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CASE REPORT

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Coexistence of nodular regenerative hyperplasia of the liver and pulmonary arterial hypertension in patients with connective tissue diseases: report of three cases and review of the literature

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Abstract Nodular regenerative hyperplasia of the liver (NRH) is known to be a rare condition in patients with connective tissue diseases (CTD). In this report, we document three patients with CTD who had both NRH and pulmonary hypertension (PH). All three patients developed PH during their course and thereafter developed NRH. The clinical course of these patients suggests that circulatory disturbance caused by PH might be a trigger for NRH.

Key words Connective tissue diseases (CTD) · Nodular regenerative hyperplasia of the liver (NRH) · Pulmonary hypertension

Introduction

Nodular regenerative hyperplasia of the liver (NRH) is histologically characterized by nodules of regenerative hepatocytes that are distributed diffusely throughout the liver, as well as atrophy of the intervening parenchyma and the absence of fibrous septae between the nodules.[1–3] Clinical studies have demonstrated that NRH progresses to noncirrhotic portal hypertension in 50% of patients.[4]

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Although the pathological characteristics of Nodular regenerative hyperplasia of the liver have been documented, its pathogenesis still remains unknown. Nodular regenerative hyperplasia of the liver rarely occurs in isolation and patients usually have various autoimmune diseases, including Felty's syndrome,[5,6] rheumatoid arthritis,[7,8] CREST syndrome,[9] systemic sclerosis (SSc),[10] polyarteritis nodosa,[11] primary Sjögren's syndrome (SjS),[12] systemic lupus erythematosus (SLE) with or without antiphospholipid syndrome (APS),[10,13–18] and primary APS.[10] A clinical association has also been documented between NRH and other systemic diseases, such as polycythemia vera,[2,19] myeloid metaplasia,[2] primary macrocryglobulinemia,[20,21] congestive heart failure,[1] infectious endocarditis,[22] primary (idiopathic) pulmonary hypertension (PPH),[23,24] and diabetes mellitus.[25]

Nodular regenerative hyperplasia of the liver is a rare hepatic condition and its prevalence in unselected autopsy series is estimated to range from 0.6% to 2.6%.[26] Matsumoto et al.[3] found three patients with the pathological features of NRH (5.8%) among 52 patients with SLE (51 autopsies and one wedge biopsy). An increasing number of NRH patients are being discovered incidentally by abdominal ultrasonography (US) or by postmortem examination. These findings suggest that the actual prevalence of NRH may be higher than has been realized.

Here we report three cases of NRH in patients with connective tissue diseases (CTD)-associated pulmonary hypertension (CTD-PH). We provide the details of these cases and review the clinical significance of NRH in patients with CTD.

Case reports

Case 1

In April 1985, a 14-year-old Japanese girl developed fever and polyarthralgia, and was admitted to Kitasato University Hospital. A diagnosis of SLE was made because she had photosensitivity, polyarthritis, pericarditis, leukopenia,

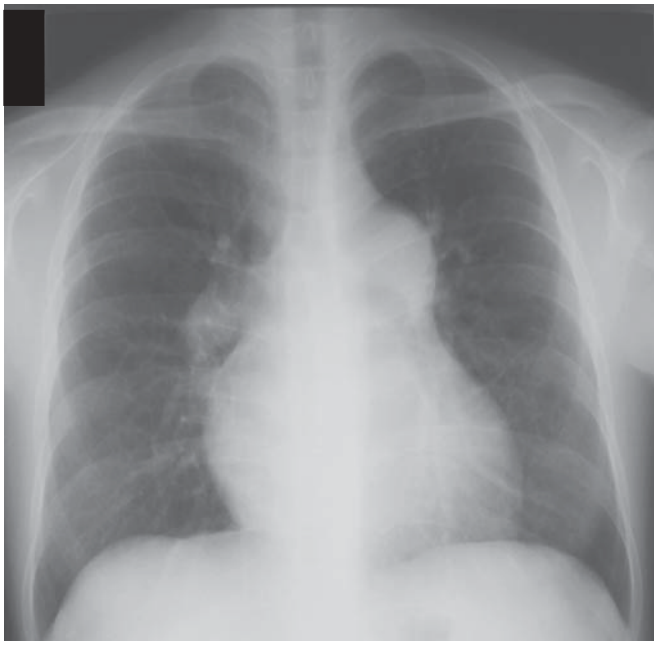

Fig. 1. Chest X-ray findings (case 1). Chest X-ray findings at the diagnosis of pulmonary hypertension (November 1990). Central pulmonary arteries are dilated and the left second arch protrudes markedly (cardiothoracic ratio; 52%)

