Nodular Regenerative Hyperplasia: Not All Nodules Are Created Equal

Preeti A. Reshamwala,[1,3] David E. Kleiner,[2] and Theo Heller[1]

Definition

Nodular regenerative hyperplasia (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. A classification system proposed by Wanless in 1990[1] provided histological criteria for the diagnosis of NRH. These included the presence of hepatocellular nodules less than 3 mm in diameter that were not surrounded by fibrosis (nodules graded 0-3+ based on the extent of nodularity noted through all fields of the biopsy), and the presence of fibrous septa (graded 0-3). Biopsy specimens that met the criteria of 3+ nodularity and 0-1 fibrous septa were classified as nodular regenerative hyperplasia. NRH has been reported to occur in association with other systemic diseases, including rheumatologic disorders, vascular disorders, and myeloproliferative disorders, as well as certain drugs.[1-10] Nodular regenerative hyperplasia may have a prolonged asymptomatic course unless it is complicated by portal hypertension and its sequelae, including variceal bleeding, ascites, and splenomegaly. In this article, the epidemiology, histology, differential diagnosis, and theories of etiology of NRH are reviewed. The diagnosis and treatment of nodular regenerative hyperplasia are also presented.

Epidemiology

Nodular regenerative hyperplasia of the liver was first described as "miliary hepatocellular adenomatatosis" by Ranstrom in 1953[11] in a patient with rheumatoid arthritis, neutropenia, and splenomegaly (Felty's syndrome). This lesion was subsequently termed *nodular regenerative hyperplasia* by Steiner,[12] who described regenerative liver nodules in a patient with congestive heart failure and tuberculosis. Several cases have since been reported in the literature, and most have been associated with long-standing systemic diseases before clinical evidence of liver disease was detected. These associations are detailed in Table 1.

A large study of 2,500 consecutive autopsies by Wanless in 1990[1] revealed that NRH was present in 64 patients (2.6%). Of these 64 cases, the majority were associated with systemic disorders. Wanless also noted that NRH was diagnosed in 5.3% of patients who were over 80 years of age at death. This prevalence was more than 7-fold higher when compared with patients who were under 60 years of age at death, likely reflecting the higher prevalence of systemic disease in an elderly population. Nevertheless, more than 20 cases of NRH have also been described in children,[13,14] and two cases have been reported in fetal liver.[15] NRH affects both males and females equally. There have been three familial cases of nodular regenerative hyperplasia reported in the literature.[16]

Pathology

On gross examination of the liver, the normally homogenous hepatic parenchyma shows a diffuse transformation into nodules of 1-3 mm in size. Unlike cirrhosis, there is no fibrosis separating nodules—each nodule presses directly against its neighbor. Although nodules greater than 15 mm have been described, these are frequently revealed to be composed of smaller nodules when examined microscopically.[1,17] The hepatocytes within the nodule are arranged in plates that are more than 1 cell thick. These cells may be enlarged and have hypertrophic nuclei. Between individual nodules, the hepatocytes are small and atrophic and are pressed together into thin, parallel plates. This compression is best visualized using a reticulin stain and may be associated with sinusoidal dilation and slitlike central veins. Immunohistochemical staining for alpha-1-antitrypsin has also been shown to be increased in the periportal areas of liver biopsies from

Abbreviation: NRH, nodular regenerative hyperplasia.

From the [1]Liver Diseases Branch, National Institutes of Diabetes and Digestive and Kidney Diseases, and the [2]Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD; and the [3]Division of Gastroenterology and Hepatology, University of Maryland Medical Center, Baltimore, MD.

Received January 27, 2006; accepted May 9, 2006.

Supported by the Intramural Research Programs of the National Institutes of Diabetes and Digestive and Kidney Diseases and the National Cancer Institute, National Institutes of Health.

Address reprint requests to: Theo Heller, M.D., Liver Diseases Branch, National Institutes of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Building 10, Room 9B-16, 10 Center Drive MSC 1800, Bethesda, MD 20892-1800. E-mail: theoh@intra.niddk.nih.gov; fax: 301-402-0491.

Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.21258

Potential conflict of interest: Nothing to report.

