

An Autopsy Case of Fulminant Hepatitis in a Patient with Multiple Sclerosis Treated by Interferon-Beta-1a

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Abstract

A 44-year-old woman with multiple sclerosis (MS) receiving interferon (IFN)-beta-1a treatment was admitted to a local hospital for severe icterus and liver injury. She was transferred to our university hospital because fulminant hepatitis (FH) was suspected. She was diagnosed with acute-type FH based on hepatic coma, severe liver injury and liver failure, and she received plasma exchange and continuous hemodiafiltration therapy. On hospital day 6, she died from liver failure despite intensive care. An autopsy revealed histological findings consistent with FH. Physicians should monitor the hepatic function of MS patients receiving IFN-beta-1a treatment, as serious events can occur in rare cases.

Key words: autopsy, fulminant hepatitis, multiple sclerosis, interferon-beta-1a

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Introduction

Interferon (IFN)-beta-1a has been widely used as the first-line treatment for relapsing-remitting multiple sclerosis (MS) (1, 2). Liver abnormalities, which are known adverse events in the early stage of IFN-beta-1a treatment, are often asymptomatic and seldom serious (3). We herein report an autopsy case of fulminant hepatitis (FH) concurrent with MS treated by IFN-beta-1a for relapse prevention.

Case Report

A 44-year-old woman was diagnosed with MS 3 months prior to admission to a local hospital because of recurrent muscle weakness of the left lower limb. At that time, magnetic resonance imaging (fluid-attenuated inversion recovery) showed several hyperintense lesions in the cerebral white

matter, cerebellum, brain stem and spinal cord (Fig. 1), and oligoclonal bands were positive in her cerebrospinal fluid. She was treated with pulsed intravenous methylprednisolone (1 g once daily for 3 days, with a repeated course after a 10-day interval). She also received intramuscular injections of IFN-beta-1a (dose gradually raised from 7.5 to 15 µg and 30 µg, once a week) for relapse prevention. Her muscle weakness in the left lower limb improved partially, but claudication remained. Blood tests were performed in this patient once a week after the initiation of IFN beta-1a at our hospital. After leaving our hospital, she never underwent any blood tests at her local hospital. She had no relevant medical history, nor any remarkable family history. She sometimes took loxoprofen and magnesium oxide for pain and constipation, respectively.

She consulted a local doctor with chief complaints of nausea and general fatigue 3 days after the 10th treatment of IFN-beta-1a. Her symptoms did not improve with stomach

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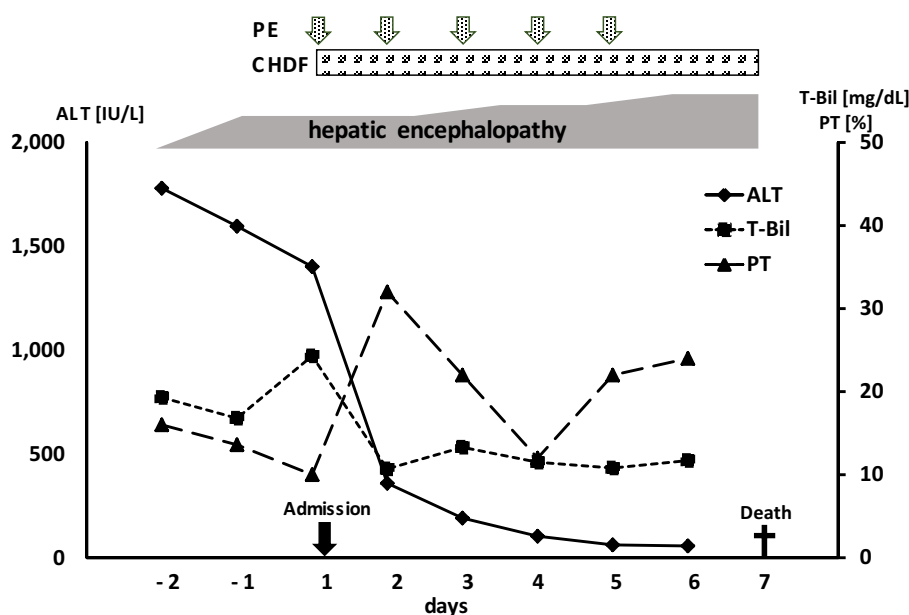


Figure 3. Clinical course of the patient. ALT: alanine transaminase, CHDF: continuous hemodiafiltration, PE: plasma exchange, PT: prothrombin time activity, T-Bil: total bilirubin

hepatitis viruses, positive anti-nuclear antibody (ANA) and normal ranges of immunoglobulin G (Table). Contrast-enhanced computed tomography showed hepatic atrophy and peripheral edema of the portal trunk and gallbladder, without remarkable changes in the brain (Fig. 2). The patient was diagnosed with acute-type FH and received combined plasma exchange (PE) and continuous hemodiafiltration (CHDF) therapy. Although we discussed living-donor liver transplantation with her family, there was no available living-donor candidate.

