Nodular Regenerative Hyperplasia of the Liver: A Rare Vascular Complication in Systemic Sclerosis

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ABSTRACT. Objective. To investigate nodular regenerative hyperplasia (NRH) as a vascular complication of systemic sclerosis (SSc) and to establish its significance in SSc vasculopathy. Methods. Cases of SSc-NRH were identified by systemic literature review and by screening the Zurich cohort. NRH had to be diagnosed by liver biopsy. Results. Literature review retrieved 22 cases. In our cohort, 1.4% of patients with SSc were diagnosed with NRH. Most had vasculopathy, were positive for anticentromere antibodies, had elevated alkaline phosphatase and gamma-glutamyl transferase levels, normal liver morphology on ultrasound yet increased stiffness on ultrasound elastography, and had portal hypertension. Conclusion. NRH might represent a rare yet potentially life-threatening vascular complication in SSc.

Key Indexing Terms:
- NODULAR REGENERATIVE HYPERPLASIA
- VASCULOPATHY
- SYSTEMIC SCLEROSIS

Nodular regenerative hyperplasia (NRH) of the liver is a rare and poorly understood liver disease. NRH is histologically defined by diffuse micronodular transformation without fibrous septa. Lack of perinuclear collagen tissue distinguishes NRH from typical regenerative nodules in the cirrhotic liver. So far, there are only about 460 reported cases, and most of the knowledge of NRH is based upon case reports rather than systematic population studies. Patients with NRH may remain asymptomatic; however, in at least 50% of reported cases, potentially life-threatening complications occur. Although the etiology is unknown, it is hypothesized that NRH develops as a result of microvascular alterations. Data indicate that damage of endothelial cells might play an important role. Clinical complications of NRH comprise manifestations of portal hypertension such as splenomegaly, ascites, and esophageal or gastric varices. Transaminases might be normal or slightly elevated, whereas cholestatic measures are often more significantly increased.

Among the autoimmune disorders, systemic sclerosis (SSc) in particular has been suggested to be associated with NRH. In SSc, microvascular injury, including damage of endothelial cells, is considered one of the earliest pathologic events, followed by inflammation and fibrosis. Therefore, it might be hypothesized that NRH represents a yet unidentified vascular alteration in SSc and possibly other autoimmune diseases with associated microvasculopathy, such as systemic lupus erythematosus or rheumatoid arthritis. So far, the prevalence of SSc-NRH is unknown, and the clinical phenotype of patients with SSc-NRH has not yet been characterized systematically. In addition, the prognosis of SSc-NRH remains elusive. Therefore, the aim of our study was to investigate the prevalence and the clinical phenotype of NRH in our SSc cohort.

MATERIALS AND METHODS

First, we performed an electronic search by systematically screening the databases Pubmed, Medline, Google Scholar, and the Cochrane Library for available literature. Combinations of medical subject headings and free text words related to “systemic sclerosis, scleroderma, nodular regenerative hyperplasia” were used. Articles published in English, Spanish, Italian, French, and German were considered from inception of the databases until December 2016. The search results were supplemented by articles found through manually screening the reference lists of identified studies. Studies were included if they were original case reports or series and reported on biopsy-proven SSc-NRH. After removal of duplicates, the search results were screened for eligibility by a team of 2 reviewers (LG/BM) sharing the retrieved citations. In case of disagreement, a third party (DO) served as referee. Next, we screened our Zurich SSc cohort, which comprised 278 patients with established SSc fulfilling the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria at the time of the data analysis. In accordance with international guidelines, the diagnosis of NRH had to be established by liver biopsy showing a characteristic diffuse micronodular transformation without fibrous septa. SSc characteristics were derived from the local SSc database in Zurich in accordance with EULAR Scleroderma Trials and Research group guidelines.
(EUSTAR) recommendations. Information on NRH was extracted from the patients’ charts. Patients with any connective tissue disease other than SSc or not fulfilling the ACR/EULAR 2013 criteria were excluded. All patients signed informed consent according to the Declaration of Helsinki, and the Cantonal Ethics Committee Zurich approved the study (PB2016_01515). To identify additional nonpublished studies of patients with SSc-NRH through expert opinion, we repeatedly conducted a questionnaire-based inquiry by contacting > 180 EUSTAR centers worldwide by e-mail between February 2015 and January 2016. However, because the eligibility of cases for our study was based on biopsy-proven NRH, no additional cases could be retrieved. For the statistical analysis, IBM SPSS software version 20 was used. Normal distribution of data was examined using the Kolmogorov-Smirnov test. For parametric nonrelated data, expressed as mean ± standard error of the mean (SEM), the unpaired 2-tailed t test was used. Nonparametric nonrelated data, expressed as median (Q1, Q3), were analyzed using the Mann-Whitney U test. P values < 0.05 were considered statistically significant.

