Nodular Regenerative Hyperplasia and Other Noncirrhotic Nodular Hyperplastic Lesions of the Liver

Contents

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Abstract

Nodular regenerative hyperplasia (NRH) of the liver is a multilobular regenerative nodular lesion that develops in a noncirrhotic liver. NRH is characterized by the presence of nodules composed of normal-looking hepatocytes that form enlarged cell plates. These nodules are not surrounded by collagenous tissue, but a compressed reticulin network is present between the nodules and adjacent parenchyma. Cells within the nodules exhibit an increased proliferative activity. NRH is a major cause of noncirrhotic portal hypertension and develops in association with several systemic and local disorders, including autoimmune and related diseases, vascular disorders of the liver, myeloid neoplasms and various lymphoproliferative disorders, various drugs (mainly immunosuppressive agents), immunodeficiency syndromes, infections, and numerous other but rare conditions. There is evidence that, as a major pathogenic pathway, obliteration of small portal venous branches that causes atrophy of downstream liver lobules is followed by compensatory hyperplasia of adjacent lobules. There are other, less common forms of noncirrhotic nodular hyperplastic lesions of the liver, including partial nodular transformation.

Nodular Regenerative Hyperplasia (NRH) of the Liver

Introduction

Nodular regenerative hyperplasia (NRH) of the liver (synonyms: micronodular transformation; nodular transformation; nodular noncirrhotic liver; noncirrhotic nodulation of the liver) is multilobular regenerative nodular lesion developing in a noncirrhotic liver. NRH is morphologically characterized by the presence of nodules of regenerating, normal-looking hepatocytes, without fibrous septa, usually distributed diffusely across the liver parenchyma (Stromeyer and Ishak 1981). NRH is a major cause of noncirrhotic portal hypertension (review: Nakanuma et al. 2001). An important pathogenic mechanism, outlined in more detail below, is that obliteration of small portal venous branches causes atrophy of downstream liver lobules followed by compensatory hyperplasia of adjacent lobules with a still intact portal blood supply (reviews: Connolly 1977; Rougier et al. 1978; Smith 1978; Alperstein et al. 1981; Stromeyer and Ishak 1981; Mones and Saldana 1984; Moran et al. 1991; Tsui and So 1993; Pettei et al. 1995; Dall'Igna et al. 1996; Trenschel et al. 2000; Kondo et al. 2004).

Epidemiology

In several reports, Rauström is credited with being the first to describe a case of NRH of the liver in 1953, however by using the term *miliary hepatocellular adenomatosis* (Rauström 1953). In 1959, Steiner coined the term *nodular regenerative hyperplasia of the liver* (Steiner 1959). The prevalence of NRH may be as high as 0.6 % on the basis of autopsy series (Wanless et al. 1980). NRH is predominantly a disease of adult subjects but is also well recognized in the pediatric age-group (). In children, NRH may follow completion of solid tumor chemotherapy and may mimic hepatic metastases (Chu and Roebuck 2003; Citak et al. 2007). There are very rare instances of familial occurrence of NRH (Dumortier et al. 1999). A trimorphic syndrome with familial idiopathic pulmonary fibrosis, bone marrow hypoplasia, and hepatic NRH has been described (Talbot-Smith et al. 2009). The causes and pathogenic pathways of NRH are discussed in more detail at the end of this chapter.

Clinical and Imaging Features

NRH may be asymptomatic (Reshamwala et al. 2006), but in autopsy studies, NRH is associated with noncirrhotic portal hypertension in part of patients with this disorder (Wanless 1990). Noncirrhotic portal hypertension has been observed in at least half of patients with NRH (Sherlock et al. 1966; Classen et al. 1970; Rougier

