

# Nodular Regenerative Hyperplasia of the Liver in Rheumatic Disease: Cases and Review of the Literature

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## Abstract

Nodular regenerative hyperplasia (NRH) is a rare disease that is characterized by benign transformation of the hepatic parenchyma into small nodules with little to no fibrosis. Nodular regenerative hyperplasia is a cause of noncirrhotic portal hypertension. Symptoms can range from asymptomatic disease to more serious complications of portal hypertension such as esophageal varices and ascites. Nodular regenerative hyperplasia has been described in association with a variety of different rheumatologic, hematologic, and oncologic diseases, as well as in immune deficiency states and with exposures to certain toxins. Diagnosis is made by histology, and the treatment involves addressing the underlying disease. The first description of this rare disease was actually described in a patient with rheumatoid arthritis, neutropenia, and splenomegaly (Felty's Syndrome). We describe 2 cases of NRH associated with underlying rheumatic disorders, in one of which NRH was actually the presenting feature of the patient's underlying autoimmune condition. Subsequently, we provide a brief review of the literature of NRH in autoimmune disease with respect to epidemiology, cause, clinical manifestations, diagnosis, and treatment.

## Keywords

nodular regenerative hyperplasia, portal hypertension, vasculopathy, autoimmune

## Introduction

Nodular regenerative hyperplasia (NRH) is a rare disease but one of the more common causes of noncirrhotic portal hypertension. NRH of the liver is characterized by diffuse micronodular transformation of the hepatic parenchyma with an absence of fibrous septa between the nodules, in contrast to the typical liver cirrhosis.<sup>1</sup> Nodular regenerative hyperplasia has been described as a form of liver disease with preserved liver function, yet with clinical, radiographical, or endoscopic signs of portal hypertension.<sup>2</sup> This rare disease was actually first described in a patient with rheumatic disease: Ranström in 1953 presented a case of what he termed "military hepatocellular adenomatosis" in a patient with rheumatoid arthritis, neutropenia, and splenomegaly (Felty's Syndrome).<sup>3,4</sup> Several years later, Steiner coined the term "nodular regenerative hyperplasia" to describe this condition characterized by diffuse transformation of hepatic parenchyma into small regenerative nodules with minimal liver

fibrosis.<sup>5</sup> Nodular regenerative hyperplasia has been described in association with a variety of different hematologic, oncologic, and rheumatic diseases, as well as in immune deficiency states and with exposures to certain toxins.<sup>3,5</sup> We describe 2 cases of NRH associated with underlying rheumatic disorders, in one of which NRH was actually the presenting feature of the patient's underlying autoimmune condition. In both cases, the liver biopsies were performed at outside institutions, but the diagnosis was made on re-review of the outside slides at our institution (often times

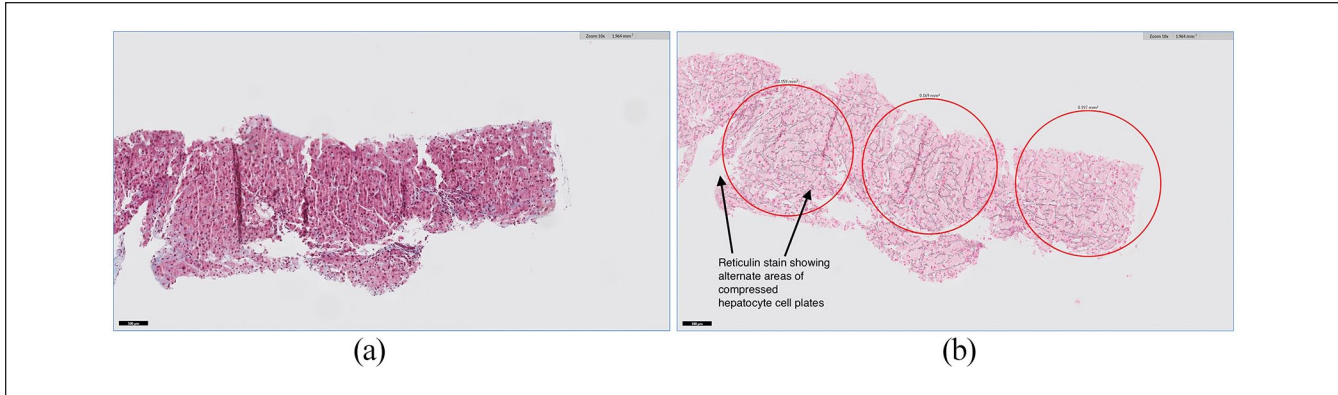
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**Figure 1.** (a) Liver biopsy slides visualized in low magnification with Masson trichrome stain, which stains for collagen, shows that there is vague nodularity present. There is an absence of fibrous septa at the periphery of the nodules, which is an important feature which distinguishes NRH from cirrhosis. (b) Reticulin stain from the same area showing nodules (annotated by circles). The reticulin stain allows for appreciation of 2 populations of hepatocytes that differ in size. The nodules themselves are composed of thickened liver cell plates whereas their boundaries consist of thin, parallel, and compressed cell plates. Abbreviation: NRH, nodular regenerative hyperplasia.

