Nodular regenerative hyperplasia: Evolving concepts on underdiagnosed cause of portal hypertension

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Abstract

Nodular regenerative hyperplasia (NRH) is a rare liver condition characterized by a widespread benign transformation of the hepatic parenchyma into small regenerative nodules. NRH may lead to the development of non-cirrhotic portal hypertension. There are no published systematic population studies on NRH and our current knowledge is limited to case reports and case series. NRH may develop via autoimmune, hematological, infectious, neoplastic, or drug-related causes. The disease is usually asymptomatic, slowly or non-progressive unless complications of portal hypertension develop. Accurate diagnosis is made by histopathology, which demonstrates diffuse micronodular transformation without fibrous septa. Lack of perinuclear collagen tissue distinguishes NRH from typical regenerative nodules in the cirrhotic liver. While the initial treatment is to address the underlying disease, ultimately the therapy is directed to the management of portal hypertension. The prognosis of NRH depends on both the severity of the underlying illness and the prevention of secondary complications of portal hypertension. In this review we detail the epidemiology, pathogenesis, diagnosis, management, and prognosis of NRH.

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INTRODUCTION

Nodular regenerative hyperplasia (NRH) belongs to the category of liver diseases responsible for non-cirrhotic intrahepatic portal hypertension (NCIPH)\[8], which include sinusoidal obstruction syndrome, perisinusoidal fibrosis, hepatorenal sclerosis and incomplete septal cirrhosis (Figure 1). In these conditions, the etiology is ascribed to an intrahepatic hypercoagulable state, possibly secondary to sinusoidal endothelial injury. In many Asian countries, the most frequent cause of NCIPH is schistosomiasis.

NRH was first defined by Steiner[5] in 1959 as a condition characterized by diffuse benign transformation of the hepatic parenchyma into small regenerative nodules distributed evenly throughout the liver with minimal or no fibrosis in the perisinusoidal or portal areas. This feature distinguishes NRH from other causes of NCIPH[8]. The presence of fibrous septa between the nodules definitively excludes NRH. However, in rare cases, one patient may exhibit histopathologic features of both NRH and other NCIPH disorders. These observations suggest that similar etiological factors may induce various adaptive liver reactions.
Over the last two decades, multiple labels have been applied to describe what we now define as NRH. Terms such as “miliary hepatocellular adenomatosis”, “non-cirrhotic nodulation”, “hepatocellular adenomatosis”, or “adenomatous hyperplasia” have been previously used. Although our current knowledge is limited to single case reports and case series, the number of patients being given the diagnosis of NRH has dramatically increased in recent years. Up to the year 2000 approximately 200 patients had been reported, whereas in the last decade more than 260 new cases of NRH were reported worldwide.

EPIDEMIOLOGY
As stated previously, our understanding of the epidemiology of NRH is based upon case reports rather than systematic population studies. In the United States National Library of Medicine/National Library of Medicine (PubMed) database (http://www.ncbi.nlm.nih.gov) 375 case reports have been published since 1975, however, not all cases meet the strict histopathologic criteria for NRH. For example, earlier publications used the term “nodular regenerative hyperplasia” as a misnomer for large regenerative nodules (LRN), associated with post-sinusoidal obstructive conditions such as congestive cardiomyopathy or Budd-Chiari syndrome.

NRH comprises 27% of all cases of non-cirrhotic portal hypertension in Europe and about 14% in Japan.[6-8] Autopsy studies indicate an overall incidence ranging between 0.72% and 2.6%.[6-8] Timely clinical diagnosis of NRH is challenging, because the majority of patients do not present with symptoms of portal hypertension. In cases where the etiology of portal hypertension was unclear the histology disclosed NRH in less than 1%.[6-8] While NRH is rare in comparison to other causes of portal hypertension, its presence is being increasingly recognized.

In the case reports we reviewed, the majority of patients were between 25 and 60 years old at diagnosis, with rare cases in children and even fetuses[1]. According to autopsy studies, the risk of development of NRH and its potential complications increases with age. In 2500 autopsies the incidence of NRH after 80 years of age was 6%, seven times greater than in people under 60 years of age.[6] One case series reported the prevalence of NRH in six siblings distributed in three unrelated families indicating the possibility of a family distribution of this disease.[31] Sex and ethnicity seem to play no role in development of NRH.

ETIOLOGY
Portal vasculopathy
NRH appears to be a result of an adaptive hyperplastic reaction of hepatocytes. Normally, the mitotic activity of hepatocytes is very low; hyperplasia is considered to be a physiological response to injury. Increased oxygen and nutrient demand, chronic inflammation, hormone-mediated dysfunction or compensation for damage or disease elsewhere play an important role in this process.