Table 1. Diseases, Drugs, and Other Conditions Associated With Nodular Regenerative Hyperplasia

Rheumatological	Hematological	Drugs	Congenital	Other
Rheumatoid arthritis[1,6,11]	Idiopathic thrombocytopenic purpura[17]	Azathioprine[8,9,10,41]	Portal vein agenesis[13]	Toxic oil syndrome[19]
Felty's syndrome[1,7,11]	Polycythemia vera[17]	6-Thioguanine[9,10]	Cardiac abnormalities[14]	Metastatic disease[1]
Systemic lupus erythematosus[1]	Essential thrombocytosis[17]	Busulfan[7]		Primary biliary cirrhosis[20,21]
Polyarteritis nodosa[1,5]	Sickle cell anemia	Doxorubicin[7]		Celiac disease[3]
Progressive systemic sclerosis[1]	Macroglobulinemia[1,4]	Cyclophosphamide[7]		Congestive heart failure[1,12]
Antiphospholipid syndrome[22,23]	Myeloid metaplasia[1,2]	Chlorambucil[7]		Tuberculosis[12]
	Chronic myelogenous leukemia[2,7]	Cytosine arabinoside[7]		
	Chronic lymphocytic leukemia[1,4]	Bleomycin[7]		
	Hodgkin's lymphoma[1]	Carmustine[7]		
	Non-Hodgkin's lymphoma[1]			

NRH patients when compared to controls.[18] This finding may be helpful in the histological evaluation of difficult cases.

Whereas the larger portal veins may be widely patent, portal venous structures in smaller radicals may be absent or occluded. Fibrosis typical of chronic liver disease is usually not present, although there may be some degree of periportal fibrosis or perisinusoidal fibrosis. The latter is frequently associated with the atrophic areas. Very thin fibrous septation may be seen between the hepatic lobules. Central veins may show veno-occlusive changes or may be compressed into narrowed slits. Sinusoidal dilation may be seen in areas of hepatocellular atrophy. There is usually little or no inflammation or cholestasis, and normal bile ducts and arteries can be easily identified. These features are illustrated in Fig. 1.

In needle biopsies of the liver, the changes of regeneration and atrophy may be very subtle on routine hematoxylin-eosin stains. Therefore, any "normal" liver biopsy specimens, particularly those from patients with portal hypertension, should be investigated further using reticulin stains. Special attention should be paid to the portal architecture and to the central veins, because NRH is usually related to underlying vascular abnormalities. At a minimum, to make the diagnosis of NRH, one should see the characteristic nodular zones of widened liver cell plates bounded by narrowed and compressed plates.

Etiology

It has been suggested that the nodular transformation in NRH of the liver is a consequence of alterations in blood flow. Morphologically, abnormalities of portal and/or central veins are frequently observed, and many drugs that are associated with NRH also cause other types of vascular injury. Several autopsy studies and case series have shown that the atrophic regions between nodules are

