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【 CASE REPORT 】

Suspected Hepatically Localized Granulomatosis with Polyangiitis

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Abstract:
The patient was a 72-year-old woman whose alkaline phosphatase levels had been elevated since she was 56 years old. Liver biopsies obtained when the patient was 64 and 66 years of age led to a suspicion of cholangitis caused by vasculitis. Furthermore, proteinase-3 anti-neutrophil cytoplasmic antibody positivity led to a suspicion of granulomatosis with polyangiitis, but subjective symptoms and disorders in other organs were absent, so this suspicion was not confirmed. Cholangitis caused by vasculitis rarely occurs without vasculitis in other organs. We herein report this case in which we obtained distinctive laparoscopic and imaging findings that raised suspicions of liver circulatory failure.

Key words: anti-neutrophil cytoplasmic antibody, anti-neutrophil cytoplasmic antibody-associated vasculitis, ischemic sclerosing cholangitis, granulomatosis with polyangiitis, arterio-portal shunt, serositis

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Introduction

Necrotizing vasculitis that primarily affects small vessels and is anti-neutrophil cytoplasmic antibody (ANCA)-positive is known as ANCA-associated vasculitis (AAV). A trend towards increasing morbidity in association with this disease has been observed in Japan in recent years. AAV includes granulomatosis with polyangiitis (GPA), which is known as Wegener's granulomatosis, microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) or Churg-Strauss syndrome (1). AAV is an immunologically mediated inflammatory disease of unknown cause. Glucocorticosteroid and cyclophosphamide treatment improves the vital prognosis of patients with AAV; however, few reports have described the prognosis in cases of hepatic involvement; hence, the prognosis of such cases remains unclear (2, 3).

AAV can occur in any organ; however, reports that describe vasculitis of the liver in detail are uncommon. Ischemic sclerosing cholangitis (ISC) is a liver disease caused by AAV (4). Posttransplantation hepatic artery thrombosis and the intra-arterial administration of antineoplastic agents are common causes of ISC, and it is rare for ISC to be induced by vasculitis.

We herein report our experience with a histologically confirmed case of cholangitis that was proteinase-3 (PR3) ANCA-positive, was not associated with any subjective symptoms or organopathy caused by vasculitis of other organs, and was thought to be a consequence of ischemic changes caused by suspected GPA, the course of which we observed for over eight years.

Case Report

The patient was a 72-year-old Japanese woman whose elevated alkaline phosphatase (ALP) level was first identified during an annual health examination when she was 56 years of age, after which she underwent regular blood tests. There were no subjective symptoms, and the cause of the

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elevated ALP level remained elusive. In 2009, at 64 years of age, the patient was examined at our institution, because imaging results had led to the suspicion of a hepatic tumor. The patient was 152 cm tall and weighed 46.7 kg. There were no abnormal vital or physical signs. The patient's medical history included cryptogenic acute pancreatitis at 16 years of age and surgery to remove a hydatidiform mole at 30 years of age, which had required blood transfusion. In addition, the patient had taken atenolol for hypertension since 62 years of age, and this was substituted with candesartan 65 years of age, which she was still taking. There was no history of smoking, drinking, or supplement use. Her sister had systemic lupus erythematosus (SLE), and there was no family history of liver disease.