The pathogenesis of NRH seems to be related to abnormalities of portal hepatic blood flow akin to the “atrophy-hypertrophy complex”. Hemodynamic disturbances at the level of the hepatic microvasculature occur either secondary to a mechanical obstruction or functional blood flow alterations. One hypothesis is that local portal venous hypoperfusion leads to apoptosis and hepatocyte atrophy, coexisting with maintained or increased blood supply to adjacent acini cells. Local hypoperfusion leads, in turn, to elevated levels of cell growth activators which act as autocrine or paracrine peptides. This hypothesis has been supported by both histopathologic examinations of liver biopsies as well as animal experiments, which showed microvascular changes involving either portal vein radicles or less frequently, arterial or hepatic vein branches. Wanless coined a “portal obliterator venopathy” phenomenon of recurrent embolization of the portal venules by platelet aggregates or thrombi originating in the portal venous system or in the spleen. The ensuing vascular inflammation and fibrosis results in reduced luminal patency of portal vein radicles and local reduction in blood supply to the liver, confirmed in 64 autopsies.[6] Nakanuma et al[6] also provided evidence of obliterated portal venules in 107 liver biopsies of patients with NRH. There are few case reports of NRH without vasculopathy[12-14], e.g. diffuse carcinoid tumor, where multifocal liver ischemia is due to a functional and not an organic cause.[10]

NRH is commonly found in patients with Abernathy’s Syndrome a condition that includes the rare anomaly of congenital absence of the portal vein. The intestinal and splenic veins drain directly into the inferior vena cava, bypassing the liver entirely. It is an extreme model of vascular pathology, where the entire liver relies upon high-pressure arterial perfusion. Rare cases of NRH were also reported in patients with thrombosis of portal vein trunk.[14,15]

Immunosuppressant and chemotherapeutic drugs
Immunosuppressive medications may induce NRH by damaging endothelial cells of small hepatic veins. There are several reports of NRH developing in response to prolonged treatment with thiopurines, including azathioprine (AZA), 6-mercaptopurine and 6-thioguanine (6-TG). NRH was found in a single case among 30 patients treated with thiopurines for Crohn’s disease. Accumulation of toxic metabolites may be a factor, as NRH was found more frequently in post-transplant patients with impaired metabolism of AZA due to the thiopurine-methyltransferase mutation.[10] In another study NRH was found on liver biopsy in three patients treated with AZA for inflammatory bowel disease for more than 1 year, who presented with elevated liver enzymes.[8] Gane et al[16] demonstrated histological regression of NRH with normalization of liver enzymes in four patients after withdrawal of AZA, after being used for an average of 64 mo. While the etiology of this remains to be elucidated, it has been stated that 6-TG, used in treatment...
of AZA-resistant forms of inflammatory bowel disease, may have a higher potential to induce NRH than other thiopurines\[19\].

Other authors reported NRH in 8% of a human immunodeficiency virus (HIV)-positive cohort receiving highly active antiretroviral therapy (HAART)\[20\]. Didanosine, a HAART drug responsible for liver injury and pulmonary hypertension, appears to induce NRH\[21\].

An analysis of 334 liver biopsies from patients with metastatic colorectal cancer demonstrated that vascular pathology (as compared to chemotherapy-associated steatohepatitis) is a predominant histopathologic finding in chemotherapy-induced liver injury\[22\]. There are numerous reports on NRH developing in patients with disseminated cancer after use of cytostatic drugs. Older reports associate NRH with use of busulphan, thioguanine or cyclophosphamide and, in more recent reports, with oxaliplatin-based therapies. Among 274 patients treated with oxaliplatin, sinusoidal obstruction syndrome and NRH were found in the histopathological study in 54% and 24.5% of patients, respectively. Peliosis and perisinusoidal fibrosis were other vasculopathy-related liver diseases\[23\]. Overall, about 70 cases of oxaliplatin-related NRH were reported in the literature (Table 1).

**Underlying disease**

NRH may develop as a result of underlying disease of autoimmune, inflammatory, neoplastic, or idiopathic origin (Table 1)\[24\]. In patients with systemic lupus erythematosus (SLE), rheumatoid arthritis, and a host of other autoimmune diseases (including sarcoidosis or other granulomatous liver diseases)\[25\], antibody reaction to the endothelial cells of small hepatic vessels combined with local hypercoagulation\[26\] may predispose to NRH. Ziol et al\[27\] found intrasinusoidal infiltrate composed of cytotoxic CD8+ T-lymphocytes in 32% of 44 patients with NRH. These T-cells were located near atrophic liver cell plates and were adjacent to endothelial cells exhibiting evidence of apoptosis. Moreover, in patients with SLE, anticardiolipin antibodies could be incriminated for portal vasculopathy leading to NRH\[28\], although this is not a universal finding in SLE\[29\].

