Isoniazid-induced Acute Liver Failure during Preventive Therapy for Latent Tuberculosis Infection

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Abstract

Treating latent tuberculosis infection is a strategy for eliminating tuberculosis, and isoniazid is recommended as preventive therapy. However, concerns have been raised regarding the application of isoniazid due to its toxicity, particularly hepatotoxicity; however, biochemical monitoring is not routinely performed during treatment. We herein present a case of fatal isoniazid-induced acute liver failure. The patient’s liver function was not periodically examined and isoniazid therapy was continued for 10 days despite the onset of symptoms associated with hepatitis. The patient died four months after hospitalization. It is essential to consider the potential toxicities of isoniazid and establish strategies to prevent acute liver failure.

Key words: isoniazid (INH), latent tuberculosis infection (LTBI), drug-induced liver dysfunction, acute liver failure, drug-induced lymphocyte stimulation test (DLST)

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Introduction

The majority of cases of active tuberculosis (TBc) in countries with a low incidence of TBc are considered to be caused by reactivated latent tuberculosis infection (LTBI) (1-3). Treating patients with LTBI in order to prevent the development of active disease is an essential strategy for eliminating TBc. In general, isoniazid (INH) therapy is recommended for 6-12 months (4, 5), with an efficacy of approximately 90% among patients who complete treatment (1). However, there are concerns regarding the application of INH due to the potential for hepatotoxicity, ranging from asymptomatic elevation of liver enzymes to severe hepatitis, although biochemical monitoring is not routinely performed. In this study, we present the case of a healthy 53-year-old Japanese man who died of acute liver failure during the course of INH therapy.

Case Report

We herein present the case of a 53-year-old Japanese man diagnosed with LTBI. The patient had previously been in good health and worked as a language teacher. However, one of his students was diagnosed with active TBc, and everyone who came into contact with the TBc patient underwent medical examinations, including chest X-ray studies and QuantiFERON-TB2 G blood tests (QFTs). Although the current patient had no symptoms of active TBc and his chest X-ray was normal, the QFT was positive. Therefore, a diagnosis of recently infected TBc was made, and the need for adequate prophylactic treatment to reduce the risk of active TBc was explained to the patient. Prior to treatment, the findings of liver function tests were normal. INH was subsequently started at a daily dose of 300 mg; however, 70 days later, he developed jaundice and general malaise. Nevertheless, the INH therapy was continued for an additional 10 days, after which the patient visited his primary care doctor and was subsequently referred and admitted to our hospital based on the suspicion of an acute hepatic disorder.

The patient was a healthy man with no history of chronic illnesses, including liver disease. He was not a heavy user of alcohol and had been taking only INH, with no other medications or supplements, before the onset of symptoms. He also advised us that he was not at risk of viral hepatitis. On a physical examination, he was 168 cm tall and weighed 54...
His blood pressure was 159/98 mmHg, his heart rate was 106 beats per minute and his body temperature was 37.4°C. He was severely jaundiced with scleral icterus; however, there was no lymphadenopathy, hepatosplenomegaly or asterixis. Due to the fact that the symptoms had started after the commencement of INH therapy, the dose of INH was promptly discontinued on admission.

The patient’s laboratory data on admission are shown in Tables 1 and 2. The white blood cell count was within the normal limits, without eosinophilia. However, the prothrombin time (PT) was prolonged and the levels of liver enzymes were extremely elevated, with an aspartate aminotransferase (AST) level of 1,581 IU/L, alanine aminotransferase (ALT) level of 2,540 IU/L, γ-glutamyl transpeptidase (γ-GTP) level of 734 IU/L, total bilirubin (T-Bil) level of 7.82 mg/dL and direct bilirubin (D-Bil) level of 5.61 mg/dL. Viral markers for hepatitis, including hepatitis A, B and C viruses, cytomegalovirus, Epstein-Barr virus and human immunodeficiency virus, were all negative, as were markers for autoimmune hepatitis. The serum immunoglobulin E level was extremely elevated at 1,739 mg/dL, and a drug-induced lymphocyte stimulation test (DLST) for INH showed a positive index [249 S.I. (>180%)]. Meanwhile, computed tomography (CT) performed on admission showed slight liver atrophy (Fig. 2a). The patient was thus diagnosed with INH-induced hepatitis.

Treatment with ursodeoxycholic acid was started at a dosage of 13 mg/kg/day.
daily dose of 600 mg. Although the AST and ALT levels began to improve, the PT and T-Bil values continued to deteriorate (Fig. 1). On the 12th day of admission, a CT scan showed advancing liver atrophy (Fig. 2b), even though the INH had been discontinued. As a matter of course, steroid pulse therapy was considered; however, we hesitated to start this therapy due to fears that he may develop active TBc. On the 13th day of admission, the patient exhibited a fever of 40.2°C, with no obvious foci of infection, and a blood culture was found to be positive for *Enterobacter aerogenes*; we prioritized treatment for the sepsis. On the 14th day of hospitalization, the patient’s clinical condition deteriorated with the onset of Grade II hepatic encephalopathy (drowsiness, possible asterixis and inappropriate behaviors), and the PT decreased to 30% [international normalized ratio (INR) = 2.05]. He was therefore diagnosed with acute liver failure with hepatic coma, subacute type according to the diagnostic criteria for acute liver failure in Japan (6).

