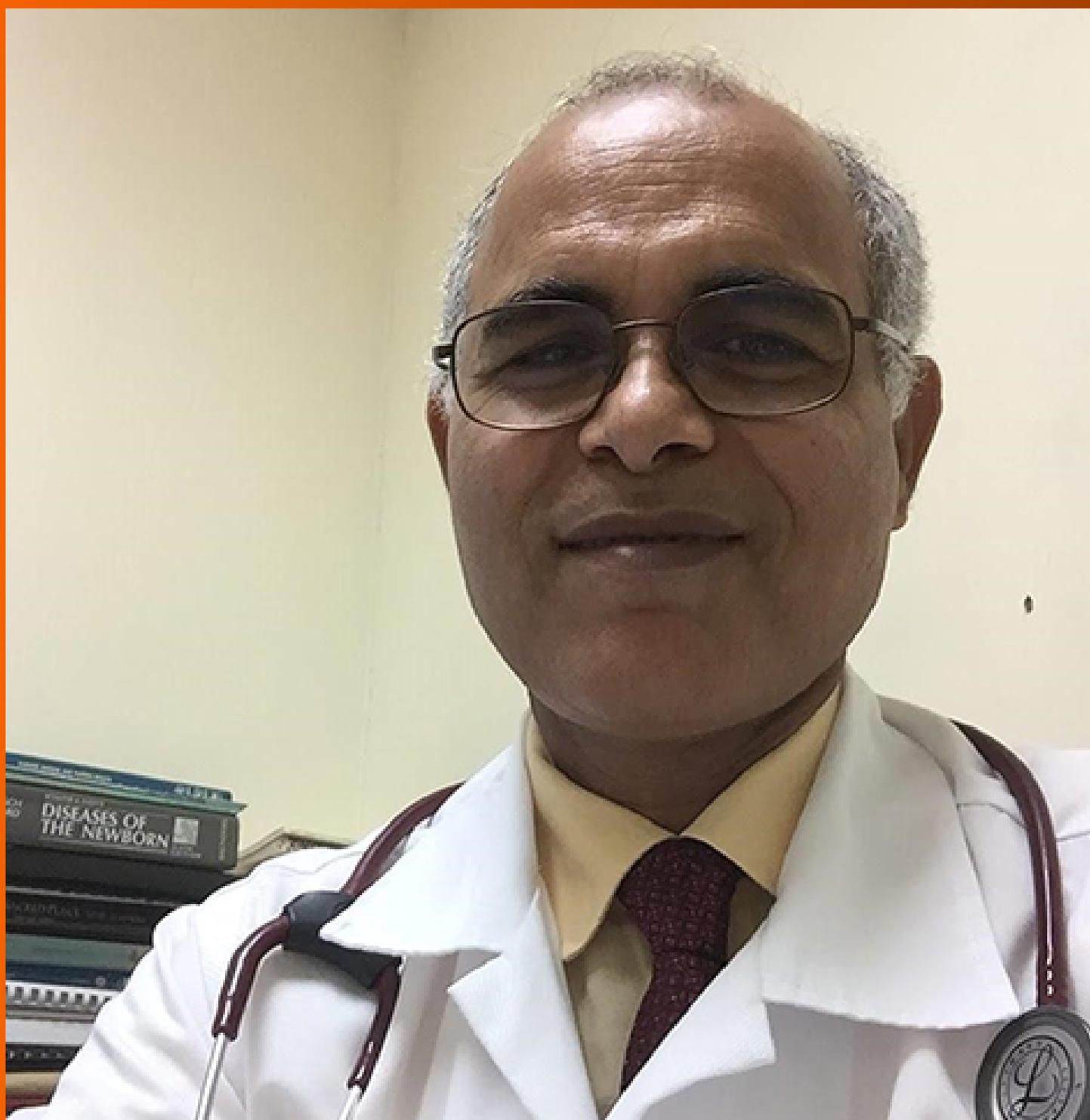


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IgA nephropathy associated with Crohn's disease

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Abstract

The relationship between IgA nephropathy (IgAN) and Crohn's disease was reported. IgAN is the most common primary glomerulonephritis and one of the leading causes of chronic kidney disease and end-stage renal failure, and up to 50% of cases progressed to end-stage renal disease within 25 years after IgAN diagnosis. However, specific and effective therapeutic strategies are still lacking. In this review, we discuss the possibility of the mechanism involved in IgAN associated with Crohn's disease based on the findings of basic and clinical studies. Although the etiology of IgAN associated with Crohn's disease is not permanent and various factors are thought to be involved, the stabilization of the disease condition of Crohn's disease is believed to help treat IgAN.

