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CASE REPORT

Liver cirrhosis in a child associated with Castleman's disease: A case report

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Author contributions: Kobayashi S and Inui A designed the report; Kobayashi S collected the patient's clinical data; Tsunoda T, Umetsu S, Sogo T, Mori M and Fujisawa T participated in study design; Kobayashi S and Inui A analyzed the data and wrote the paper; Shinkai M performed a lymph node biopsy; all authors have finally approved the version of the article to be published.

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Abstract

BACKGROUND

Castleman's disease (CD) is a lymphoproliferative disorder. TAFRO syndrome is classified as a variant of CD based on its key clinical manifestations of thrombocytopenia, anasarca (generalized edema and pleural effusion), fever (pyrexia), reticulin fibrosis in the bone marrow and the proliferation of megakaryocytes, and organomegaly (such as hepatosplenomegaly and multiple lymphadenopathies); TAFRO syndrome is mainly reported in Japanese patients. To our knowledge, this is the first pediatric case report detailing a CD-associated disorder progressing to cirrhosis.

CASE SUMMARY

A 10-year old male patient presented with fever and anemia. Six months before hospitalization, he had remarkable abdominal distention. Subsequently, he visited a clinic for a fever that lasted 5 d. The physical findings were marked hepatosplenomegaly and cervical lymphadenopathy. A blood test revealed leukocytosis, microcytic anemia, aspartate aminotransferase-dominant transaminase elevation, high levels of C-reactive protein, polyclonal hypergammaglobulinemia, and high levels of interleukin-6 and vascular endothelial growth factor. Abdominal contrast computed tomography and magnetic resonance imaging suggested cirrhosis, which was confirmed by liver histology. Histological findings in the enlarged hepatic lymph nodes revealed both hyperplasia and atrophy of lymphoid follicles with some vascular hyperplasia and moderate plasmacytosis between the lymphoid follicles, which is compatible with lymph node histology in TAFRO syndrome. Prednisolone was

Pharmaceutical Co., Ltd., and Asahikasei Pharmaceutical Co." Other authors declare that there is no conflict of interest. Even though there is a COI to disclose as of January 2020, this will not prevent the submission from proceeding.

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not effective in reducing the patient's symptoms; therefore, the patient was prescribed tocilizumab. To date, the patient remains free of fever and continues to receive tocilizumab.

CONCLUSION
We described the clinicopathological features of TAFRO syndrome to highlight the clinical presentation of this rare disease in a pediatric case.

Key words: Castleman disease; Case report; Multi-centric Castleman's disease; Liver cirrhosis; Tocilizumab; Child

Core tip: Castleman disease (CD) is a lymphoproliferative disorder of unknown cause. TAFRO syndrome is classified as a variant of CD based on its key clinical manifestations of thrombocytopenia, anasarca (generalized edema and pleural effusion), fever (pyrexia), reticulin fibrosis (reticulin fibrosis in the bone marrow and the proliferation of megakaryocytes), and organomegaly (*e.g.*, hepatosplenomegaly and multiple lymphadenopathies). To our knowledge, this is the first pediatric case report detailing a CD-associated disorder progressing to cirrhosis.

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INTRODUCTION

Castleman's disease (CD) is a lymphoproliferative disorder with an unknown cause, classified into unicentric (unicentric distribution of the disease) and multicentric (multicentric distribution of the disease) types. While in Western countries, the human herpesvirus 8 (HHV-8) infection-related multicentric CD is common[1,2], majority of the CD cases in Japan are idiopathic[3,4]. The clinical features include anemia, multiple lymphadenopathy, increased inflammatory response, polyclonal hypergammaglobulinemia, and thrombocythemia. Histologically, the hyaline vascular type (HV type) is common in the unicentric type, and multicentric types are further classified into plasma cell type (PC-type) and mixed-type[5]. Patients with the mixed-type idiopathic multicentric Castleman's disease (MCD), characterized by thrombocytopenia, anasarca (generalized edema and pleural effusion), fever (pyrexia), reticulin fibrosis in the bone marrow and the proliferation of megakaryocytes, and organomegaly (such as hepatosplenomegaly and multiple lymphadenopathies), are considered to have TAFRO syndrome (thrombocytopenia, anasarca, fever, renal impairment or reticulin fibrosis, and organomegaly) and often follow a more severe course[6]. There are no case reports of children with CD or TAFRO syndrome who subsequently develop cirrhosis. We presented this pediatric case to expand our understanding of this disease.

