Nodular regenerative hyperplasia of the liver: a cause of noncirrhotic portal hypertension[1]

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Nodular regenerative hyperplasia of the liver is described in a case report of a 59-year-old man who presented with hematemesis and varices. He had a 20-year history of severe rheumatoid arthritis and a three-year history of Felty's syndrome. Nodular regenerative hyperplasia is a cause of noncirrhotic portal hypertension.

Index terms: Hypertension, portal · Liver, hyperplasia · Pathology features

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Portal hypertension with varices is usually secondary to cirrhosis of the liver. Cirrhosis of the liver is always preceded by liver cell necrosis and is characterized by fibrosis and nodular regeneration. However, portal hypertension can also be associated with a variety of other causes that have not resulted in liver cell necrosis and cirrhosis. Nodular regenerative hyperplasia, characterized by nodular regeneration without fibrosis and without prior liver cell necrosis, is one of those causes; it was first described in 1953 by Ranström as "miliary hepatocellular adenomatosis," and the initial case was also associated with Felty's syndrome.[1]

Case report

A 59-year-old white man was first seen at the Cleveland Clinic in May 1983 for a second opinion concerning the diagnosis of pancytopenia. He presented with a hemoglobin of 7.7 gm/dL, white blood cell (WBC) count of 670/mL, and platelet count of 57,000/mL. A reticulocyte count was 5.7%. He had a 20-year history of severe rheumatoid arthritis and had been pancytopenic with splenomegaly for three years. The patient admitted a heavy ethanol intake in the past, but had quit drinking in January 1983. On physical examination, he was noted to have hepatomegaly (3 finger breadths) as well as splenomegaly (5 finger breadths). No spider angiomata or petechiae were noted. There was no ascites. Pedal edema (+1) was present. Laboratory data included: antinuclear antibody (ANA), 1:320; rheumatoid factor (RF), 1:296; erythrocyte sedimentation rate (ESR), 152 mm/min; Coombs' test, negative; lupus erythematosus (LE) cell, negative; anti-DNA, negative; anti-smooth muscle, negative; and cryoglobulins, 189 μg/mL (mixed cryoglobulins with all Ig classes present). Serum protein electrophoresis showed marked elevation of the gamma globulins with a polyclonal distribution. Liver function studies included: serum glutamic oxaloacetic transaminase (SGOT), 37 IU/L; alkaline phosphatase, 206 IU/L; and bilirubin, 1.8 mg/dL.

The patient was thought to have pancytopenia on the basis of Felty's syndrome; however, the enlarged liver raised the possibility of cirrhosis. The patient's hemoglobin was stable after blood transfusion, and we decided to follow the patient and to consider splenectomy only if serious bleeding occurred in the future. The patient was discharged on a regimen of iron, multivitamins, and a thiazide diuretic.

Three months later, the patient had an episode of hematemesis. Endoscopy revealed varices, but no bleeding site was seen. He was given 7 U of packed red blood cells and 10 U of pooled platelets. An angiogram revealed a normal hepatic vein with a pressure of 15 mm Hg and a wedged hepatic vein pressure of 24 mm Hg. These changes were thought to be consistent with intrahepatic sinusoidal portal hypertension. The patient underwent laparotomy, and an enlarged finely nodular liver was seen. The initial portal vein pressure was 37.5 cm H_2O, and after splenectomy, the portal vein pressure was 27.0 cm H_2O. No portal vein shunt was performed because it was thought that the elevated portal vein pressure was probably caused by increased splenic blood flow. The preoperative pancytopenia responded to splenectomy. When the patient was discharged in September 1983, the hemoglobin was 10.6 g/dL; WBC, 5,700/mL; and platelets, 352,000/mL.

