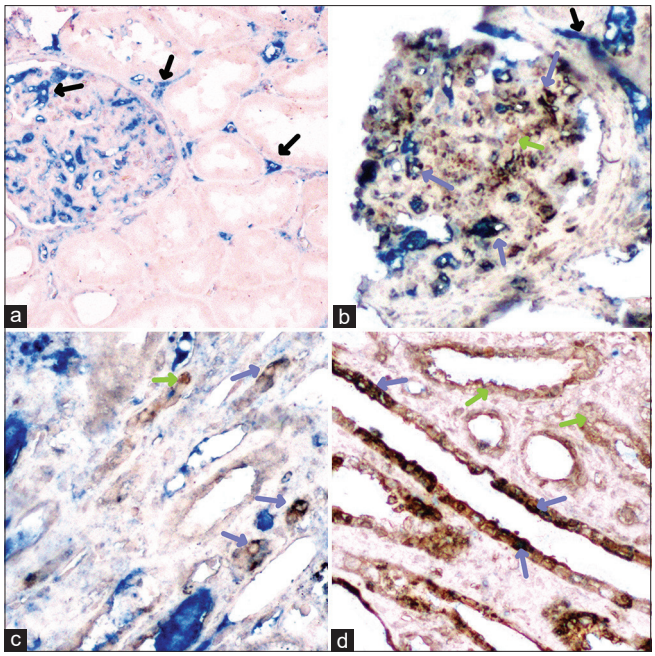

Figure 2: Figure A shows IgA anti-tTG2 dual immunohistochemical staining in a control kidney biopsy. Only IgA positivity in glomerular and peri-tubular capillaries are noted (black arrows) [A × 200]. Kidney biopsy from a patient with IgAN in figure B shows prominent bluish-brown IgA anti-tTG2 antibody deposits (purple arrows) in the glomerular capillary walls and mesangium [isolated anti-TG2 stain (brown)- green arrow; isolated IgA stain (blue)- black arrow] [B × 200]. Kidney biopsies from patients with IgAN in figures C and D show patchy deposits of IgA anti-TG2 colocalized deposits in the tubular wall and peritubular capillaries (purple arrows) [isolated anti-TG2 stain (brown)- green arrow; isolated IgA stain (blue)- black arrow] [C × 100, D × 200]

deposits by dual-color immunohistochemistry (IHC) and dual-color immunofluorescence (IF) colocalization techniques. Normal-looking kidney parenchyma samples, away from renal tumor mass in nephrectomy specimens, were also included as normal controls (n = 10). However, serum anti-tTG Ab sero-titer was not available in the latter [Figure 1].

Demonstration IgA anti-TG2 antibody deposits by dual-color immunohistochemistry technique

From the retrieved FFPE blocks, 4-micron thick sections were obtained, which were then subjected to dual-color IHC staining using peroxidase-labeled rabbit polyclonal anti-human anti-TG2 antibody (1:400 dilution, ab421; ABCAM; chromogen: DAB [Spring Bio, UK]) and alkaline phosphatase labeled monoclonal mouse anti-human IgA antibody (1:1000 dilution, clone M24A; MERCK; chromogen: Vector Blue [Vector Lab, Burlingame, USA]. The IgA/anti-TG2 dual deposits were then analyzed based on stain intensity as follows: negative (0), mild (1), moderate (2), and strongly positive (3). At first, scores were calculated individually in different areas of the biopsies in which dual deposits were noted, like glomeruli, tubules, and interstitial spaces/capillaries. These were then summed up to a cumulative score which was finally graded as grade 0 (cumulative score of 0–3; negative or mild positive); grade 1 (cumulative score: 4–6; moderately positive); grade 2 (cumulative score: 6–9, strongly positive). Isolated anti-tTG2 antibody deposits were highlighted as brown positivity and IgA tissue deposits appeared as blue positivity, while the IgA anti-TG2 colocalized antibody deposits appeared as a unique dirty bluish-brown positivity [Figure 2]. Similarly, IgA anti-TG2 deposits were also analyzed in the duodenal biopsies [Figure 3].

Demonstration of IgA anti-TG2 antibody deposits by dual direct immunofluorescence technique

