

[ CASE REPORT ]

## Cartilage-hair Hypoplasia Complicated with Liver Cirrhosis Due to Chronic Intrahepatic Cholestasis

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### Abstract:

We herein report a rare case of cartilage-hair hypoplasia (CHH) complicated with liver cirrhosis. A 20-year-old Japanese man with CHH was found incidentally to have liver cirrhosis and an esophageal varix. This patient had been treated for infections due to immunodeficiency since early childhood. He ultimately died of liver failure at 31 years of age. An autopsy revealed an abnormality of the interlobular bile ducts and intrahepatic cholestasis. Liver cirrhosis was thought to have been caused by chronic intrahepatic cholestasis due to biliary duct hypoplasia and changes in the intestinal microbiome. Therefore, CHH may cause biliary cirrhosis due to multiple effects.

**Key words:** cartilage-hair hypoplasia, chronic intrahepatic cholestasis, liver cirrhosis, agammaglobulinemia, biliary hypoplasia

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### Introduction

Cartilage-hair hypoplasia (CHH) is an extremely rare, congenital, autosomal recessive metaphyseal chondrodysplasia manifested by short-limbed dwarfism, hypoplastic hair, and defective immunity and erythropoiesis (1-3). Mutations in the RNA component of the mitochondrial RNA processing endoribonuclease (*RMRP*) gene are associated with CHH (4, 5). This genetic disease has a relatively poor prognosis due to a spectrum of disorders with protean clinical manifestations (6). Therefore, careful attention to monitoring the complications is prudent.

To our knowledge, this is the first report of a CHH case complicated with agammaglobulinemia and chronic intrahepatic cholestasis with a fatal course after complications involving an esophageal varix and hepatic ascites.

### Case Report

A 20-year-old Japanese man was found incidentally to be suffering from liver cirrhosis and an esophageal varix on an abdominal ultrasound evaluation following lower abdominal discomfort. He had been admitted for his first consultation with our hospital eight years ago for *Streptococcus pneumoniae* meningitis and recurrent respiratory tract infections. At the first admission, the patient's history of repetitive infections and physical features led us to suspect CHH. Polymerase chain reaction testing of *RMRP* was performed using blood DNA. Consequently, new *RMRP* mutations (16-bp dup at +1 on the paternal allele, and 168G>A on the maternal allele) and clinical phenotypes were detected (4).

The patient had a history of agammaglobulinemia symptomatic of CHH. Therefore, regular and careful intravenous immunoglobulin at 400 mg/kg body weight was adminis-

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**Table. Summary of the Laboratory Data.**

		Normal range	Previous procedure
<b>Complete blood count</b>			
<b>White blood cells</b>			
Neutrophils	%	30-97	36
Haemoglobin	g/dL	36.6-79.9	70.7
Platelet counts	$\times 10^4/\mu\text{L}$	13.1-17.6	16.8
		12.4-30.5	4.3
<b>Biochemistry</b>			
Total bilirubin	mg/dL	0.1-1.2	1.6
Aspartate aminotransferase	IU/L	12-35	54
Alanine aminotransferase	IU/L	6-40	43
Lactate dehydrogenase	IU/L	119-229	256
$\gamma$ -glutamyl transpeptase	IU/L	0-48	121
Alkaline phosphatase	IU/L	115-359	634
Blood-urea-nitrogen	mg/dL	7.4-19.5	12
Creatinine	mg/dL	0.5-1.2	0.4
Total protein	g/dL	6.4-8.3	6.6
Albumin	g/dL	3.8-5.2	4.6
Sodium	mEq/L	135-147	142
Potassium	mEq/L	3.4-4.8	4.1
Ammonia	$\mu\text{g/dL}$	12-66	36
IgG	mg/dL	861-1,797	505
IgA	mg/dL	93-393	<2
IgM	mg/dL	33-183	<3
<b>Coagulation</b>			
PT-INR		0.89-1.12	1.18
APTT	s	23.6-31.3	88.2
<b>Tumor marker</b>			
Alpha-fetoprotein	ng/mL	0-10	2
PIVKA-II	mAU/mL	0-39	45
<b>Serology</b>			
Hepatitis B surface antigen		(-)	(-)
Hepatitis C virus antibody		(-)	(-)
Anti-nuclear antibody		<40	<40

PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, PIVKA-II: protein induced by vitamin K absence-II

tered. His family history revealed hepatocellular carcinoma in his paternal grandfather and heart disease in his paternal grandmother. He was a non-smoker, did not drink alcohol, and had no food or drug allergies.