Key Words: Crohn's disease; IgA nephropathy; Immunological abnormalities; Mucosal-associated lymphoid tissue; Gut-associated lymphoid tissue; Nasopharynx-associated lymphoid tissue

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Core Tip: The relationship between IgA nephropathy (IgAN) and Crohn's disease was reported. Crohn's disease (CD) immunological abnormalities may promote and activate the IgAN inflammatory process. Although the etiology of CD-IgAN is not fixed and various factors are thought to be involved, the stabilization of the disease condition of CD is believed to help treat IgAN.

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INTRODUCTION

Intestinal diseases include chronic nonspecific inflammatory diseases of the gastrointestinal tract. Inflammatory bowel disease (IBD) is a chronic and recurrent inflammatory disease of the gastrointestinal tract that includes Crohn's disease (CD) and ulcerative colitis (UC).

In addition to intestinal inflammation, CD has numerous extraintestinal manifestations of IBD. Extraintestinal complications of renal and urological diseases in CD include internal fistula lesions such as enterovesical fistula and enterovaginal fistula, urolithiasis, and renal disease. Urolithiasis is relatively common in 19% of patients with IBD; however, comorbid renal disease is relatively rare. Interstitial nephritis and secondary renal amyloidosis caused by 5-aminosalicylic acid (5-ASA) are renal diseases that show a clear causal relationship with CD treatment or CD itself; however, glomerulonephritis has been reported in few cases, and the lack of a causal relationship is difficult to prove. Among them, the relationship between IgA nephropathy (IgAN) and CD was reported[1,2].

IgAN is the most common primary glomerulonephritis and one of the leading causes of chronic kidney disease and end-stage renal failure. Up to 50% of cases progressed to end-stage renal disease (ESRD) within 25 years after the diagnosis of IgAN. However, at present, specific and effective therapeutic strategies are still lacking[3,4]. Thus, this paper discusses the possibility of the mechanism involved in IgAN associated with CD (CD-IgAN) based on the findings of basic and clinical studies.

ABNORMAL MUCOSAL IMMUNITY AND IGAN

Because IgAN exacerbates nephropathy after upper respiratory tract infection, it has been hypothesized that mucosal immunity is involved in the pathogenesis of IgAN. IgA is an immunoglobulin that mainly acts on the mucosa, and renal glomerular IgA is a mucosal multimeric IgA1 containing a secretory component[5-8], and multimeric IgA1 is also increased in the serum[9,10]. These have also supported these hypotheses.

Conversely, which mucosal-associated lymphoid tissue (MALT) is the main responsible site for IgAN is unclear. The involvement of nasopharynx-associated lymphoid tissue (NALT) is assumed to be mainly responsible for IgAN because it worsens after upper respiratory inflammation. Gut-associated lymphoid tissue (GALT) has a huge mucosal area and is the main production site of mucosal IgA; however, its involvement in the pathology of IgAN is controversial. In addition, the exacerbation of IgAN after a mucosal infection suggests the involvement of foreign antigens; however, many points are unclear about how infection is involved.

Recently, the activation of the innate immune system triggered by infection is involved in the onset and progression of various types of nephritis, along with mechanisms such as molecular mimicry and epitope spreading[11]. However, the specific mechanism of IgAN has not been elucidated.

IgAN leads to ESRD, IgAN recurrence in approximately half of the patients who underwent kidney transplantation, and vice versa. IgAN disappears when the kidney is transplanted as a donor, suggesting that the main cause of IgAN is not kidney-specific cells but the systemic IgA immune system [5].

The facts suggesting the involvement of mucosal immunity are as described above; however, bone marrow abnormalities have also been pointed out in patients with IgAN. van den Wall Bake *et al*[12] reported that the ratio of IgA-producing plasma cells (IgA + PC) increased in the bone marrow of patients with IgAN, and IgA1 production was enhanced. These suggest that glomerular IgA1 is derived from the bone marrow[13].

