Immunoglobulin A Nephropathy in Association with Inflammatory Bowel Diseases: Results from a National Study and Systematic Literature Review

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Nizar Joher[1,2], Clément Gosset[3], Dominique Guerrot[4], Evangeline Pillebout[5], Aurélie Hummel[6], Jean-Jacques Boffa[7], Stanislas Faguer[8], Marion Rabant[9], Sarah Higgins[9], Anissa Moktefi[10], Yahsou Delmas[11], Alexandre Karras[12], Nathanaël Lapidus[13,14], Aurélien Amiot[15], Vincent Audard[1,2], Khalil El Karoui[1,2].

[1]Département de Néphrologie et Transplantation, Centre de Référence Maladie Rare « Syndrome Néphrotique Idiopathique », Hôpital Universitaire Henri Mondor, Assistance Publique-Hôpitaux de Paris AP-HP, Créteil, France

[2]Université Paris Est Créteil UPEC, Institut National de la Santé et de la Recherche Médicale INSERM U955, Institut Mondor de Recherche Biomédicale IMRB, Equipe 21, Créteil, France

[3]Département de Pathologie, Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris AP-HP, Paris, France

[4]Département de Néphrologie, Hôpital Universitaire de Rouen, Rouen, France

[5]Département de Néphrologie, Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris, Paris, France

[6]Département de Néphrologie, Hôpital Necker, Assistance Publique-Hôpitaux de Paris, Paris, France

[7]Département de Néphrologie, Hôpital Tenon, Assistance Publique-Hôpitaux de Paris, Paris, France

[8]Département de Néphrologie, Hôpital Rangueil, Centre Hospitalo-Universitaire de Toulouse, Toulouse, France

[9]Département de Pathologie, Hôpital Necker, Assistance Publique-Hôpitaux de Paris, Paris, France

[10]Département de Pathologie, Hôpital Henri Mondor, Assistance Publique-Hôpitaux de Paris, Créteil, France

[11]Département de Néphrologie, Hôpital Universitaire de Bordeaux, Bordeaux, France

[12]Département de Néphrologie, Hôpital Européen Georges Pompidou, Paris, France

[13]Département de Santé Publique, Hôpital Saint Antoine, Assistance Publique-Hôpitaux de Paris, Paris, France

[14]Institut Pierre Louis d'Epidémiologie et de Santé Publique IPLESP, INSERM, Sorbonne Université, F75012 Paris, France

[15] Département de Gastro-Entérologie, Hôpital Henri Mondor, Assistance Publique-Hôpitaux de Paris, Créteil, France

Corresponding author: Dr Khalil EL KAROUI, Département de Néphrologie, Hôpital Henri Mondor, Assistance Publique-Hôpitaux de Paris APH-HP, 51 Avenue du Maréchal de Lattre de Tassigny 94010 Créteil, France. E-mail: khalil.el-karoui@aphp.fr .

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ABSTRACT

Background Little is known about clinical characteristics and kidney outcome in patients with biopsy-proven immunoglobulin A nephropathy (IgAN) in a context of inflammatory bowel disease (IBD).

Methods We conducted a retrospective multicenter study with centralized histological review, to analyze the presentation, therapeutic management and outcome of 24 patients suffering from IBD associated IgAN relative to a cohort of 134 patients with primary IgAN without IBD.

Results Crohn's disease and ulcerative colitis accounted for 75% and 25% of IBD-associated IgAN cases, respectively. IBD was diagnosed before IgAN in 23 cases (a mean of 9 years previously) and was considered active at IgAN onset in 23.6% of patients. Hypertension was present in 41.7% of patients. Urinary protein-to-creatinine ratio exceeded 100 mg/mmol in 70.8% of patients (mean: 254 mg/mmol). Estimated glomerular filtration rate (eGFR) exceeded 60 ml/min/1.73m^2 in 13/24 patients and only one patient required dialysis. In the Oxford MEST-C classification of renal biopsies, 57% were M1, 48% E1, 76% S1, 57% T1+T2 and 38% C1+C2. Steroids were administered in 50% of cases. After a mean follow-up of 7.2 years, four patients (16.7%) had a poor kidney outcome: end-stage renal disease (n=3) or a > 50% decrease in eGFR from initial values (n=1). A similar evolution was observed in patients with primitive IgAN.

Conclusions This first case series suggests that IBD-associated IgAN have frequent inflammatory lesions at onset and variable long-term outcome.

Keywords: IgA nephropathy; chronic kidney disease; inflammatory bowel disease; Crohn's disease; ulcerative colitis

KEY LEARNING POINTS

IgA nephropathy (IgAN) has been associated with inflammatory bowel diseases (IBD) on the basis of single case reports. No detailed studies of the clinical, biological and pathological characteristics or management of patients with IgAN and IBD have been published to date.

This first case series suggests that IBD-associated IgAN have frequent inflammatory lesions at onset and variable long-term outcome. We did not detect any association between IBD activity and IgAN evolution in our study. No IBD related factor, including TNFalpha blockade agents, was associated with renal evolution.

INTRODUCTION

Immunoglobulin A nephropathy (IgAN), the most common primary glomerulonephritis[1], is characterized by mesangial deposition of IgA and C3. IgAN has a highly variable clinical presentation and course, ranging from asymptomatic microscopic hematuria to rapidly progressive glomerulonephritis[2]. Thus, despite the relatively high prevalence of IgAN, the most appropriate therapeutic strategy for various forms of the disease remains a matter of debate[3–6]. There is a need to characterize the various phenotypes associated with IgAN more precisely and to facilitate improvements in therapeutic management. Recent advances have highlighted the role of the gut-kidney axis in IgAN pathogenesis: dysregulation of the interplay between intestinal immunity, diet and microbiota can lead to the production of mis-galactosylated IgA[7]. The gut-kidney axis hypothesis is also supported, in some patients, by the association between IgAN and inflammatory bowel disease (IBD)[8–25]. IgAN is the most frequent abnormal finding on kidney biopsy (24%) in IBD patients, with a significantly higher prevalence compared to biopsy-proven kidney diseases in patients without IBD[26]. However, it remains unclear whether the association of these two conditions is merely fortuitous, given the high frequency of subclinical kidney IgA deposition[27]. In addition, the clinical features of IBD-associated IgAN have been described exclusively on the basis of single-case reports[8–25], and no case series investigating long-term outcomes has ever been published. Furthermore, little is known about the similarities or differences between primary IgAN and IBD-associated IgAN in terms of clinical, biological, and pathological characteristics or prognosis.

