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Acute Elevation of Liver Enzymes Following Anti-thymocyte Globulin Treatment in a Patient with Aplastic Anemia: A Case Report

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Abstract

Background & Objective: Plastic anemia, a rare hematological disorder resulting in pancytopenia, is primarily managed through immunosuppression. Anti-thymocyte globulin (ATG), a polyclonal antibody derived from equine or lapine sources, is one such immunosuppressive treatment. While common side effects of ATG include allergic reactions, thrombocytopenia, headache, and myalgia, more severe but less frequent adverse effects encompass dyspnea and chest pain. The incidence and severity of liver function test abnormalities associated with ATG administration remain subjects of ongoing debate; however, most cases present with mild and transient enzyme elevations.

Case: We present the case of a 13-year-old male child diagnosed with aplastic anemia (AA) who was admitted to the hematology clinic for ATG treatment. Three days after the initiation of ATG therapy, following the third dose, the patient developed severe hepatotoxicity. The patient experienced symptoms including chest pain, icterus, myalgia, and abdominal tenderness. Laboratory investigations revealed a significant elevation in liver enzymes and serum bilirubin levels. Upon discontinuation of ATG, the symptoms resolved within six days, accompanied by a marked reduction in liver enzymes and bilirubin levels. Subsequently, the patient received the fourth dose of ATG without adverse reactions.

Conclusion: Our patient developed frank symptomatic hepatitis, manifesting as icterus and right upper quadrant pain. Given the existing literature, this presentation does not appear to be common and warrants increased vigilance.

Keywords: Aplastic anemia, Liver dysfunction, Anti-thymocyte globulin

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Introduction

Aplastic anemia (AA) is a rare bone marrow disorder characterized by pancytopenia. This condition may result in hemorrhage, anemia, and infection, thereby posing a significant risk to the patient's life. Treatment modalities for this disease include corticosteroids, hematopoietic growth factors, and immunosuppressants (1). Anti-thymocyte globulin (ATG), a polyclonal antibody derived from either equine ATG

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(eATG) or rabbit ATG (rATG) sources, is one such immunosuppressant. Utilized for over three decades, ATG is believed to reduce lymphocyte counts through complement-dependent lysis of blood cells and lymphoid cells, as well as T-cell activation and apoptosis (2, 3). In addition to its application in AA, ATG is employed in solid organ and hematopoietic stem cell transplantation, as well as in the management of graft-versus-host disease (4).

While common side effects of ATG include allergic reactions, thrombocytopenia, headache, and myalgia, more serious but less frequent adverse effects comprise dyspnea and chest pain (5). The precise incidence of liver function test abnormalities following ATG administration remains a subject of debate, with varying estimates reported in the literature (6, 7). Moreover, the severity of this adverse effect is not well-established (8). However, according to the drug's FDA monograph and other reports, liver enzyme elevations in AA are typically described as mild to moderate and transient in nature, rarely causing symptoms in patients. Severe elevations of hepatic enzymes are considered uncommon (6, 7, 9-12). Herein, we report a case of acute significant hepatotoxicity accompanied by jaundice, an uncommon occurrence in a pediatric patient with AA, following treatment with ATG.

Case Presentation

A 13-year-old male child, previously diagnosed with AA, was admitted to our hematology service for ATG treatment. This therapeutic approach was selected due to the patient's inadequate response to a three-month course of oxymetholone at 1 mg/kg/day. Concurrently, the patient received tranexamic acid at 10 mg/kg every eight hours and folic acid at 1 mg daily.

Following the successful completion of an intradermal ATG test (0.02 mg of ATG diluted 1:1000 in 0.9% sodium chloride), the patient commenced rATG therapy at 5 mg/kg/day, administered intravenously once daily over an eight-hour infusion period for four consecutive days. Concomitant medications included methylprednisolone at 5 mg/kg/dose intravenously every six hours and cyclosporine at 10 mg/kg/day orally, divided into four equal daily doses. Premedication, consisting of hydroxyzine 10 mg and acetaminophen 10 mg/kg, was administered 30 minutes prior to each ATG infusion. Furthermore, in consideration of the patient's initial white blood cell count (Table 1), granulocyte-stimulating factor was administered subcutaneously at 10 mcg/kg daily. Three days following the initiation of ATG therapy, the patient developed acute chest pain, icterus, myalgia, and abdominal tenderness in the right upper quadrant. The patient became tachycardic (110 beats/minute) and tachypneic (30 respirations/minute), necessitating the immediate cessation of the ATG infusion. The patient's oxygen saturation remained within normal limits, and both the electrocardiogram and chest radiograph were unremarkable. The patient's laboratory data at this time are presented in Table 1.

