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IgA Vasculitis With Underlying Liver Cirrhosis: A French Nationwide Case Series of 20 Patients

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ABSTRACT. ***Objective.*** Immunoglobulin A 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 7 (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 g/L 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 nonalcoholic steato-hepatitis (n = 2), chronic viral hepatitis (n = 1), hemochromatosis (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 deaths were related to IgAV.

Conclusion. We report the first case series of IgAV patients with underlining cirrhosis, to our knowledge, which was mainly alcohol related. The liver disease did not seem to affect baseline vasculitis characteristics. Physicians should investigate the existence of liver cirrhosis at IgAV diagnosis, especially in the context of alcohol abuse.

Key Indexing Terms: alcohol, cirrhosis, Henoch-Schönlein purpura, IgA vasculitis, liver

Immunoglobulin A vasculitis (IgAV), formerly known as Henoch-Schönlein purpura, is a systemic small-vessel vasculitis characterized by IgA deposits in small arterial walls and nonlymphoid 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 (GI) 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 Ig A1 (IgA1) in both IgAV and IgAN[7]. Indeed, in IgAV, IgA1 hinge regions are galactose-deficient, and such modified IgA1 are more

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prone to immune complex formation and deposition, thereby leading to enhanced inflammation[8,9], most likely through alternative complement 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 through 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, increased CD89 expression on mononuclear cells, and decreased immune complex hepatic clearance[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 the intestinal tight junction barrier; this disruption enhances bacterial translocation[14,15,16]. To date, only a few isolated case reports have focused on the concomitancy of IgAV and liver cirrhosis but without aggregating and analyzing epidemiological data to determine a real relationship between both diseases[17,18,19]. In undertaking this study, we hypothesized that the abnormal higher production of hypoglycosylated IgA in liver cirrhosis could contribute to IgAV pathogeny, and speculated that this late dysmetabolic and dysimmunitary condition could display a different clinical phenotype in the presentation of vasculitis. 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, which collects primary cases of IgAV excluding IgAV-associated cancer.

MATERIALS AND METHODS

Patients. We conducted a multicentric retrospective study at a French university and at 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 the Caen University Hospital Center (approval number 00-20181116-01R1). The inclusion criteria for the study were age > 18 years, and the diagnosis of liver cirrhosis and IgAV 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. 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 the 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 the study, 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], esophageal varices, portal hypertension gastropathy, portal thrombosis, and eventual hepatocellular carcinoma. Laboratory assessments included determination of serum creatinine, C-reactive protein, albumin, IgA, factor V, bilirubin levels, prothrombin ratio, urinalysis to screen for hematuria, and a 24-h urine protein examination. Renal failure was defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2, assessed with the Modified Diet in Renal Disease equation[21]. Proteinuria was defined as a 24-h urinary protein excretion rate of > 0.5 g/day, and hematuria was defined as > 10 red cells/mm^3 in the urine, which was designated as macroscopic if there were > 1500 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 leukocytoclastic vasculitis. Further recorded information included C3 deposits, extracapillary proliferation, mesangial sclerosis, and fibrinoid necrosis.

Response to therapy. Response to 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), GI signs, and renal involvement (eGFR, levels of proteinuria and hematuria). A complete response was defined as an improvement in all baseline clinical manifestations, and in cases of renal involvement, by a proteinuria < 0.5 g/day, the disappearance of hematuria, and a decrease in the 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 a decrease in the GFR no greater than 20% from baseline. All other patients were classified as nonresponders.

Relapse. Relapse was defined as the reappearance of clinical signs of IgAV, occurring after a symptom-free period of at least 1 month. Minor relapse was defined as an increase in prednisone no greater than 20 g/day, and major relapse was defined as the addition of an immunosuppressive drug or an increase in prednisone > 20 mg/day.

Statistical analysis. Descriptive statistics included the mean ± SD values or median (IQR) for continuous variables and frequency (percentage) for categorical variables. Univariate analysis included Fisher 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, 7 (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 involvement (35% vs 62%, $P = 0.03$). Though not reaching statistical significance, GI

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

	IgAV Patients, n = 20	IGAVAS Patients, n = 260	*P*
Demographics			
Female	7 (35)	96 (37)	0.9
Age at diagnosis, yrs, mean ± SD	62.7 ±11	50.1 ± 18	**< 0.01**
Clinical manifestations			
Constitutional symptoms			
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 (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 edema	9 (45)	49 (27)	**0.01**

Values are n (%) unless otherwise indicated. Significant values are in bold. GI: gastrointestinal involvement; IgA: immunoglobulin A.

involvement, defined as the presence of abdominal pain, ileus, or GI bleeding, tended to be less frequent in patients with liver cirrhosis than in those from the IGAVAS registry (35% vs 53%, $P = 0.2$).