et al. 1978; Stromeyer and Ishak 1981; Naber et al. 1991; Arvanitaki and Adler 2001; Gentilucci et al. 2011; review: Hartleb et al. 2011). Noncirrhotic portal hypertension is also caused by NRH in the pediatric age-group (Alperstein et al. 1981). Hemodynamic studies have suggested that portal hypertension in NRH is primarily sinusoidal, similar to that seen in liver cirrhosis (Ueno et al. 1996). In a more recent study of 24 NRH patients with symptomatic portal hypertension analyzing wedged hepatic vein, inferior vena cava, and portal vein pressures, findings were those of a presinusoidal component to portal hypertension, probably related to compression of portal venules by the regenerative nodules (Bissonnette et al. 2012). Rarely, NRH was associated with pulmonary arterial hypertension (Yutani et al. 1988; Bedossa et al. 1990). NRH may be associated with elevated serum AFP levels, caused by the regenerative hepatocyte response (Mneimneh et al. 2011). The prognosis of NRH is thought to be related more to the severity of underlying disease or systemic disorder than to the hepatic involvement itself (Colina et al. 1989).

The nodules of NRH have variable echogenicity on sonography, with hyperechoic or hypoechoic lesions (Casillas et al. 1997). In many cases, the reflexion pattern of the nodules is similar to that produced by cirrhotic liver, but in contrast to cirrhosis, the liver surface is smooth and free from the typical nodularity found in cirrhosis, and the coarsening or thickening of the lower edge of the liver is absent (Classen et al. 1970). By use of contrast-enhanced ultrasound (CEUS), distinct coral atoll-like lesions were detected in predisposed patients (Caturelli et al. 2011). Multiple small echogenic masses with occasional anechoic centers corresponding to hemorrhagic foci within the nodules may be encountered (Dachman et al. 1987). Radiologically, multiple small to medium-sized nodules and larger masses caused by conglomerate nodules on a background of a noncirrhotic liver are visible (Reynolds and Wanless 1984). The imaging features of multiple NRH lesions may mimic hepatic metastases (Clouet et al. 1999). These findings may be associated with splenomegaly and/or ascites on plain films or upper gastrointestinal series, and esophageal varices in barium studies, features of portal hypertension (Dachman et al. 1987). On CT images, the nodules are often hypodense without significant enhancement. The lack of enhancement is an important finding to distinguish NRH from large regenerative liver nodules which exhibit enhancement in a large proportion of cases (Ames et al. 2009). In a larger series, masses seen on CT images measured 0.2–10 cm in diameter, the latter representing conglomerate nodules (Dachman et al. 1987). Conglomerate lesions may produce a pseudotumoral aspect (Patriarche et al. 1988; Casillas et al. 1997). T1-weighted MR images of the liver show high-signal nodular lesions with central hypointense foci, while T2-weighted images reveal that the nodular lesions are isointense with central hyperintense foci (Siegelman et al. 1995; Horita et al. 2002; Wang et al. 2008; Leung et al. 2009). The nodules may take up technetium sulfur colloid (reviews: Dachman et al. 1987; Kobayashi et al. 2009). Angiographically, the findings were strikingly similar to what has been reported in cases of idiopathic portal hypertension (Shedlofsky et al. 1980). In splenoportography, an abrupt reduction in the contrast density of the smallest hepatic branches was seen, typical for a block at the level of hepatic microcirculation (Classen et al. 1970). Detection in intranodular Kupffer cells with superparamagnetic iron oxide enhanced MR imaging is an important indicator that a nodule is regenerative rather than neoplastic (Kobayashi et al. 2009).

Pathology

Macroscopy

At autopsy, livers with NRH often show a smooth capsule, in contrast to cirrhosis. However, in cases with advanced disease and formation of conglomerate nodules, the macroscopic features may resemble liver cirrhosis, also on small biopsy samples (Fig. 1; Qizilbash and Castelli 1980). On cut surfaces the picture varies considerably, ranging from an apparently preserved lobular