Histopathology

A needle biopsy performed at operation re-

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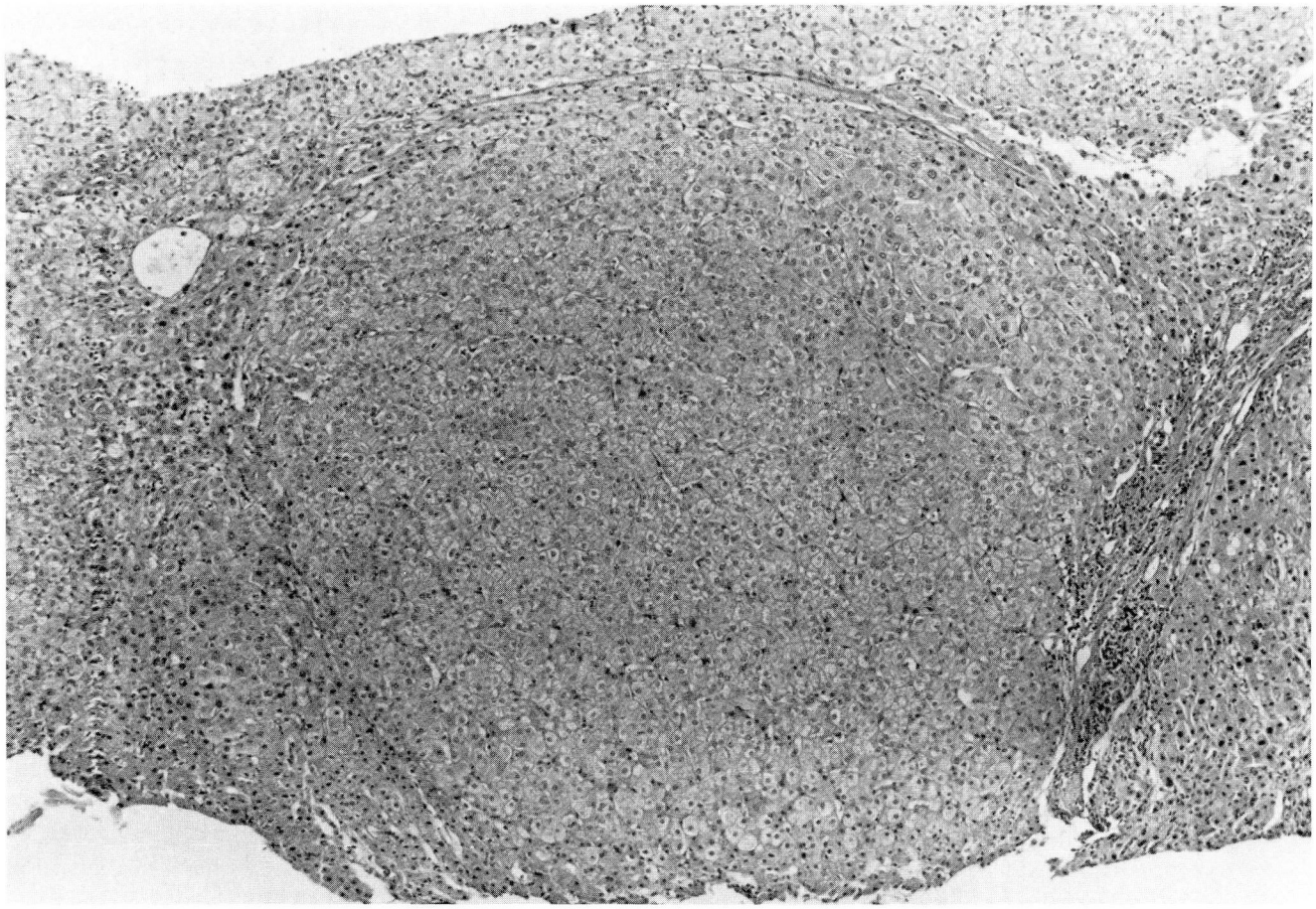

Fig. 1. A rounded, regenerating nodule involves the periportal and midzonal regions of the liver. The portal tract is at lower right and the central vein is at upper left (PAS stain, ×40).

