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【 CASE REPORT 】

Tocilizumab, a Humanized Anti-interleukin-6 Receptor Antibody, Induces Hepatic Iron Overload in a Susceptible Patient

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Abstract:
A 75-year-old woman visited to our hospital with liver dysfunction. The patient's liver function was normal. She had been treated with tocilizumab for rheumatoid arthritis for two years. One year after initiation of tocilizumab treatment, liver dysfunction was observed. Serum ceruloplasmin concentration was low. We diagnosed hepatic iron overload because of a high ferritin concentration and a liver biopsy. The cessation of tocilizumab and phlebotomy improved the liver function. We believe that tocilizumab induced iron accumulation. We should be aware of the possibility that tocilizumab induces iron overload in susceptible patients and monitor iron status in patients treated with tocilizumab.

Key words: ceruloplasmin, hemochromatosis, hepcidin-25, iron, rheumatoid arthritis, tocilizumab

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Introduction

Iron overload disorders include a variety of conditions that lead to the accumulation of iron in the body and organ damage. These include hereditary hemochromatosis, secondary hemochromatosis, aceruloplasminemia, and chronic liver diseases (1, 2).

Hereditary hemochromatosis is a heterogeneous disease induced by abnormal hepcidin-25 activity (1, 3-5). This disease is caused by mutations in at least five genes [*HFE*, *HJV*, *HAMP*, *TFR2* and *SLC40A1* (3-5)] induced by insufficient hepcidin production or resistance to hepcidin activity. Hepcidin is a peptide synthesized by hepatocytes and is the master regulator of systemic iron metabolism (3-5). It reduces iron absorption by enterocytes and iron release from macrophages by decreasing the membrane expression of ferroportin, an iron transporter (3). Hepcidin production is regulated by iron homeostasis, hypoxia, erythropoiesis and inflammation (6, 7).

Interleukin-6 (IL-6) is an important inducer of hepcidin production, and the IL-6-gp130-STAT3 pathway is important for hepcidin production (6). Hepcidin production increases under conditions of iron overload (6, 7). Of note, ceruloplasmin stabilizes ferroportin in the plasma membrane (8, 9).

The introduction of biological drugs that target inflammatory cytokines, such as tumor necrosis factor (TNF) or IL-6, has been very useful for the treatment of rheumatoid arthritis (RA) (10, 11). Tocilizumab is a widely used biological originator disease-modifying antirheumatic drug (DMARD) and a recombinant humanized anti-IL-6 receptor monoclonal antibody that inhibits IL-6 signal transduction (12).

We herein report a case of secondary hemochromatosis (hepatic iron overload) induced by tocilizumab treatment for RA.

Case Report

A 75-year-old Japanese woman was admitted to our hospital because of a liver function abnormality of unknown etiology. Two years later, the liver function test results were normal. She had been diagnosed with rheumatoid arthritis

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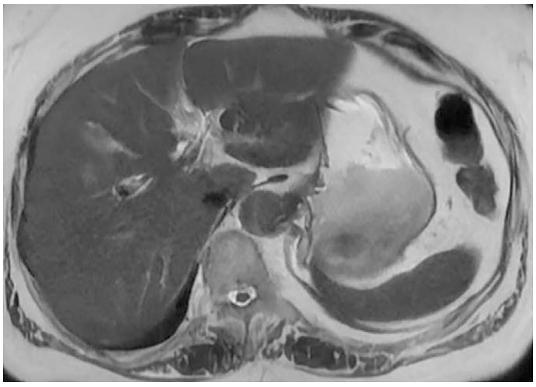

Figure 1. Magnetic resonance imaging (MRI; T2-weighted image). MRI did not reveal a low T2-weighted signal of the liver.

(RA), hypertension, and dyslipidemia and started on treatment with tocilizumab two years previously by a local orthopedic surgeon for RA. Other medications being used included azilsartan, amlodipine, and ezetimibe. The patient was not receiving any iron supplements. She had no history of blood transfusion, and she was not a habitual drinker.

The patient's body mass index was 27.2 kg/m^2. Ultrasonography revealed a mildly steatotic liver. A biochemical examination showed mild elevation of transaminase (AST/ALT=140/215 U/L). Hepatitis virus markers were negative. The antinuclear antibody was weakly positive, and IgG concentration was normal. Tests for anti-mitochondrial antibodies were negative. serum ferritin level was 1,000 ng/mL. The transferrin saturation was 48%. The serum ceruloplasmin concentration was 15 mg/dL. Urinary copper excretion levels were normal.

