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Case Report
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Severe Liver Injury Induced by Minocycline in Hepatitis B Patient: A Case Report

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Abstract

Drug-induced liver injury is an acute and potentially severe adverse effect. There are few reports on the adverse reactions caused by minocycline. It has been reported that long-term high-dose minocycline causes liver injury, which is characterized by abnormal liver function and elevated alanine aminotransferase. However, there are few reports of severe liver dysfunction caused by minocycline in short-term conventional doses. This article introduces relevant cases for clinical reference.

A 32-year-old female patient took minocycline for acne, resulting in subacute hepatic failure. After treatment, coagulation function and liver function have improved.

Keywords: Minocycline; Drug-induced liver injury; Double plasma molecular adsorption system; Chronic Hepatitis B; Immunomodulatory

Introduction

Drug-Induced Liver Injury (DILI) is a common adverse drug reaction, and it can lead to liver failure and even death. DILI is traditionally classified as intrinsic (or direct) *vs.* idiosyncratic [1]. Intrinsic DILI is typically dose-related, but idiosyncratic DILI is not. Minocycline-induced liver injury belongs to idiosyncratic DILI. The pathogenesis of DILI is related to the chemical properties of the drug, especially lipophilicity and drug biotransformation. This exposes the liver to reactive metabolites which can covalently bind to proteins, induce oxidative stress, activate signal transduction pathways and result in organelle stress, interfere with bile acid transport and either lead to lethal consequences or induce adaptive responses which dampen these processes [1].

In mainland China, the annual incidence of DILI in the general population is estimated at 23.80 per 100,000 persons, higher than that reported from Western countries. Hepatocyte injury (51.39%) occurred in most DILI cases, followed by mixed injury (28.30%) and cholestatic injury (20.31%). The incidence of chronic DILI was 13.00%, and 1.08% of patients progressed to hepatic failure [2].

Minocycline is a semi-synthetic antimicrobial which, in addition to its role in infectious disease, has garnered roles in the management of acne vulgaris, acne rosacea, and a variety of novel clinical applications [3]. In the context of a potentially expanding population on protracted treatment courses, immune-mediated adverse effects, although rare, remain important to recognize. Such reactions were first described in the 1990s, when the spectrum of reactions was subdivided into four categories: systemic lupus erythematosus-like, autoimmune-like hepatitis, vasculitis, and hypersensitivity reactions [4].

From the clinical side, DILI can result in illness, hospitalization and even life-threatening liver failure, death or need for liver transplantation. Besides, diagnosis of DILI is one of the most challenging liver disorders faced by hepatologists because of its relatively low incidence, the variety in its clinical phenotype, as well as the absence of specific biomarkers.

Case Presentation

A 32-year-old Chinese female complained of negligence, lack of strength, and yellowing of her skin and eyes. A week ago, she started taking minocycline capsules 50 mg twice a day and vitamin B6 tablets 10 mg twice a day to treat acne. During the treatment, she noticed that her skin and urine were yellow-stained, and she was accompanied by bloating. She said that no other drugs were used

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during the taking of minocycline capsules and vitamin B6 tablets. The patient said she was a healthy carrier of hepatitis B virus. More importantly, the patient's annual physical examination report showed normal liver and kidney function. She reported no previous history of hypertension, diabetes, or coronary heart disease. She denied that she had a history of infectious diseases such as tuberculosis. She also denied a history of surgical trauma, blood transfusions, and drug allergies.

The patient was afebrile (temperature 36.5°C). Her pulse rate was 104 Beats/min, and blood pressure was 118/78 mmHg. On physical examination, the patient's skin color was dark and yellow, and the color of the sclera was slightly yellow. No other abnormalities were found in other physical examination.

In the abdominal scan CT-assisted examination, the patient was found to have fatty liver, cirrhosis, and possible nodules in the liver parenchyma. B-ultrasound examination revealed peritoneal effusion, gallbladder wall edema and thickening, and cirrhosis.

Significantly elevated transaminase levels with Aspartate Aminotransferase (AST) of 639 U/L and Alanine Aminotransferase (ALT) of 581 U/L were found. The patient's Alkaline Phosphatase (ALP) was 177U/L. Total bilirubin was 184.7 μmol/L (direct bilirubin of 86.8 μmol/L, indirect bilirubin of 97.9 μmol/L). The albumin content was 25.60 g/L. Coagulopathy test results showed that plasma Prothrombin Time (PT) of 28.90 sec, PT-INR of 2.58, PTA of 22.30%, Activated Partial Thromboplastin Time (APTT) of 49.50 sec, Plasma Fibrinogen (Fbg) of 0.75 g/L and plasma Thrombin Time (TT) of 28.90 sec.