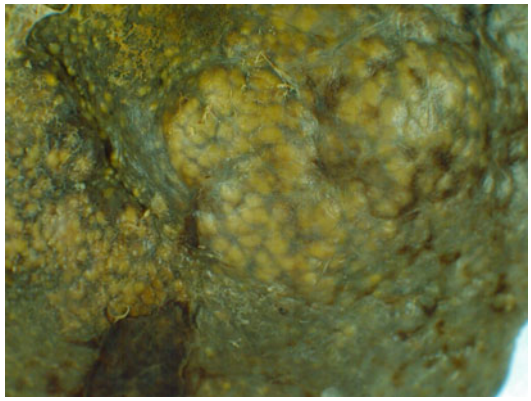

Fig. 1 Marked nodular regenerative hyperplasia of the liver

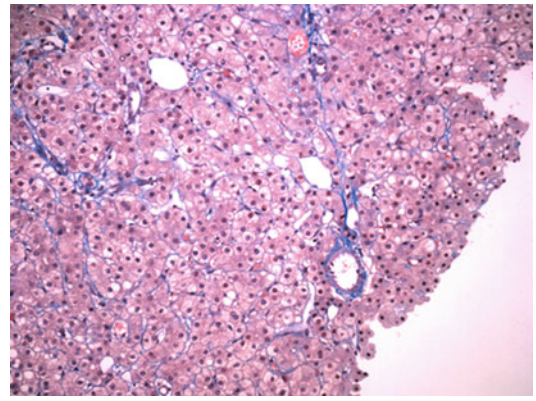

Fig. 3 Nodular regenerative hyperplasia of the liver. As seen in this collagen stain, the nodular lesion is not surrounded by fibrosis (CAB stain)

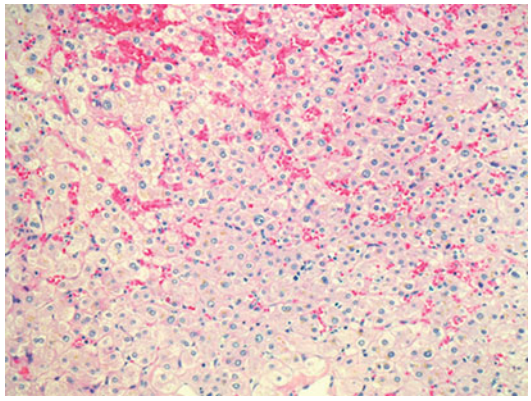

Fig. 2 Nodular regenerative hyperplasia of the liver. Hyperplastic areas show enlarged liver cell plates, darker cells and nuclear unrest (*center* of figure, hematoxylin and eosin stain)

architecture without visible nodular structures to multiple round to polygonal nodules, sometimes resulting in a picture resembling liver cirrhosis. The nodules typically measure 1–3 mm in diameter, but a macronodular aspect of the liver may also be found. In most instances, the nodules are more or less spherical, have a color identical or similar to the background parenchyma, and do not bulge from the cut surface. In contrast to cirrhotic nodules, the borders of the nodular structures are blurred or ill defined, because they are not delimitated by a fibrous shell (Stromeyer and Ishak 1981; Solis Herruzo et al. 1985; Wanless 1990; Forbes et al. 1991). Rarely, conglomerate nodules may be formed, resulting in lesions approaching 10 cm in diameter or even pseudotumoral presentation (Casillas et al. 1997). At abdominal surgery, granularity of the liver surface has been described (Blendis et al. 1970). Laparoscopically, histologically proven NRH grossly presented as a non-nodular undulated liver surface, a recognizable lobular pattern, and a hepatic consistency softer than normal to palpation (Cano-Ruiz et al. 1985).

Histopathology

The pertinent histological features of NRH have been described in detail (Weinbren and Mutum 1984). The salient presentation is that of well-circumscribed or vague hepatocyte nodules without associated fibrosis, whereby the nodularity is finer than the macroscopic appearance of granularity in cases of diffuse NRH (Figs. 2 and 3). NRH can develop in a focal pattern or may exist as diffuse NRH occupying the entire liver (diffuse regenerative hyperplasia, DNRH; Colina et al. 1989), depending on the underlying causes. The diameter of the nodules ranges from minute spherical hepatocyte clusters that may not be seen easily without a reticulin stain to macronodules that can be seen with naked eye (Trenschel et al. 2000). The hepatocyte plates within the nodules exhibit a characteristic thickening, the plates having three or four rows instead of two.