Based on these findings, we suspected hemochromatosis and thus performed magnetic resonance imaging (MRI). However, MRI did not reveal a low T2-weighted signal in the liver (Fig. 1). Therefore, we performed a liver biopsy, which revealed mild steatosis, scattered ballooned hepatocytes sometimes containing Mallory-Denk bodies, moderate inflammatory infiltrates in the hepatic lobules, and an expanded portal area with bridging and pericellular fibrosis. The nonalcoholic fatty liver disease activity score (NAS) was 4 (steatosis, 1; inflammation, 2; ballooning, 1). These findings indicated a diagnosis of metabolic dysfunction-associated steatohepatitis (MASH) (Fig. 2A, B). Berlin blue staining demonstrated the deposition of iron in the liver, especially in the sinusoidal lining cells (Fig. 2C).

Because the serum ceruloplasmin level was low, we measured the hepatic copper content, which was a normal value (27.9 μg/dry·g). We then examined the serum hepcidin-25 concentration because serum hepcidin-25 levels are low in patients with hereditary hemochromatosis. Serum hepcidin-25 levels were quantified using a liquid chromatography-tandem mass spectrometry-based assay (13, 14). Her serum hepcidin-25 concentration was 25.4 ng/mL. The normal level of serum hepcidin is 20.0±12.0 ng/mL (15). Therefore, hereditary hemochromatosis was deemed unlikely.

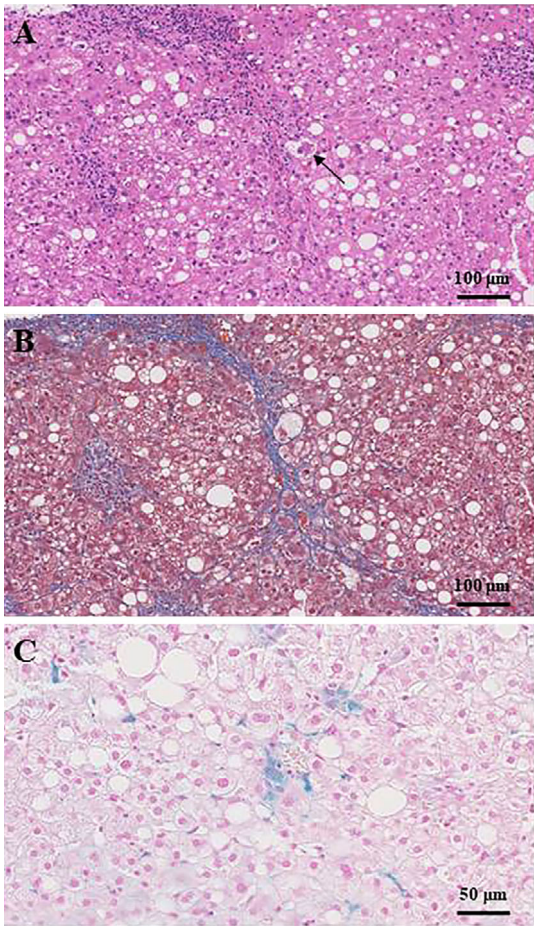

Figure 2. Pathological findings of the liver biopsy. A: Hematoxylin and Eosin staining, B: Azan staining. C: Berlin blue staining. A liver biopsy revealed mild steatosis, scattered ballooned hepatocytes sometimes containing Mallory-Denk bodies (arrow), moderate inflammatory infiltrates in the hepatic lobules, and an expanded portal area with bridging and pericellular fibrosis (A, B). Berlin blue staining demonstrated iron deposition in the liver, especially in the sinusoidal lining cells.

We administered vitamin E for the treatment of MASH. However, the liver function did not improve. We then performed phlebotomy (400 mL/month) 4 times at 4 months after the initial visit to 8 months. Phlebotomy gradually decreased the serum ferritin and ALT concentrations. We suspected that the abnormal liver function was due to excess iron, which might have been associated with tocilizumab. We therefore asked the surgeon to stop the use of tocilizumab for RA. In response, the doctor changed the treatment for RA from tocilizumab to filgotinib maleate six months after the initial visit. After cessation of tocilizumab and four phlebotomies, her serum ferritin concentration and liver function stabilized.

The clinical course, including changes in transaminase and ferritin concentrations, is shown in Fig. 3. Now, her liver function remained stable without phlebotomy. Transferrin saturation was 30% at 10 months after the initial visit.

