

## Successful Treatment of Acute Hepatitis-Associated Aplastic Anemia in a Young Boy: a case report

 Mirna Natalija Anicic,<sup>1,2</sup>  Matija Bakos,<sup>1</sup>  Ana Petrovic Gluscic,<sup>1</sup>  Marijana Ćorić,<sup>2,3</sup>  
 Jurica Vukovic<sup>1,2</sup>

<sup>1</sup>Department of Pediatrics, University Hospital Centre Zagreb, Zagreb, Croatia

<sup>2</sup>University of Zagreb School of Medicine, Zagreb, Croatia

<sup>3</sup>Department of Pathology and Cytology, University Hospital Centre Zagreb, Zagreb, Croatia

### ABSTRACT

**Background:** Acute hepatitis-associated aplastic anemia (AHAAA) is a rare clinical syndrome characterized by the development of aplastic anemia 2–3 months following an episode of acute hepatitis. Several immunosuppressive agents, but not mycophenolate mofetil (MMF), and bone marrow transplantation are the standard treatment options for AHAAA.

**Case Report:** In this report, we present a case of a young boy with AHAAA manifesting as acute liver failure. The etiology was type 1 autoimmune hepatitis responsive to the second-line therapeutic combination of steroids and MMF. The liver has fully recovered, but bone marrow failure ensued. After 4 months, Clinical and laboratory improvement occurred without the need for bone marrow transplantation. An important aspect of this case is the full recovery of aplastic anemia without calcineurin inhibitors, anti-thymocyte globulin utilization, or bone marrow transplantation.

**Conclusion:** Our case history supports MMF as a potentially crucial adjunctive therapy for patients with AHAAA who poorly respond to standard procedures.

**Keywords:** Autoimmune hepatitis, aplastic anemia, children, immunosuppression, treatment.



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#### Address for correspondence:

Matija Bakos.  
Department of Pediatrics,  
University Hospital Centre  
Zagreb, Zagreb, Croatia  
**Phone:** +385 989567615  
**E-mail:** mbakos11@gmail.com

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### INTRODUCTION

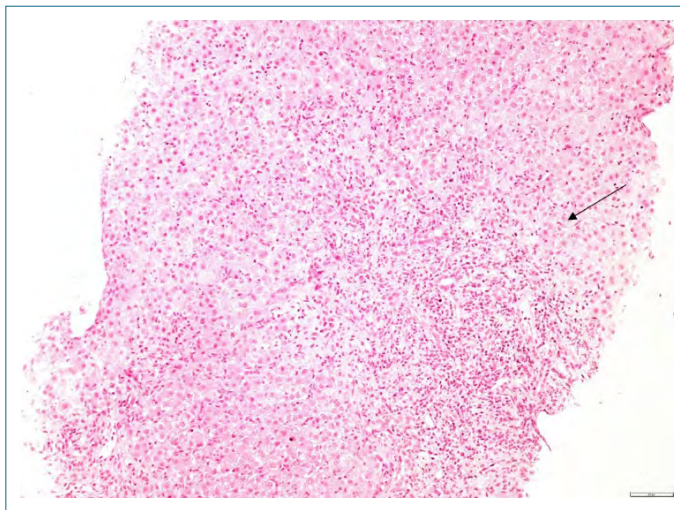
Acute hepatitis-associated aplastic anemia (AHAAA) presents as a rare clinical syndrome in which aplastic anemia usually develops 2–3 months following an episode of acute hepatitis.<sup>1</sup> It is more prevalent in adolescent boys and has a poor prognosis if left untreated.<sup>2,3</sup> Despite the extensive workup, the etiology remains unknown in the majority of patients. Presumably, aplastic anemia is caused by immune dysregulation due to infection, which induces cytokine production and damages hematopoietic stem cells.<sup>2</sup> Immunosuppressive therapy, including corticosteroids, calcineurin inhibitors, anti-thymocyte globulin, anti-lymphocyte globulin, and bone marrow transplantation, is currently used to treat severe AHAAA.<sup>1</sup> We present a case of a 10-year-old boy who developed AHAAA, which was successfully treated with corticosteroids and mycophenolate mofetil (MMF).

### CASE REPORT

A healthy 10-year-old boy was admitted to Pediatric Department, Division for Gastroenterology and Hepatology, University Hospital Center Zagreb, with symptoms of jaundice and nausea. Laboratory findings revealed elevated aminotransferases (AST 2089 U/L, ALT 3228 U/L) and conjugated hyperbilirubinemia (total bilirubin 391 μmol/L, conjugated fraction 302 μmol/L). The synthetic liver function was still preserved. Infectious, toxic, ischemic, and metabolic causes of acute hepatitis were excluded.

