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Case Report

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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

Abstract
The immune response has largely been implicated in the pathogenesis of inflammatory bowel disease (ulcerative colitis and Crohn's disease) and immunoglobulin A nephropathy. We present a 26-year-old woman with a long past history of asymptomatic macroscopic hematuria who later developed several episodes of bloody stools and abdominal pain. A colonic biopsy disclosed ulcerative colitis and a renal biopsy was consistent with immunoglobulin A nephropathy. Immunoglobulin A nephropathy is the most common glomerulonephritis, being end-stage renal disease a rare but the most serious complication. It can be primary or secondary, but the association between both entities is unusually observed. We discuss the possible immunologic mechanisms involved and believe the initial immunologic derangement originates in the bone marrow. We suggest both conditions must be considered when either a patient with ulcerative colitis and micro- or macrohematuria or with renal involvement and a past history of diarrhea or abdominal pain presents.

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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 immunodefi-

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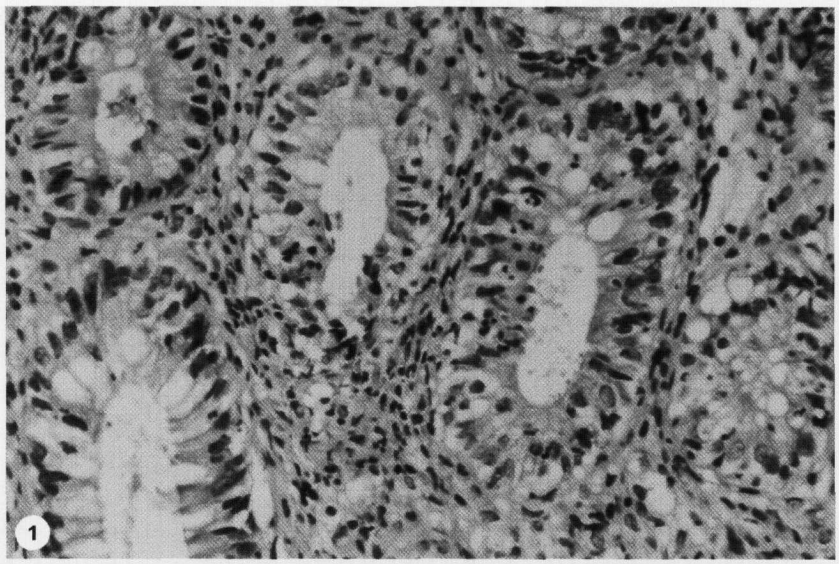

Fig. 1. Mucosal rectal biopsy showing cryptitis. HE. × 235.

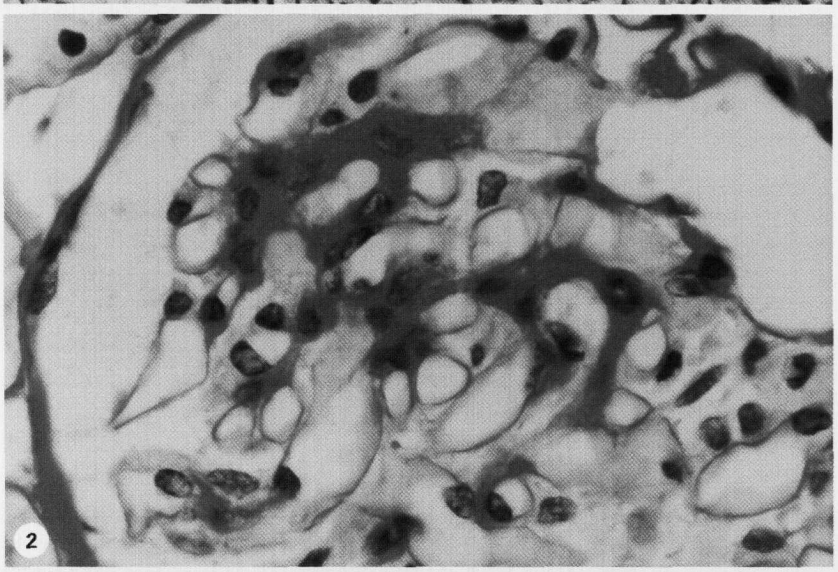

Fig. 2. Renal biopsy with mesangial expansion and mild hypercellularity. PAS. × 590.

