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CASE REPORT

Generalized crystal-storing histiocytosis with noncirrhotic portal hypertension: an autopsy case report

Yasunao Numata[1] · Shigeru Sasaki[1] · Kazufumi Magara[2] · Akira Takasawa[2] · Taro Sugawara[3] · Naruki Ohara[1] · Noriyuki Akutsu[1] · Tadashi Hasegawa[3] · Makoto Osanai[2] · Hiroshi Nakase[1]

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Abstract

Crystal-storing histiocytosis (CSH) is a rare disease associated with the accumulation of histiocytes containing crystalline matter within their cytoplasm. Herein, we present the case of a female patient who was diagnosed with Tolosa–Hunt syndrome at 45 years of age and idiopathic retroperitoneal fibrosis when she was 48 years. She developed portal hypertension (PH), but did not present with cirrhosis; as such, the cause of PH was not identified. Her PH gradually worsened when she was 54 years, and at the age of 60 years, she died from an acute subdural hematoma. Autopsy revealed retroperitoneal fibrosis with severe fibrosis extending around the hepatic veins and into the porta hepatis. Histologically, the retroperitoneal tissue showed a dense infiltrate of eosinophilic histiocytes with crystal structures in the cytoplasm, which was pathologically diagnosed as CSH. Nodular regenerative hyperplasia was observed in the liver parenchyma, whereas cirrhosis was not. In the present case, CSH caused fibrosis, which was believed to be the cause of PH. In addition, we considered that nodular regenerative hyperplasia caused by the altered hepatic blood flow due to treatment of gastric varices contributed to worsening PH. Hence, CSH should be considered as an underlying disease in noncirrhotic portal hypertension.

Keywords Noncirrhotic portal hypertension · Crystal-storing histiocytosis · Tolosa–Hunt syndrome · Retroperitoneal fibrosis · Nodular regenerative hyperplasia

Introduction

Portal hypertension (PH) is most commonly caused by underlying cirrhosis, which accounts for approximately 90% of cases [1, 2]. However, there are cases of noncirrhotic portal hypertension (NCPH) that cause PH even in the absence of cirrhosis [3, 4].

Crystal-storing histiocytosis (CSH) is a very rare disease, in which crystalline material accumulates in the cytoplasm of histiocytes, often with lymphoproliferative or plasma cell disorders as the underlying pathology [5]. Most cases of CSH are asymptomatic [6], but in very rare instances, fibrosis may accompany the disease [7]. However, there have been no reports of PH caused by CSH. Herein, we present a case, in which CSH caused fibrosis in the retroperitoneum, hepatic veins, and porta hepatis, leading to NCPH.

Case report

The patient was a 49-year-old woman who was referred to our department for further evaluation and treatment of ascites. When she was 45 years, she became aware of eye pain and an orbital mass, and was subsequently diagnosed with Tolosa–Hunt syndrome (THS). She was started on prednisolone (PSL), and her symptoms improved. When she was 48 years, she developed abdominal distention; computed tomography (CT) showed ascites and peritoneal thickening (Fig. 1a). She was diagnosed with idiopathic retroperitoneal fibrosis (RPF) by the histological examination of peritoneal biopsy. She then received steroid pulse therapy and partially responded to it. Thereafter, she received tamoxifen

✉ Shigeru Sasaki
ssasaki@sapmed.ac.jp

1 Department of Gastroenterology and Hepatology, Sapporo Medical University School of Medicine, Minami 1-Jo Nishi 16-Chome Chuo-Ku, Sapporo 060-8543, Japan

