

Nodular regenerative hyperplasia of the liver associated with systemic lupus erythematosus: three cases

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Nodular regenerative hyperplasia of the liver, characterised by regenerative nodules distributed throughout the liver in the absence of fibrosis, is a rare but important complication of systemic lupus erythematosus. The main consequence of nodular regenerative hyperplasia of the liver is non-cirrhotic portal hypertension. This condition is probably underdiagnosed, as many of these patients may remain asymptomatic. Furthermore, nodular regenerative hyperplasia of the liver may be misdiagnosed as cirrhosis. We describe three female patients with nodular regenerative hyperplasia of the liver associated with systemic lupus erythematosus. All three patients have clinical manifestations of portal hypertension, and all were initially misdiagnosed as having cryptogenic cirrhosis.

Introduction

Nodular regenerative hyperplasia (NRH) of the liver is an uncommon condition characterised by regenerative nodules lacking a fibrous rim that are distributed throughout the liver.¹ The nodules typically measure 1 to 3 mm, but conglomerate nodules forming large masses have also been described.^{1,2} The main consequence of this condition is portal hypertension. The absence of fibrosis distinguishes NRH from cirrhosis. A variety of systemic autoimmune diseases and haematological disorders have been associated with NRH; these include rheumatoid arthritis, Felty's syndrome, scleroderma, systemic lupus erythematosus (SLE), polyarteritis nodosa, anti-phospholipid syndrome, myeloproliferative disorders, and lymphoproliferative disorders.¹⁻⁴ Certain drugs, in particular azathioprine and a number of chemotherapeutic agents, have also been linked to NRH.⁴ In this report, we describe three cases of NRH of the liver in patients with SLE.

Case reports

Case 1

A 54-year-old Chinese female was diagnosed with SLE at the United Christian Hospital in 1980. She had a malar rash, polyarthritis, nephrotic syndrome, positive anti-nuclear antibodies (ANA), and elevated anti-double-stranded DNA (anti-dsDNA) antibodies. Treatment with prednisolone and azathioprine was commenced at that time with a complete response. Azathioprine was maintained for 4 months and has not been used since then; the prednisolone was continued. She had several lupus flare-ups during follow-up, which responded to a temporary increase in her steroid dosage.

In 1994, ascites and splenomegaly were found incidentally during a physical examination. At that time, her full blood count showed mild anaemia and mild thrombocytopenia: her haemoglobin was 106 g/L, platelet count 138×10^9 /L, and white cell count 4.5×10^9 /L. Both her prothrombin time and activated partial thromboplastin time were normal. Her serum biochemistry was normal apart from a mild elevation of her liver enzymes: alkaline phosphatase (ALP) level of 120 IU/L (reference range, 30-85 IU/L), γ -glutamyltransferase (GGT) 97 IU/L (7-32 IU/L), and alanine aminotransferase (ALT) 58 IU/L (4-33 IU/L). Other investigations, including testing for the hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibodies, anti-mitochondrial antibodies (AMA), and smooth muscle antibodies (SMA) were negative. Transabdominal ultrasonography (USG) showed a liver with a coarse echotexture and nodular outline, moderate splenomegaly, mild ascites, patent hepatic and portal veins, and the presence of gall bladder stones. Oesophagogastroduodenoscopy (OGD) detected small oesophageal varices. A wedge liver biopsy was obtained during a cholecystectomy for symptomatic gallstones performed later in the same year. The pathologist reported mild non-specific regenerative changes without evidence of fibrosis or cirrhosis in the liver specimen. Nevertheless, the patient was labelled as having cryptogenic cirrhosis, and propranolol was initiated for control of

Key words

Focal nodular hyperplasia; Hypertension, portal; Liver; Lupus erythematosus, systemic

