CASE REPORT

Nodular regenerative hyperplasia of the liver: coral atoll-like lesions on ultrasound are characteristic in predisposed patients

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ABSTRACT. Nodular regenerative hyperplasia (NRH) is an uncommon liver disease characterised histologically by numerous small hyperplastic nodules that are not separated by fibrotic tissue. It is thought to be the result of obliterator vasculopathy, and it has been associated with chronic use of medications, toxic substances and a wide variety of systemic diseases. Imaging diagnosis of early-stage NRH remains problematic. The nodules are rarely discerned and their appearance and behaviour before and after contrast medium administration are heterogeneous and not specific. A review of the literature shows that ultrasound has succeeded on occasion in revealing small focal liver lesions in patients with NRH. To our knowledge, there has been no published data on the performance in this setting of last-generation ultrasound scanners and techniques such as contrast-enhanced ultrasound (CEUS). The question is an important one because abdominal ultrasound is widely used as a first-line imaging technique for the evaluation of liver disease, and this makes it particularly suitable as a potential tool for the early diagnosis of NRH. Owing to the prolonged subclinical period and the limited help provided by imaging, the diagnosis in vivo of NRH is currently frequently missed, and it is still made exclusively on the basis of liver biopsy. In conclusion, this report describes 4 cases of biopsy-proven NRH that have been diagnosed over the past 2 years by our group. All were characterised by known comorbidities that confer a predisposition to NRH and by a peculiar parenchymal ultrasound pattern that we refer to as the “atoll sign”.

Nodular regenerative hyperplasia (NRH) is an uncommon liver disease characterised histologically by numerous small (usually 1–3 mm) hyperplastic nodules that are not separated by fibrotic tissue [1]. It is thought to be the result of obliterator vasculopathy, and it has been associated with chronic use of certain medications, toxic substances and a wide variety of systemic diseases that disturb hepatic blood flow, particularly myeloproliferative and immunological disorders. NRH rarely affects protein synthesis in the liver, so most patients remain asymptomatic with normal liver function for years. For this reason, as late as 1990 virtually all reported cases of NRH had been diagnosed on autopsy [1]. However, nodular compression of the sinusoids can cause portal hypertension with upper gastrointestinal bleeding, generally related to oesophageal varices.

Imaging diagnosis of early-stage NRH remains problematic. The nodules are usually quite small, and none of the major imaging techniques, including ultrasound, CT scanning, MRI and scintigraphy, reveal significant changes in the appearance of the liver, other than enlargement and/or parenchymal inhomogeneity. The nodules themselves are rarely discerned and, on such occasions, their appearance and behaviour before and after contrast medium administration are heterogeneous and not specific. Moreover, there is also the possibility that previous reports [2, 3] had grouped together patients with NRH and large regenerative nodules, so that the rare nodules evidenced in those series by CT and MRI could only be the latter. Large regenerative nodules are larger (diameter ranging from 5 to 50 mm) and usually enhance after contrast medium administration [4]. A review of the literature shows that ultrasound has succeeded on occasions in revealing small focal liver lesions in patients with NRH. The appearance of these lesions varied from hypoechoic [5, 6] to isoechoic [2] or hyperechoic [2, 5, 7]. However, these reports date back to the 1980s and 1990s, when ultrasound technology was far less refined than it is today. To our knowledge, there are no published data on the performance in this setting of last-generation ultrasound scanners and techniques like contrast-enhanced ultrasound (CEUS). The question is an important one because abdominal ultrasound is widely used as a first-line imaging technique for the evaluation of liver disease (and a variety of other conditions as well), and this makes it particularly

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suitable as a potential tool for the early diagnosis of NRH, particularly in predisposed patient groups. In fact, owing to the prolonged subclinical period and to the limited help given from imaging, the diagnosis in vivo of NRH is currently frequently missed, and it is still made exclusively on the basis of liver biopsy [8].

This report describes four cases of biopsy-proven NRH that have been diagnosed over the past 2 years by our group. All were characterised by known comorbidities that confer a predisposition to NRH and by a peculiar parenchymal ultrasound pattern that we refer to as the "atoll sign".

All ultrasound examinations were performed with an Aloka Prosound SSD 5500 ePHD (extended pure harmonic detection) scanner (Aloka, Tokyo, Japan) and multifrequency convex array transducers (3.0–6.0 MHz).

All biopsy were performed with a cutting technique using a 21-gauge needle (Biomol, Hospital Service, Milan, Italy).

Case report 1

A 36-year-old male presented with intense epigastric pain. He had a 5 year history of type 2 diabetes, which he treated on an irregular basis with a biguanide/sulfonylurea combination. 4 years before admission, he had undergone open cholecystectomy for gallstones. Admission laboratory tests revealed markedly elevated serum lipase (2346 U l\(^{-1}\); normal values, 23–300) and amylase levels (668 U l\(^{-1}\); normal values, 30–110), a \(^{1}\text{L}-\text{glutamyl-transpeptidase level of 101 Mu ml}^{-1}\) (normal values, 8–78), mildly elevated transaminase levels and hyperglycaemia (256 g l\(^{-1}\)). The white blood cell count was 13,000 mm\(^{-3}\). Total bilirubin, alkaline phosphatase levels and other routine blood chemistryparameters were within normal limits.

