ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

AZATHIOPRINE INDUCED HEPATIC VENO-OCCLUSIVE DISEASE

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ARTICLE INFO

Key words: Hepatic veno-occlusive disease, Jaundice, Hepatomegaly

Access this article online
Website: https://www.jgtps.com/
Quick Response Code:

ABSTRACT

A patient of 46 years of age was admitted in the gastroenterology department with severe complaints of tiredness, jaundice and urinary complaints. He had been taking azathioprine since 16 years after his renal transplantation surgery. He was subjected to different laboratory investigations and was diagnosed with hepatic veno-occlusive disease.

INTRODUCTION

Hepatic veno occlusive disease (HVOD) or sinusoidal obstructionis a rare adverse drug reaction of Azathioprine. It occurs normally in immunodeficient individuals and a potentially fatal disorder in which a part of the liver's tiny veins become clogged. It is a side effect of high-dose chemotherapy given before a bone marrow transplant, as well as excessive exposure to pyrrolizidine alkaloids, which are hepatotoxic. Classic signs include weight increase due to fluid retention, an enlarged liver, and raised bilirubin levels in the blood. It has an impact on both children and adults. Painful hepatomegaly, jaundice, and fluid retention manifesting as weight gain, edemas, and ascites characterize the clinical manifestation. Hepatic insufficiency with coagulopathy and hepatic encephalopathy is a possibility. Renal insufficiency with functional impairment is very prevalent. Multiple organ failure or serious bacterial infections may develop in severe situations.

HVOD is most typically associated with the conditioning regimen for hematopoietic stem cell transplantation, with 10 to 60 percent of transplant patients suffering from the disease. HVOD is a well-known complication of allogeneic and autologous hematopoietic stem cell transplantation and is classified as a condition-related toxicity. Depending on the diagnostic criteria used, the population studied and the differences in conditioning therapy used, the incidence of the condition ranges from less than 5% to as high as 70% in different reports. Understanding the pathophysiology of HVOD and creating innovative preventative and therapy strategies are crucial since it causes significant morbidity and mortality in patients receiving stem cell transplantation. The general treatment for azathioprine induced liver damage is a fibrinolytic drug Defibrotide which can act on the occluded area, lysis of the clog formed thereby increasing the blood flow to liver.

DESCRIPTION

A 46 years old male patient was admitted in the gastroenterology department with complaints of excessive tiredness, jaundice, and urinary incontinence. He had undergone renal transplantation 16 years back, his mother was the donor. He had been on treatment for diabetes, dyslipidaemia, and hypertension along with the immunosuppressants since last 16 years. His past medication history included Tab. Clonidine 0.1mg, T. Prednisolone 5mg, T. Ecospirin 75mg, T. Atenolol 50mg, T. Azathioprine 100mg, T. Atorvastatin 10mg, T. Metformin 1gm, and T. Gabapentin 300mg. the vitals were all normal for the patient. But the weight of the patient was increasing day by day from 42.1 kg from the first day to 48.6 kg in the 10^{th} day. The provisional diagnosis was Wilson's disease. But later after taking the Ceruloplasmin, Copper, and anti- mitochondrial antibody testing, the diagnosis was confirmed as immunosuppressant induced liver damage. The laboratory parameters of the patient showed declined WBC (3300cells/mm^3), the liver function tests were taken and it showed elevated bilirubin (T. Bilirubin – 14.55mg/dl, D.Bilirubin- 13.06mg/dl, I. Bilirubin – 1.49mg/dl) elevated SGOT – 119mg/dl, SGPT- 117mg/dl, ALP – 78U/L. Declined levels of albumin about 2.1g/dl and total protein declined to 4.8g/dl were found. Renal function tests showed a reduced sodium levels of 131 meq/L.

The patient was having an increased blood glucose levels and he has been switched over to insulin therapy from the day 2 since his FBS was found to be 295mg/dl. He has been treated with Inj. H. Actrapid for the next 9 days of hospital stay. The USG abdomen of the patient was taken and found that there is chronic parenchymal liver injury, along with moderate ascites and hepatocellular necrosis. On the basis of subjective and objective evidences the case was diagnosed as azathioprine induced hepato-veno-occlusive disease or sinusoidal obstructive syndrome.