CASE PRESENTATION

Chief complaints

A 10-year-old Japanese boy presented with fever and anemia.

History of present illness

Six months before his hospitalization, the patient experienced remarkable abdominal distention. Subsequently, he visited a clinic for fever that persisted for 5 d. His blood test results were as follows: White blood cell 13.2 × 10^3/μL (white blood cell normal range: 3.5 × 10^3/μL-8.5 × 10^3/μL), hemoglobin 9.8 g/dL (hemoglobin normal range: 11.5-15.0 g/dL), and C-reactive protein (CRP) 8.6 mg/dL (CRP normal range: 0.03 mg/dL or less). Therefore, he was referred to our hospital.

Past illness and family history

His family history did not reveal anything of significance to his present condition. He was diagnosed with Kawasaki disease when he was 1 year old and treated with intravenous immunoglobulin therapy and antiplatelet drugs. He had a fever of unknown origin when he was 7 years old.

Physical examination

His physical examination revealed no growth disorder. His height and weight were 141.0 cm (+ 1.0 SD) and 34.5 kg (0.0 SD), respectively. His body temperature was 36.3 °C. Redness of the pharynx and bleeding spots in the soft palate were observed, and his lymph nodes were palpable in the cervical region. The patient's abdomen was slightly distended. Upon investigation, his liver was palpable 10 cm below the right costal margin and his spleen 6 cm below the left costal margin.

Laboratory examinations

Laboratory examinations were performed and are summarized in Table 1. A blood test revealed neutrophil-dominant leukocytosis, microcytic hypochromic anemia, elevation of aspartate aminotransferase (AST)-dominant transaminase, high CRP, polyclonal hypergammaglobulinemia, and high interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF).

Imaging examinations

Abdominal ultrasound revealed a rough texture of the liver. Abdominal contrast computed tomography (CT) detected hepatosplenomegaly and heterogeneous reduction of the density of the liver, suggesting advanced cirrhosis. Multiple lymphadenopathies were found in the hepatic portal, and the mesenteric and celiac arteries. A small number of ascites was observed in the pelvis (Figure 1). Multiple nodules were observed in the liver. However, the abdominal enhanced magnetic resonance imaging (MRI) did not show washout of the contrast agent in the nodules during the late phase of the contrast enhancement, which suggested regenerative nodules (Figure 2).

Further diagnostic work-up

Upon bone marrow examination, no monoclonal cell proliferation was observed. In positron emission tomography with CT, the standardized uptake values for the right hepatic lobe, hepatic portal, and intestinal membrane were about 2.0-3.0. Upper gastrointestinal endoscopy revealed esophageal varices. Liver histology showed sinusoidal dilation in the hepatic lobule, significant inflammatory cell infiltration, bile ductular proliferation, and fibrotic expansion in portal areas (Figure 3). When testing for high serum immunoglobulin G4 (IgG4) levels (191 mg/dL), a special immunohistological staining of the liver tissue was negative for IgG4. Endoscopic retrograde cholangiopancreatography showed no evidence of sclerosing cholangitis, leading to the negative diagnosis of Langerhans cell histiocytosis- or immunodeficiency-related sclerosing cholangitis. Intraoperative findings from laparoscopy revealed roughness of the liver surface, suggesting liver cirrhosis (Figure 4). Laparoscopic lymph node biopsy revealed both hyperplasia and atrophy of lymphoid follicles, lymphoid proliferation with some vascular hyperplasia, and moderate interfollicular plasmacytosis (Figure 5).

