IgA Vasculitis with Underlying Liver Cirrhosis: a French Nationwide Case Series of 20 Patients

Ines Elhani[1], Evangéline Pillebout[2], Benjamin Terrier[3,4,5], Antoine Hankard[1], François Vrtovsnik[6], Noémie Jourde-Chiche[7], Sophie Greillier[7], Matthieu Groh[8], Nabil Belfeki[9], Adrien Bigot[10,11], Hubert de Boysson[1], Georges-Philippe Pageaux[12], Loïc Raffray[13], Geoffrey Urbanski[14], Isabelle Ollivier[15,] Francois Maillot[10,11], Achille Aouba[1], Alexandra Audemard-Verger[10,11] on behalf of the French Vasculitis Study Group (FVSG) and the HSPrognosis group.

[1]*Department of Internal medicine, Caen, Normandie Univ, UNICAEN, CHU de Caen Normandie, France.*
[2]*Department of Nephrology, Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France.*
[3]*Université Paris Descartes, Paris.*
[4]*Department of Internal Medicine, Hôpital Cochin, Paris.*
[5]*National Referral Center for Systemic and Autoimmune Diseases, Hôpital Cochin, Paris, France.*
[6]*Department of Nephrology, Bichat-Claude Bernard Hospital, AP-HP, and Inserm U1149 - CRI, University of Paris, France*
[7]*Aix-Marseille Univ, C2VN, INSERM, INRA, Centre de Néphrologie et Transplantation Rénale, CHU de la Conception, AP-HM, Marseille.*
[8]*Department of Internal Medicine, National Referral Center for Hypereosinophilic Syndrome (CEREO), Suresnes, France..*
[9]*Department of Internal Medicine, Groupe Hospitalier Sud Ile de France, Melun, France.*
[10]*Department of Internal Medicine and Clinical Immunology, CHRU Tours, Tours, France.*
[11] *University of Tours, Tours, France.*
[12] *Liver Transplantation Unit, Digestive Department, Saint Eloi University Hospital, University of Montpellier, France.*
[13]*Department of Internal Medicine, Centre Hospitalier Universitaire de la Réunion, Réunion, France.*
[14]*Department of Internal Medicine, Centre Hospitalier Universitaire d'Angers, Angers, France.*
[15]*Department of Hepato-Gastroenterology and Nutrition, Caen University Hospital, France.*

CORRESPONDING AUTHOR

Dr AUDEMARD-VERGER Alexandra, MD-PhD, Department of Internal Medicine and Clinical Immunology, CHRU Tours, Tours, France, University of Tours, Tours, France.

Email: a.audemard-verger@chu-tours.fr

ORCID id: orcid.org/0000-0002-0226-5016

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ABSTRACT

Objectives. IgA vasculitis (IgAV) and nephropathy (IgAN) share common immunological mechanisms. Liver cirrhosis is well-known to be associated with IgAN. Here, we aimed to describe the presentation and outcome of IgAV patients with underlying cirrhosis.

Methods. We conducted a French nationwide retrospective study of adult patients presenting with both IgAV and cirrhosis. Baseline characteristics were compared to those of the 260 patients included in the French nationwide IgAV registry (IGAVAS).

Results. Twenty patients were included, and seven (35%) were female. The mean ±SD age was 62.7 ±11 years. At baseline, compared with IGAVAS' patients, patients with underlying cirrhosis were older (62.7 ±11 vs. 50.1 ± 18; p<0.01) and displayed more constitutional symptoms (weight loss 25 vs. 8%; p= 0.03). Patients with underlying cirrhosis were also more likely to exhibit elevated serum IgA levels (5.6 vs. 3.6 g/L; p=0.02). Cirrhosis and IgAV were diagnosed simultaneously in 12 patients (60%). Cirrhosis was mainly related to alcohol intake (n=15, 75%), followed by non-alcoholic steato-hepatitis (n=2), chronic viral hepatitis (n=1), haemochromatosis (n=1) and autoimmune hepatitis (n=1). During follow-up with a median of 17 months [IQR 12-84]), 10/13 (77%) exhibited IgAV remission at month 3. One patient presented a minor relapse. Six patients died, but no death was related to IgAV.