RESULTS
The literature review provided 1698 citations. After screening and checking for duplicates, 17 reports evaluating 22 patients with SSc-NRH remained. In the Zurich cohort, 4 out of 278 patients with established SSc were diagnosed with biopsy-proven NRH (Figure 1), resulting in a prevalence of symptomatic NRH of 1.4%. An additional questionnaire-based EUSTAR inquiry did not retrieve additional results based on eligibility. The majority of those 26 patients were women (75%) with an average age of 46 ± 11.9 at diagnosis of SSc. Mean disease duration of SSc was 6.5 ± 5.6 years when NRH was diagnosed. NRH occurred both in diffuse (n = 12, 54.5%) and limited cutaneous SSc (n = 8, 36.4%), as well as in 2 patients without skin involvement (9.1%). In 4 published cases, the extent of skin involvement was not reported. Of note, in most patients, vascular features of SSc were present at the time of NRH diagnosis, including digital ulcers (ever 100%, active 71.4%), an active pattern on nailfold capillaroscopy (100%), and pulmonary hypertension (63%). The most prevalent autoantibodies were anticentromere (50%) and anti-U1nRNP (33%). In most patients, an elevation of alkaline phosphatase (AP, 85%) and gamma-glutamyl transferase (GGT, 60%) was observed, whereas transaminases were not increased. Melena and hematemesis occurred in 71% and 56% of patients, respectively. Ultrasound detected ascites (75%) and splenomegaly (82%), but no pathologic liver morphology. However, an increased stiffness [kPa 14(5,21), reference ≤ 7.5 kPa] was diagnosed by ultrasound elastography (FibroScan by EchoSens; 75%).

Figure 1. Nodular regenerative hyperplasia on liver biopsy (A) shows subtle nodularity from liver parenchyma stained with H&E; panels B and C demonstrate discrete hypotrophic hepatocyte plates (asterisk) juxtaposed to slightly hypertrophic hepatocyte plates (arrow) using H&E and reticulin staining; in (D), Sirius Red staining demonstrates the absence of significant fibrosis; (E) highlights the relative rarefaction of capillaries visualized by immunohistochemical staining of endothelial cells (von Willebrand factor–positive, brown DAB staining).
Portal hypertension, defined as hepatic venous pressure gradient ≥ 5 mmHg measured by catheter during transjugular liver biopsy under fluoroscopic guidance, was diagnosed in 90% of patients and had esophageal varices (77%) and variceal hemorrhage (58%) as main complications, which were the reasons for which most patients underwent liver biopsy. The presence of hepatitis B, C, or human immunodeficiency virus, and primary biliary cholangitis were excluded by serologic tests and liver biopsies. The main characteristics of all 26 patients (as far as available) are provided in Table 1.

**DISCUSSION**

The data derived from our own SSc cohort as well as from the literature support the hypothesis of NRH as a rare vascular complication of SSc, especially in ant centromere–positive patients. Consistently, all patients had a history of digital ulcers, with 70% even having active ulcers at the time of NRH diagnosis. Pulmonary arterial hypertension (PAH), renal crisis, and active nailfold capillaroscopy, all vascular complications of SSc, were also present in most patients from our local cohort. Immunosuppression and treatment with cytotoxic agents, particularly within the context of autoimmune diseases, and organ or stem cell transplantation, is discussed as another contributing factor for the development of NRH. Although 28% of patients (5/18, no data available for 7) were treated with immunosuppressive agents (including corticosteroids ≤ 10 mg/d, mycophenolate mofetil, rituximab, cyclosporine, methotrexate, cyclophosphamide, and human immunoglobulins), none were under treatment with azathioprine, which has been predominantly suggested for patients who either have autoimmune diseases or have undergone organ transplantation, and particularly in cases with decreased thiopurine methyltransferase activity. As our limited data suggest, the prevalence in SSc might be higher because in most patients with NRH, only late-stage complications owing to portal hypertension lead to the diagnosis. This is especially true because liver enzymes (apart from measures of cholestasis) and ultrasound findings are not pathologic in most patients. Ultrasound elastography or hepatic magnetic resonance imaging findings might raise suspicion, however. Even then, liver biopsies are often not performed before the onset of bleeding complications and/or the development of ascites. Therefore, we suggest that an extended diagnostic investigation be performed in patients with SSc who have persisting elevation of GGT and AP in the presence of other risk factors such as female sex, established SSc, microvasculopathy (peripheral, PAH), and positivity for ant centromere or anti-U1RNP antibodies. This assessment should include the performance of a liver ultrasound to screen for signs of portal hypertension, ultrasound elastography to evaluate the presence of fibrosis/cirrhosis, and in cases of upper gastrointestinal bleeding, a gastroscopy. Depending on the obtained results, a liver biopsy under fluoroscopic guidance, was diagnosed in 90% of patients and had esophageal varices (77%) and variceal hemorrhage (58%) as main complications, which were the reasons for which most patients underwent liver biopsy. The presence of hepatitis B, C, or human immunodeficiency virus, and primary biliary cholangitis were excluded by serologic tests and liver biopsies. The main characteristics of all 26 patients (as far as available) are provided in Table 1.

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biopsy should be performed to establish the final diagnosis by simultaneously excluding the presence of primary biliary cholangitis (PBC), which occasionally occurs in patients with (anticentromere–positive) SSc, although most often it is additionally characterized by the presence of antimitochondrial and anti-M2 antibodies.

NRH might represent a rare yet clinically important, potentially life-threatening complication in patients with SSc, especially in those with prominent vascular features and positivity for anticientromere antibodies. Mildly to moderately elevated levels of AP and GGT (i.e., 2–3× upper limit of normal), ascites, as well as splenomegaly by ultrasound (> 11 x 4 x 7 cm) and increased stiffness by ultrasound elastography (> 7.5 kPa) might indicate the presence of NRH as another important differential diagnosis to PBC, as illustrated by our case series. Therefore, if suspected, the diagnosis should be confirmed by liver biopsy.

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REFERENCES