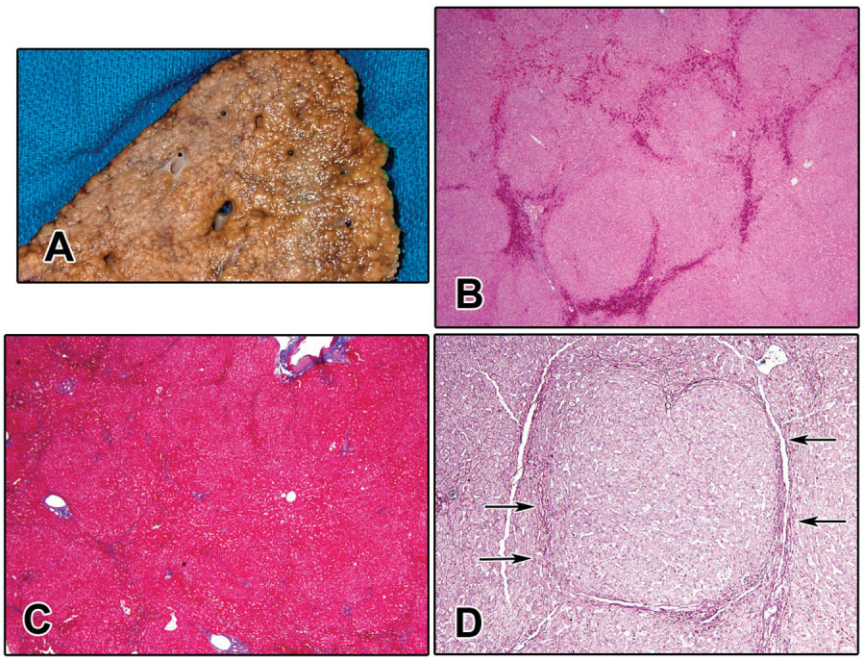

Fig. 1. (A) Gross photograph of a resected specimen showing NRH. The liver parenchyma is diffusely transformed into nodules approximately 1 mm in size. There is a superficial resemblance to cirrhosis; however, the nodules are not separated by fibrosis. (B) Low magnification examination shows vague nodularity on routine staining, here enhanced by congestion in areas of atrophy between the nodules (hematoxylin-eosin; original magnification ×4). (C) Staining for collagen with a Masson trichrome shows that there is no significant fibrosis present. (Masson trichrome; original magnification ×4). (D) The diagnosis is most easily made using a reticulin stain, which demonstrates nodules with expanded liver cell plates surrounded by zones of reticulin compression (arrows), where the liver cells are small, atrophic, and pressed together (reticulin; original magnification ×10).

