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Case report

Azathiorpine-induced Idiosyncratic Liver-injury

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ABSTRACT:
Autoimmune hepatitis is a rare autoimmune disorder. The regular treatments for this disease is the administration of regular immunosuppressants like Azathiorpine, Metabolic Mycophenolic Acid in addition to steroids. The adverse effects of these immunosuppressants are poorly described in the literature. Here is the description of one case report where the patient had maximum level of severity of autoimmune hepatitis within weeks of exposure to Azathiorpine.

KEYWORDS: Autoimmune hepatitis; Azathiorpine.

CASE REPORT

A 56-year old man was admitted because of sudden increase of total and conjugated bilirubin content and abnormal increase of liver enzymes. This particular patient was admitted to the hospital with the problems of anorexia and passage of yellow-coloured urine. He was regularly treated with heptral tablets (400 mgs) to improve his liver conditions. With time, he has been diagnosed with massive ascites, peripheral edema and splenomegaly. Furthermore, he has been detected with probable autoimmune hepatitis by excluding other factors of liver injuries. The other factors include biochemical tests for anti-HAV (Hepatitis A virus), HCV (Hepatitis C virus) and HAE (hepatic artery embolization), with all results being negative in this case. Thus, azathiorpine (AZA, Generic name: Imuran) along with prednisolone was prescribed to him to improve his conditions. In addition, he had no history of heavy alcohol consumption.

Physical examination shows massive ascites, cirrhosis and total organ failure after the azathiorpine uptake. Biochemical tests show increased amount of liver enzymes (SGOT and SGPT) and increased prevalence of autoantibodies (ANA and ASMA). Notably, the bilirubin content is highly increased during the treatment. He was diagnosed with the diabetic problem. That is why; carbohydrate-restricted diet was medicated to him. Initially, he was diagnosed with relatively lesser amount of total and conjugated bilirubin (7.8 and 5.2 mg/dl). This was intensively increased during the course of study *viz,* 23.21 and 15.51 mg/dl at the end stage of liver disease as explained in Fig. 1 and Table 1. After the initial exposure of Imuran (50 mg), the systemic function of kidney ceased with a severe drop in blood pressure. Most dangerously, neuronal ammonia content has rapidly increased from 13 umol/L to 158 mcg umol/L finally leading to severe and deadly hepatic encephalopathy. Other clinical investigations showed related with this comatose 'on ventilatory support' patient: PT

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(Prothrombin Time)- 26.3, INR (International normalization ratio)- 2.37, Na^+- 144.1, K^+- 3.59 mEq/L; Creatinine- 1.46, Urea- 82 mg/dl; DCs(Dendritic Cells) showing polymorphonuclear leukocytosis, TLC (Total Lung Capacity)- 15,800/cumm; raised Temp; Icterus (++); Respiratory rate - 25/min; Pulse- 90/min; Blood Pressure- 130/90 mm of Hg as explained in Box 1. Within 2-weeks of commencing this immunosuppressant, there was no remission of inflammation, but rather other organs of the patients like kidney and blood vessels started to severely affect progressing to hepatic encephalopathy, acute kidney injury and sepsis. Thus, this patient was considered to be a true non-responder to the standard treatment. There was no chance for the alternative therapies like employing the other immunosuppressant or liver transplantation because in one week he was recognized as 'Code Blue' and all the other organs fail to work within next one week.

Figure 1.Increasing amount of conjugated bilirubin with increasing amount of azathiopurine.

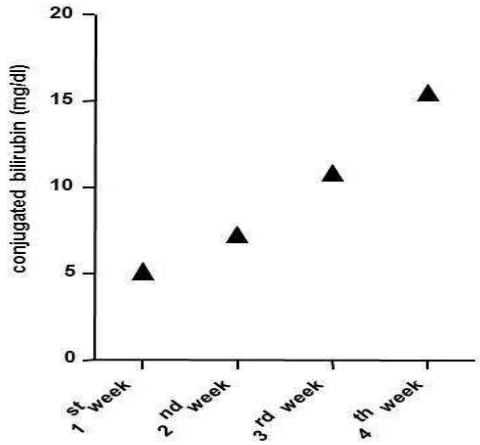

Table 1.Description features of biochemical features of liver.

Weeks	Conj. Bil. (mg/dl)	Total Bil.(mg/dl)	SGOT	SGPT	Physical features
1st week	5.2	7.8	increased	increased	Anorexia and yellow-coloured urine
2nd week (Start of AZA)	7.6	13.2	increased	Increased	ascites
3rd week	12.2	18.6	no particular mention	no particular mention	kidney failure, blood pressure drop and sepsis
4th and final week	15.51	23.21	no particular mention	no particular mention	autoimmune encephalopathy and death

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Medication: Azathiorpine (50 mg daily)

Severity: highest level

Latency: none

Recovery: none

Other medications:

- **Hydrocortisone drug Efcorlin and injection (both 100 mgs)**
- **Wysolone (10, 20 followed by 30 mgs)**
- **Lasilactone (50 mgs) and Spilactone (50 mgs) for improving cirrhotic condition**
- **Actrapid insulin injection and Eltroxin drug (50 mgs)**
- **Inderal and Dytor (10 mgs) to treat blood pressure**

In most of the cases, the use of AZA leads to increase of serum aminotransferases while using for longer duration[1,2]. This particular report describes the malice effect of this immunosuppressant within weeks of exposure.

Azathiorpine is an imidazolyl derivative and prodrug (a precursor of active drug) of 6-mercaptopurine and 6-thioinosinic acid. This conversion into mercaptopurine and finally active metabolite takes place in liver and it inhibits lymphocyte functions by antagonizing purine metabolism. With its anti-inflammatory activity, it inhibits T cell proliferation and hypersensitivity reaction. In simple words, this drug is used to decrease body's natural immunity. That is why; it is used in case of transplantation patients, where the normal immune system needs to be suppressed to prevent rejection of transplanted organs. Additionally, this drug is also used in several inflammatory conditions (e.g. rheumatoid arthritis, inflammatory muscle diseases) and autoimmune disorders (e.g. inflammatory bowel disorder, psoriasis and autoimmune hepatitis). According to previous studies, AZA is leading to milder hepatotoxicity like elevations of liver enzymes[1,2]. It is also seen that this immunosuppressant leads to severe problems when used for other non-hepatic disorders like, psoriasis[3], rheumatoid arthritis(RA)[4] and Crohn's disease[5, 6]. In most of the case, it leads to intrahepatic cholestatic injury with long-term use in case of transplant patients[7, 8] and sinusoidal dilation for RA patients[9]. All of these effects are seen after the chronic use of this drug. There is only one report where the disease is finally culminating into end-stage liver disease after the medication AZA for 8 long years[10].

This is a case report which describes the adverse effects of immunosuppressant drug Azathiorpine. In other words, the physicians should be careful while medicating this drug. There should be also a concern if AZA should be used for suppressing liver-related autoimmune disorders. As an alternative, MMF (Mycophenolate Mofetil) can be medicated.

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