vealed several rounded aggregates of liver cells that were not surrounded by fibrous tissue. The rounded aggregates or nodules of liver cells were seen with hematoxylin and eosin, trichrome, and periodic acid-Schiff (PAS) (*Figs. 1* and *2*) stains, but were best seen with a reticulin stain (*Figs. 3* and *4*). Seventeen portal tracts and central veins were present for examination. A few of the portal tracts showed mild focal stellate fibrosis and mild, nonspecific chronic inflammation. There was no piecemeal necrosis. Bile ducts and portal veins were both present and unremarkable. The nodules were near the portal tracts and involved the periportal and midzonal portions of the liver parenchyma (Rappaport's zones 1 and 2). In contrast, the central zones showed atrophy; the liver cells were small and often appeared attenuated next to the expanding nodules (*Figs. 2* and *4*). Lipofuscin pigment granules were present in the cytoplasm of the centrizonal liver cells, but absent in the regenerating liver nodules (*Fig. 4*). In contrast, glycogen was detected by periodic acid-Schiff stain before diastase digestion within hepatocytes in the regenerating nodules, but was absent in the atrophic centrizonal liver cells (*Fig. 2*). No mitotic figures were identified. There was mild anisonucleosis, but no more than usually seen in adult livers. There was no cytologic dysplasia. The iron stain was negative. The orcein stain was negative for hepatitis B surface antigen and copper-binding protein. There was no fatty change. Occasional clusters of hepatocytes within regenerating nodules contained intracytoplasmic structures consistent with megamitochondria. No intracytoplasmic hyalin (Mallory's hyalin) was identified.

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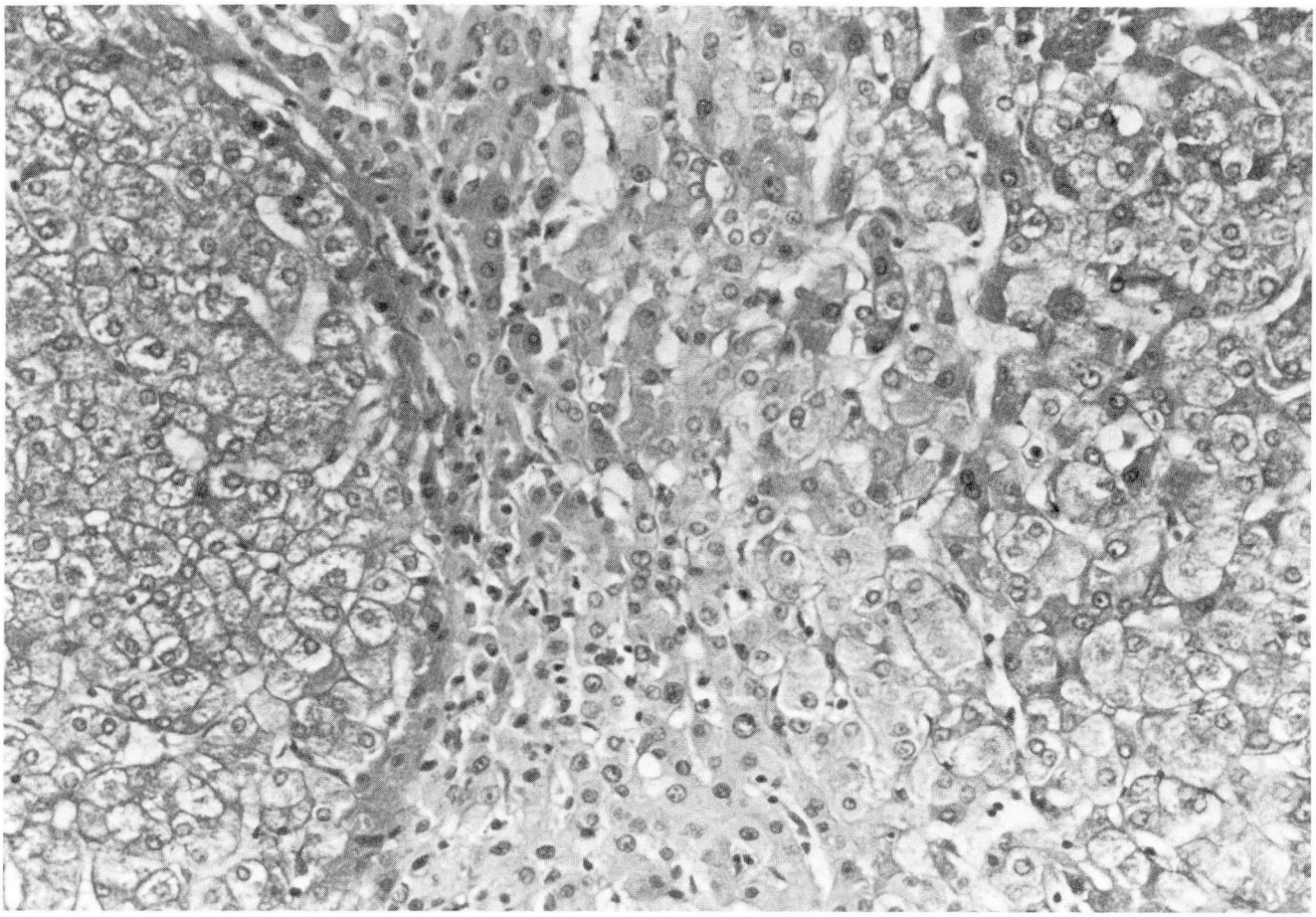