Moreover, in patients with IgAN, IgA1 was significantly higher with the production of peripheral blood mononuclear cell IgA[12]. By contrast, Harper *et al*[14] reported that J-chain mRNA-positive mucosal-type IgA + PC increased in the bone marrow of patients with IgAN. Another study reported that when leukemia develops in a patient with IgAN and the patient undergoes bone marrow transplantation, not only leukemia but also IgAN improves[15]. In other words, in patients with IgAN, mucosal-type IgA + PC, which is involved in the pathology, increased in the extramucosal bone marrow, suggesting the excessive production of mucosal-type multimeric IgA1[5].

Approximately 30 years ago, van den Wall Bake *et al*[16] hypothesized the existence of "mucosa-bone marrow axis" abnormalities in IgAN[5]. Moreover, the homing mechanism of immunocompetent cells to the effective tissue was clarified. This hypothesis became more realistic because mucosa-derived effector cells were found to be translocated and stored in the lymphatic tissue.

Studies using mouse models of spontaneous IgAN have also shown that cells responsible for the abnormal IgA production related to renal onset are present in the bone marrow and spleen[17-19]. Active cell migration and immune information exchange take place between the mucosal tissue and bone marrow. However, whether the cells responsible for IgAN migrate between the MALT and bone marrow or whether only relatively localized mucosal tissue is involved is unclear.

Moreover, we discuss the possible involvement of GALT and NALT in pathologies with IgAN. Serum IgA is mainly produced in the bone marrow, and intestinal mucosa-derived IgA is thought to be scarce. Conversely, in GALT, large amounts of IgA are produced and secreted in the mucosa, which contribute

to intestinal immunity. Unlike mucosal IgA, the physiological role of serum IgA is largely unknown. Although there are IgA1 and IgA2 subclasses in humans, 80%-85% of serum IgA is IgA1[20].

As shown in the IgA1 and IgA2 ratios of IgA + PC in the mucosal execution phase, IgA2 + PC was high (30%-65%) in the intestinal mucosa, whereas it was low (7%-25%) in the peripheral lymph nodes and respiratory tract mucosa[20]. In particular, IgA2 + PC is dominant in the ileum and colon[21-24].

Human IgA2 Lacks amino acids, which are the recognition sites of hinge-specific proteases derived from intestinal bacteria, and is protease resistant, which is thought to work favorably in intestinal immunity[24]. The organogenesis mechanisms of Peyer's patch (PP) and NALT are significantly different.

In the PP, the number of CD3⁻CD4⁺CD45⁺ inducer cells increased from the embryonic period and decreased until 3 wk after birth. In NALT, the number of inducer cells increased because of postnatal stimulation with foreign antigens and peaks at 3 wk after birth[25]. The molecular mechanisms involved in the organogenesis of the two are also different[26]. These facts suggest the difference in the basic roles and needs of both in the mucosa.

The polymeric immunoglobulin receptor (pIgR) is a protein expressed on the basolateral side of mucosal secretory epithelial cells that carry IgA and IgM produced in the mucosa to the mucosal surface.

In GALT, IgA and IgM produced from the PC of the lamina propria (LP) form dimeric IgA and pentameric IgM by the J-chain produced at the same time. pIgR easily binds to multimeric IgA and IgM containing this J-chain and efficiently transports them to the mucosal surface. The transported multimeric IgA and IgM trap antigens in the mucosa and act as a non-inflammatory mucosal immune defense mechanism[27,28].

In IBD, IgA is actively produced in the LP. Conversely, inflammatory pIgR expression and dysfunction occur, inhibiting its secretion on the mucosal surface. Therefore, mucosal IgA, which increased in the LP, was also thought to increase in the blood[29]. Mucosal IgA in the blood is increased in patients with IBD such as UC and CD[30].

The lymphotoxin-β receptor (LTβR) is essential for the formation of mucosal lymphoid tissue[31] and plays an important role in IgA production in the small intestine[32].

LIGHT is a ligand for LTβR and is expressed on activated T cells[33]. In LIGHT transgenic mice (LIGHT Tg), sustained stimulation of LIGHT *via* LTβR on T cells causes the over-induction of IgA + PC in the LP, and increased expression of MAdCAM-1 by stimulation from LTβR leads to the activation of inflammatory cells, causing severe enteritis[30].

Impaired pIgR expression and excessive IgA production caused by this intestinal inflammation induce mucosal multimeric IgA, which is not transported to the mucosa, to enter and increase their presence in the blood circulation. Because these multimeric IgAs have high affinity to the kidney, they are deposited in the kidney and cause IgAN[30].

