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Case Report

Budesonide for Relapsed/Persistent Hepatitis in Two Patients with Hepatitis-Associated Aplastic Anemia Treated with Antithymocyte Globulin and Cyclosporine A Case Report

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1. Abstract

Flares of hepatitis with activity similar or even higher than peak activity during initial presentation are rare in patients with Hepatitis-Associated Aplastic Anemia (HAAA). We describe two children with HAAA in whom hepatitis with high transaminases activity persisted or relapsed after a course of antithymocyte globulin (ATG) + cyclosporine A(CsA)/tacrolimus and methylprednisolone and subsided after oral budesonide 9 mg daily was added. Budesonide was successfully stopped in one patient, whereas the second patient requires low-dose maintenance. We conclude that use of budesonide may be the approach of choice when hepatitis in HAA does not subside with IST or relapses after initial resolution.

What is known:

- Hepatitis-associated aplastic anemia (HAAA) is the most prevalent form of nonidiopathic aplastic anemia.
- The most common scenario of HAA development is onset of pancytopenia coinciding with a decrease in or normalization of serum aminotransferases and bilirubin.
- Residual hepatitis activity typically resolves after combined immunosupression with ATG and CsA.

What is new:

- In very rare patients hepatitis and pancytopenia relapse soon after initial resolution and hepatitis persists, despite hematopoiesis recovery after second course of ATG and substitution of tacrolimus for CsA.
- Administration of budesonide results in hepatitis resolution or significant alleviation.

2. Introduction

Hepatitis-Associated Aplastic Anemia (HAAA) is the most prevalent form of nonidiopathic aplastic anemia, accounting for 6% of all AA cases in European populations and 12-18% in Eastern and South Eastern Asian populations [1, 2]. No infectious agent causing hepatitis associated with AA has been identified [3]. Given the good response to Immunosuppressive Therapy (IST) with Antithymocyte Globulin (ATG), AA is believed to result from immune T cell-mediated attack directed against Hematopoietic Stem Cells (HSCs). Target antigens for this attack are not shared between hepatocytes and HSCs, as hepatitis and bone marrow aplasia onset is usually discordant.

The most common scenario of HAA development is an abrupt or gradual concordant decrease in granulocytes, platelets, red blood cells and reticulocytes, generally coinciding with a decrease in or

normalization of serum aminotransferases and bilirubin. Less frequently, moderate hepatitis persists after pancytopenia onset and resolves only after IST either in the context of allogeneic bone marrow transplantation or combined immunosuppression [4].

In both types of treatment, ATG and prolonged cyclosporine A (CsA) constitute essential components of therapeutic regimens. The least common scenario in the hepatitis course is full-blown relapse after initial improvement or complete resolution, occurring either spontaneously or after IST.

Here, we describe two patients with HAA in whom hepatitis persisted or relapsed after a course of ATG+CsA/tacrolimus+methylprednisolone and subsided after budesonide was added.

3. Case 1

A 3.5-year-old boy of gypsy origin experienced anorexia, fatigue, vomiting and jaundice. He was admitted to the Pediatric Infectious Disease Department, where hepatomegaly +3 cm below the costal margin, indirect hyperbilirubinemia 114 μmol/l and an increase in ALAT/ASAT to 314/322 U/l were detected. Hepatitis A, B, C and HIV were ruled out by serology and PCR. Complete blood counts were normal, with Hb 11.8 g/dl, WBC 6300/μl, granulocytes 3000/μl and platelets 223000/μl. Prednisolone was administered intramuscularly for 1 week, and transaminase activity was normalized. Ten days after discharge, fatigue recurred, and cutaneous purpura appeared. Physical examination was unremarkable, and CBC showed anemia 6.3 g/dl, reticulocytopenia 0%, leukopenia 1200/μl, agranulocytosis 30/μl and platelets 0/μlʌ. ALT/AST activity was normal at 28/24 U/l, and total bilirubin was 8.3μmol/l.

Bone marrow smears revealed severe hypocellularity, with only scarce lymphocytes present, and trephine biopsy showed total replacement of hematopoietic spaces by adipose tissue. PNH clones were not detected by flow cytometry, and karyotyping and diepoxybutane tests failed due to low cellularity. RW, HIV, hepatitis C and B serology were negative, and extensive PCR analyses for other hepatotropic viruses such as CMV, EBV, HHV-6, and ParvoB19 were negative. Blood chemistry showed ALT/AST activity 9/14 U/l; total bilirubin was 11.0μmol/l, γGTP 26U/l, alkaline phosphatase 234 U/l, and LDH 115U/l.

Based on the classical clinical and laboratory picture of very severe HAAA, in April 2017, three months after hepatitis onset, immunosuppressive therapy with horse ATG (ATGAM, Pfizer, USA) in cumulative dose 160 mg/kg and CsA combined with eltrombopag 2 mg/kg b.w. day were commenced. A complete hematological response was achieved by day 59 after ATG start, with Hb 9,9 g/dl, reticulocytes 1,2%, WBC 3740/μl, granulocytes 2300/μl and platelets 176000/μl. On day 68, increases in ALT/AST to 864/974 μ/l and bilirubin to 48, 6 μmol/l were detected; pancytopenia developed during the next week. Thus, relapse of HAAA was diagnosed.