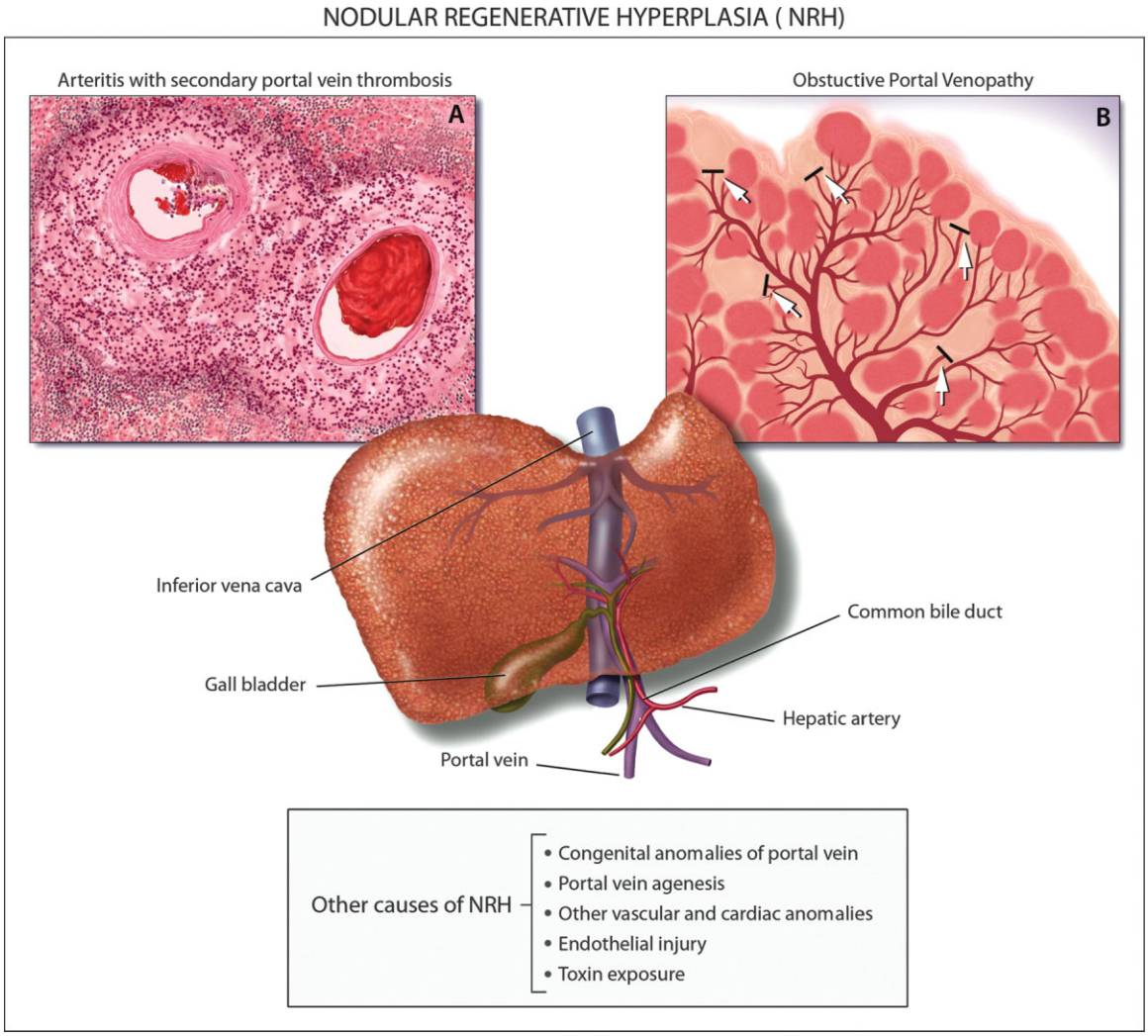

Fig. 2. Proposed causes of NRH. (A) Acute on chronic arteritis with adjacent secondary portal vein thrombosis. Note the extensive inflammatory exudate and thick-walled artery indicating the chronicity of the arteritis. (B) Liver tissue infused with radiopaque latex. Note the nodules of regeneration. Arrows mark sharp cutoffs in portal vein branches, resulting in atrophic internodular areas. Modified and reprinted from *The American Journal of Medicine, Vol. 70,* Wanless et al., Nodular regenerative hyperplasia, pages 1203-1209, © 1981, with permission from Excerpta Medica, Inc.

associated with obliterative changes in the portal veins, leading to decreased blood flow in the supplied acini.[1,17] The nodular areas are believed to be a hypertrophic response to normal or slightly increased blood flow. This was demonstrated by Wanless et al.[4] in their report of a 37-year-old man with connective tissue disorder, hyperviscosity syndrome, arthritis, and pulmonary hypertension. The patient was diagnosed with NRH after presenting with hematemesis due to esophageal varices that developed in the setting of portal hypertension that was not associated with cirrhosis. His underlying diseases were treated, but he died 4 years later of recurrent massive bleeding from varices. At autopsy, the investigators infused radiopaque latex via the portal vein in a slice of liver tissue. The resulting image revealed that nodules were well perfused and atrophic areas were not, with sharp cut-offs of portal venous branches, suggesting that nodular regenerative hyperplasia resulted from obliterative portal venopathy. These changes are illustrated in Fig. 2.

A morphometric study performed by Wanless et al. in 1980[17] compared the portal vein to portal space area in patients with NRH with a control group. A portal vein to portal space ratio of less than 0.08 was used to define an abnormal portal space. The investigators found that the portal vein to portal space ratio was significantly lower in NRH patients, suggesting damage or destruction of portal veins when compared with controls.

Drugs have also been associated with the development of NRH. Azathiaprine, a purine analog, is the most commonly associated drug, as noted in case reports of patients receiving this drug for immunosuppression after liver transplantation.[8] Patients receiving this medication for

inflammatory bowel disease have also been reported to develop NRH.[9,10] Thioguanine has been implicated in vascular damage with early fibrosis and collagen deposition in the space of Disse. In a study by Breen et al.[8] in 65 liver transplant recipients, two patients with thiopurine methyltransferase 3A mutations developed NRH, suggesting that polymorphisms in genes encoding thiopurine methyltransferase may be linked to development of nodular regenerative hyperplasia, probably through altered drug metabolism.