Conclusion. We reported the first case series of IgAV patients with underlining cirrhosis, which was mainly alcohol-related. The liver disease did not seem to impact baseline vasculitis' characteristic. Physicians may investigate the existence of liver cirrhosis at IgAV diagnosis, especially in the context of alcohol abuse.

KEY MESSAGES

- We report the first case series of IgA vasculitis patients with underlying cirrhosis**.**
- Liver cirrhosis did not seem to impact baseline characteristics of the vasculitis.
- Physicians may investigate the existence of liver cirrhosis at IgAV diagnosis, especially in the context of alcohol abuse.
- Patient with cirrhosis may develop IgAV, and not only IgAN. The occurrence of vasculitis features such as purpura and arthritis in patients with cirrhosis should call for the screening or renal and/or gastro-intestinal involvement of IgAV.

INTRODUCTION

Immunoglobulin A (IgA) vasculitis, formerly known as Henoch-Schönlein purpura, is a systemic small-vessel vasculitis characterized by IgA deposits in small arterial walls and non-lymphoid tissues (1,2). IgAV is the most common systemic vasculitis in children but is less frequent in adults (1). The clinical spectrum of the disease encompasses purpura, glomerulonephritis, enteritis and arthralgia and/or arthritis (3). In adults, renal and gastrointestinal involvement can constitute life-threatening manifestations (4). The pathogenesis of IgAV remains unclear, and current knowledge is extrapolated from data driven from IgA nephropathy (IgAN) (5,6). During the last decade, many studies have highlighted a pivotal role of abnormal circulating immunoglobulin A1 (IgA1) in both IgAV and IgAN (7). Indeed, in IgAV, IgA1 hinge regions are galactose-deficient, and such modified IgA1 are more prone to immune complex formation and deposition, thereby leading to enhanced inflammation (8,9), most likely through complement alternative pathway activation. This mechanism also sustains the hypothesis of the inducing role of infectious events in the occurrence of the disease. IgA1 could also activate neutrophils via the IgA Fc receptor FcalphaRI (CD89), thereby inducing neutrophil migration and related tissue damage (8). Unlike IgAV, which is usually described as a primary vasculitis even though it is possibly triggered by a usual acute infection (10), IgAN is regarded as either primary or secondary to various chronic diseases whose pathogeny could proceed from the increase in serum IgA levels, including liver cirrhosis (11).

Liver cirrhosis, especially alcohol-related cirrhosis, is associated with IgA metabolism abnormalities such as galactose deficiency, CD89 expression increase on mononuclear cells, and immune complex hepatic clearance decrease (12,13). Altogether, these abnormalities spontaneously induce the formation of immune complexes (IgA-CD89) similar to those observed in IgAV. Moreover, alcohol intake increases the serum amounts of IgA through the disruption of intestinal barrier tight junctions that enhance bacterial translocation (14–16). To

date, only a few isolated case reports have focused on the concomitancy of IgAV and liver cirrhosis but without aggregating and analytic epidemiological data in favour of a real relationship between both diseases (17–19). Hypothesizing that the abnormal higher production of hypoglycosylated IgA in liver cirrhosis could contribute to IgAV pathogeny and speculating that this late dysmetabolic and dysimmunitary condition could print a different clinical phenotype on the presentation of vasculitis, we undertook this study. The aim of the present study was to describe and compare the presentation, outcome and prognosis of a series of patients exhibiting both IgAV and liver cirrhosis with those of the French "IGAVAS" registry that collects primary cases of IgAV excluding associated cancer.