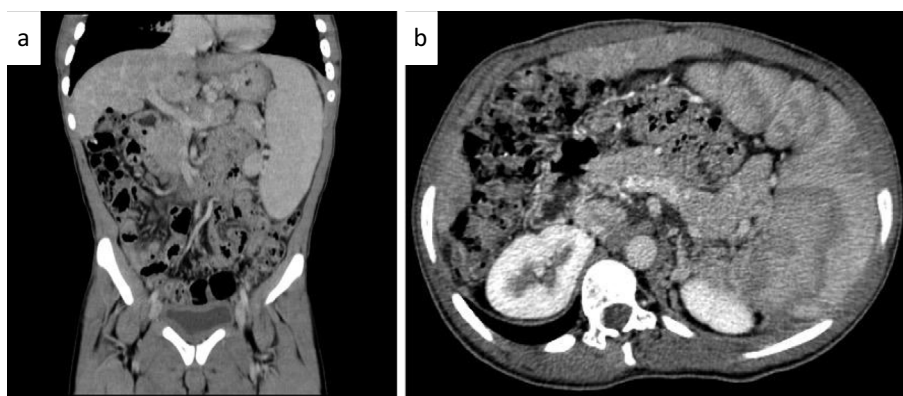
On a physical examination at a referral visit to our department, he appeared well. His axillary temperature, heart rate, blood pressure, and respiratory rate were 35.6°C, 90 beats/min, 132/67 mmHg, and 12 breaths/min, respectively. His height was 101.6 cm, weight 21.8 kg, and body mass index 21.4. He had severe short stature, disproportionate short-limbed dwarfism, and short and puffy hands. Hyperextensibility of the joints was not detected. Scalp hair and eyebrows were observed, but the eyelashes, armpit hair, and pubic hair were fair, very fine, and sparse, respectively. No nail dysplasia or dental abnormalities were found. No conjunctival pallor, icterus, or cyanosis were detectable. Cardiovascular and respiratory examinations revealed normal heart sounds with no detectable murmurs, and the breath sounds were without crackle. An abdominal examination revealed a non-palpable liver and palpable spleen two fingers below the

rib arch. There were no stigmata of liver disease nor spider nevi or caput medusae. His bowel sounds were normal, but mild ascites was present.

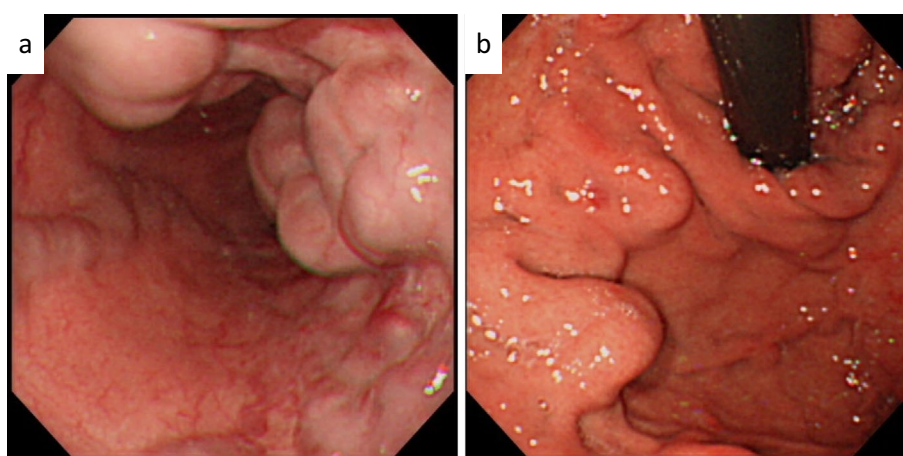
Table shows the laboratory data at the referral visit. The platelet count was extremely low. Anti-nuclear antibodies were negative. Serology detected anti-hepatitis B (HB) and anti-HB core (HBc) antibodies, but not HB virus DNA. The outstanding finding was extremely low  $\gamma$ -globulin.