2 Department of Pathology, Sapporo Medical University School of Medicine, Sapporo, Japan

3 Department of Surgical Pathology, Sapporo Medical University School of Medicine, Sapporo, Japan

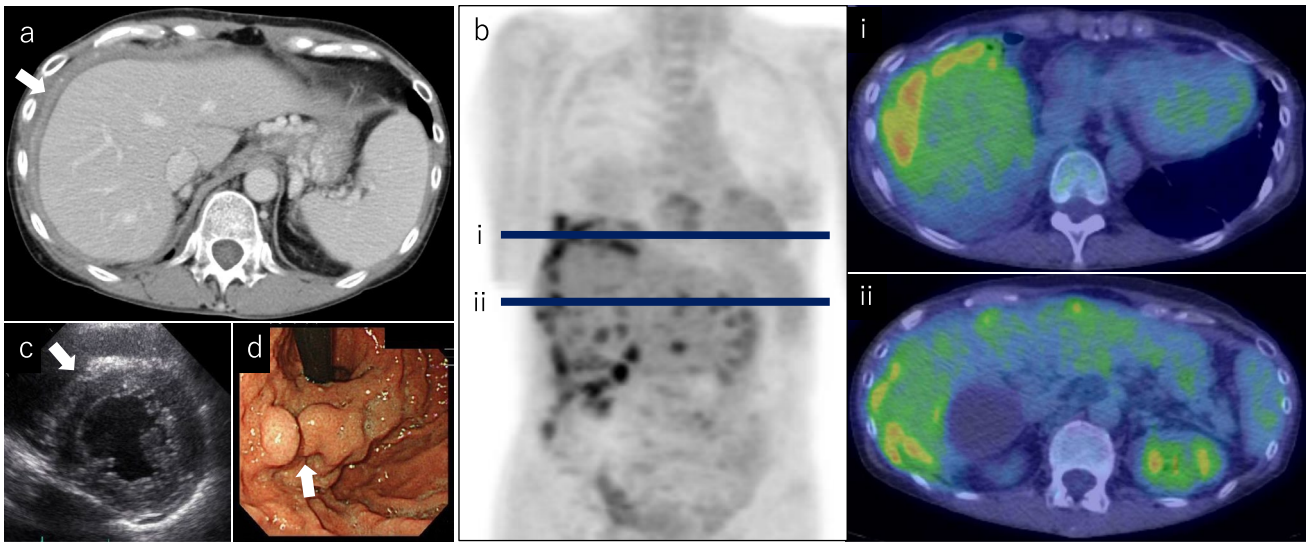


Fig. 1 **a** Computed tomography shows thickened peritoneum and ascites (white arrow). **b** PET imaging with FDG shows FDG uptake in the perihepatic region, omentum, and mesentery. **c** Echocardiography shows cardiac hypertrophy (white arrow). **d** Upper gastrointestinal endoscopy shows gastric varices (white arrow)

Table 1 Ascitic fluid analysis

Complete blood count		*Biochemistry*		*Serological tests*	
WBC	16.4×10^3/μL	TP	7.5 g/dL	ANA	(–)
Neu	92.9%	Alb	2.8 g/dL	SS-A	(–)
Lym	5.0%	T-Bil	0.7 mg/dL	MPO-ANCA	< 10 EU
RBC	4.24×10^6/μL	AST	29 U/L	RF	< 10 U/mL
Hb	12.0 g/dL	ALT	24 U/L	CH50	65.6 U/mL
Hct	37.7%	ALP	551 U/L	IgG	2720 mg/dL
Plt	262×10^3/μL	LDH	135 U/L	IgG4	18.6 mg/dL
		γ-GTP	61 U/L	IgM	104 mg/dL
Coagulation test		ChE	179 U/L	IgA	261 mg/dL
PT	87.8%	TG	181 mg/dL	κ FLC	13.6 mg/L
PT-INR	1.08	TC	199 mg/dL	λ FLC	22.2 mg/L
APTT	28.8 s	BUN	12 mg/dL	FLC κ/λ	0.61
		Cre	0.5 mg/dL		
Viral markers		Na	136 mEq/L		
HBs-Ag	(–)	K	4.4 mEq/L		
HCV-Ab	(–)	CRP	7.85 mg/dL		
		FER	306.3 ng/mL		