Dual-color direct IF staining was performed on FFPE kidney biopsies, by using already standardized protocols (1, 12). Anti-tTG2 staining was evaluated using rabbit polyclonal antibody against human TG2 (1:400 dilution, ab421; Abcam, Cambridge, USA) and was detected by goat anti-rabbit IgG (Heavy + Light chains) cross-adsorbed secondary antibody labeled with Alexa Fluor 594 (1:200 dilution, A-11012; Invitrogen). The same sections were thereafter stained with fluorescein isothiocyanate (FITC) conjugated mouse anti-human monoclonal IgA antibody, clone M24A, heavy chain (1:1000 dilution, CBL 114F; MERCK, New York, USA). 4', 6'-diamidino-2-phenylindole (DAPI) was used as a nuclear stain. The IgA/anti-tTG2 dual deposits were then analyzed via confocal microscopy using the NIKON NIS AR software. Recordings of the Pearson's value (ranging from − 1 to + 1) as calculated by the software were graded as follows: 0 (none + mild) (Pearson's index <0.3), 1+ (moderate) (Pearson's index >0.3–<0.6), and 2+ (strong) (Pearson's index >0.6–1). Grades of 1 + and 2 + positivity were considered as evidence of IgA anti-TG2 dual deposits. Anti-TG2 deposits were indicated by red immunofluorescence, green immunofluorescence indicated IgA deposits, while yellow immunofluorescence was evinced as colocalized IgA anti-TG2 tissue deposits [Figures 3 and 4]. Similarly, IgA anti-TG2 deposits were also analyzed in the duodenal biopsies.

Statistical analyses

In this prospective study, as per the study design the screened patients with IgAN who had increased sero titer, pathological changes in duodenal biopsies and IgA anti-TG2 antibody deposits, were only a few of the whole cohort. We descriptively represented the data and did not perform statistical analyses.

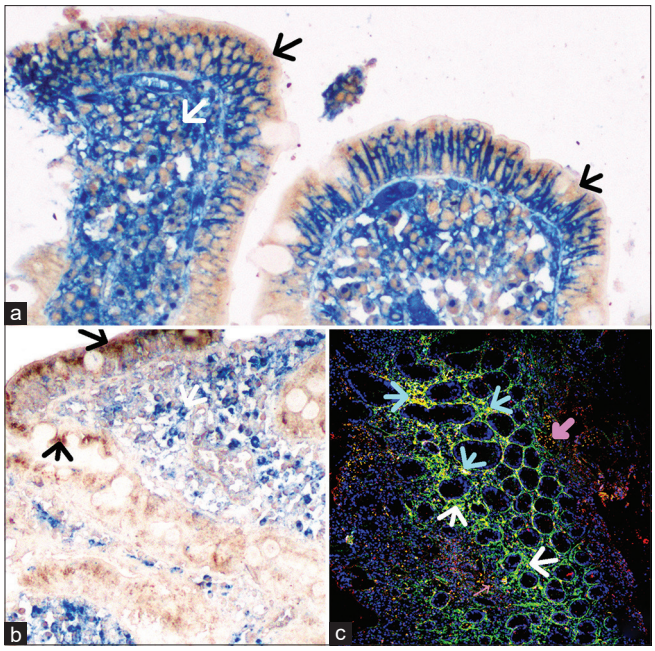

Figure 3: Duodenal biopsy in figure A from a control shows IgA stain positivity in lamina propria plasma cells (white arrow) and excretion of IgA through epithelial paracellular junctions. Anti-TG2 stain (brown) is noted in epithelial cell cytoplasm (black arrows), however, IgA anti-TG2 Ab deposits (bluish brown) are not seen [A × 400]. Corresponding duodenal biopsy from a patient with IgAN in figure B shows IgA anti-TG2 colocalized deposits (dirty brownish blue) in the epithelial cell cytoplasm (black arrows). IgA positivity is noted in lamina propria plasma cells (white arrows) [× 200]. Confocal microscopy image of the duodenal biopsy in figure C, stained with IgA anti-TG2 dual-color immunofluorescence staining, shows yellow IgA anti-TG2 colocalized Ab deposits in the pericrypt stroma, epithelial cells, and capillary walls (sky blue arrows), while green IgA positivity is noted in lamina propria plasma cells and capillary walls (white arrows), and red anti-tTG2 stain is noted in epithelial cells (pink arrows), subepithelial basement membrane and in muscularis mucosae [D × 100]

RESULTS

Clinical details, serological and intestinal biopsy evaluation of the IgAN patients

Of 151 patients with IgAN, only 32 patients gave consent to undergo screening for CeD using serum anti-tTG antibody. Anti-tTG Ab was assessed using ELISA kits (Aesku Diagnostics, Germany) and a titer greater than 18U/mL was considered positive. Five of these 32 patients were found to have high anti-tTG Ab titers as follows: 19.7, 22, 22, 97, and 153 U/mL, respectively. The age of these five patients ranged from 25 to 48 years. Three of these patients were females while two were males. Data of all-other patients of IgAN, as well as non-IgAN, were also collected from the adult Nephrology clinic and their ages were comparable. Of the five consenting patients, on counseling, only two patients (with anti-tTG Ab titers of 97 and 153 U/mL) agreed to undergo UGIE duodenal biopsies and both had villous abnormalities of modified Marsh grade 3b [Table 1]. They were put on a gluten-free diet under the supervision of a nutritionist [Figure 1].