PATIENTS AND METHODS

Patients

We conducted a multicentric retrospective study at French university or general hospital departments of internal medicine, nephrology and hepatogastroenterology. The study was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Institutional Review Boards of the University of Caen Normandie and of the Caen University Hospital Center (Approval number 00-20181116-01R1). The inclusion criteria for the study were as follows: age>18 years and liver cirrhosis and IgAV diagnosed between January 1997 and June 2019. Liver cirrhosis diagnosis should have been performed by the practitioner in charge of the patient. The diagnosis should have been based on the clinical, biological and radiological characteristics of cirrhosis. Liver biopsies were not required. All usual causes of liver cirrhosis were considered, including alcohol consumption, as well as viral, metabolic genetic and/or drug-related causes. The diagnosis of IgAV was defined by the

association of palpable purpura and histopathological findings of small vessel vasculitis associated with IgA deposits on skin, kidney or digestive biopsy.

Clinical, biological and histological data of recruited patients were compared to those of patients included in the IGAVAS registry patients. The IGAVAS registry included 260 IgAV adult patients, with the exclusion of associated cancer and cirrhosis conditions and has been previously published (3). Briefly, the inclusion criteria were age >18 years and diagnosis of histologically proven IgAV.

Clinical and biologic data

Data on the clinical and biological characteristics of vasculitis and cirrhosis were recorded using a standardized form for each patient at the time of the initial evaluation, during and at the end of follow-up. Clinical assessments included determination of skin, rheumatic, renal or digestive manifestations. Cirrhosis evaluation included Child-Pugh score (20), oesophageal varices, portal hypertension gastropathy, portal thrombosis and eventual hepatocellular carcinoma. Laboratory assessments included determination of serum creatinine, C-reactive protein (CRP), albumin, IgA, Factor V, and bilirubin levels, prothrombin ratio, urinalysis to screen for haematuria and a 24-hour urine protein examination. Renal failure was defined as an eGFR of <60 ml/minute/1.73 m^2, assessed with the Modified Diet in Renal Disease equation (21). Proteinuria was defined as a 24-hour urinary protein excretion rate of >0.5 g/day, and haematuria was defined as >10 red cells/mm^3 in the urine, which was designated as macroscopic if there were >1,500 red cells/mm^3. Elevated IgA levels were defined as an IgA level of >3.5 mg/L.

Histologic data

Data regarding histologic features (findings from skin and renal biopsies) were recorded at the time of diagnosis. Histology was considered compatible with IgA vasculitis in the presence of

IgA deposits and leuckocytoclastic vasculitis. Further recorded information included C3 deposits, extracapillary proliferation, mesangial sclerosis and fibrinoid necrosis.

Response to therapy

Response therapy was defined as a combination of clinical and biological signs following the definitions used in the IGAVAS registry to allow comparison, including: skin involvement (purpura), joint manifestations (arthralgias and/or arthritis), gastrointestinal signs, and renal involvement (eGFR, levels of proteinuria and haematuria). A complete response was defined as an improvement in all baseline clinical manifestations and in case of renal involvement by a proteinuria <0.5 g/d, the disappearance of haematuria and a decrease in the glomerular filtration rate (GFR) no greater than 20% as compared to baseline. A partial response was defined as an improvement in at least one-half of the baseline clinical manifestations, and in cases of renal involvement, as an improvement in proteinuria > 50% of the baseline value, and no decrease in the GFR greater than 20% from baseline. All other patients were classified as non-responders.

Relapse

Relapse was defined as the reappearance of clinical signs of IgA vasculitis, occurring after a period free of symptoms of at least one month. Minor relapse was defined by an increase in prednisone no greater than 20 mg/day, and major relapse was defined by the addition of an immunosuppressive drug or an increase in prednisone greater than 20 mg/day.

Statistical analysis

Descriptive statistics included the mean+/-SD values or median with interquartile range (IQR) as appropriate for continuous variables and the frequency (percentage) for categorical variables.

Univariate analysis included Fisher's exact test as appropriate for comparing categorical variables and the nonparametric Mann-Whitney test to compare continuous variables.