When she visited our hospital at 64 years of age, the patient's blood test results showed a slightly elevated white blood cell (WBC) count and C-reactive protein level and the presence of anemia (Table 1). While her transaminase levels were normal, her ALP, leucine aminopeptidase, and gamma-glutamyl transpeptidase levels were elevated, and the ALP isoenzyme test results showed that her hepatic ALP level was elevated. Immunological tests determined that the patient's immunoglobulin G, 50% hemolytic complement activity, complement 3, and PR3-ANCA levels were elevated, and that the tests for other autoantibodies were negative, including those for anti-nuclear antibody, rheumatoid factor, matrix metalloproteinase-3, anti-double-stranded DNA antibody, anti-ribonucleoprotein antibody, anti-Smith antibody, anti-Sjögren's-syndrome (SS)-related antigen A/Ro antibody, anti-SS-related antigen B/La antibody, anti-liver kidney microsome type I antibody, anti-smooth muscle antibody, M2 anti-mitochondrial antibody, anti-thyroglobulin antibody, myeloperoxidase-ANCA, and anti-cardiolipin antibody. Furthermore, no abnormalities were found with respect to the indicators of the patient's blood coagulation ability, including the prothrombin time and the antithrombin III, protein C, and protein S levels. In addition, no anomalies were found in the indocyanine green test results at 15 min, thyroid hormone and tumor marker levels, or urinary analysis results. The test results for anti-hepatitis B surface antigen, anti-hepatitis B core antibody, anti-hepatitis C virus antibody, and anti-human immunodeficiency virus antibody were negative. With the exception of a slightly elevated hyaluronic acid level (76.4 ng/mL, ≥50), the test results for the markers of fibrosis, including those for sialylated carbohydrate antigen, procollagen III peptide, and type IV collagen, were negative.

These results suggested that, while the hepatic functional reserve was maintained, there was sustained inflammation in the bile duct. In addition, while the patient tested positive for PR3-ANCA, no abnormalities were found during head and chest computed tomography (CT) scanning, or in the urinalysis. Furthermore, given that there were no subjective symptoms, polyangiitis caused by GPA, sinusitis, respiratory disease, and renal disease was ruled out.

Abdominal CT showed slight atrophy of the left hepatic lobe, mild splenomegaly, and a splenorenal shunt, but there were no abnormalities in the gall bladder or pancreas. In the arterial phase, heterogeneous contrast enhancement was found in the hepatic parenchyma, and the contrast in the portal vein revealed the presence of an arterio-portal (AP) shunt. While the AP shunt was considerable in the atrophied left hepatic lobe, only one part of the right hepatic lobe was affected, suggesting that there were pronounced differences in the level of internal impairment. The contrast enhancement continued in the portal phase and to the periphery of the portal tract. In the late phase, similar contrast enhancement was evident surrounding the hepatic parenchyma, which was likely an effect of the AP shunt, thereby ruling out a neoplastic lesion. Furthermore, there was no blockage of the portal vein (Fig. 1). Magnetic resonance imaging (MRI) revealed enlargement of the portal tract in the left hepatic lobe, and there was an iso-signal at the left lateral sector on T1-weighted imaging and iso- to slight hyperintensity on T2-weighted imaging. While no abnormalities were found using magnetic resonance cholangiopancreatography (MRCP), slight atrophy of the left hepatic lobe, blunting of the hepatic wedge, and a liver lobe with an irregular surface were found during an ultrasound investigation. Given the considerable enlargement of the portal tract and the elevated echo level found in the portal tract, inflammatory changes were suspected. The intrahepatic bile duct was slightly enlarged in the left hepatic lobe compared with that in the right hepatic lobe, and the bile duct wall was slightly thickened. A contrast-enhanced ultrasound investigation using perflubutane showed the presence of contrast enhancement in the portal tract in the early arterial phase and some dense specks in the central hepatic parenchyma of the left hepatic lobe. In the late vascular phase, homogeneous contrast enhancement was found in the hepatic parenchyma, and the portal tract appeared as a continuous non-enhanced region (Fig. 2). Although abnormalities were found in the portal tract of both hepatic lobes during these imaging examinations, the damage to the left hepatic lobe was clearly more severe. We suspected a bile duct abnormality, specifically cholangitis, based on the aforementioned imaging and the blood test results, so we conducted endoscopic retrograde cholangiopancreatography (ERCP) and a bile duct biopsy. ERCP did not reveal any abnormalities in the pancreatic duct or the extrahepatic bile duct, and while slight straightening of the intrahepatic bile duct was suspected, no clear abnormalities were evident, as indicated by the findings from the MRCP (Fig. 3). During ERCP, biopsies were obtained from the left and right forks of the hepatic bile duct and from the common bile duct; however, a histopathological evaluation did not reveal any abnormalities in the epithelium, which had a minimal number of lymphocytes and no plasma cells or eosinophils. A diagnosis could therefore not be established.