In August 2017, 100 days after the first course, the second course of ATGAM was initiated. On day 45 after the second course of ATG began, tacrolimus was substituted for CsA due to persistent hepatitis (ALT/AST 588/406 U/L). On day 59, a complete hematological response was achieved again, but high transaminase activity persisted (ALT/AST 1130/2018 U/l). Needle liver biopsy showed moderate hepatitis (Knodl index 4) but no fibrosis. Budesonide 6 mg/day was added, and the hepatitis gradually subsided, with halving of transaminase activity every two weeks and complete normalization at 90 days after budesonide was started. Side effects were mild and consisted of hyperthichosis as well as moon face, which disappeared shorty after budesonide cessation. The total duration of treatment with budesonide was 110 days, after which it was electively interrupted. No relapse of the hepatitis occurred. The patient has completed 2 years of maintenance therapy with tacrolimus uneventfully and stayed in complete hematological remission.

4. Case 2

A 15-year-old boy presented in June 2016 with jaundice, dark urine and clear stool. Blood chemistry revealed hyperbilirubinemia at 260 μmol/l and high ALAT and ASAT, at 1534 and 1370 U/l, respectively. Complete blood counts were normal at Hb 13.2 g/dl, WBC 3300/μl, and platelets 182000/μl. Serologic and PCR testing for hepatitis A, B and C, as well as for CMV, HHV-6, HCV1/2, and VZV, was negative. Thereafter, CBC began to decline, and in one month, severe pancytopenia developed, with Hb 8.0/dl, WBC 100/μl and platelets 18000/μl while levels of ALAT and ASAT remained very high at 2342 U/l and 1726 U/l, respectively. Pulse therapy with methylprednisolone 10 mg/kg day intravenously for three days was delivered, and the patient was referred to our center.

At admission, the patient was pale with jaundice and fatigued but afebrile. Physical examination was unremarkable, and the liver margin was not palpable.CBC showed severe pancytopenia with Hb 7.9/dl, WBC 60/μl and platelets 19000/μl. Total bilirubin was 198 μmol/l and direct bilirubin 129 μmol/l; ALAT and ASAT were 658 U/l and 140 U/l, respectively.

Bone marrow aspirate was acellular, with only some lymphocytes present, and bone marrow trephine biopsy showed total replacement of the marrow by fat. Virologic work-up was repeated, and no viral cause of hepatitis was established. Thus, a diagnosis of hepatitis-associated aplastic anemia was made, and combined IST with horse ATG (ATGAM, Pfizer, USA) in cumulative dose 160 mg/kg and cyclosporine A was started, together with stimulation of granulocytopoiesis using pegylated filgrastim.

Transaminases normalized on day 9 after IST, but complete normalization of bilirubin was delayed until day 65. On day 103 after starting IST, eltrombopag was added due to the absence of any hematologic improvement, but no response was achieved. The second course of the same brand of ATG was started at 173 days after the

first course. Transaminase activity remained normal. In July 2017, 6 months after the second ATG course, a partial hematologic response was achieved, with Hb>8.0 g/dl, granulocytes > 1000/µl, platelets > 30000/µl and transfusion independence. However, at that time, transaminase activity rose again and fluctuated 3- to 10-fold above the upper limits of normal. Repeated testing for a large panel of hepatotropic viruses was negative. Based on the presumption of recurrent immune-mediated hepatitis, budesonide 3 mg t.i.d. was started, and tacrolimus was substituted for cyclosporine A. This change resulted in a decrease in ALAT and ASAT activity below the upper normal value. Gradually, his hematologic response improved, and blood counts stabilized, with Hb>14.0 g/dl, granulocytes > 2000/µl and platelets > 40000/µl, meeting the criteria for very a good partial response. However, several attempts to stop budesonide resulted in a rapid rise in transaminase activity above 150 U/l. At the time of writing, the patient was continuing treatment with tacrolimus 6 mg/daily and budesonide 3 mg every three days and had not experienced any glucocorticoid-related side effects.

5. Discussion

Although a causal association between "seronegative" hepatitis and aplastic anemia was demonstrated several decades ago, little is known about the pathophysiological mechanisms of AA development [5].

The response of HAA and hepatitis to intensive IST indicates that both processes result from cytotoxic attack of hematopoietic progenitors and hepatocytes, respectively. Interestingly, there is no direct correlation between hepatitis severity and the hazard of AA development, as very severe HAAA may occur even after very mild subclinical hepatitis. In a typical scenario, however, rapid development of pancytopenia occurs when severe hepatitis is resolving or has already resolved completely. Less commonly, hepatitis persists after AA onset and subsides only after immunosuppression with ATG, steroids and CsA; flares of hepatitis with activity similar or even higher than peak activity during initial presentation are rare [4].

Treatment of hepatitis in HAA resistant to intensive IST with ATG and CsA is challenging, and there are no standard approaches. Classical immune suppression with cyclophosphamide, methotrexate or mycophenolate is undesirable due to the hazard of additional myelosuppression, necessitating nonmyelotoxic immunosuppressants. Substitution of tacrolimus for CsA is attractive, as tacrolimus accumulates at especially high concentrations in the liver, and has been beneficial in ameliorating inflammation in autoimmune hepatitis, refractory to conventional immunesupression [6]. In our two patients, however, this did not allow the complete control of hepatitis. The second attractive option in such circumstances is budesonide, a powerful glucocorticoid that undergoes extensive first-pass hydroxylation by P450(CYP) 3A and exhibits active enterohepatic circulation, avoiding undesirable systemic side effects while retaining high activity in the intestinal lumen and liver [7]. Budesonide has been tested with success in children with autoimmune hepatitis [8].

In the patients reported herein, budesonide administration proved to be effective and led to a complete resolution of hepatitis in the first patient and stable lowering of hepatitis biochemical activity in the second patient. The side effects of budesonide are usually mild, as seen in our patients, but can be more pronounced when P450(-CYP) 3A inhibitors are used simultaneously. We thus conclude that prolonged use of budesonide may be the approach of choice when hepatitis in HAA does not subside with IST or relapses after initial resolution.

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