Five cases of NRH associated with toxic oil syndrome have been reported.[19] In 1981, in northern Spain, the ingestion of contaminated olive oil caused a syndrome characterized by severe myalgias, pulmonary infiltrates, and eosinophilia. Over 20,000 people were affected, and over 300 deaths have been reported. A large number of these patients have developed chronic diseases, including neuropathies, musculoskeletal pain, diabetes mellitus, hypothyroidism, and obesity. Five patients are known to have developed NRH. This complication was noted a mean of 2.5 years after consuming the adulterated oil. These patients had a combination of hepatomegaly, jaundice, elevated aminotransferases, and symptoms of portal hypertension. The authors suggested that NRH was initiated by a diffuse, nonnecrotizing endothelial injury with a possible autoimmune component that resulted in microcirculatory disturbances.[19]

NRH has also been reported to occur in cases of congenital anomalies of the portal vein.[13] Only 17 cases of congenital absence of the portal vein have been reported in the literature. Of these, four cases have reported the development of NRH of the liver. Microscopic examination of liver biopsy specimens shows an absence of portal veins and an arterial vascularization of the lobule with resulting nodularity. This is consistent with the theory that obliteration of portal veins leads to NRH. Other vascular abnormalities such as atrial septal defects, ventricular septal defects, abnormal junction of pulmonary veins, and other congenital anomalies are reported in children diagnosed with NRH, strengthening the argument that NRH may result from microcirculatory derangements.[13]

The association of NRH with systemic diseases has been previously discussed. Many of these diseases involve a vasculitic process including polyarteritis nodosa and rheumatoid arthritis. Morphometric studies of these cases suggest that acute and chronic inflammation of intrahepatic arteries leads to secondary portal venous obliteration and thrombosis of the adjacent portal veins, which may result in NRH.[5,6,17] This is also illustrated in Fig. 2.

A few studies have also described an association between the early (stage I or II) histological stages of primary biliary cirrhosis and nodular regenerative hyperplasia.[20,21] The largest of these studies evaluated the liver biopsies of 64 patients with early primary biliary cirrhosis and found that 43% of these biopsies had some degree of nodular transformation without fibrosis. Approximately 54% of the liver biopsies with NRH had evidence for a vascular lesion (decreased portal vein luminal diameter due to intimal fibrosis or thrombotic occlusion[20]). The authors also reported an increased incidence of portal hypertension with splenomegaly and one patient with esophageal varices in this subset of patients with NRH and early primary biliary cirrhosis. In this situation, it was possible that the nodular transformation was contributing to portal hypertension.

Multiple reports have described an association between NRH and the antiphospholipid syndrome.[22,23] The antiphospholipid syndrome is a rhematological condition associated with venous and arterial thrombosis, thrombocytopenia, and recurrent pregnancy loss in women with the presence of antiphospholipid antibodies in the serum. More than 10 cases of patients with histologically confirmed NRH and evidence for primary or secondary antiphospholipid syndrome have been described in the literature. The majority of these patients presented with elevated liver enzymes or signs or symptoms of portal hypertension such as variceal bleeding and/or hepatosplenomegaly. Retrospective analysis for the presence of antiphospholipid antibodies in the serum—specifically anti-cardiolipin antibody—showed a significantly higher number of patients with these antibodies in histologically confirmed cases of nodular regenerative hyperplasia when compared with matched controls of patients with autoimmune forms of liver disease and normal patients.[23] The likely pathogenesis of NRH in association with antiphospholipid syndrome is believed to be through small vessel occlusion resulting from the coagulopathy associated with the antiphospholipid syndrome, leading to uneven hepatic perfusion and subsequent nodularity and portal hypertension.[22]

Recently, the inactivation of Notch1 was shown to be associated with the development of nodular regenerative hyperplasia in mice.[24] Although constitutive deletion of Notch1 is lethal, mice with inducible inactivation of Notch1 developed increased hepatocellular proliferation. A careful microscopic search for portal vein lesions failed to identify a vascular cause for the hyperplasia, which suggests that in special circumstances NRH may develop without associated vascular abnormalities.

Clinical Features

Nodular regenerative hyperplasia may remain clinically asymptomatic for many years. Laboratory parame-

ters including serum aminotransferases, albumin, prothrombin time/international normalized ratio, and bilirubin levels are usually normal. Approximately 25% of cases reported in the literature note an elevated alkaline phosphatase level.[1,25] Excessive alcohol use, viral hepatitis, and markers of chronic liver disease are typically absent. Current literature on NRH may be biased toward symptomatic patients, as 73 of 135 patients reported in case series prior to 1990 had clinical complications of the disease, whereas only 1 of 64 patients diagnosed with NRH at autopsy in the Wanless study was known to have complications of NRH.[1] Portal hypertension and its complications dominate the clinical presentation and course of disease. Patients can present with hepatosplenomegaly and gastroesophageal variceal bleeding. Ascites is also seen, but is not as common, because patients typically have normal synthetic function of the liver with normal albumin levels. Treatment is aimed at removing the offending agent, if applicable, and managing complications of portal hypertension.

