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Trimethoprim-Sulfamethoxazole-Induced Hepatitis in Mixed Connective Tissue Disease

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ABSTRACT

Trimethoprim-Sulfamethoxazole (*TMP-SMZ*) *is associated with severe hepatic toxicity or liver failure. We present a case of severe hepatic toxicity for whom TMP-SMZ was prescribed as part of treatment for mixed connective tissue disease* (*MCTD*). *TMP-SMZ was used to prevent complications from steroid therapy*, *but fever and hepatic toxicity developed with repeated TMP-SMZ medication. While the drug lymphocyte stimulation test* (*DLST*) *for TMP-SMZ showed negative*, *the genotype for N-acetyltransferase* 2 (*NAT*2) *showed type* *6/*7, *which is the slow acetylating type for NAT*2 *activity. This finding for NAT*2 *genotype and the patient's clinical history lead us to speculate that her fever and hepatic toxicity were caused by TMP-SMZ.*

***Keywords*:** *Hepatic Toxicity*, *Mixed Connective Tissue Disease*, *N-Acetyltransferase* 2, *Trimethoprim-Sulfamethoxazole*

1. Introduction

Hepatic side effect of Trimethoprim-Sulfamethoxazole (TMP-SMZ) is recognized in clinical, and usually mild [1,2]. Severe hepatic damage by TMP-SMZ is rarely seen, however, the cause of which is difficult to be traced, because of the complexity of clinical course [3]. On the other hand, it is not clear whether the patient with collagen disease, especially mixed connective tissue disease (MCTD), is easier to complicate hepatic toxicity by TMP-SMZ. We present a case report of MCTD, who complicated fever and hepatic toxicity, and this toxicity were caused by TMP-SMZ.

2. Case Report

A 14-year-old Japanese woman developed the subjective symptoms of Raynaud's phenomenon in February 2007 and was complicated with butterfly rush, muscle power weakness and arthralgia. The patient had no previous history of illness, nor was anyone with collagen disease in her family. She came to the outpatient clinic of the Department of Clinical Immunology, Saiseikai Nakatsu Hospital, in May 2007. Laboratory examination results showed positivity for anti-nuclear antigen (x2560), and anti-U1-RNP antibody (167.6 Index). Other antibody findings were: anti-DNA antibody, 3.1 IU/ml; anti-Sm antibody: 41.4 Index. The patient was diagnosed with Mixed Connective Tissue Disease (MCTD), and further examination revealed that she was complicated with pulmonary artery hypertension. Steroid therapy with a dosage of 1mg/kg/day of prednisolone was initiated on June 26th. Several oral drugs were used in combination for the prevention of complications caused by the steroid therapy, that is, TMP-SMZ (Bactar®) (480 mg/day) for PCP, atorvastatin calcium (Lipitor®) for hyperlipidemia, and warfarin potassium for vessel thrombosis. Beraprost sodium was used for treatment of pulmonary hypertension. On August 8th, the patient developed chills and high fever (38˚C) and showed abnormal hepatic transaminase data (max AST/ALT, 1393/1550 IU/l). She was transferred to the Clinical Immunology Division, Kobe University Hospital, on August 13th for further examinations.

On physical examination at the time of her transfer, we noted overall slight redness of the skin, moon face with butterfly rash on her face, and swelling of the fingers. The liver edge was palpable at one finger's breadth below the central costal margin. The rest of the physical examination test showed no abnormalities. Vital signs were: blood pressure, 100/58 mmHg; pulse rate, 96/min; body temperature, 37.9˚C; respiratory rate, 16/min. The blood count test showed white blood cells, 7100/μl; hemoglobin, 11.4 g/dl; platelet count, 14.1 × 10^4/μl. The serological test results included some abnormal data: AST, 283 IU/l; ALT, 769 IU/l; ALP, 432 IU/l; total

