Acute-onset Autoimmune Hepatitis in a Patient with Selective Immunoglobulin M Deficiency

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Abstract:
Selective immunoglobulin M deficiency (SIGMD) is an uncommon primary immunodeficiency disorder. We herein report an SIGMD patient with autoimmune hepatitis. A 21-year-old Japanese man was transferred to our hospital because of acute liver dysfunction. His serum IgM level was low, whereas those of IgG and IgA were normal, indicating that he had SIGMD. We diagnosed him with acute-onset autoimmune hepatitis, and his liver function test findings gradually recovered with corticosteroid administration. Although SIGMD with autoimmune diseases has been reported, the clinical features and pathogenesis have not yet been clarified. We have summarized previous reports on SIGMD patients with autoimmune diseases.

Key words: autoimmune hepatitis, selective immunoglobulin M deficiency

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Introduction
Selective immunoglobulin M deficiency (SIGMD) is a rare primary immunodeficiency disease associated with serious infectious diseases, autoimmune diseases and malignancies (1). In SIGMD patients, the serum immunoglobulin M (IgM) level is below two standard deviations of the mean, and the IgG and IgA levels are normal (1). Although a number of patients with SIGMD have been reported after Hobbs et al. first described young patients with SIGMD in 1967 (2), few large-scale studies have explored the prevalence of SIGMD.

Autoimmune hepatitis (AIH), which is predominant in middle-age and elderly women, is a liver disease caused by the loss of tolerance to autoantigens (3). Although several studies have shown that autoimmune diseases are frequently present in adults with SIGMD, few SIGMD patients with AIH have been reported.

We herein report a young patient with SIGMD who experienced acute-onset AIH and review previous reports on SIGMD patients with autoimmune diseases.

Case Report
A 21-year-old Japanese man presented to a local hospital with fatigue and nausea. He had frequently experienced symptoms of a common cold for one year before visiting the hospital. Regarding his medical history, he had atopic dermatitis. He had no history of regular alcohol intake or smoking. He was not regularly taking any medicines, supplements, or illicit drugs.

He was admitted to the hospital because of liver dysfunction with high levels of serum aspartate aminotransferase (AST, 977 U/L) and alanine aminotransferase (ALT, 2,191 U/L) (Table 1). He was negative for hepatitis B surface antigen, hepatitis C virus antibody, anti-nuclear antibody (ANA), and anti-liver kidney microsome type 1 (anti-LKM-1) antibody. His serum level of IgM [reference range (RR) in the hospital: 33-190 mg/dL] was low (2 mg/dL), whereas those of IgG (RR: 870-1,700 mg/dL) and IgA (RR: 110-410 mg/dL) were normal (1,095 and 175 mg/dL, respectively). Abdominal computed tomography (CT) revealed periportal collar signs and edematous thickening of the gallbladder wall, indicating the presence of acute hepatitis (Fig. 1). CT

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did not show any signs of malignant disease. A percutaneous liver biopsy was performed nine days after his admission, and the histological examination did not show lobular/portal plasma cell infiltration, fibrosis, or centrilobular inflammation/necrosis, but moderate lobular inflammation and interface hepatitis in the portal areas was found (Fig. 2). No emperipolisis, cobblestone appearance, or rosette formation of hepatocytes was noted.

He was diagnosed with acute-onset AIH based on the pathological findings, and steroid therapy with prednisolone (PSL, 50 mg/day) was started, with the dose later tapered (Fig. 3). However, while his liver function gradually recovered, the serum aminotransferase levels were still abnormal despite the patient taking 30 mg/day PSL. At 36 days after his admission, he was transferred to our hospital for further examinations and treatment.

On admission to our hospital, he was 170 cm in height and 53.8 kg in weight with a blood pressure of 103/67 mmHg, pulse 62 beats per minute and regular, and body temperature 36.4°C. His consciousness was lucid. He did not have icterus or abdominal symptoms.

Regarding laboratory data, his serum IgM level (RR in our hospital: 33-183 mg/dL) was extremely low (<4 mg/dL) although the serum IgG (RR: 861-1,747 mg/dL) and IgA (RR: 93-393 mg/dL) levels were almost normal (867 mg/dL and 150 mg/dL, respectively), as the laboratory data from the previous hospital had shown. A flow cytometric analysis of the peripheral blood revealed normal rates of CD4+ and CD8+ T lymphocytes (36.8% and 26.3%, respectively) and CD19+ B lymphocytes (28.1%). He was positive for anti-Epstein Barr virus capsid antigen IgG, and anti-Varicella Zoster Virus IgG, indicating that his specific IgG producibility was normal. Lymphocyte blastoid transformation by process hazard analysis (PHA) did not show dysfunction of T cells (PHA+: 16,604 cpm, control: 113 cpm). These results indicated that he had SIGMD as the underlying disease.