On the contrary, the bias of Th2 cytokines may be involved in the glycosylation of IgA in the intestinal tract. Even a small amount of IgA released into the blood from the intestinal tract may cause nephropathy[34-36]. Thus, induction of glomerular deposition of intestinal IgAN is theoretically possible if conditions such as inflammation-associated pIgR dysfunction are met.

However, clinically, most patients with IgAN do not have IBD or gastrointestinal symptoms, and the so-called secondary IgAN associated with intestinal abnormalities occurs in a small proportion of patients. The involvement of IBD in IgAN is considered limited, at least in terms of IgAN in Japan.

COMPARISON OF HISTOLOGICAL FINDINGS BETWEEN CD-IgAN AND COMMON IgAN

Virchows Archiv investigated the clinical and pathological differences CD-IgAN and common IgANs (NOS-IgAN) associated with upper airway inflammation such as tonsillitis[37]. The PCs of the upper airway mucosa mainly produce IgA1[38]. However, the intestinal mucosa, especially PP, is thought to predominantly secrete IgA2 (approximately 60% in mucosal cells) rather than IgA1[39]. For IgAN with CD, intestinal IgA2 is deposited in the glomerular mesangium and may be involved in IgAN induction and progression. However, among the deposited IgA subclasses, the IgA1 subclass was predominant in both the CD-IgAN and NOS-IgAN groups, and no significant difference in the staining intensity of IgA2 was found between the two groups. Then, they examined the deposition of galactose-deficient IgA1 (Gd-IgA1) in the glomerulus of primary IgAN[40].

Gd-IgA1 is an abnormal IgA1 of the IgA1 subclass, exhibiting a structure in which the o-linked glycans in the hinge lack galactose and expose N-acetylgalactosamine (GalNAC)[41,42]. They found no difference in the extent of Gd-IgA1 deposition in the glomeruli, irrespective of CD complications, and a significant difference in Gd-IgA1 deposition was found between CD-IgANs and NOS-IgAN. CD-IgANs were suggested to share the same pathogenesis as primary IgANs. Furthermore, negative views have emerged regarding the disease specificity of Gd-IgA1[43]. In their renal histological findings, patients with CD-IgAN were found to have significantly more severe glomerulosclerosis, arteriolar hyalinosis grade, tubular atrophy, and interstitial fibrosis than those with NOS-IgAN.

A comparison of the Oxford Classification MEST-C scores revealed that the T-scores representing tubular atrophy and interstitial fibrosis were significantly higher in CD-IgANs than in NOS-IgANs. To confirm this trend, they performed a meta-analysis comparing MEST-C scores using a large cohort of patients with IgAN reported in previous studies[44,45]. The incidence of T1 and T2 was higher in CD-IgANs than in IgANs. These histological differences were speculated to be related to the following factors: (1) CD pathophysiology (*i.e.*, diarrhea and dehydration); (2) Therapeutic agents for CD; and (3) Systemic inflammation, including the gut.

First, in the course of CD, dehydration due to diarrhea, reduced fluid intake, and surgery can reduce the circulating blood volume, which can lead to tubulointerstitial damage and glomerulosclerosis. In addition, undernutrition and hypokalemia have been reported to cause chronic tubulointerstitial injury [46]. The possible reason is that the reduced effective circulating blood volume stimulates the renin-angiotensin-aldosterone system, which in turn enhances the activation of angiotensin II, which can lead to arteriolar contraction, glomerular ischemia, and interstitial fibrosis[47,48]. In addition, evidence showed that hyperuricemia, common in CD, may exacerbate glomerulosclerosis[49].

Second, this factor is related to the effect of treatment. 5-ASA remains the main treatment for CD, and its adverse renal effects are collectively called mesalamine-associated kidney disease[50]. The mechanism by which mesalamine promotes renal injury appears to be through the salicylic acid inhibition of intrarenal prostaglandin synthesis, which is a vasoactive mediator of intrarenal blood flow and uncouples mitochondrial oxidative phosphorylation[46,51].

Several studies have also reported that mesalamine promotes histologically renal injury through interstitial nephritis[52], and similar findings have been reported in patients with CD, not on 5-ASA [53]. Therefore, distinguishing whether interstitial nephritis is due to drugs or CD is challenging.