IgA anti-TG2 deposits in the kidney biopsies

In the kidney biopsies, IgA anti-TG2 Ab deposits were noted in the glomeruli, predominantly in the mesangium, but also in the peri-glomerular area around the Bowman's capsule, proximal and distal tubules, and peri-tubular capillaries in interstitial space [Figures 2 and 4]. While 3 of the 5 patients with high serum anti-tTG Ab titer showed IgA anti-TG2 deposits with dual-color IHC technique, 4 of them showed colocalization by dual direct immunofluorescence technique [Figure 4]. In two patients of IgAN with high sero-titer in whom duodenal biopsies were done, IgA anti-TG2 deposits were observed in both the corresponding duodenal and kidney biopsies [Table 1, Figure 3]. The kidney biopsies of the rest of the 27 patients with IgAN with normal anti-tTG sero-titer did not show IgA anti-TG2 Ab deposits by both techniques. The two IgAN patients with serum and biopsy confirmed CeD were put on GFD under a nutritionist, however, they were lost to follow-up.

One patient out of non-consenting 105 patients with IgAN showed moderate IgA anti-TG2 deposits with dual-confocal technique, but not with dual-IHC technique. Serum anti-tTG titer was however not available in these patients. Among the non-IgA nephropathies (as disease controls) none by dual IHC technique showed IgA anti-TG2 deposits, however, three patients including two with features of membranoproliferative glomerulonephritis and one with membranous glomerulonephritis showed moderate (1+) IgA anti-tTG2 Ab deposits by confocal IF

Table 1: Table showing detailed findings of duodenal biopsy and IgA anti-TG2 antibody deposits in the kidney and duodenal biopsies in the seropositive patients of IgAN in this cohort

Sex	Kidney Biopsy	Serum TTG value (U/mL)	Serum TTG cut off (U/mL)	D2 Biopsy	Marsh Grade in D2/3 Biopsy	IgA anti-TG2 IHC in kidney biopsy	IgA anti-TG2 IF in kidney biopsy	IgA anti-TG2 IHC in D2 biopsy	IgA anti-TG2 IF in D2 biopsy
F	IgAN	19.7	18	-	N/A	0	0	N/A	N/A
F	IgAN	22.04	18	-	N/A	0	1+	N/A	N/A
F	IgAN	22.40	18	-	N/A	1+	2+	N/A	N/A
M	IgAN	97	18	+	3b	2+	2+	2+	2+
M	IgAN	154	18	+	3b	2+	2+	2+	2+

N/A- not applicable

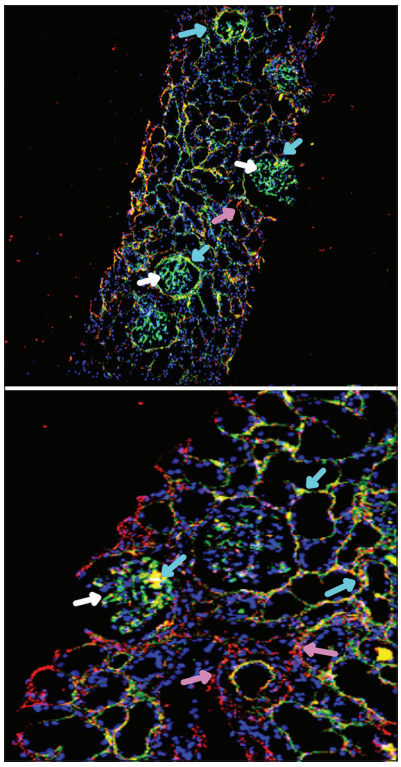

Figure 4: Confocal microscopy image of kidney biopsies from patients with IgAN stained with IgA anti-TG2 dual-color immunofluorescence staining in figures A (and amplified); B show yellow IgA anti-TG2 Ab deposits in the glomerular capillary wall, mesangium, tubular wall, peritubular capillaries, focally in Bowman's capsule, and afferent arterioles (sky blue arrows); while green fluorescence indicates IgA positivity (white arrows) and red immunofluorescence indicates anti-TG2 positivity (pink arrows) [A × 100, B × 400]

technique. None of the healthy kidney tissues included showed IgA anti-tTG2 Ab deposits.

DISCUSSION

Of 32 patients with IgAN who underwent anti-tTG sero-screening, five had high sero-titer and two of them agreed to undergo UGIE duodenal biopsies. Duodenal biopsies from both of these patients showed modified Marsh 3b changes in duodenal mucosa. In these two identified patients with celiac-associated IgAN, IgA anti-tTG2 deposits were identified both in the corresponding renal biopsies and duodenal biopsies by dual-color IHC as well as by dual-IF confocal techniques. IgA anti-TG2 antibody deposits were not identified in the rest of the 27 patients with IgAN who were screened negative for CeD.