Abdominal enhanced computed tomography showed a rough liver with blunted margins and atrophy of the right lobe. Splenomegaly was noted with retrogastric varices and a splenorenal shunt. There was no obstruction in the bilateral intrahepatic ducts and no significant lymph node swelling, but mild ascites was observed (Fig. 1). Upper gastrointestinal endoscopy showed varices with blue and cherry-red spots in the lower esophagus. There was no compression when air was insufflated. Furthermore, extension of the gastric varices was found in the cardia toward the greater curvature and into the gastric fundus (Fig. 2).

The patient was diagnosed with liver cirrhosis and



**Figure 1.** (a) A coronal view of abdominal computed tomography (CT) shows the rough inside, blunted margins, and atrophy of the right lobe of the liver. (b) An axial view of abdominal CT shows splenomegaly and a splenorenal shunt.



**Figure 2.** (a) Esophageal varices [Ls, F3, Cb, RC (+)] are present from the upper esophagus to the esophagogastric junction. (b) Gastric varices [Lg-c, F2, Cb, RC (-)] are present in the gastric cardia.

esophageal varices complicated with CHH. To prevent varix rupture, he was treated with endoscopic variceal band ligation. Despite  $\beta$ -blocker therapy and eight additional endoscopic variceal band ligation sessions following discharge, a follow-up endoscopy revealed multiple fundic varices with cherry-red spots. Ten years after the diagnosis of liver cirrhosis, his liver function gradually deteriorated, and the patient ultimately died of liver failure at 31 years old. An autopsy was performed to determine the correlation between CHH and liver cirrhosis.

### Autopsy findings

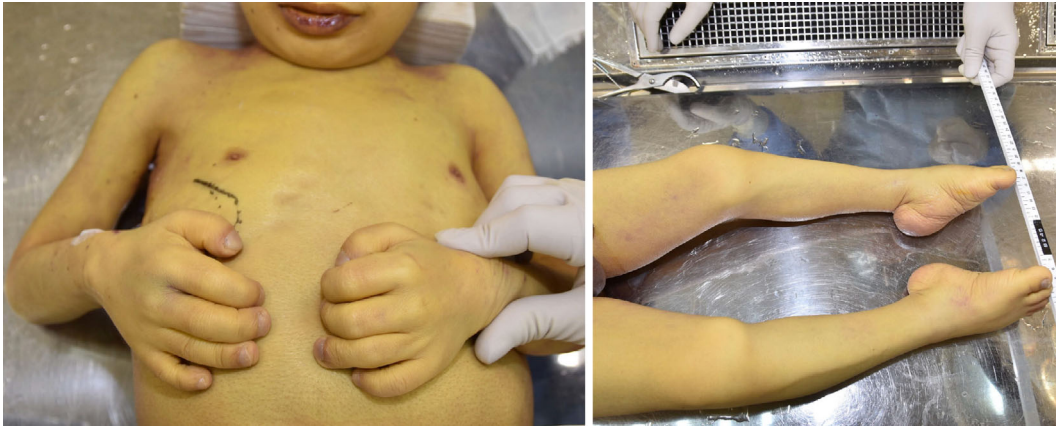
On a gross examination, the autopsy confirmed the general findings of liver cirrhosis and splenomegaly, mild ascites (0.4 L), and gastric and esophageal varices. The liver weight was 334 g with a coarse surface, and macroscopic portal tract fibrosis and cirrhosis (Fig. 3, 4). A histopathological examination of the liver showed perivenular and pericellular fibrosis along with regenerating parenchymal nodules separated by dense fibrotic bands. In the nodules, there was widespread irregular hepatocyte shedding and necrosis, which was consistent with acute or chronic liver fail-

ure (Fig. 5). As a characteristic finding, neither focal necrosis nor interface hepatitis was observed. However, chronic intrahepatic cholestasis was found, and the 20% of interlobular bile ducts was disappeared in the portal tract. (Fig. 6). Lymphocytes had mainly infiltrated into the fibrotic areas. Immunohistochemical staining of the lymphocytes revealed a predominant CD8+ infiltrate (Fig. 7). In addition, the HB antigen was detected, suggesting HB virus infection (Fig. 8). A histopathological examination of the spleen showed thickening of the splenic column and hemophagocytic images, which was consistent with portal hypertension. Finally, the white pulp of the spleen was obscured (Fig. 9).