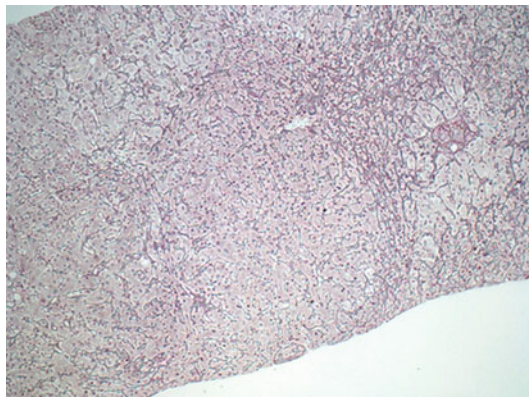

Fig. 4 Nodular regenerative hyperplasia of the liver. The nodular lesion is best visualized in reticulin stains (*middle* of figure; Gomori silver stain)

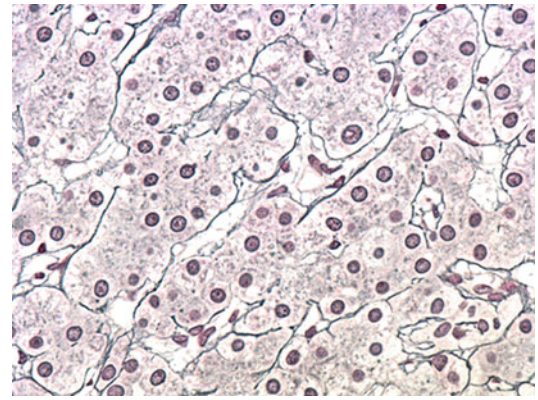

Fig. 6 Nodular regenerative hyperplasia of the liver. In this reticulin stain, an enlargement of hepatocyte plates (more than two cells in width) is seen (Gomori silver stain)

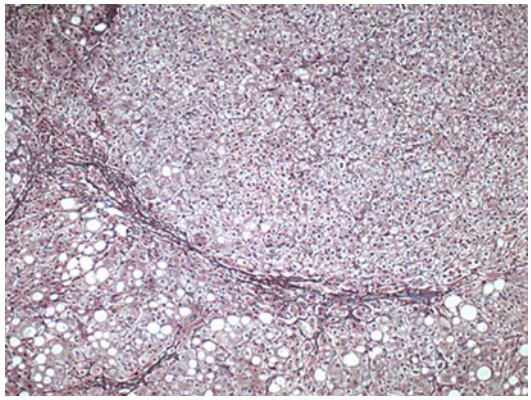

Fig. 5 Nodular regenerative hyperplasia of the liver may induce compression of adjacent liver tissue and condensation of reticulin fibers (Gomori silver stain)

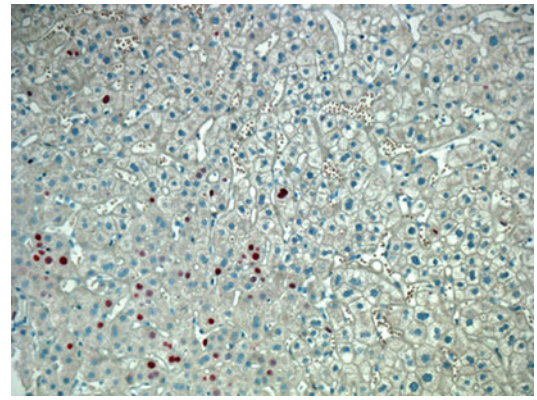

Fig. 7 Nodular regenerative hyperplasia of the liver. In areas with hyperplasia, hepatocytes exhibit an increased proliferative activity (*left half* of figure; MIB1 immunostain)

This feature is particularly well visualized in a reticulin stain (Figs. 4, 5 and 6). Thick hepatocyte plates are a constant and striking feature and represent the result of regenerative cell proliferation (Fig. 7; Weinbren and Mutum 1984). Within the nodules and their conglomerates, sinusoids are commonly narrow and the number of branches of the hepatic vein are reduced. Portal tracts may be trapped within nodules, producing a pattern of reversed lobulation, but this a rather rare finding. Portal tracts entrapped within regenerative nodules may show a mild lymphocytic infiltration and some fibrosis, even with incomplete septa. Obliterative portal phlebopathy may be in evidence (Nakanuma et al. 1996). Typically, the parenchyma adjacent to the nodules reveals a preserved lobular architecture, i.e., without any cirrhotic remodeling, but it manifests varying degrees of atrophy, with compression and thinning of hepatocyte plates, best seen in reticulin stains. Due to the expansion of nodules, the reticulin network is compressed and therefore more dense, a feature that has not to be confounded with true fibrosis. In and around the nodules of NRH, sinusoids may be significantly dilated in the absence of a hepatic venous outflow disorder (Kakar et al. 2004). Sinusoids of livers with NRH may contain increased