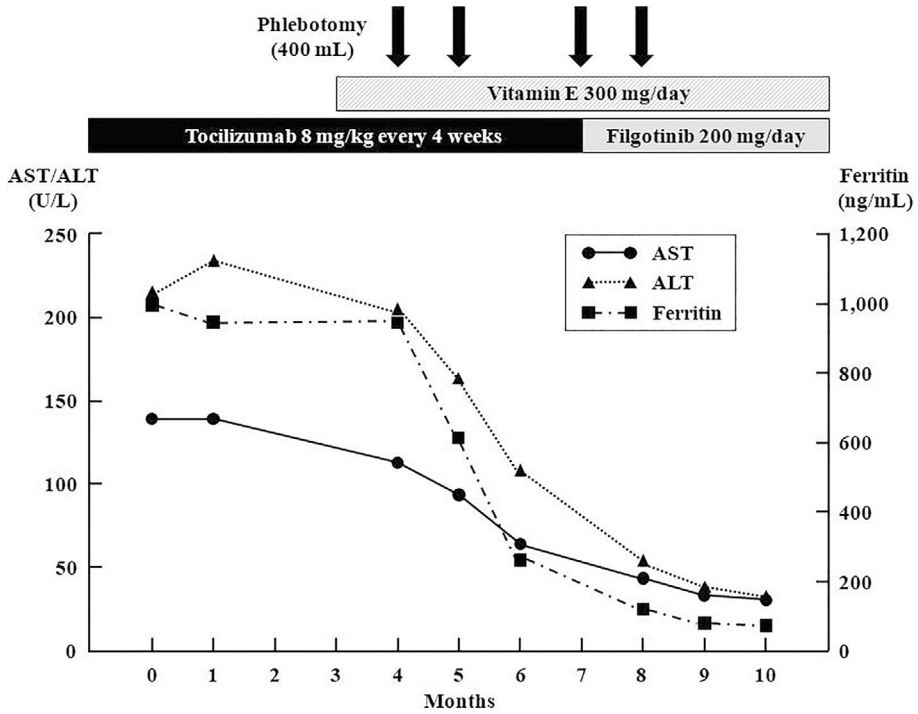

Figure 3. **Clinical course of the patient.**

Discussion

We encountered a patient with tocilizumab-induced secondary hemochromatosis with MASH. Although the serum ceruloplasmin concentration was low, the urinary copper excretion and hepatic copper content were normal. Therefore, Wilson's disease was ruled out. Vitamin E did not affect the liver function, and phlebotomy rapidly improved the abnormal liver function. Therefore, excess iron is the main cause of liver injury. After cessation of tocilizumab, the serum ferritin concentration and liver function tests were stable. These findings suggest that tocilizumab-induced iron overload may lead to liver dysfunction.

Hepcidin-25-mediated abnormal iron metabolism contributes to anemia in chronic disorders, such as Castleman disease and RA (13, 15). Tocilizumab decreases serum hepcidin-25 levels and improves anemia in patients with Castleman disease and RA (13, 15). Tocilizumab decreases the expression of hepcidin-25 in liver-derived cultured cells (13) and also suppressed hepcidin-25 production and improved anemia in a monkey model (16). The present patient's serum hepcidin-25 level was 25.4 ng/mL. This value is within the normal range but was still rather low, despite the high concentration of ferritin and hepatic iron deposition. Because expression of hepcidin-25 is regulated by iron levels in the body, especially in hepatocytes (6). The relationship between hepcidin-25 and liver iron has also been demonstrated in humans (7, 17). Therefore, the hepcidin-25 concentration of this patient was rather low for the iron status.

Tocilizumab does not usually induce hemochromatosis (10). The association between tocilizumab and hepatic iron overload has not been reported; however, there are some reports on the association between iron metabolism and tocilizumab (14). The serum ceruloplasmin levels were low in this patient. The ferroxidase activity of ceruloplasmin is important for the oxidation of ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}) and for the stability of cell surface ferroportin (8, 9). The absence of ceruloplasmin results in iron accumulation in various organs (9). Ceruloplasmin stabilizes ferroportin in the plasma membrane. Therefore, this patient was likely rendered susceptible to iron accumulation due to various stimuli.

MRI is useful in demonstrating iron overload (1, 2). However, MRI did not reveal iron overload in the present patient. Our previous study demonstrated that MRI was not always useful for demonstrating iron overload in patients with ferritin concentrations below 2,000 ng/mL (18). Therefore, a liver biopsy is still the gold standard for demonstrating iron overload in the liver, and it was also able to reveal accompanying abnormalities, such as steatotic liver disease in the present patient.

In conclusion, we encountered a patient with hepatic iron overload induced by tocilizumab, an anti-IL-6 receptor antibody. Therefore, we should be aware that tocilizumab can induce iron overload (secondary hemochromatosis) in susceptible patients, such as those with chronic hepatic diseases or a low ceruloplasmin concentration. The iron status should be monitored in patients treated with tocilizumab.

The patient provided her written informed consent for this study.

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

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