FINAL DIAGNOSIS

Based on the abovementioned findings, the final diagnosis was CD-associated disease.

TREATMENT AND OUTCOME

According to the treatment regimen for CD, 1 mg/kg per day of prednisolone (PSL) was administered for 4 wk. However, there was no improvement in fever and serum CRP. Finally, the patient was switched from PSL to 8 mg/kg per day of tocilizumab, and the fever subsided.

DISCUSSION

CD is a rare lymphoproliferative disorder first reported by Castleman *et al*[7] in 1956. To date, there has been no epidemiological study of the disease in children. However,

Table 1 Laboratory findings on admission

Blood cell count	
WBC	8.49 × 10^3/μL
NET%	76.1%
LYP%	19.8%
MONO%	2.7%
EOS%	1.3%
RBC	423 × 10^4/μL
Hb	9.5 g/dL
Ht	31.2%
MCV	73.8 fL
MCH	22.5 pg
MCHC	30.4%
PLT	17 × 10^4/μL
Biochemical and immune serum examination	
TP	8 g/dL
Alb	3.1 g/dL
T-bil	1 mg/dL
D-bil	0.6 mg/dL
AST	95 U/L
ALT	63 U/L
LDH	289 U/L
γ-GTP	132 U/L
ALP	3152 U/L
Glu	97 mg/dL
BUN	7.5 mg/dL
Cr	0.39 mg/dL
CRP	6.83 mg/dL
Fe	24 μg/dL
TIBC	299 μg/dL
UIBC	286 μg/dL
Ferritin	65.9 ng/mL
NH_3	36 μg/dL
AFP	1.3 ng/mL
IgG	2265 mg/dL
IgG4	191 mg/dL
IgA	469 mg/dL
IgM	399 mg/dL
Blood coagulation examination	
PT ratio	60.5%
APTT	32.2 s
Fib	328 mg/dL
FDP	6.6 μg/mL
D-dimer	2.8 μg/mL
Cytokine/VEGF	
IL-6	40 pg/mL
VEGF	49.2 pg/mL
Virologic test	
HIV antibody	(-)
HHV-8 PCR	(-)

WBC: White blood cell; RBC: Red blood cell; Hb: Hemoglobin; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; PLT: Blood platelet; CRP: C-reactive protein; TP: Total protein; ALP: Albumin; Glu: Glucose; BUN: Blood urea nitrogen; TIBC: Total iron binding capacity; UIBC: Unsaturated iron binding capacity; AFP: Alpha fetoprotein; VEGF: Vascular endothelial growth factor; HIV: Human immunodeficiency virus; PCR: Polymerase chain reaction.