An upper abdominal ultrasound scan revealed multiple round focal lesions, up to 11 mm in diameter, scattered throughout both lobes. All appeared isoechoic with thin hyperechoic rims and no mass effect (Figure 1a,b). The intrahepatic biliary tree and the common bile duct were not dilated, and the pancreas was normal in size. No fluid collections were observed. CEUS and contrast-enhanced CT scans showed no signs of focal liver lesions in the vascular phases. The CT scan confirmed the normal appearance of the biliary tree and pancreas.

The patient was diagnosed with acute pancreatitis, probably owing to the passage of sludge through the common bile duct. His condition improved rapidly, and 5 days after admission an ultrasound-guided fine-needle biopsy was obtained from an area of the liver that functioned as a predisposing factor in the development of the disease.

Case report 2

A 74-year-old female had a 12 year history of essential thrombocythaemia. She was taking hydroxyurea and allopurinol orally and her platelet counts ranged from 400,000 to 520,000 mm\(^{-3}\). The complete blood count was otherwise normal, as were all routine blood chemistryparameters (including those reflecting liver function). An annual abdominal ultrasound scan (performed as part of the disease surveillance protocol) revealed that both liver lobes contained multiple isoechoic lesions with thin hyperechoic rims and a maximum diameter of around 12 mm (Figure 2a). No focal lesions were seen on the CEUS scan. Our experience with the previous case prompted us to obtain an ultrasound-guided fine-needle biopsy, which confirmed our suspicion of NRH (Figure 2b).

Case report 3

A 65-year-old female with coeliac disease was being treated with a gluten-free diet. Abdominal ultrasound was performed to investigate the presence of thrombocytopenia (platelet count: 74,000 mm\(^{-3}\)). Apart from this, all liver function tests were within the normal range. The ultrasound scan revealed massive splenomegaly and multiple round lesions in the liver. The lesions measured 10 mm in diameter and were isoechoic with thin hyperechoic rims (Figure 2c). CEUS showed no evidence of focal liver lesions. An ultrasound-guided fine-needle biopsy diagnosed NRH (Figure 2d).

Case report 4

A 12-year-old female presented with an episode of upper gastrointestinal bleeding. 9 years earlier she had been treated with vincristine for a nephroblastoma. Apart from thrombocytopenia (platelet count: 85,000 mm\(^{-3}\)) and a mild increase in the serum alkaline phosphatase levels, liver function tests were within normal limits. An abdominal ultrasound scan showed round focal lesions (13 mm in diameter) in both liver lobes. The lesions appeared isoechoic with thin hyperechoic rims (Figure 2e), and they were associated with portal vasodilatation and splenomegaly. A contrast-enhanced abdominal CT scan revealed signs of portal hypertension but no evidence of focal liver lesions. The diagnosis of NRH was made once again on the basis of ultrasound-guided fine-needle biopsy findings (Figure 2f).

Discussion

The term "nodular regenerative hyperplasia" was coined by Steiner in 1959 [9], although the condition it refers to was first described in 1953 by Ramstrom [10], who reported what he called "miliary hepatocellular adenomatosis" in a patient with Felty’s syndrome. Similar histopathological findings were later reported by other authors under a wide variety of names, including "liver adenomatosis" [5], "multiple adenomas" [11], "nodular transformation" [12], "non-cirrhotic nodular transformation" [13], "partial nodular transformation" [14], "non-cirrhotic nodulation" [15], and "non-cirrhotic portal hypertension" [16]. Finally, in 1995 the decision was made to use the term NRH to refer to all of these conditions [17, 18]. In a histopathological study of
liver biopsies and autopsy specimens obtained from 107 patients with non-cirrhotic portal hypertension, 14% were diagnosed as NRH, 23% as “incomplete septal cirrhosis,” 2% as “partial nodular transformation,” and the remaining 62% as “idiopathic portal hypertension.” The authors noted that the pathological features of these four conditions are similar and suggested that they may represent different stages of a single disorder [19].

As its various names suggest, the pathological hallmark of NRH is the presence of small adenoma-like nodules composed of hyperplastic hepatocytes. They usually range in diameter from 1 to 3 mm. Nodules measuring over 15 mm have also been described, but they appear to be composed of smaller nodules [1, 18, 20]. The hepatocytes within the nodules are arranged in plates more than one cell thick, a clue that is best revealed by reticulin staining. Fibrosis is minimal or absent between one nodule and another, and this element distinguishes NRH from cirrhosis. Sometimes this condition may be very difficult to distinguish from adenomas as both are composed of hyperplastic hepatocytes but for the fact that NRH is a multifocal process and adenomas tend to be solitary or rarely several lesions.