Diagnosis

The diagnosis of nodular regenerative hyperplasia is made by liver biopsy—either needle biopsy or open wedge biopsy. This must be performed in the appropriate clinical setting, usually as an evaluation of unexplained portal hypertension, not associated with cirrhosis. As noted above, portal hypertension may only be discovered after an episode of gastroesophageal variceal bleeding or the development of progressive thrombocytopenia without a hematological cause. Cirrhosis needs to be ruled out, as do other causes of chronic liver disease. In theory, as suggested by Wanless, the portal hypertension should be presinusoidal in nature (portal venopathy).[1] However, in practice, two groups have evaluated portal pressure measurements in a small number of patients with NRH and have found that they were more consistent with a sinusoidal portal hypertension.[26,27] It is possible that in later stages of this disease the diffuse nodularity may be compressing the sinusoids, causing sinusoidal portal hypertension similar to that seen in cirrhosis. Sensitive imaging modalities such as contrast-enhanced computed tomography and magnetic resonance imaging can help characterize various nodular liver lesions; however, histological evaluation is the only way to make a definitive diagnosis of NRH and rule out conditions such as hepatocellular carcinoma and cirrhosis. In the case of needle biopsy, the gauge of the needle is an important consideration. Regenerative nodules may be missed if the needle is too narrow, as is often the case with transjugular liver biopsy, thus making the diagnosis of NRH difficult. A reticulin stain is often essential to visualize the changes of hyperplasia and atrophy.

Differential Diagnosis

As imaging capabilities have expanded over the recent years, detection of nodular liver lesions has become more prevalent. Magnetic resonance imaging and computed tomography are increasingly being employed to evaluate liver disease, and abnormalities should be considered in terms of a complete differential diagnosis. Occasionally, NRH and cirrhosis may be difficult to distinguish, particularly on clinical grounds and radiographic imaging. The radiographic features that can be present in NRH are shown in Fig. 3 and can be quite similar to features often seen in cirrhosis. However, it is important to differentiate between causes of portal hypertension that are or are not associated with cirrhosis, because prognosis and treatment options are vastly different.

Nodular regenerative hyperplasia, a distinct entity in the spectrum of benign nodular disorders of the liver, must be differentiated from other nodular disorders of the liver, including hepatic adenoma, focal nodular hyperplasia, partial nodular transformation, large regenerative nodule, incomplete cirrhosis, and cirrhosis. The International Working Party has published guidelines and definitions for these nodular hepatic lesions.[28] The characteristics of these lesions are compared in Table 2.[29-32] This table does not review cystic, malignant, or infectious etiologies of hepatic nodules. It is important to note that more than one type of nodular lesion can coexist in the same liver; for example, NRH and hepatic adenoma may both be present in the same patient. This is an important distinction clinically, because portal hypertension may result from NRH, whereas disabling pain or hemorrhage may be due to hepatic adenoma, and different treatment options would be offered for each situation. Histologically, patients with portal hypertension not associated with cirrhosis may present with NRH, hepatoportal sclerosis (portal venopathy), central venous obliteration, sinusoidal dilation, or some combination of these lesions.[33] The pathologist should take care to exclude these findings, which may be subtle, before concluding that there are no histological abnormalities.