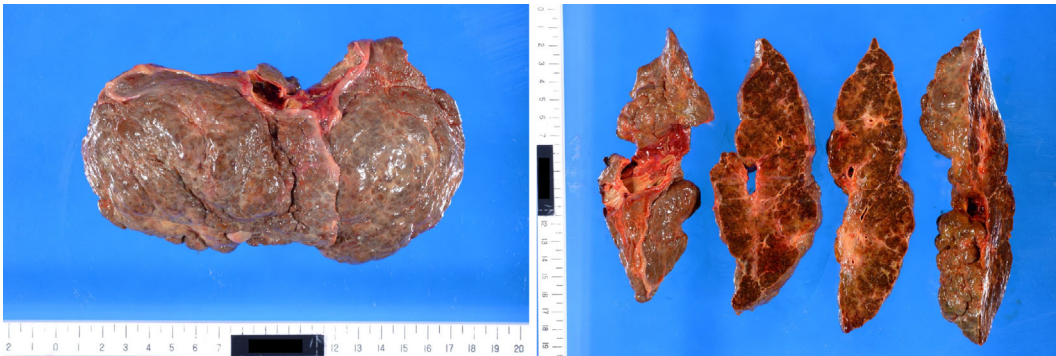
### Discussion

To our knowledge, this is the first report of a case of CHH complicated with end-stage liver disease. CHH was first reported by McKusick et al. (7) in a child with cartilage-hair dysplasia immunocompromised to chickenpox in 1964. This congenital disease is an autosomal-recessive disorder caused by mutations in *RMRP* (8, 9). *RMRP* functions as a nuclear reservoir for a group of long non-coding

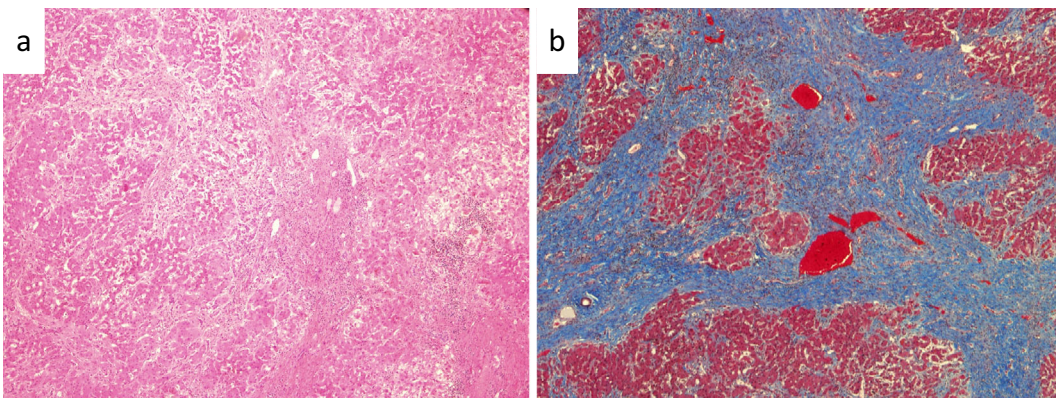




**Figure 3.** The patient has a severe short stature, disproportionate short-limbed dwarfism, and short and puffy hands. The scalp hair and eyebrows are present, but the eyelashes, armpit hair, and pubic hair are fair, very fine, and sparse, respectively.



**Figure 4.** (a) Gross examination findings. The liver weight was 334 g, and the surface was coarse with macroscopic portal tract fibrosis or cirrhosis. (b) Cross section view.