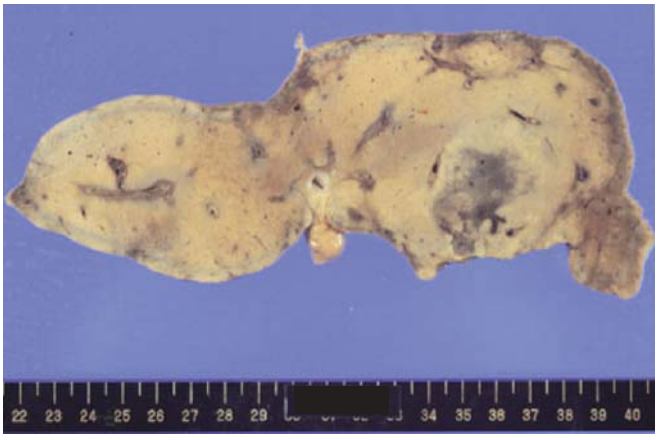

Fig. 2. Macroscopic appearance of the liver in case 1. There is nodular regenerative hyperplasia of the liver. The cut surface of the liver shows multiple nodular lesions throughout the parenchyma

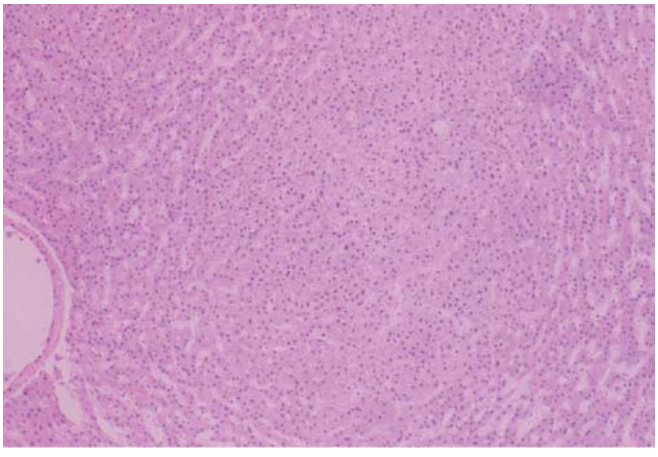

Fig. 3. Microscopic features of the liver in case 1. There is nodular hyperplasia without hepatocellular dysplasia. Hepatocytes at the borders of the nodules show atrophy. No fibrosis is seen around the nodules. The hepatic lobe is destroyed by hyperplastic nodules. No hepatocellular abnormalities are seen in the central areas of the nodules (H&E stain, ×100)