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肝結節狀再生性增生症伴系統性紅斑狼瘡的 三個病例報告

肝結節狀再生性增生症是一個罕有卻很重要的系統性紅斑狼瘡併發症，特徵是再生結節會佈滿整個肝臟但沒有纖維化。此病的主要後果是非肝硬化性門靜脈高壓症。由於很多患者沒有症狀，此病往往被忽略。此外，肝結節狀再生性增生症可能會被誤診為肝硬化。本文報告三名女病人患有肝結節狀再生性增生症伴系統性紅斑狼瘡，並呈現門靜脈高壓的臨床症狀，但起初卻被誤診為隱源性肝硬化。

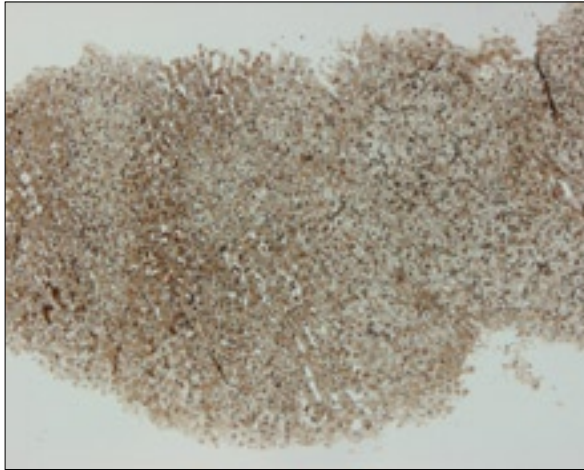


FIG 1. Photomicrograph of the liver biopsy specimen showing nodules of hyperplastic hepatocytes with no significant fibrosis (reticulin silver stain, x40)

her portal hypertension. She subsequently suffered two episodes of gastric variceal bleeding in 2000 and 2003 respectively, both of which were successfully controlled with endoscopic histoacryl injections. Her oesophageal varices were eradicated using repeated endoscopic band ligation. Her liver function has remained relatively stable over the years, although a progressive increase in spleen size was documented by serial ultrasonographic measurements, and her ascites has worsened. During this time her lupus has been kept quiescent with maintenance prednisolone of about 10 mg daily. A review of her liver histology in 2006 demonstrated features consistent with NRH (Fig 1). Subsequent testing for lupus anticoagulant (LA) and anti-cardiolipin (aCL) antibodies were both negative. A computed tomographic (CT) scan of the liver did not show any focal hepatic lesions, but magnetic resonance imaging (MRI) of the liver demonstrated multiple non-enhancing hepatic nodules (Fig 2). The patient was last seen in April 2008 when she remained well, apart from intractable ascites.

Case 2

A 56-year-old Chinese female was diagnosed as having

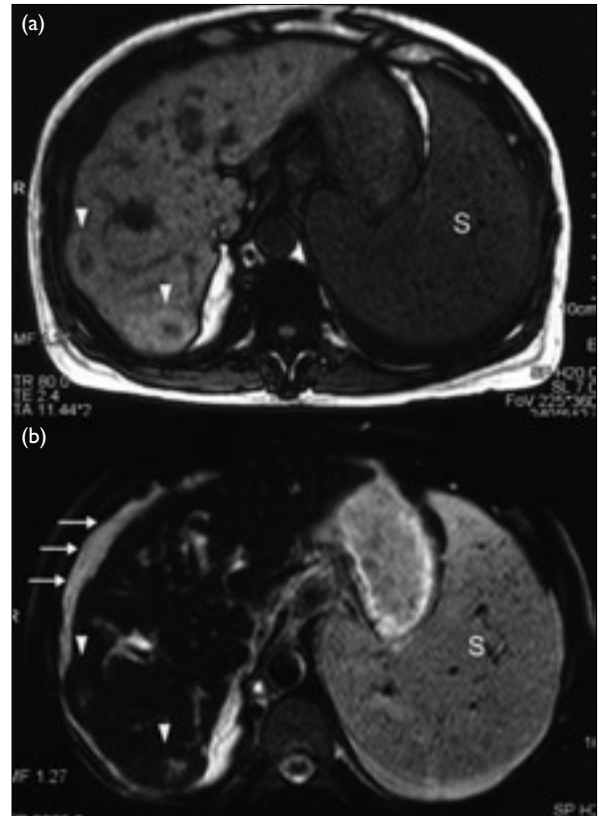


FIG 2. (a) T1-weighted magnetic resonance image of the liver showing high-signal nodular lesions with central hypointense foci (arrowheads). (b) T2-weighted magnetic resonance image showing that the nodular lesions are isointense with central hyperintense foci (arrowheads). Massive splenomegaly (S) and ascites (arrows) are present