Laparoscopy and a needle biopsy were next conducted. Serositis and severe circulatory disturbance were suspected based on the atrophy and strong adhesions found in the left

Table 1. Laboratory Data.

Complete blood count		Blood chemistry results		Immunoserological test results	
White blood cell count	8.8×10³ /μL	Total protein	8.8 g/dL	IgG	3,259 mg/dL
Neutrophils	58.8 %	Alpha-1 globulin	0.3 g/dL	IgG1	1,370 mg/dL (320-748 mg/dL)
Lymphocytes	32.0 %	Albumin	3.9 g/dL	IgG2	1,370 mg/dL (208-754 mg/dL)
Eosinophils	2.3 %	Total bilirubin	0.35 mg/dL	IgG3	71.6 mg/dL (6.6-88.3 mg/dL)
Basophils	0.5 %	Aspartate aminotransferase	21 U/L	IgG4	97.5 mg/dL (4.8-105 mg/dL)
Monocytes	6.4 %	Alanine aminotransferase	12 U/L	IgA	324 mg/dL
Red blood cell count	4.14×10⁶ /μL	Lactate dehydrogenase	136 U/L	IgM	47 mg/dL
Hemoglobin	11.4 g/dL	ALP	607 U/L (117-335 U/L)	IgE	85 IU/L
Hematocrit	35.0 %	ALP1	5 %	CH50	73.6 CH50/mL (33-48 CH50/mL)
Platelet count	32.3×10⁴ /μL	ALP2	83 % (36-74%)	C3	156 mg/dL (44-102 mg/dL)
		ALP3	10 % (25-59%)	C4	32 mg/dL
		ALP5	2 % (0-16%)	ACE	5.4 IU/L (8.3-21.4 IU/L)
		Leucine aminopeptidase	102 U/L (39-94 U/L)	MPO-ANCA	>10 EU
		Gamma-glutamyl transpeptidase	99 U/L (12-73 U/L)	PR3-ANCA	43 EU (>10 EU)
		Total cholesterol	183 mg/dL	HLA-DR	4/8
		Triglyceride	114 mg/dL		
		Blood urea nitrogen	10.6 mg/dL		
		Creatinine	0.5 mg/dL		
		C-reactive protein	2.7 mg/dL		

Note: The underlined figures denote abnormal values. The normal ranges are shown in parentheses.

ALP: alkaline phosphatase, ACE: angiotensin-converting enzyme, HLA: human leukocyte antigen, Ig: immunoglobulin, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase 3-anti-neutrophil cytoplasmic antibody, CH50: 50% hemolytic complement activity, C: complement