WBC white blood cell, *Neu* neutrophils, *Lym* lymphocytes, *RBC* red blood cell, *Hb* hemoglobin, *Hct* hematocrit, *Plt* platelets, *PT* prothrombin time, *PT-INR* prothrombin time-international normalized ratio, *APTT* activated partial thromboplastin time, *HBs-Ag* hepatitis B surface antigen, *HCV-Ab* hepatitis C virus antibody, *TP* total protein, *Alb* albumin, *T-Bil* total bilirubin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *LDH* lactate dehydrogenase, *γ-GTP* γ-glutamyl transpeptidase, *ChE* cholinesterase, *TG* triglycerides, *TC* total cholesterol, *BUN* blood urea nitrogen, *Cre* creatinine, *Na* natrium, *K* potassium, *CRP* C-reactive protein, *FER* ferritin, *ANA* antinuclear antibody, *SS-A* anti-SS-A antibody, *MPO–ANCA* myeloperoxidase–antineutrophil cytoplasmic antibody, *RF* rheumatoid factor, *CH50*: 50% hemolytic complement activity, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19–9, *κ FLC*: kappa free light chain, *λ FLC* lambda free light chain, *FLC κ/λ* free light chain kappa lambda ratio

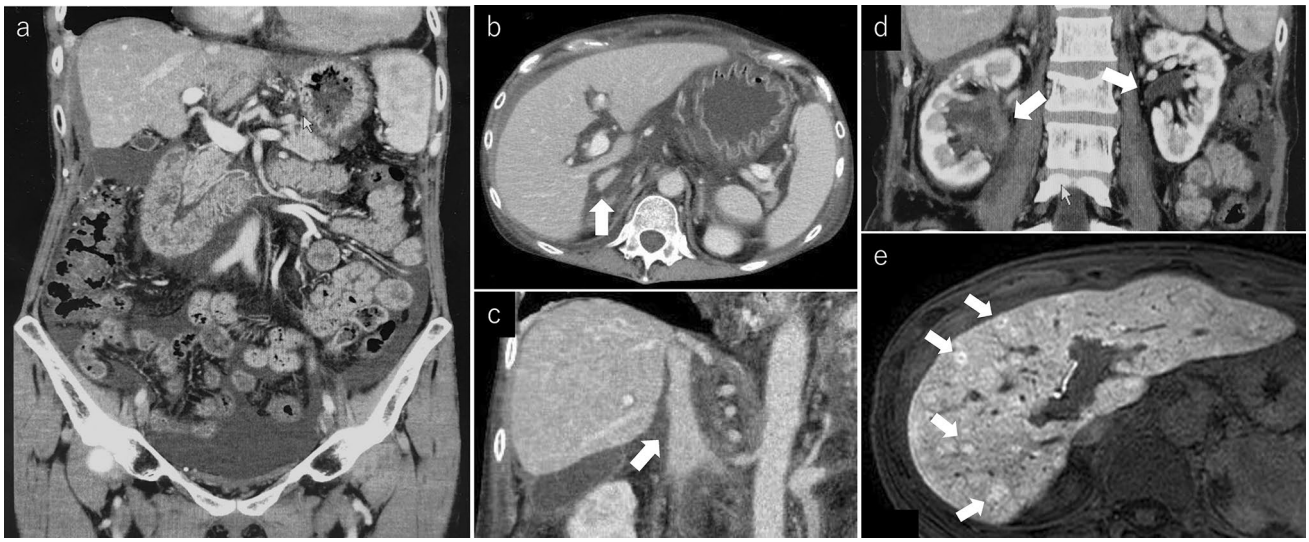


Fig. 2 **a** Computed tomography shows increased ascites. **b**, **c** Compressed inferior vena cava surrounded by soft tissue shadow (white arrow). **d** Dilation and wall thickening of the right and left renal pelvis (white arrows). **e** Ethoxybenzyl-magnetic resonance imaging shows multiple nodules in the liver (white arrows)

and methotrexate; however, these drugs did not necessarily relieve her symptoms.