SLE in 1974 on the basis of a malar rash, polyarthrits, thrombocytopenia, positive ANA, and elevated anti-dsDNA antibodies. She underwent splenectomy for profound thrombocytopenia in 1990. In 1992, she presented to the United Christian Hospital with bleeding oesophageal varices successfully treated by endoscopic injection sclerotherapy. She was labelled as having cryptogenic cirrhosis from that time on. She had another episode of variceal bleeding from gastric varices in 2000 that was successfully controlled by endoscopic histoacryl injection. She was on prednisolone until around 1993, and her lupus has remained quiescent since stopping steroids. Her liver function tests and liver enzyme levels have been normal all along, and she has never had ascites or hepatic encephalopathy. Blood tests for HBsAg, HCV antibodies, AMA, SMA, LA and aCL antibodies were all negative. Her liver appeared small with a nodular outline on USG. Magnetic resonance imaging of the liver showed multiple non-enhancing hepatic nodules that were isointense with a central hypointense area on T1-weighted images and isointense with a central hyperintense area on T2-weighted images. A transcutaneous needle

liver biopsy was performed in 2006 to investigate a possible non-cirrhotic cause of portal hypertension, revealing NRH. She was last seen in April 2008 when she remained well.

Case 3

A 56-year-old Chinese female was diagnosed with SLE at the United Christian Hospital in 1996 based on a cutaneous rash, polyarthrititis, pericardial effusion, haemolytic anaemia, and the presence of ANA and elevated anti-dsDNA antibodies. Treatment with prednisolone and azathioprine was initiated with a good clinical response. The azathioprine was maintained for about 30 months until 1999, and the prednisolone was continued. Five years after the initial SLE diagnosis, she was labelled as having cryptogenic cirrhosis on the basis of hypersplenism (thrombocytopaenia with a platelet count of $79 \times 10^9/L$ and splenomegaly on USG), small oesophageal varices detected by OGD, and ultrasonographic features of a liver with a coarse echotexture and nodular outline. Her serum biochemistry was normal apart from mild elevation of her liver enzymes (ALT 55 IU/L, ALP 104 IU/L, and GGT 285 IU/L). Blood tests for HBsAg, HCV antibodies, AMA, SMA, LA and aCL antibodies were all negative. Magnetic resonance imaging of the liver demonstrated multiple non-enhancing hepatic nodules that were hyperintense on T1-weighted images and isointense on T2-weighted images. A transcutaneous needle biopsy of the liver was done in 2006 and revealed NRH. She was last seen in April 2008; her lupus remained quiescent while she was on prednisolone 8 mg daily.

Discussion

Although the liver is not a usual target for damage in patients with SLE, biochemical liver function abnormalities are a common phenomenon and are mostly attributable to drug-related toxicity, steatosis, congestion or non-specific hepatitis reflecting lupus activity.⁵ Other liver abnormalities that have been encountered less frequently include Budd-Chiari syndrome, hepatic rupture, primary biliary cirrhosis, idiopathic portal hypertension, and NRH.⁶ According to Japanese autopsy registry data for 1468 patients with SLE, the frequency of SLE complicated by NRH is only 0.3%.⁷ To our knowledge, fewer than 25 cases of NRH occurring in association with SLE have been reported in the English literature.^{3,7-15} Nevertheless, NRH is probably underdiagnosed, as many patients may remain asymptomatic, especially in the early stages of the disease,¹ and establishment of the diagnosis of NRH requires histological examination of liver tissue. Moreover, this lesion can be overlooked or misinterpreted in a routinely processed needle biopsy specimen. The main histological feature of

NRH is the presence of nodules of hyperplastic hepatocytes without surrounding fibrosis. Such nodularity may be inconspicuous in liver specimens acquired through needle biopsy because of sampling error. Furthermore, lack of awareness of this condition may also contribute to misdiagnosing it as cirrhosis.

