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

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1 **IgA nephropathy in association with inflammatory bowel diseases:**
2 **Results from a national study and systematic literature review**

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61 **ABSTRACT**

62

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

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

69 **Results** Crohn's disease and ulcerative colitis accounted for 75% and 25% of IBD-associated
70 IgAN cases, respectively. IBD was diagnosed before IgAN in 23 cases (a mean of 9 years
71 previously) and was considered active at IgAN onset in 23.6% of patients. Hypertension was
72 present in 41.7% of patients. Urinary protein-to-creatinine ratio exceeded 100 mg/mmol in
73 70.8% of patients (mean: 254 mg/mmol). Estimated glomerular filtration rate (eGFR) exceeded
74 60 ml/min/1.73m² in 13/24 patients and only one patient required dialysis. In the Oxford
75 MEST-C classification of renal biopsies, 57% were M1, 48% E1, 76% S1, 57% T1+T2 and
76 38% C1+C2. Steroids were administered in 50% of cases. After a mean follow-up of 7.2 years,
77 four patients (16.7%) had a poor kidney outcome: end-stage renal disease (*n*=3) or a > 50%
78 decrease in eGFR from initial values (*n*=1). A similar evolution was observed in patients with
79 primitive IgAN.

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

82

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

85

86 **KEY LEARNING POINTS**

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

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

94

95 INTRODUCTION

96 Immunoglobulin A nephropathy (IgAN), the most common primary glomerulonephritis¹, is
97 characterized by mesangial deposition of IgA and C3. IgAN has a highly variable clinical
98 presentation and course, ranging from asymptomatic microscopic hematuria to rapidly
99 progressive glomerulonephritis². Thus, despite the relatively high prevalence of IgAN, the most
100 appropriate therapeutic strategy for various forms of the disease remains a matter of debate³⁻⁶.
101 There is a need to characterize the various phenotypes associated with IgAN more precisely
102 and to facilitate improvements in therapeutic management. Recent advances have highlighted
103 the role of the gut-kidney axis in IgAN pathogenesis: dysregulation of the interplay between
104 intestinal immunity, diet and microbiota can lead to the production of mis-galactosylated IgA⁷.
105 The gut-kidney axis hypothesis is also supported, in some patients, by the association between
106 IgAN and inflammatory bowel disease (IBD)⁸⁻²⁵. IgAN is the most frequent abnormal finding
107 on kidney biopsy (24%) in IBD patients, with a significantly higher prevalence compared to
108 biopsy-proven kidney diseases in patients without IBD²⁶. However, it remains unclear whether
109 the association of these two conditions is merely fortuitous, given the high frequency of
110 subclinical kidney IgA deposition²⁷. In addition, the clinical features of IBD-associated IgAN
111 have been described exclusively on the basis of single-case reports⁸⁻²⁵, and no case series
112 investigating long-term outcomes has ever been published. Furthermore, little is known about
113 the similarities or differences between primary IgAN and IBD-associated IgAN in terms of
114 clinical, biological, and pathological characteristics or prognosis.

115 In this retrospective study, we assessed the clinical significance of this association, by
116 reviewing clinical, histological, and therapeutic data, and outcomes for 24 patients with biopsy-
117 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

121 **MATERIALS AND METHODS**

122 **Study population**

123 Patients with biopsy-proven IgAN occurring in a context of IBD were retrospectively identified
124 by asking all French nephrology academic departments. The inclusion criteria were the
125 presence of biopsy-proven IgAN² and a diagnosis of either CD or UC, on the basis of
126 radiological and endoscopic evidence in addition to pathological criteria^{28,29}. A poor kidney
127 outcome was defined as follows: ESRD, defined as CKD stage V or the need for kidney
128 replacement therapy, or a > 50% decrease in eGFR from initial values³⁰. IBD-associated IgAN
129 was compared to a control group of 134 patients with primary IgAN diagnosed from 2003 to
130 2014. The inclusion criteria were the presence of biopsy-proven IgAN², without history of
131 autoimmune or inflammatory disease especially from rheumatic or gastrointestinal system such
132 as IBD, malignancy and infection such as infection by Human Immunodeficiency Virus or
133 current bacteremia. Data were recorded in the control group using the same method as for IBD-
134 associated IgAN group.