numbers of lymphocyte. CD8+ cytotoxic T lymphocytes were detected in 14 of 44 NRH patients. The cells were located near atrophic liver cell plates. Significantly more granzyme B+ and CD57+ lymphocytes were observed in NRH than chronic hepatitis C samples with quantitatively similar CD8+ lymphocyte infiltrates. It was suggested that CD8+ cytotoxic cells may damage sinusoidal endothelial cells and participate in the pathogenesis of NRH (Ziol et al. 2004). NRH may be associated with other histological liver alterations, depending on the type of underlying disease. In certain hematologic disorders, including myeloproliferative syndromes, obliterative portal venopathy is found in association with NRH (Wanless et al. 1980). NRH occurring in the setting of primary hypogammaglobulinemia was often associated with accumulation of lymphocytes in hepatic sinusoids (Malamut et al. 2008).

Immunohistochemistry

In one report, periportal immunostaining of hepatocytes for alpha-1-antitrypsin was more frequent in biopsies showing NRH than in non-NRH samples, suggesting that this staining may be useful in confirming the needle biopsy diagnosis of NRH (Nakhleh and Snover 1988).

Causes of Nodular Regenerative Hyperplasia

The causes of NRH cover a broad spectrum. Many if not most causative factors operate through a pathway involving vascular damage. The mode of progression or the reversibility of NRH are currently unknown. Known causes and associations of NRH are compiled in Table 1.

Drugs

Drug-induced NRH is common form of this disorder, probably amounting to more than 60 % of cases (Colina et al. 1989; Ghabril and Vuppalanchi 2014), but the underlying cause is

Table 1 Known causes and associations of nodular regenerative hyperplasia

Autoimmune and related disorders
Rheumatoid arthritis
Felty's syndrome
Systemic lupus erythematodes (SLE)
Sclerderma
Sjögren's syndrome
Polyarteritis nodosa
Immune complex-induced microvasculitis
Mixed cryoglobulinemia
Inflammatory bowel disease (IBD)
Celiac disease
Primary biliary cirrhosis (with or without CREST)
Antiphospholipid syndrome
Membranous and membranoproliferative glomerulonephritis
Drugs (mostly used as immunosuppressants)
Vascular disorders of the liver
Portal vein agenesis
Portal vein thrombosis and other obliterative lesions (portal obliterative venopathy)
Patent ductus venosus
Congenital extrahepatic portosystemic shunts
Veno-occlusive disease
Budd-Chiari syndrome
Hepatic arteritis/vasculitis
Hereditary hemorrhagic telangiectasia
Hematologic disorders
Acute leukemias
Myeloproliferative disorders
Non-Hodgkin's lymphomas
Hodgkin lymphoma
Castleman's disease
Hypereosinophilic syndromes
Aplastic anemia
Immunodeficiency syndromes
Hypogammaglobulinemia
Solid organ and cell transplantation (post-transplant NRH)
Liver transplantation
Renal transplantation
Bone marrow transplantation
Infections
HIV infection
Tuberculosis
Hepatic granulomatous disorders
Sarcoidosis
Microcirculatory disorders caused by hepatic tumors or metastases
Thorotrastosis

(*continued*)

Table 1 (continued)

Inborn errors of metabolism
Cystinosis
Hyperhomocysteinemia
Krabbe's disease
Other congenital disorders
Turner syndrome
Multiple malformations
Familial pulmonary fibrosis
Familial nodular regenerative hyperplasia

often the disorder treated with the implicated drugs. In fact, the drugs involved are mostly immunosuppressive agents used in the treatment of autoimmune disorders, inflammatory bowel disease and transplantation, and agents employed in cancer chemotherapy.