Fig. 2. Rounded expansile nodules abut an atrophic centrilobular zone. The granular cytoplasm of hepatocytes in the nodules represents glycogen (PAS stain, ×200).

Discussion

Noncirrhotic portal hypertension may be classified into four categories: extrahepatic portal and splenic vein obstruction, such as thrombosis; periportal and sinusoidal obstruction by space-occupying lesions and infiltrates, such as sarcoidosis or early chronic active hepatitis; hepatoportal sclerosis, such as after vinyl chloride exposure and hypervitaminosis A; and hepatic vein obstruction, such as seen in veno-occlusive disease and congenital anomalies of the hepatic vein.[2] Nodular regenerative hyperplasia best fits the second category.

It is important to distinguish between cirrhotic and noncirrhotic portal hypertension because complications of esophageal variceal rupture and hemorrhage are more likely in the former. In cirrhotic portal hypertension, hepatocellular function is poorly preserved, and therefore, ascites, jaundice, encephalopathy, and death may follow episodes of bleeding. Conversely, in noncirrhotic portal hypertension, hepatocellular function is maintained and patients tolerate variceal bleeding much better.[2]

The patient described here demonstrated the classical changes of nodular regenerative hyperplasia.[3,4] At operation, the liver appeared diffusely and finely nodular. The histopathologic examination revealed multiple small nodules only slightly larger than normal liver lobules. The nodules were present without surrounding fibrosis and were primarily located in the periportal and midzonal (Rappaport's zones 1 and 2) areas of the liver parenchyma. The centrilobular liver cells appeared atrophic and were devoid of stainable glycogen. This atrophy may be secondary to