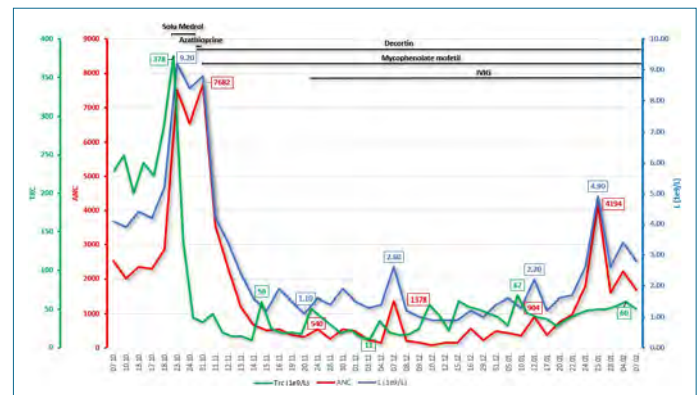


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**Figure 1.** The portal tract exhibits a marked lymphocytic infiltrate with piecemeal necrosis (arrow) and necroinflammatory changes throughout the lobule (hematoxylin and eosin, original magnification  $\times 100\times$ ).

Anti-smooth muscle antibodies were positive in two successive tests (1:20), although hypergammaglobulinemia was not present. Typical pathological findings of acute hepatitis were discovered on liver biopsy (Fig. 1). The course of the illness was progressive, and the patient developed acute liver failure (INR 2.6). Therapy for autoimmune hepatitis (AIH) was started (corticosteroids 2 mg/kg and azathioprine 1 mg/kg). After confirming the decreased activity of the enzyme thiopurinmethyltransferase (TPMT), azathioprine was replaced with MMF. Subsequently, his synthetic liver function completely recovered, and both aminotransferases and bilirubin levels returned to normal. Severe thrombocytopenia ( $<20 \times 10^9/L$ ), neutropenia ( $<100 \times 10^6/L$ ), and anemia were observed 6 weeks after the initial presentation (Fig. 2). Bone marrow biopsy revealed heterogeneous hypocellularity, with some areas showing total aplasia and others being 30% hypocellular. The CD4/CD8 cell ratio in peripheral blood was reduced (0.06%; normal range 0.9%–3.1%). Due to the presence of *Pneumocystis carinii* in sputum and the reactivation of cytomegalovirus and varicella zoster virus, trimethoprim–sulfamethoxazole and valganciclovir were initiated along with antifungal therapy for oral candidiasis. Multiple platelet transfusions, as well as filgrastim, were required. Two months after the first symptoms, the patient's bone marrow showed the first signs of recovery. Four months after the initial presentation, the patient was discharged from the hospital with normal liver function tests and normal white and red blood cell counts, but with mild thrombocytopenia ( $99 \times 10^9/L$ ). Three years after the initial presentation, the patient remains well on MMF, completely recovering from AHAAA.



**Figure 2.** Laboratory values of thrombocytes, leukocytes, and absolute neutrophil count during the course treatment and introduction of different therapy.

## DISCUSSION

Our patient showed a typical clinical presentation of AHAAA, as previously described in the literature. Hematological complications are occasionally observed in several patients with acute or chronic liver disease.<sup>4</sup> AHAAA is a distinct clinical syndrome in which pancytopenia develops, usually 2–3 months after an episode of acute hepatitis.<sup>5</sup> The mortality rate is up to 85% when full-blown fulminant hepatitis is followed by aplastic anemia.<sup>3</sup> Although AIH is a relatively uncommon condition in children, the diagnosis should be suspected whenever a typical combination of clinical signs, symptoms, and laboratory findings are found, and a liver biopsy should remain mandatory.<sup>6</sup> Some of the common causes of hepatitis, such as metabolic, hereditary cholestatic, or drug-induced liver failure, should be excluded during the workup.<sup>6</sup>

The scoring system from the International Autoimmune Hepatitis Group from 2017 relies on four diagnostic parameters: the presence of autoantibodies, IgG levels, histological findings, and the absence of viral hepatitis.<sup>7</sup> Although the initial IgG levels were not increased, anti-smooth muscle antibodies (SMA; 1:20) were positive on two occasions. On the liver biopsy, acute hepatitis and interface (piecemeal necrosis and lymphocytic infiltration) hepatitis were found. There is no exclusive histological feature for AIH, but typically, interface hepatitis is present.<sup>7</sup> In AHAAA, several immunological abnormalities have been described. An activated CD8+ T lymphocyte could be cytotoxic to myelopoietic cells in the bone marrow in patients with aplastic anemia, which results in a decreased ratio of CD4/CD8 cells in peripheral blood.<sup>2,4</sup> Kemme et al.<sup>9</sup> described four children with seronegative AHAAA; all had evidence of increased systemic inflammation and immune dysregulation (decreased NK cell function and CD8+ T cell activation) as well as hyperinflammation demonstrated on liver histology. Extensive marrow failure evaluation and genetic causes of immune dysregulation were examined, where one patient had a genetic mutation predisposing to immune-mediated disease (TNFRSF13B, variant c.542C>A (TAC1) previously reported in association

with common variable immunodeficiency and autoimmunity.<sup>9</sup> Further genetic investigations can reveal a subgroup of patients with acute hepatitis susceptible to developing aplastic anemia.

The standard treatment for AIH in children includes corticosteroids and azathioprine. Second-line treatment of AIH presents cyclosporine, MMF, and tacrolimus.<sup>6</sup> In our patient, azathioprine was introduced immediately after transaminase levels were persistently high during the steroid treatment only. The patient's condition further deteriorated after azathioprine was introduced, possibly because of decreased TPMT function, and it was switched to MMF until the patient's condition and laboratory results improved.