In this retrospective study, we assessed the clinical significance of this association, by reviewing clinical, histological, and therapeutic data, and outcomes for 24 patients with biopsy-proven IgAN occurring in a context of Crohn's disease (CD) or ulcerative colitis (UC). These

118 patients were compared to 134 patients with primary biopsy-proven IgAN and 19 patients with
119 IBD-associated IgAN identified through a systematic literature review.
120

MATERIALS AND METHODS

Study population

Patients with biopsy-proven IgAN occurring in a context of IBD were retrospectively identified by asking all French nephrology academic departments. The inclusion criteria were the presence of biopsy-proven IgAN[2] and a diagnosis of either CD or UC, on the basis of radiological and endoscopic evidence in addition to pathological criteria[28,29]. A poor kidney outcome was defined as follows: ESRD, defined as CKD stage V or the need for kidney replacement therapy, or a > 50% decrease in eGFR from initial values[30]. IBD-associated IgAN was compared to a control group of 134 patients with primary IgAN diagnosed from 2003 to 2014. The inclusion criteria were the presence of biopsy-proven IgAN[2], without history of autoimmune or inflammatory disease especially from rheumatic or gastrointestinal system such as IBD, malignancy and infection such as infection by Human Immunodeficiency Virus or current bacteremia. Data were recorded in the control group using the same method as for IBD-associated IgAN group.

IBD phenotype was characterized according to the Montreal classification[31]. Disease activity was assessed with the Harvey–Bradshaw index for CD and the partial Mayo score for UC[32]. We considered IBD to be active for a Harvey–Bradshaw index (HBI) > 4 for CD and a partial Mayo score > 3 for UC.

This multicenter study was performed in accordance with the Declaration of Helsinki and was approved by our local institutional review board (IRB 412 Mondor No. 00003835) and by the *Comité de Protection des Personnes d'Ile de France IV* (No. 2016/25NICB).

Renal pathology studies

The histological diagnosis of IgAN was made as previously described[33]. We considered histological features to be severe if more than one of the MEST-C criteria for M1, E1, S1, T1-2, and C1-2 were met[33].

Literature review

We performed a systematic review of the literature from 1980 to 2019 to identify previous cases of IBD-associated biopsy-proven IgAN without confounding factors. We searched MEDLINE via PubMed for all articles published in French or English using the keywords or MeSH terms "Glomerulonephritis, IGA", "Inflammatory Bowel Diseases", "Crohn Disease", "Colitis,Ulcerative". Only reports for which clinical, biological, and renal histological data and outcomes were available were included. At the time of the review, 19 cases were identified[8–25].

Statistical analysis

The descriptive statistics recorded included the mean (±SD standard deviation) or the median [IQR, interquartile range: 25%-75%], as appropriate, for continuous variables, and frequency (percentage) for categorical variables. Data were compared with Student's *t* tests or Mann-Whitney tests for continuous variables and with chi-squared or Fisher's exact tests for categorical variables, as appropriate. Distributions of survival without poor kidney outcome were compared in a univariate analysis, with log-rank tests. Hazard ratios for prognostic factors were estimated with 95% confidence intervals (95%CI), with a proportional hazards models ($_{PH}$HR) or the Mantel-Haenszel approach ($_{MH}$HZ) if the assumption of proportional hazards was violated or there was a lack of convergence. Survival without poor kidney outcome was compared between IBD-associated IgAN and primary IgAN, with proportional hazards models. In a sensitivity analysis, we improved the comparability between cohorts, by three controls to

one IBD-associated IgAN individual matching on the basis of baseline characteristics and steroid therapy, using Mahalanobis distance. The small sample size and low frequency of poor kidney outcome precluded multivariable analysis and tests of interaction between prognostic factors and IBD-associated IgAN. *P* values below 0.05 were considered significant. Results were analyzed with Graph Pad Prism software version 7.

Detailed materials and methods are provided in supplementary methods.

RESULTS

In this retrospective study, we identified 24 subjects (16 men and 8 women) with IBD-associated IgAN, diagnosed between 1985 and 2015 at seven nephrology departments. Detailed descriptions of each patient are provided in supplemental table S1.

Demographic, clinical and biological features of patients with IBD-associated IgAN

At the time of renal biopsy, the mean age of patients with IBD-associated IgAN was 37 years (±15 years; range: 13 to 73; Table 1). Twenty-two patients were of Caucasian origin and the other two were of Afro-Caribbean ancestry. Only one patient was diagnosed with IBD after IgAN (9 months after IgAN diagnosis). In the remaining 23 patients, IgAN was diagnosed after IBD (mean of 9 ±6 years after IBD diagnosis).

Seventeen (70.8%) had a uPCR exceeding 100mg/mmol, (mean 254 mg/mmol). Three patients had nephrotic syndrome. Hypertension was present in 41.7% of patients. CKD disease stages are summarized in Table 1.

Pathological characteristics of IBD-associated IgAN

Pathology findings are shown in Table 1. The mean number of glomeruli was 18 ± 11. The mean rate of globally sclerotic glomeruli was 21.5%, with values ranging from 0 to 80%. Mesangial IgA deposits were associated with C3 deposits in all cases. The most frequent patterns for the criteria of the Oxford classification were M1 (57%), E0 (52%), S1 (76%), T1 (48%), and C0 (62%). A severe histological pattern (> 1 MEST-C criterion) was found in 14/21 (66.7%) patients. Only four of the 12 patients with a T1 or T2 criterion had previously received 5-ASA therapy.

Management of IgAN and outcome of patients with IBD-associated IgAN

Mean follow-up was 87±70 months after IgAN diagnosis. Renin-angiotensin system (RAS) inhibitor therapy was initiated at the time of IgAN diagnosis in 16/24 (66.7%) patients and used in 19/24 patients (79.2%) at last follow-up (Table 2). Steroid therapy was administered, for a mean duration of 14.3 ± 10 months, in 12 patients. In 6/12 patients, steroids were initially administered intravenously, and in all cases, oral treatment was initiated at a dose of 1 mg/kg/day with progressive tapering. No other immunosuppressive agents were introduced for specific control of IgAN.

The proportion of patients with uPCR > 100 mg/mmol decreased from 70.8% to 26.1% at last follow-up. Four patients with IBD-associated IgAN (16.7%) met the composite criterion for poor renal outcome. Two of these patients underwent kidney transplantation, and one required chronic hemodialysis. No recurrence was observed on renal allograft biopsy during a mean follow-up of 7.5 months after kidney transplantation. Two deaths were recorded during follow-up: one from bladder cancer before reaching the composite outcome and one from endocarditis due to *Streptococcus bovis* after kidney transplantation.

IBD pattern of patients with IBD-associated IgAN

The mean age at IBD diagnosis was 28 ±14 years. IBD consisted predominantly of Crohn's disease (CD) (18/24 patients; ulcerative colitis (UC) was found in 6/24 patients; Table 3). Only four patients with CD (22.2%) had pure ileal disease; 14 had colonic involvement, which was isolated in four cases and associated with ileal involvement in 10 cases. After a mean follow-up of 15.6 ±7.5 years, the phenotype was mostly non-stricturing and non-penetrating, in 11 (61.1%) cases. Others extra-intestinal manifestations, not involving the kidney, were present in 11 patients (45.8%). They included arthritis (*n*=6), purpura (*n*=6), bullous dermatosis (*n*=1) and eye involvement (*n*=3). IBD was diagnosed before IgAN in all (mean of 8.7 ±6.4 years) but one

case. At the time of IgAN diagnosis, IBD was active in 5 of the 19 (26.3%) cases of CD (Harvey – Bradshaw index > 4), but none of those with UC (partial Mayo score > 3). Median C-reactive protein level at IgAN onset was 2.15 mg/L [IQR 4.4 –11.9]. Following IgAN diagnosis, the annual rate of IBD relapse (number of relapses/year of follow-up) decreased significantly (0.6 ± 0.5 vs. 0.1 ± 0.2, $p < 0.001$), and there was a trend towards a decrease in annual steroid requirement (number of steroid uses/years of follow-up) (0.2 ± 0.3 vs 0.1 ± 0.2, p = 0.06).