Classical thiopurines (azathioprine and 6-mercaptopurine) are commonly used as immunosuppressants in transplanted patients and patients with inflammatory bowel disease (IBD), in both Crohn's disease and ulcerative colitis. Hepatotoxicity is considered to be a relatively rare adverse event and is generally characterized by an increase in routine liver test parameters without clinical symptoms and signs. However, azathioprine (AZA) is well documented to cause NRH as a hepatic side effect (Duvoux et al. 1991; Mion et al. 1991; Russmann et al. 2001; Daniel et al. 2005; Seiderer et al. 2006; Schumann et al. 2008; Blogowski et al. 2011; Seksik et al. 2011; review: Musumba 2013). Male gender seems to be a major risk factor by providing a predisposing pharmacogenetic profile of purine analogue metabolism (Daniel et al. 2005). Several studies have shown NRH in IBD patients treated with AZA (Ehmsen et al. 2008), but has also been found in other disorders treated with this agent, including multiple sclerosis (Mion et al. 1991). In patients with inflammatory bowel disease treated with AZA, NRH is however an uncommon complication. In a study of 1888 consecutive IBD patients treated with AZA, the cumulative incidence of NRH was 1.28 % at 10 years (Seksik et al. 2011). A vascular effect may be involved in AZA-induced NRH, as NRH has been found in association with veno-occlusive disease in one patient with AZA-treated ulcerative colitis (Russmann et al. 2001).

NRH has been reported as a complication of 6-thioguanine therapy, both when used as a cancer therapy agent and as an immunosuppressive agent. In IBD patients, NRH has been increasingly found in azathioprine- or 6-mercaptopurine-intolerant patients using 6-thioguanine as a rescue drug (Shepherd et al. 1991; Dubinsky et al. 2003; Geller et al. 2004; Shastri et al. 2004; de Boer et al. 2005; Seiderer et al. 2005; De Bruyne et al. 2006; Ravikumara et al. 2006; Ferlitsch et al. 2007; Teml et al. 2007). 6-thioguanine is closely related to 6-mercaptopurine and azathioprine and has principally been used in the treatment of hematological malignancies. It has been reported to cause hepatocyte damage and necrosis and veno-occlusive disease, the latter being the most characteristic hepatic side effect caused by 6-thioguanine. The prevalence of NRH in patients treated with 6-thioguanine varies considerably, being 27.1 % (Teml et al. 2007), 39 % (Zech et al. 2007), and 76 % of patients undergoing liver biopsy in a group of IBD patients with hepatic laboratory abnormalities (Dubinsky et al. 2003). Among patients with inflammatory bowel disease treated with 6-thioguanine, 53 % of those who had a liver biopsy showed NRH in the reticulin stain, whereas only 11 % of the NRH cases were identified in H&E sections (Geller et al. 2004). It was proposed that NRH in the setting of 6-thioguanine therapy may well be dose or level dependent, NRH being less common under low-dose therapy. In a prospective multicenter study of inflammatory bowel disease patients using low-dose 6-thioguanine for at least 30 consecutive months, 28 liver biopsies were analyzed. In 93 % of biopsies, no signs of NRH were found, and in 2 patients the findings were not conclusive (de Boer et al. 2008a). On the other, NRH also develops in thiopurine-naïve patients with inflammatory bowel disease. In one study having analyzed 83 liver specimens (61 % of them from Crohn's disease patients), NRH was observed in 6 % of the samples, suggesting that NRH is occurring in IBD without specific therapy (de Boer et al. 2008b).

NRH occurs in patients with colorectal carcinoma liver metastases treated with cycles of neoadjuvant 5-fluorouracil and oxaliplatin before major liver surgery (Hubert et al. 2007; van den Broek et al. 2009; Wicherts et al. 2011; Morris-Stiff et al. 2014). Pathogenetically, a disturbance of hepatic microvascular circulation caused by chemotherapeutic agents may be considered. It was found that patients treated by oxiplatin more often had NRH compared with oxiplatin-naïve patients with metastatic colorectal cancer (Wicherts et al. 2011). Oxaliplatin-based chemotherapy has been shown to cause severe hepatic sinusoidal obstruction (the so-called sinusoidal obstruction syndrome; Arotçarena et al. 2006; Rubbia-Brandt et al. 2006; Rubbia-Brandt et al. 2010), and microvascular hepatic changes were found to be significantly associated with oxiplatin therapy in patients with metastatic colorectal cancer (Ryan et al. 2010).