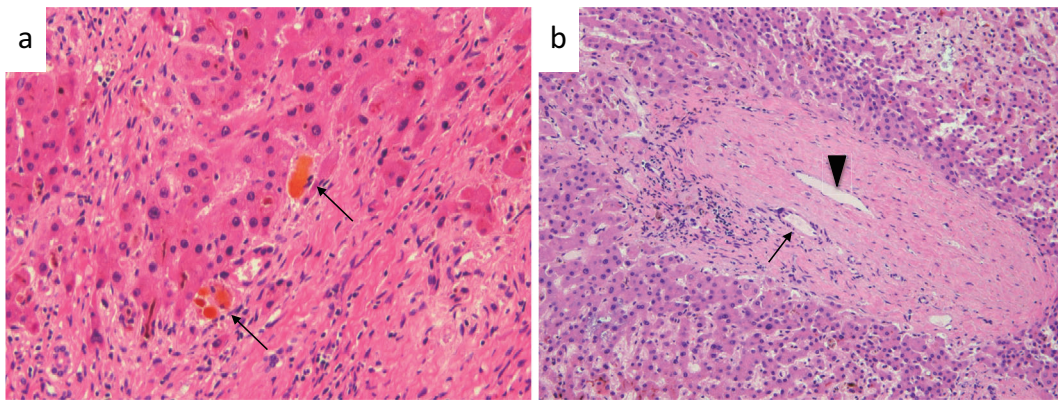


**Figure 5.** (a) Histological findings of the liver biopsy specimen (Hematoxylin and Eosin staining,  $\times 40$ ). Perivenular and pericellular fibrosis with regenerating parenchymal nodules separated by dense fibrotic bands are present. Mild periportal inflammation comprised of lymphocytes and hepatocytes is observed. In the nodules, there is widespread irregular hepatocyte shedding and necrosis. (b) Bridging fibrosis and fibrotic expansion of the portal tract are observed (Masson trichrome stain,  $\times 40$ ).

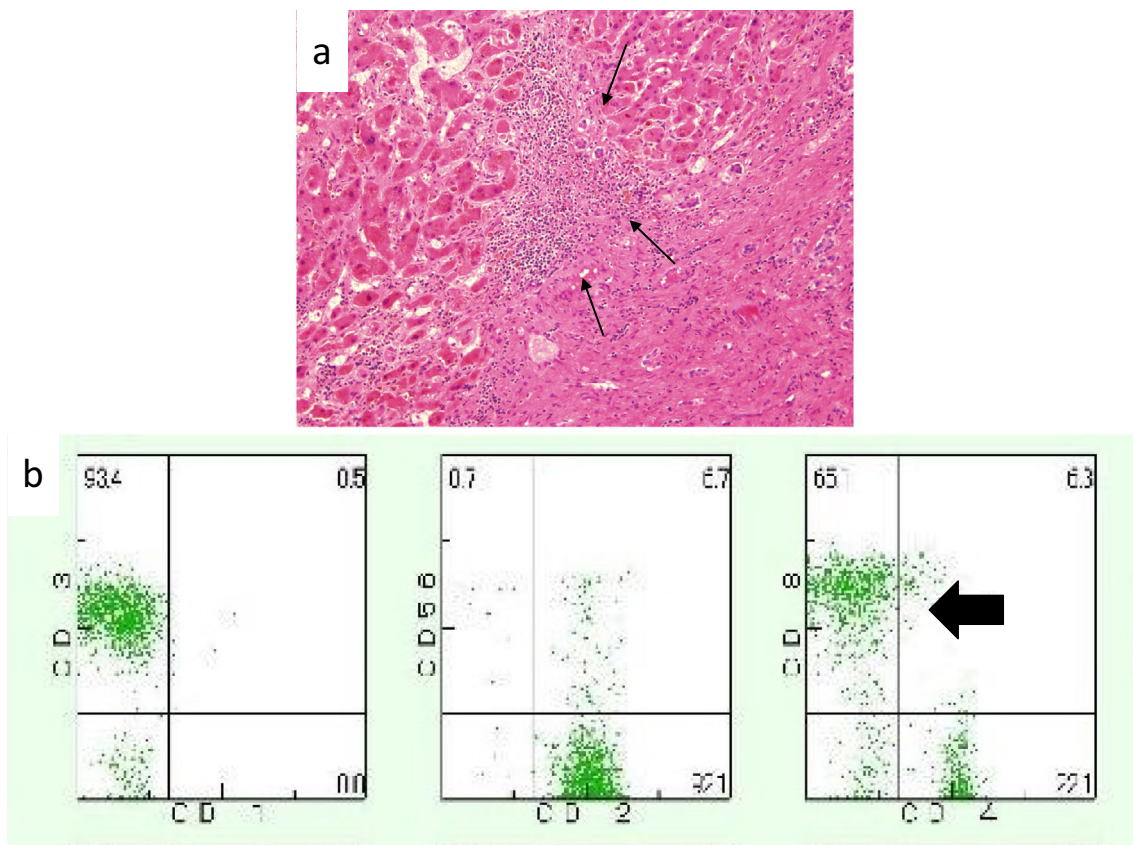
RNAs with gene-silencing activity. Gene targets include those with functions related to bone and cartilage growth. In the present case, *RMRP* mutations, 16-bp dup at +1 on the