Although we found no guidelines for treating patients with AHAAA, treatment options include immunosuppressive therapy and bone marrow transplant.<sup>1</sup> Osugi et al.<sup>8</sup> analyzed the outcomes of 44 children with AHAAA who received immunosuppressive therapy with anti-thymocyte globulin (ATG) and cyclosporine (CsA) as a standard of care. One-third of them (31.8%) achieved a complete response, and 38.6% achieved a partial response. Seven nonresponders received bone marrow transplantation from an HLA-matched unrelated donor, and six out of seven are alive.<sup>8</sup> Since AHAAA is a rare condition, a limited number of allogeneic bone marrow transplants have been done, but at the moment, it appears to be an acceptable last treatment option for patients with AHAAA. In the study by Kemme et al.,<sup>9</sup> three cases were treated initially with corticosteroids and tacrolimus, and one patient with corticosteroids and azathioprine with minimal response, two of which underwent hematopoietic stem cell transplantation, and all of them received ATG and MMF. Often, various combinations of immunosuppressive agents are necessary for establishing remission in AHAAA. It is hard to comprehend the role of MMF in this case study since all the patients also received ATG.

One could argue whether the introduction of MMF when aplastic anemia develops could provide the same benefit (possible benign course) on this rare phenomenon, as we have observed in our patient. It presumably worked that way before the development of aplastic anemia when it was initiated as a second-line treatment for AIH type 1. We advise its implementation in patients with AHAAA who poorly respond to standard conservative therapy as an additional treatment modality. A few outstanding questions remain to be answered as we collect new insights into this rare phenomenon.

## CONCLUSION

The important aspect of our case is the full recovery of bone marrow aplasia without using calcineurin inhibitors, ATG, or bone marrow transplantation. The question remains whether the early introduction of MMF treatment has changed the course of the disease. Our case history supports the argument that MMF may be considered a potentially beneficial adjunctive therapy, at least for patients with AHAAA who poorly respond to standard procedures.

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**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Author Contributions:** Concept – MNA, MB, JV; Design – MB, JV; Supervision – MNA, JV; Resource – MNA, MB, APG, MĆ, JV; Materials – MNA, MB, APG, MĆ, JV; Data Collection and/or Processing – MNA, MB, APG, MĆ, JV; Analysis and/or Interpretation – MNA, MB, APG, MĆ, JV; Literature Search – MNA, MB, APG, MĆ, JV; Writing – MNA, MB, APG, MĆ, JV; Critical Reviews – MNA, MB, APG, MĆ, JV.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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## REFERENCES

1. Alshabani A, Dufour C, Risitano A, de Latour R, Aljurf M. Hepatitis-associated aplastic anemia. *Hematol Oncol Stem Cell Ther* 2022; 15(2): 8–12.
2. Patel KR, Bertuch A, Sasa GS, Himes RW, Wu H. Features of hepatitis in hepatitis-associated aplastic anemia: Clinical and histopathologic study. *J Pediatr Gastroenterol Nutr* 2017; 64(1): e7–e12. [\[CrossRef\]](#)
3. Gonçalves C, Ferreira S, Nobre S, Gonçalves I. Long-term follow-up of hepatitis-associated aplastic anaemia. *BMJ Case Rep* 2017; 2017: bcr2017221434. [\[CrossRef\]](#)
4. Qureshi K, Sarwar U, Khallafi H. Severe aplastic anemia following acute hepatitis from toxic liver injury: Literature review and case report of a successful outcome. *Case Reports Hepatol* 2014; 2014: 216570. [\[CrossRef\]](#)
5. Rauff B, Idrees M, Shah SA, Butt S, Butt AM, Ali L, Hussain A, et al. Hepatitis associated aplastic anemia: a review. *Virology* 2011; 8: 87. [\[CrossRef\]](#)
6. Pathak S, Kamat D. Autoimmune hepatitis in children. *Pediatr Ann* 2018; 47(2): e81–6. [\[CrossRef\]](#)
7. Mieli-Vergani G, Vergani D, Baumann U, Czubkowski P, Debray D, Dezsofi A, et al. Diagnosis and management of pediatric autoimmune liver disease: ESPGHAN hepatology committee position statement. *J Pediatr Gastroenterol Nutr* 2018; 66(2): 345–60. [\[CrossRef\]](#)
8. Osugi Y, Yagasaki H, Sako M, Kosaka Y, Taga T, Ito T, et al; Japan Childhood Aplastic Anemia Study Group. Antithymocyte globulin and cyclosporine for treatment of 44 children with hepatitis associated aplastic anemia. *Haematologica* 2007; 92(12): 1687–90. [\[CrossRef\]](#)
9. Kemme S, Stahl M, Brigham D, Lovell MA, Nakano T, Feldman AG, et al. Outcomes of severe seronegative hepatitis-associated aplastic anemia: A pediatric case series. *J Pediatr Gastroenterol Nutr* 2021; 72(2): 194–201.