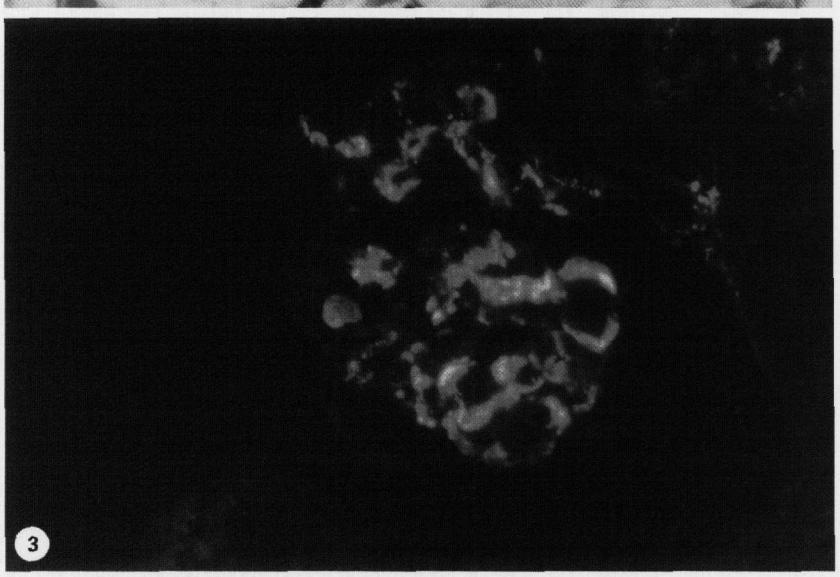

Fig. 3. Diffuse mesangial granular immunofluorescence with an anti-IgA antibody. × 235.

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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 colonic 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 proteinura. 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-helper 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-

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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 hypergammaglobulinemia 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 tissular 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 acetyl sulfapyridine [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.

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References

1 Langholz E, Munkholm P, Davidsen M, Binder V: Course of ulcerative colitis: Analysis of changes in disease activity over years. Gastroenterology 1994;107:3–11.

2 Das K: Relationship of extraintestinal involvements in inflammatory bowel disease: New insights into autoimmune pathogenesis. Dig Dis Sci 1999;44:1–13.

3 Monsen U, Sorstad J, Hellers G, Johansson C: Extracolonic diagnoses in ulcerative colitis: An epidemiological study. Am J Gastroenterol 1990;85:711–716.

4 Greenstein A, Janowiz H, Sachar D: The extraintestinal complications of Crohn's disease and ulcerative colitis. A study of 700 patients. Medicine 1976;55:401–412.

5 Dard S, Kenouch S, Mery J, Baumelou A, Beaufils H, Baglin A: A new association: Ankylosing spondylitis and Berger's disease. Kidney Int 1983;24:129.

6 Bruneau C, Villiaurney J, Avouac B, et al: Seronegative spondyloarthropathies and IgA glomerulonephritis: A report of four cases and a review of the literature. Semin Arthritis Rheum 1986;15:179–184.

7 Iida H, Asaka M, Izumino K, Takata M, Sasayama S, Tanaka M: IgA nephropathy complicated by ulcerative colitis. Nephron 1989;53: 285–286.

8 Peeters A, van der Wall-Bake L, Daha M, Breedveld F: Inflammatory bowel disease and ankylosing spondylitis associated with cutaneous vasculitis, glomerulonephritis, and circulating IgA immune complexes. Ann Rheum Dis 1990;49:638–640.

9 Imasawa T, Nagasawa R, Utsunomiya Y, et al. Bone marrow transplantation attenuates murine IgA nephropathy: Role of a stem cell disorder. Kidney Int 1999;56:1809–1817.

10 Noris M, Remuzzi G: IgA nephropathy: A stem cell disease? Kidney Int 1999;56:1964–1966.

11 Van Es L, De Fijter J, Daha M: Pathogenesis of IgA nephropathy. Nephrology 1997;3:3–12.

12 Matsuura T, West G, Youngman K, Klein J, Fiocchi C: Immune activation genes in inflammatory bowel disease. Gastroenterology 1993; 104:448–458.

13 Fiocchi C, Battisto J, Farmer R: Studies on isolated gut mucosal lymphocytes in inflammatory bowel disease. Detection and activated T cells and enhanced proliferation to *Staphylococcus aureus* and lipopolysaccharides. Dig Dis Sci 1981;26:728–736.

14 Van den Wall Bake A, Daha M, Haaijman J, Radl J, van der Ark A, van Es L. Elevated production of polymeric and monomeric IgA1 by the bone marrow in IgA nephropathy. Kidney Int 1989;35:1400–1404.