the diagnosis can be easily missed on initial pathology review). Subsequently, we provide a brief review of the literature with respect to epidemiology, cause, clinical manifestations, diagnosis, and treatment. It is critical that rheumatologists and hepatologists consider NRH as a rare but important cause of noncirrhotic portal hypertension in patients with underlying systemic illnesses and unexplained ascites.

## Case Presentation

### Case 1

A 56-year-old woman was referred to our rheumatology clinic for evaluation Raynaud phenomenon and a positive antinuclear antibody (ANA). She was in her usual state of health until 1 year prior when she began to develop bilateral lower extremity edema and abdominal distention. Gynecologic evaluation included a transvaginal ultrasound that showed ascites and a slightly elevated serum CA-125 level, thought to be related more to ascites and not to ovarian cancer. Shortly thereafter, she presented to a local emergency department for worsening abdominal distention and was found to have a serum creatinine of 4.4 mg/dL. Over the next several months, she underwent numerous hospitalizations and was evaluated by multiple subspecialists without a unifying diagnosis for the ascites and kidney injury. Renal biopsy revealed a thrombotic microangiopathy with both acute and long-term features. Liver biopsy was initially read as normal without evidence of cirrhosis. She underwent bilateral salpingo-oophorectomy with lymph node dissection for possible Meig syndrome, but ascites persisted requiring weekly large-volume paracentesis.

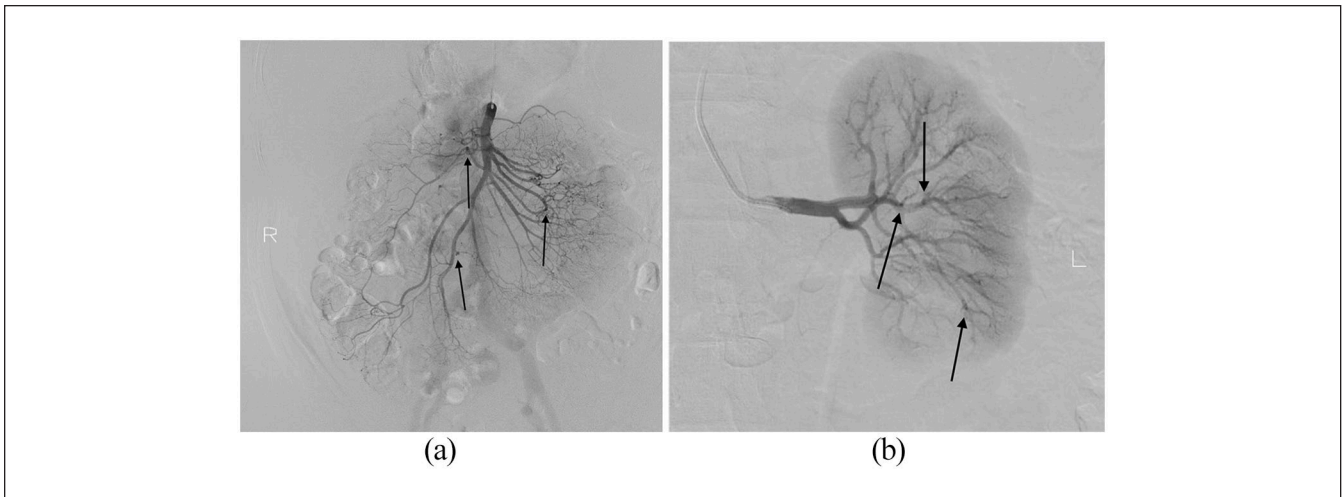
Around the same time that her other symptoms began, she also developed Raynaud phenomenon. She was referred to Rheumatology for evaluation of possible scleroderma;