thrombocytopenia, positive fluorescent antinuclear antibody (FANA) (speckled type), positive anti-dsDNA antibody, and positive anti-U1 RNP antibody (123.5 index, normal: <15 index). She was treated with prednisolone (PSL) at 60 mg/day and soon improved. She subsequently developed CNS lupus in June 1989 and was treated with methylpredonisolone (mPSL) pulse therapy followed by PSL at 50 mg/day. She was also given received oral azathiopurine (AZP) at 50 mg/day because of high serum levels of anti-dsDNA antibodies and hypocomplementemia. In November 1990, she presented with chest pain and PH was diagnosed (the pulmonary artery pressure was 46/22(30) mmHg) by right heart catheterization (Fig. 1). She was treated with intravenous cyclophosphamide (IVCY) twice and with mPSL pulse therapy, followed by antithrombotic therapy. Dyspnea on exertion was noted from July 1994, and the mean pulmonary artery pressure (mPAP) was estimated to have reached 79 mmHg by echocardiography. Thereafter, she was treated with home oxygen therapy (HOT) and active prostaglandin I_2 analogue (beraprost sodium). In July 1995, she presented with hepatomegaly and abdominal US showed two space-occupying lesions in her liver with diameters of several centimeters. The tumors showed slight contrast enhancement on computed tomography scans. Because of the presence of esophageal varices with red color (RC) sign, she was repeatedly treated with endoscopic injection sclerotherapy (EIS) without administration of anticoagulant. She died of pulmonary hemorrhage in April 1997. Postmortem examination revealed the presence of NRH in the liver and alveolar capillaritis with diffuse pulmonary hemorrhage (Figs. 2 and 3). Throughout her clinical course, clinical findings of systemic sclerosis, myositis, and anti-phospholipid antibodies (aPL) were not observed.

Case 2

In 1993, a 71-year-old Japanese woman presented with dry eyes, polyarthritis, hypergammaglobulinemia, positive FANA (discrete speckled type, homogeneous type), positive anti Ro/SS-A antibody, and positive anticentromere antibody (ACA) (185 units, normal: <20 units). She had no manifestations of CREST syndrome, and she was diagnosed as having primary SjS with ACA. In January 1995, she showed elevated serum levels of hepatobiliary enzymes (AST 27 IU/l, ALT 16 IU/l, ALP 362 IU/l, γ-GTP 140 IU/l), and hepatomegaly was detected by US. Antimitochondrial antibody was not detected.

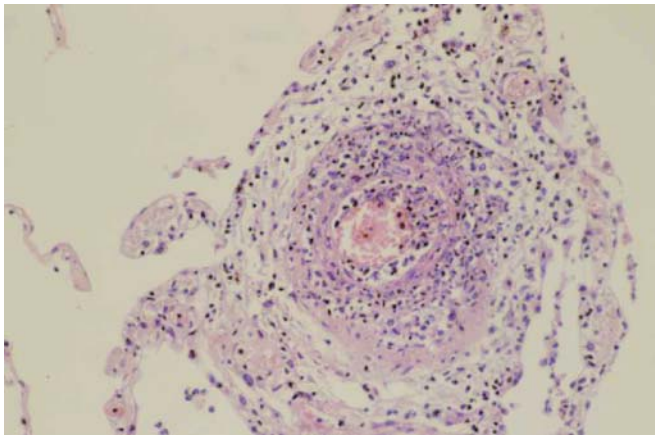

Fig. 4. Pulmonary histological findings (case 2). Histopathological changes of the pulmonary arterioles are shown. Inflammatory cell infiltration and necrotizing angiitis with fibrinoid necrosis are seen in the medium-sized pulmonary arteries to arterioles. These changes were not found outside for the lungs (H&E stain, ×200)

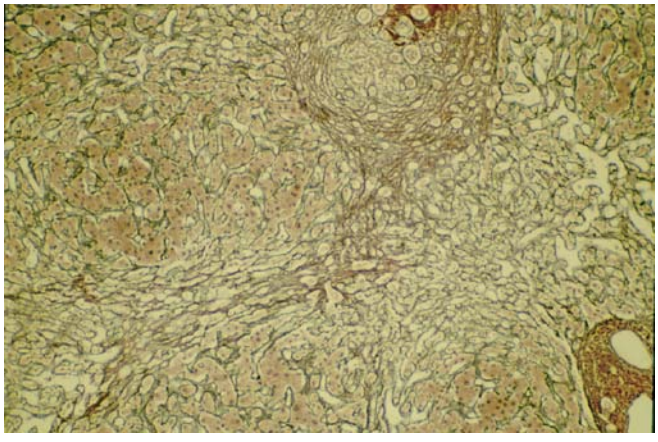

Fig. 5. Microscopic features of the liver in case 2. Grossly, nodular lesions (5 mm in diameter) are scattered throughout the liver. These nodules are found around portal regions and consist of hyperplastic hepatocytes, while hepatocytes near the central vein are compressed and atrophic. No fibrous septae are noted (Elastica von Gieson stain, ×100)