The patient was diagnosed with hepatitis B from Hepatitis B testing (hepatitis B surface antigen quantification of 247.980 IU/L, hepatitis B surface antibody quantification of 0.000 mIU/L, hepatitis B e antigen quantification of 18.796S/ CO, Hepatitis B e antibody quantification of 1.720S/CO, Hepatitis B core antibody quantification of 8.000S/CO). Hepatitis A and hepatitis E test results were negative.

Immunoglobulin reports showed lg G of 21.19 g/L, lg A of 4.66 g/L, lg M of 1.96 g/L, complement 3 of 0.13 g/L and complement 4 of 0.04 g/L. The test results of other types of antibodies were all negative.

The Thromboelastogram (TEG) results suggested that the patient's fibrinogen function and platelet function were diminished.

Diagnosis

(1) Chronic hepatitis B; (2) subacute liver failure

The patient's complexion was dark yellow and the yellow sclera suggested abnormal liver function. Liver function tests, CT results, and B-ultrasound results were consistent with clinical symptoms. Although the patient had hepatitis B, we can learn from the health check that her liver function was normal. In addition, when asked about the patient's medication history, we did not find any drugs that affect liver function. Therefore, the patient was a healthy carrier of hepatitis B virus. The patient's working environment, eating habits, living conditions and other factors will not induce hepatitis B.

Recently, the patient reported she took minocycline capsules 50 mg twice daily for the treatment of acne. However, Health Canada had received three reports of adverse reactions to liver injury induced by minocycline in adolescents [5]. The Roussel Uclaf Causality Assessment Method (RUCAM) score [6] of 6 indicated that the patient's DILI was probable. Combined with clinical symptoms, laboratory tests, and patient medication history, we highly suspect that the patient's liver injury was induced by minocycline. Initially, the patient's R [1] of 8.2 indicated hepatocellular pattern.

Figure 1: The picture of patient undergoing DPMAS in combination with RRT.

Treatment

Patients underwent comprehensive treatment in the ICU, which included restoring liver function, reducing bilirubin, correcting coagulation. Therapeutic drugs included acetylcysteine injection, reduced glutathione injection, adenosylmethionine injection, polyene phosphatidylcholine injection, entecavir dispersible tablet.

During the hospital stay, we received 16 reports of patient's coagulation function reaching critical value. The patient received a total of 12 blood transfusions. A total of 2,350 ml of type A Rh-positive frozen fresh plasma and 57 IU of cryoprecipitate were infused. After targeted transfusion, supplementation of coagulation factors, coagulation function was improved.

The patient's blood type has type A Rh-negative blood. Plasma matching was difficult when the patient received plasmapheresis. Therefore, we used Double Plasma Molecular Adsorption System (DPMAS) in combination with RRT (Renal Replacement Therapy).

We performed a puncture procedure in the patient's right femoral vein to place a vascular access. DPMAS was applied using the Prisma FLEX device (Gambro Lundia AB, Sweden). Briefly, the blood first flowed through the TPE2000 plasma separator (Gambro Dialysatoren GmbH, Shanghai) after being pumped out of the body, and the plasma then flowed sequentially through the ion exchange resin (BS330, Zhuhai Jianfan Biotechnology Co., Ltd) and the neutral macroporous adsorption resin (HA330-II, Zhuhai Jianfan Biotechnology Co., Ltd), and was mixed with the blood cells and infused back into the patient. Blood pumping speed was 120 mL/min, the plasma separating speed was 37.5 mL/min, and the plasma separation ratio was 22%. The plasma volume for a single treatment by DPMAS was approximately 5.7 L. DPMAS consists of blood and plasma circuits and is shown in Figure 1.