At the first examination, she had spontaneous pain from the right lateral abdomen to the right costal region. On physical examination, her liver was palpable in the right costal region up to three fingerbreadths. Stiffness and tenderness were noted in her right quadriceps and pericardial region. Laboratory findings demonstrated hypoalbuminemia (2.8 g/dL; range 3.7–5.2), increased C-reactive protein levels (7.85 mg/dL; range 0.00–0.30), and elevated immunoglobulin G levels (IgG) (2720 U/L; range 815–1800) but normal IgG4 levels (18.6 mg/dL; range 4.8–105.0), antinuclear antibodies, and free light chain κ/λ ratio (Table 1). No monoclonal immunoglobulins were detected in serum immunoelectrophoresis. ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)–CT showed FDG uptake in the perihepatic region, omentum, and mesentery (Fig. 1b). Electrocardiography revealed ST depression and negative T waves in leads V5 and V6. Echocardiography presented left ventricular and right ventricular hypertrophy (Fig. 1c). Upper gastrointestinal endoscopy revealed moderately enlarged, beady gastric varices (Fig. 1d), which were classified as F2 according to the Japan Society for Portal Hypertension classification [8]. The presence of ascites and gastric varices suggested PH. However, no imaging findings were suggestive of cirrhosis.

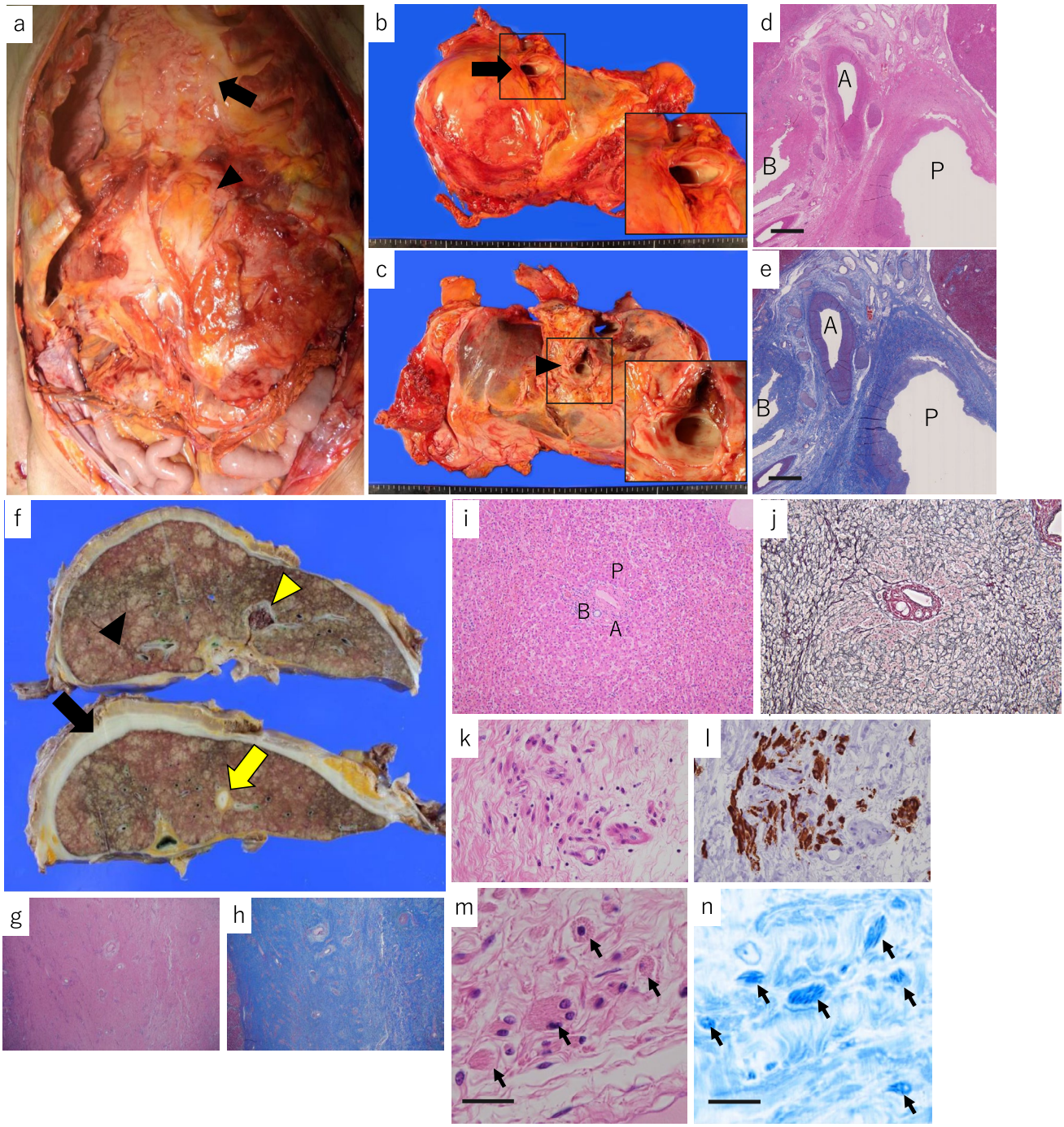
PET–CT findings suggested that the abdominal pain was caused by inflammation due to idiopathic RPF. Treatment with tocilizumab ameliorated her abdominal symptoms, ascites, and inflammatory response. We were able to reduce the dose of PSL and eventually discontinued it 5 years after tocilizumab administration. To investigate the cause of her cardiac enlargement, she underwent myocardial biopsy, which revealed no amyloid deposits or infiltration of IgG4-positive cells. She was diagnosed with secondary myocarditis and treated with β blockers and diuretics. The gastric varices worsened and were treated with balloon-occluded retrograde transvenous obliteration.