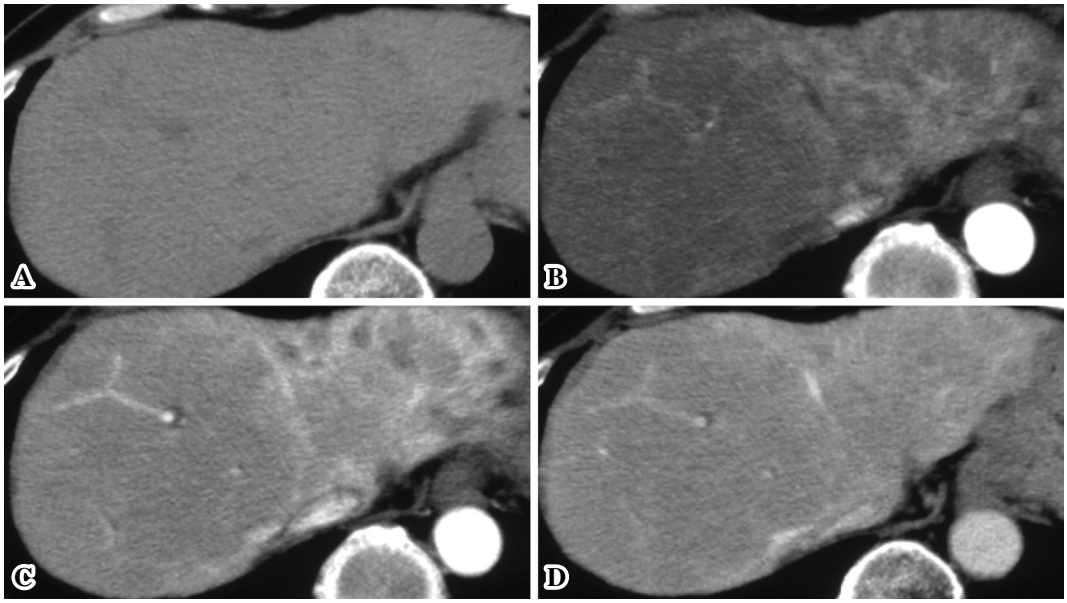

Figure 1. Liver CT imaging. (A) Slight atrophy of the left hepatic lobe was observed on plain CT. (B) During the arterial phase, heterogeneous contrast enhancement was apparent in the hepatic parenchyma, and the presence of an arterio-portal shunt was determined from the contrast in the portal vein. (C) The contrast enhancement persisted during the portal phase and continued to the periphery of the portal tract. (D) During the late phase, similar contrast enhancement was observed surrounding the hepatic parenchyma. CT: computed tomography

lateral sector of the liver and membrane hyperplasia, which was white; furthermore, surface irregularities were found over the entire surface of the liver. Membrane hyperplasia was also present in part of the right hepatic lobe, but this was less marked than that in the left hepatic lobe, and the lesions were not widespread. The surface of the right hepatic lobe was slightly uneven and interspersed with shallow, linear recesses. Using a 16-gauge needle, a transcutane-

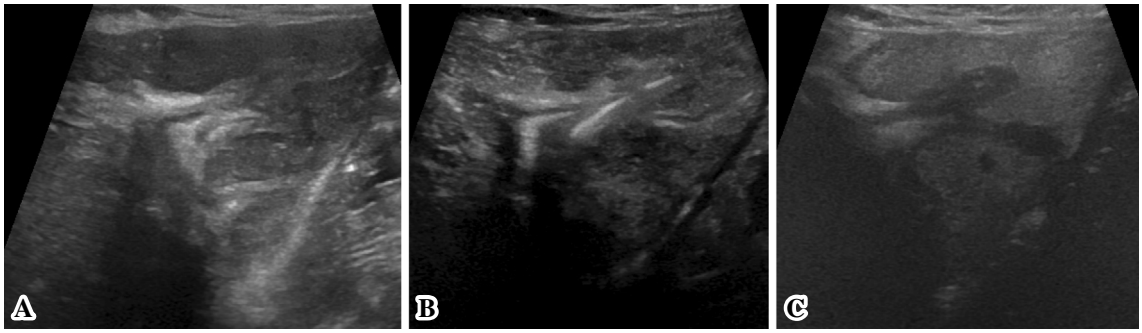

Figure 2. **Ultrasound images of the liver. (A) Enlargement of the portal tract and an elevated echo level in the portal tract detected using B-mode imaging. (B) Contrast-enhanced ultrasound using perflubutan detected the presence of contrast enhancement in the portal tract in the early arterial phase, and some dense specks were found in the central hepatic parenchyma of the left hepatic lobe. (C) During the late vascular phase, homogeneous contrast enhancement was found in the hepatic parenchyma, and the portal tract appeared as an uninterrupted non-enhanced region.**

