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Autoimmune Haemolytic Anaemia in Patients With Chronic Liver Disease: Case Series

Dorien Pint[1,2] | Abid Suddle[2] | M. Mansour Ceesay[3]

[1]University Hospital Antwerp, Edegem, Belgium | [2]Institute of Liver Studies, King's College Hospital, London, UK | [3]Department of Haematological Medicine, King's College Hospital, London, UK

Correspondence: Dorien Pint (dorien.pint@uza.be)

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Chronic anaemia frequently accompanies chronic liver disease (CLD), contributing to increased morbidity and mortality rates [1]. In up to 53% of cases, the aetiology of anaemia in CLD remains unknown [2]. Autoimmune haemolytic anaemia (AIHA) is characterised by the destruction of red blood cells by circulating autoantibodies directed against erythrocytes. AIHA is a rare autoimmune disorder affecting approximately one to three per 100,000 annually [3]. AIHA has a female predisposition with a female-to-male ratio of approximately 2:1 to 3:1 [4]. The diagnosis of AIHA has additional challenges in CLD, as all these laboratory values can be distorted due to the CLD. For instance, haptoglobin is low in CLD due to poor synthetic function, and similarly, LDH is often raised without haemolysis [5]. Autoimmune liver and bile duct diseases such as autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and primary biliary cholangitis (PBC) often coexist with other autoimmune disorders, though AIHA is a rare comorbidity.

We conducted a retrospective study from 2002 to 2022 investigating patients with concomitant CLD and AIHA managed in King's College Hospital Institute of Liver Studies and the Department of Haematological Medicine. The patients were identified using search criteria for various causes of CLD combined with AIHA diagnosis. The diagnosis of AIHA was based on laboratory parameters. The review aimed to evaluate the relationship between AIHA and CLD as well as review the diagnostic and therapeutic challenges. Due to the retrospective nature of this study, we were unable to determine the exact number of patients with CLD seen in our institution during the study period. As a result, we could not establish a denominator for AIHA prevalence in this population. However, our objective was not to perform an epidemiological assessment but rather to describe the clinical complexities in diagnosing and managing these rare cases.

A total of 10 patients were included in this study (Table 1). The median age for the diagnosis of chronic liver disease was 34 years (range 6–72), and the median age of AIHA diagnosis was 43 (19–72 years). The median interval between CLD diagnosis and onset of AIHA was 6 (range 0–17) years. There was female predominance with 70% being female. All patients had classical features of haemolysis with an elevated unconjugated bilirubin (mean 88.5 μmol/L), increased LDH (mean 496 U/L), reduced haptoglobin, and positive direct antiglobulin test (DAT). The most common underlying liver disease was AIH in four patients. Seven patients had cirrhosis, and five received an orthotopic liver transplantation (OLT). Among the five transplanted patients, three developed AIHA after their liver transplant. Indications for liver transplantation were AIH in two patients, and primary sclerosing cholangitis (PSC) and alcohol-related liver disease (ArLD) both in one patient.

Corticosteroids were used in all the patients, while intravenous immunoglobulin (IVIG) and rituximab at 375 mg/m^2 weekly for

Clinical Registration: There is no clinical trial registration as this was a retrospective study.

TABLE 1 | Study patients' characteristics, treatments and outcomes.

	Age (y) at CLD diagnosis	Age (y) at AIHA diagnosis	Gender	Ethnicity	Liver disease	Cirrhosis	OLT	AIHA after OLT	Cofactors AIHA	Treatment	Treatment outcome
Patient 1	6	21	Female	White	AIH	Yes	Yes	No	CMV reactivation	(1) Prednisolone (2) IVIG	Long-term remission
Patient 2	72	72	Female	White	AIH	No	No	N/A	—	Prednisolone	Remission of AIHA; remains on prednisolone for AIH, no flair-up
Patient 3	22	39	Male	Asian	PSC	Yes	Yes	Yes	Crohn's disease	(1) Prednisolone (2) Rituximab (3) MMF added	Refractory AIHA now maintained on low dose corticosteroids, tacrolimus, and MMF
Patient 4	51	58	Female	White	ArLD	Yes	No	N/A	COVID positive	(1) Prednisolone	Deceased
Patient 5	54	54	Female	White	AIH	No	No	N/A	COVID positive	(1) Prednisolone (2) IVIG	Remission; remains on Azathioprine for AIH
Patient 6	6	23	Male	Black African	ALF, viral	No	Yes	Yes	—	(1) Prednisolone (2) Rituximab	Remission; remains on IS for OLT (tacrolimus)
Patient 7	48	51	Female	White	ArLD	Yes	No	N/A	—	(1) Prednisolone (2) IVIG	Refractory AIHA Deceased
Patient 8	14	19	Male	Arab/African	Cryptogenic	Yes	No	N/A	COVID positive	(1) Prednisolone (2) Rituximab (3) MMF	Refractory AIHA Deceased: end stage liver failure and AIHA
Patient 9	28	29	Female	White	ArLD	Yes	Yes	No	—	Prednisolone	Remission
Patient 10	39	45	Female	White	AIH	Yes	Yes	Yes	—	(1) Rituximab (2) Prednisolone (3) MMF	Refractory AIHA now maintained on low dose prednisolone, tacrolimus and MMF