however, her clinical findings were not consistent with a diagnosis of scleroderma. Laboratory evaluation upon presentation revealed white blood cell  $6 \times 10^9/L$ , hemoglobin 10.2 g/dL, creatinine 1.45 mg/dL, and normal liver function tests. Immunologic profile revealed a positive ANA at a titer of 1:160 (homogeneous pattern) with negative anticentromere antibodies, as well as negative testing for SSA, SSB, Scl-70, RNP, and Anti-Jo 1 auto-antibodies. Review of the original liver biopsy revealed focal nodular formation on the reticulin stain consistent with a diagnosis of NRH (Figure 1).

She was treated with prednisone 10 mg daily. Although she now had a diagnosis of biopsy-proven NRH, a connection with her renal disease had yet to be established. Over the following year with extensive collaboration between rheumatology and nephrology, polyarteritis nodosa (PAN) was proposed as a possible unifying diagnosis that could explain both the NRH and the thrombotic microangiopathy. The patient therefore underwent mesenteric angiography (Figure 2) for further evaluation, and this revealed multiple microaneurysms within the hepatic, splenic, superior mesenteric, and bilateral renal arterial vasculature consistent with a diagnosis of PAN. With the diagnosis of PAN, Prednisone dose was increased, and immunosuppression was initiated with monthly intravenous cyclophosphamide resulting in improvement in her abdominal pain, ascites, and renal function. With this treatment, she has not required paracentesis in over a year.

### Case 2

A 58-year-old man with a complicated past medical history presented to our clinic for evaluation. Several years prior, he developed symptoms of Raynaud phenomenon, skin tightening in his fingers and toes, as well as dysphagia and esophageal reflux symptoms. He was referred to a local rheumatologist who diagnosed limited cutaneous systemic



**Figure 2.** Mesenteric angiography demonstrating microaneurysms in the ileal branches of the superior mesenteric artery (a) and upper pole of the left kidney (b), as seen in polyarteritis nodosa.

sclerosis. A few years into his illness, he began experiencing abdominal fullness and shortness of breath. Abdominal ultrasound revealed a cirrhotic morphology of the liver, and chest imaging revealed a large right-sided pleural effusion. Over the next several months, he required large volume paracenteses and thoracenteses for symptomatic relief of his refractory ascites and pleural effusions. His wife estimated that he had undergone roughly 12 large volume paracenteses and upward of 55 thoracenteses over a period of 8 months. He had undergone a liver biopsy for workup of his ascites that did not show cirrhosis; however, esophagogastroduodenoscopy (EGD) revealed esophageal varices. Due to suspicion for NRH, his liver biopsy slides were re-reviewed and deemed to be consistent NRH. Transhepatic venogram revealed normal portal pressures but an elevated direct portal pressure. He underwent a transjugular intrahepatic portosystemic shunt (TIPS) placement for refractory ascites. His postoperative course was complicated by hepatic encephalopathy and congestive heart failure, but he had remarkable improvement in his ascites and symptoms after the procedure. Both his hepatic encephalopathy and congestive heart failure are now well controlled with medical management, and he has not required either a paracentesis or thoracentesis since having the TIPS procedure more than 4 years ago.

