【 CASE REPORT 】

An Autopsy Case of Multicentric Castleman Disease Presenting with Severe Jaundice

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Abstract:
A 70-year-old man with multicentric Castleman disease (MCD) was admitted to our hospital with jaundice and ascites. Elevations in his bilirubin and interleukin-6 levels were noted, and computed tomography revealed hepatic atrophy and portal vein and bile duct disorders. Steroid therapy was started for MCD, but he died of hepatic failure. An autopsy revealed that the MCD activity was mild, but advanced fibrosis and cholestasis were observed in the liver. Mild infiltration of interleukin-6-positive plasma cells was noted in the highly fibrotic area of the liver. Although rare, liver and biliary tract damage may be also considered organ disorders of MCD.

Key words: autopsy, multicentric Castleman disease, severe jaundice, interleukin-6

Introduction

Castleman disease is an uncommon lymphoproliferative disease described in the 1950s by Dr. Benjamin Castleman (1). Castleman disease has two types, namely unicentric Castleman disease and multicentric Castleman disease (MCD), and histological variants include hyaline-vascular type, plasma-cell type, mixed type, plasmablastic type, and hypervascular type (2-4). MCD is usually associated with the plasma cell variant and often presents with generalized lymphadenopathy, a fever, weight loss, fatigue, edema, anemia, and hypoalbuminemia (5). Severe patients may develop hepatosplenomegaly, massive ascites, pleural effusions, or organ failure (6), but severe jaundice or liver failure can occur in rare cases.

We herein report an autopsy case of MCD presenting with severe jaundice.

Case Report

A 70-year-old man consulted a local doctor with a chief complaint of right flank pain 8 years ago. Abdominal contrast-enhanced computed tomography (CT) revealed poorly marginated and irregularly enhanced tumor-like lesions in the left hepatic lobe, atrophy of the left hepatic lobe, disappearance of the left branch of the portal vein, and multiple enlarged lymph nodes (Fig. 1a, b). The patient was referred to our hospital for a further examination.

Fluorodeoxyglucose-position emission tomography showed an abnormal uptake in multiple enlarged lymph nodes. The laboratory findings showed elevation of cholestatic liver enzymes, hypergammaglobulinemia and high levels of C-reactive protein (CRP) but no elevation of total bilirubin (T-Bil), tumor markers or immunoglobulin G (IgG) 4. Histological findings on a liver biopsy revealed inflammatory changes accompanied by marked hepatocellular loss, advanced fibrosis, and fibroblast proliferation without IgG4-positive plasma cell infiltration (Fig. 1c, d). In addition, the histological findings of the supradiaphragmatic lymph nodes by a thoracoscopic biopsy revealed multiple lymphoid follicles with germinal centers, vascular hyperplasia with hyalinization in germinal centers, and high plasma cell infiltration between follicles (Fig. 1e, f). According to these find-
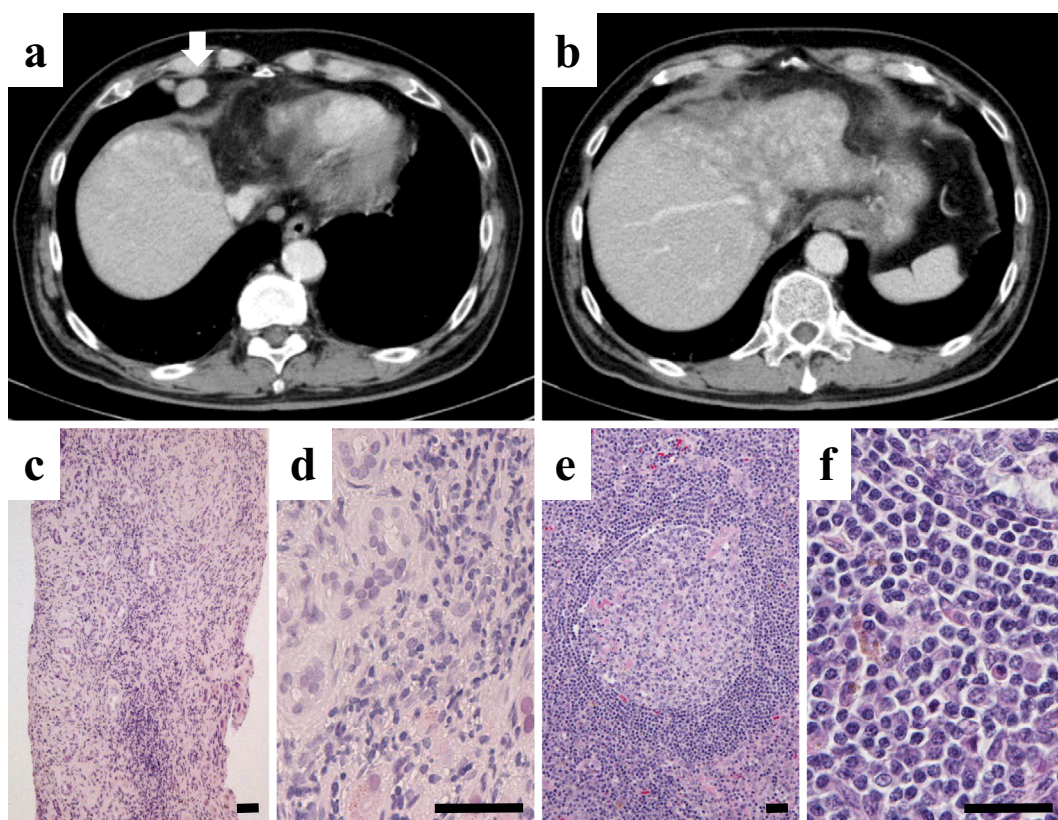
Figure 1. Abdominal contrast-enhanced computed tomography (CT) and histological findings at the diagnosis. (a, b) Abdominal CT at the diagnosis revealed multiple enlarged lymph nodes (white arrow), poorly marginated and irregularly enhanced tumor-like lesions in the hepatic lobe, atrophy of the left hepatic lobe, and disappearance of the left branch of the portal vein. (c, d) A liver biopsy revealed inflammatory changes accompanied by marked hepatocellular loss, advanced fibrosis, and fibroblast proliferation; Hematoxylin and Eosin (H&E) staining, scale bar, 50 μm. (e, f) A thoracoscopic biopsy of the supradiaphragmatic lymph nodes revealed multiple lymphoid follicles with germinal centers, vascular hyperplasia with vitrification in germinal centers, and high plasma cell infiltration between follicles; H&E staining, scale bar, 50 μm.