Third, in CD pathogenesis, immune abnormalities may be involved. Macrophages and T cells produce large amounts of interleukin-23 and tumor necrosis factor (TNF)- α in immune diseases such as CD and are thought to play a central role in CD pathophysiology[54]. These cytokines also contribute to the exacerbation of IgAN tubulointerstitial lesions[54]. A study has also reported a mechanism by which dysfunctional macrophages promote intestinal fibrosis[55].

In recent years, the mechanisms and systemic responses of B cell immune abnormalities in CD have been elucidated[56-58]. Interstitial inflammation in chronic kidney disease involving IgAN was reported to involve B cell-mediated immune dysfunction[59], and immune dysfunction in CD was found to be associated with IgAN in terms of immune dysfunction, which may act as an aggravating factor for renal function. Moreover, in IgAN, complement activity was thought to promote glomerulosclerosis and interstitial fibrosis[60,61].

Previous studies have shown that in patients with CD, activated complement (predominantly C3b) stains strongly in the intestinal mucosa[62] and that resected ileocecal specimens show increased expression of complement C3 mRNA[63]. The effects of CD-associated complement activation may influence glomerular and tubulointerstitial inflammations in IgAN.

COMMON KEY GENES ASSOCIATED WITH CD AND IGAN

Several common genetic predispositions to CD and IgAN have been reported. *HLA-DR1* in IgAN[64] and *HLA-DR1 DQw5* in CD[65] are characteristic genetic predispositions. Moreover, *HLA-DR1*-positive patients may have an increased risk of IgAN and CD[66]. A genome-wide association study found that *CARD9*, *HORMAD2*, and *HLA-DQB1* susceptibility genes for IgAN were also associated with IBD. These IgAN loci encode a protein involved in maintaining the intestinal barrier and regulating mucosal immune responses to pathogens[67-70]. Yuan *et al*[71] reported that the gene for *CXCL2* is critically linked to immune infiltration during CD and IgAN. *CXCL2*, also known as macrophage inflammatory protein-2, belongs to the CXC subfamily. It is secreted by many cell types, including monocytes, macrophages, endothelial cells, and hepatocytes, in response to infection and injury. It primarily affects the recruitment of polymorphonuclear leukocytes to sites of injury or infection, thereby modulating immune and inflammatory responses. The analysis of the relationship between *CXCL2* and immune cell infiltration in CD and IgAN diseases suggested that *CXCL2* is involved in immune infiltration, thereby contributing to the pathogenesis of the two diseases.

PATHOGENESIS OF IGAN ASSOCIATED WITH CROHN'S DISEASE

Recent research has revealed that the apoptosis inhibitor of macrophages (AIM) is involved in the pathogenesis of renal failure through the function of macrophages, a type of leukocytes. AIM deposited in the same sites as IgA in the glomeruli in human IgAN and a spontaneous mouse model of IgAN. As a result, AIM deficiency in the spontaneous IgAN mouse model, although IgA deposition in the glomeruli was observed, did not develop IgAN. Subsequently, when AIM was administered to mice, IgG and IgM were co-deposited in the glomeruli, proteinuria and occult blood appeared, and nephropathy was confirmed. From this, IgA deposition in the glomerulus alone does not progress to nephropathy. In