RESULTS

Baseline characteristics of IgA patients with associated cirrhosis

Of the 23 patients assessed for eligibility, 20 patients were included. Three patients were excluded because of the lack of IgAV histological proof. The main baseline characteristics of the patients exhibiting IgAV with associated liver cirrhosis and the comparison to the 260 patients of the nationwide cohort IGAVAS are shown in **Table 1**. Of the 20 patients included, seven (35%) were females. The mean age was 62.7 ±11 years. At baseline, compared to the 260 patients of the IGAVAS registry, patients with associated cirrhosis were older (62.7 ±11 vs. 50.1 ± 18, $p<0.01$) and displayed more constitutional symptoms (weight loss 25 vs. 8%; p=0.03) and less joint involvements (35 vs. 62%, p= 0.03). Though not reaching statistical significance, GI involvement, defined by presence of abdominal pain, ileus or gastrointestinal bleeding tended to be less frequent in patients with liver cirrhosis than in those from the IGAVAS registry (35 vs. 53%; p=0.07).

The main biological and histological characteristics of IgAV patients with associated cirrhosis are shown in **Table 2**. Histopathological characteristics of skin and renal biopsies were available in 10 and 13 patients, respectively.

At baseline, compared to the 260 patients included in the IGAVAS registry, patients with cirrhosis exhibited higher serum IgA levels (5.6 vs. 3.6 g/L; p=0.02). Regarding renal function, eGFR was slightly lower in patients with underlying cirrhosis compared to those included in the IGAVAS survey (72.5 vs 88; p=0.03 ml/mn/1.73 m). However, no evidence indicated a higher rate of glomerular involvement, either on histological examination, including

extracapillary proliferation, fibrinoid necrosis or glomerular sclerosis, or regarding urinary protein excretion. On skin biopsy, C3 deposits were more frequent in patients with underlying cirrhosis (80 vs. 21%, p=0.002).

Characteristics of liver cirrhosis at IgAV diagnosis

Characteristics of liver cirrhosis at IgA diagnosis are reported in **Table 3**. The diagnoses of liver cirrhosis and IgAV were simultaneous in 12 patients (60%), whereas the diagnosis of cirrhosis preceded that of IgAV in the 8 remaining patients, and therefore, no case of vasculitis occurrence had preceded the clinical diagnosis of the hepatic disorder.

The median time between the diagnoses of the 2 diseases was 60 months [IQR 4-120]. Child-Pugh scores were as follows: A in 6 patients (30%), B in 12 patients (60%) and C in 2 patients (10%). Cirrhosis was mainly related to alcohol intake (n=15, 75%), followed by non-alcoholic steato-hepatitis (n=2), Hepatitis B and C co-infection (n=1), haemochromatosis (n=1) and autoimmune hepatitis (n=1). Eleven patients (52%) presented with alcohol abuse at IgAV diagnosis. At IgAV diagnosis, 9 patients displayed ascites (45%), 4 had portal hypertensive gastropathy (20%), and another had acute alcoholic hepatitis (5%). The median albumin level was 29 g/l [IQR 22-33], and the median factor V was 75% [IQR 65-81]. No case of hepatocarcinoma was reported.

Patient management and outcome

The management and outcome of IgAV patients are shown in **Table 4**. Fourteen patients (70%) received a specific treatment targeting vasculitis: all fourteen received oral glucocorticoid (n=14) motivated by renal involvement, and one received colchicine (n=1). One patient underwent liver transplant.

The median follow-up was 17 months [IQR 12-84]. At last follow-up, data regarding the course of vasculitis were available for 13/20 patients. Among them, 10 (77%) exhibited a clinical response at month 3: 5 had a complete response and 5 had a partial response. During follow-up, one patient presented with a minor relapse, and six others died. No death was related to vasculitis. Two deaths were directly related to the cirrhosis condition, and the other deaths were due to sepsis (n=2), pancreaticoduodenal artery aneurysm rupture (n=1) and heart failure (n=1).

