Immunoglobulin A Nephropathy and Ulcerative Colitis: A Focus on Their Pathogenesis

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Key Words
Immunoglobulin A nephropathy · Ulcerative colitis · Complement · T lymphocyte · Hematuria

Introduction

Ulcerative colitis (UC) is characterized by recurring episodes of inflammation limited to the mucosal layer of the colon, invariably involving the rectum and extending in a proximal and continuous pattern to other portions of the colon. Clinically, symptoms may vary from intermittent rectal bleeding associated with the passage of mucus and diarrhea in the mild spectrum of the disease, to the more frequent loose, bloody stools, abdominal pain, fever, anemia and malnourishment observed in the more severe forms [1]. UC may be associated with a number of extraintestinal complications, involving almost any organ system. Approximately 25% of patients have a combination of extraintestinal manifestations [2, 3]. The organs most commonly involved include the skin (erythema nodosum, pyoderma gangrenosum, aphthous ulcers), joints (ankylosing spondylitis and reactive arthritis), biliary tract (sclerosing cholangitis, bile duct carcinoma, autoimmune chronic hepatitis) and eyes (uveitis, episcleritis, corneal ulcers) [2–4]. However, renal and genitourinary tract manifestations are quite rare, particularly glomerulonephritis. Herein we describe a patient with UC and chronic intermittent episodes of indolent macrohematuria. A kidney biopsy diagnosed immunoglobulin A nephropathy (IgAN). IgAN can be primary (most cases) or secondary (associated with: seronegative arthritis, hepatic cirrhosis, celiac disease, vasculitis, human immunodefici-
Fig. 1. Mucosal rectal biopsy showing cryptitis. HE. × 235.

Fig. 2. Renal biopsy with mesangial expansion and mild hypercellularity. PAS. × 590.

Fig. 3. Diffuse mesangial granular immunofluorescence with an anti-IgA antibody. × 235.
ciency virus (HIV), etc.) but is rarely associated with UC [5–8]. Although elevated immunoglobulin levels have been documented in both entities, it has been suggested that altered T-helper cells’ function might be the initial common derangement of both UC and IgAN [9–13]. In IgAN such alteration in CD4-positive T cells causes a nonspecific stimulus on plasma cells in the bone marrow to secrete polymeric IgA1 into the circulation [14–17] (ultimately causing IgAN) and of IgG1 and IgG3 in UC [18, 19] culminating in both cases with a common state of local cytokine secretion and tissue inflammation.

Case Report

A 26-year-old woman with a past history of undiagnosed bouts of asymptomatic macrohematuria experienced in the last 2 years several episodes of diffuse abdominal pain and diarrhea. During one severe attack she was admitted to the hospital due to bloody stools, and a colon biopsy was consistent with UC (Fig. 1). She was started on mesalazine 2 g/day with good results. The patient was normotensive and well nourished; she had normal renal function and the urinalysis showed 10–15 red blood cells/HPF, with 80% of dysmorphic erythrocytes and 3% of acanthocytes without proteinuria. Other laboratory results included negative tests for hepatitis B, C; HIV, rose Regan, antinuclear antibody, perinuclear and cytoplasmic antinuclear cytoplasmic antibody and cryoglobulins; complement levels were within normal limits, IgA levels were 470 mg/dl (normal 150–350), HLA profile: A3, A25; B51, B7; DR 12, 15, 52, 53. A renal ultrasound was normal and a kidney biopsy was consistent with IgAN (Fig. 2, 3). After 4 months of follow-up, she was doing well and was free of symptoms, with normal renal function and persistent asymptomatic microhematuria.

Discussion

The patient described herein presents with the uncommon association of IgAN and UC [5–8]. Such association may be supported by their common complications such as ankylosing spondylitis, scleritis and dermatitis herpetiformis [2–4, 15] and by the important fact that in both entities immunological derangements have been implicated [7, 9, 10, 15, 20–22].

IgAN, the most frequent cause of glomerulonephritis, was initially considered to be a benign disease until it was recognized than annually, 1–2% of patients have a progressive course to end-stage renal disease requiring dialysis, 3% at 5 years and 8% at 10 years [23, 24]. Almost 50% of patients with IgAN have elevated serum IgA levels, especially of the polymeric IgA1 subclass derived from bone marrow and later deposited in the glomeruli [15, 23, 25]. The pathogenesis of IgAN is unknown [15]. IgA antibodies to dietary components (gluten, bovine albumin) may be found in some patients [26]. No infectious pathogen has been identified, despite the recurrence of acute disease after infectious pharyngitis [25]. The presence of granular deposits of IgA and the third component of complement (C3) in the mesangium shows that it is a circulating immune complex-mediated disease involving activation of the alternative complement pathway. IgA1 molecules are low-affinity antibodies generated by T-helper lymphocyte stimulation of bone marrow plasma cells [15, 27] or circulating B lymphocytes [28] that are capable of activating the alternative pathway of complement [29]. Several studies have reported increased fractions of peripheral B lymphocytes expressing surface IgA [15, 25]. However, it is unlikely that the excess circulating IgA is the sole cause of IgA renal deposition, as indicated by the rate occurrence of IgAN in states of high IgA levels. In addition, the number of T-helpe cells, which are endowed with the capacity to switch B cells from IgM to IgA synthesis, is increased in patients with IgAN [14, 15]. Recently, IgA from patients with IgAN has been found to exhibit abnormal glycosylation, modifying the stability of the IgA1 molecule and leading to different degrees of cytokine-mediated glomerular inflammation [30]. Still other patients with IgAN manifest abnormalities with clearance of IgA immune complexes [31] and diminished number of macrophages with receptors for the Fc portion of IgA [32]. Interestingly, in some patients with IgAN who were later transplanted, IgAN recurred in the grafts (50%) without loss of graft function [33, 34]. Additionally, when a kidney with IgAN was inadvertently transplanted into a patient whose renal insufficiency was unrelated to IgAN, the deposits disappeared, meaning that an intrinsic circulating factor, presumably formed in the bone marrow, caused the IgA mesangial deposition [35]. It has recently been observed that a patient with IgAN and chronic myeloblastic leukemia who underwent bone marrow transplantation cured both the leukemia and the IgA deposits, again suggesting that anomalies of bone marrow stem cells may also be involved in the pathogenesis of IgAN [9]. The continuing debate over the site of origin of polymeric IgA1 is not resolved, albeit most of the available data now indicate the bone marrow a candidate [9, 36]. IgA appears to be an epiphenomenon and recent data suggest that abnormal T-lymphocyte function drives the increased IgA production by B cells [37–39].