15 Van Es L: Pathogenesis of IgA nephropathy. Kidney Int 1992;41:1720–1729.

16 Feehaly J: IgA nephropathy – A disorder of IgA production? Q J Med 1997;90:387–390.

17 Feehaly J: Immune mechanisms in glomerular IgA deposition. Nephrol Dial Transplant 1988; 3:361–378.

18 Scott M, Nahm M, Macke K, et al: Spontaneous secretion of IgG subclasses by intestinal mononuclear cells: Differences between ulcerative colitis, Crohn's disease and control subjects. Clin Exp Immunol 1986;66:209–216.

19 Kett K, Rognum T, Brandzaeg P: Mucosal subclass distribution of immunoglobulin G-producing cells is different in ulcerative colitis and Crohn's disease of the colon. Gastroenterology 1987;93:919–924.

20 Broberger O, Perlmann P: Autoantibodies in human ulcerative colitis. J Exp Med 1959;110: 657–662.

21 Greenwald B, James S: Immunology of inflammatory bowel disease. Curr Opin Gastroenterol 1997;13:293–297.

22 Emancipator S: IgA nephropathy: Morphologic expression and pathogenesis. Am J Kidney Dis 1994;23:451–462.

23 Donadio J, Grande J: Immunoglobulin A nephropathy: A clinical perspective. J Am Soc Nephrol 1997;8:1324–1332.

24 Radford M, Donadio J, Berstralh E, Grande J: Predicting renal outcome in IgA nephropathy. J Am Soc Nephrol 1997;8:199–207.

25 Gall J: IgA nephropathy. Kidney Int 1995;47: 377–387.

26 Nagy J, Scott H, Brandtzaeg P: Antibodies to dietary antigens in IgA nephropathy. Clin Nephrol 1988;29:275–278.

27 Drew P, Nieuwhof W, Clarkson A, Woodroffe A: Increased concentration of serum IgA antibody to pneumococcal polysaccharides in patients with IgA nephropathy. Clin Exp Immunol 1987;67:124–129.

28 Schena F, Mastrolitti G, Fracasso A, et al: Increased immunoglobulin secreting cells in the blood of patients with active idiopathic IgA nephropathy. Clin Nephrol 1986;26:163–168.

29 Conley M, Cooper M, Michael A: Selective deposition of immunoglobulin A1 in immunoglobulin A nephropathy, anaphylactoid purpura nephritis and systemic lupus erythematosus. J Clin Invest 1980;66:1432–1435.

30 Sterzel R, Rupprecht H: Glomerular mesangial cells; in Nielsen E, Couser W (eds): Immunologic Renal Diseases. Philadelphia, Lippincott-Raven, 1977, p 595.

31 Sancho J, Egido J, Rivera F, Hernando L: Immune complexes in IgA nephropathy: Presence of antibodies against diet antigens and delayed clearance of specific polymeric IgA immune complexes. Clin Exp Immunol 1983;54: 194–199.

32 Schena F, Pastore A, Sinico R, et al: Studies on the mechanisms producing solubilization of immune precipitates in the serum of patients with primary IgA nephropathy. Semin Nephrol 1987;7:336–342.

33 Bumgardner G, Amend W, Ascher N, Vincenti F: Single-center long-term results of renal transplantation for IgA nephropathy. Transplantation 1998;65:1053–1060.

34 Kotanko P, Pusey C, Levy J: Recurrent glomerulonephritis following renal transplantation. Transplantation 1997;63:1045–1052.

35 Silva F, Chander P, Pirani C, Hardy M: Disappearance of glomerular mesangial IgA deposits after renal allograft transplantation (letter). Transplantation 1982;33:241–246.

36 Harper S, Allen A, Pringle J, Feehally J: Increased dimeric IgA producing B cells in the bone marrow in IgA nephropathy determined by in situ hybridization. J Clin Pathol 1996;49: 38–42.

37 Wu H, Zhang G, Clarkson A, Knight J: Conserved T-cell receptor beta chain CDR3 sequences in IgA nephropathy biopsies. Kidney Int 1999;55:109–119.

38 Cagnoli L, Beltrandi E, Pasquali S, et al: B- and T-cell abnormalities in patients with IgA nephropathy. Kidney Int 1985;28:646–652.

39 Imasawa T, Utsonomiya Y, Kawamura T, Nagasawa R, Maruyama N, Sakai O. Evidence suggesting the involvement of hematopoietic stem cells in the pathogenesis of IgA nephropathy. Biochem Biophys Res Commun 1998;249: 605–611.