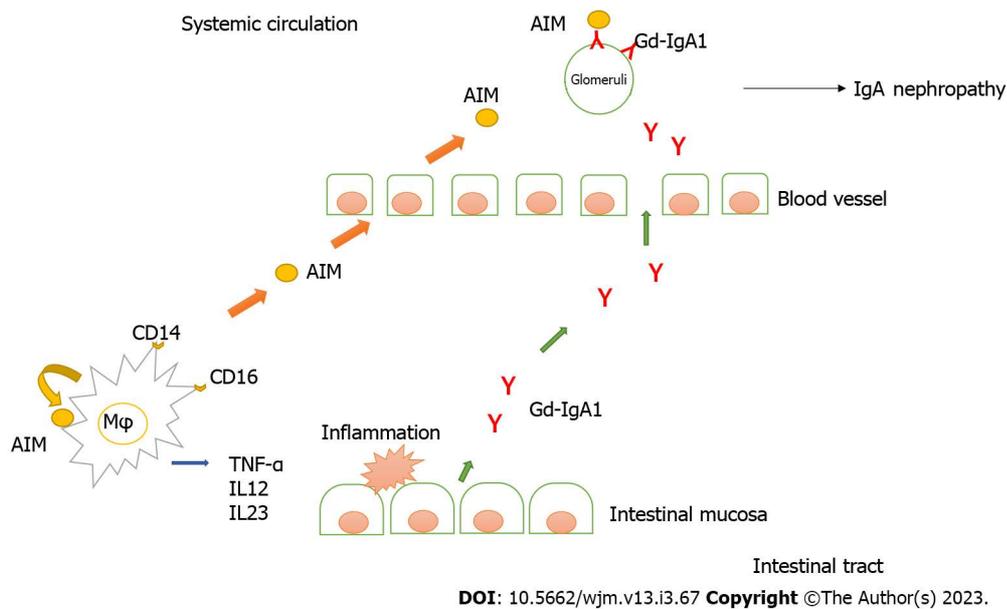


Figure 1 Intestinal mucosal barrier disruption due to Crohn's disease enhances the production of glycosylated IgA. Apoptosis inhibitor of macrophages (AIM) produced by resident macrophages in the intestinal tissue contributes to intestinal inflammation, and active macrophage-derived AIM in the gut leads to elevated serum AIM levels. AIM is involved in the recruitment of inflammatory macrophages *via* autocrine and paracrine and induces inflammatory cytokine (TNF- α) in mesenteric adipose tissue in Crohn's disease. AIM influences the pathogenesis of Crohn's disease by inhibiting apoptosis of active intestinal macrophages and enhancing the expression of TNF- α in these mesenteric adipose tissues. Intestinal mucosal barrier disruption due to Crohn's disease enhances the production of glycosylated IgA. In IgA nephropathy, it was clarified that the deposition of IgA in the glomerulus is essential as the first step, and that AIM leads to inflammation as the second step. AIM: Apoptosis inhibitor of macrophages; CD: Crohn's disease; M ϕ : Macrophages.

addition, glomerular deposition of AIM, IgG, and IgM was not induced in IgA-deficient mice. These results demonstrate that IgAN involves the deposition of IgA into the glomeruli as the first step and that co-deposition of IgG and IgM *via* AIM leads to inflammation as the second step. Furthermore, in human IgAN, AIM was co-deposited with glomerular IgA, IgG, IgM, and complement (C3). Therefore, AIM is a key molecule that initiates inflammation in IgAN[72].

Ono *et al*[73] showed that serum AIM levels were higher in patients with CD than in patients with UC, patients with intestinal BD, and healthy controls. Furthermore, AIM is expressed in CD14- and CD16-positive macrophages in the intestinal tissue.

AIM produced by resident macrophages in the intestinal tissue was believed to contribute to intestinal inflammation and that active macrophage-derived AIM in the intestine results in elevated serum AIM levels. AIM is taken up by the adipocytes *via* CD36-mediated endocytosis, which subsequently induces lipolysis[74,75]. Therefore, it may be involved in the recruitment of inflammatory macrophages and induce TNF- α in mesenteric adipose tissue in CD.

AIM may affect the pathogenesis of CD by not only inhibiting the apoptosis of active intestinal macrophages but also enhancing TNF- α expression in these mesenteric adipose tissues.

Inoue *et al*[76] reported that glycosylated IgA is produced in the gastrointestinal mucosa of CD and that glycosylated IgA correlates with CD disease activity. These results are crucial because they not only indicate that CD induced IgAN but also serve as evidence of the correlation between CD and IgAN.

We hypothesized the pathogenesis of IgAN associated with Crohn's disease (Figure 1).

IGAN: CD-ASSOCIATED OR ADALIMUMAB-INDUCED?

We searched PubMed for studies on CD with IgAN (Supplementary Figure 1). Twenty-five cases have been reported[77-92], including a self-case, with an average age of 27.5 (9-39) years, male-to-female ratio of 20:5 (male 80%), seven cases with underlying IgAN, and seven cases with underlying CD. Moreover, 17 patients had comorbidities, and one case had a simultaneous onset (Table 1).

However, certain cases had urinalysis abnormalities such as proteinuria and microscopic hematuria, which have been pointed out before the definitive diagnosis of IgAN. Because CD also progresses preclinically, identifying the time of onset of CD and IgAN is very difficult.