## Discussion

NRH is a rare condition characterized by transformation of normal liver parenchyma into regenerative nodules. This subsequently leads to the development of noncirrhotic portal hypertension. Noncirrhotic portal hypertension is seen when there are clinical signs of portal hypertension such as splenomegaly, varices, ascites, and portovenous collaterals. Laboratory testing reflects normal serum transaminases,

albumin, prothrombin time/international normalized ratio (INR), and normal bilirubin levels. Exclusion of long-term liver disease by serologic work up and exclusion of cirrhosis on liver biopsy are also necessary for diagnosis of NRH. Other conditions that can cause portal hypertension such as congenital liver fibrosis, schistosomiasis, and sarcoidosis must be ruled out. In addition, there must be confirmation that there is patency of the portal and hepatic veins. In 1990, Wanless developed a new histologic criterion for diagnosis of NRH. This included the presence of hepatic nodules less than 3 mm in diameter and not surrounded by fibrous septa between nodules.<sup>6</sup> Biopsies that met the criteria of 3+ nodularity and 0 to 1 fibrous septa were classified as consistent with NRH. Nodular regenerative hyperplasia can be seen in association with a variety of systemic diseases, including myeloproliferative, hematologic, vascular, and rheumatologic disorders.<sup>1-8</sup> The disease course is variable, ranging from asymptomatic disease to complications of portal hypertension including ascites, variceal bleeding, and hepatosplenomegaly. The diagnosis is often missed on biopsy, which contributes to challenges in management.

The exact prevalence of NRH, especially in the setting of autoimmune disease, has not been determined. Liver dysfunction in patients with rheumatic disease is sometimes assumed to be secondary to medication side effects and liver biopsies are often not performed. In addition, NRH is likely underdiagnosed as the histology can be missed in routinely processed specimens, particularly if a reticulin staining is not performed.<sup>9</sup> Some autopsy studies, which looked at consecutive autopsy livers without hepatic necrosis, fibrosis, cirrhosis or tumors, indicate an overall incidence between 0.72 and 2.6%.<sup>10</sup> A large cohort study of 2,500 consecutive autopsies in Canada by Wanless in 1990 revealed that NRH was present in 64 patients (2.6%).<sup>6</sup> In this cohort, 93.8% of patients

with NRH were noted to be above the age of 60, likely reflecting the higher prevalence of systemic diseases in older individuals. Men and women were equally affected. NRH was found to be associated with a variety of different underlying conditions and malignancy was commonly noted (42.2%). The most commonly associated rheumatologic conditions included rheumatoid arthritis (6.2%), Felty's syndrome (3.1%), polymyalgia rheumatica (3.1%), systemic sclerosis (1.6%), PAN (1.6%), and systemic lupus erythematosus (SLE) (1.6%).<sup>6</sup> Other studies noted similar numbers, including Graf and colleagues who studied NRH in systemic sclerosis.<sup>5</sup> Considered a rare condition, the literature on NRH in autoimmune disease largely consists of case reports and case series so the true prevalence is not known.

Hepatocytes normally have a very low mitotic activity with hyperplasia occurring in response to cellular injury or abnormalities in blood flow. Nodular regenerative hyperplasia is thought to occur as a physiologic response to cellular injury and hemodynamic disturbances at the level of the microvasculature.<sup>3</sup> Hypoperfusion at the level of the portal vein is thought to lead to apoptosis and hepatocyte atrophy. This, in turn, is thought to lead to increased blood supply and upregulation of cellular growth factors in adjacent cells, leading to hypertrophy.<sup>3</sup> This hypothesis is supported by histopathologic data from liver biopsies as well as animal models showing microvascular changes involving the portal vein. Wanless, therefore, coined the term "portal obliterative venopathy" to describe the underlying pathophysiology of NRH.

Although NRH is ultimately a result of local hyperplastic response of hepatocytes and underlying vascular irregularities, the mechanism by which this occurs can vary slightly depending upon the trigger. For example, medications (primarily immunosuppressive drugs or chemotherapy) may induce NRH by injuring the endothelial cells of small hepatic veins. In those with underlying autoimmune disease, NRH is thought to occur as a result of an antibody reaction to the endothelial cells of small hepatic vessels, along with local inflammation and hypercoagulation.<sup>11</sup> In patients with lupus, for example, anticardiolipin antibody has been hypothesized as being a precipitant for portal vasculopathy, although this is not a universal finding in SLE.<sup>12</sup> In addition, it has been postulated that NRH pathogenesis may imply a hypercoagulable state and subsequent hepatic vessel thrombosis.<sup>13</sup> Specifically, it has been hypothesized that long-term inflammation of intrahepatic arteries leads to secondary portal venous obliteration and thrombosis of adjacent portal veins, such as might be seen in PAN leading to NRH.<sup>14</sup>