The pathogenesis of NRH complicating SLE is believed to be vasculitis of intrahepatic arteries leading to secondary portal venous obliteration and thrombosis of the adjacent portal veins.¹ Alternatively, occlusion of intrahepatic small vessels may result from coagulopathy in patients with an associated anti-phospholipid syndrome.¹⁶ It has been suggested that anti-phospholipid antibodies may play a pathogenic veno-occlusive role in the pathogenesis of NRH, especially in those cases associated with an anti-phospholipid syndrome.^{3,16}

Clinically, patients with NRH may be asymptomatic or they may present with altered liver function tests, symptoms and signs of portal hypertension (hepatosplenomegaly, ascites, or oesophageal variceal bleeding).^{1,2} Rarely, patients may progress to hepatic failure.² Most patients have liver function tests showing normal bilirubin and albumin levels, reflecting preserved hepatic synthetic function.^{2,3} Elevated levels of ALP and GGT are common, and may be accompanied by a slight increase in aminotransferase levels.¹⁻³

The radiological features of NRH, including nodularity of the liver surface, hepatic regenerative nodules, and extrahepatic signs related to portal hypertension, such as splenomegaly, portosystemic collaterals and ascites, can be quite similar to features often seen in cirrhosis. Magnetic resonance imaging is more sensitive than CT scan or USG for detecting the regenerative nodules of NRH, which typically appear hyperintense on T1-weighted images and isointense or hypointense on T2-weighted images.^{12,13} Hypointense nodules with central hyperintense foci on T2-weighted images have also been described in NRH,¹⁴ and are probably the result of infarction within the regenerative nodules. We have also reported a case of NRH showing a unique hepatic imaging pattern of periportal tubular structures with enhancement during the portal venous phase on both the CT scan and MRI.¹⁵

There is no specific treatment for NRH. At present the mainstay of treatment is management of the underlying systemic disorder and control of portal hypertension.⁴ With regard to the treatment of NRH associated with SLE, previous reports indicate that steroid therapy may not be helpful.^{7,8} In our patients, the use of steroids did not appear to be useful as a means of preventing the development or progression of portal hypertension. In another patient with NRH associated with SLE, whose case we have reported previously,¹⁵ progression to development

of portopulmonary hypertension was observed, despite the lupus activity being kept quiescent with steroids. Anticoagulation should be considered in those patients whose disease is associated with an anti-phospholipid syndrome.⁴ Another treatment consideration is that azathioprine should be avoided as this drug has been linked to NRH. Studies on the optimal therapy for NRH-related non-cirrhotic portal hypertension are lacking due to the uncommon nature of this condition. Treatment strategies are generally extrapolated from the algorithm employed in the treatment of cirrhotic portal hypertension; these include the use of non-selective β -blockers, endoscopic variceal sclerotherapy or band ligation, transjugular intrahepatic portosystemic shunting, and surgical portosystemic shunting.⁴ The incidence of hepatic encephalopathy after portosystemic shunting is low as NRH is usually associated with well-preserved hepatic synthetic function.⁴ Liver transplantation may be indicated for those rare patients who progress to hepatic failure.⁴

Conclusions

We have presented three new cases of NRH of the liver associated with SLE. All three patients were initially misdiagnosed as having cryptogenic cirrhosis, and the underlying diagnosis was only revealed after careful evaluation of their liver histology. Nodular regenerative hyperplasia of the liver should be considered in patients with SLE who develop clinical manifestations of portal hypertension. Elevated liver enzymes (particularly ALP and GGT) and radiological evidence of hepatic regenerative nodules are compatible with the diagnosis, but ultimately, histological confirmation is required to make a diagnosis of NRH of the liver. It is important to differentiate between those cases of portal hypertension related to NRH and those caused by cirrhosis because the prognosis is vastly different. Furthermore, treatment options may differ as patients with NRH are better candidates for portosystemic shunting procedures.

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