ings, the patient was diagnosed with mixed hyaline vascular and plasma cell-type MCD.

The elevated levels of CRP and interleukin 6 (IL-6) improved slightly after supradiaphragmatic lymph node dissection, so he was followed up in the Department of Hematology. Esophageal varices were noted by upper gastrointestinal endoscopy five years after the diagnosis, and he was referred to our department. Abdominal CT revealed marked atrophy of the left lobe of the liver, splenomegaly, and collateral circulation (Fig. 2a, b). Based on his history of substantial drinking up to five years ago, he was diagnosed with portal hypertension associated with alcoholic liver cirrhosis and underwent endoscopic esophageal varix sclerotherapy. In addition, follow-up was continued for MCD without an increase in lymph node swelling.

Nine months before admission to another hospital, the patient developed jaundice (T-Bil 9.9 mg/dl) and ascites and improved with symptomatic treatment, such as abdominal puncture and the administration of a diuretic agent. He was referred to our department because of the appearance of jaundice again two weeks ago without any cause and was

admitted to our department because of marked jaundice and ascites. He had a medical history of chronic gastritis and duodenal ulcer due to *Helicobacter pylori* infection, so he received eradication treatment for *H. pylori*. His sister had diabetes and liver cirrhosis as a family history. He had been consuming 150 g of alcohol a day for 30 years until 8 years ago and 20 cigarettes a day for 45 years until 3 years ago.