135 IBD phenotype was characterized according to the Montreal classification³¹. Disease activity
136 was assessed with the Harvey–Bradshaw index for CD and the partial Mayo score for UC³².
137 We considered IBD to be active for a Harvey–Bradshaw index (HBI) > 4 for CD and a partial
138 Mayo score > 3 for UC.

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

142

143 **Renal pathology studies**

144 The histological diagnosis of IgAN was made as previously described³³. We considered
145 histological features to be severe if more than one of the MEST-C criteria for M1, E1, S1, T1-
146 2, and C1-2 were met³³.

147 **Literature review**

148 We performed a systematic review of the literature from 1980 to 2019 to identify previous cases
149 of IBD-associated biopsy-proven IgAN without confounding factors. We searched MEDLINE
150 via PubMed for all articles published in French or English using the keywords or MeSH terms
151 “Glomerulonephritis, IGA”, “Inflammatory Bowel Diseases”, “Crohn Disease”,
152 “Colitis,Ulcerative”. Only reports for which clinical, biological, and renal histological data and
153 outcomes were available were included. At the time of the review, 19 cases were identified⁸⁻²⁵.

154

155 **Statistical analysis**

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

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

172 Detailed materials and methods are provided in supplementary methods.

173

174 **RESULTS**

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

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

179 At the time of renal biopsy, the mean age of patients with IBD-associated IgAN was 37 years
180 (± 15 years; range: 13 to 73; Table 1). Twenty-two patients were of Caucasian origin and the
181 other two were of Afro-Caribbean ancestry. Only one patient was diagnosed with IBD after
182 IgAN (9 months after IgAN diagnosis). In the remaining 23 patients, IgAN was diagnosed after
183 IBD (mean of 9 ± 6 years after IBD diagnosis).

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

187 *Pathological characteristics of IBD-associated IgAN*

188 Pathology findings are shown in Table 1. The mean number of glomeruli was 18 ± 11 . The
189 mean rate of globally sclerotic glomeruli was 21.5%, with values ranging from 0 to 80%.
190 Mesangial IgA deposits were associated with C3 deposits in all cases. The most frequent
191 patterns for the criteria of the Oxford classification were M1 (57%), E0 (52%), S1 (76%), T1
192 (48%), and C0 (62%). A severe histological pattern (> 1 MEST-C criterion) was found in 14/21
193 (66.7%) patients. Only four of the 12 patients with a T1 or T2 criterion had previously received
194 5-ASA therapy.

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

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

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

210 ***IBD pattern of patients with IBD-associated IgAN***

211 The mean age at IBD diagnosis was 28 ± 14 years. IBD consisted predominantly of Crohn's
212 disease (CD) (18/24 patients; ulcerative colitis (UC) was found in 6/24 patients; Table 3). Only
213 four patients with CD (22.2%) had pure ileal disease; 14 had colonic involvement, which was
214 isolated in four cases and associated with ileal involvement in 10 cases. After a mean follow-
215 up of 15.6 ± 7.5 years, the phenotype was mostly non-stricturing and non-penetrating, in 11
216 (61.1%) cases. Others extra-intestinal manifestations, not involving the kidney, were present in
217 11 patients (45.8%). They included arthritis ($n=6$), purpura ($n=6$), bullous dermatosis ($n=1$) and
218 eye involvement ($n=3$). IBD was diagnosed before IgAN in all (mean of 8.7 ± 6.4 years) but one

219 case. At the time of IgAN diagnosis, IBD was active in 5 of the 19 (26.3%) cases of CD (Harvey
220 – Bradshaw index > 4), but none of those with UC (partial Mayo score > 3). Median C-reactive
221 protein level at IgAN onset was 2.15 mg/L [IQR 4.4 –11.9]. Following IgAN diagnosis, the
222 annual rate of IBD relapse (number of relapses/year of follow-up) decreased significantly (0.6
223 ± 0.5 vs. 0.1 ± 0.2 , $p < 0.001$), and there was a trend towards a decrease in annual steroid
224 requirement (number of steroid uses/years of follow-up) (0.2 ± 0.3 vs 0.1 ± 0.2 , $p = 0.06$).