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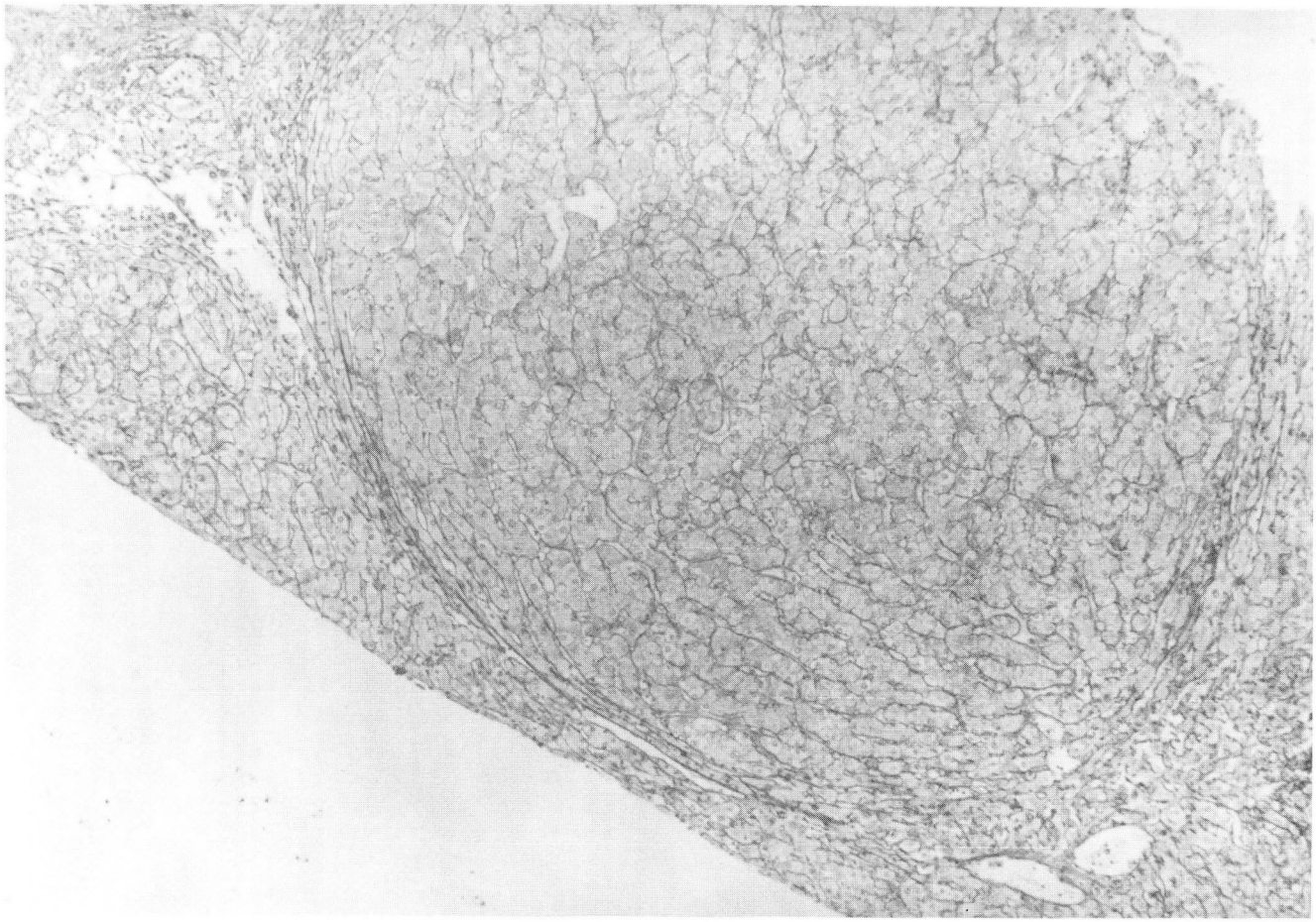

Fig. 3. The reticulin stain demonstrates the expansile nature of the nodule with compression of preexisting reticulin, but no fibrosis (reticulin stain, ×20).

compression by the adjacent expanding nodules, but also might be related to some other factor in the etiology and pathogenesis of this disorder. The patient had a history of drinking, but there was no evidence of fatty change, intracytoplasmic hyalin, or centrilobular fibrosis. Focal clusters of hepatocytes within the nodules revealed structures consistent with megamitochondria. The positive drinking history and presence of megamitochondria alone could not account for the portal hypertension and were probably unrelated causally to the nodular regenerative hyperplasia. In addition, there was only mild focal nonspecific portal fibrosis associated with mild chronic inflammation. The degree of inflammation and fibrosis also was insufficient to cause portal hypertension.

In 1981, Wanless et al[5] reported four cases of nodular regenerative hyperplasia and stated that "more than half of the portal triads displayed obliteration of the portal vein." The portal vein changes described by Wanless et al are similar to those described as "obliterative portal venopathy of the liver" by Nayak and Ramalingaswami[6] in patients without cirrhosis, but with portal hypertension. In those patients, changes of nodular regenerative hyperplasia were not seen. In the case reported here, 17 portal tracts were present, and no abnormal veins were identified.

The patient described here had a 20-year history of severe rheumatoid arthritis and a three-year history of Felty's syndrome. The original case reported by Ranström occurred in a patient with Felty's syndrome, and several other reports are found in the literature of nodular regenerative hyperplasia occurring in Felty's syn-