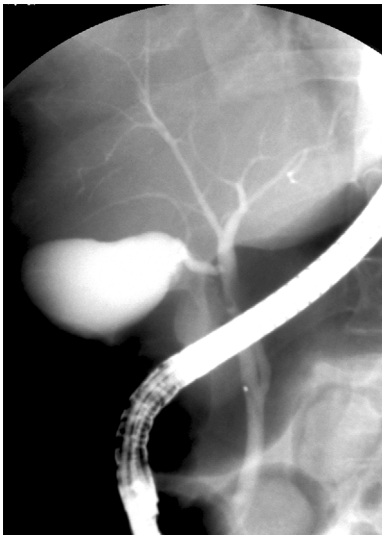

Figure 3. **Endoscopic retrograde cholangiography imaging. While slight straightening of the intrahepatic bile duct was suspected, no clear abnormalities were evident on endoscopic retrograde cholangiography.**

ous biopsy of the right hepatic lobe was performed, revealing slight membrane hyperplasia, and the histopathological findings showed that the marked expansion of the portal tract was accompanied by severe fibrosis. Mild regenerative changes were found in the hepatic parenchyma, but there was no infiltration of inflammatory cells. In contrast, mild inflammatory cell infiltration and cholangiole hyperplasia were found in the portal tract.

Portal hypertension was suspected based on the splenomegaly and the presence of the splenorenal shunt detected during the imaging examinations; however, upper gastrointestinal endoscopy did not detect any esophageal varices, and lower gastrointestinal endoscopy, gallium scanning, and echocardiography did not reveal any abnormalities. The patient was prescribed oral ursodiol to promote biliary excretion and vitamin B12 to improve the peripheral circulation. The patient's ALP and gamma-glutamyl transpeptidase levels in the blood did not improve, and no noteworthy changes were observed in other laboratory data or CT, MRI, or ultrasonography findings. Given the ongoing transition in relation to inflammation that was signified by a WBC count of 7,000-10,000/μL and a C-reactive protein level of 2-4 mg/dL, we were concerned that the condition might be progressing. Consequently, at 66 years of age and approximately 1.5 years after the first biopsy, the patient underwent a wedge biopsy of the left lateral sector of the liver, which was the region in which the imaging assessments had indicated the presence of severe inflammation. At this stage, the external appearance of the liver did not differ markedly from the time of the first laparoscopic examination, and it appeared that the disease had not progressed (Fig. 4).

The histopathological findings from the tissue sample obtained from the second biopsy showed that the liver contained a portal tract with fibrotic expansion at the level of the large bile ducts (Fig. 5A arrow) and the liver parenchyma was not damaged (Fig. 5A). Thickening of the hepatic serosa was also observed (Fig. 5A arrowhead). The bile duct and the peribiliary glands had irregular morphologies due to the presence of fibrosis, and mild cellular infiltration was present (Fig. 5B). Furthermore, vasculitis was apparent, which had manifested as fibrotic occlusion of the portal vein (arrow) and inflammatory cell infiltration, comprising neutrophils and histiocytes, within the artery (arrowhead) (Fig. 5C-E). Lamina elastic interna was noted in the inflamed artery (Fig. 5D). Bile duct loss was evident in the peripheral interlobular connective tissues, and in some regions, the bile ducts accompanying the artery were completely absent (arrow) (Fig. 5F). Serositis was present in the hepatic serosa, caused by the inflammatory cell infiltration, which was severe in some areas, and fibrosis and vasculitis were suspected in one area. These findings led us to speculate that the patient had vasculitis with secondary sclerosing cholangitis. The liver tissue comprised a mixture of normal and pathological areas, and the fibrotic expansion of the