225 Anti-TNF α treatment was used to manage IBD in 11 and was initiated before the diagnosis of
226 IgAN in 9 patients. Anti-TNF α therapy followed a first line of immunosuppressive agents in
227 6/11 cases, but was initiated as a first-line treatment in the other 5. At the time of IgAN
228 diagnosis, 5 patients were on azathioprine or methotrexate treatment and 5 were on anti-TNF α
229 therapy. The median time between the first administration of anti-TNF α agents and IgAN
230 diagnosis was 6.3 ± 4.3 years. Anti-TNF α treatment was not modified or discontinued following
231 the diagnosis of IgAN. Clinical and biological presentation at the time of renal biopsy and
232 disease course did not differ significantly between patients with and without anti-TNF α therapy
233 (Supplemental table S3).

234 ***Prognosis factors***

235 No IBD-related factors were identified as significantly associated with kidney outcome in
236 univariable analysis (Table 4). Only uPCR > 150 mg/mmol at IgAN onset was associated with
237 a poor kidney outcome ($MHR = 8.0$, 95%CI: [1.1 – 57], $p = 0.04$). A severe histological pattern
238 (> 1 MEST-C criteria) was not associated with the occurrence of the composite outcome (PHR
239 = 1.8, 95%CI: [0.59 – 57], $p = 0.09$). Interestingly, steroid use was significantly associated with
240 better kidney survival ($MHR = 0.12$, 95%CI: [0.01 – 1.1], $p = 0.02$).

241 ***Comparison between IBD-associated IgAN and primary IgAN***

242 The comparison of demographic, clinical, pathological and biological characteristics between
243 patients with IBD-associated IgAN and patients with primary IgAN is summarized in Table 1.
244 Mean initial eGFR was 70.4 ml/min/1.73m² in IBD-associated IgAN and 66.7 ml/min/1.73m²
245 in primary IgAN ($p = 0.61$), with no difference in proteinuria or hematuria. Pathological
246 features diverged between the two conditions: M1 lesions were observed in 57% of cases of
247 IBD-associated IgAN versus only 28% of cases of primary IgAN ($p=0.03$), whereas T2 lesions
248 were observed in 9% of cases of IBD-associated IgAN and 34% of cases of primary IgAN
249 ($p=0.02$). The frequencies of E, S and C lesions were similar in the two conditions.

250 We then compared therapeutic management and outcome between the two groups (Table 2).
251 Follow-up duration was 82 and 61months in IBD-IgAN and primary IgAN respectively
252 ($p=0.23$). Almost 80% of the patients in both cohorts were treated with RAS inhibitors. Steroid
253 use was 50% and 35% in IBD-IgAN and primary IgAN respectively ($p=0.23$). As shown in
254 Figure 1, kidney survival did not differ significantly between the two groups ($p_{\text{HR}} = 0.67$,
255 95% CI: [0.23 –1.9], $p=0.46$). Individual matching between IBD patients and controls to
256 improve comparability did not markedly change this estimate ($p_{\text{HR}} = 0.75$, 95% CI: [0.14 –
257 4.0], $p=0.75$).

258

259 **DISCUSSION**

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

264 We performed a literature review and identified 19 cases of IBD-associated IgAN for
265 whom sufficient data were available for analysis⁸⁻²⁵⁸⁻²⁵ (Table 5 and Supplemental Table S2).
266 The mean age of the patients in published studies of IBD-associated IgAN was 30 years, from
267 11 to 72 years. We identified three pediatric cases in literature review, and one in the current
268 cohort. As observed in our study, the predominance of male patients was greater among patients
269 with IBD-associated IgAN than in typical IBD cohorts, possibly due to a confounding bias
270 relating to the preponderance of men in IgAN cohorts². Overall, renal presentation was similar
271 to that in the previously reported cases, with frequent hematuria, proteinuria and moderately
272 altered renal function. An analysis of previous case reports revealed a higher rate of steroid use
273 (75%) than in our cohort (50%). Given the limited duration of follow-up (mean = 22 months),
274 none of the previously reported cases reached the composite outcome. Interestingly, IBD was
275 considered to be in an active phase in 13 of the 19 (68%) previously reported cases of IBD-
276 associated IgAN but in only 26.3% of the patients in this cohort. This difference may be
277 explained by a selection bias towards the reporting of single cases with a similar course for both
278 diseases. This bias was probably limited in our cohort by the inclusion of patients with IBD-
279 associated IgAN independently of IBD activity. The features of IBD in previous cases were
280 similar to those of our cohort in terms of IBD type, extra-intestinal manifestations and
281 frequency of surgical procedures. One divergence concerned the non-surgical approach to IBD