bilirubin, 1.3 IU/l; CRP, 1.41 mg/dl. Hepatic image test consisting of CT and ultrasound echogram showed only the presence of fatty change of the liver. It was difficult at that time to find out the exact cause of hepatic toxicity. After admission, the patient was prescribed TMP-SMZ (480 mg/day), and warfarin for protection against pneumocystis pneumonia, and warfarin for prevention from embolism of pulmonary hypertension. On August 24th, she an attack of high fever (40˚C), which was again complicated with abnormal transaminase levels. After cessation of administration of these two drugs, her body temperature and hepatic function returned to normal. Warfarin was prescribed again there were no clinical symptoms of toxicity. The drug lymphocyte stimulation test (DLST) for TMP-SMZ showed negative results. The genotype analysis for N-acetyltransferase 2 (NAT2), performed by BML, Inc. (Tokyo, Japan), showed that the patient's NAT2 type was *6/*7, which is the slow acetylating type for NAT2 activity. In view of the NAT2 genotyping result and the patient's clinical history, we speculate that her fever and hepatic toxicity were due to TMP-SMZ (**Figure 1**).

3. Discussion

The case presented here involved the occurrence of complicating hepatic toxicity during the treatment for Mixed Connective Tissue Disease (MCTD). We speculate that TMP-SMZ was the causative drug for the severe hepatic toxicity.

The incidence of hepatic toxicity for TMP-SMZ is not notably higher than that for other antibiotics with a risk of 0.3 - 1/10,000 [3,4]. On the other hand, numerous cases of severe hepatic toxicity or fulminant hepatitis caused by TMP-SMZ have been reported [5-9], most of which were complicated by the use of TMP-SMZ as an anti-biotic drug for infectious disease. The mechanism of TMP-SMZ-induced hepatitis remains to be clarified [3], but several possibilities have been put forward. The first one is that in cases proven by the positive DLST results, TMP-SMZ-induced hepatitis is likely to be connected with the immune-mediated mechanism [10]. The second one is that some other cases can be explained in terms of idiosyncrasy, which accounts for differences among individuals in terms of drug metabolization. For the third possible mechanism, a genetic predisposition has been postulated [11].

As for the genetic factor, N-acetyltransferase 2 (NAT2) is the representative gene for the metabolization of TMP-SMZ [12], and plays an important role in the metabolization of sulfamethoxazole to N-acetylsulfamethoxazole. Theoretically, a decrease in NAT2 enzymatic activeity would result in the side effect, and this enzymatic activity depends on the NAT2 genotype. In fact, NAT2