On hospital day 5, the patient had a more severe hepatic coma event and suffered respiratory failure and hemorrhagic shock due to bleeding from the nasal cavity and digestive tract. Following this, the patient's condition never improved despite intensive care that included a fifth instance of combined PE and CHDF, blood transfusion and a ventilator. She died from liver failure on hospital day 6 (Fig. 3). We planned to register the patient for brain death liver transplantation, however, the patient died before we could complete the registration process. An autopsy was performed on the same day.

In the macroscopic findings, we noted multiple patchy lesions in the cerebral white matter, cerebellum, brain stem and spinal cord (Fig. 4A). In the microscopic findings, we noted extensive lesions of myelin pallor in the cerebral white matter, cerebellum, brain stem and spinal cord, with both clear and unclear boundaries in Klüver-Barrera's staining, indicating demyelinating lesions (Fig. 4B). These demyelinating lesions contained proliferation of reactive astrocytes and infiltration of lymphocytes and histiocytes in the peripheral vessels (Fig. 4C). Immunohistochemically, glial fibrillary acidic protein (GFAP) staining revealed only mild gliosis (Fig. 4D). These findings were compatible with MS.

Grossly, the liver was remarkably atrophic, and the weight

was 740 g (Fig. 5A). Histologically, there were massive necrotic lesions in the liver without periportal fibrosis or lymphocyte infiltration (Fig. 5B). These histological findings showed typical FH and were not compatible with autoimmune hepatitis (AIH).

Discussion

Liver injury incurred during MS treatment is known to be caused by therapeutic agents, AIH or autoimmune thyroiditis (3-6). IFN-beta treatment for the relapse prevention of MS has been reported to cause drug-induced liver injury (DILI) (3, 6). The majority of IFN-beta-induced liver injury occurred during the first 3-6 months of treatment (3, 6). As these hepatic abnormalities were mild and asymptomatic, only <1% of the patients with hepatic abnormalities discontinued IFN-beta treatment (3, 6). Thus far, no case reports have described FH induced by IFN-beta-1a (Avonex[®]) or IFN-beta-1b (Betaferon[®]) in Japan, although some cases of IFN-beta-induced severe hepatotoxicity leading to liver transplantation have been reported in other countries (7, 8). Based on our PubMed search, we concluded that our patient was the first case of IFN-beta-1a-induced FH concurrent with MS confirmed by autopsy.

In the present case, the causes of liver injury were probably DILI and/or AIH due to the recent introduction of IFN-beta-1a (less than three months), lack of other habitual drugs, negative makers for viral hepatitis, normal thyroid function and positive ANA findings. It has been reported that IFN-beta induced or exacerbated AIH in MS patients (4, 7, 9); however, the relationship between IFN-beta and AIH in patients without MS is unknown. The prevalence of AIH is reportedly higher in patients with untreated MS (0.17%) than in the general population (0.017%) (10).