282 management, with different rates of steroid use and anti-TNF α administration between
283 previously published cases (60% and 13.3%, respectively) and our cohort (16.7% and 45.8%,
284 respectively). The most frequently observed CD phenotype in our cohort was the non-
285 stricturing and non-penetrating phenotype, which is usually uncommon after follow-up for
286 more than 10 years²⁹.

287 The clinic-biological parameters, and evolution of IBD-IgAN were similar to those of
288 our primary IgAN group. Our findings are also consistent with those of previous studies on
289 other cohorts of European patients with IgAN³⁰. In the VALIGA study, clinico-biological
290 characteristics (including age, blood pressure, initial eGFR, initial proteinuria and time-averaged
291 proteinuria) were similar to our control group, and the composite end point (>50% eGFR loss
292 or ESRD) was observed in 16,7% patients after 56 months of follow-up, which is close to 16.8%
293 after 82 months of follow up (Table 2) observed in our control group. Moreover, the treatments
294 were also similar (immunosuppression used in 46% and 35% patients, and RAS blockers in
295 86% and 79% patients, in the VALIGA study and our control group, respectively).

296 However, histological lesions differed between IBD-associated IgAN and primary
297 IgAN, with a higher frequency of M lesions and a lower frequency of T2 lesions in IBD-IgAN.
298 It should be noted that T1-T2 lesions were frequent in both IBD-IgAN and our control group,
299 which may reflect the biopsy policy in France. This differential pattern may be related to the
300 earlier diagnosis of kidney dysfunction in patients already followed for IBD. In addition, a
301 larger proportion of patients with IBD than of patients in the control group received steroids
302 and/or immunosuppressive agents before IgAN diagnosis. These therapeutic interventions may
303 have led to a decrease in inflammatory burden in the course of kidney disease⁶. Our univariate
304 analysis demonstrated that steroids were associated with a lower incidence of poor kidney

305 outcome. There remains much debate about the impact of steroids in patients with primary
306 IgAN³, but the use of these drugs seems to be most beneficial in patients with inflammatory
307 lesions and limited fibrosis⁴, as ~~reported~~ observed in this series of patients with IBD-associated
308 IgAN.

309 TNF α blockade has been associated with the development of systemic vasculitis and
310 IgA-dependent diseases, including IgAN³⁴. However, anti-TNF α therapy has also been reported
311 to induce IgAN remission³⁵. We identified no specific characteristics of patients previously
312 treated with anti-TNF α agents in our cohort. Further studies on larger patient cohorts are
313 required to determine whether anti-TNF α therapy is beneficial or deleterious in IBD-associated
314 IgAN.

315 The pathophysiological processes involved in IBD-associated IgAN remain to be
316 determined. Many similarities between these two diseases, in terms of genetics, environmental
317 factors, and immune system dysregulation, have been documented⁷. First, the overstimulation
318 of mucosal B cells in established IBD lesions skews immunoglobulin production away from
319 IgA2 towards IgA1³⁶. Furthermore, an aberrant O-linked glycosylation of IgA, characterized
320 by a decrease in N-acetylgalactosamine is observed in CD patients³⁷, and this is also the first
321 step in IgAN pathogenesis. Indeed, a recent study demonstrated an absence of difference
322 between 32 patients with primary IgAN and 100 patients with secondary IgAN, including UC,
323 in terms of the levels of circulating IgA1 and glomerular IgA1 with galactose-deficient O-
324 glycans³⁸. This pattern of glycosylation in IgAN may be explained by lower levels of production
325 and activity for a key glycosyltransferase, C1GalT1, due to lower levels of expression of its
326 chaperone, encoded by *COSMC*⁷. Interestingly, *COSMC* expression is strongly inhibited in
327 circulating B lymphocytes from IgAN patients cocultured with lipopolysaccharide, suggesting