In September, she developed exertional dyspnea and echocardiography indicated the presence of PH (PAP was estimated as 88 mmHg). She was treated with HOT and beraprost sodium. In May 1997, she was hospitalized for exacerbation of dyspnea. Although she was treated with intravenous prostaglandins, as well as digitalis and vasodilators, she died of right heart failure. Postmortem examination revealed the presence of necrotizing angiitis in the pulmonary arterioles and NRH in the liver (Figs. 4 and 5). She was not treated with either PSL or immunosuppressants during her course.

Case 3

In December 1971, a 16-year-old Japanese girl was admitted to our hospital due to Raynaud's phenomenon and skin thickening. She showed sclerodactyly, skin pigmentation, and areas of hypopigmentation on the forearms. Investigations revealed lower esophageal dilatation, polyarthritis, and hypergammaglobulinemia, but she was negative for FANA. A diagnosis of SSc was made. Exertional dyspnea developed from February 1977. A chest X-ray film showed pulmonary artery dilatation without any evidence of pulmonary fibrosis. Right heart catheterization revealed an increased PAP (48/22 (31) mmHg). Echocardiographic analysis was performed thereafter and PAP decreased under 40 mmHg. In 1987, prominent hepatosplenomegaly without any space-occupying lesion was found by US.

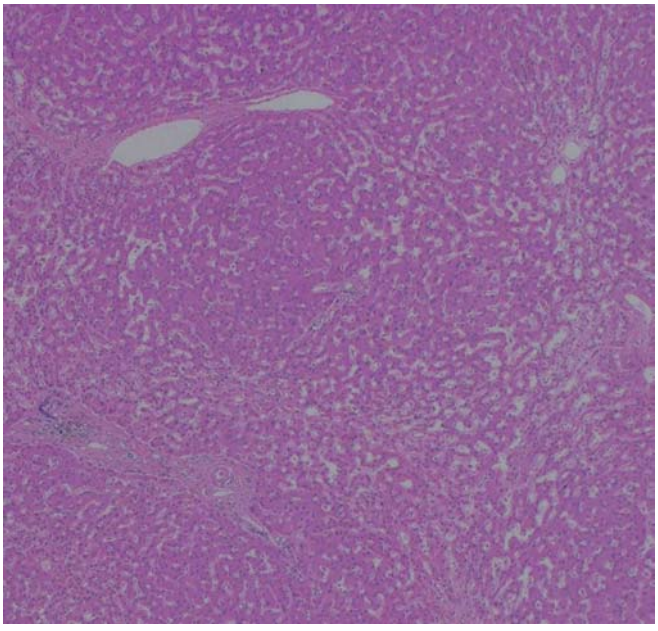

Fig. 6. Microscopic features of the liver in case 3. Hepatocytes showed nodular hyperplasia without atypia. (H&E stain, ×100)

In September 1989, she developed generalized lymphadenopathy, and thrombocytopenia (8.3×10^4/μl), as well as becoming positive for FANA, anti-DNA antibody (840 U/ml), anti-U1 RNP antibody (83.4 index), and hypocomplementemia (CH50 18 U/ml, normal: 20–50 U/ml). We then diagnosed as SLE/SSc overlap syndrome and started administration of PSL at 50 mg/day. On admission, she had massive hepatosplenomegaly despite normal hepatic enzyme levels. Liver biopsy was done via laparoscopy and revealed NRH of the liver (Fig. 6). She was treated with EIS because of the presence of esophagogastric varices with the RC sign. In 2005, she had dyspnea on exertion, but was otherwise well. aPL has not been detected throughout her course.