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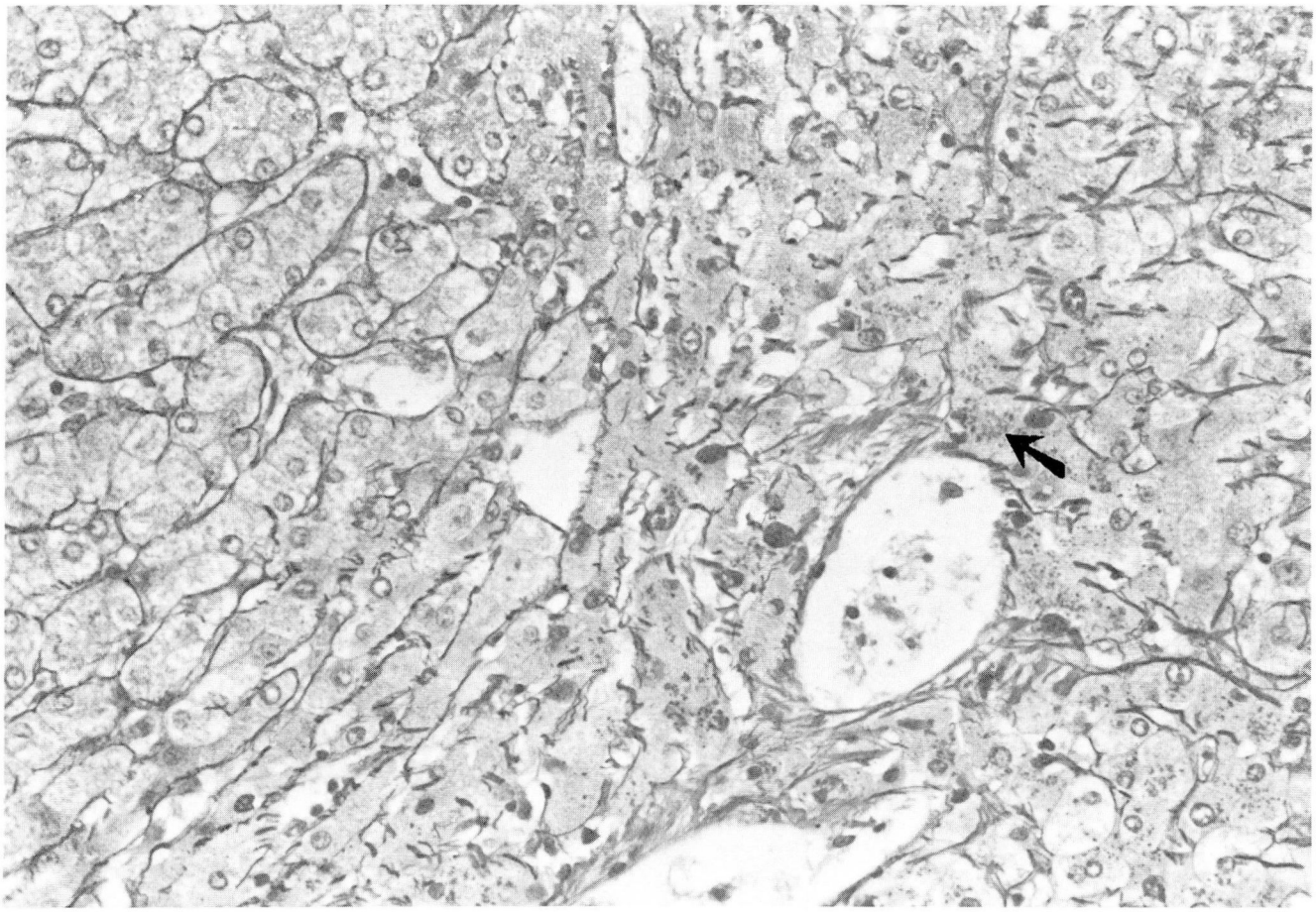

Fig. 4. An expansile nodule (left) compresses centrilobular liver cells. Note black intracytoplasmic granules of lipofuscin within centrilobular cells (*arrow*) (reticulin stain, ×200).

drome[1,3,4] and in rheumatoid disease alone.[4,7] Nodular regenerative hyperplasia has also been reported with other connective tissue diseases such as lupus erythematosus and the CRST (calcinosis cutis, Raynaud's phenomenon, sclerodactyly, and telangiectasia) syndrome.[4] However, those associated with Felty's syndrome, rheumatoid disease, and other connective tissue diseases comprise a minority of the cases. Many examples have been reported with the use of drugs such as corticosteroids, oral contraceptives, and antineoplastic agents.[4] Cases have been reported with other multiple unrelated associations, and cases have also been reported without any recognized association at all.[4,8] Some patients with Felty's syndrome may have portal hypertension on the basis of noncirrhotic nodular regenerative hyperplasia; however, the exact causal relationship with Felty's syndrome has yet to be determined.

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