Nodular regenerative hyperplasia of the liver presenting with ascites in a woman with limited systemic sclerosis

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CASE
A 57-year old Caucasian female was being followed for a 30-year history of limited systemic sclerosis. Her disease first presented with Raynaud’s phenomenon in 1980, and she subsequently developed digital calcinosis, dysphagia and esophageal reflux, sclerodactyly, and widespread telangiectasia.

In 2003, she developed progressive dyspnea on exertion accompanied by chest tightness and a single episode of syncope. Physical examination was significant for a split S2 with a loud pulmonic component. Pulmonary function testing showed a decreased diffusion capacity. RVSP was found to be elevated on 2D-Echocardiogram. These findings supported a diagnosis of pulmonary arterial hypertension (PAH) secondary to scleroderma. She received continuous IV prostacyclin infusion in combination with an oral prostacyclin analogue. Sildenafil was added in 2007, due to worsening exercise tolerance. She underwent evaluation for lung transplantation, but a decision was reached to defer the procedure unless her status worsened further.

In 2007, the patient began to experience intermittent episodes of dull and diffuse RUQ pain. Her abdomen was noted to be protuberant on several occasions. However, repeated laboratory tests and imaging of abdomen and liver remained normal. An upper GI endoscopy was performed in 2008 and showed no significant abnormalities.

In June of 2011 she presented to the ER with increasing RUQ pain, abdominal fullness, and weight gain of 10 lbs despite decreasing appetite over the last 2-3 months. There was no icterus or pedal edema. AST and ALP were mildly elevated (45 IU/L and 161 IU/L respectively), with normal albumin and INR. Abdominal ultrasound showed ascites, splenomegaly and bilateral pleural effusions, and she was admitted to hospital for further evaluation. Paracentesis revealed a serum-to-ascites albumin gradient of 11 with no evidence of infection. Hepatic venous pressure gradient was at the upper limit of normal (5 mmHg). Gastroscopy showed marked portal hypertensive gastropathy with no significant varices. Cardiac RVSP was measured at 96 mmHg (N<40 mmHg) on 2D-echochardiogram, which had remained stable at this level for the past few years.

A transjugular liver needle biopsy was then performed. This revealed loss of small portal veins and nodularity of the hepatic parenchyma with minimal fibrosis, no fibrous septa and no evidence of cirrhosis or other disease. Of note, bile ducts were present in normal numbers and appeared normal, with no observed cholestasis. These histological changes were diagnostic for Nodular Regenerative Hyperplasia (NRH) of the liver.

The treating physicians felt that this patient’s presentation of RUQ pain with ascites was the result of non-cirrhotic portal hypertension secondary to NRH, which was further exacerbated by severe PAH. The patient was treated with gentle diuresis and supportive management, and over the course of her admission her ascites diminished moderately and pleural effusions resolved. It was recognized that aggressive diuresis, therapeutic paracentesis or a transjugular intrahepatic portosystemic shunt (TIPS) procedure were all contraindicated given her fragile cardio-pulmonary status secondary to PAH. She was discharged after two weeks on spironolactone, a no added salt diet, and continued close monitoring of fluid balance. Unfortunately, this complication of her disease will limit her suitability for future lung transplantation.

DISCUSSION
Systemic sclerosis (SSc) or scleroderma is a rare disease characterized by progressive fibrosis of cutaneous, vascular and/or visceral connective tissue. The pathogenesis is linked to sustained immune-mediated activation of fibroblasts and endothelial cells. The ‘limited’ or ‘diffuse’ subtypes of SSc differ with respect to the extent of skin fibrosis, organ involvement, antibody production, and survival. Features of limited SSc (I-SSc) include the CREST syndrome (calcinosis cutis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) and anti-centromere antibodies. Patients with either subtype require continuous monitoring for specific organ complications, and supportive treatment targeted towards affected tissues.

Nodular regenerative hyperplasia (NRH) is a pathological description for abnormal regenerative nodules within the hepatic parenchyma in the absence of fibrosis. NRH is rare diagnosis, known to develop in the context of autoimmune, hematologic and malignant disorders as well as certain drug exposures. In a case series of 42 patients with NRH, one quarter had an underlying rheumatologic disorder, and a recent review found 7 reports of NRH associated with SSc or CREST syndrome.

The regenerative nodules in NRH are thought to be a reactive process of hepatocytes secondary to disrupted vascular flow. Clinically, NRH belongs to a heterogeneous group of disorders causing non-cirrhotic portal hypertension, characterized by elevated portal pressures, ascites, or varices in the absence of cirrhosis or significant liver dysfunction. The pathogenesis of non-cirrhotic portal hypertension likely involves pre-sinusoidal and portal vessel injury, fibrosis, and thrombosis. The chronic inflammation, auto-antibodies, and pro-thrombotic state present in rheumatic diseases may precipitate this process. In SSc, the abnormal fibroblast activity responsible for cutaneous thickening may also be present in...
the portal tracts.10

Although non-specific liver abnormalities are common in SSc,11 intrinsic liver disease is seen infrequently.12 Primary Biliary Cirrhosis (PBC), involving progressive obliteration and fibrosis of intrahepatic bile ducts, is the liver disease most commonly associated with l-SSc.9,11,15 Conversely, NRH is a very rare complication12,14, and only case reports exist in the literature.3 Interestingly, NRH has been reported as an overlap syndrome with PBC in patients with CREST.15,16 In this patient, a minimally elevated ALP in the presence of normal bile ducts in the biopsy specimen makes a diagnosis of overlapping PBC unlikely.15

NRH should be considered in the context of preserved liver function, minimally elevated liver enzymes, and no evidence of cirrhosis.3 The diagnostic gold standard for NRH is liver biopsy14; imaging and other non-invasive tests are less helpful diagnostically.3,17 Management consists of treating the underlying condition(s) and preventing or treating portal hypertension, as these are the main prognostic factors in this condition.5,6

Portal hypertension will eventually develop in 50% of patients with NRH, but it is uncommon for manifestations such as ascites to be present at the time of diagnosis.6,15 One of the factors that likely contributed to this patient’s dramatic presentation was her long-standing pulmonary arterial hypertension (PAH), which is estimated to affect 10-25% of SSc patients.18 Prostaglandyn analogues, endothelin-receptor antagonists and PDE-5 inhibitors have been shown to improve function and delay progression in patients with PAH-SSc19,20, but it remains the leading cause of mortality in patients with l-SSc.18 Interestingly, there have been numerous reports of NRH co-existing with PAH in patients with SSc and other diseases, suggesting that a common vascular pathogenesis may underlie these conditions.5,15,21,22 Alternatively, PAH may be responsible for producing the circulatory disturbance that initiates the development of NRH.22

This is an example of a rare condition, Nodular Regenerative Hyperplasia of the Liver, presenting in a relatively rare disease, scleroderma. The initially subtle signs and lack of laboratory abnormalities further confounded efforts to identify the underlying problem. Our patient had a prolonged stay in hospital, and the ability to make the diagnosis and provide appropriate care required the collaboration with, and expertise of hepatologists, gastroenterologists and respirologists. This case highlights the need for multidisciplinary management of patients with complex rheumatic disorder, particularly in the setting of diagnostic and therapeutic dilemmas. Further research is warranted to investigate the relationship between pulmonary hypertension and the vascular pathogenesis of NRH.

REFERENCES


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