Anti-TNFα treatment was used to manage IBD in 11 and was initiated before the diagnosis of IgAN in 9 patients. Anti-TNFα therapy followed a first line of immunosuppresive agents in 6/11 cases, but was initiated as a first-line treatment in the other 5. At the time of IgAN diagnosis, 5 patients were on azathioprine or methotrexate treatment and 5 were on anti-TNFα therapy. The median time between the first administration of anti-TNFα agents and IgAN diagnosis was 6.3 ±4.3 years. Anti-TNFα treatment was not modified or discontinued following the diagnosis of IgAN. Clinical and biological presentation at the time of renal biopsy and disease course did not differ significantly between patients with and without anti-TNFα therapy (Supplemental table S3).

Prognosis factors

No IBD-related factors were identified as significantly associated with kidney outcome in univariable analysis (Table 4). Only uPCR > 150 mg/mmol at IgAN onset was associated with a poor kidney outcome ($_{MH}$HR = 8.0, 95%CI: [1.1 – 57], $p = 0.04$). A severe histological pattern (> 1 MEST-C criteria) was not associated with the occurrence of the composite outcome ($_{PH}$HR = 1.8, 95%CI: [0.59 – 57], $p = 0.09$). Interestingly, steroid use was significantly associated with better kidney survival ($_{MH}$HR = 0.12, 95%CI: [0.01 – 1.1], $p = 0.02$).

Comparison between IBD-associated IgAN and primary IgAN

The comparison of demographic, clinical, pathological and biological characteristics between patients with IBD-associated IgAN and patients with primary IgAN is summarized in Table 1. Mean initial eGFR was 70.4 ml/min/1.73m^2 in IBD-associated IgAN and 66.7 ml/min/1.73m^2 in primary IgAN (p = 0.61), with no difference in proteinuria or hematuria. Pathological features diverged between the two conditions: M1 lesions were observed in 57% of cases of IBD-associated IgAN versus only 28% of cases of primary IgAN (p=0.03), whereas T2 lesions were observed in 9% of cases of IBD-associated IgAN and 34% of cases of primary IgAN (p=0.02). The frequencies of E, S and C lesions were similar in the two conditions.

We then compared therapeutic management and outcome between the two groups (Table 2). Follow-up duration was 82 and 61months in IBD-IgAN and primary IgAN respectively (p=0.23). Almost 80% of the patients in both cohorts were treated with RAS inhibitors. Steroid use was 50% and 35% in IBD-IgAN and primary IgAN respectively (p=0.23). As shown in Figure 1, kidney survival did not differ significantly between the two groups ($_{PH}$HR = 0.67, 95% CI: [0.23 –1.9], p=0.46). Individual matching between IBD patients and controls to improve comparability did not markedly change this estimate ($_{PH}$HR = 0.75, 95% CI: [0.14 – 4.0], p=0.75).

DISCUSSION

IgAN has been identified as part of the spectrum of renal manifestations in IBD patients. However, no detailed studies of the clinical, biological and pathological characteristics or management of these patients have been published. In this nationwide retrospective study, we identified 24 patients with IBD-associated IgAN, whose data were analyzed in detail.

We performed a literature review and identified 19 cases of IBD-associated IgAN for whom sufficient data were available for analysis[8–258–25] (Table 5 and Supplemental Table S2). The mean age of the patients in published studies of IBD-associated IgAN was 30 years, from 11 to 72 years. We identified three pediatric cases in literature review, and one in the current cohort. As observed in our study, the predominance of male patients was greater among patients with IBD-associated IgAN than in typical IBD cohorts, possibly due to a confounding bias relating to the preponderance of men in IgAN cohorts[2]. Overall, renal presentation was similar to that in the previously reported cases, with frequent hematuria, proteinuria and moderately altered renal function. An analysis of previous case reports revealed a higher rate of steroid use (75%) than in our cohort (50%). Given the limited duration of follow-up (mean = 22 months), none of the previously reported cases reached the composite outcome. Interestingly, IBD was considered to be in an active phase in 13 of the 19 (68%) previously reported cases of IBD-associated IgAN but in only 26.3% of the patients in this cohort. This difference may be explained by a selection bias towards the reporting of single cases with a similar course for both diseases. This bias was probably limited in our cohort by the inclusion of patients with IBD-associated IgAN independently of IBD activity. The features of IBD in previous cases were similar to those of our cohort in terms of IBD type, extra-intestinal manifestations and frequency of surgical procedures. One divergence concerned the non-surgical approach to IBD

management, with different rates of steroid use and anti-TNFα administration between previously published cases (60% and 13.3%, respectively) and our cohort (16.7% and 45.8%, respectively). The most frequently observed CD phenotype in our cohort was the non-stricturing and non-penetrating phenotype, which is usually uncommon after follow-up for more than 10 years[29].

The clinic-biological parameters, and evolution of IBD-IgAN were similar to those of our primary IgAN group. Our findings are also consistent with those of previous studies on other cohorts of European patients with IgAN[30]**.** In the VALIGA study, clinico-biological characteristics (including age, blood pressure, intial eGFR, initial proteinuria and time-averaged proteinuria) were similar to our control group, and the composite end point (>50% eGFR loss or ESRD) was observed in 16,7% patients after 56 months of follow-up, which is close to 16.8% after 82 months of follow up (Table 2) observed in our control group. Moreover, the treatments were also similar (immunosuppression used in 46% and 35% patients, and RAS blockers in 86% and 79% patients, in the VALIGA study and our control group, respectively).

However, histological lesions differed between IBD-associated IgAN and primary IgAN, with a higher frequency of M lesions and a lower frequency of T2 lesions in IBD-IgAN. It should be noted that T1-T2 lesions were frequent in both IBD-IgAN and our control group, which may reflect the biopsy policy in France. This differential pattern may be related to the earlier diagnosis of kidney dysfunction in patients already followed for IBD. In addition, a larger proportion of patients with IBD than of patients in the control group received steroids and/or immunosuppressive agents before IgAN diagnosis. These therapeutic interventions may have led to a decrease in inflammatory burden in the course of kidney disease[6]. Our univariate analysis demonstrated that steroids were associated with a lower incidence of poor kidney

outcome. There remains much debate about the impact of steroids in patients with primary IgAN[3], but the use of these drugs seems to be most beneficial in patients with inflammatory lesions and limited fibrosis[4], as ~~reported~~ observed in this series of patients with IBD-associated IgAN.

