Rare Case of Drug Induced Autoimmune Hepatitis

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Introduction

World Journal of Hepatology emphasizes Drug Induced Autoimmune Liver Disease (DIALD) is a poorly defined, under reported and underestimated liver disease emphasizing the importance of reporting such case reports. The cause is unknown, but known to be triggered by external factors such as drugs, viruses and herbs.[1]

Figure 1 shows a list of drugs associated with DIALD. Symptoms can range from being asymptomatic, to anorexia, fatigue, abdominal pain, itching and weight loss. Drug induced liver injury is characterized according to three types; hepatocellular, cholestatic, or a mixed injury type. Each determined by lab abnormalities as seen below:

Hepatocellular injury
- Elevation of serum aminotransferases > alkaline phosphatase
- Serum bilirubin may be elevated

Cholestatic Injury
- Elevation of serum aminotransferases < alkaline phosphatase
- Serum bilirubin may be elevated, at times very high levels

Acute Liver injury defined as abnormal liver tests for less than 3 months and chronic if longer than three months. Diagnosis requires thorough history and details of drug dosing. Also important to obtain imaging to rule out biliary obstruction and to exclude venous outflow obstruction, such as Budd- Chiari Syndrome.

Females are more susceptible to DIALD, especially if antinuclear antibody positive. Additionally, patients with the human-leukocyte antigen class II, specifically the DRB1 locus, are more susceptible to AIH.[2] If patient presents with hypersensitivity reaction, may have peripheral eosinophilia, compared to those with mononucleosis like illness, may have lymphocytosis and atypical lymphocytes.

Well Established Drugs: Minocycline, Nitrofurantoin, Oxyphenisatin, alpha-methyl-dopa, clometacin
Emerging Drugs: Statins
Biologic Agents: Infliximab
Others: adalimumab, etanercept, efalizumab, ipilimumab
Less frequently reported: Atomoxetine, diclofenac, fenofibrate, pemoline, phenprocoumon, dihydralazine, tielinic acid, benzarone

Figure 1: Drugs associated with DIALD

Case Description

65 year old female, with history of hypertension, alcohol use but quit in October 2021 and sigmoid diverticulosis, presented to the office clinic with dark urine, unintentional 10lb weight loss as of 2 months ago, pale colored loose stools and new abnormal lab findings as seen in Figure 2. Patient's abdominal ultrasound showed cholelithiasis and hepatic hemangioma. Patient's home medications included Lipitor, which had a dose increase from 10mg to 40mg in August 2021. Additionally, the patient was started on Norvasc 5mg in August 2021. Both medications were discontinued on 12/10/2021. Patient had resolution of liver enzymes after discontinuation of medications as seen in Figure 2.

	12/14/2021	12/23/2021		12/14/2021
AST	699	379	**IgG**	1885
ALT	657	519	**IgM**	298
ALP	1079	731	**ANA**	POSITIVE
Total Bilirubin	7.3	2.1	**Anti-Smooth Muscle**	53
Direct Bilirubin	6.04	1.4	**Anti-Mitochondrial**	115

Figure 2: Timeline of patient's lab abnormalities

Discussion

In 2011, classifications of the combination of drug induced liver injury (DILI) and autoimmune hepatitis (AIH) were established. AIH with DILI is a reactivation of known AIH. DI-AIH, no diagnosis prior to presentation, immune reaction that becomes chronic requiring immunosuppressants. Immune mediating-DILI presents as acute or chronic liver injury, depending on duration of drug intake. Liver injury may resolve with drug withdrawal or hepatocellular or mixed type liver damage that does not improve after drug withdrawal.[3] The latter requires immunosuppressants and is the most common presentation seen.[4]

Liver biopsy to assess the histology is not necessary for the diagnosis does assist in ruling out other causes of hepatitis, such as Wilson disease and hemochromatosis as seen in Figure 3 and 4.

A rise in DIALD has resulted from growing use of drugs like statins.[1] Statins are a well known drug in preventing cardiovascular events. There was an increase in statin use from 18 to 26% from 2003 to 2012, additionally, 93% of patients with hyperlipidemia were found to be taking a statin.[5] Clinical studies have shown adverse hepatic function with statins, representing 0.5 to 3% of patients taking them.[6]

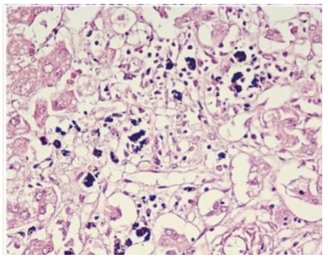

Figure 3

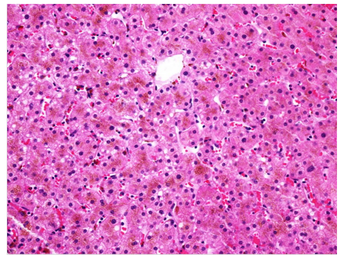

Figure 4

Figure 3: Wilson's disease, cytoplasmic coarsely granular cola-colored granules stained with orcein demonstrating copper[10]
Figure 4: iron-rich granules are distributed around bile canaliculi[11]

Amongst statin induced DI-AIH, more cases involving atorvastatin have been reported.[7] There are reports of DI-AIH arising after 16 months of atorvastatin and 3 months of ezetimibe therapy, in which symptoms resolved after cessation of both drug and another report of DI-AIH after 3 months of atorvastatin therapy despite the patient having been treated with other statins for over 3 years.[8]

Currently, there are cases of amlodipine causing DI-AIH, in one case, an isolated liver enzymes elevation was noted within 4 days of use and resolved after 5 days of cessation.[9] The exact mechanism is not known, although, other similar case reports have been noted.

Conclusion

As there is a lack of information regarding DIALD and with the rise of cases, it is becoming increasingly important to report such cases. More specifically, with the increased use of statins and very few cases reported of amlodipine causing DIALD, more awareness should be made regarding these commonly used drugs.

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