The treatment given to the patient included acetyl cysteine 600mg, T. Ursodeoxycholic acid 300 mg, T. Silimarin 140mg, and multivitamins. From the 4^{th} day onwards Azathioprine was stopped and prednisolone 5mg was changed to 10 mg, then after confirmation of medicine induced liver injury from the 7^{th} day Mycophenolate sodium and Tacrolimus were added instead of Azathioprine. Due to a declining albumin level about 2.1g/dl, the patient was treated with Inj. Albumin 30% from the 4^{th} day. After switching over from Azathioprine to Tacrolimus and Mycophenolate, the patient's symptoms got improved.

He was discharged on 10^{th} day and discharge medications included, Inj. H.Mixtard 30/70, T. Tacrolimus 0.5mg, T. Aspirin 75mg, T. Ursodeoxycholic acid 300mg, T. Atenolol 50mg, T. Pantoprazole 40mg, T. Clonidine 0.1mg, T. Atorvastatin 10mg, T. Prednisolone 10mg and T. Metformin 1 gm.

Table 1: Description of HVOD and symptoms severity in patient

HEPATIC VENO OCCLUSIVE DISEASE	SEVERITY OF SYMPTOMS IN PATIENT
Latency of onset- subacute (weeks/months)/ chronic(years)	Chronic
Abdominal pain	+++
Swelling	+
Weight gain	+++ (42.3----48.6kg)
Ascites/edema/varices	++ (moderate ascites in USG abdomen)
Jaundice	++++ (bilirubin – 14.55mg/dl)
Fluid retention	++
ALT & AST elevation	+++

Mild to minimal increase in ALP	++
Damage to endothelial cells in liver, hepatocellular necrosis	Chronic parenchyma damage seen in USG abdomen
Sinusoidal obstruction in MRI	MRI NOT TAKEN

+ Indicates the presents and severity of symptoms

DISCUSSION

HVODis not merely caused by azathioprine, it can also be caused by different drugs like busulfan, cyclophosphamide, melphalan, carmustine including herbal drugs**.** These drugs may form occlusions in the pathway to the liver due to oxidative stress and this will lead to reduced oxygen in the liver cells, thereby causing liver damage. Azathioprine and its metabolites 6-Mercaptopurines may damage the endothelial cells that line the sinusoids by activated, damaged, and inflammatory. Sinusoids containing small capillary like blood vessels can form clog easily due to the smaller diameter. Narrowing of the blood vessels may be an asymptomatic change in the patients and hence the patient may develop symptoms even after the complete closure of the sinusoidal vessels, which eventually develop liver damage.

Azathioprine-induced HVOD has been reported in several studies including the patients having rheumatoid arthritis and other serious illness. It is a fatal effect of azathioprine which brings out the complete reduction in liver function. Azathioprine causes the obstruction on chronic use whereas obstruction caused by other drugs will be acute or sub-acute.

REFERENCES

1. Lemley DE, Azathioprine induced hepatic veno-occlusive disease in rheumatoid arthritis. Ann Rheum Dis. 1989; 48(4):342-346
2. Barker, C., Incidence, survival and risk factors for the development of veno-occlusive disease in pediatric hematopoietic stem cell transplant recipients. Bone Marrow Transplant 2003; 32, 79–87
3. Ortega JA, Donaldson SS, Ivy SP et al. Venoocclusive disease of the liver after chemotherapy with vincristine, actinomycin D and cyclophosphamide for the treatment of rhabdomyosarcoma. Cancer 1997; 79: 2435–39.
4. Meresse V, Hartmann O, Vassal G et al. Risk factors for hepatic veno-occlusive disease after high-dose busulfan-containing regimens followed by autologous bone marrow transplantation: a study in 136 children. Bone Marrow Transplant 1992; 10: 135–41.
5. Bisogno, A et al. Veno-occlusive disease of the liver in children treated for Wilms' tumor. Med PediatrOncol 1997; 29: 245–51.
6. Kullendorff, Hepatic veno-occlusive disease in Wilms' tumor. Eur J PediatrSurg 1996; 6: 338–40.
7. Carreras E, Bertz H, et al, Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for Blood and Marrow Transplantation. European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party. Blood. 1998 ;92(10):3599-604
8. Mohty, M., Prophylactic, preemptive, and curative treatment for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a position statement from an international expert group. Bone Marrow Transplant2020; 55**,** 485–495.
9. Fan-CQ, Sinusoidal obstruction syndrome (hepatic veno-occlusive disease). J. Clin. Exp. Hepatol**.** 2014; 4(4), 332–346
10. Helmy A. Review article: updates in the pathogenesis and therapy of hepatic sinusoidal obstruction syndrome. Aliment Pharmacol. Ther. 23(1), 11–25 (2006