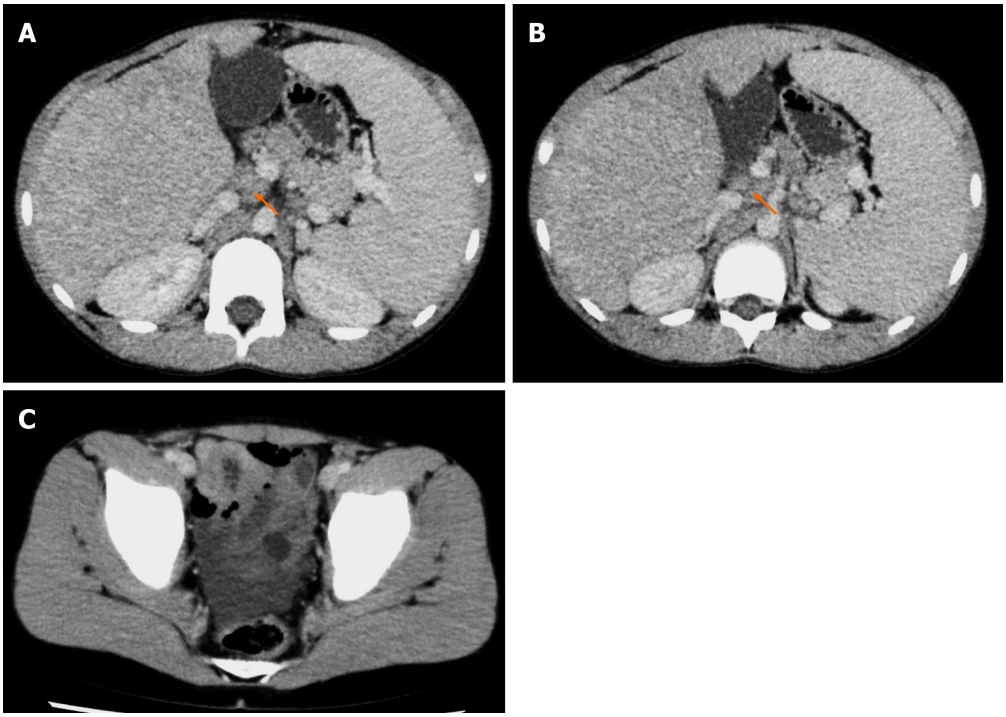

Figure 1 Abdominal contrast computed tomography. A and B: Arrow represents hepatic lymphadenopathy; C: A small number of ascites was observed.

a study conducted in the United States estimated the annual incidence of CD to be 0.24 per million[8]. A study conducted in Japan estimated the prevalence and annual incidence to be approximately 1500 and 1 per million, respectively[9]. Regarding pathological types, the syndrome can be classified into hyaline-vascular type (HV-type), plasma cell type (PC-type), and mixed type. Regarding clinical characteristics, CD can be roughly classified into single (localized) and multiple (systemic). Lymphadenopathy is most frequently observed in the mediastinum, while rare in the hepatic portal region[10]. The close relationship of MCD with HIV and HHV-8 has been emphasized in Western countries[1,2]. However, the relationship is seldom mentioned in studies conducted in Japan[3,4]. Fajgenbaum *et al*[11] reported HHV-8-negative MCD as idiopathic MCD (iMCD). In Japan, most patients with MCD are classified as having iMCD. In 2010, Takai *et al*[6] named the TAFRO syndrome based on its key clinical manifestations of thrombocytopenia, anasarca (generalized edema and pleural effusion), fever (pyrexia), reticulin fibrosis (reticulin fibrosis in the bone marrow and the proliferation of megakaryocytes), and organomegaly (*e.g.*, hepatosplenomegaly and multiple lymphadenopathies). The histology of lymph nodes in patients with TAFRO syndrome revealed CD-like (*i.e.*, mixed-type or HV-type) characteristics. Therefore, some researchers classify TAFRO syndrome, which is rare in western regions, as a type of MCD. In most cases, patients with TAFRO syndrome have increased gamma globulin levels, decreased platelet levels, smaller lymph nodes, and significant subacute development of pleural effusion and edema, and follow a progressive (sometimes lethal) course[12,13].

In the present case, the findings from the histopathological examination of the lymph node biopsy, which was performed by a pathologist, Dr. Kojima, a member of the Castleman disease, TAFRO, and related disease research group, indicated a diagnosis of TAFRO syndrome. However, despite the presence of mild ascites, no renal dysfunction, reticulin fibrosis in the bone marrow, general anemia, or thrombocytopenia (100000/μL) were found at the first visit. Thus, the symptomology did not meet the diagnostic criteria for TAFRO syndrome. In addition, the patient had intermittent fever, but he was in good general condition. The patient not presenting with all the symptoms of the TAFRO syndrome might be because he has been receiving treatment early in the disease process due to early diagnosis. Marked hepatosplenomegaly and cirrhosis were particularly dominant in this case. There are 8 case reports of patients with MCD or TAFRO syndrome complicated by hepatobiliary disorders[14-20] (Table 2). Case reports by Baruch *et al*[14] included the description of cirrhosis in patients with Budd-Chiari syndrome. On the other hand, a study has reported diffuse liver fibrosis, cholangitis, and nodular regenerative hyperplasia (NRH)[17], suggesting that liver disease is associated with MCD and related diseases.