DISCUSSION

The results of this study, call for consideration that, beyond a simple fortuitous association between both conditions, liver cirrhosis belongs in the spectrum of underlying diseases of IgAV, in addition to infectious processes. Even though our hypothesis that liver cirrhosis may contribute to the occurrence of IgAV is in line with these data, due to the small size of our series, we were not able to assess the correlation between the respective severities of the two conditions.

IgAV patients with underlying cirrhosis did not seem to display a distinct phenotypical baseline pattern. Patients with underlying cirrhosis were older and displayed more constitutional symptoms, which can certainly be linked to cirrhosis. On the other hand, we hypothesized that the lower representation of gastrointestinal and rheumatologic involvement in the present series is age-related. Indeed, older age seems to be correlated with lesser rheumatologic and gastrointestinal manifestations at diagnosis of IgAV (unpublished data). Finally, renal involvement does not seem to be overrepresented in patients with underlying cirrhosis. Decreased eGFR and more frequent tubulo-nephritis on renal biopsy in patients with cirrhosis, which may be explained by the older age of patients in this series, which is associated with a higher prevalence of atheroembolic diseases, but also of the expostion to Drug-induced

nephrotoxicity (22). In the end, the older age, the biological and histopathological features consisting of higher serum IgA and more frequent complement system consumption found in skin lesions should be the real and independent aetiopathogenic factors differentiating underlying liver disease patients from primary IgAV. In addition, it is interesting to note the temporality of the diagnoses of the two diseases, in which liver cirrhosis consistently either preceded or was revealed simultaneously to the onset of IgAV. Though there was a wide range in delay between the diagnoses of the two diseases, cirrhosis, is often asymptomatic entity and could have developed months or years before diagnosis (23). In fact, the temporal factor, higher serum IgA levels and complement consumption in the vasculitis process strengthen the causative role of liver cirrhosis in the IgAV process, which is analogous to the infectious process that is well established as a causal factor or the occurrence of vasculitis. Notably, it should be highlighted that no hepatocarcinoma was observed. In the last decade, neoplasia is a well-documented condition associated with IgAV.

The high rate of mortality in our series, which was in no case related to IgAV, highlights the frailty of patients with cirrhosis, which was responsible for 1/3 of the deaths reported. In addition, one patient patients died from infectious diseases, and one from acute heart failure while treated with corticosteroids for IgAV. The decision of treatment of IgAV with systemic steroids should hence be carefully balanced in these fragile patients, especially since long-term benefits of corticosteroids for IgAV have not been demonstrated in large-scale prospective studies.

An analogy of a real pathogenic association between IgAV and liver cirrhosis can be considered with the current well-documented relationship between cirrhosis and IgAN, which prevalence is estimated to be 9% in IgAN patients (11); It is well known that IgAN, which shares numerous pathological features with IgAV (5,24,25), can be secondary to liver cirrhosis (11,26,27). Thus, we can speculate that the pathogenic mechanism of cirrhosis-associated IgAN

can also be applied to IgAV. As previously mentioned, the occurrence of IgAN in liver cirrhosis patients involves the presence of an abnormal glycosylated IgA1 subtype that exhibits a higher affinity for its soluble receptor than that of normal IgA1 found in healthy subjects, which could enhance the formation of IgA-CD89 complexes. Clearance of this abnormal IgA1 is further decreased in liver cirrhosis patients, since CD89 expression on intra-hepatic macrophages is reduced, and endocytic functions are thus impaired (12). It is also believed that these large immune complexes cannot enter the liver via the Disse space (5,28,29). A decrease in IgA clearance could also be directly related to alcohol consumption, which decreases galactosyltransferase and sialyltransferase activities (12). In the present series, the vast majority of cirrhosis were alcohol-related, which could illustrate the implication of alcohol in the pathogenesis of associated IgAV, though it might simply reflect the dominance of alcoholic cirrhosis in France (30). Interestingly, Hommos and El-Zoghby reported favourable renal outcomes in 14 patients with IgAN after liver transplant without any therapy for IgAN (31). Portal hypertension could also be involved in the occurrence of IgAV through a portacaval shunt, as suggested by reports of patients with cirrhotic or non-cirrhotic portal hypertension who developed IgAN, which resolved rapidly after medical or surgical correction of portal hypertension (32–34). Some aspects of IgAN occurrence in patients with liver cirrhosis remain unclear. Indeed, liver cirrhosis is associated with elevated serum IgA levels (35,36) and IgA tissue deposits (37–39); however, only a minority of patients subsequently develop IgAN. Further studies are needed to understand the causes of this shift from IgA non-symptomatic deposits to inflammatory IgA deposits leading to IgA-related disease.