A hematological examination at admission revealed severe jaundice (T-Bil 22.7 mg/dl); elevations in ALP, CRP, and IL-6; and renal impairment (Table). Abdominal CT (Fig. 2c, d) and magnetic resonance cholangiopancreatography showed marked atrophy of the left lobe of the liver, atrophy of the right lobe of the liver, narrowing of the right branch of the portal vein and discontinuous stenosis and dilations of the intrahepatic bile ducts (Fig. 2e). We considered intrahepatic cholestasis to be the main cause of his severe jaundice, rather than obstructive jaundice, and did not perform biliary drainage. Furthermore, we suspected that active MCD might affect intrahepatic cholestasis and administered prednisolone (1 mg/kg) as a treatment for MCD and severe jaundice. Subsequently, in response to steroid therapy, his IL-6 and
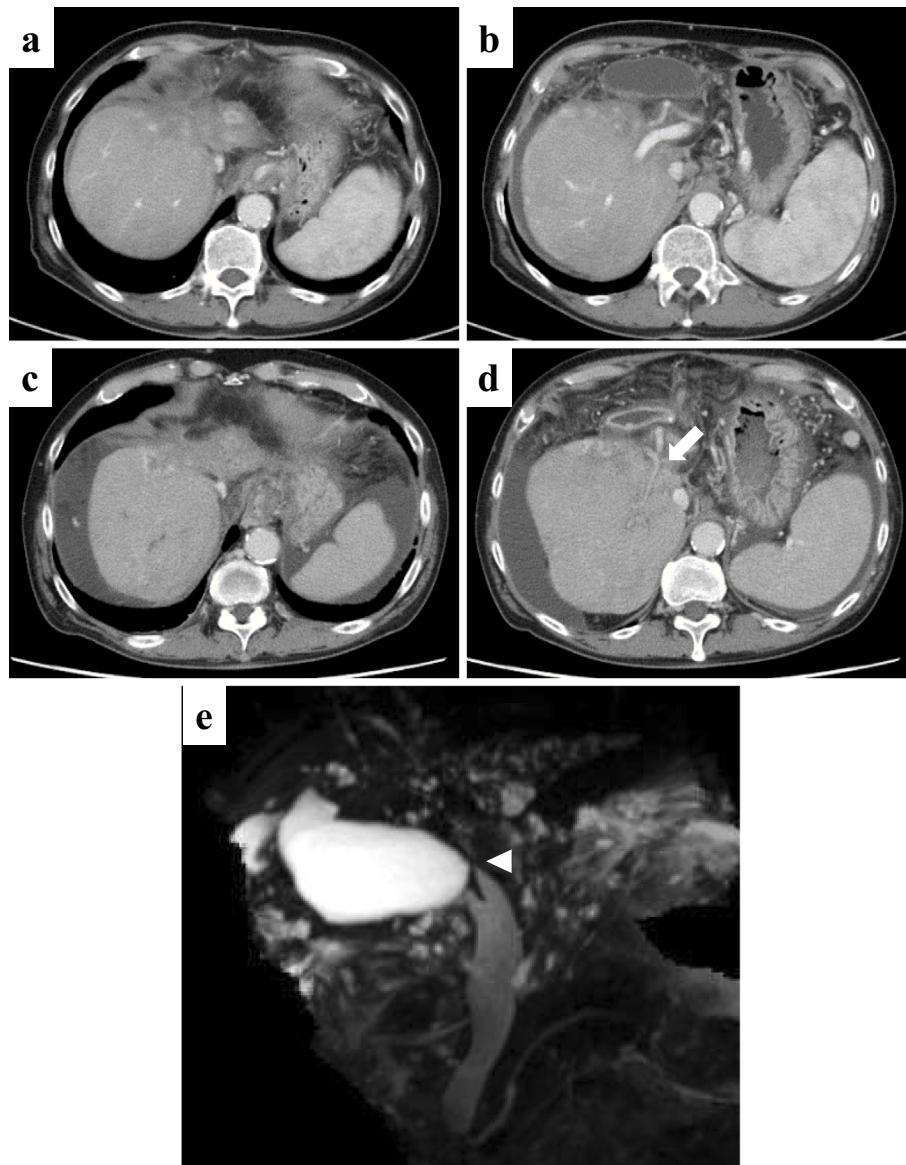
Figure 2. Abdominal CT and magnetic resonance cholangiopancreatography (MRCP) at the progressive stage. (a, b) Abdominal CT five years after the diagnosis revealed marked atrophy of the left hepatic lobe, splenomegaly, and collateral circulation. (c, d) In addition, abdominal CT eight years after the diagnosis revealed atrophy of the right hepatic lobe, narrowing of the right branch of the portal vein (white arrow), and discontinuous dilation of the intrahepatic bile duct. (f) MRCP showed narrowing of the right hepatic duct (white arrowhead) and discontinuous dilation of the intrahepatic bile duct.

CRP levels decreased, but the jaundice and renal damage did not improve, and on the night of the 27th hospital day, he developed hematemesis due to rupture of the esophageal varices. Despite hemostasis with endoscopic varicose ligation, he developed liver and renal failure and died on the 28 th hospital day.