Natural History

There are very little data available on the long-term prognosis and outcome of patients with NRH. The literature appears to emphasize symptomatic cases, because many patients present with dramatic evidence of portal hypertension with variceal bleeding, hepatosplenomegaly, or altered liver enzymes. However, as noted in the autopsy study published by Wanless, only 64 cases of NRH were discovered in 2,500 consecutive autopsies (2.6%).[1] Of these 64 patients, only 1 was diagnosed with NRH prior to death. In the same study,

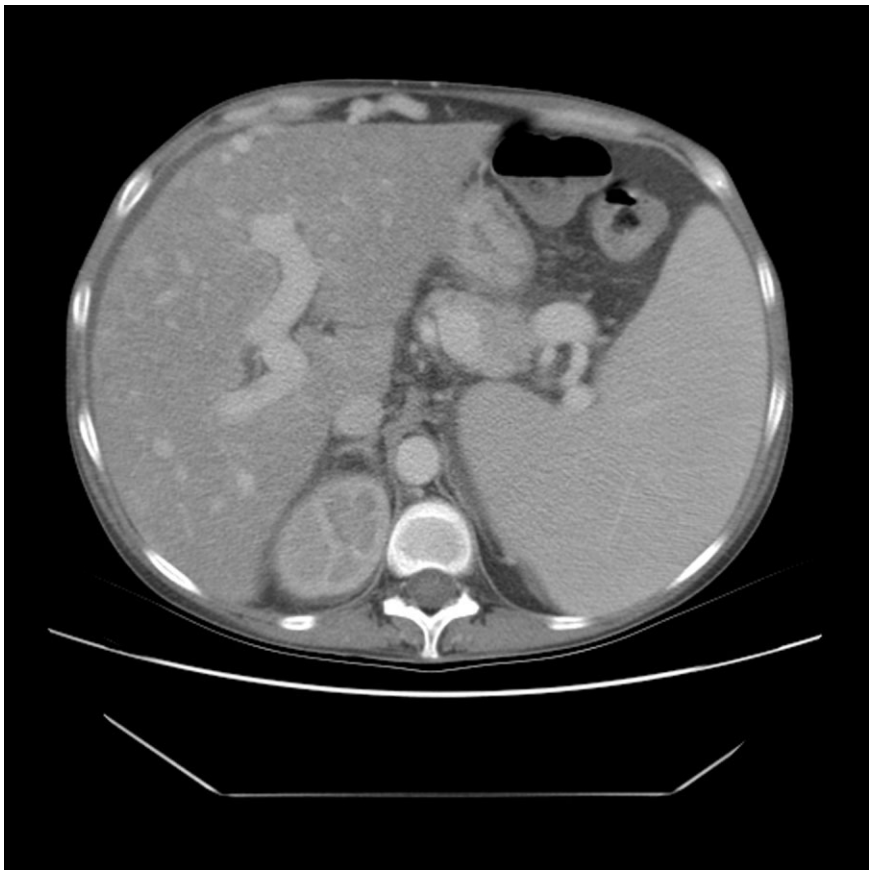

Fig. 3. Computed tomography imaging of NRH. There is a suggestion of nodularity and heterogeneous hepatic parenchyma with features of significant portal hypertension, including an enlarged portal vein measuring 16 mm in size, a recannulized umbilical vein, a small amount of ascites, and splenomegaly. Note the similarities between this patient and imaging of patients with cirrhosis.

esophageal varices were only discovered in one of five patients who had an endoscopy prior to death, and no mention is made of symptoms attributable to NRH in these documented cases. Therefore, the natural history of nodular regenerative hyperplasia is likely much more indolent than is evident in the literature. A few cases of surgical decompression of portal hypertension with portosystemic shunts has been attempted with some success; however, shunt thrombosis and recurrent variceal hemorrhaging have been noted in a minority of these patients.[26] Rare cases of hepatic and renal failure necessitating orthotopic liver transplantation and renal transplantation have also been reported.[16] NRH has also been reported to occur after liver transplantation. It is not known whether NRH is a reversible process once the presumed cause is removed, such as might occur with stopping a drug. This is an intriguing possibility given the recent literature suggesting the reversal of even significant hepatic fibrosis.[34]

Treatment

Management of patients with NRH is directed at treating the underlying disorder, if identified, and treating the complications of portal hypertension. Given the uncommon nature of NRH, there is scant literature on the natural history of this disease, and treatment strategies are based on experience with other, more common causes of portal hypertension.

The initial treatment should be directed at identifying an etiologic agent and removing it, if possible. Treatment beyond that depends on the presentation of the patient. A fundamental concept is that the synthetic function of the liver is generally intact in NRH, despite the potential for the development of significant portal hypertension. Liver transplantation is therefore not a conventional therapy for NRH. The approach to the patient with complications of portal hypertension as a result of NRH can be divided into short and long-term solutions.