Investigations

In light of the elevated liver enzymes and bilirubin levels, the patient underwent a comprehensive evaluation for viral hepatitis and portal vein thrombosis. The viral hepatitis panel yielded negative results for hepatitis A, B, and C, cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus. Additionally, the patient's influenza polymerase chain reaction (PCR) test was negative. Given the presence of anemia, a history of blood transfusion, and elevated total bilirubin levels, a Coombs test was performed to exclude autoimmune hemolysis which also yielded negative results.

Abdominal and pelvic ultrasonography revealed no evidence of portal vein thrombosis. After eliminating all aforementioned possibilities, drug-induced acute liver injury

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Table 1. Laboratory parameters of the patient at baseline and days after administration of ATG

		Day (since ATG initiation)					
		Baseline (2 days prior to ATG)	Day 3 ATG was held	Day 8	Day 9 (ATG re-initiation)	Day 10	Day 19 (discharge)
Laboratory tests	Leukocytes, /x10^9/L	1.8	0.85	3.8	2.35	1.1	8.85
	Hemoglobin, g/dL	10.4	5.8	9.1	8.9	6.5	9.9
	Platelet count, ×10^3/µL	6	31	8	66	27	35
	AST, U/L	55	45	20	56	57	13
	ALT, U/L	47	42	74	118	91	20
	Total bilirubin, mg/dL	.7	**13.5**	6.49	3.7	5.67	2.15
	Direct bilirubin, mg/dL	.08	8.5	4.72	3.14	4.29	1.5
	BUN, mg/dL	13	18	17	11	12.2	15.8
	Cr, mg/dL	.5	.4	.5	.5	.61	.6
	CRP, mg/dL	-	-	5	36.3	35	-
	ESR, 1h	-	-	34	98	110	-
	PTT, secs	-	24	32	36	34	-
	PT, secs	-	13	12	13	12	-
	INR	-	1.12	.99	1.04	.99	-

Abbreviations: Aspartate transaminase (AST), Alanine transaminase (ALT), bilirubin (Bili), blood urea nitrogen (BUN), Creatinine (Cr), PTT (Partial thromboplastin time, PT (Prothrombin time), International normalized ratio (INR), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR).

was deemed the most probable diagnosis. The patient's plasma cyclosporine level was 128 ng/ml (sample obtained 72 hours post-cyclosporine initiation), and the possibility of this medication being the causative agent was dismissed in favor of ATG.

ATG and cyclosporine administration was suspended, and the patient was initiated on the following regimen: lactulose 10 ml every 8 hours, silymarin 140 mg oral tablet every 12 hours, ursodeoxycholic acid 200 mg daily, oral metronidazole 250 mg every 8 hours, and oral vitamin K 5 mg daily. The elevation in liver enzymes persisted until day 6 (post-ATG initiation); however, on day 8, a significant reduction was observed (all measurements are presented in Table 1). In view of the improvement in the patient's icterus and bilirubin levels, he was rechallenged with the fourth dose of ATG on day 9, which he tolerated without

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complications. Cyclosporine and prednisolone doses were tapered to 100 mg every 8 hours and 12.5 mg every 12 hours, respectively, on day 13. Subsequently, the patient was discharged from the hospital on a regimen of cyclosporine 100 mg twice daily and prednisolone 12.5 mg daily, without further complications. At a follow-up visit three months later, the patient exhibited no signs of icterus and demonstrated white blood cell and platelet counts of 2 x 10^9/L and 20 x 10^9/L, respectively. The patient is currently managed with cyclosporine 100 mg every eight hours and receives packed red blood cell transfusions every two to three months.

