Coeliac sprue-associated membranoproliferative glomerulonephritis (MPGN)

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Abstract
Coeliac sprue (CS) may occur in association with immune complex-mediated diseases, including IgA nephropathy, dermatitis herpetiformis and thyroiditis. An association of CS with membranoproliferative glomerulonephritis (MPGN) type 1 is rare, with only two prior cases reported. Here we describe a 45-year-old man with no prior medical history who presented initially with microhaematuria, subnephrotic proteinuria and hypocomplementaemia. A renal biopsy revealed MPGN type 1 with negative serologic workup for secondary causes. The patient was treated conservatively with angiotensin-converting enzyme inhibitors. Several months later, he developed daily non-bloody diarrhoea and was found to have worsening hypoaalbuminaemia, hypophosphataemia and severe iron deficiency anaemia. A diagnosis of CS was established based on elevated tTGA (IgA anti-tissue transglutaminase) antibody and positive IgA antiendomysial antibody titres. Proteinuria resolved completely following the initiation of a gluten-free diet, without the use of immunosuppressive therapy and despite tapering of angiotensin-converting enzyme inhibitor. This case illustrates that CS-associated MPGN may precede overt clinical evidence of coeliac disease and may respond to gluten-free diet, without resort to immunosuppressive therapy.

Keywords: coeliac sprue; glomerular disease; glomerulonephritis; membranoproliferative; MPGN

Introduction
Coeliac sprue (CS) has been reported in association with several immune complex-mediated diseases, including IgA nephropathy, dermatitis herpetiformis and thyroiditis. Immune complexes originating from the small intestinal mucosa have been hypothesized to deposit in various organs to initiate disease. In 1978, Katz et al. reported the first case of CS-associated membranoproliferative glomerulonephritis (MPGN) [1]. A second case was described by Scholey et al. in 1986 [2]. Here we report the third case of biopsy-documented MPGN type 1 associated initially with subclinical CS. The clinical resolution of renal disease following treatment directed to CS supports a direct aetiologic association.

Case report
A 45-year-old Caucasian man was in normal state of health, without any known prior medical conditions, until he developed proteinuria of 2.1 g/day that was detected on a routine physical examination in February 2005. He had no significant past medical history. A review of the system was negative. Initial physical examination was normal except for trace pitting oedema of the lower extremities. Laboratory investigation revealed a BUN of 7.8 mmol/L (2.8–7.0 mmol/L) and creatinine of 97 µmol/L (35–88.4 µmol/L), with calculated creatinine clearance of 1.3 mL/s. Urinalysis revealed 2+ dipstick-positive proteinuria and microscopic haematuria and hypocomplementaemia. A diagnosis of CS was established based on elevated tTGA (IgA anti-tissue transglutaminase) antibody and positive IgA antiendomysial antibody titres. Proteinuria resolved completely following the initiation of a gluten-free diet, without the use of immunosuppressive therapy and despite tapering of angiotensin-converting enzyme inhibitor. This case illustrates that CS-associated MPGN may precede overt clinical evidence of coeliac disease and may respond to gluten-free diet, without resort to immunosuppressive therapy.

Keywords: coeliac sprue; glomerular disease; glomerulonephritis; membranoproliferative; MPGN

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Fig. 1. A representative glomerulus displays global mesangial hypercellularity and double contours of the glomerular capillary walls with few infiltrating mononuclear leukocytes. Between the double contours, there were focal PAS-positive deposits. Some glomerular capillaries also contained infiltrating mononuclear leukocytes. No intracapillary deposits, necrotizing features or crescents were identified. There was minimal focal (~5%) interstitial inflammation by lymphocytes and monocytes. No arteritis, tubular atrophy, interstitial fibrosis or foam cells were identified. There was mild focal intimal sclerosis of small arteries. Arrow points to double contouring (Periodic acid–Schiff, ×1000).

Fig. 2. There are global granular mesangial and peripheral capillary wall deposits for IgG (immunofluorescence, ×400).

The renal biopsy findings were consistent with MPGN type 1. Given the low C3 and a negative workup for secondary causes of MPGN, a diagnosis of idiopathic MPGN type 1 was considered as a diagnosis of exclusion.