A pathological autopsy was performed on the same day to evaluate the disease state of MCD and search for the cause of his severe jaundice. A macroscopic evaluation revealed marked jaundice and 1,500 ml of yellowish clear ascites in the abdominal cavity. A globular and slightly lobulated liver was observed, but the left lobe was not confirmed, and advanced fibrosis was observed in the hilar region (Fig. 3a). The liver was somewhat hard, its surface was smooth, and

fibrous thickening of the capsule was noticeable. There was no swelling of the hilar lymph nodes. He had congestive splenomegaly and mild swelling of the superior thymus pole and abdominal peri-aortic lymph nodes. Histopathologically, lymphoid follicles were diffusely distributed in the central part of the enlarged lymph node, but the lymphatic follicles were highly atrophic, and secondary follicles were not clear. A few plasma cells had infiltrated between the follicles, and fibrotic thickening of the lymphatic sinuses was noticeable (Fig. 3b). The spleen had notable fibrotic thickening of the capsule, the red pulp had expanded, and the white pulp was atrophic. Fibrotic thickening and congestion of the splenic cord were noted. The high degree of plasma cell infiltration that had been observed at the time of the diagnosis as MCD

Table. **Laboratory Findings on Admission.**

Hematology		Biochemistry		Immunological test	
Hb	12.2 g/dL	TP	8.3 g/dL	ANA	(-)
RBC	397×10⁴ /μL	Alb	2.2 g/dL	AMA	(-)
Ht	36.7 %	T-Bil	22.7 mg/dL	PR3-ANCA	(-)
WBC	8,100 /μL	D-Bil	18 mg/dL	MPO-ANCA	(-)
Plt	13.3×10⁴ /μL	AST	50 IU/L	IgG	3,234 mg/dL
		ALT	26 IU/L	IgM	90 mg/dL
Coagulation test		LDH	160 IU/L	IgG4	80 mg/dL
PT(%)	63	ALP	1,077 IU/L	IL-6	97 pg/mL
APTT	45.2 s	γ-GTP	24 IU/L		
Fbg	316 mg/dL	ChE	50 U/L	Virus marker	
AT-III	46.5 %	BUN	35 mg/dL	HBsAg	(-)
FDP	28.1 ug/mL	Cre	1.37 mg/dL	HBcAb	(-)
D-dimer	10.7 ug/mL	Na	136 mEq/L	HBsAb	(-)
		K	5 mEq/L	HCV Ab	(-)
Tumor marker		Cl	104 mEq/L	HIV Ab	(-)
AFP	1.1 ng/mL	CRP	5.72 mg/dL	CMV IgM Ab	(-)
PIVKA-II	272 AU/mL	NH3	36 ug/mL		
CEA	3.2 ng/mL				
CA19-9	25 U/mL				

AFP: α-fetoprotein, Alb: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AMA: anti-mitochondrial antibody, ANA: anti nuclear antibody, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, AT-III: antithrombin-III, BUN: blood urea nitrogen, CA19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, ChE: cholinesterase, Cl: chloride, CMV IgM Ab: cytomegalovirus antibody immunoglobrin M, Cre: creatinine, CRP: C-reactive protein, D-Bil: direct bilirubin, Fbg: fibrinogen, FDP: fibrinogen degradation product, γ-GTP: γ-glutamyl transferase, Hb: hemoglobin, HBcAb: hepatitis B core antibody, HBsAg: hepatitis B surface antigen, HBsAb: hepatitis B surface antibody, HCV Ab: hepatitis C virus antibody, HIV Ab: human immunodeficiency virus antibody, Ht: hematocrit, IgG: immunoglobrin G, IgG4: immunoglobulin G isotype 4, IgM: immunoglobrin M, Il-6: interleukin-6, K: potassium, LDH: lactate dehydrogenase, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibody, Na: sodium, NH3: ammonia, PIVKA-II: protein induced by vitamin K absence or antagonist-II, Plt: platelet count, PR3-ANCA: serine proteinase3-anti-neutrophil cytoplasmic antibody, PT%: percentage of prothrombin, RBC: red blood cell count, T-Bil: total bilirubin, TP: total protein, WBC: white blood cell count