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 g/L 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 registry (71.5 vs 88 mL/min/1.73 m^2, $P = 0.03$). 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: Class A in 6 patients (30%), Class B in 12 patients (60%), and Class C in 2 patients (10%). Cirrhosis was mainly related to alcohol intake (n = 15, 75%), followed by nonalcoholic steato-hepatitis (n = 2), hepatitis B and C coinfection (n = 1), hemochromatosis (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 14 received oral glucocorticoid (n = 14) motivated by renal involvement, and 1 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 3 months: 5 had a complete response and 5 had a partial response. During follow-up, 1 patient presented with a minor relapse, and 6 others died. No deaths were related to vasculitis. Two deaths were directly related to cirrhosis, 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 a consideration that, beyond a simple fortuitous association between the 2 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 2 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 GI and rheumatologic involvement in the present series is age-related. Indeed, older age seems to be correlated with lesser rheumatologic and GI manifestations at diagnosis of IgAV (unpublished data). Finally, renal involvement does not seem to be overrepresented in patients with underlying cirrhosis.In our present study, we found decreased eGFR and more frequent tubulo-nephritis on renal biopsy in patients with cirrhosis,

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

	IgA Patients, n = 20	IGAVAS Patients, n = 260	*P*
Biological features			
Serum IgA > ULN	11/13 (85)	85/159 (53)	**0.04**
Serum IgA, g/L	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/min/1.73m^2	71.5 (7–134)	88 (55–103)	**0.03**
C-reactive protein, mg/dL	28.3 (36–91)	27 (8–60)	0.5
Proteinuria, g/day	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)	0.05
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**

Values are n (%) or median (IQR) unless otherwise indicated. Significant values are in bold. eGFR: estimated glomerular filtration rate; IgA: immunoglobulin A; ULN: upper limit of normal.

which may be explained by the older age of patients in this series. This finding is associated with a higher prevalence of atheroembolic diseases, as well as the exposure to drug-induced nephrotoxicity[22]. In the end, older age, 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 etiopathogenic factors differentiating underlying liver disease patients from those with primary IgAV. In addition, it is interesting to note the temporality of the diagnoses of the 2 diseases, in which liver cirrhosis consistently either preceded or was revealed simultaneously with the onset of IgAV. Though there was a wide range in delay between the diagnoses of the 2 diseases, cirrhosis is often an 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 for the occurrence of vasculitis. Notably, it should be highlighted that no hepatocarcinoma was observed. In the last decade, neoplasia has been a well-documented condition associated with IgAV.

The high rate of mortality in our series, which was in no manner related to IgAV, highlights the frailty of patients with cirrhosis, which was responsible for one-third of the deaths reported. In addition, 1 patient died from infectious diseases, and 1 from acute heart failure while being treated with corticosteroids for IgAV. The decision regarding 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.

The analogy of a real pathogenic association between IgAV and liver cirrhosis can be considered with the current well-documented relationship between cirrhosis and IgAN, in 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 patients with liver cirrhosis 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 and could enhance the formation of IgA-CD89 complexes. Clearance of this abnormal IgA1 is further decreased in patients with liver cirrhosis, since CD89 expression on intrahepatic macrophages is reduced and endocytic functions are thus impaired[12]. It is also believed that these large immune complexes cannot enter the liver through 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 cases 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 favorable 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,

Table 3. Liver cirrhosis characteristics at IgAV diagnosis.

	n = 20
Demographics	
Synchronous IgAV and cirrhosis diagnosis	12 (60)
Time between cirrhosis and IgAV, median (IQR), months	60 (4–120)
Child-Pugh	
Class A	6 (30)
Class B	12 (60)
Class C	2 (10)
Etiology of liver cirrhosis	
Alcohol related	15 (75)
HCV and HBV coinfection	1 (5)
Nonalcoholic 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, median (IQR)	
Albumin, g/L	29 (22–33)
Prothrombin time, %	69 (61–78)
Factor V, %	75 (65–81)
Total bilirubin, µmol/L	19 (9–36.5)
Conjugated bilirubin, µmol/L	11 (7–18.5)

Values are n (%) unless otherwise indicated. IgAV: immunoglobulin A vasculitis; HBV: hepatitis B virus; HCV: hepatitis C virus.

Table 4. Treatments and outcomes of IgAV patients.

	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)
Nonresponders	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)

Values are n (%) unless otherwise indicated. IgAV: immunoglobulin A vasculitis.

as suggested by reports of patients with cirrhotic or noncirrhotic portal hypertension who developed IgAN, which resolved rapidly after medical or surgical correction of portal hypertension[32,33,34]. 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[37,38,39]; however, only a minority of patients subsequently develop IgAN. Further studies are needed to understand the causes of this shift from IgA nonsymptomatic deposits to inflammatory IgA deposits leading to IgA-related disease.

In this series, the levels of glycosylation of IgA1 could not have been measured because it is not a routine test and, therefore, we cannot affirm that patients in this series displayed such IgA. However, abnormally glycosylated IgA were previously identified in patients with cirrhosis and further studies should confirm this finding[12].

Liver cirrhosis affects 300 in 100,000 inhabitants in France[30] 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 this did not permit exhaustive inclusion of IgAV patients with cirrhosis. Further, mild IgAV with cutaneous and/or digestive manifestations occurring in patients with cirrhosis could have remained undiagnosed.

The strength of our study is the number of patients included in the context of a rare disease and the comparison cohort that included 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, to our knowledge, we report the first case series of IgA patients with underlying cirrhosis; this latter condition did not seem to affect baseline vasculitis characteristics. 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, IgAV diagnosis should be considered at the occurrence of purpura in patients with cirrhosis.

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