Abbreviation: AIH, autoimmune hepatitis; AIHA, autoimmune haemolytic anaemia; ALF, acute liver failure; ArLD, alcohol related liver disease; CLD, chronic liver disease; CMV cytomegalovirus; IVIG, intravenous immunoglobulins; IS, immunosuppression; MMF, mycophenolate mofetil; OLT, orthotopic liver transplantation; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

4 weeks were both used in four patients. Of the four patients treated with rituximab, only one patient achieved remission of haemolysis. All three patients who developed AIHA after their liver transplant were treated with rituximab. A total of four patients were refractory to treatment, two of whom developed AIHA after their liver transplant.

Possible cofactors for AIHA development that were identified were COVID-19 infection in three patients, cytomegalovirus (CMV) reactivation in one patient, and Crohn's disease in one patient. Eight patients presented with chronic liver disease before AIHA. Three patients died all of whom had liver cirrhosis. The cause of death was decompensated cirrhosis in all three, with concomitant COVID infection in one patient.

Our study confirms that AIHA in CLD patients is rare but challenging. We observed a significant female predominance, with 70% female predominance. This aligns with existing literature indicating a higher susceptibility of females to autoimmune disorders, including AIHA. The aetiology of CLD in our cohort varied, with AIH being the most common underlying condition present in four patients (40%). ArLD accounted for three cases (30%). Although the correlation between AIHA and ArLD is not clearly established, we found that 30% of the patients had concomitant AIHA and ArLD, suggesting a possible underestimation of AIHA in this patient group. Our study identified several cofactors that may influence the development of AIHA in patients with CLD. COVID-19 infection was noted in three patients (30%), CMV reactivation in one patient, and Crohn's disease in one patient. The temporal overlap of AIHA presentations with the COVID-19 pandemic explains the high concordance and highlights the potential impact of infectious triggers on autoimmune pathogenesis.

Interestingly, 80% of the patients in this cohort presented with chronic liver disease before the onset of AIHA. This suggests that there may be underlying immunological triggers associated with CLD that predispose patients to develop AIHA. Current literature supports the notion that chronic inflammatory conditions, including liver diseases, can alter immune tolerance and potentially trigger autoimmune responses such as AIHA [6].

Corticosteroids remain the cornerstone of treatment for AIHA, administered to all patients. Intravenous immunoglobulins were used in four patients and can provide a rapid increase in haemoglobin. It is often used in cases where corticosteroids alone are insufficient or relatively contraindicated. However, its use is contraindicated in post-transplant patients due to the risk of enhanced immune activation and increased risk of infection. Rituximab, a monoclonal antibody targeting CD20 on B cells, can be used with high-dose corticosteroids in severe AIHA or in steroid-refractory or relapsed cases. Rituximab was administered to four patients, and only one of them went into remission. Although the number of patients in this series is small, this would indicate poor response to rituximab. Three of these patients were post-liver transplant. In our series, two of the three patients who developed AIHA after their liver transplant remained refractory despite rituximab and triple immunosuppression with corticosteroids, tacrolimus, and MMF. AIHA after solid organ transplantation is often severe and difficult to treat and requires more aggressive treatment modalities [7].

All the patients in our study exhibited classical haemolytic features, emphasising the importance of recognising and diagnosing AIHA accurately. It is crucial to exclude other potential causes of haemolysis, such as infections, drug-induced haemolysis, and spur cell anaemia to ensure appropriate management and treatment. Standard workup should contain haemolytic parameters, a meticulous review of medications, and if there is diagnostic uncertainty, a bone marrow examination should be performed.

The treatment landscape for AIHA in patients with chronic liver disease, particularly those who have undergone transplantation, requires careful consideration of the unique challenges and contraindications associated with each therapeutic option. Our findings underscore the necessity for further research to better understand the role of chronic liver disease as an immunological trigger for AIHA. Investigating the pathways linking liver inflammation and immune dysregulation could provide valuable insights into the pathogenesis of AIHA in patients with CLD as well as patients developing AIHA post-liver transplantation. Additionally, exploring the impact of various cofactors, including viral infections and autoimmune conditions, may help in developing targeted therapeutic strategies.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article.

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