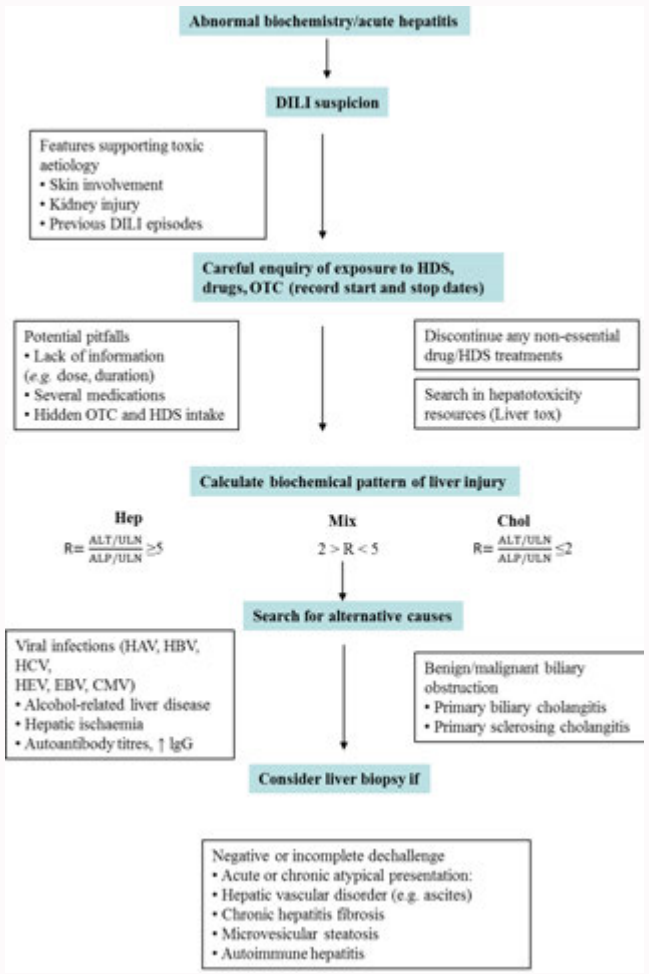

Figure 2: Stepwise approach to Drug-induced liver injury diagnosis. ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; Chol: Cholestatic Injury Pattern; CMV: Cytomegalovirus; EBV: Epstein-Barr Virus; HAV: Hepatitis A Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HDS: Herbal and Dietary Supplements; Hep: Hepatocellular Injury Pattern; HEV: Hepatitis E Virus; IgG: Immunoglobulin G; Mix: Mixed Injury Pattern; OTC: Over-the-Counter Drugs; ULN: Upper Limit of Normal

After DPMAS treatment, the patient received Renal Replacement Therapy (RRT) treatment in the form of Continuous Venous-Venous Hemodiafiltration (CVVHDF). The blood flow rate was 200 ml/min, the pre-dilution speed was 2000 ml/h, the post-dilution speed was 600 ml/h, the dialysis rate was 600 ml/h, and the calcium chloride rate was 8 ml/h to 12 ml/h. The RRT treatment time was 8 h.

On the third, fourth, and sixth days after hospitalization, the patient received three DPMAS treatments. Coagulation function and liver function were the focus of monitoring during treatment.

Discussion

Because of the diversity of DILI clinical phenotype, and the lack of specific biomarkers, how to accurately diagnose DILI is critical. Meanwhile, factors such as age, gender, ethnicity, alcohol and pregnancy, chronic disease, drug dosage and metabolism all contribute to the incidence of DILI. These factors increase the difficulty of distinguishing DILI (Figure 2).

The potential immunomodulatory effects of tetracycline antibiotics have also been reported in recent years. Minocycline

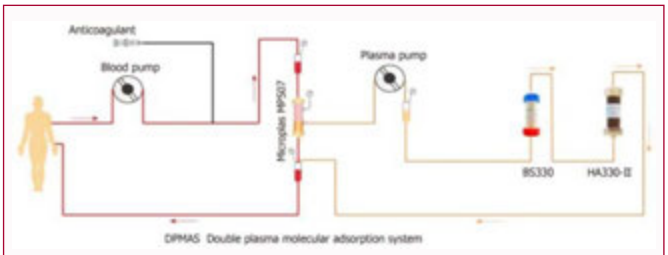

Figure 3: Double plasma molecular absorption system flowchart.

Table 1: Summary of liver function tests.

NO.	ALT (U/L)	AST (U/L)	ALP (U/L)	R
1st	307	272	94	8.2
2nd	151	108	48	7.9
3rd	83	53	40	5.2
4th	73	45	48	3.8
5th	58	49	52	2.8
6th	54	50	56	2.4
7th	63	110	80	2
8th	70	137	87	2
9th	65	127	77	2.1

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; ULN: Upper Limit of Normal

inhibits the proliferation of T lymphocytes, inhibits the proliferation of microglia, monocytes/macrophages [7], and inhibits the chemotaxis of neutrophils [8]. Garrido-Mesa et al. [9] found that minocycline can significantly inhibit the formation of some chemokines and pro-inflammatory factors, such as IL-6, IL-8, IL-17, TNFα, IL-1β. Compared with other tetracyclines, minocycline showed significant immunomodulatory effects. These studies suggested a potential immunosuppressive effect of minocycline.