We determined that, following the treatment of sepsis, liver transplantation (LT) was the only modality that offered a cure. Preparations for LT were thus started, and the need for LT was explained to the patient and his family. Unfortunately, no blood relations were able to donate a section of their liver, and the patient was therefore registered as a LT...
recipient on the Japan Organ Transplant Network. We subse-
quently performed plasma exchange with hemodiafiltration
(HDF) as artificial liver support for three days, and the pa-
tient’s hepatic encephalopathy improved to Grade I. Mean-
while, although the transaminase and T-Bil levels gradually
decreased, they remained abnormally high. On the 18th day
of hospitalization, CT showed further liver atrophy and asc-
cites (Fig. 2c); the liver injury was remarkable and irrever-
sible. While the patient and his family initially consented to
LT, they later rejected this course of treatment, and he died
of liver failure four months after admission.

**Discussion**

It is important to treat LTBI in order to eliminate TBc. Among
LTBI patients who do not receive treatment, approxi-
mately 5% go on to develop active TBc within two
years. INH has an efficacy rate of approximately 90% in
individuals who complete treatment and remains the main
agent of treatment for LTBI (1). Unfortunately, INH therapy
carries a serious side effect of hepatotoxicity, the manifesta-
tions of which are variable, ranging from asymptomatic ele-
vation of liver enzymes to severe hepatitis. The proportion
of patients with an AST level more than five times the up-
per limit of normal during INH therapy has been reported to
be 0.56% (19/3,377), while that of patients with an AST
level more than 10 times the upper limit is 0.30% (10/
3,377) (7). In most cases, the liver injury improves after
withdrawing the drug, although some cases progress to se-
vere hepatitis. In patients intolerant to INH, rifampicin
(RFP) is an alternative treatment for LTBI (8).

The largest study conducted by the United States Public
Health Service reported eight deaths due to hepatitis among
nearly 14,000 patients taking INH (9). A number of studies
were subsequently performed to evaluate the risk of hepato-
toxicity. Notably, a high incidence of INH-induced hepatox-
ity was reported in patients over 35 years of age (10),
patients with a history of alcohol consumption, especially
drinking on a daily basis (9) and carriers of HCV and/or hu-
man immunodeficiency virus (HIV) (11, 12). Current studies
have also shown that differences in the rate of INH-induced
hepatotoxicity in individuals can be attributed to genetic
variability at several loci that code for drug-metabolizing en-
zymes; for example, the slow-acetylator status of N-acetyl
transferase 2 and cytochrome P450 2E1 C/D or C/C geno-
type together are associated with a higher frequency of he-
patotoxicity (13).

INH-induced hepatotoxicity occurs with variable la-
tency (14), with a latency period of approximately one week
to three months in most cases, although the disease can oc-
cur up to one year later or more (7). In general, symptoms
associated with hepatotoxicity include fatigue, weakness, ab-
dominal pain, loss of appetite, itching and jaundice. How-
ever, hepatotoxicity is not always associated with such
symptoms, and it has been reported that 73% of patients
with a transaminase level exceeding five times the upper
limit of normal are asymptomatic (15). Our patient did not
report having jaundice or general malaise before the 70th
day of INH therapy and was not periodically examined us-
ing liver function tests. It is possible that the liver dysfunc-
tion in this case occurred early on during the course of INH
therapy. In this event, early detection would have led to INH
discontinuation before the onset of overt hepatitis. It is in-
adequate to perform the liver function tests only when the
patient experiences symptoms of hepatic illness. Periodic
liver function tests should therefore be scheduled in such pa-
tients in order to detect hepatotoxicity at a reversible stage;
in the early stages of disease, liver injury improves by the
second or third week after drug withdrawal. Some experts
recommend that INH be withheld if a patient’s transaminase
level exceeds three times the upper limit of normal in asso-
ciation with symptoms and five times the upper limit of nor-
mal if the patient is asymptomatic (1). In addition to the
current case, other fatal cases in which treatment with INH
was continued for several weeks after the onset of symp-
toms associated with hepatitis have been reported (16-18). It
has also been demonstrated that a T-Bil level above 2.5 mg/
DL is associated with a high mortality rate (9). Delays in
INH discontinuation may result in irreversible hepatic de-
struction. The prognosis of acute liver failure may be im-
proved by LT; however, if this therapy is not an option, the
prognosis of patients with acute liver failure is poor (19). LT
recipients must be treated with immunosuppressive drugs to
avoid rejection and are thus at a higher risk of developing
TBc than the general population (20). Hence, it is important
that physicians make every effort to prevent the develop-
ment of severe hepatitis in patients receiving preventive ther-
apy for LTBI.

Japanese guidelines recommend the use of liver function
tests once every two weeks during the first two months of
treatment (21). However, one study reported that the propor-
tion of patients examined using liver function tests more
than once during the course of treatment for LTBI is only
47.6% (371/779) (22). Biochemical monitoring is not rou-
tinely performed in such cases, as the frequency of fatal
hepatitis is low and these tests are thus not considered to be
cost effective. Furthermore, asymptomatic patients are less
likely to attend clinical check-ups. Physicians should there-
fore impress upon their patients the need for regular hospital
visits and correspondence when side effects occur. In par-
icular, patients who experience signs and symptoms of he-
patotoxicity should promptly terminate INH therapy and
visit the hospital (23).

We herein presented a case of fatal INH-induced acute
liver failure. INH-induced hepatotoxicity may occur in the
absence of symptoms, and this therapy should be combined
with careful clinical monitoring, including liver function
tests once every two weeks, at least during the first three
months of treatment. The best way to prevent fatal INH-
induced hepatitis is with the early detection of hepatotoxic-
ity, and physicians should counsel their patients regarding
the dangers of hepatotoxicity resulting from INH therapy.
The authors state that they have no Conflict of Interest (COI).

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