However, despite tocilizumab treatment, PH worsened 6 years later. Gradually, ascites worsened and became refractory (Fig. 2a). Paracentesis was performed and the ascitic fluid was analyzed, which showed a high serum-ascites

Table 2 Ascitic fluid analysis

Aspect	Serous, clear
Color	Pale-yellow
Specific gravity	1.011
Protein	1.0 g/dL
Albumin	0.5 g/dL
SAAG	2.2 g/dL
LDH	33 U/L
Glucose	114 mg/dL
Cell count	63/μL
Neurophilis count	6%
Leukocyte count	83%
Others	11%
RBC count	0.0×10^4/μL
Bacterial culture	Sterile
Cytology	Negative for malignant cells

SAAG serum-ascitic albumin gradient, *LDH* lactate dehydrogenase, *RBC* red blood cell



albumin gradient of 2.2 g/dL, consistent with transudate, and no evidence of malignancy or infection (Table 2). In addition, compressed inferior vena cava surrounded by the soft tissue shadow and dilation and wall thickening of the renal pelvis became apparent on CT imaging (Fig. 2b–d). She was found to have multiple hyperplastic nodules in her liver on ethoxybenzyl-magnetic resonance imaging (Fig. 2e), and esophageal varices were classified as F2 [8] on upper gastrointestinal endoscopy. She underwent repeated treatment for esophageal varices with endoscopic variceal ligation and abdominal paracentesis, but died from a cerebral hemorrhage and subdural hematoma when she was 60 years, 11 years after receiving tocilizumab.

A pathological autopsy was performed with the consent of the family. The abdominal cavity was filled with a large amount (4800 mL) of pale-yellow clear ascites. Severe fibrosis was observed mainly around the upper abdominal organs, such as the liver and spleen. Moreover, the fibrosis extended to the retroperitoneal tissue around both kidneys, which was considered a salient finding of RPF (Fig. 3a). Histologically,

◂**Fig. 3** **a** Thoracolaparotomy findings show severe fibrosis from the anterior mediastinum to the upper abdomen. **b** Macroscopic image of thehepatic vein shows white to yellowish-white firm fibrosis surrounding the vein (black arrow). **c** Macroscopic image of the portal vein shows fibrous tissue surrounding it and the hepatic vein (black arrow head). **d**, **e** Pathology of the hepatic hilum shows fibrosis extending from the periportal to the portal vein wall (**d** Hematoxylin and eosin staining. **e** Masson's trichrome staining. A: hepatic artery, B: bile duct, P: portal vein, bar; 2 mm). **f** Macroscopic findings of the liver show thick fibrosis surrounding the liver (black arrow) and multiple diffuse nodular lesions in the liver parenchyma (black arrow head). Portal vein thrombosis (yellow arrow head) and the round ligament of the liver (yellow allow) were also observed. **g**, **h** Pathology of the perihepatic area shows severe fibrosis (**g** Hematoxylin and eosin staining, 2×. **h** Masson's trichrome staining, 2×). **i**, **j** Pathology of nodular regenerative hyperplasia shows a hepatocellular nodular lesion with the central portal vein area. There is no fibrous septum around the nodule or conspicuous congestion in the sinusoids surrounding the nodule (**i** Hematoxylin and eosin staining, 100×. **j** Gitter staining, 100×. A: hepatic artery, B: bile duct, P: portal vein). **k**, **l** Pathology of the perihepatic fibrosis shows collagen fibrils with cocooning of eosinophilic spindle-shaped cells, which are positive for CD68 immunostaining and are considered histiocytes (**g** Hematoxylin and eosin staining, 40×. **h** CD68 staining, 40×). **m**, **n** Pathology of the histiocytes shows a crystalline structure (black arrows) within the eosinophilic cytoplasm on hematoxylin and eosin staining, and a clear accumulation of needle-like crystals on toluidine blue staining (**m** Hematoxylin and eosin staining. **n** Toluidine blue staining. bar; 25 μm)