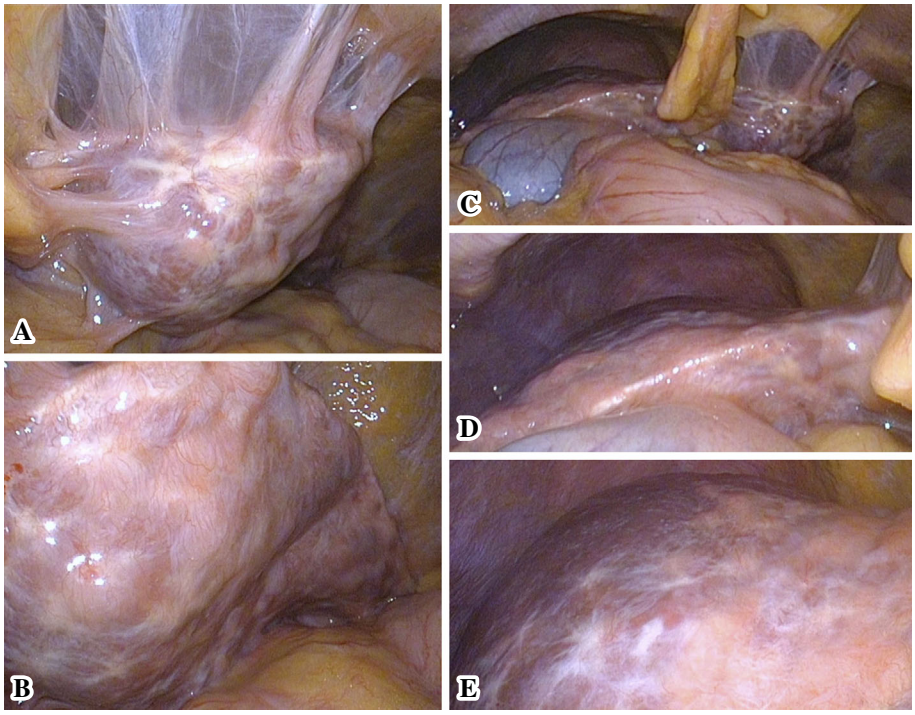

Figure 4. **Laparoscopic images of the liver. (A and B) View of the left lateral sector; (C) Overall distant view; (D and E) View of the right lobe. (A and B) Serositis and severe circulatory disturbances were suspected based on the atrophy and the strong adhesions found in the left lateral sector of the liver. (A-E) Membranous hyperplasia with white areas and surface irregularities over the entire surface of the liver. (D and E) The surface of the right hepatic lobe was slightly uneven and interspersed with shallow, linear recesses.**