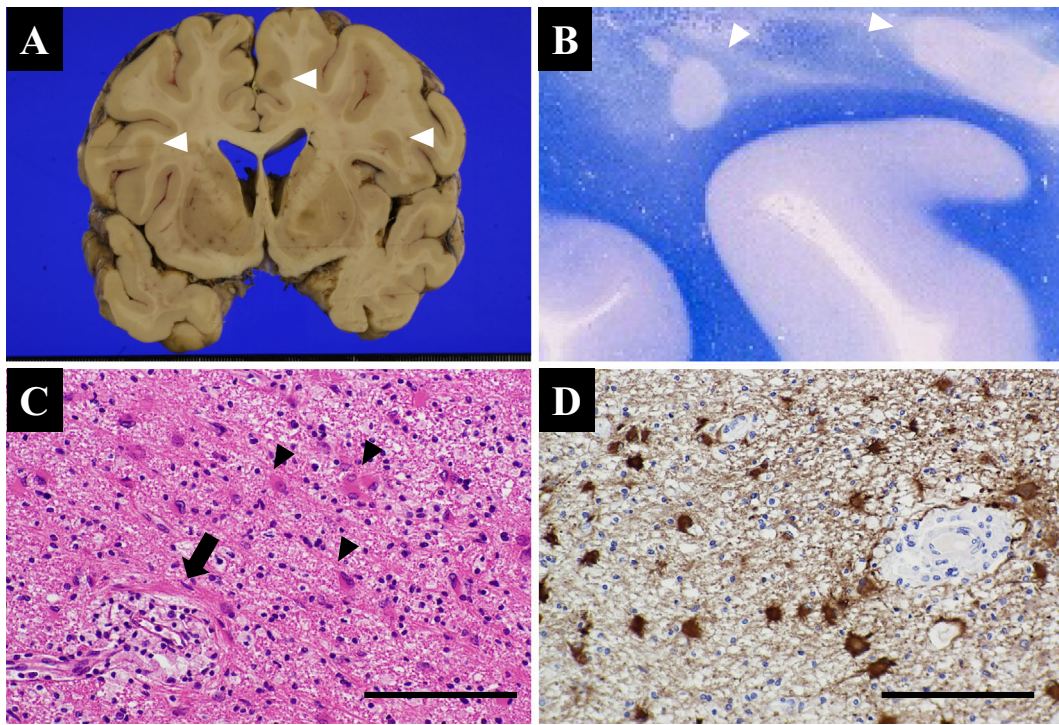


Figure 4. Autopsy findings of the brain. **A:** Grossly, there are multiple patchy lesions in the cerebral white matter (white arrowheads). **B:** Klüver-Barrera's staining shows well-demarcated myelin pallor in the cerebral white matter (white arrowheads). **C:** Histologically, the demyelinating lesions in the cerebral white matter contain proliferating reactive astrocytes (black arrowheads) and infiltration of lymphocytes and histiocytes in the peripheral vessels (black arrow) (Hematoxylin and Eosin staining). **D:** Glial fibrillary acidic protein (GFAP)-positive cell numbers are increased in the lesions with mild gliosis (GFAP antibody staining). Scale bar, 100 μ m.

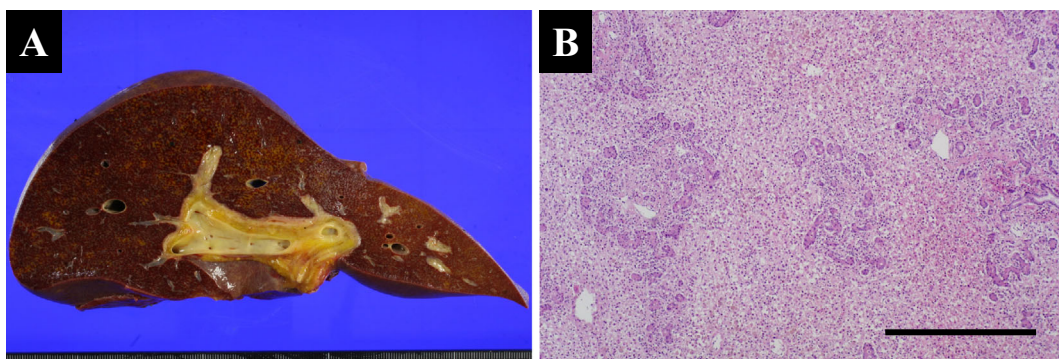


Figure 5. Autopsy findings of the liver. **A:** The macroscopic appearance of the liver shows remarkable atrophy. **B:** A histopathological examination of the liver shows massive necrotic lesions in the liver without periportal fibrosis or lymphocyte infiltration (Hematoxylin and Eosin staining). Scale bar, 500 μ m.

Therefore, IFN-beta-1a might have induced the FH related to AIH in our patient. In either case, there is a high probability that IFN-beta-1a therapy was related to the development of FH.

The autopsy revealed histological findings consistent with typical FH with massive hepatocyte necrosis. These findings are compatible with DILI rather than AIH because they did not include periportal fibrosis or interface hepatitis, indicating chronic hepatitis or liver cirrhosis. We were unable to

diagnose AIH based on the International AIH scoring system, but we were able to diagnose highly possible DILI by IFN-beta-1a based on the diagnostic criteria for DILI in Japan (11, 12). Furthermore, the brain pathological findings were useful for determining a definite diagnosis of MS, and IFN treatment for relapse prevention was confirmed to be necessary for this patient.

In conclusion, we herein report the first autopsy case of FH concurrent with MS treated by IFN-beta-1a in Japan.

Physicians should monitor the hepatic function and keep in mind that IFN-beta-1a-induced liver injury is common during the first several months of treatment, and serious events can occur in rare cases.

The authors state that they have no Conflict of Interest (COI).

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