Discussion

Hepatic involvement has been documented in CTD and hepatomegaly is occasionally found by physical examination or US. In the present study, we reported three CTD

Table 1. Clinical features of CTD patients with PH and NRH

Case no.	Sex	Dx	Raynaud's phenomenon	Esophageal varices	Age of onset for CTD	Age of onset for PH	Age of onset for NRH	Age at death	Immunosuppressive therapy until NRH
1.	F	SLE	(+)	(+)	14y 10m	21y 7m	25y 2m	26y 11m	PSL, CY, AZP
2.	F	Primary SjS	(–)	(–)	71y 3m	72y 11m	74y 7m	74y 7m	(–)
3.	F	SLE+SSc	(+)	(+)	16y 4m	21y 6m	34y 1m	Alive	AZP

Dx, diagnosis; CTD, connective tissue disease; PH, pulmonary hypertension; NRH, nodular regenerative hyperplasia; SLE, systemic lupus erythematosus; SjS, Sjögren's syndrome; SSc, systemic sclerosis; PSL, prednisolone; CY, cyclophosphamide; AZP, azathiopurine; y, years; m, months

Table 2. Laboratory data of CTD patients with PH and NRH

Case no.	Dx	Findings at the onset of NRH	Autoantibodies		
			FANA	ENA	aPL
1.	SLE	Cytopenia (–) AST 35, ALT 34, ALP 327, γGTP 84	1:1280	U1 RNP	(–)
2.	Primary SjS	Cytopenia (–) AST 30, ALT 18, ALP 572, γGTP 241	1:5120	ACA, SS-A	NE
3.	SLE+SSc	Cytopenia Normal liver enzymes	1:320	U1 RNP	(–)

FANA, fluorescent antinuclear antibody; ENA, antibodies against extractable nuclear antigen; aPL, antiphospholipid antibody; ACA, anticentromere antibody; NE, not examined; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γGTP, gamma-glutamyltranspeptidase

patients who had both NRH and PH. From a 35-year (1971–2005) retrospective review of archival records of Kitasato University Hospital, we made diagnoses of three cases with NRH (3.1%) in 96 patients with CTD-PH. The clinical manifestations and laboratory findings of these cases are summarized in Tables 1 and 2. The patients were SLE (case 1), primary SjS (case 2), and SLE/SSc overlap syndrome (case 3) as the underlying disease and NRH was diagnosed histopathologically (two autopsy cases and one biopsy). All three patients developed PH during their disease course and subsequently developed NRH. The average interval from the onset of PH to that of NRH was 5.9 years (range: 1.7–12.6 years). Two patients died at an average of 3.5 years (range: 1.7–5.3 years) after the diagnosis of PH. Concerning the use of corticosteroid therapy before the onset of NRH, case 1 was treated with long-term steroids, but case 2 did not receive any immunosuppressive agents including steroids, and case 3 was started on steroid therapy after the diagnosis of NRH (Table 2). Two patients had esophagogastric varices. Anti-U1 RNP antibodies were detected in two patients, but aPL were negative in the two patients (cases 1 and 3) who were examined (Table 2).

Although the pathological features of NRH are well established, the pathogenesis remains unknown. Steiner[1] demonstrated that NRH was frequently complicated by severe congestive heart failure, and he hypothesized that circulatory disturbance, especially right heart dysfunction, may lead to the development of NRH. Stromeyer and Ishak[4] documented the possible role of drugs, such as steroids, anticancer agents, immunosuppressants, and contraceptives in the development of NRH. Wanless and colleagues[2,26] demonstrated that obliteration of lobular veins by portal thrombi (obliterative portal venopathy) might promote hepatic nodule formation, and they concluded that it was a secondary and nonspecific tissue response to aberrant distribution of blood flow rather than specific disease entity. At present, this hypothesis of circulatory disturbance is generally accepted as being involved in the pathogenesis of NRH. An association of aPL with NRH in patients who have SLE or primary APS has been shown by Perez-Ruiz et al.[27] If NRH is initiated by the cumulative effects of microthrombi, it is possible that aPL may contribute to its development. However, the association of aPL with NRH remains controversial because of the small number of CTD patients who develop NRH. Two of our three patients in this series did not become positive for aPL during their course. We also could not find any association between NRH and immunosuppressants, including steroids.