NRH is considered an uncommon disease. Its prevalence in general autopsy series ranges from 0.6% to 2.6% [1, 20], but higher figures have been reported in some patients. In fact, NRH has been increasingly linked...
Figure 2. (a) Case 2, upper abdominal ultrasound scan on the right hepatic lobe (using a 3.5 MHz convex probe). Multiple lesions, isoechoic with a thin hyperechoic rim, are visible (arrows), the larger diameter of such lesions is 12 mm. (b) Case 2, histological sample from ultrasound-guided fine-needle biopsy on one of the focal lesions of the right liver lobe. Regenerative hyperplastic hepatocytes are arranged in micronodules with microacinar appearance (arrows) (HE stain, 40×). (c) Case 3, upper abdominal ultrasound scan on the right hepatic lobe (using a 3.5 MHz convex probe). Some round isoechoic lesions with a thin hyperechoic rim, with a larger diameter of 10 mm, are present (arrows). (d) Case 3, histological sample from ultrasound-guided fine-needle biopsy on one of the focal lesions of the right liver lobe. The nodular arrangement of multilayered regenerative hyperplastic hepatocytes is evident. Some of them show hypertrophic nuclei (HE 40×). (e) Case 4, upper abdominal ultrasound scan on the right hepatic lobe (3.5 MHz convex probe). Rare round focal lesions, isoechoic with a hyperechoic rim, with a larger diameter of 13 mm, are visible (arrows). (f) Case 4, reticulin staining clearly reveals both the nodular arrangement of hepatocytes and the absence of fibrosis between the nodules (40×).
The focal lesions of nodular regenerative hyperplasia resemble the ring-shaped coral island known as an atoll (aerial view of Ari atoll, Maldives).

to haematological diseases, including myeloproliferative disorders (essential thrombocythaemia, polycythaemia vera, chronic myelogenous leukaemia and myeloid metaplasia) [20–23], lymphoproliferative diseases (multiple myeloma, non-Hodgkin’s lymphoma, chronic lymphocytic leukaemia and Hodgkin’s disease) [21], spherocytosis [21] and sickle cell disease [23]. It has also been seen in patients with immunological diseases, such as Felty’s syndrome [24], rheumatoid vasculitis [25], polyarteritis nodosa [26] and hypogammaglobulinaemia [27], and with a variety of other conditions (neoplastic disease [28], diabetes [29], coeliac disease [30] and renal or bone marrow transplantation [31]). Finally, it has been associated with the use of diverse drugs (chemotherapy agents [23, 32], azathioprine [33] and antiretroviral agents [34]) and with exposure to toxic agents.

The most widely accepted view is that NRH is the result of obliterator vascular disease. Depending on the nature of the underlying systemic illness, the primary endothelial damage can affect the portal radicles or branches of the hepatic artery. In the latter case, portal vessel occlusion is caused by the extension of the damage from an adjacent arterial branch. In either case, the portal occlusion produces acinar atrophy, and this is thought to lead to a compensatory regenerative-hyperplastic response in nearby areas that have been unaffected by the portal vessel obliteration [20, 35].

The fact that NRH occurs mostly in patients affected with predisposing disease should facilitate early diagnosis, but thus far no reliable method has been developed for this purpose. CT and MRI are not suitable in this setting [2–4], and they are also fairly expensive. Ultrasound has the advantages of being widely available, relatively easy to perform and less costly than other imaging methods. In the mid-1990s [7], our group described two cases of NRH presenting with a fairly non-specific ultrasound pattern consisting of multiple confluent hyperechoic liver lesions. Later-generation scanners and transducers allow higher-resolution imaging, and this has undoubtedly improved our ability to identify NRH lesions. The peculiar finding of small, round isoechoic lesions with a thin hyperechoic rim found in the first patient of our series resembles the ring-shaped coral-reef configuration known as an atoll (Figure 3). It was later encountered in three other patients and immediately raised the suspicion of NRH. All three were suffering from conditions known to be associated with NRH, and the diagnosis was subsequently confirmed by liver biopsy. The ultrasound diagnosis thus meant we avoided additional imaging studies.

Regenerative-hyperplastic nodules are usually smaller than 3 mm, but diameters of up to 15 mm have been reported. The lesions identified on ultrasound in our patients appear to represent only the larger nodules. It is important to emphasise that neither CEUS nor contrast-enhanced CT proved useful in detecting the focal lesions of NRH in the four cases described above. This is consistent with the experience of other authors [4], and it probably reflects not only the small size of the nodules, but also their arterial and portal vascularisation patterns, which are similar to those of the normal liver parenchyma.

Although intranodular haemorrhage is more typical of adenomas, such an event has been occasionally described in NRH [2, 3, 21]. Imaging features of intrasplenic haemorrhage consist, on CT, of hyperdense areas within hypodense nodules, while, on MRI, foci of high signal on $T_1$ may be present internally to isointense nodules.

**Conclusion**

The presence on ultrasound of the atoll-like pattern described in this report should raise the suspicion of NRH if the patient has one of the diseases known to be associated with this condition.

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**References**