TNFα blockade has been associated with the development of systemic vasculitis and IgA-dependent diseases, including IgAN[34]. However, anti-TNFα therapy has also been reported to induce IgAN remission[35]. We identified no specific characteristics of patients previously treated with anti-TNFα agents in our cohort. Further studies on larger patient cohorts are required to determine whether anti-TNFα therapy is beneficial or deleterious in IBD-associated IgAN.

The pathophysiological processes involved in IBD-associated IgAN remain to be determined. Many similarities between these two diseases, in terms of genetics, environmental factors, and immune system dysregulation, have been documented[7]. First, the overstimulation of mucosal B cells in established IBD lesions skews immunoglobulin production away from IgA2 towards IgA1[36]. Furthermore, an aberrant O-linked glycosylation of IgA, characterized by a decrease in N-acetylgalactosamine is observed in CD patients[37], and this is also the first step in IgAN pathogenesis. Indeed, a recent study demonstrated an absence of difference between 32 patients with primary IgAN and 100 patients with secondary IgAN, including UC, in terms of the levels of circulating IgA1 and glomerular IgA1 with galactose-deficient O-glycans[38]. This pattern of glycosylation in IgAN may be explained by lower levels of production and activity for a key glycosyltransferase, C1GalT1, due to lower levels of expression of its chaperone, encoded by *COSMC*[7]. Interestingly, *COSMC* expression is strongly inhibited in circulating B lymphocytes from IgAN patients cocultured with lipopolysaccharide, suggesting

328 a potential role of the gut microbiota in *COSMC* downregulation in IgAN[39]. Indeed, low levels
329 of gut microbiota diversity and an increase in intestinal permeability have been reported in both
330 diseases[7]. However, such increase in intestinal permeability is also observed in other types of
331 glomerulonephritis without IgA glycosylation impairment[40]. Nevertheless, the gut microbiota
332 may drive B-cell activation in a T cell-independent manner, via B-cell activation factor of the
333 TNF family (*BAFF*). *BAFF* is overexpressed in colon biopsy specimens from IBD patients[41]
334 and serum *BAFF* levels are high in IgAN patients[42]. Transgenic mice overexpressing *BAFF*
335 develop mesangial IgA deposits, together with high serum levels of aberrantly glycosylated
336 IgA, which are not observed in axenic conditions[43]. Microbiota-reactive circulating IgA
337 antibodies were found in these mice. Moreover, T cells may also play a crucial role, given their
338 contribution to IBD, through the expansion of Th17 cells and decreases in T regulatory cell
339 (Treg) levels[28,29]. In IgAN, Treg differentiation is inhibited by micro-RNA *miR-133b*[44], which
340 is strongly expressed in the bowel tissues of IBD patients[45]. Furthermore, in Peyer's patches,
341 Th17 cells can acquire a follicular helper T-cell phenotype, inducing the formation of IgA-
342 producing germinal center B cells, suggesting a close relationship between IBD and IgAN[46]. It
343 has recently been shown *in vitro* that interleukin-17 can promote the production of
344 underglycosylated IgA1 in a B-cell lineage[47]. Wang et al. developed a mouse model of IgAN
345 and bowel inflammation similar to CD[48], by dysregulating the expression on T cells of LIGHT,
346 a ligand for the lymphotoxin beta receptor. These results further highlight the potential
347 contribution of T cells to the pathogenesis of both IgAN and IBD.

348 Our work has several limitations. The centralized review of renal biopsies was possible
349 in only 146 of 158 cases. The retrospective collection of data may have resulted in biases,
350 relating to the activity score obtained in 19/24 cases and the course of IBD, which began a mean

of nine years before kidney biopsy. Finally, the relatively small sample size and limited number of events provided a power sufficient only for the detection of major prognostic factors. These limitations make it impossible to draw definitive conclusions regarding therapeutic strategies for IBD-associated IgAN and comparison of IBD-IgAN and primitive IgAN.

In conclusion, we report the presentation and outcome of the first case series of IBD-associated IgAN. Interestingly, IgAN diagnosis was not associated with IBD flare. TNFα blockade had no impact on presentation and course of IBD-IgAN in our series. Prospective studies are required to decipher the exact molecular links between gut inflammation and IgAN.

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Conflict of interest statement

The authors had no conflict of interest

Authors' contributions

NJ, AA, VA and KEK designed the study, analyzed the data and wrote the manuscript. CG, MR and SH performed histological analyses. NJ, DG, EP, AH, JJB, SF, YD, AK, AA and KEK were responsible for patient care. All the authors carefully reviewed the manuscript.

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Data Availability statement

The data underlying this article are available in the article and in its online supplementary material.

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TABLES

Table 1. Demographic data, kidney features and pathological characteristics at presentation

Characteristic	IBD-IgAN n = 24	Primary IgAN n = 134	*p* *
Demographic data			
Age at kidney biopsy (years), mean ±SD	37 ± 15	39 ± 12	*0.46*
Female, n (%)	8 (33.3)	35 (26.1)	*0.46*
Kidney features at IgAN onset			
Hypertension, n (%)	10 (41.7)	56 (41.8)	*1.00*
Systolic blood pressure (mmHg), mean ±SD	137 ± 16	136 ± 20	*0.80*
Diastolic blood pressure (mmHg), mean ±SD	78 ± 10	81 ± 13	*0.55*
uPCR > 50 mg/mmol, n (%)	23 (95.8)	103 (80.5)[x]	*0.07*
uPCR > 100 mg/mmol, n (%)	17 (70.8)	81 (63.3)[x]	*0.64*
uPCR > 150 mg/mmol, n (%)	13 (54.2)	50 (39.1)[x]	*0.18*
uPCR (mg/mmol), mean ±SD	254 ± 242	174 ± 165	*0.14*
Serum albumin (g/L), mean ±SD	35 ± 7	38 ± 6	**0.04**
Nephrotic syndrome, n (%)	3 (12.5)	5 (3.7)	*0.10*
eGFR (mL/min/1.73m^2), mean ±SD	70.4 ± 29	66.7 ± 31	*0.61*
Kidney replacement therapy at IgAN onset, n (%)	1 (4.2)[°]	5 (5.3)[x]	*1.00*
CKD stages, n (%)			
I / II	13 (54.2)	73 (57.5)[x]	
III	9 (37.5)	38 (29.9)[x]	
IV	1 (4.15)	13 (10.2)[x]	
V	1 (4.15)[°]	3 (2.4)[x]	
Histopathological characteristics	**n = 21**	**n = 130**	
Severe pattern (>1 MEST-C criteria), n (%)	14 (66.7)[x]	99 (73.8)	*0.59*
Glomeruli (n), mean ± SD	18 ± 11	15 ± 8	*0.30*

Sclerotic glomeruli (%), mean ± SD	21.5 ± 23	23.8 ± 22	*0.52*
M0/M1, n	9/12	94/36	**0.03**
E0/E1, n	11/10	91/39	*0.13*
S0/S1, n	5/16	24/106	*0.56*
T0/T1/T2, n	9/10/2	67/19/44	**0.02**
C0/C1/C2, n	13/8/0	84/37/9	*0.36*

Chronic kidney disease (CKD) stages defined according to the 2012 KDIGO guidelines, eGFR: glomerular filtration rate estimated with the CKD-EPI formula and expressed in ml/min/1.73m^2; Hypertension, defined as systolic blood pressure > 140 mmHg or diastolic blood pressure > 80 mmHg; IBD: inflammatory bowel disease; IgAN: IgA nephropathy; MEST-C according to the Oxford classification; nephrotic syndrome defined as a serum albumin concentration < 30 g/L and proteinuria > 3 g/day; uPCR: urinary protein-to-creatinine ratio.