The patient was treated conservatively from March 2005 with valsartan 80 mg/day and the dose was slowly increased to 120 mg/day. He was placed on a low-potassium, low-salt and 1 g/kg protein diet. In the next few months, he was not able to tolerate this low-dose therapy due to hyperkalaemia and was switched to lisinopril 10 mg/day in October 2005. Subsequently, his renal function remained stable but his anaemia worsened to haemoglobin of 6.64 mmol/L, which was first detected in September 2005. Based on his worsening anaemia, a workup for non-renal causes of anaemia was initiated. The patient reported daily non-bloody diarrhoea, worsening lower extremity oedema and a 10 kg weight loss. His albumin had decreased to 12 g/L by December 2005 despite the reduction in proteinuria to 0.8 g/24 h. His other laboratory data showed hypophosphataemia of 0.64 mmol/L (0.7–1.4 mmol/L) and total protein of 38 g/L (55–80 g/L). Haematologic workup disclosed low iron level of 3.7 µmol/L (9–28 µmol/L), transferrin saturation of 14% (13–53%), low folate of 6.6 nmol/L (9–45 nmol/L) and vitamin B12 level <148 pmol/L (132–680 pmol/L). Stool cultures for ova and parasites were negative for infectious aetiologies.
Malabsorption syndrome was considered as a possible unifying diagnosis. A colonoscopy revealed only external and internal haemorrhoids. Given a recent acute coronary syndrome, an endoscopy was not performed due to the risk of discontinuing clopidogrel to perform the procedure. Serological testing for CS was performed. The tTGA (IgA anti-tissue transglutaminase) antibody was >100/mL (<5/mL), the IgA antiendomysial antibody titre was strongly positive at 1:640 (<1:5) and the antigliadin IgA was strongly positive at >100/mL (<11/mL). The patient was placed on a gluten-free diet by January 2006.

Within 3–6 months of initiation of gluten-free diet, the patient's anaemia, diarrhoea, oedema and hypoalbuminaemia resolved. Two years after starting a gluten-free diet, his listipril was reduced to 5 mg/day, and urinary protein was only 156.2 mg/24 h with serum creatinine 79.5 μmol/L, haemoglobin 8.9 mmol/L and erythrocyte sedimentation rate 7 mm/h. His haematuria has also resolved. Repeat complement levels were unchanged. Repeat tTGA antibody in May 2009 was 9/mL (<5/mL), significantly lower than his initial test, and antigliadin peptide antibody IgA was 3/mL (<11/mL).

### Discussion

CS was first described in 1888 by Samuel Gee [3]. The basic disorder is a sensitivity to gluten, the component of wheat and related grains such as oat, barley and rye, which contain the protein gliadin. When unrecognized and untreated, CS is associated with a high mortality [4]. The classic presentation includes symptoms of malabsorption such as steatorrhoea, weight loss or other signs of nutrient or vitamin deficiency including hypoalbuminaemia. In our case, there was weight loss, along with protein, iron, folic acid and other vitamins and electrolyte losses. The resolution of CS usually occurs within several weeks to months following initiation of a gluten-free diet, as occurred in our case [3]. The association between CS and other immune disorders may be due to sharing of a common genetic predisposition, the HLA-DQw2 histocompatibility antigen. Other autoimmune disorders associated with this disease include dermatitis herpetiformis [3], diabetes mellitus type 1 [4], primary biliary cirrhosis [5], autoimmune thyroiditis [6] and microscopic colitis [7].

Testing should begin with serological evaluation. Serum IgA endomysial and tissue transglutaminase antibody testing have the highest diagnostic accuracy [8]. The IgA and IgG antigliadin antibody tests are less sensitive and specific [8]. All of these serologies were performed in our patient, but only the first two were positive, leading to a serologic diagnosis of CS. Typically, patients with a positive IgA endomysial or transglutaminase antibody tests should undergo a small bowel biopsy. Grossly, the small intestinal mucosa appears atrophic with loss of folds, development of fissures and nodular contours [8]. Microscopically, the lamina propria and epithelium of the small intestine are typically infiltrated by numerous B lymphocytes and plasma cells, leading to villous flattening. The diagnosis can be established when there is concordance between the serologic results and small bowel biopsy findings and is confirmed when symptoms resolve on a gluten-free diet [8]. Given our patient's cardiac risk, it was prudent to forego a small bowel biopsy, especially because a diagnosis of CS could be made based on evidence of malabsorption, laboratory data, strong serological evidence and resolution of symptoms with a gluten-free diet. A kidney biopsy revealed an immune complex-mediated glomerulonephritis with features of MPGN type I and dominant glomerular deposits of IgG and IgM. Based on the negative serologies and lack of other clinical signs and symptoms, the most common secondary causes [9] of MPGN (such as hepatitis C, cryoglobulinaemia, dysproteinemia and autoimmune disease) were ruled out.