The pathogenesis may be explained by the overproduction of IL-6 by the germinal

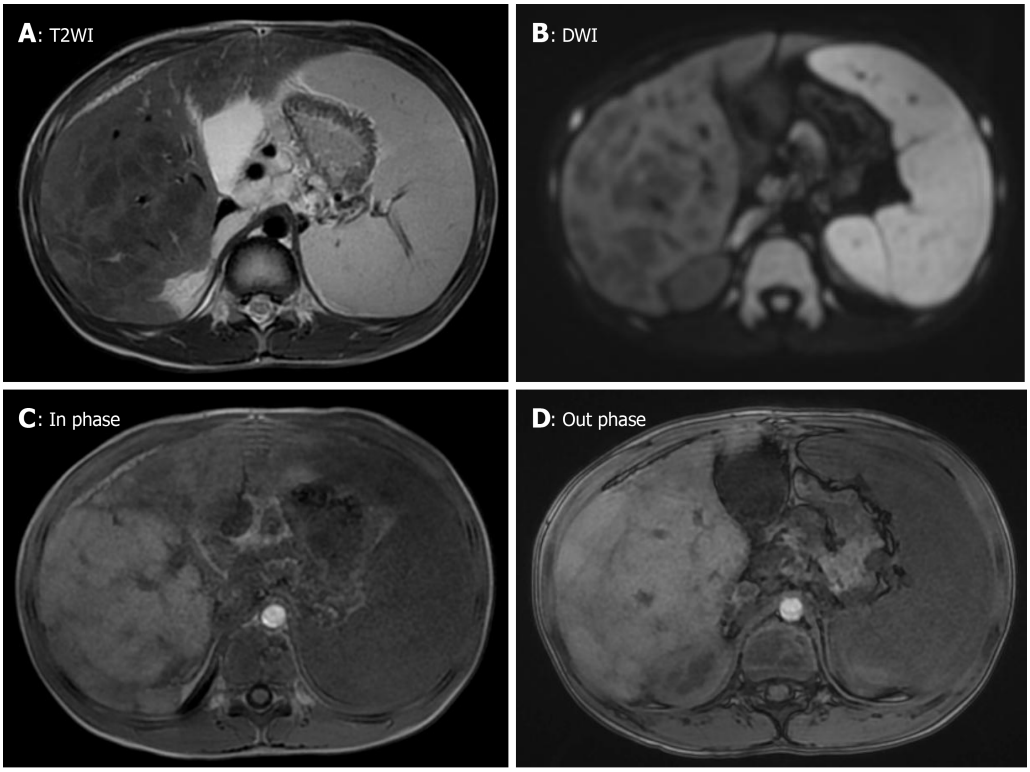

Figure 2 Abdominal enhanced magnetic resonance imaging. A and B: Multiple nodules were observed in the liver; C and D: No washout of the contrast agent in the nodules was detected in the late phase of contrast enhancement.

center of the lymph nodes. The detailed mechanisms of MCD and TAFRO syndrome are unknown. However, some patients respond to tocilizumab (humanized anti-human IL-6 receptor monoclonal antibody), suggesting that IL-6 is involved[21,22]. The overproduction of IL-6 promotes differentiation into plasma cells, which in turn produce VEGF and bind to hepatocyte receptors, promoting endothelial permeability and neovascularization. Hypoxia due to blood vessel remodeling, impaired blood flow, and imbalance between demand and supply of oxygen promotes collagen synthesis[23-25] and leads to fibrosis, suggesting that there is a relationship between VEGF and fibrosis.

