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, brainstem 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...
Figure 1. Magnetic resonance imaging (fluid-attenuated inversion recovery) at the time of the multiple sclerosis diagnosis shows several hyperintense lesions in the cerebral white matter and cerebellum (white arrows).

Table. Laboratory Findings on Admission.

| Hematology | Biochemistry | Immunological Test |
|------------|--------------|--------------------|
| Hb 13.9 g/dL | TP 5.4 g/dL | IgG 1,134 mg/dL |
| RBC 472×10^4 μL | Alb 3.3 g/dL | IgM 259 mg/dL |
| Ht 39.7% | T-Bil 18.1 mg/dL | ANA <40 |
| WBC 11,000 μL | D-Bil 11.8 mg/dL | AMA (-) |
| PLT 17.6×10^4 μL | AST 1,069 IU/L | |
| ALT 1,402 IU/L | | |

| Coagulation Test | Biochemistry | Immunological Test |
|-----------------|--------------|--------------------|
| PT <10 sec | LDH 497 IU/L | HBs Ag (-) |
| APTT 63.8 sec | ALP 661 IU/L | Hbc Ab (-) |
| Fbg 54 mg/dl | γ-GTP 264 IU/L | HBs Ab (-) |
| AT-III 14.9% | AMY 125 mg/dl | HCV Ab (-) |
| FDP 2 μg/mL | BUN 5 mg/dl | IgM-HA Ab (-) |
| D-dimer 1.4 μg/mL | Cr 0.43 mg/dl | IgM-Hbc Ab (-) |
| | Na 137 mEq/L | IgA-HEV Ab (-) |
| | K 3.1 mEq/L | HBV-DNA (-) |
| | Cl 96 mEq/L | HCV-RNA (-) |
| | CRP 0.51 mg/dl | EBV-IgM Ab (-) |
| TSH <0.1 μg/mL | | |
| free T3 1.89 ng/mL | NH3 214 μg/mL | CMV-IgM Ab (-) |
| free T4 1.74 pg/mL | | |

Figure 2. Abdominal computed tomography on admission shows hepatic atrophy and peripheral edema of the portal trunk and gallbladder.

medication (saikokeishito and rebamipide), and she was admitted to a local hospital for severe icterus and liver injury 1 day after the 11th treatment with IFN-beta-1a. Two days after admission, FH was suspected because of flapping tremor, hepatic coma and hyperammonemia. The patient was therefore transferred to our university hospital.

On admission, her level of consciousness was E4 V3 M4. Her body temperature was 36.6°C, blood pressure was 113/68 mmHg, pulse was 116 beats/min, respiratory rate was 15/min and SpO₂ was 97%. A general physical examination revealed severe icterus. A neurological examination showed muscle weakness of the left lower limb and flapping tremor. Laboratory studies showed severe liver injury and failure (Table). Immunological tests revealed negative markers for
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 fibrillar 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 periporal 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).
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).

References

1. Cross AH, Naismith RT. Established and novel disease-modifying treatments in multiple sclerosis. J Intern Med 275: 350-363, 2014.
2. Leary SM, Miller DH, Stevenson VL, Brex PA, Chard DT, Thompson AJ. Interferon beta-1a in primary progressive MS: an exploratory, randomized, controlled trial. Neurology 60: 44-51, 2003.
3. Francis GS, Grumser Y, Alteri E, et al. Hepatic reactions during treatment of multiple sclerosis with interferon-beta-1a: incidence and clinical significance. Drug Saf 26: 815-827, 2003.
4. Villamil A, Mallen E, Cacciato P, Gadano A. Interferon beta 1a-induced severe autoimmune hepatitis in patients with multiple sclerosis: report of two cases and review of the literature. Ann Hepatol 14: 273-280, 2015.
5. Caraccio N, Dardano A, Manfredonia F, et al. Long-term follow-up of 106 multiple sclerosis patients undergoing interferon-beta 1a or 1b therapy: predictive factors of thyroid disease development and duration. J Clin Endocrinol Metab 90: 4133-4137, 2005.
6. Fontana RJ, Hayashi P, Bonkovsky HL, et al. Presentation and outcomes with clinically apparent interferon beta hepatotoxicity. Dig Dis Sci 58: 1766-1775, 2013.
7. Yoshida EM, Rasmussen SL, Steinbrecher UP, et al. Fulminant liver failure during interferon beta treatment of multiple sclerosis. Neurology 56: 1416, 2001.
8. Kozielewicz D, Pawlowska M. Acute liver failure and liver transplantation in a patient with multiple sclerosis treated with interferon beta. Neurol Neurochir Pol 49: 451-455, 2015.
9. Pietrosi G, Mandala L, Vizzini GB, et al. Fulminant hepatic failure and autoimmune disorders in patient with multiple sclerosis on interferon beta 1a: a fatal combination? Transpl Int 21: 502-504, 2008.
10. de Seze J, Canva-Delcambre V, Fajardy I, et al. Autoimmune hepatitis and multiple sclerosis: a coincidental association? Mult Scler 11: 691-693, 2005.
11. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 31: 929-938, 1999.
12. Takikawa H. Recent status of drug-induced liver injury. Hepatol Res 39: 1-6, 2009.

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