The pathogenesis of IgAN is complex and characterized by dysregulated IgA response to a wide range of antigenic stimuli and formation and mesangial deposition of polymeric IgA1 antibody.[3,16,17] An association between IgAN and CeD has been proposed for more than a decade now.[4-11] While an association has been described, it is yet to be established whether this association is casual or causal. Papista *et al*.,[8] in a study of humanized mice, have demonstrated that early treatment of mice with a GFD prevented mesangial IgA deposits, indicating a role of dietary gluten in the pathogenesis of IgAN. In isolated case reports, a complete clinical remission of IgAN was demonstrated with GFD in whom an associated CeD was suspected clinically.[6]

Since the tTG enzyme is present in most cells and comes out in an extra-cellular environment on cell damage, IgA type of anti-tTG Ab staining in duodenal and extra-intestinal organs was thought to be a marker of tissue damage in CeD.[14] Therefore, it is essential to demonstrate IgA type of anti-tTG Ab deposits in the tissues to confirm the deposition of circulating IgA type of anti-TG2 antibody in the affected organ. IgA anti-tTG2 Ab can be demonstrated in the tissues using an antibody colocalization technique using either dual-color IHC or confocal IF microscopy.[1,12] IgA anti-TG2 co-localization was identified in the duodenal biopsies of patients with CeD, potential CeD, and even seronegative CeD, and biopsies from other extra-intestinal biopsies such as liver, skin, lymph node, brain, and appendix.[18-20] In kidney biopsies also, IgA anti-TG2 Ab deposits were demonstrated in IgAN patients.[4,11] This study is the first planned prospective study on a cohort of IgAN patients to identify the co-existence of CeD and confirm the association with IgA anti-TG2 Ab deposits in kidney tissue.

IgA anti-TG2 Ab colocalization in this study was explored by both dual-color immunohistochemistry and dual-color immunofluorescence techniques in the corresponding kidney and duodenal mucosal biopsies. The staining protocols of both these techniques were optimized on FFPE tissue so that the technique can be performed on archived tissue blocks, whenever deemed necessary.[1,12] IgA anti-TG2 colocalization was identified in 3 of 5 sero-positive IgAN patients with dual-color IHC technique, and in 4 of 5 patients by dual direct IF technique. One patient with IgAN with high anti-tTG sero-titer did not show colocalization of IgA anti-TG2 Ab in the kidney biopsy, and in this patient the serum anti-tTG sero-titer was less than 2 times the upper limit of normal (anti-tTG Ab titer: 19.7 IU/L; cut-off value 18 IU/L). Strong colocalization of IgA anti-TG2 Ab was observed in the corresponding kidney and duodenal biopsies in two patients of celiac-associated IgAN, identified in this prospective cohort. None of the 27 anti-tTG seronegative IgAN patients had IgA anti-TG2 Ab deposits in renal biopsies. Nurmi R *et al*.,[4] suggested IgA anti-TG2 Ab deposits (3/9 patients) in the kidney are

not celiac associated-IgAN specific, as they identified these Ab deposits in three anti-tTG sero-negative patients also. It is important to mention that in two of these three patients with IgA anti-TG2 Ab deposits, a diagnosis of CeD was established a year later.[4] While the kidney biopsies of three patients with non-IgAN, which showed IgA anti-TG2 Ab deposits in the index study, could not be screened for CeD, as informed consent was not available.

While the present prospectively planned study adds to the body of evidence of a causal relationship between IgAN and CeD; limited availability of informed consent for anti-tTG sero-screening and UGIE biopsy in sero-positive patients for further evaluation was a limitation. Furthermore, the two newly diagnosed patients of celiac-associated IgAN in this cohort were advised GFD but were lost to follow-up. However, the need of following up on patients with CeD who are put on GFD cannot be disregarded, especially in patients with extra-intestinal involvement to prove the association. However, it is not always easy to counsel patients and convince them and their family members on the importance of follow-up, as they may not have any significant morbidity related to the gastrointestinal tract. This is probably the reason both of our patients discontinued following up in the celiac disease clinic. In literature, non-compliance has been reported in 25–50% of children and adolescents.[21-24] Keeping this in mind, our study findings become more relevant, as detecting IgA anti-TG2 deposits in the archival tissue itself is quite an effective technique in establishing an association with CeD in such patients. However, we do not deny that non-availability of follow-up data is a limitation in this study. Koivuviita *et al*.[6] and Slavin *et al*. in their corresponding case reports showed reversal of dysregulated parameters in a patient with CeD-associated IgAN who were put on GFD for 5 years. However, we could not demonstrate this aspect.[24]

In conclusion, IgA anti-tTG2 Ab colocalization study in kidney biopsies of patients with suspected celiac-associated IgA nephropathy can establish their causal link. A small proportion of patients with IgAN have associated CeD.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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