In the literature, the pathological findings of CD-complicated nephritis and IgAN with CD also tended to have a higher T-score, which represents tubular atrophy and interstitial fibrosis, than IgAN without CD. Five patients developed IgAN during biologic therapy, and CD and proteinuria improved after biologics were discontinued or changed.

Table 1 Reported cases of Crohn's disease with IgA nephropathy

Age (yr)	Sex	Clinical course	CD disease type	IgAN MEST-C grade	CD treatment	IgAN treatment	CD and IgAN worsened simultaneously
20	Female	CD(y)→IgAN(y)	Ileocolitis	NR	SASP	nothing	+
25	Male	CD(4y)→IgAN(12y)	Ileocolitis	NR	ED only	NR	+
18	Male	IgAN(NR)→CD(2y)	colitis	NR	5-ASA	ACE-I	NR
24	Male	CD(NR)→IgAN(3y)	NR	NR	5-ASA	NR	-
38	Male	CD(NR)→IgAN(6y)	NR	NR	PSL+5-ASA →IFX	ACE-I	+
40	Female	CD(NR)→IgAN(5y)	colitis	NR	5-ASA	ARB	+
38	Male	CD(NR)→IgAN(16y)	Ileocolitis	NR	5-ASA	NR	NR
40	Male	CD(NR)→IgAN(12y)	NR	NR	PSL+5-ASA	PSL	+
34	Female	IgAN(4y)→CD(5y)	Ileocolitis	NR	ED only	PSL	+
25	Male	CD(25y)→IgAN(33y)	NR	M1E1S1T1C1	ADA	MPT→PSL, ACE-I	-
24	Male	CD(22y)→IgAN(24y)	Ileitis	M1E0S1T1C2	IFX →UST	MPT→PSL	-
10	Male	CD(1y)→IgAN(7y)	colitis	M1E0S0T0C0	IFX	IFX→ADA, PSL	+
40	Male	CD(NR)→IgAN(39y)	NR	M1E0S1T0C1	AZA	PSL	-
31	Male	CD(16)→IgAN(18y)	Ileocolitis	M1E0S1T1C0	PSL+5-ASA	PSL	+
46	Male	IgAN(17y)→CD(40y)→IgAN(46y)	NR	M1E0S0T0C1	5-ASA, AZA, IFX	PSL	+
15	Female	CD(16)→IgAN(18y)	NR	NR	5-ASA, PSL	IFX	+
13	Male	IgAN(10y)→CD(13y)	NR	M1E0S0T0C1	PSL, SASP	PSL, CPA, ACE-I	+
9	Male	CD(9)→IgAN(11y)	Ileitis	M1E0S0T1C0	ADA	ADA →AZA; MPT, PSL, ACE-I	-
39	Female	CD(32)→IgAN(39y)	NR	M1E0S1T0C0	ADA, AZA	ARB, ADA→IFX	+
27	Male	IgAN(22y)→CD(27y)	NR	M1E0S1T2C1	5-ASA, IFX	MPT, MMF, CsA	+
18	Male	CD(9)→IgAN(11y)	NR	M1E1S1T1C2	5-ASA	PSL, CPA	+
22	Male	IgAN(8y)→CD(22y)	NR	M1E1S1T1C0	SASP, AZA	PSL, 5-ASA	+
36	Male	CD(30)→IgAN(36y)	NR	M1E0S0T2C0	5-ASA, AZA	ACE-I	-
29	Male	IgAN(24y)→CD(29y)	colitis	NR	PSL	non	+
10	Male	CD(30)→IgAN(36y)	Ileocolitis	M1E0S0T0C0	ADA, AZA, budesonide	PSL	+

CD: Crohn's disease; IgAN: IgA nephropathy; ED: Elemental diet; PSL: Prednisolone; MPT: Methylprednisolone pulse therapy; SASP: Salazosulfapyridine; 5-ASA: 5-aminosalicylic acid; CPA: Cyclophosphamid; AZA: Azathioprine; IFX: Infliximab; ADA: Adalimumab; UST: Usutekinumab; CsA: Cyclosporin; MMF: Mycophenolate mofetil; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; NR: Not reported.

Simultaneous exacerbation of both diseases was observed in 17 of 23 patients, and many studies have reported that the disease activity of both diseases was related, suggesting that IgAN is an extraintestinal complication of CD. This tendency was also observed in our case (Figure 2). Considering that the disease progression of both diseases is the same, controlling the disease progression of CD is also important to prevent the progression of renal failure.