In this series, the levels of glycosylation of igA1 could not have been measured as it is not a routine test and therefore we cannot affirm that patients in this series displayed such IgAs. However abnormally glycosylated IgAs were previously identified in patients with cirrhosis and further studies should confirm this findings (12).

Liver cirrhosis affects 300 in 100000 inhabitants in France and is largely related to alcohol consumption (70%). Given the high prevalence of the disease, a higher number of associated IgAV could have been expected. Several factors could account for this result. First, in France there is no national registry of adult IgAV and did not permit exhaustive inclusion of IgAV patients with cirrhosis. Furthermore, mild IgAV with cutaneous and/or digestive manifestations occurring in patients with cirrhosis could have remained undiagnosed.

The strength of our work is the number of patients included in the context of a rare disease and the comparison of the patients included with a large series of 260 IgAV patients. However, our study presents some limitations: its retrospective nature and short follow-up. Moreover, in the IGAVAS survey, patients were not systematically screened for cirrhosis, and among the 260 patients, it cannot be ruled out that some patients had cirrhosis.

In conclusion, we reported the first case series of IgA patients with underlining cirrhosis, this latter condition did not seem to impact baseline vasculitis' characteristic. However, this study should encourage physicians to investigate the existence of liver cirrhosis at IgAV diagnosis, notably in the presence of a history of alcohol abuse in elderly patients exhibiting higher IgA serum levels. Conversely, the occurrence of purpura in patients with cirrhosis should lead to consider the diagnosis of IgAV

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CONFLICTS OF INTEREST

None

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Table 1. Clinical characteristics of IgA vasculitis (IgAV) patients with underlying cirrhosis, and comparison with the French nationwide multicentric cohort of primary IgAV (IGAVAS)

Characteristics	n=20	n=260	p
Demography			
Female	7 (35)	96 (37)	0.9
Age at diagnosis (years), mean ± SD	62.7 ±11	50.1 ± 18	**<0.01**
Clinical manifestations			
Constitutional symptoms, n (%)			
Fever	5 (25)	39 (15)	0.21
Asthenia	6 (30)	54 (21)	0.4
Weight loss	5 (25)	22 (8)	**0.03**
Skin involvement	19 (95)	260 (100)	**0.07**
Purpura	19 (95)	260 (100)	0.07
Lower limb	19 (95)	258 (99)	0.2
Upper limb	7 (35)	93 (36)	1
Abdomen	7 (35)	63 (24)	0.3
Face	1 (5)	8 (3)	0.5
Necrosis	6 (30)	68 (26)	0.8
Joint involvement	7 (35)	160 (62)	**0.03**
Arthralgia	7 (35)	159 (100)	**0.03**
Arthritis	2 (10)	26 (16)	1
GI involvement	7 (35)	137 (53)	0.2
Abdominal pain	6 (30)	135 (99)	0.07
Vomiting	2 (10)	26 (19)	1
Diarrhea	4 (20)	36 (26)	0.5
Ileus	0	13 (9)	0.6
Bleeding	2 (10)	43 (31)	0.8
Kidney involvement	13 (65)	182 (70)	0.62
Arterial hypertension	7 (35)	40 (22)	**0.05**
Pitting oedema	9 (45)	49 (27)	**0.01**

SD: standard deviation; GI: gastrointestinal involvement

Table 2. Biological and histological characteristics of IgAV patients with underlying cirrhosis and comparison with the French nationwide multicentric cohort (IGAVAS)