NRH has also been associated with hematologic disorders, especially myeloproliferative diseases and congenital thrombophilias, where the hypercoaguable state may induce a progressive splenic and portal vein thrombosis and subsequent portal hypertension\[30\].

| Disease | No. of cases | Ref. |
|---------|-------------|-----|
| Pulmonary hypertension | 32 | [27,28,76-78] |
| Rheumatoid arthritis/Felty’s syndrome | 30 | [5,36-40] |
| Human immunodeficiency virus infection | 20 | [5,36-40] |
| Lupus erythematosus | 12 | [77,46-57] |
| Crohn’s disease/ulcerative colitis | 13 | [88,90] |
| Celiac disease | 9 | [114,115] |
| Scleroderma/CREST | 7 | [88,90] |
| Antiphospholipid syndrome | 11 | [90] |
| Sarcoidosis | 9 | [88,90] |
| Post-transplant | 18 | [82,125,126] |
| Extravascular cancers | 26 | [28,120,121] |
| Dysfibrotic enteropathy | 12 | [125,126] |
| Macroglobulinemia | 5 | [101,105] |
| Mixed cryoglobulinemia | 3 | [121,122] |
| ITP/Aplastic anemia | 4 | [25,120,121] |
| Primary biliary cirrhosis | 6 | [125,120,121] |
| Krabbe disease | 4 | [125,120] |
| Congenital absence of portal vein | 4 | [125,120] |
| Portal vein thrombosis | 2 | [125,120] |
| Familial pulmonary fibrosis | 4 | [125,120] |
| Chronic glomerulonephritis | 5 | [125,120,121] |
| Cystinosis | 2 | [28] |
| Myasthenia | 2 | [101,105] |
| Polyarteritis nodosa | 2 | [101,105] |
| Common variable immunodeficiency syndrome | 2 | [101,105] |
| Turner’s syndrome | 2 | [101,105] |
| Castleman’s disease | 2 | [79,144] |
| Idiopathic eosinophilic syndrome | 2 | [101,105] |

Table 1 Diseases and conditions coexisting with nodular regenerative hyperplasia

\[1\] only associations reported in the literature twice or more have been shown. ITP: Idiopathic thrombocytopenia. CREST: Calcinosis, raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia.
DIAGNOSIS

One should consider a diagnosis of NRH in all patients with clinical symptoms of portal hypertension (splenomegaly, esophageal varices, ascites) but with normal transaminases and no manifestations of cirrhosis (gynecomasia, palmar erythema, spider nevi). There are mildly increased liver enzymes, usually alkaline phosphatase, in 11%-25% of patients. It is estimated that NRH is complicated by clinically overt portal hypertension in at least 50% of cases, with an augmented hepatic venous pressure gradient confirming sinusoidal obstruction. Close surveillance of patients with predisposing conditions is important for early diagnosis, especially in situations where drug toxicity may play a role. In patients on AZA for autoimmune hepatitis, the occurrence of splenomegaly should alert the clinician to the development of portal hypertension secondary to NRH.

In all cases of NCIPH, more common treatable causes (viruses, alcohol, metabolic and autoimmune disorders) should be eliminated first, followed by an assessment of the usual exposures (acetaminophen, vitamin A, copper sulfate, vinyl chloride, arsenic salt). Portal and hepatic venous thrombosis may be excluded on radiographic imaging.

Imaging

Imaging methods have poor sensitivity and specificity for NRH. A diffusely heterogeneous hepatic parenchyma may be the only imaging abnormality. On ultrasound, regenerative nodules are usually not visible due to a small size or isoechogenicity. The presence of well-delineated hypoechoic or isoechoic tiny lesions with a sonoluscent rim are indistinguishable from metastases. Hyperechoic nodules have been reported in very rare cases of NRH. On computed tomography (CT), regenerative nodules remain isodense or hypodense in both arterial and portal venous phases, distinguishing NRH from focal nodular hyperplasia and adenomas.

The significance of magnetic resonance imaging in the diagnosis of NRH is still controversial, although because of its inherent propensity to resolve soft tissue details it may be superior to CT in visualization of regenerative nodules. NRH lesions appear hypointense on T1-weighted images and iso- or hypointense on T2-weighted images, with a sensitivity and specificity of 70%-80% when using gadolinium contrast, others found more disappointing results.

Histopathology

Grossly, NRH presents as diffuse fine nodularity of the liver with 1-3 mm diameter nodules. Granularity of the hepatic surface may resemble micronodular cirrhosis. Rarely, nodules are larger, and may coalesce into a large tumor, NRH nodules appear paler than the surrounding normal hepatic tissue. Mild hepatomegaly may be present.