Generally, the clinical manifestations of NRH are related to the complications of portal hypertension. The diagnosis should be considered in patients with signs and symptoms of portal hypertension (ascites, esophageal varices, and splenomegaly) but without other clinical manifestations of cirrhosis or hyper-estrogenism (palmar erythema, spider angioma, and gynecomastia). In most cases, NRH is slowly progressive

and related to the severity of the associated underlying disease. Similarly, the long-term prognosis is overall uncertain and is related to the underlying autoimmune, myeloproliferative, or hematologic process.

The diagnosis of NRH is made by liver biopsy. Diagnosis requires a high index of suspicion, especially when evaluating unexplained portal hypertension not associated with cirrhosis. The diagnosis can be challenging because the presentation can be widely variable and most patients present without significant laboratory abnormalities, although mild abnormalities in liver function tests can be seen, especially elevations in alkaline phosphatase which are reported in 1 of 10 patients.<sup>15</sup> Imaging modalities, such as contrast-enhanced computed tomography and magnetic resonance imaging, can sometimes be helpful by characterizing the liver nodules and identifying features of portal hypertension. Typically, portal hypertension is presinusoidal with hepatic venous pressure gradient measurements being falsely low (<10 mmHg) in the vast majority of patients.<sup>16</sup> Although imaging modalities can support the diagnosis, liver biopsy is the only way to make a definitive diagnosis.<sup>9</sup> Needle biopsy or open-wedge biopsy are preferred, although diagnosis can be missed in needle biopsy if the needle is too narrow. A reticulin stain is often essential to make the diagnosis as the changes on pathology can be subtle. On gross examination of the liver, the hepatic parenchyma, which is normally homogenous, appears as though it has transformed into diffuse nodules 1 to 3 mm in size. Unlike cirrhosis, no perisinusoidal or portal fibrosis is seen, and each nodule is pressed directly against its neighbor.<sup>17</sup> The hepatocytes within the nodules themselves are arranged in thick plates which are usually 2 to 3 cells thick. These hepatocytes may be enlarged and have hypertrophic nuclei. However, the cells between the nodules are small, atrophic, and pressed together in thin, parallel plates.<sup>18</sup> This compression between cells is best visualized using a reticulin stain, which is often required to visualize the nodular architecture, hepatocyte atrophy, and alternating thickened and atrophic plates.<sup>17,18</sup> Studies, such as that by Jharap and colleagues, reveal that even when liver biopsies are reviewed by experienced pathologists, the interobserver agreement on the histologic diagnosis of NRH was poor.<sup>15</sup> Therefore, the diagnosis requires a high degree of clinical suspicion because one cannot always rely on the histology alone, especially on gross examination, as is evidenced by our 2 cases.

As is the dogma in many secondary disease processes, initial treatment of NRH is to address the underlying disease and the manifestations of portal hypertension. Concomitant diseases should be treated simultaneously and with consideration to minimizing drug toxicity. It should be noted that mortality by variceal hemorrhage in noncirrhotic portal hypertension is considerably lower than that observed in cirrhotic patients, likely because of a preserved liver function.<sup>14</sup> Outcome and prognosis are related to the severity of both portal hypertensive complications and the underlying associated diseases.

We conclude that the presence of NRH should generate considerable interest for clinical investigation. The medical community should appreciate that the current knowledge of NRH and relationship to autoimmune disease is lacking and needs further investigation. Likewise, patients with autoimmune disease who have signs and symptoms of portal hypertension but a negative workup for cirrhosis should prompt the clinician to consider NRH and initiate appropriate work up for this condition. Patients who suffer from portal hypertension from any cause should be managed by current guidelines as they have significant physiologic cause for increased morbidity and mortality.<sup>14</sup>

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### Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

### Informed Consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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