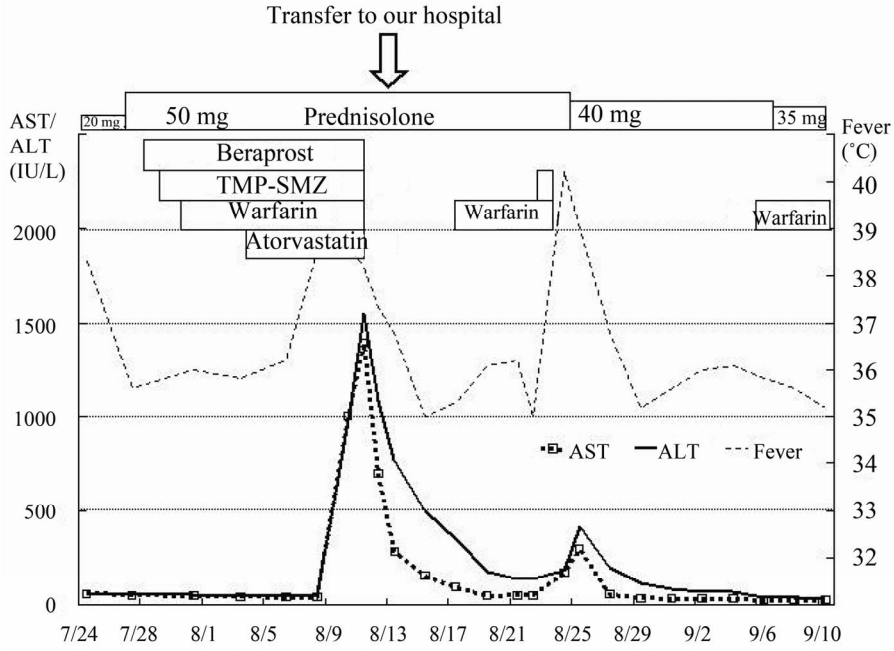

Figure 1. Clinical course: Fever and elevation of liver transaminase recurred in conjunction with the TMP-SMZ medication. On August 8th, the patient developed high fever, and showed hepatic dysfunction under the subscription of beraprost sodium, TMP-SMZ, warfarin potassium, and atorvastatin. These for subscription were stopped soon. After the re-administration of TMP-SMZ and warfarin potassium, high fever and hepatic dysfunction were occurred again on August 24th. These two drugs were stopped again. There was no fever under use of warfarin only which was started to be taken on September 5th.

consists of four genotypes, *i.e.* NAT2*4, NAT2*5, NAT2*6, NAT2*7, with NAT2*4 being the fast metabolizing genotype in comparison with the other three genotypes. Some studies have demonstrated the relationship between NAT2 genotype and NAT2 activity [12,13], in which the genotype without NAT2*4 is low in activity compared with the genotype carrying NAT2*4. The slow acetylator type, which is defined as the genotype without NAT2*4, is strongly connected with the adverse effect of TMP-SMZ; for example, 90% of patients complicated with hypersensitivity reactions to TMP-SMZ were identified as possessing the slow acetylator [7]. These findings imply that analysis for NAT2 genotype can be useful for prediction of adverse reactions to TMP-SMZ.

For the application of the NAT2 analysis to collagen disease, it is important that some drugs are involved in NAT2 metabolization. Salazosulfapyridine (SASP) is an effective drug for treating rheumatoid arthritis, while isoniazid, also known as isonicotinylhydrazine (INH), is also a key drug for preventing tuberculosis during immunosuppressive therapy for collagen disease. These two drugs are known to metabolize via the NAT2 pathway, in other words, the NAT2 genotype affects the efficacy of SASP [14], or the serum drug concentration of INH [15]. However, to the best of our knowledge, there are very few studies about the relationship between TMP-SMZ and NAT2 metabolization in collagen disease. Soejima *et al*. [16] reported on the rate of severe adverse effects caused by daily oral TMP-SMZ prescription in 57 SLE patients, of whom the ones possessing the slow acetylator suffered significantly adverse effects including hepatic toxicity. Since only 10% of the Japanese are classified as possessing the NAT2 slow acetylator type [17], the specific population of patients will be suffered by this adverse effect.

In the case reported here, the NAT2 genotype was the hetero type consisting of *6/*7, which is classified as a slow acetylator. The findings for our case are compatible with those previously reported in that they showed high frequency of hepatic toxicity for the NAT2 slow acetylator genotype [7,12,16]. In view of the growing need for TMP-SMZ medication to prevent pneumocystis jiroveci pneumonia infection in collagen disease, further studies are required to investigate the relationship between NAT2 genotype and the adverse effects of TMP-SMZ. On the basis of our investigation, we recommend using the NAT2 genotype test before administering TMP-SMZ to determine the risk of adverse effects.

4. Conclusions

We reported a case of MCTD, who complicated fever and hepatic toxicity, and this toxicity were caused by TMP-SMZ. We recommend using the NAT2 genotype test before administering TMP-SMZ to determine the risk of adverse effects.

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Abbreviations:

ALT, alanine aminotransferase;

AST, aspartate aminotransferase;

Atrovastatin, atrovastatin calcium;

Beraprost, beraprost sodium;

TMP-SMZ, Trimethoprim-Sulfamethoxazole;

Warfarin, warfarin potassium.