*Statistical tests were performed to compare the IBD-IgAN cohort with a primary IgAN cohort. *P* values below 0.05 were considered significant.

(%)^x: % for available data

° : patient requiring hemodialysis at IgAN onset, with recovery of renal function

511 **Table 2. Management and outcome at last follow-up**

Characteristic	IBD-IgAN n = 24	Primary IgAN n = 134	*p* *
Follow-up (months), mean ±SD	82 ± 70	61 ± 40	*0.23*
RAS inhibitors, n (%)	19 (79.2)	69 (78.4)[x]	*1.00*
Steroid to treat IgAN, n (%)	12 (50)	29 (35)[x]	*0.23*
Initiated intravenously, n (%)	6 (50)	-	
Duration (months), mean ±SD	14.3 ± 10	-	
Composite Outcome, n (%)	4 (16.7)	21 (16.8)[x]	*1.00*
ESRD, n	3	17	
Decline > 50% of initial eGFR, n	1	4	
Hypertension, n (%)	9 (39.1)[x]	19 (21.8)[x]	*0.10*
uPCR> 50 mg/mmol, n (%)	13 (56.5)[x]	39 (39.4)[x]	*0.16*
uPCR> 100 mg/mmol, n (%)	6 (26.1)[x]	26 (26.3)[x]	*0.99*
uPCR> 150 mg/mmol, n (%)	5 (21.7)[x]	16 (16.2)[x]	*0.54*
uPCR (mg/mmol), mean ±SD	114 ± 159	88 ± 123	*0.43*
eGFR (mL/min/1.73m^2), mean ±SD	62 ± 35	63.7 ± 33	*0.78*
CKD stages, n (%)			
I/II	10 (45.4)[x]	53 (50.5)[x]	
III	8 (36.4)[x]	31 (29.5)[x]	
IV	1 (4.6)[x]	14 (13)[x]	
V	3 (13.6)[x]	7 (6)[x]	
Dialysis therapy, n (%)	1 (4.2)	13 (10.5)[x]	*0.46*
Kidney transplantation, n (%)	2 (8.4)	-	
Severe infections, n (%)	3 (12.5)	-	
Death, n (%)	2 (8.4)	-	

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513 Chronic kidney disease (CKD) stages defined according to the 2012 KDIGO guidelines, eGFR:
514 glomerular filtration rate estimated with the CKD-EPI formula and expressed in
515 ml/min/1.73m^2; ESRD: end-stage renal disease; hypertension defined as systolic blood pressure

> 140 mmHg or diastolic blood pressure > 80 mmHg; IgAN: IgA nephropathy; MEST-C based on the Oxford classification; nephrotic syndrome defined as serum albumin concentration < 30 g/L and proteinuria > 3 g/day; RAS: renin-angiotensin system; uPCR: urinary protein-to-creatinine ratio.

*Statistical tests were performed to compare the IBD-IgAN cohort and a primary IgAN cohort. *P* values below 0.05 were considered significant.

(%)[x]: % for available data

544 **Table 3. IBD features of patients with IBD-associated IgAN**

Characteristic	IBD-IgAN (n = 24)
Demographic data	
Age at IBD diagnosis (years), mean ±SD	28 ± 14
Female, n (%)	8 (33.3)
Smoker, n (%)	6 (25)
Body-mass index (kg/m^2), mean ±SD	24.8 ± 5.5
IBD pattern	
Familial history of IBD, n (%)	8 (33.3)
IBD diagnosed before nephropathy, n (%)	23 (95.8)
Crohn's disease, n (%)	18 (75)
Montreal classification	
A1/A2/A3, n	3/11/3
B1/B2/B3/+p, n	11/4/3/+9
L1/L2/L3/L4, n	4/4/10/3
Ulcerative Colitis, n (%)	6 (25)
Montreal classification	
A1/A2/A3, n	0/5/0
E1/E2/E3, n	1/4/1
Other extraintestinal manifestations, n (%)	11 (45.8)
Purpura, n	6
Arthritis, n	6
Other, n	4
Serum C - Reactive protein level at IgAN onset (mg/L), median	2.15
Active IBD at IgAN onset, n (%)	5 (26.3%)[x]
Harvey-Bradshaw index > 4, n	5
Partial Mayo score > 3, n	0
IBD treatment	
Steroid to treat IBD, n (%)	4 (16.7)

Local administration, n	1
Systemic administration, n	3
Anti-TNFα, n (%)	11 (45.8)
Before IgAN, n	9
Ongoing at IgAN onset, n	5
Adalilumab, n	2
Infliximab, n	11
5-aminosalicylic acid, n (%)	5 (20.8)
Azathioprine or methotrexate, n (%)	11 (45.8)
Surgery, n (%)	10 (41.7)

IBD: Inflammatory bowel disease; IgAN: IgA nephropathy; Montreal classification with age at diagnosis (<16/ 17-40/ > 40 years noted A1/ A2/ A3), disease location (ileal/ colonic/ ileocolonic/ upper gastrointestinal location, noted L1/ L2/ L3/ L4, for Crohn's disease and proctitis/ left-sided colitis/ extensive colitis, noted E1/ E2/ E3, for ulcerative colitis) and disease phenotype (non-stricturing and non-penetrating/ stricturing/ penetrating/ perianal disease noted B1/ B2/ B3/ +p for Crohn's disease); TNFα: tumor necrosis factor α