Kondo et al.[28] evaluated the pathological features of their cases with nodular lesions and reported that pathological changes of the arteries or bile ducts indicating portal thrombosis were not predominant. They emphasized that obliterative portal venopathy was only an exacerbating factor promoting thrombosis and angiitis during nodule formation. They proposed the hypothesis that regenerating nodules arose as a result of immunological dysfunction or due to vascular remodeling in other organs that brought about hepatic circulatory disturbance and parenchymal injury.[29] Through a Medline search for English-language articles published between 1966 and 2005, two PPH cases with NRH[23,24] and six CTD-PH patients with NRH including our

cases[13] were found. Because the number of reported cases of NRH complicated by PPH or congestive heart failure appears to be smaller than the number of patients who have NRH with CTD, autoimmune diseases may be a causative factor in the development of NRH. Although an association of NRH with CTD has been often shown, the coexistence of NRH and PH in patients with CTD is rare. Kuramochi et al.[13] have reported three patients with SLE who developed both NRH and PH. Coexistence of NRH and PH was found in one patient at postmortem, while another two patients had SLE and developed NRH after the onset of PH. Our three patients in this series also developed NRH after the onset of PH. Therefore, it is reasonable to speculate that circulatory disturbance related to right heart dysfunction may lead to the development of NRH, as Steiner first suggested.[1]

Perez-Ruiz et al.[10] stated that the serum levels of aminotransferases (AST and/or ALT), alkaline phosphatase (ALP), and γ-glutamyltranspeptidase (γGTP) were increased in 50%, 75%, and 65% of patients with NRH, respectively. As shown in Table 2, the increase of biliary enzymes was more prominent than that of aminotransferases in these two patients.

The multiple hepatic nodules that occur in NRH may have variable echogenicity and are often of low density without significant enhancement on computed tomography scans.[30,31] Dynamic computed tomography scanning shows multiple enhancing nodules in the hepatic arterial phase, as well as isodense nodules in the portal venous and delayed phases.[32] When viewed by magnetic resonance imaging, the nodules often have a diffuse high signal intensity on T1-weighted images and isointensity on T2-weighted images, and range from a few millimeters to several centimeters in diameter.[33,34] Since hyperplastic regenerative nodules consist of normal hepatocytes and Kupffer cells that take up contrast agents, they do not show up as defects on superparamagnetic iron oxide-enhanced MRI (SPIO-MRI).[35] These findings are helpful for making a differential diagnosis between NRH and hepatocellular carcinoma.

Histopathological detection of diffusely distributed regenerating nodules without fibrous septa is essential for the diagnosis of NRH.[36] Dachman et al.[30] recommended multiple needle biopsies, laparoscopically guided needle biopsy, or wedge liver biopsy to make a definite diagnosis in patients with the radiological features of NRH. Although one patient (case 3) had hepatosplenomegaly with normal liver function tests and did not show any topographic lesions on various imaging studies, we made a diagnosis of NRH with laparoscopic liver biopsy.

It is well known that the frequency of PH is far higher in patients with CTD than in normal populations. Our three cases developed CTD-PH. Pulmonary angiitis found in cases 1 and 2 on postmortem examination may contribute to the development of PH. Pulmonary hypertension is a life-threatening disorder and the median survival time is reported to be 2.8 years.[37] Home intravenous prostacyclin infusion therapy has recently become available for PH in Japan, so we expect that not only the quality of life but also the long-term prognosis of patients with PH will be improved. Anticoagulant therapy as well as home oxygen therapy and administration of prostaglandin I_2 analogues are recommended for patients with PH.[38,39] In two patients (cases 1 and 3), we discontinued anticoagulant therapy because of the high risk of bleeding from esophageal varices caused by NRH-induced portal hypertension. Therefore, coexistence of NRH may lead to deterioration of PH in patients with CTD.

Patients with CTD often develop hepatomegaly and elevated levels of liver enzymes. It is not easy to diagnose NRH because there are no specific laboratory findings apart from those on pathological examination. Thus, rheumatologists should consider NRH as a possible liver disease in CTD patients with PH who develop hepatomegaly and liver dysfunction.

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