the retroperitoneal tissue had dense infiltration of eosinophilic histiocytes with crystal structures in the cytoplasm. Immunohistochemically, the crystalline structures were strongly positive for both kappa and lambda light chains, and no obvious light chain restriction was identified. Histopathologically, no lymphoplasmacytic neoplasms were detected.

Neither the hepatic vein nor the portal vein was occluded; however, the fibrous tissue surrounding them was tightly adherent, such that it was difficult to peel off (Fig. 3b–e). Thick fibrosis was further observed surrounding the liver (Fig. 3f–h).

Hepatocellular hyperplastic nodules up to 10 mm in diameter were diffusely developing within the liver parenchyma and were diagnosed as nodular regenerative hyperplasia (NRH) (Fig. 3i, j). Mild infiltration of inflammatory cells and fibrous expansion was observed in the portal region of the liver parenchyma. However, there were no histiocytes containing crystalline structures in the liver parenchyma, as observed in the retroperitoneal tissue, and the liver was not cirrhotic. No crushing, narrowing, or abnormal blood circulation of the portal branch was observed in the portal vein area. In the heart, both ventricles were highly thickened, and their lumens were markedly narrowed. The ventricular wall had fibrosis and fatty infiltration circumferentially in all layers. Histologically, there was an increase in collagen fibers and a dense infiltration of eosinophilic histiocytes similar to those identified in the retroperitoneal tissue (Fig. 3k, l). Granular or crystalline structures were observed in the cytoplasm of some of the histiocytes, as in those in the retroperitoneum (Fig. 3m, n). Similar findings were observed in the bone marrow, heart, and anterior mediastinum. With these lesions present in multiple organs, the patient was diagnosed with generalized CSH.

Discussion

The patient was diagnosed with generalized CSH, with histiocytic infiltration of the retroperitoneum, perihepatic tissue, heart, mediastinum, and bone marrow. In addition, the patient was diagnosed with idiopathic RPF due to marked fibrosis, which led to ascites and gastric and esophageal varices. To our knowledge, there have been no prior reports on NCPH due to CSH.

CSH is a rare disease caused by the accumulation of crystalline material within the cytoplasm of histiocytes [6]. In 76–90% of CSH cases, there is an underlying disease expressing monoclonal immunoglobulin (mainly Ig kappa light chain), such as multiple myeloma and lymphoplasmacytic lymphoma [9]. In contrast, just under 10% of cases occur in association with inflammatory diseases, such as rheumatoid arthritis, lung infections, and Crohn's disease [5]. In addition, clofazimine, a drug used in the treatment of leprosy, is reported to be associated with CSH [5]. The elevated polyclonal immunoglobulin levels observed in this case were reported to be a characteristic more commonly observed in female patients with inflammatory diseases [5]. This suggests that the patient may have had some inflammatory disease that we were unable to identify.