Clear evidence exists for the activation of the immune response in inflammatory bowel diseases [12, 13]. Similarly to what has been postulated with IgAN, many hypotheses have emerged: Microbial pathogens as anti-
genic triggers; some common dietary antigens against which the patient mounts an abnormal vigorous immune response and finally an autoimmune theory, in which the antigenic trigger could be located on the patient's own intestinal epithelial cells [40–42]. Nevertheless, bearing in mind the fact that UC is associated with many other autoimmune diseases (thyroid disease, diabetes mellitus, pernicious anemia) [43] and the recent isolation of certain circulating antibodies in UC patients, suggest that the origin of this disorder may lie outside the colon [44]. An increased number of circulating B cells and autoantibodies in UC patients [20, 21] may indicate that abnormal B-cell regulation may be involved [12, 45]. Circulating T cells from patients with UC show increased proliferation to antigens in vitro [13, 46]. Although the number of T cells is increased in intestinal mucosa of UC patients, the CD4/CD8 ratio is conserved, but the degree of activated T cells is high [47]. C3 and its activated fragment C3b have been found in UC mucosa along the epithelial basement membrane [48]. Moreover, macrophage functional aberrations involving both complement receptors and Fc receptors have also been identified in UC [49].

CD4-positive lymphocytes regulate immunoglobulin production by B cells: In UC patients there are markedly increased levels of IgM and IgG1 and IgG3 (but not IgA) [8, 18, 19], whereas in IgAN, IgA levels are increased [15, 23, 25] and IgG can also be found in glomeruli together with IgA and C3 molecules. Noteworthy, we have retrospectively performed immunohistochemistry studies on the colonic biopsy of our patient searching for IgA molecules in the colonic mucosa. Despite IgA high levels in our patient, no IgA molecules were observed in the colonic biopsy, in agreement with other authors [50]. Therefore, the origin of both diseases appears to be in CD4-positive T-cell dysregulation of B-cell secretion, regardless of the type of immunoglobulin secreted. Both IgG in UC and IgA1 in IgAN [29] are capable of complement activation. These states of hyperimmunoglobulinemia and complement activation appear to be the consequences rather than the causes of these entities. IgAN and UC have many downstream inflammatory processes in common that contribute to tissue damage. Many of these mediators are shared by UC and IgAN: interleukin (IL)-1, IL-2, IL-5, IL-6, tumor necrosis factor, interferon-γ, transforming growth factor-β [2, 30]. Finally, both diseases have been related to human leukocyte antigens (HLA): HLA DR2 with UC [51] and HLA A2, B12, B27, B35 and DR4 with IgA [52–54], but our patient lacked these antigens. Noteworthy, in extraintestinal manifestations of UC, HLA antigens A2, DR1 and DQw5 have been associated [51].

UC rarely affects the kidney. Renal tubular damage has been described as a possible association [55] and glomerulonephritis is unusual. In the English literature only 4 cases of IgAN and UC have been described [5–8], the first by Dard et al. [5] in 1983. One of the reasons why both diseases are not found more frequently may be due to underdiagnosis, as patients with isolated hematuria (the most common presentation of IgAN) are not always biopsied, and intermittent mild states of diarrhea are only treated symptomatically and not investigated in depth. Moreover, this underdiagnosis of IgAN has led to confusion in the interpretation of the natural history of this common entity, recently reviewed by D’Amico [56] and thus few, if any, valid therapeutic approaches have been appropriately assessed. Of the 4 cases, in only 1 IgAN preceded UC [7], but in all hematuria plus proteinuria were present. It is known that proteinuria represents a more advanced state of IgAN, suggesting that (as in our patient) it may develop before UC, when asymptomatic microhematuria is the first sign of the disease and not referred by the patient or not studied by the physician. In 2 of the cases, ankylosing spondylitis was also present [5, 6]. Finally, the simultaneous occurrence of both entities together does not appear to modify the clinical course or outcome of each disease separately. Sulphasalazine, an option for UC management, can be nephrotoxic through its metabolite sulfapyridine causing interstitial nephritis [57, 58], renal tubular acidosis associated with interstitial nephritis [59], or urolithiasis, being the stone composed of acetylsulfapyridine [60]. The use of 5-aminosalicylic acid (5-ASA or mesalazine), the active moiety of sulphasalazine, has greatly replaced the use of sulphasalazine. Although 5-ASA has a significantly reduced toxicity compared to sulphasalazine, there have been reports of nephrotoxicity, therefore presenting a dilemma regarding its use as maintenance therapy in this setting [61].

In summary, IgAN and UC have several features in common. Both diseases have been associated with other autoimmune disorders, possess CD4-positive T-cell dysregulation and B-cell overproduction of immunoglobulins and complement activation; their origins may be a common immunologic derangement that appears to be in the bone marrow.
References