(%)^{x}: % for available data

Table 4. Univariate analysis for predictive factors in IBD-associated IgAN

Factors analyzed	Hazard ratio [95%CI]	*p* *
Epidemiological factors		
Age > 60 years at IgAN onset	4.4 [0.1 - 208]	*0.15*
Male	3.4 [0.5 - 24]	*0.18*
Tobacco exposure	1.7 [0.2 - 13]	*0.60*
IBD-related factors		
Crohn disease subtype	4 [0.3 - 51]	*0.28*
Active IBD at IgAN onset	6.6 [0.6 - 64]	*0.10*
Use of Anti-TNFα agents	0.45 [0.06 - 3.3]	*0.45*
History of surgery	4.9 [0.6 - 37]	*0.12*
Kidney-related factors at IgAN onset		
Hypertension	0.45 [0.06 - 3]	*0.48*
uPCR > 100 mg/mmol	5.2 [0.6 - 40]	0.19
uPCR > 150 mg/mmol	8.0 [1.1 - 57]	**0.04**
eGFR < 60 mL/min/1.73m^2	2.8 [0.4 - 20]	*0.34*
Severe pathologic pattern (> 1 MEST-C criteria)	1.8 [0.6 - 57]	*0.09*
Sclerotic glomeruli > 20 %	3.3 [0.3 - 33]	*0.18*
Management		
Use of steroid to treat IgAN	0.12 [0.01 - 1]	**0.02**

eGFR: glomerular filtration rate estimated with the CKD-EPI formula and expressed in ml/min/1.73m^2; hypertension, defined as systolic blood pressure > 140 mmHg or diastolic blood pressure > 80 mmHg; IBD: inflammatory bowel disease; IgAN: IgA nephropathy; MEST-C based on the Oxford classification; uPCR: urinary protein-to-creatinine ratio; TNFα: tumor necrosis factor α

*Hazard ratios were estimated with 95% confidence interval (95%CI), with a proportional hazards model or the Mantel-Haenszel approach if the proportional hazards assumption was violated or there was a lack of convergence. *P* values below 0.05 were considered significant.

566 **Table 5. Summary of published data for IBD-associated IgAN**

Characteristic	Literature review (n = 19)
Demographic data	
Age at kidney biopsy (years), mean ±SD	30 ± 15
Female, n (%)	5 (26.3)
IBD pattern	
IBD present before nephropathy, n (%)	11 (57.9)
Crohn's disease, n (%)	12 (66.7)[x]
Ulcerative colitis, n (%)	6 (33.3)[x]
Other extraintestinal manifestations, n (%)	6 (37.5)[x]
Purpura, n	0
Arthritis, n	4
Other, n	3
Active IBD at IgAN onset, n (%)	13 (81.2)[x]
IBD treatment	
Steroid to treat IBD, n (%)	9 (60)[x]
Local administration, n	2
Systemic administration, n	7
Anti-TNFα agents, n (%)	2 (13.3)[x]
Before IgAN, n	1
Adalilumab, n	0
Infliximab, n	2
5-aminosalicylic acid, n (%)	11 (73.3)[x]
Azathioprine or methotrexate, n (%)	1 (7.7)[x]
Kidney features at IgAN onset	
Hypertension, n (%)	0
Hematuria, n (%)	14 (87.5)[x]
Macroscopic hematuria, n	3

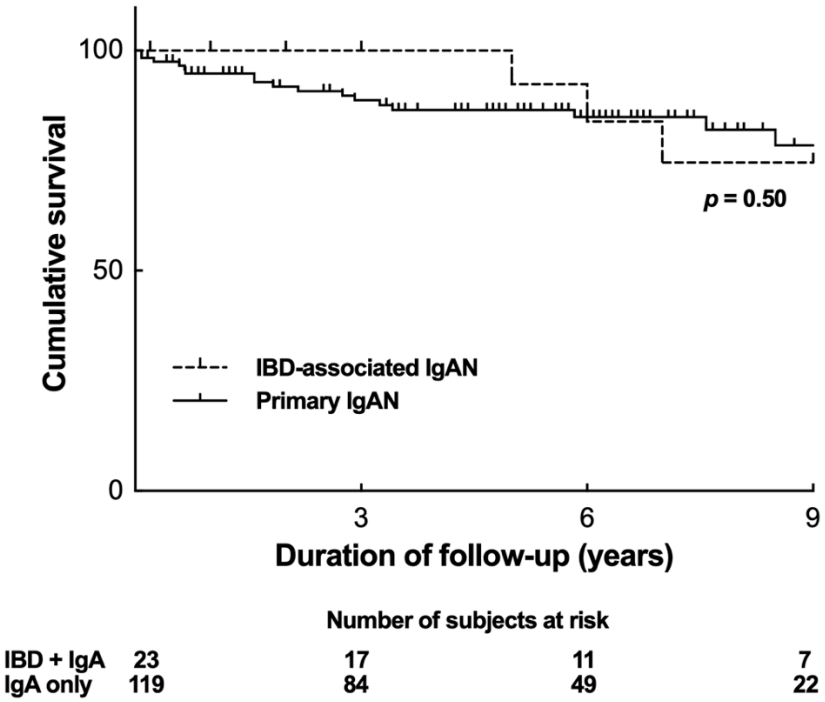
Proteinuria > 0.5 g/day, n (%)	9 (52.9)[x]
Proteinuria (g/day), mean ±SD	1.34 g/day ± 1.6
Nephrotic syndrome, n (%)	0
eGFR (mL/min/1.73m^2), mean ±SD	63 ± 40
Kidney replacement therapy at onset IgA, n (%)	0
CKD stages, n I/II – III – IV – V	11 – 3 – 4 – 1
Management and outcome	
Follow-up (months), mean ±SD	22 ± 22
Steroid to treat IgAN, n (%)	12 (75)[x]
Composite outcome, n (%)	0
Similar course between IBD and IgAN, n (%)	13 (81.2)[x]
Proteinuria > 0.5 g/day, n (%)	3 (18.7)[x]
Proteinuria (g/day), mean ±SD	0.75 g/day ± 0.7
eGFR (mL/min/1.73m^2), mean ±SD	79 ± 35
CKD stages, n I/II – III – IV – V	12 – 3 – 1 – 0
Death, n	0

CKD stages defined according to the 2012 KDIGO guidelines, eGFR: glomerular filtration rate estimated with the CKD-EPI formula and expressed in ml/min/1.73m^2; ESRD: end-stage renal disease; hypertension, defined as systolic blood pressure > 140 mmHg or diastolic blood pressure > 80 mmHg; IBD: inflammatory bowel disease; IgAN: IgA nephropathy; MEST-C based on the Oxford classification as described in the methods; nephrotic syndrome defined as serum albumin concentration < 30 g/L and proteinuria > 3 g/day; uPCR: urinary protein-to-creatinine ratio. (%)[x]: % for available data

Legends to figure

Figure 1. Kaplan–Meier renal survival curves for patients with IBD-associated IgAN and primary IgAN

Kidney survival, defined as not reaching ESRD or having a decline of > 50% in eGFR from initial values during follow-up. IBD: inflammatory bowel disease, IgAN: IgA nephropathy. Bars represent the date on which data were censored. Log-rank tests were used to compare survival curves. *P* values below 0.05 were considered significant.



SUPPLEMENTAL MATERIALS

Supplemental materials and methods

Study population

We conducted this retrospective study by sending a questionnaire to all French nephrology departments asking them to identify patients with biopsy-proven IgAN occurring in a context of IBD. Patients consulting from 1985 to 2016 were retrospectively identified. The inclusion criteria were the presence of biopsy-proven IgAN[2] and a diagnosis of either CD or UC according to standard guidelines, on the basis of radiological and endoscopic evidence in addition to pathological criteria[28,29]. The exclusion criteria included a lack of available clinical/biological data and the absence of a kidney biopsy. Relevant clinical and biological data were recorded for each patient at the time of IgAN diagnosis (i.e. kidney biopsy), and at the end of follow-up (i.e. last visit, date of death, date of ESRD). The use of drugs usually administered during the course of IgAN, such as steroids and renin-angiotensin system inhibitors, was recorded for all patients. Glomerular filtration rate (eGFR) was estimated with the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (CKD-EPI). CKD stages were defined according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. A poor kidney outcome was defined as follows: ESRD, defined as CKD stage V or the need for kidney replacement therapy, or a > 50% decrease in eGFR from initial values.