Cytosine arabinoside and daunorubicine used for leukemia treatment has caused NRH (Rosen et al. 1991). Transcatheter arterial embolization therapy of hepatocellular carcinoma can be followed by NRH due to disturbance of vascular supply (Kobayashi et al. 1993).

NRH is observed in HIV-infected patients (Fernandez-Miranda et al. 1993; Arey et al. 2007; Tateo et al. 2008; Bihl et al. 2010; Kochin et al. 2010) and is thought to be related to antiretroviral drugs, e.g., ART therapy and IL-2 therapy, probably caused by the known capillary toxicity of high-dose IL-2 leading to decreased hepatic sinusoidal blood flow in murine models (Podevin et al. 2006; Arey et al. 2007; Sandrine et al. 2007; Maida et al. 2008). Didanosine therapy is implicated in HIV-associated NRH (Sood et al. 2014). NRH in HIV-infected patients seem to be related to age and the cumulative exposure to nucleoside and nucleotide analogues (Cotte et al. 2011).

Autoimmune and Related Disorders

NRH develops in several collagen vascular disorders and has been found in rheumatoid arthritis (Rauström 1953; Harris et al. 1974; Reynolds and Wanless 1984; Goritsas et al. 2001; Ebert and Hagspiel 2011) and in patients with Felty's syndrome (Ellman et al. 1955; Blendis et al. 1974, 1978; Reisman et al. 1977; Belaiche et al. 1978; Guarda and Hales 1981; Thorne et al. 1982; Young et al. 1992; Moots et al. 1994). Rheumatoid vasculitis accompanying these disorders seems to play a significant role in pathogenesis (Young et al. 1992). Several reports document the development of NRH in patients with systemic lupus erythematosus /SLE (Kuramochi et al. 1982; Klemp et al. 1986; Perez Ruiz et al. 1990; van Hoek 1996; Matsumoto et al. 2000; Horita et al. 2002; Park et al. 2006; Leung et al. 2009; Vaiphei et al. 2011; Grover et al. 2014). In an older study of 33 histologically proven cases of SLE, the spectrum of liver diseases included cirrhosis, but not NRH (Runyon et al. 1980). Pathogenetically, vasculitic changes induced by SLE may be considered. Some reports document NRG in the setting of systemic sclerosis (Friguet et al. 1984; Matsumoto et al. 2000) and Sjögren's syndrome (Gonzalez-Alvaro et al. 1994). Also the rare instance of NRH associated with mixed cryoglobulinemia, cryoglobulin-induced obliterative vasculitis may be pathogenetically involved (Garcia Buey et al. 1987).

NRH was observed in association with hepatobiliary autoimmune disorders. Numerous observations document the association between NRH and primary biliary cirrhosis, a disorder rather often associated with portal hypertension already in early-stage disease (Kew et al. 1971; Lebrec et al. 1976; Nakanuma and Ohta 1987; Nakanuma et al. 1989; Castellano et al. 1992; Sasaki et al. 2006). In part of the patients, CREST syndrome was found in association with NRH and primary biliary cirrhosis, suggesting an overlap syndrome (McMahon et al. 1989; Riviere et al. 2010). Patients with autoimmune disorders and other diseases of the bile duct system undergoing liver transplantation may present with portal hypertension already in the precirrhotic stage of liver disease. A study of 306 liver explants of such cases has shown that NRH is a major cause of this form of portal hypertension; in patients in whom portal hypertension was the major

indication for OLT, NRH was detected in 73 % and obliterative portal venopathy in 55 % of explants (Abraham et al. 2006).

NRH has been found in association with mesangiocapillary glomerulonephritis and idiopathic membranous glomerulonephritis (McCulloch et al. 1981; Haratake et al. 1987; Haboubi et al. 1991).