Discussion

Hepatitis, irrespective of its etiology, is generally characterized by a broad spectrum of clinical manifestations, including fatigue, abdominal pain, icterus, nausea, and vomiting (13). Drug-induced liver injury (DILI) represents an infrequent but severe complication associated with numerous medications. This adverse effect may manifest as an asymptomatic, mild elevation in liver enzymes detectable only through laboratory testing, or it may precipitate overt liver failure or even mortality (14). The drug-induced damage, whether direct or indirect, may result in hepatic cell necrosis, cholestasis, and sinusoidal and endothelial involvement. Regardless of the pathological findings, a valuable diagnostic feature in many cases is the restoration of hepatic markers to baseline levels following discontinuation of the offending medication (6). ATG-induced liver enzyme elevation is reported to vary in duration and severity; however, the majority of cases are expected to be mild and transient, irrespective of its use in solid organ transplantation or other indications such as aplastic anemia. Notably, approximately one-third of patients receiving ATG for AA experience a mild elevation of liver enzymes (15).

Some sources estimate that the severity of enzyme elevation is mild in the majority of cases. According to these references, icterus is generally not anticipated following this enzyme elevation (15). Conversely, some reports indicate a high prevalence of grade 3 and 4 enzyme elevations (exceeding 7 times the upper limit of normal) after receiving rabbit-ATG for stem cell transplantation (8). This elevation typically occurs after the first dose of ATG and resolves within 7 days, with no icterus observed (2). The precise mechanism underlying ATG-induced hepatotoxicity remains elusive. While some researchers have proposed a cytotoxic effect of the antibodies on liver cells, as a mechanism questioned by others due to the transient nature of the reaction and the prolonged elimination half-life of the medication (8, 15).

The prevalence of hepatotoxicity appears to vary among different products and the indications for which the medication is used. Interestingly, Al-Anazi et al. reported a case of enzyme elevation with horse-ATG in a patient receiving an allogeneic stem cell transplant, which resolved upon discontinuation and subsequent switch to the rabbit product (4). The exact mechanism for this adverse reaction remains to be elucidated and warrants further investigation; however, the binding of ATG to hepatocytes has been postulated as a potential mechanism (7).

It is noteworthy that our patient developed frank symptomatic hepatitis, leading to icterus and right upper quadrant pain. In light of the available literature, this presentation does not appear to be common. Our patient tolerated a rechallenge with the same product after the hepatitis was managed, without further complications.

As evidenced in Table 1, our patient's baseline liver enzymes were not within normal limits, and the observed pattern was cholestatic rather than hepatocellular. The changes in liver enzymes and bilirubin levels did not correlate with each other. The discrepancy between our

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patient's presentation and other case reports may be attributable to the prior treatment with oxymetholone before receiving ATG, as oxymetholone is known to induce a cholestatic pattern of hepatotoxicity. Although the timeline of symptom presentation does not correlate with toxicity caused solely by oxymetholone, the cholestasis in our patient may have developed as a result of synergistic toxicity between oxymetholone and ATG treatment. This hypothesis may account for the discrepancy between liver enzyme and bilirubin changes (16).

It is noteworthy that the incidence of hepatotoxicity has been studied for various immunosuppressant regimens in the treatment of AA. Patients receiving ATG monotherapy have been reported to experience elevations in liver enzymes normalized subsequently. Cyclosporine monotherapy did not induce liver toxicity, while some patients receiving both ATG and cyclosporine exhibited liver enzyme elevations that returned to normal after several weeks. Given that our patient was receiving cyclosporine, the ATG-cyclosporine combination may have partially contributed to the significant enzyme alterations (6). The clinical presentation observed in our patient warrants heightened vigilance for signs and symptoms of hepatotoxicity in patients with aplastic anemia who have previously undergone androgen therapy and are candidates for ATG treatment.

Conclusion

In conclusion, hepatotoxicity resulting from the use of immunosuppressive medications among AA patients is generally mild and transient, while being fatal in rare instances. The degree of liver toxicity can vary considerably, ranging from transient to long-lasting effects. Individual or population-specific susceptibilities to side effects may exist, and the occurrence of adverse reactions may also depend on the particular immunosuppressive agent employed.

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Ethical Approval

This research was conducted in accordance with the guidelines delineated in the Declaration of Helsinki and was approved by the Research Ethics Committee of Urmia University of Medical Sciences (approval number: IR.UMSU.REC.1402.096). The patient has provided explicit consent for the publication of this case report.

Competing interests

The authors declare that they have no conflicts of interest.

Authors' Contribution:

- Conceptualization: ZG
- Data Curation: MMA, NE
- Methodology: ZG, FG
- Investigation: MMA, NE
- Supervision: ZG, FG
- Validation: ZG, FG
- Writing—Original Draft Preparation: MMA, NE
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