The information about IBD extracted from the gastroenterologist's records included: timing of the occurrence of IBD relative to IgAN onset, the type of IBD, the parts of the digestive tract affected, extra-intestinal manifestations other than kidney involvement, and specific treatments received by the patient (surgery, immunosuppressive agents and/or biotherapy, such as anti-

TNFα agents). IBD phenotype was characterized according to the Montreal classification[31]. Disease activity was assessed with the Harvey–Bradshaw index for CD and the partial Mayo score for UC[32]. We considered IBD to be active for a Harvey–Bradshaw index (HBI) > 4 for CD and a partial Mayo score > 3 for UC. Serum C-reactive protein concentration was also recorded at the time of kidney biopsy. The two diseases were considered to have occurred simultaneously if their diagnoses were separated by less than six months.

This study aimed at describing the patients with IBD-associated IgAN and to compare them to a control group of patients with primary IgAN. All consecutive IgAN patients diagnosed from 2003 to 2014 in the Pathology department of Necker Hospital (Paris, France) were evaluated to inclusion in this control group. This pathology department is in charge of analysing renal biopsy specimens from 4 different centres in the Paris, France area. The inclusion criteria were the presence of biopsy-proven IgAN[2], without history of autoimmune or inflammatory disease especially from rheumatic or gastrointestinal system such as IBD, malignancy and infection such as infection by Human Immunodeficiency Virus or current bacteremia. Data were recorded in the control group using the same method as for IBD-associated IgAN group.

Renal pathology studies

The histological diagnosis of IgAN was based on the presence of IgA-dominant or co-dominant immune deposits within glomeruli[33] on immunofluorescence analysis. The kidney biopsy specimens used for the initial pathological diagnosis of IgAN were reassessed centrally by a nephropathologist blind to clinical data. Samples were processed for light microscopy, for the determination of MEST-C score according to the updated Oxford classification[33]. Kidney biopsy specimens were not available for 12/158 patients. Five of these cases were analyzed on the basis of the initial histological report, in which a precise MEST-C score was noted; no definitive MEST-C score could be obtained for the remaining seven cases. We considered

histological features to be severe if more than one of the MEST-C criteria for M1, E1, S1, T1-2, and C1-2 were met.

Literature review

We performed a systematic review of the literature from 1980 to 2019 to identify previous cases of IBD-associated biopsy-proven IgAN without confounding factors (including malignancies, infections, or other autoimmune ofr inflammatory diseases). We searched MEDLINE via PubMed for all articles published in French or English using the keywords or MeSH terms "Glomerulonephritis, IGA", "Inflammatory Bowel Diseases", "Crohn Disease", "Colitis, Ulcerative". Only reports for which clinical, biological, and renal histological data and outcomes were available were included.

61 **Supplemental Table S1. Main characteristics of IBD-associated IgAN in the French retrospective cohort**

Subject	Epidemiological data			First diagnosis	IBD pattern			Kidney features at IgAN onset					Management and outcome				
	Age	Sex	Origin		Type	Other EIM	AntiTNFα	HBP	Hematuria	uPCR	eGFR	Histology	Duration of follow-up	Steroid for IgAN	uPCR	eGFR	Outcome
1	47	♂	Caucasian	IBD	UC	No	No	Yes	Micro	472	37	M0S0E0T2C0	-	No	-	-	+
2	27	♂	African	IBD	CD	No	No	No	Micro	174	95	M0S1E1T1C1	72	No	432	5	ESRD - Dialysis
3*	36	♀	Caucasian	IBD	UC	No	No	Yes	No	200	93	M0S1E0T0C0	18	No	80	58	+
4*	42	♂	Caucasian	IBD	CD	No	Infliximab	No	Micro	71	58	M1S1E0T0C0	36	No	62	53	+
5	45	♂	Caucasian	IBD	CD	No	Infliximab	No	Micro	161	54	M0S1E0T0C0	60	No	221	9	ESRD - KT
6	23	♂	Caucasian	IBD	CD	No	Infliximab	Yes	No	72	69	M1S1E0T1C0	62.2	No	33,9	64	+
7	35	♀	Caucasian	IBD	UC	No	No	No	Micro	184	116	M1S0E0T0C0	156	No	80	95	+
8	64	♂	Caucasian	IBD	CD	No	No	Yes	No	466	30	M1S1E1T1C1	84	No	300	14	Decline eGFR > 50%
9	46	♂	Caucasian	IBD	CD	Arthritis	Infliximab	Yes	No	760	78	M0S0E0T0C0	36	No	90	80	+
10	51	♂	Caucasian	IBD	CD	No	Infliximab	Yes	No	260	52	M0S1E0T1C0	60	No	0	30	+
11*	25	♂	Caucasian	IBD	CD	No	No	No	No	79	97	-	72	No	0	105	+
12	61	♂	Caucasian	IBD	CD	Arthritis / Uveitis	Adalimumab / Infliximab	No	Macro	12	98	M0S0E0T0C0	24	No	0	91	+
13	27	♀	Caucasian	IBD	CD	Purpura / Keratitis	Infliximab	Yes	Micro	250	63	M1S1E0T1C0	61.9	Bolus first	57	52	+
14	13	♀	African	IBD	CD	Arthritis / Episcleritis	No	No	No	304	123	M1S1E1T1C1	24	Bolus first	20	150	+
15*	36	♂	Caucasian	IBD	UC	No	No	Yes	No	134	94	M1S1E1T0C1	192	Bolus first	637	57	+
16*	27	♀	Caucasian	IBD	CD	Arthritis/ Purpura	No	No	Macro	760	35	M1S1E1T1C1	216	Yes	15	-	ESRD - KT
17	32	♀	Caucasian	IBD	CD	Purpura	Adalimumab / Infliximab	No	Micro	900	59	M1S1E1T0C1	84	Yes	6	94	+
18	73	♂	Caucasian	IBD	CD	Purpura	No	No	No	120	17	M1S1E1T1C0	2,4	Bolus first	100	57	+

19	21	♀	Caucasian	IBD	CD	Arthritis	Infliximab	Yes	Micro	80	81	M0S0E0T0C0	264	Yes	60	44	+
20*	38	♂	Caucasian	IBD	CD	Arthritis	Infliximab	Yes	No	90	77	-	180	Yes	50	69	+
21	48	♀	Caucasian	IBD	CD	No	No	No	Micro	183	111	M0S1E1T1C0	36	Yes	0	81	+
22*	21	♂	Caucasian	IBD	CD	No	No	No	No	140	47	-	120	Yes	117	47	+
23	22	♂	Caucasian	IBD	UC	Bullous dermatosis	Infliximab	No	Micro	118	48	M1S1E1T1C1	36	Bolus first	260	97	+
24*	27	♂	Caucasian	IgAN	UC	Purpura	No	No	Micro	100	57	M1S1E1T2C1	108	Bolus first	16	35	+