The immediate approach to variceal bleeding and ascites in the patient with NRH does not differ from that of any other patient with variceal bleeding or ascites. The management of gastroesophageal variceal bleeding has been reviewed elsewhere.[35-38] A lasting treatment would be to reverse the portal hypertension in NRH with a portosystemic shunt.[26] For individuals who have cirrhosis, the choice of portosystemic shunts in patients who are candidates for liver transplantation is guided by the need for a bridge to transplant. In the case of those with NRH where the shunt is the end in itself, different factors come to bear. The shunt should not need revision, and a higher initial complication rate in return for greater long-term

Table 2. Comparison of Nodular Liver Lesions

	Nodular Regenerative Hyperplasia	Focal Nodular Hyperplasia	Hepatic Adenoma	Partial Nodular Transformation	Large Regenerative Nodule	Cirrhosis
Location/distribution of nodules	Numerous; diffuse	Usually single	Usually single	Single or multiple; hepatic hilum or large portal areas	Single or multiple; diffuse	Numerous; diffuse
Typical size of nodules	1-3 mm	<5 cm	3-15 cm	>3-5 cm	>3-5 cm	Variable
Fibrosis	Absent to minimal perisinusoidal fibrosis	Present in septae of central scar; remainder of liver normal	Absent to minimal	Absent to minimal	Absent to minimal	Present, significant
Imaging characteristics	CT: may be normal or have diffuse nodularity in heterogeneous hepatic parenchyma; may see evidence of portal hypertension	CT/MRI: central feeding artery with enhancement in arterial phase; rapid washout and isointensity to liver in delayed imaging	CT: heterogeneous nodule due to necrosis, fat, hemorrhage; early arterial enhancement	CT: nonspecific nodule near hepatic hilum; may enhance in portal phase	CT: nonspecific hypodense nodule	CT/MRI: diffuse nodularity; may see evidence of portal hypertension
Portal hypertension	May be present	None	None	May be present	May be present	May be present
Histology	Presence of nodules <3 mm in diameter without surrounding fibrosis	Normal-appearing hepatocytes; dense central stellate scar with radiating septa; proliferating bile ductules	Large plates of normal-appearing hepatocytes; dilated sinusoids; no true capsule; no bile ductules	Normal-appearing hepatocytes in nodules near hepatic hilum; no significant fibrosis	Normal-appearing hepatocytes in nodules; no significant fibrosis within or surrounding nodule	Small or large nodules; hepatocytes may have dysplastic features; nodules surrounded by fibrosis

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

patency is acceptable. Thus, a surgical shunt might be preferable to a transjugular intrahepatic portosystemic shunt in NRH. The caveat is that surgical shunts are difficult operations, and expertise in this procedure is dwindling. The bias toward surgical shunts might change as transjugular intrahepatic portosystemic shunt technology changes and restenosis rates and maintenance needs drop with newer covered stents. Experience with orthotopic liver transplantation in NRH is very limited.[16,39,40]

Lastly, there are case reports of hepatocellular carcinoma occurring in NRH.[41,42] There are theoretical reasons why NRH might be a risk factor for hepatocellular carcinoma.[43] There is no consensus in terms of whether this is so, nor is there a consensus in terms of screening. Should hepatocellular carcinoma occur, it is treated according to standard methods.[44-46]

Conclusion

Nodular regenerative hyperplasia is believed to be a hyperproliferative response to an obstructive portal venopathy and the resulting uneven perfusion of the hepatic parenchyma. NRH should be included in the differential diagnosis of patients who present with unexplained portal hypertension. The hepatologist should have a high index of suspicion in patients with systemic diseases known to be associated with NRH or in patients who have had an exposure to drugs that have been associated with NRH. Liver biopsy is essential for diagnosis, and at present the mainstay of treatment is management of the underlying disorder and control of portal hypertension. Understanding the pathophysiology of NRH might elucidate understanding of regenerative nodules in cirrhosis. As understanding of NRH and the mechanisms underlying it are developed, novel treatment strategies are likely to emerge for NRH—and possibly other liver diseases as well.

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