The laboratory data also showed high levels of serum AST (66 U/L) and ALT (188 U/L). According to the revised scoring system of the International Autoimmune Hepatitis Group (IAIHG) (4), he was scored as probable AIH (score 12). Because some human leucocyte antigen (HLA) types have been reported to be risk factors for AIH, we determined his HLA haplotype, and it was revealed that he had SIGMD as the underlying disease.

Table 1. Laboratory Data on Admission to the Previous Hospital.

| WBC       | 7.100 ×10^9/μL | Neut | 60.8 % | TSH | 0.77 μU/dL |
|-----------|----------------|------|--------|-----|------------|
| Eosi      | 20.1 %         | T4   | 2.65 pg/mL |     |            |
| Baso      | 0.6 %          | Na   | 1.16 ng/dL |     |            |
| Mono      | 9.1 %          | K    | 4 mm/dL |     |            |
| Lymp      | 9.4 %          | Cl   | 103 mm/dL |     |            |
| RBC       | 4.87 ×10^12/μL | Glucose | 105 mg/dL |     |            |
| Hb        | 14.5 g/dL      | HbA1c | 5.6 % |     |            |
| Hct       | 43.8 %         | IgG  | 1.095 mg/dL |     |            |
| PLT       | 17.7 ×10^12/μL | IgA  | 175 mg/dL |     |            |
| PT%       | 96.5 %         | IgM  | 2 mg/dL |     |            |
| APTT      | 31.9 sec       | ANA  | <40 x  |     |            |
| Fibrinogen| 207 mg/dL      | Anti-LKM-I Ab | <5.0 index |   |            |
| T-Bil     | 1.6 U/L        | Anti-ds DNA Ab | 2.4 U/mL |     |            |
| D-Bil     | 0.8 U/L        | Anti-Sm Ab | <1.0 U/mL |     |            |
| AST       | 977 U/L        | AMA  | <20 x  |     |            |
| ALT       | 2,191 U/L      | P-ANCA | <1.0 U/mL |     |            |
| LDH       | 435 U/L        | HBsAg | -     |     |            |
| ALP       | 828 U/L        | HBsAb | -     |     |            |
| Che       | 208 U/L        | HBeAb | -     |     |            |
| Amylase   | 114 U/L        | HBV DNA | -     |     |            |
| BUN       | 13.7 mg/dL     | HCV Ab | -     |     |            |
| Creatinine| 0.69 mg/dL     | HCV RNA | -     |     |            |
| UA        | 6.6 mg/dL      | HAV IgM | -     |     |            |
| TP        | 6.8 mg/dL      | HEV IgA | -     |     |            |
| Albumin   | 4.4 mg/dL      | EBV EA IgG | -     |     |            |
| TG        | 135 mg/dL      | EBV VCA IgM | -     |     |            |
| T-Cholesterol | 157 mg/dL | EB VCA IgG | (+) |     |            |
| Ferritin  | 991 ng/mL      | EB EBNA | -     |     |            |
| NH3       | 39 μg/dL       | HSV IgM | -     |     |            |
| AFP       | 2.6 mg/dL      | VZV IgM | -     |     |            |
| CEA       | 2.0 mg/dL      | VZV IgG | (+) |     |            |
| CA19-9    | 9.7 U/mL       | B19 IgM | -     |     |            |
| CMV IgM   |                | (−) |     |     |            |

WBC: white blood cell, Neut: neutrophil, Eosi: eosinophil, Baso: basophil, Mono: monocyte, Lymp: lymphocyte, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, PLT: platelet, PT: prothrombin time, APTT: activated partial thromboplastin time, T-Bil: total bilirubin, D-Bil: direct bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, ChE: cholinesterase, BUN: blood urea nitrogen, UA: uric acid, TP: total protein, TG: triglycerides, T-Ch: total cholesterol, AFP: alpha-fetoprotein, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, TSH: thyroid-stimulating hormone, Ig: immunoglobulin, ANA: anti-nuclear antibody, Anti-LKM-1 Ab: anti-liver kidney microsome type 1 antibody, Anti-ds DNA Ab: anti-double stranded DNA IgG antibody, Anti-Sm Ab: anti-Smith antibody, AMA: anti-mitochondrial antibody, p-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibody, HBsAg: hepatitis B surface antigen, anti-VCA: virus capsid antigen, EBNA: EBV nuclear antigen, HSV: herpes simplex virus, VZV: varicella-zoster virus, B19: Parvovirus B19, CMV: cytomegalovirus.
in a cohort of 55 patients with SIGMD, only 4 patients had complete absence of serum IgM (1).