The use of immunomodulators to maintain remission in both diseases is an option. In addition, because TNF-α induces glomerular inflammation and enhances permeability[93], anti-TNF-α antibodies are theoretically expected to improve proteinuria.

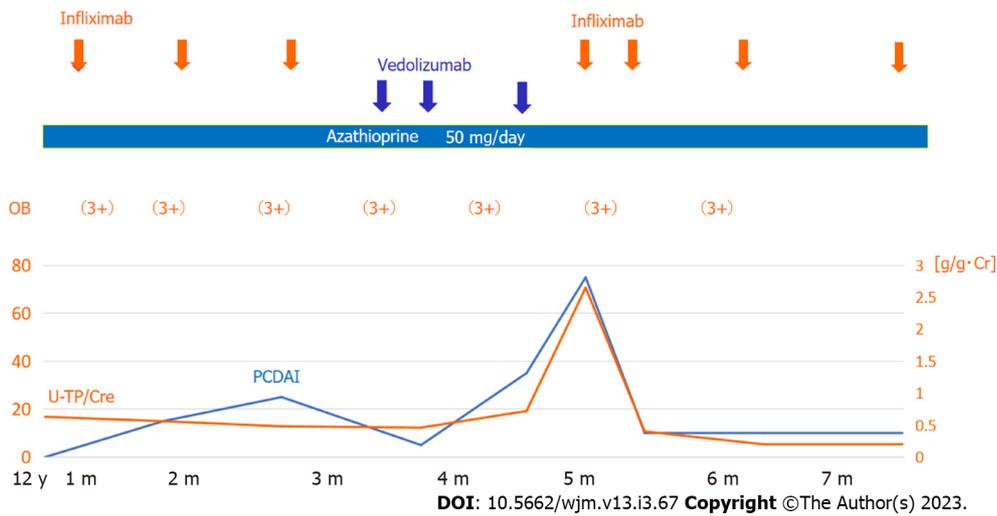


Figure 2 Clinical course after the appearance of hematuria. Hematuria and proteinuria persisted, and IgA nephropathy was suspected. Since there were some reports of IgA nephropathy caused by infliximab, we switched from infliximab to vedolizumab. After the change to vedolizumab, Crohn’s disease worsened, and there was a marked increase in proteinuria. Fever and abdominal symptoms worsened, and infliximab was administered again. Thereafter, Crohn’s disease improved rapidly, and decrease in the urinary protein level was noted. OB: Occult blood urine; U-TP/Cr: Urinary protein creatinine ratio; PCDAI: Pediatric Crohn’s disease activity index; y: years; m: Months.

However, TNF- α inhibitors were also reported to induce systemic vasculitis and several types of glomerulonephritis, such as minimal-change disease group, membranous nephropathy, IgAN, and lupus nephritis[94-98].

Although the following hypotheses have been suggested and the following possibilities have been proposed, the mechanism of vasculitis associated with anti-TNF α therapy is unclear: (1) TNF α /anti-TNF α immune complexes may deposit in small blood vessels and induce local complementary activation [94]; (2) A cytokine imbalance with a shift from a Th1 profile to a Th2 profile could induce symptoms associated with antibody-mediated immunity[95]; and (3) In glomerulonephritis, immune complexes are thought to form by cross-reactivity of Gd-IgA1 and anti-drug antibodies to the glycan structures of TNF α inhibitors. They are deposited in the mesangium and can induce IgAN[96].

The reported detection rate of antinuclear antibodies in patients treated with anti-TNF α ranged from 29% to 76.7%. Immunological abnormalities can lead to glomerulonephritis, including membranous glomerulonephritis and lupus nephritis[97,98].

CONCLUSION

In many cases, proteinuria progressed simultaneously with CD; moreover, it is possible that IgAN and Crohn’s disease occur in parallel. The factors governing the simultaneous occurrence of IgAN and Crohn’s disease is still unknown; however, the involvement of biologics has been pointed out. Although the etiology of CD-IgAN is not fixed and various factors are thought to be involved, the stabilization of the disease condition of CD is believed to help treat IgAN.

FOOTNOTES

Author contributions: Tamura H reviewed the patient’s clinical data, wrote the initial draft of the manuscript, contributed to writing the manuscript, and revised the final version of the manuscript.

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