paternal allele and 168G>A on the maternal allele, were detected.

CHH is a spectrum disorder with protean clinical mani-



**Figure 6.** (a) The accumulation of bilirubin is observed in hepatocytes (arrow) [Hematoxylin and Eosin (H&E) staining,  $\times 400$ ]. Chronic cholestasis is present. (b) Branches of the hepatic artery (arrow) and portal vein (star shape) are present in the portal tract. Interlobular bile ducts are absent. In this portal tract, mild chronic inflammatory infiltrate, including lymphocytes, is observed (H&E staining,  $\times 200$ ).



**Figure 7.** (a) Lymphocytes are mainly concentrated in the fibrotic area (Hematoxylin and Eosin staining,  $\times 200$ ). (b) The lymphocyte surface marker analysis shows that CD8+lymphocytes are predominant (arrow).

festations including immunodeficiency, an abnormal/malfunctioning musculoskeletal system, and gastrointestinal abnormalities (10-12). Furthermore, this genetic disease is associated with T-cell and B-cell immunodeficiency, which is the leading cause of death in this syndrome (13). Therefore, surveillance for immunodeficiency is important to perform for all CHH patients, and immunoglobulin replacement is

required in some individuals with hypogammaglobulinemia.

The present case was treated for immunodeficiency using an intravenous immunoglobulin preparation and closely monitored for complications. Consequently, no serious infections occurred. However, this case was fatal owing to liver failure complicated with varix rupture and hepatic ascites. To our knowledge, the liver has not been reported as an or-



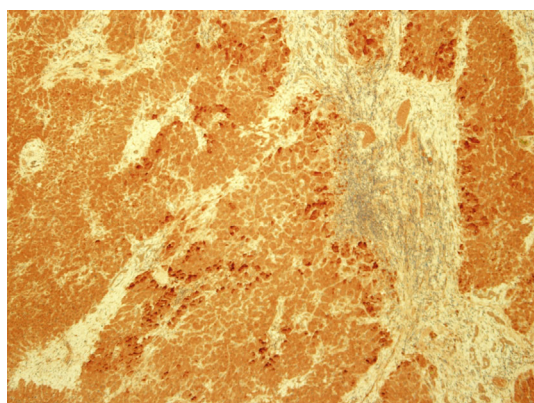
gan exhibiting clinical manifestations caused by mutations in *RMRP*. Initially, we suspected that the cause of cirrhosis was hepatitis virus infection, as the hepatocytes were positive for the HB antigen. However, a histopathological examination did not reveal any characteristic findings of a hepatitis virus infection, such as either focal necrosis or interface hepatitis. One characteristic finding was the loss of bile duct structure without destructive cholangitis in 20% of the interlobular bile ducts in the portal tract. In addition, liver histopathology revealed ductular proliferation and expansion of the portal areas due to fibrotic nodular transformation that correlated with the development of secondary biliary cirrhosis from intrahepatic cholestasis. Furthermore, widespread and irregular hepatocyte shedding and necrosis were observed. The hepatocyte shedding and necrosis was complicated by pneumonia, suggesting the involvement of an infection. As a result, we speculated that the patient had developed acute or chronic liver failure due to rapid hepatocellular necrosis caused by infection, against a background of biliary cirrhosis.