The diagnosis of NRH is secured by histopathology demonstrating regenerative nodules without parietal thickening of portal venules, and no or minimal perisinusoidal and portal fibrosis on reticulin staining. Hepatocytes commonly show feathery degeneration of cytoplasm suggesting impairments of bile production or transport. Two morphologically distinct populations of hepatocytes coexist within the nodules: hypertrophied hepatocytes centrally surrounded by atrophic hepatocytes peripherally. Hypertrophic cells may compress terminal hepatic venules, which frequently appear shrunken and may be undetectable. Heterogeneity may be explained by uneven perfusion. Dilated sinusoids and thrombosed portal vein radicles are occasionally present.

If a dominant large regenerative nodule is sampled, adenoma-like features with discrete cytoplasmatic and/or nuclear atypia can be seen. Therefore, sampling a single nodule may yield an incorrect diagnosis and multiple liver sampling becomes necessary. Dysplastic large hepatocytes were seen in 42% of NRH samples, without high-degree dysplasia. NRH should also be distinguished from LRN occurring in livers with disturbed hepatic venous outflow (e.g. Budd-Chiari syndrome, veno occlusive disease, or congestive pericarditis) but well developed compensatory arterIALIZATION and preserved hepatic venous collaterals.

It should be kept in mind that in small biopsy samples histologic features of NRH may be lacking or incomplete. The diagnosis can be made after careful examination by the experienced hematopathologist with a high index of suspicion. In justified cases a laparoscopy with open wedge biopsy should be done.

Overlap syndromes, involving both NRH and portal or pericentral fibrosis due to hepatitis C viral infection, alcoholic, or non-alcoholic liver disease, can occur and in such cases the diagnosis of NRH may be easily overlooked. Fibroscan or fibrotest panels may rule out cirrhosis, but have limited clinical value.

TREATMENT

Treatment of NRH therapy is directed towards elimination of the causative factor, once established. Concomitant diseases should be treated appropriately and with attention to minimizing drug toxicity. Long-term anticoagulation treatment is usually indicated in the thrombophilias. Anticoagulation therapy was found to be beneficial in early stages of NRH induced by HAART in HIV-infected patients.

In patients with NRH, the mainstay of management is directed primarily to prevention and treatment of complications related to portal hypertension, i.e. variceal bleeding, the main source of mortality. Treatment of portal hypertension is standard: low sodium diet, diuretics, and endoscopic banding of esophageal varices. Spleenectomy is not indicated. A portosystemic surgical shunt may offer a significant therapeutic benefit, especially in the case of severe recurrent esophageal variceal hemorrhage. Liver transplantation is rarely necessary and is reserved for patients with hepatic failure.
NATURAL HISTORY AND PROGNOSIS

Generally, the prognosis of NRH is better than that of chronic liver disease and is related to the complications of portal hypertension and the severity of the associated diseases, if present. In most cases the disease is slowly progressive, although the rate of nodular growth may be accelerated for unknown reasons. The long-term prognosis is uncertain and considers the level of underlying myeloproliferative, thrombophilic, or autoimmune processes. There are several case reports demonstrating the presence of both NRH and hepatocellular carcinoma without underlying cirrhosis, although a neoplastic process has yet to be proven.

CONCLUSION

NRH is a rare condition of NCIPH liver diseases. Our understanding of the epidemiology of NRH is based upon case reports rather than systematic population studies. Timely diagnosis is challenging, because the majority of patients do not present with overt signs of portal hypertension. The pathogenesis of NRH is not well established, but an adaptive hyperplastic reaction of hepatocytes appears to be related to abnormalities of hepatic venous perfusion. Immunosuppressive medications may induce NRH by damaging endothelial cells of small hepatic veins. NRH may also develop as a result of underlying autoimmune, inflammatory, neoplastic, or idiopathic disease.

The knowledge on tumorigenesis in NRH is virtually non-existent as compared with hepatocellular carcinoma, adenoma and even cirrhotic regeneration. Genetic studies indicate that RASSF1A, a gene acting in the proapoptotic pathway, is increasingly methylated in hepatocellular hyperplastic hepatocytes. Moreover, in ceramide synthesis 2 null mice that are unable to synthesize very long acyl chain ceramides, an extensive hepatocellular anisocytosis with widespread formation of regenerative nodules composed of hyperplastic hepatocytes was found. This finding emphasizes the role of ceramide synthase 2 activity and altered hepatic sphingolipid profile for liver proliferative homeostasis.

Common causes of extrahepatic and intrahepatic portal hypertension should be excluded before making a diagnosis of NRH. Imaging may be helpful during the initial clinical encounter with liver biopsy as the gold standard for diagnosis. An accurate diagnosis can only be made on histopathology, which shows diffuse micronodular transformation without fibrous septa. Management is directed primarily for prevention and treatment of complications related to portal hypertension. Outcome and prognosis is related to the severity of both portal hypertensive complications and the underlying associated diseases. Further studies may be helpful to elucidate a molecular mechanism for the vasculopathy that appears to play a central role in the adaptive hyperplastic reaction universally seen in NRH.

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