CONCLUSION

CD associated disorder should be suspected in patients with fever of unknown origin, hepatosplenomegaly, lymphadenopathy, or polyclonal hypergammaglobulinemia. To date, there is no detailed study of liver pathology in patients with CD-associated disorder. Further understanding of CD-associated disorder may help clarify the mechanism of CD.

Table 2 Patients with multicentric Castleman's disease/TAFRO syndrome complicated by hepatobiliary diseases

Year	Age/sex	Diagnosis	Type	Pathological findings of the liver	Outcome	Ref.
1991	22/F	CD	Mixed	Liver cirrhosis associated with Budd-Chiari syndrome, an underlying disease	Liver transplantation waiting for Budd-Chiari syndrome	[14]
1995	50/M	CD	PC	Diffuse fibrosis	Death due to thrombocytopenia and massive gastrointestinal bleeding	[15]
	35/M	CD	PC	Cholestasis and peliosis hepatis	Unknown	
2003	54/M	CD	Mixed	Nodular cirrhosis	Perform liver transplantation and maintain remission	[16]
2005	45/M	CD	PC	Nodular regenerative hyperplasia	PSL effective	[17]
2013	51/M	CD	-	Liver amyloidosis	Symptoms persist even after lymph node dissection	[18]
2016	56/M	TAFRO	Mixed	Expansion of portal area, interface hepatitis, pseudo biliary hyperplasia and cholangitis	Steroid pulse, PSL, tocilizumab, rituximab	[19]
2017	26/F	CD	PC	Fibrosis and plasma cell infiltration	PSL effective	[20]
This case	10/M	CD or TAFRO	Mixed	Portal vein area fibrosis, inflammatory cell infiltration, bile duct hyperplasia	PSL ineffective, tocilizumab improves inflammatory response	

CD: Castleman's disease; PC: Plasma cell; PSL: Prednisolone.