Although familial cases of SIGMD have been reported (9), no inheritance patterns or responsible genes have yet been identified. The European Society for Immunodeficiencies Registry defines SIGMD as a serum IgM level repeatedly below two standard deviations of normal with normal levels of serum IgA, IgG, and IgG subclasses, an absence of T cell defects, and an absence of causative external factors (http://www.esid.org). Our case showed a complete absence of serum IgM repeatedly and almost normal IgG and IgA. In addition, a flow cytometric analysis of peripheral blood revealed almost normal rates of CD4+ and CD8+ T lymphocytes and CD19+ B lymphocytes, and lymphocyte blastoid transformation by PHA showed no dysfunction of T cells. External factors causing SIGMD were not found. Based on these findings, we diagnosed the present patient with SIGMD.

AIH is a disease of the hepatic parenchyma that can present in acute or chronic forms, in common with many auto-immune diseases. AIH is associated with non-organ-specific antibodies in the context of hepatic autoimmunity (10). In Japan, a study in a certain region revealed that the incidence and prevalence of AIH were 2.23 and 23.4 per 100,000, respectively (age-standardized to the Japanese population) (11). AIH often presents as a chronic disease; however, it can also have an acute presentation (12). A nationwide survey in Japan revealed that acute hepatitis was seen in 11.7% of patients with AIH (13). Acute AIH has some characteristics: (a) recent onset (<30 days), (b) significant clinical symptoms, (c) remarkable biochemical elevations (serum bilirubin level and/or aminotransferase levels) (12). Although serum IgG or autoantibody levels are frequently elevated in chronic AIH, they may not be elevated in patients with acute-onset AIH (12, 14-16). Therefore, these laboratory data are sometimes not reliable. The histological features are also varied, and previous studies have reported that lobular/portal inflammation and interface hepatitis were frequently observed in patients with acute-onset AIH (17, 18). The
IAIHG criteria have been often used for the diagnosis of AIH (4), but the scoring system may be also unreliable in patients with acute-onset AIH. A previous study reported that the frequency of an overall diagnosis of AIH by the IAIHG system among 70 patients with fulminant liver failure caused by acute-onset AIH was 40% (19). Therefore, the diagnosis of acute-onset AIH needs to be made comprehensively from various viewpoints.

The present patient showed acute-onset clinical symptoms of fatigue and nausea and markedly elevated serum aminotransferase levels, suggesting he had acute hepatitis. Evidence of a viral infection, alcoholic hepatitis, drug-induced liver injury, or other liver diseases was absent. Although he showed atypical findings of AIH, with the absence of elevated levels of serum IgG and autoantibodies, he was defined as probable AIH according to the revised IAIHG scoring system, and the histological findings were consistent with the features of AIH. Furthermore, he had HLA-DR/DQ types, which have been reported to be associated with AIH in Japan (5). In addition, autoimmune diseases are more frequent in patients with SIGMD than in the general population (1), with an estimated rate of 8% according to a long-term follow-up study (6). Given the above, we diagnosed him with acute-onset AIH and started corticosteroid therapy. A previous study noted that, in acute-onset AIH, the response rate to PSL therapy ranges from 36% to 100% (12). In our case, the reaction to corticosteroid treatment was relatively good, and his serum aminotransferase levels have remained adequate with oral low-dose of PSL. This good response to steroid therapy also supports the diagnosis of AIH.

Previous reports of autoimmune diseases associated with SIGMD on PubMed are presented in Table 2 (20-30). Although collagen diseases or thyroid diseases with SIGMD have been reported relatively frequently, there is only one case report of AIH with SIGMD. No other cases of AIH accompanied by the “complete” absence of serum IgM have been reported.