328 a potential role of the gut microbiota in *COSMC* downregulation in IgAN³⁹. Indeed, low levels
329 of gut microbiota diversity and an increase in intestinal permeability have been reported in both
330 diseases⁷. However, such increase in intestinal permeability is also observed in other types of
331 glomerulonephritis without IgA glycosylation impairment⁴⁰. 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 patients⁴¹
334 and serum *BAFF* levels are high in IgAN patients⁴². 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 conditions⁴³. 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 patients⁴⁵. 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 IgAN⁴⁶. It
343 has recently been shown *in vitro* that interleukin-17 can promote the production of
344 underglycosylated IgA1 in a B-cell lineage⁴⁷. Wang et al. developed a mouse model of IgAN
345 and bowel inflammation similar to CD⁴⁸, 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

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

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

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361 of the patients included in this study.

362

363 **Conflict of interest statement**

364 The authors had no conflict of interest

365

366 **Authors' contributions**

367 NJ, AA, VA and KEK designed the study, analyzed the data and wrote the manuscript. CG,

368 MR and SH performed histological analyses. NJ, DG, EP, AH, JJB, SF, YD, AK, AA and KEK

369 were responsible for patient care. All the authors carefully reviewed the manuscript.

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371 None

372 **Data Availability statement**

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

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

Characteristic	IBD-IgAN n = 24	Primary IgAN n = 134	<i>p</i> *
Demographic data			
Age at kidney biopsy (years), mean \pm SD	37 \pm 15	39 \pm 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 \pm SD	137 \pm 16	136 \pm 20	0.80
Diastolic blood pressure (mmHg), mean \pm SD	78 \pm 10	81 \pm 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 \pm SD	254 \pm 242	174 \pm 165	0.14
Serum albumin (g/L), mean \pm SD	35 \pm 7	38 \pm 6	0.04
Nephrotic syndrome, n (%)	3 (12.5)	5 (3.7)	0.10
eGFR (mL/min/1.73m ²), mean \pm SD	70.4 \pm 29	66.7 \pm 31	0.61
Kidney replacement therapy at IgAN onset, n (%)	1 (4.2) ^o	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) ^o	3 (2.4) ^x	
Histopathological characteristics			
Severe pattern (>1 MEST-C criteria), n (%)	14 (66.7) ^x	99 (73.8)	0.59
Glomeruli (n), mean \pm SD	18 \pm 11	15 \pm 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

498

499 Chronic kidney disease (CKD) stages defined according to the 2012 KDIGO guidelines, eGFR:
500 glomerular filtration rate estimated with the CKD-EPI formula and expressed in
501 ml/min/1.73m²; Hypertension, defined as systolic blood pressure > 140 mmHg or diastolic
502 blood pressure > 80 mmHg; IBD: inflammatory bowel disease; IgAN: IgA nephropathy;
503 MEST-C according to the Oxford classification; nephrotic syndrome defined as a serum
504 albumin concentration < 30 g/L and proteinuria > 3 g/day; uPCR: urinary protein-to-creatinine
505 ratio.

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

508 (%)^x: % for available data

509 ^o : patient requiring hemodialysis at IgAN onset, with recovery of renal function

510

Table 2. Management and outcome at last follow-up

Characteristic	IBD-IgAN	Primary IgAN	<i>p</i> *
	n = 24	n = 134	
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)	-	

512

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/1.73m²; ESRD: end-stage renal disease; hypertension defined as systolic blood pressure

516 > 140 mmHg or diastolic blood pressure > 80 mmHg; IgAN: IgA nephropathy; MEST-C based
517 on the Oxford classification; nephrotic syndrome defined as serum albumin concentration < 30
518 g/L and proteinuria > 3 g/day; RAS: renin-angiotensin system; uPCR: urinary protein-to-
519 creatinine ratio.