was not recognized in any lymphoid tissue at the autopsy, and the possibility of modification by steroid treatment was considered. The right hepatic lobe was highly fibrotic with pseudolobules, cholestasis, lymphocytic infiltration, loss of some interlobular bile ducts, and ductular proliferation (Fig. 3c, d). In the area near the portal region, which was presumed to be the atrophic left liver, several peripheral nerve fiber bundles were densely mixed in the fibrotic foci, and mild lymphocytic infiltration was observed (Fig. 3e). Massive elastic fiber clumps were also found, and the portal vein at the hilar region had collapsed and was occluded. Fat deposits and a high degree of fibrosis from the center of the lobule, which are characteristic findings of alcoholic liver cirrhosis, were not observed. Although obliterative portal venopathy, defined as obliteration or stenosis with fibrosis of portal vein branches, was observed, nodular regenerative hyperplasia and incomplete septal cirrhosis, which are considered to be characteristic of idiopathic portal hypertension (IPH), were not observed (7). IL-6 immunostaining revealed IL-6-positive cells in the hilar lymph node tissue (Fig. 3f), and similar IL-6-positive cells were also found in highly fibrotic parts of the liver (Fig. 3g).

Discussion

MCD typically presents with clinical symptoms of a fever, lymph node swelling, and anemia due to hyper-IL-6 emia, often with a chronic course (5). In Japan, in cases with no symptoms of MCD, we follow patients without treatment, and if organ damage due to MCD is noted, we treated them with steroids and tocilizumab (6, 8). Organ damage, such as kidney damage, lung damage or heart failure, is an index of severity of MCD, but jaundice or liver damage is not such an index, according to the international and Japanese guidelines for MCD (6, 8). Thus, in this case, liver damage and marked atrophy of the left lobe of the liver were observed at the time of diagnosis, but they were not considered to be organ damage due to MCD; therefore, the patient had to be followed, as he had no symptoms and no organ damage.

Several papers have reported that the causes of jaundice in MCD are biliary obstruction due to direct exclusion of
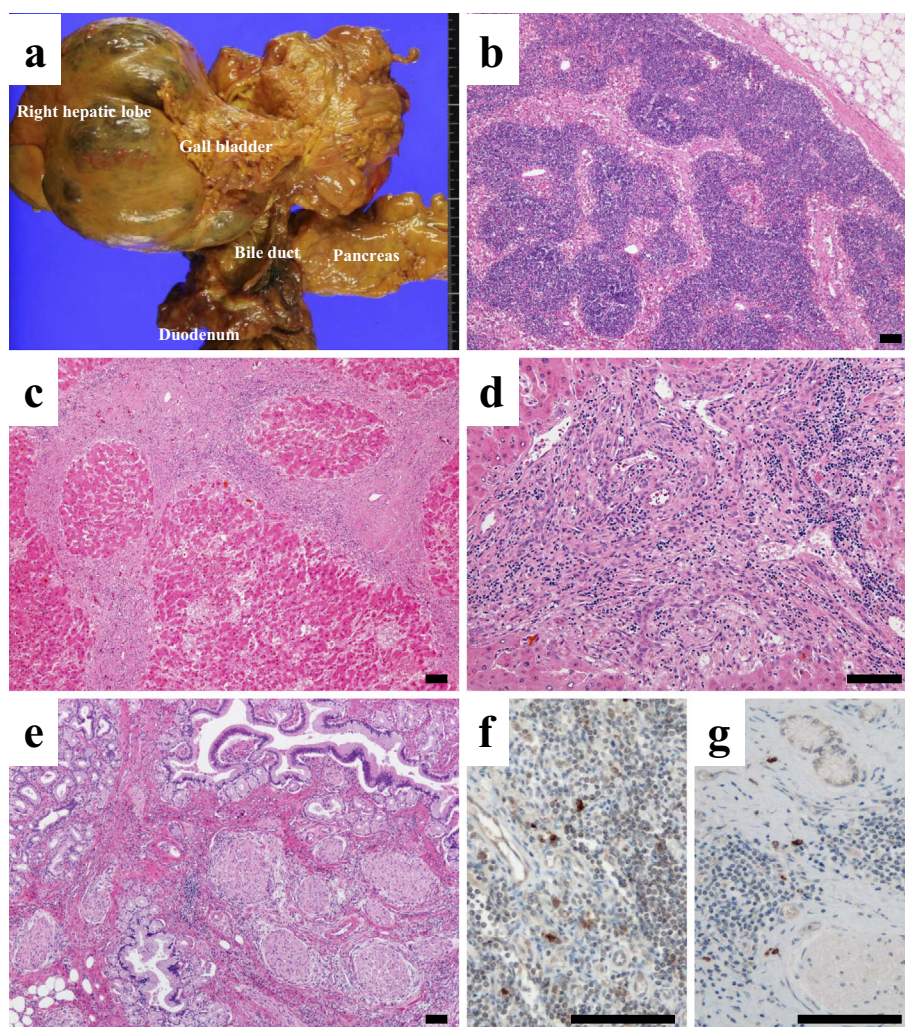
Figure 3. Autopsy findings. (a) Macroscopically, a globular and slightly separated liver was observed, the left lobe was not confirmed, and advanced fibrosis was observed in the hilar region. (b) Histopathologically, lymphoid follicles were diffusely distributed in the central part of the enlarged lymph node, but the lymphatic follicles were highly atrophic, and secondary follicles were not clear. There were a few plasma cells infiltrating between the follicles, and fibrotic thickening of the lymphatic sinuses was noticeable; Hematoxylin and Eosin (H&E) staining, scale bar, 100 μm. (c, d) The right hepatic lobe was highly fibrotic, with pseudolobules, cholestatic findings, lymphocytic infiltration, loss of some interlobular bile ducts, and ductular proliferation; H&E staining, scale bar, 100 μm. (e) In the area near the portal region, which was presumed to be the atrophic left liver, several peripheral nerve fiber bundles were densely mixed in the fibrotic foci, and mild lymphocytic infiltration was observed; H&E staining, scale bar, 100 μm. (f) IL-6-positive cells were found in the hilar lymph node tissue; IL-6 antibody staining, scale bar, 100 μm. (g) There were similar IL-6-positive cells in the highly fibrotic parts of the liver; IL-6 antibody staining, scale bar, 100 μm.