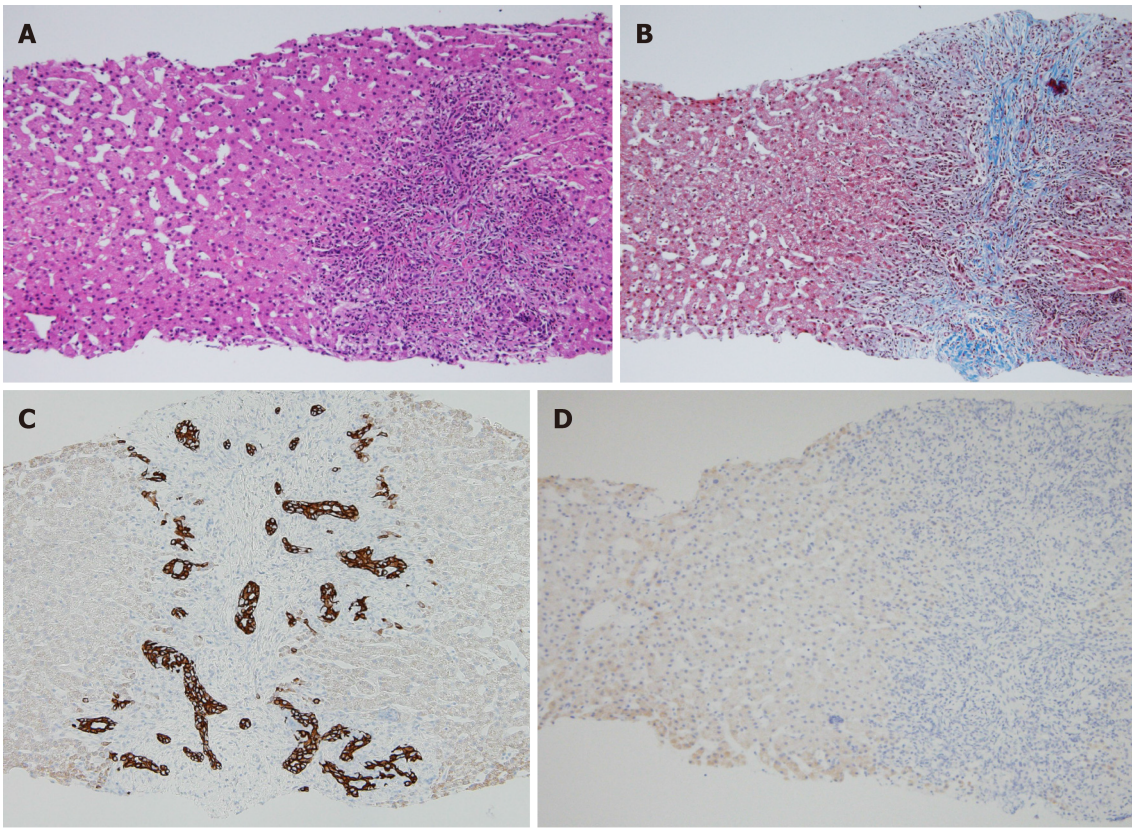

Figure 3 Liver histopathology. A: Hematoxylin and eosin staining (magnification, 100 ×); Dilated sinusoids and fibrotic expansion of the portal area, as well as marked inflammatory cells infiltration, were observed; B: Masson trichrome staining (magnification, 100 ×); Fibrosis was observed in the portal area; C: CK7 staining (magnification, 100 ×); Bile duct hyperplasia was observed; D: IgG4 staining (magnification, 100 ×); IgG4 was not stained.