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

522 (%)^x: % for available data

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

Characteristic	IBD-IgAN (n = 24)
Demographic data	
Age at IBD diagnosis (years), mean \pm SD	28 \pm 14
Female, n (%)	8 (33.3)
Smoker, n (%)	6 (25)
Body-mass index (kg/m ²), mean \pm SD	24.8 \pm 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%)*
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-TNF α , n (%)	11 (45.8)
Before IgAN, n	9
Ongoing at IgAN onset, n	5
Adalimumab, n	2
Infliximab, n	11
5-aminosalicylic acid, n (%)	5 (20.8)
Azathioprine or methotrexate, n (%)	11 (45.8)
Surgery, n (%)	10 (41.7)

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

552 (%)^x: % for available data

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

Factors analyzed	Hazard ratio [95%CI]	<i>p</i> *
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-TNF α 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

556

557 eGFR: glomerular filtration rate estimated with the CKD-EPI formula and expressed in
558 ml/min/1.73m²; hypertension, defined as systolic blood pressure > 140 mmHg or diastolic
559 blood pressure > 80 mmHg; IBD: inflammatory bowel disease; IgAN: IgA nephropathy;
560 MEST-C based on the Oxford classification; uPCR: urinary protein-to-creatinine ratio; TNF α :
561 tumor necrosis factor α

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

565

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

Characteristic	Literature review (n = 19)
Demographic data	
Age at kidney biopsy (years), mean \pm SD	30 \pm 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-TNF α agents, n (%)	2 (13.3) ^x
Before IgAN, n	1
Adalimumab, 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

567

568 CKD stages defined according to the 2012 KDIGO guidelines, eGFR: glomerular filtration rate
569 estimated with the CKD-EPI formula and expressed in ml/min/1.73m²; ESRD: end-stage renal
570 disease; hypertension, defined as systolic blood pressure > 140 mmHg or diastolic blood
571 pressure > 80 mmHg; IBD: inflammatory bowel disease; IgAN: IgA nephropathy; MEST-C
572 based on the Oxford classification as described in the methods; nephrotic syndrome defined as
573 serum albumin concentration < 30 g/L and proteinuria > 3 g/day; uPCR: urinary protein-to-
574 creatinine ratio. (%)^x: % for available data

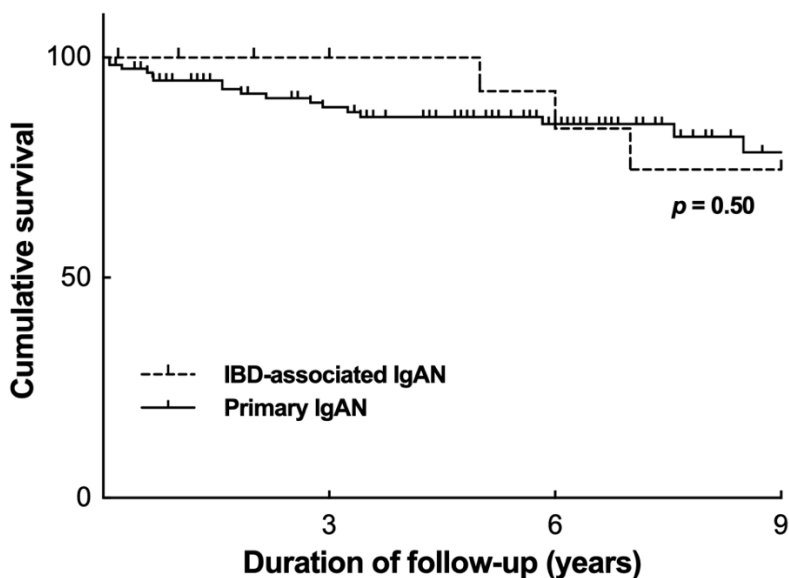
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576 **Legends to figure**

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

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

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		Number of subjects at risk			
		3	6	9	
IBD + IgA	23	17	11	7	
IgA only	119	84	49	22	

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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 IgAN² 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-

27 TNF α agents). IBD phenotype was characterized according to the Montreal classification³¹.
28 Disease activity was assessed with the Harvey–Bradshaw index for CD and the partial Mayo
29 score for UC³². We considered IBD to be active for a Harvey–Bradshaw index (HBI) > 4 for
30 CD and a partial Mayo score > 3 for UC. Serum C-reactive protein concentration was also
31 recorded at the time of kidney biopsy. The two diseases were considered to have occurred
32 simultaneously if their diagnoses were separated by less than six months.