*: Kidney sample not centrally reviewed; Age in years; CD: Crohn's disease; eGFR: glomerular filtration rate estimated with the CKD-EPI formula and expressed in ml/min/1.73m^2; EIM: extraintestinal manifestation; HBP: High blood pressure, defined as systolic pressure > 140 mmHg or diastolic pressure > 80 mmHg; IBD: inflammatory bowel disease; IgAN: IgA nephropathy; KT: kidney transplantation; MEST-C according to the Oxford classification; UC: ulcerative colitis; TNFα: Tumor necrosis factor α; uPCR: urinary protein-to-creatinine ratio expressed in mg/mmol

Supplemental Table S2. Main characteristics of IBD-associated IgAN in cases from the literature review

Ref.	Publication date	Epidemiological data			First diagnosis	IBD pattern			Kidney features at IgAN onset					Management and outcome				
		Age	Sex	Origin		Type	Other EIM	AntiTNFα	HBP	Hematuria	Proteinuria	eGFR	Histology	Duration of follow-up	Steroid for IgAN	Proteinuria	eGFR	Outcome
8	1984	22	♀	-	IBD	CD	-	-	-	-	1.5	90	-	-	Bolus first	-	-	+
8	1984	43	♂	-	IBD	UC	-	-	-	-	7	85	-	-	Bolus first	3	-	+
9	1989	21	♂	Asian	IgAN	UC	No	No	No	Micro	0.3	100	-	24	No	<0.5	100	+
10	1990	35	♂	-	IBD	-	Arthritis	No	No	Micro	0.6	90	-	-	-	0.5	90	+
11	1992	31	♂	-	IBD	CD	No	-	-	No		5	-	3	Bolus first	-	40	+
12	1994	21	♂	-	IBD	CD	-	-	-	-	1.1	'Normal'	-	24	Bolus first	0.25	'Normal'	+
13	1996	12	♀	Caucasian	IBD	CD	Eye	No	No	Macro	2	15	-	2	No	<0.5	'Normal'	+
14	1997	11	♀	Caucasian	IgAN	CD	Arthritis	No	-	Micro	0.3	'Normal'	Segmental sclerosis	84	Bolus first	<0.5	'Normal'	+
15	2001	26	♀	-	Concomitant	UC	No	No	No	Micro	0.3	'Normal'	-	4	No	<0.5	'Normal'	+
16	2002	13	♂	Asian	IgAN	CD	No	No	No	Macro	1.2	55	Crescent	24	Yes	<0.5	95	+
17	2005	29	♂	-	IgAN	CD	No	No	-	Macro		'Normal'	-	60	Bolus first		'Normal'	+
18	2006	72	♂	-	IBD	UC	Arthritis	No	-	Micro	0.5	20	-	35	-	<0.5	30	+
19	2006	25	♂	-	IBD	UC	Arthritis Eye	No	No	Micro	0.6	125	-	24	-	<0.5	125	+
20	2010	31	♂	Caucasian	IBD	CD	No	No	No	No	0.5	50	TI damage	20	Bolus first	0.5	70	+
21	2012	18	♂	Asian	Concomitant	CD	No	No	No	Micro		25	Crescent/Segmental sclerosis/TI damage	10	Bolus first	<0.5	40	+
22	2012	38	♀	Hispanic	IBD	UC	Eye	No	No	Micro	1.5	70	Crescent	3	Bolus first	1.5	95	+
23	2012	62	♂	Caucasian	Concomitant	CD	No	No	No	Micro	2.5	25	-	12	Yes	1.5	50	+
24	2015	22	♂	Asian	IBD	CD	No	Infliximab	No	Micro	0.2	130	-	9	No	<0.5	135	+
25	2016	46	♂	Asian	IgAN	CD	No	Infliximab	No	Micro	1.4	60	Crescent/TI damage	12	Yes	0.3	-	+

Age in years; CD: Crohn's disease; eGFR: glomerular filtration rate estimated with the CKD-EPI formula and expressed in ml/min/1.73m^2; EIM: extraintestinal manifestation; HBP: high blood pressure, defined as systolic BP > 140 mmHg or diastolic blood pressure > 80 mmHg; IBD: inflammatory bowel disease; IgAN: IgA nephropathy; proteinuria expressed in g/day; TI: tubular and interstitial; UC: ulcerative colitis.

Supplemental Table S3. Clinical and biological presentation and course of IBD-associated IgAN with and without anti-TNFα treatment

Characteristic	Anti-TNF*α* + n = 11	Anti-TNF*α* - n = 13	*p* *
Age (years), mean ±SD	37 ± 13	37 ± 17	*0.97*
Female, n (%)	3 (27.3)	5 (38.5)	*0.68*
Crohn's disease, n (%)	10 (91)	8 (62)	*0.16*
Active IBD at IgAN onset, n (%)	5 (45)	0[x]	*0.05*
Extraintestinal manifestations, n (%)	7 (63)	4 (31)	*0.22*
High blood pressure at IgAN diagnosis, n (%)	4 (36)	6 (46)	*0.70*
Hematuria at IgAN diagnosis, n (%)	5 (45)	8 (61)	*0.68*
uPCR (mg/mmol) at IgAN diagnosis, mean ±SD	252 ± 297	255 ± 197	*0.97*
eGFR (mL/min/1.73m^2) at IgAN diagnosis, mean ±SD	67 ± 15	73 ± 36	*0.61*
Severe histologic pattern (>1 MEST-C criteria), n (%)	6 (60)[x]	8 (73)[x]	*0.66*
M0/M1, n	5/5	4/7	
E0/E1, n	8/2	3/8	
S0/S1, n	3/7	2/9	
T0/T1/T2, n	6/4/0	3/6/2	
C0/C1/C2, n	8/2/0	8/2/0	
Composite outcome, n (%)	1 (9)	3 (23)[x]	*0.60*
Use of Anti-TNFα related Hazard ratio [$_{95\%}$CI]	0.45 [0.06 - 3.3]		*0.45*

Composite outcome: end-stage renal disease or > 50% decrease in eGFR (glomerular filtration rate estimated with the CKD-EPI formula and expressed in ml/min/1.73m^2); high blood pressure defined as systolic pressure > 140 mmHg or diastolic pressure > 80 mmHg; IgAN: IgA nephropathy; MEST-C according to the Oxford classification; TNFα: tumor necrosis factor α; uPCR: urinary protein-to-creatinine ratio.

*Statistical tests were performed to compare IBD-IgAN patients who received anti-TNFα treatment with IBD-IgAN patients who did not receive antiTNFα treatment. *P* values below 0.05 are considered significant.

(%)[x]: % for available data