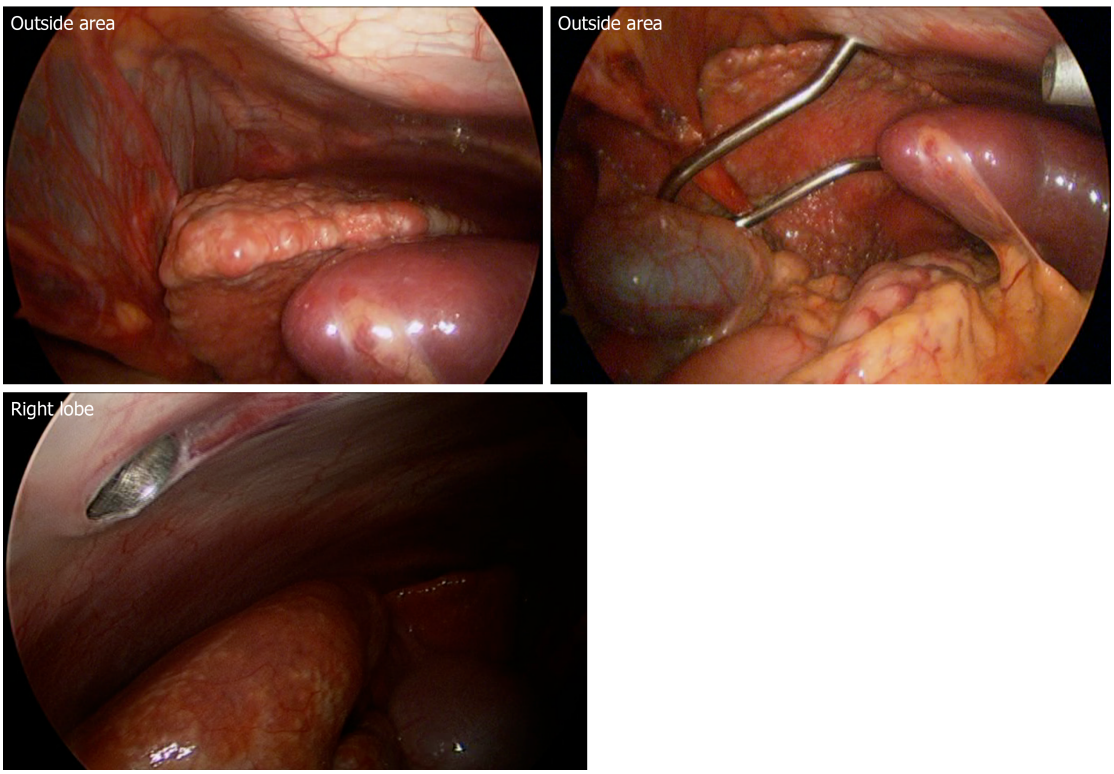

Figure 4 Intraoperative findings of porta hepatis lymph nodes.

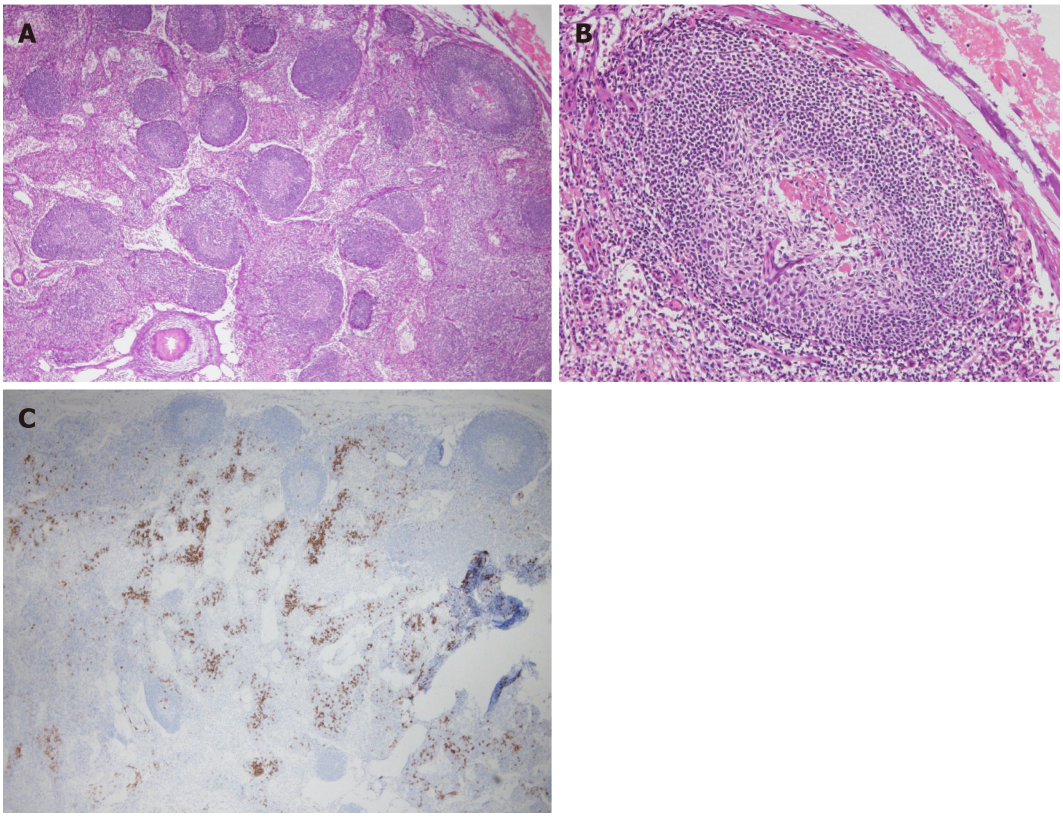

Figure 5 Lymph node tissue in the porta hepatis. A: Hematoxylin and eosin staining (magnification, 40 ×); Hyperplasia and atrophy of lymphoid follicles were observed; B: Hematoxylin and eosin staining (magnification, 100 ×); Lymphoid proliferation with some vascular hyperplasia was observed; C: CD21 staining (magnification, 200 ×); Moderate plasmacytosis was observed in the lymphoid follicles.

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