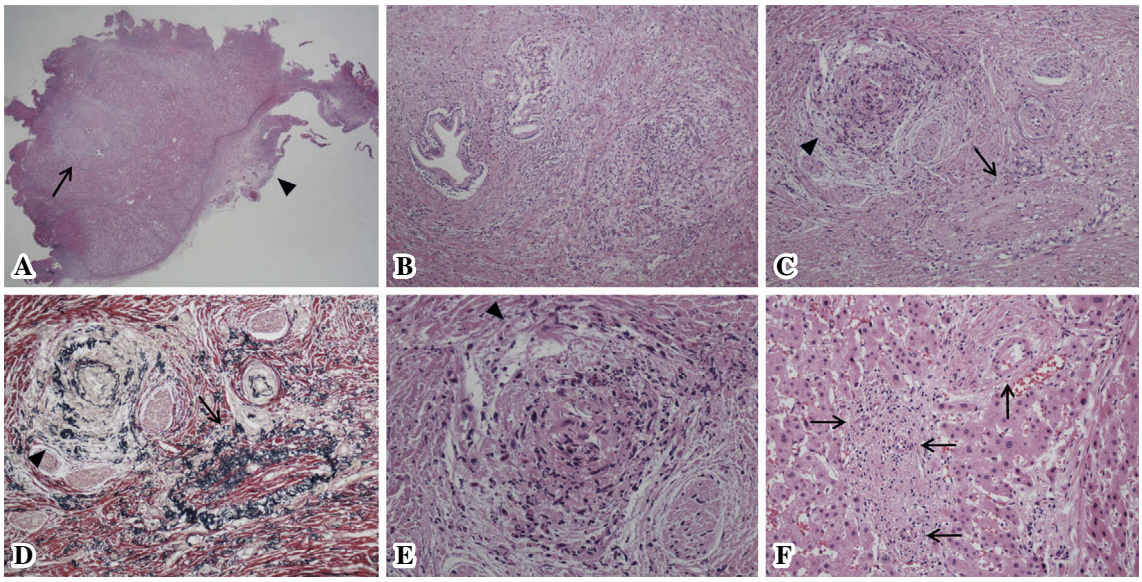

Figure 5. **Histopathological findings from the liver. (A-C, E, and F) Hematoxylin and Eosin staining and (D) Elastica van Gieson staining. (A) A portal tract with fibrotic expansion at the level of the large bile ducts (indicated by arrow) and thickening of the hepatic serosa were observed (indicated by arrowhead). Liver cirrhosis was ruled out, as the relationship between the portal tract and central veins was maintained (×1.25). (B) The bile duct and peribiliary glands had irregular morphologies, fibrosis was evident, and mild cellular infiltration was present (×10). (C-E) Apparent vasculitis with fibrotic occlusion of the portal vein (indicated by arrow) and inflammatory cell infiltration of the artery, which included neutrophils and histiocytes (indicated by arrowhead). Lamina elastic interna was noted in the inflamed artery (D) (C and D ×20; E ×40). (F) Bile duct loss was evident in the peripheral interlobular connective tissue, and in some regions, the bile ducts accompanying the artery were absent. Interlobular arteries are indicated by the arrow (×20).**

Table 2. Case Reports Describing Anti-neutrophil Cytoplasmic Antibody-associated Vasculitis Confirmed Liver Biopsies.

Case no.	Age, years	Gender	Diagnosis of vasculitis	Type of ANCA	Liver histology		Other organ involvement	Clinical symptoms	Liver function abnormality	Imaging findings**	Reference number
					Vasculitis	Additional findings					
1	58	Female	MPA	MPO	+	Irregular arrangement of bile duct	Kidney	Fever	Elevated ALP, normal ALT	No abnormalities	5
2	32	Male	EGPA	p/MPO	-	Epithelial lymphoplastic infiltration around bile ducts	Lung, heart	Chest pain, shortness of breath, fever, abdominal pain, etc	Elevated ALP, normal ALT	No abnormalities	6
3	58	Male	GPA	PR3	-	Focal lobular hepatitis	Lung	Dry cough, fever, rhinitis, fatigue, appetite loss	Elevated ALT	No abnormalities	7
4	72	Female	GPA	Negative	-	Necrotizing granuloma	Lung, skin, parotid gland	Weight loss	Elevated ALT and gamma-GT	Multiple hepatic lesions up to 4 cm	8
5*	78	Female	s/o MPA	p/MPO	+	Cholangitis, nodular regenerative hyperplasia	Kidney	Fever, malaise, arthralgia	Elevated ALP, normal ALT	No abnormalities	4
Our case	64	Female	s/o GPA	PR3	+	Small bile duct damage	None	None	Elevated ALP, normal ALT	No abnormalities	

*Microscopic polyangiitis suspected based on the new diagnosis criteria. **Abdominal CT or ultrasonography or endoscopic retrograde cholangiopancreatography.

ALP: alkaline phosphatase, ALT: alanine aminotransferase, ANCA: anti-neutrophil cytoplasmic antibody, EGPA: eosinophilic granulomatosis with polyangiitis, gamma-GT: gamma-glutamyl tanspeptidase, GPA: granulomatosis with polyangiitis, MPA: microscopic polyangiitis, MPO: myeloperoxidase, p: perinuclear, PR3: proteinase 3, s/o: suspicion of

portal tract was the most profound in the tissue sample obtained from the left lateral sector of the liver.