The mechanisms underlying autoimmunity with SIGMD are unknown. One suggested possibility is cross-linking of IgM Fc receptor (FcμR) and B-cell receptor (BCR) by IgM autoantibody-self-antigen complexes, causing the induction of anergy (20). Mouse mutants for FcμR showed impairment in specific responses of IgG antibodies against T-dependent and T-independent antigens, resulting in the development of autoimmunity (31). In addition, the deficiency of CXCR3+ B-cells in SIGMD patients and a relationship between CXCR3+ cells and autoimmunity have been reported (32, 33). Other potential mechanisms reported in the literature include the loss of central tolerance as a result of BCR editing, loss of peripheral tolerance due to a deficiency of isotype-specific regulatory lymphocytes, and an impaired clearance of apoptotic cells (1). In the present AIH case, high levels of serum IgG or autoantibodies were not seen, probably because AIH was caused by the loss of tolerance or an impairment of anergy resulting from a deficiency in IgM by the mechanisms described above, which differed from those in patients with typical AIH.

We herein report a rare case of a young man who developed acute-onset AIH with SIGMD. Corticosteroid therapy has been effective, and the state of AIH has been well-controlled. Although the risk of serious infections is regarded as smaller in adult patients with SIGMD than in pediatric patients (1), an adult patient with a life-threatening infection has been reported (34). We should carefully treat the complications of infectious diseases because of the need for low-dose long-term corticosteroid administration. Because cases of autoimmune diseases, especially AIH, accom-
Table 2. Reported Cases of Autoimmune Diseases with SIGMD.

| Age (years) | Gender | Associated disease | IgM (mg/dL) | IgG (mg/dL) | Reference |
|------------|--------|--------------------|-------------|-------------|-----------|
| 51         | Female | SLE                | 10          | 2,340       | (21)      |
| 43         | Female | SLE                | 5           | 1,426       | (22)      |
| 37         | Female | SLE                | 15          | 1,506       | (22)      |
| 33         | Female | SLE                | 17          | 1,532       | (22)      |
| 47         | Female | SLE                | 23          | 1,567       | (22)      |
| 41         | Female | SLE                | 25          | 1,900       | (22)      |
| 42         | Female | SLE                | 28          | 1,316       | (22)      |
| 36         | Male   | SLE                | 30          | 1,267       | (22)      |
| 59         | Female | SLE                | 32          | 2,546       | (22)      |
| 30         | Female | SLE                | 37          | 1,109       | (22)      |
| 63         | Female | SLE                | 43          | 1,319       | (22)      |
| 36         | Female | SLE                | 44          | 1,226       | (22)      |
| 55         | Female | SLE                | 44          | 1,441       | (22)      |
| 29         | Female | SLE                | 25          | 1,597       | (23)      |
| 30         | Male   | SLE                | 6           | 936         | (23)      |
| 59         | Female | SLE                | 12          | 1,180       | (24)      |
| 30         | Female | SLE                | 18          | 1,120       | (24)      |
| 23         | Male   | Celiac disease     | 48          | 2,100       | (25)      |
| 26         | Male   | Celiac disease     | 27          | 1,700       | (25)      |
| 75         | Male   | Celiac disease     | 48          | 1,700       | (25)      |
| 52         | Male   | Celiac disease     | <32         | NA          | (20)      |
| 63         | Female | Sjögren’s syndrome | <5          | 3,030       | (24)      |
| 53         | Female | Sjögren’s syndrome | 16          | 1,500       | (24)      |
| 70         | Male   | Hashimoto’s disease| <3          | 1,972       | (25)      |
| 50         | Female | Hashimoto’s disease| 34          | 921         | (26)      |
| 39         | Female | Hypothyroidism     | 16          | 729         | (26)      |
| 65         | Male   | Hypothyroidism     | <5          | 1,350       | (24)      |
| 67         | Male   | Hypothyroidism     | 27          | NA          | (27)      |
| 53         | Female | Rheumatoid arthritis| 17       | 2,159       | (23)      |
| 46         | Female | Rheumatoid arthritis| 39        | 985         | (26)      |
| 68         | Female | CREST syndrome     | 37          | NA          | (27)      |
| 57         | Male   | Autoimmune glomerulonephritis| 34 | 1,500 | (28) |
| 34         | Male   | Psoriasis pustulosa| 1           | 1,314       | (29)      |
| 64         | Female | Autoimmune hepatitis| 11       | 2,942       | (30)      |
| 21         | Male   | Autoimmune hepatitis| 2           | 1,095       | Present case |

SIGMD: selective immunoglobulin M deficiency, IgM: immunoglobulin M, IgG: immunoglobulin G, SLE: systemic lupus erythematosus, NA: not available

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

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