CSH often involves a single organ or site (localized CSH), but may involve multiple organs or sites (generalized CSH) [10]. The former is reported in 58–82% of cases and the latter in 18–42% of cases [5]. Various organs and sites have been reported as having lesions in CSH; the bone marrow is the most common lesion site at 50% of cases, followed by the head and neck at 31%, kidney at 23%, lung at 20%, and liver at 8% of cases [11]. There have been rare reports of cases involving the peritoneum and heart [7]. In the present case, THS first occurred, which is a rare idiopathic granulomatous inflammatory disease with unknown etiology that occurs in the cavernous sinus, superior orbital fissure, or orbit, and is associated with ocular pain and ocular muscle paralysis [12]. THS in this case could be a sign of CSH, because autopsy revealed systemic CSH lesions.

Furthermore, this case developed RPF with CSH. RPF is characterized by the presence of chronic inflammation and pronounced fibrosis in the retroperitoneal tissue. In addition, a fibroinflammatory soft tissue mass surrounding the abdominal aorta, ureters, or other organs is frequently found [13, 14]. More than two-thirds of RPF cases are idiopathic,

whereas the remaining are related to other factors, such as neoplasms, infections, and use of certain drugs [14]. Idiopathic RPF is believed to be an immune-mediated disorder, which may develop alone or in association with other autoimmune diseases and/or fibroinflammatory disorders [13]. CSH has been reported to complicate myelofibrosis and cause systemic fibrosis [7], and RPF in this case may have been developed in association with CSH.

Considering that there was no evidence of cirrhosis and that there was severe fibrosis at the roots of the inferior vena cava and hepatic veins, PH in this case was believed to be NCPH, caused by disturbance of blood flow due to RPF. Compression of veins (mainly the inferior vena cava) is not rare, and this can cause lower limb edema [15, 16]. In addition, several reports of esophagogastric variceal ruptures caused by RPF indicate that RPF was the cause of the esophageal varices [17–19].

The primary treatment for RPF is PSL, which produces remission in 75–95% of cases [15, 20]. Unfortunately in this case, the patient did not respond to PSL treatment. However, the ascites decreased after initiation of tocilizumab. Tocilizumab is an anti-interleukin-6 (IL-6) agent that modulates immune function and suppresses inflammation [21]. Moreover, it is reported that IL-6 is involved in fibrosis and that tocilizumab reduces the fibrosis observed in systemic scleroderma and pulmonary fibrosis [22, 23]. Therefore, IL-6 is involved in the pathophysiology of RPF, and we considered that tocilizumab could have improved the patient's symptoms by suppressing the progression of IL-6-dependent fibrosis.

This case was complicated by NRH during the course of the disease. NRH of the liver is an uncommon condition characterized by the diffuse transformation of normal hepatic parenchyma into small, regenerative nodules with little to no fibrosis [24]. NRH has been reported to be associated with congestive liver due to non-compensated heart failure, rheumatic diseases, hematologic diseases, and systemic diseases, such as primary cholangitis [24, 25]. NRH is one of the causes of NCPH and accounts for 14–27% of all NCPH cases [26]. The pathogenesis of NRH seems to be related to abnormalities of the portal hepatic blood flow, a hemodynamic disturbance at the level of the hepatic microvasculature that occurs either secondary to mechanical obstruction or to functional blood flow alterations [27]. Drugs, such as steroids and immunosuppressive agents, may also induce NRH by injuring the endothelial cells of hepatic microvasculature [28]. In this case, the increased portal hepatic blood flow resulting from treatment of gastric varices and long-term use of steroids and immunosuppressive drugs may have contributed to the formation of NRH [29]. Therefore, it is possible that NRH was involved in the refractory ascites during the patient's clinical course.

In conclusion, we report a case of NCPH caused by generalized CSH. This is the first case to report generalized CSH as a cause of NCPH. Further studies are required to elucidate the pathogenesis of NCPH caused by generalized CSH.

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Author contributions YN, SS, NO, NA, and HN contributed to the study conception and design. YN, KM, AT, TS, NA, TH, and MO contributed to material preparation, data collection, and analysis. The manuscript was mainly written by YN. All authors read and approved the final manuscript.

Declarations

Conflict of interest Yasunao Numata, Shigeru Sasaki, Kazufumi Magara, Akira Takasawa, Taro Sugawara, Naruki Ohara, Noriyuki Akutsu, Tadashi Hasegawa, Makoto Osanai, and Hiroshi Nakase declare that they have no conflict of interest.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the patient's family.

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