33 This study aimed at describing the patients with IBD-associated IgAN and to compare them to
34 a control group of patients with primary IgAN. All consecutive IgAN patients diagnosed from
35 2003 to 2014 in the Pathology department of Necker Hospital (Paris, France) were evaluated to
36 inclusion in this control group. This pathology department is in charge of analysing renal biopsy
37 specimens from 4 different centres in the Paris, France area. The inclusion criteria were the
38 presence of biopsy-proven IgAN², without history of autoimmune or inflammatory disease
39 especially from rheumatic or gastrointestinal system such as IBD, malignancy and infection
40 such as infection by Human Immunodeficiency Virus or current bacteremia. Data were
41 recorded in the control group using the same method as for IBD-associated IgAN group.

42 **Renal pathology studies**

43 The histological diagnosis of IgAN was based on the presence of IgA-dominant or co-dominant
44 immune deposits within glomeruli³³ on immunofluorescence analysis. The kidney biopsy
45 specimens used for the initial pathological diagnosis of IgAN were reassessed centrally by a
46 nephrologist blind to clinical data. Samples were processed for light microscopy, for the
47 determination of MEST-C score according to the updated Oxford classification³³. Kidney
48 biopsy specimens were not available for 12/158 patients. Five of these cases were analyzed on
49 the basis of the initial histological report, in which a precise MEST-C score was noted; no
50 definitive MEST-C score could be obtained for the remaining seven cases. We considered

51 histological features to be severe if more than one of the MEST-C criteria for M1, E1, S1, T1-
52 2, and C1-2 were met.

53 **Literature review**

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

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63 *: Kidney sample not centrally reviewed; Age in years; CD: Crohn's disease; eGFR: glomerular filtration rate estimated with the CKD-EPI formula
64 and expressed in ml/min/1.73m²; EIM: extraintestinal manifestation; HBP: High blood pressure, defined as systolic pressure > 140 mmHg or
65 diastolic pressure > 80 mmHg; IBD: inflammatory bowel disease; IgAN: IgA nephropathy; KT: kidney transplantation; MEST-C according to the
66 Oxford classification; UC: ulcerative colitis; TNF α : Tumor necrosis factor α ; uPCR: urinary protein-to-creatinine ratio expressed in mg/mmol

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68 **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
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	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	-	+

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70 Age in years; CD: Crohn's disease; eGFR: glomerular filtration rate estimated with the CKD-EPI formula and expressed in ml/min/1.73m²; EIM:
 71 extraintestinal manifestation; HBP: high blood pressure, defined as systolic BP > 140 mmHg or diastolic blood pressure > 80 mmHg; IBD:
 72 inflammatory bowel disease; IgAN: IgA nephropathy; proteinuria expressed in g/day; TI: tubular and interstitial; UC: ulcerative colitis.

73 **Supplemental Table S3. Clinical and biological presentation and course of**
 74 **IBD-associated IgAN with and without anti-TNF α treatment**

Characteristic	Anti-TNF α +	Anti-TNF α -	<i>p</i> *
	n = 11	n = 13	
Age (years), mean \pm SD	37 \pm 13	37 \pm 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*	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 \pm SD	252 \pm 297	255 \pm 197	0.97
eGFR (mL/min/1.73m ²) at IgAN diagnosis, mean \pm SD	67 \pm 15	73 \pm 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-TNF α related Hazard ratio [95%CI]	0.45 [0.06 - 3.3]		0.45

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76 Composite outcome: end-stage renal disease or > 50% decrease in eGFR (glomerular filtration
 77 rate estimated with the CKD-EPI formula and expressed in ml/min/1.73m²); high blood
 78 pressure defined as systolic pressure > 140 mmHg or diastolic pressure > 80 mmHg; IgAN: IgA
 79 nephropathy; MEST-C according to the Oxford classification; TNF α : tumor necrosis factor α ;
 80 uPCR: urinary protein-to-creatinine ratio.

81 *Statistical tests were performed to compare IBD-IgAN patients who received anti-TNF α
 82 treatment with IBD-IgAN patients who did not receive anti-TNF α treatment. *P* values below
 83 0.05 are considered significant.

84 (%)^x: % for available data