40 Andresen A: Ulcerative colitis – An allergic phenomenon. Am J Dig Dis 1942;9:91–99.

41 Truelove S: Ulcerative colitis provoked by milk. Br Med J 1961;i:154–156.

42 Jewell D, Snook J: Immunology of ulcerative colitis and Crohn's disease; in Allan R, Keighley M, Alexander-Williams J, Hawkins C (eds): Inflammatory Bowel Diseases, ed 3. Edinburgh, Churchill Livingstone, 1990, pp 127–146.

43 Snook J, de Silva H, Jewell D: The association of autoimmune disorders with inflammatory bowel disease. Q J Med 1989;72:835–841.

44 Halstensen T, Das K, Brandtzaeg P: Epithelial deposits of immunoglobulin G1 and activated complement colocalise with the M(r) 40 kD putative autoantigen in ulcerative colitis. Gut 1993;34:650–657.

45 Naparstek Y, Plotz P: The role of autoantibodies in autoimmune disease. Annu Rev Immunol 1993;11:79–104.

46 Chott A, Probert C, Gross G, Blumberg R, Balk S: A common TCR beta-chain expressed by CD8+ intestinal mucosa T cells in ulcerative colitis. J Immunol 1996;156:3024–3035.

47 Voiglio E, Salle B, Lemaitre D, Cloix P, Bancel B, Cozon G: Activation of T-lymphocytes in Crohn disease and in ulcerative hemorrhagic rectocolitis. Therapeutic implications. Pathol Biol 1996;44:287–292.

48 Uckei T, Mizuno M, Uesu T, et al: Distribution of activated complement, C3b, and its degraded fragments, iC3b/C3dg, in the colonic mucosa of ulcerative colitis. Clin Exp Immunol 1996;104:286–292.

49 Ekdahl N, Loof L, Ahrenstedt O, Nilsson U, Nilsson B: Defective elimination of C3b/iC3b-coated autologous erythrocytes in patients with primary biliary cirrhosis, alcoholic cirrhosis, and ulcerative colitis. J Lab Clin Med 1997; 130:285–292.

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50 Cicalese L, Duerr R, Nalesnik M, Heeckt P, Lee K, Scharaut W: Decreased mucosal IgA levels in ileum of patients with chronic ulcerative colitis. Dig Dis Sci 1995;40:805–811.
51 Roussomoustakaki M, Satsangi J, Welsh K, et al. Genetic markers may predict disease behavior in patients with ulcerative colitis. Gastroenterology 1997;112:1845–1853.
52 Julian B, Quiggins P, Thompson J, Woodford S, Gleason K, Wyatt R: Familial IgA nephropathy. Evidence of an inherited mechanism of disease. N Engl J Med 1985;312:202–208.
53 Moore R: MHC gene polymorphism in primary IgA nephropathy. Kidney Int 1993;43:S9–S12.
54 Freedman B, Spray B, Heise E: HLA associations in IgA nephropathy and focal and segmental glomerulosclerosis. Am J Kidney Dis 1994;23:352–357.
55 Kreisel W, Wolf L, Grotz W, Grieshaber M: Renal tubular damage: An extraintestinal manifestation of chronic inflammatory bowel disease. Eur J Gastroenterol Hepatol 1996;8:461–468.
56 D'Amico G: Natural history of idiopathic immunoglobulin A nephropathy: Role of clinical and histological prognostic factors. Am J Kidney Dis 2000;36:227–237.
57 Behrens R, Ruder H: Chronic inflammatory intestinal disease and nephritis (abstract). Klin Pädiatr 1992;204:61–64.
58 Dwarakanath A, Michael J, Allan R: Sulphasalazine-induced renal failure. Gut 1992;33:1006–1007.
59 Hamling J, Raedler A, Helmchen U, Shreiber S: 5-Aminosalicylic acid-associated renal tubular acidosis with decreased renal function in Crohn's disease. Digestion 1997;58:304–307.
60 Tanagisawa R, Kamijo T, Nagase Y: A case of drug-induced urolithiasis composed of acetyl sulphapyridine associated with ulcerative colitis (abstract). Nippon Hinyokika Gakkai Zasshi 1999;90:462–465.
61 Agharazii M, Marcotte J, Boucher D, Noel R, Lebel M: Chronic interstitial nephritis due to 5-aminosalicylic acid. Am J Nephrol 1999;19:373–376.

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