The renal disease most commonly associated with CS is IgA nephropathy [9–13]. Such patients with IgA nephropathy often have circulating IgA-antigliadin antibodies. Oral immunization with gliadin can induce IgA nephropathy in mice [11]. Only a few cases of reported IgA nephropathy had well-documented CS and showed remission or improvement of renal disease after withdrawal of gluten from the diet. Although our patient had glomerular deposits of IgA (2+ intensity), these IgA deposits were less intense than those for IgG (3+) and IgM (3+), and therefore did not reach a diagnostic threshold for IgA nephropathy.

There are only two prior reports of MPGN associated with CS [1,2]. The first patient with immune complex glomerulonephritis and CS was recorded by Katz et al. [1] in 1978. Circulating immune complexes and precipitating serum antibodies to gluten and gliadin were present. After institution of a gluten-free diet, circulating immune complexes and antigliadin antibodies disappeared from the patient's serum. Although a repeat biopsy was not performed, the resolution of diarrhoea and proteinuria indicated simultaneous improvement in the CS and glomerulonephritis. Swarbrick et al. [14] described a 15-year-old boy with CS, mesangiocapillary glomerulitis with electron dense deposits and chronic active hepatitis. Adoption of a gluten-free diet also resolved the diarrhoea, hepatitis and renal failure. Scholey et al. [2] reported a case of biopsy-proven CS and MPGN type I. After the initiation of a gluten-free diet, diarrhoea and oedema quickly resolved but improvement in proteinuria was slower. Although, there was persistent hypocomplementaemia, our patient clinically responded well to a gluten-free diet, with reduction in proteinuria to <200 mg/24 h and negative repeat antigliadin IgA and tTGA antibodies at most recent follow-up. The mild membranoproliferative pattern, absence of glomerular scarring and absence of chronic tubulointerstitial disease can be considered favourable prognostic features in our case, despite the heavy load of immune deposits detected by immunofluorescence and electron microscopy.

This case illustrates the importance of identifying secondary causes of MPGN, especially in the adult patient, an age group where idiopathic MPGN type I is uncommon. The possibility of CS should not be overlooked, particularly in the setting of disproportionately severe anaemia, diarrhoea and hypoalbuminaemia relative to the mild level of renal dysfunction and the subnephrotic proteinuria.

The precise mechanism of glomerular immune deposition in CS is unknown. The association of CS with other autoimmune disorders suggests a potential role for dysreg-
ulated immune responses, possibly occurring in susceptible individuals with a genetic predisposition. Persistent stimulation by cytokines such as IFN-γ and TNF-α could promote dietary or autoantigen presentation to T cells and B cells followed by production of specific antibodies. Complexing of antibodies to local or circulating antigens presumably leads to chronic immune complex deposition in the glomerulus, where complement activation could promote hypocomplementaemia. A membranoproliferative pattern of glomerulonephritis usually indicates the presence of a chronic immune stimulus with continuous or episodic levels of circulating immune complexes [15]. In our case, the close temporal association between initiation of a gluten-free diet and the resolution of proteinuria (without use of immunosuppressive therapy and despite tapering of angiotensin enzyme inhibitor) strongly supports an aetiologic association. This case illustrates that MPGN may precede overt clinical evidence of CS, via subclinical disease mediated by chronic antigen stimulation. Importantly, CS-associated MPGN can resolve clinically following initiation of gluten-free diet, without resort to immunosuppressive therapy.

Conflict of interest statement. None declared.

References


Received for publication: 9.6.09; Accepted in revised form: 25.6.09

Haemolytic uraemic syndrome caused by factor H mutation: is single kidney transplantation under intensive plasmatherapy an option?

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Abstract

Complement factor H (CFH) mutation is one of the causes of atypical haemolytic uraemic syndrome (aHUS). Patients with CFH mutation-associated aHUS progress often to end-stage renal disease despite plasma exchange therapy. When such patients are transplanted, aHUS recurs almost invariably and causes graft failure making the rationale of single kidney allograft transplantation questionable. Since CFH is synthesized mostly by the liver, combined liver–kidney transplantation has been recommended. However, fatal outcomes have been reported using this strategy. We report a case of successful single kidney allograft transplantation in a patient with a CFH gene mutation (R1210C), who had end-stage renal failure after three flares of aHUS treated...