Characteristics	n=20	n=260	p
Biological features			
Serum IgA >ULN, n (%)	11/13 (85)	85/159 (53)	**0.04**
Serum IgA (g/L), median [IQR]	5.6 [4.81-8.8]	3.6 [2.7-4]	**0.02**
Serum creatinine level, µmol/l	72.5 [64-180]	80 [67-116]	0.2
eGFR, ml/mn/1.73m²	71.5 [7-134]	88 [55-103]	**0.03**
C-reactive protein (mg/dL), median [IQR]	28.3 [36-91]	27 [8-60]	0.5
Proteinuria (g/day), median [IQR]	2.53 [0.35-3.2]	1.5 [0.6-3]	0.2
Albumin level (g/l)	29 [22.6-33]	33.5 [10-48]	0.052
Skin biopsy	10 (50)	220 (85)	
Leukocytoclastic vasculitis	10 (100)	205 (92)	1
IgA deposits	9 (90)	174/216 (81)	0.7
C3 deposits	8 (80)	47/222 (21)	**0.0002**
Fibrinoid necrosis	6 (60)	59/222 (27)	0.03
Renal biopsy	13 (65)	144/182	
IgA mesangial deposits	13 (100)	142/144	1
Extracapillary proliferation	7(54)	59/144 (41)	0.05
Fibrinoid necrosis	6 (46)	46/144 (32)	0.3
Glomerular sclerosis	1 (8)	47/144 (33)	0.1
Tubulointerstitial nephritis	8 (62)	44/144 (31)	**0.03**

IQR: interquartile range; ULN: upper the limit of normal; eGFR: estimated glomerular filtration rate.

Table 3. Liver cirrhosis characteristic at IgAV diagnosis

Characteristics	n=20
Demography	
Synchronous IgAV and cirrhosis diagnosis, n (%)	12 (60)
Time between cirrhosis and IgAV, median [IQR], m	60 [4-120]
Child-Pugh, n (%)	
Class A	6 (30)
Class B	12 (60)
Class C	2 (10)
Aetiology of liver cirrhosis	
Alcohol-related	15 (75)
HCV and HBV co-infection	1 (5)
Non-alcoholic steato-hepatitis	2 (10)
Hemochromatosis	1 (5)
Autoimmune hepatitis	1 (5)
Active alcohol consumption	11 (52)
Complications	
Ascites	9 (45)
Hepatic encephalopathy	0
Portal hypertensive gastropathy	4 (20)
Hepatocellular carcinoma	0
Ascitic fluid infection	0
Acute alcoholic hepatitis	1 (5)
Portal vein thrombosis	0
Gastrointestinal bleeding	0
Hepatorenal syndrome	1 (5)
Biological features	
Albumin, median [IQR], g/l	29 [22-33]
Prothrombin time, median [IQR], %	69 [61-78]
Factor V, median [IQR], %	75 [65-81]
Total bilirubin, median [IQR], µmol/l	19 [9-36,5]
Conjugated bilirubin, median, [IQR], µmol/l	11 [7-18.5]

M: months; SD: standard deviation; IQR: interquartile range

Table 4. Treatment and outcome of IgAV patients

Outcome	n=20
Vasculitis treatment	
Corticosteroids	14 (70)
Methylprednisolone pulses	7 (35)
Colchicine	1 (5)
Treatment duration, median [IQR], months	4 [4-4]
Cirrhosis treatment	
Liver transplant	1(5)
Follow-up, median [IQR], months	17[12-84]
Response at 3 months	
Complete	5/13 (38)
Partial	5/13 (38)
Non-responders	3/13 (23)
Relapses	
Minor	1/13 (8)
Major	0/13 (0)
Death	6 (30)
IgAV-related death	0
Cirrhosis-related death	2 (33)
Infectious disease	2 (33)
Rupture of pancreaticoduodenal artery aneurysm	1 (17)
Heart failure	1 (17)