Although eight years have passed since this patient was first examined, subjective symptoms remain absent. The blood test results have not shown any noteworthy changes, the slight elevations of the WBC count and C-reactive protein level continue, and the ALP level remains two- to four-fold higher than the normal upper limit. In addition, while the imaging studies suggest a slight progression in the atrophy of the left hepatic lobe, this is not concurrent with esophageal varices, nor is it accompanied by pulmonary disease, renal disease, sinusitis, or neuritis. Treatments, including corticosteroids and cyclophosphamide, have not been administered because the patient refused these treatments based on concerns about their adverse effects.

Discussion

We speculate that, in this case, the ISC occurred concurrently with the development of an AP shunt because of a reduction in the arterial blood flow supplying the bile duct, which was caused by successive changes initiated by vascu-

litis. The PR3-ANCA positivity, arteriolar arteritis, and granule formation in the hepatic tissues led to the suspicion of GPA as the cause of the vasculitis, but given that there was no involvement or signs of inflammation in the respiratory tract, lungs, kidneys, and skin, we did not diagnose GPA.

The blood test results in around half of the cases of AAV have confirmed liver function abnormalities, and while liver function abnormalities have been reported to be significantly more frequent in GPA than in MPA and EGPA (3), no large-scale detailed studies on the causes of the liver function abnormalities have been conducted. We conducted a search of published case reports that were written in English and described the confirmatory liver histology in cases of AAV with liver dysfunction, and we excluded those reports that described autopsy studies. Table 2 summarizes the selected case studies (4-8). None of these cases had icterus at the onset of the disease, and imaging studies of all of these cases, with the exception of case number 4, did not detect liver abnormalities. Similar to our case, the ALP levels were elevated in three other cases, and these patients were thought to have cholangitis caused by vasculitis. Cases of AAV concurrent with primary biliary cirrhosis (9-11) and incomplete septal cirrhosis concurrent with SS (12) have also been described. However, cases with and without vasculitis of the liver tissue have been described, and whether there is an immunological relationship with these diseases and AAV or whether it is just coincidence remains unclear.

The patient described in this report had a sister who had SLE, and given that vasculitis is present in SLE, AAV must be distinguished from SLE. The vasculitis associated with SLE, rheumatoid arthritis, and SS is often a periarteritis nodosa-type necrotizing arteritis, and the patients are negative for ANCA (13). Furthermore, none of the findings in the current case were indicative of SLE, and all of the autoantibody test results were negative; we therefore think it unlikely that the vasculitis in the current case was caused by SLE or rheumatoid arthritis.

Imaging detected abundant blood flow, which was related to the presence of an AP shunt in the dilated portal tract and serosa, primarily in the left hepatic lobe; this led to heterogeneity in the vascular phase that was caused by differences in the amount of blood flowing in the hepatic parenchyma. Since considerable membrane hyperplasia was found that was accompanied by serositis and circulatory disturbances, particularly in the left hepatic lobe, and the laparoscopic examination revealed the presence of shallow, linear recesses on the surface of the liver, it seems likely that the distinctive findings were related to the dilated portal tract and the fibrosis that are associated with ISC and the AP shunt that accompanies circulatory disturbances and serositis.

To date, only one report has described cholangitis caused by vasculitis that did not include vasculitis of the other organs, and that patient presented with abdominal pain that was caused by leucocytoclastic vasculitis (14). The present case of suspected ISC had a course of around eight years without any symptoms; the patient was not administered glucocorticoids or immunosuppressive therapies, and this case is the first of its kind to be reported. One report described the correlations between the ANCA titers and the levels of vasculitis activity (15). Continuous, slight CRP level elevation occurred in the present case, and the patient's PR3-ANCA values transitioned from 10 to 104 EU (normal range: >10 EU). The PR3-ANCA level elevation may have suppressed the onset of AAV and progression of the pathology in the liver. However, the possibility of disease progression in the future and the onset of vasculitis in other organs cannot be ruled out. Furthermore, given that hepatic failure (7, 12) and ruptured hepatic aneurysms (16, 17) have caused death in patients with AAV, these patients must be monitored carefully.

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

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