enlarged lymph nodes (9-11) or stricture due to biliary lesions with plasma cell infiltration (12) and that excision of enlarged lymph nodes or steroid therapy was effective for jaundice. In this case, no significant infiltration of plasma cells was observed in the liver biopsy specimen at the time of the diagnosis, and there was no clear evidence of compression of the enlarged lymph nodes into the bile duct on imaging findings when jaundice was noted. The coexistence of alcoholic liver cirrhosis, IPH, or biliary diseases, such as primary sclerosing cholangitis or IgG4-related diseases, was considered a differential disease, but these diseases were ruled out by blood tests, imaging findings, and liver tissue findings at the diagnosis and autopsy. Thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly (TAFRO) syndrome, which is well known to be refractory and lethal, was also considered as a differential diagnosis but was ruled out because the patient had hypergammaglobulinemia and no thrombocytopenia (13).

With regard to the effect of hyper-IL-6 emia on the liver, a sharp rise in IL-6 levels has hepatoprotective effects, such as antifibrosis, anti-inflammatory, and liver regeneration effects, while a chronic rise causes inflammation and hyper-

plasia of fibroblasts and promotes liver injury and liver fibrosis (14, 15). In addition, IL-6 acts as a neurotrophic factor on neural tissue to promote oligodendrocyte differentiation and regeneration of peripheral nerves (16). We speculated that chronic hyper-IL-6 emia might cause inflammatory changes accompanied by hyperfibrosis and fibroblast proliferation and peripheral nerve fiber bundles, which were observed on liver histopathology at the diagnosis and autopsy. There have been no reports on the involvement of hyper-IL-6 emia in biliary tract lesions in MCD, but some reports have indicated that approximately 20% of cases with IgG4-related disease, which is a differential disease due to its similar pathological condition to MCD, had hyper-IL-6 emia and that IL-6 might be involved in liver and biliary tract disorders of IgG4-related disease (17, 18). We speculated that, similar to IgG4-related disease with hyper-IL-6 emia, IL-6 might cause chronic inflammation and severe fibrosis in the liver and biliary tract of patients with MCD and result in the narrowing of not only the intrahepatic bile duct but also the portal vein.

In conclusion, we experienced an autopsy case of MCD with severe jaundice. We suspect that intrahepatic cholestasis due to inflammation and severe fibrosis in the liver caused by chronic hyper-IL-6 emia might have been the main cause of severe jaundice. Although rare, liver and biliary tract damage, such as liver injury and cholestasis, may also be considered organ disorders of MCD.

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

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