Previous studies have reported hepatic injury in primary hypogammaglobulinemia patients. They revealed histological cholestasis without destructive cholangitis that was associ-

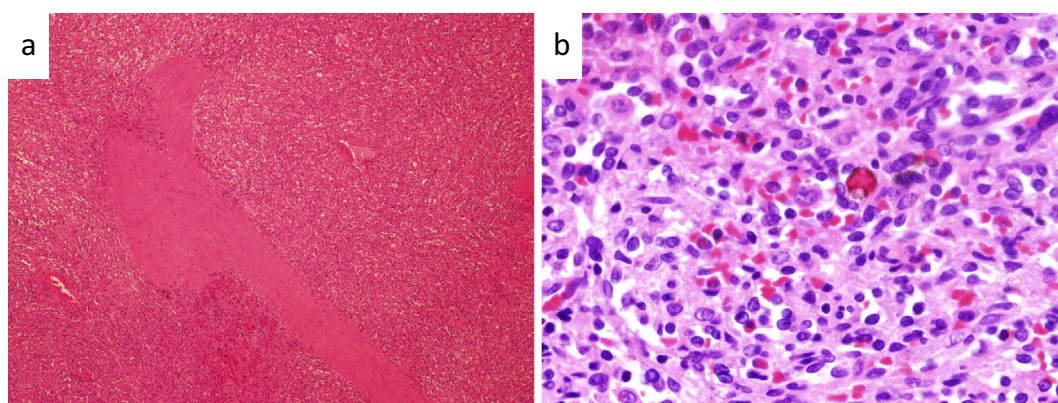
ated with poorly described liver lesions. Furthermore, cholestasis, mainly anicteric, and portal hypertension were reported to be the main hepatic manifestations in patients with hypogammaglobulinemia (14).

The diagnosis of the present case required eliminating other conditions associated with chronic cholestasis (15, 16). The most common causes of chronic progressive cholestasis in adults are primary biliary cirrhosis (PBC) and primary sclerosing cholangitis. In the present case, comprehensive laboratory tests targeting PBC and primary sclerosing cholangitis were negative. Furthermore, the pathology from the autopsy revealed intrahepatic biliary hypoplasia rather than typical bile duct destruction, as found in PBC. Another disease associated with chronic cholestasis is idiopathic adulthood ductopenia (IAD), which is defined as the loss of  $\geq 50\%$  of the interlobular and septal bile ducts among  $\geq 20$  portal tracts in an adult. However, this was a case of chronic intrahepatic cholestasis due to the loss of interlobular and septal bile ducts of approximately 20%, which does not meet the diagnostic criteria for IAD. (17-19). Therefore, the above factors were deemed insufficient as causes leading to biliary cirrhosis.

Other studies have also reported that, when the composition of the intestinal microbiome is altered (dysbiosis), excess bacterial fragments and products can reach the liver through the portal system, contributing to chronic inflammation and liver fibrosis (20). Changes in the intestinal microbiome contribute to the early stages of diseases, such as hepatic steatosis and fibrosis, especially during the development of alcoholic liver disease and non-alcoholic fatty liver disease (21). Furthermore, alterations in the intestinal microbiome have been associated with liver cirrhosis and its complications, such as esophageal varices (22). The present patient had been treated for infections due to immunodeficiency since early childhood. As a result of these treatments, there may have been changes in the intestinal microbiome that affected the liver and contributed to the liver fibrosis. Therefore, the present case is most likely related to agammaglobulinemia with a background of congenital ductopenia



**Figure 8.** Cells are positive for anti-hepatitis B antigen (Orcein staining,  $\times 200$ ).



**Figure 9.** (a) A histopathological examination of the spleen shows thickening of the splenic column and hemophagocytic images, which is consistent with portal hypertension [Hematoxylin and Eosin (H&E) staining,  $\times 40$ ]. (b) The white pulp of the spleen is obscured (H&E staining,  $\times 400$ ).

and multiple effects, such as cholestasis, portal hypertension, and changes in the intestinal microbiome.

### Conclusion

To our knowledge, this is the first reported case of CHH complicated with end-stage liver disease due to chronic intrahepatic cholestasis. Because CHH may be a liver disorder manifesting with intrahepatic cholestasis due to bile duct hypoplasia or immunodeficiency, patients with CHH and immunodeficiency should be closely monitored for chronic intrahepatic cholestasis.

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

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