The patient took minocycline capsules to treat acne without knowing that she had chronic hepatitis B, which led to the induction of chronic hepatitis B outbreak by minocycline. In the early stage of hepatitis B, the patient's liver function deteriorated rapidly, the coagulation function was impaired or even reached an extreme value, and bilirubin was elevated to the point where conventional treatment cannot be used. The patient's symptoms and laboratory tests confirmed this inference.

The artificial liver support system is based on the strong regenerative capacity of hepatocytes. Through mechanical, physicochemical and biological devices *in vitro*, it removes all kinds of harmful substances, supplements essential substances, improves the internal environment, and creates conditions for liver cell regeneration and liver function recovery. DPMAS is one of the Non-Bio Artificial Liver (NBAL). The principle of DAPAS is to use plasma separation technology to filter plasma and then adsorb it through a perfusion device to treat diseases such as liver failure and hyperbilirubinemia (Figure 3). A series of studies have shown that DPMAS has a strong advantage in improving patients' clinical symptoms, coagulation function and liver function, and improving treatment efficiency. In addition, DPMAS can enhance the elimination of harmful substances such as inflammatory mediators, save plasma resources, and reduce the phenomenon of simple plasma exchange rebound. DPMAS avoids the risk of allergic and blood-borne diseases caused by plasma exchange and significantly improves the patient's prognosis and

Table 2: Summary of coagulation function tests.

NO.	PT (sec)	PT-INR	PT% (%)	APTT (sec)	APTT_rati	Fbg (g/L)	TT (sec)
1st	28.9	2.58	22.3	49.5	1.74	0.75	28.9
2nd	46.3	4.2	13.1	>180.00	/	0.68	>150.00
3rd	>150.00	/	/	>180.00	/	0.5	55.3
5th	35.7	3.21	17	>180.00	/	1.48	49.3
6th	27.4	2.45	23.9	119.7	4.21	1.64	36.5
7th	>150.00	/	/	>180.00	/	1.2	>150.00
8th	22.8	2.02	30.3	53.2	1.87	1.42	21.4
9th	25.5	2.27	26.2	52.1	1.83	1.51	19.6
10th	30.3	2.71	22.4	121	4.26	1.23	42
11th	32.4	2.91	19.3	>180.00	/	1.19	>150.00
12th	21.1	1.87	33.4	50.3	1.77	1.8	22.1
13th	29	2.59	22.2	92.5	3.26	1.28	55.6
14th	21.4	1.9	32.8	52.7	1.86	1.28	20.9
15th	26.6	2.37	24.9	69.1	2.43	0.69	24.9
16th	25.4	2.26	26.4	81	2.85	0.61	26.8
17th	26.6	2.37	24.9	75.6	2.66	0.7	35.8
18th	29	2.59	22.2	79.7	2.81	0.68	36.72
19th	27.5	2.45	23.8	104.4	3.68	1	44.5
20th	23.7	2.11	30.5	65.8	2.32	0.88	28.8
21st	24.7	2.2	27.3	80.3	2.83	1.07	28.9

PT: Prothrombin Time; PT-INR: Prothrombin Time International Normalized Ratio; APTT: Activated Partial Thromboplastin Time; Fbg: Fibrinogen; TT: Plasma Thrombin Time

Table 3: Summary of serum bilirubin content.

NO.	Total bilirubin (μmol/L)	Direct bilirubin (μmol/L)	Indirect bilirubin (μmol/L)
1st	184.7	86.8	97.9
2nd	234.2	102.6	131.6
3rd	165.6	62.8	102.8
4th	143	51.5	91.5
5th	207.8	72.9	134.9
6th	169.7	67.8	101.9
7th	176.9	68.5	108.4
8th	170.3	80.6	89.7
9th	173.1	73.2	99.9
10th	181.5	76.6	104.9

promotes the treatment of liver failure [10,11].

After treatment, the patient's ALT value decreased significantly, from hepatocellular injury pattern to cholestatic injury pattern (Table 1). Although the patient's current coagulation test index is still above the upper limit, the coagulation function tends to be stable and has significantly improved compared with the time of admission (Table 2). Due to the impaired status of primitive liver function in patients with hepatitis B, the patient's bilirubin is still overrun (Table 3).

This case report highlights the importance of a detailed drug history when faced with a patient with liver dysfunction and the significant hepatotoxic potential of a widely used drug such as minocycline. After finding the cause, an effective treatment can control the patient's condition, preventing the further deterioration of health, and also attainment of enough recovery time.

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