Antiphospholipid Syndromes

IgG and IgA antiphospholipid syndromes (APS) are systemic autoimmune disorders characterized by the combination of arterial and/or venous thrombosis, thrombocytopenia, and presence of antiphospholipid antibodies in serum. Antiphospholipid antibodies (aPL) form a heterogeneous group of circulating autoantibodies found in the sera of healthy individuals and patients with autoimmune and infectious diseases. aPL are directed against anionic phospholipids or protein/phospholipid complexes, usually containing beta2-glycoprotein I or prothrombin, but also other proteins involved in coagulation, including protein C, protein S, and annexin V. Several reports document the association of APS and NRH (Keegan et al. 1994; Cadranel et al. 1996; Perez-Ruiz and Zea-Mendoza 1998; Klein et al. 2003; Gaya et al. 2005). An association between NRH and circulating aPL was also observed in patients with systemic lupus erythematosus and suggested to play a role in the pathogenesis of NRH of the liver, probably via thrombotic obliterative changes taking place in small portal vein branches (Perez Ruiz et al. 1990). Part of HIV-infected patients show acquired autoimmune protein S paucity and secondary thrombophilia, associated with obliterative portal venopathy and NRH (Mallet et al. 2009).

Vascular Disorders of the Liver

NRH can develop in several types of portal venopathies. It has been found in portal vein thrombosis (Fukai et al. 1992; Terayama et al. 1995) and portal obliterative venopathy associated with myeloproliferative syndromes (Wanless et al. 1980; Wanless 1987). In a study of 64 NRH cases detected among 2500 autopsies, obliteration of many small portal veins was seen in all cases, but only 4.7 % of these had evidence of portal hypertension (Wanless 1990). Several studies reported on the development of NRH in congenital absence of the portal vein (Arana et al. 1997; Tanaka et al. 2003; Tsuji et al. 2005; Peker et al. 2009). Congenital absence of portal vein occurs in association with other hyperplastic hepatic lesions, specifically focal nodular hyperplasia/FNH (De Gaetano et al. 2004; Schmidt et al. 2006). Hepatic nodular lesions corresponding to NRH were seen in patients with patent ductus venosus (Kim et al., 2004a) and congenital extrahepatic portosystemic shunts (Abernethy type 2 malformation; Lisovsky et al. 2011). Congenital portosystemic shunts can be associated with NRH (Pupulim et al. 2013). NRH was also observed in obliterative portal phlebopathy, e.g., induced by macroglobulinemia (Wanless et al. 1981). Extensive obliteration of portal vein branches by cancer cell emboli can cause NRH (Turk et al. 2013). NRH can develop in Budd-Chiari syndrome (Castellano et al. 1989; de Sousa et al. 1991; Rha et al. 2000). In a systematic study of Budd-Chiari syndrome based on 17 explanted livers, obstructive portal venopathy associated with NRH was a constant finding, supporting the view that Budd-Chiari syndrome is associated with complex disturbances of hepatic arterial and portal circulation and their sequelae (Cazals-Hatem et al. 2003). However, large nodular hyperplastic lesions, FNH-like nodules, and FNH are more common complications of Budd-Chiari syndrome than NRH. A well-established cause of NRH is veno-occlusive disease involving the small and terminal hepatic veins (Snover et al. 1989). NRH can occur in the setting of hereditary hemorrhagic telangiectasia (Wanless and Gryfe 1986; Scardapane et al. 2013).

Hepatic vasculitis may cause NRH, including polyarteriitis nodosa (Nakanuma et al. 1984; Matsumoto et al. 2000; Tanaka et al. 2012), vasculitis in collagen vascular disorders, in particular

SLE, but also vasculitis/hepatic arteritis in rheumatoid arthritis (Reynolds and Wanless 1984), Felty's syndrome (Reisman et al. 1977), and microvasculitis in idiopathic hypereosinophilic syndrome (Baker et al. 1991). Similar to other vascular disorders, blood vessel stenosis or obliteration in vasculitis is thought to promote a hepatocyte regenerative response.

Granulomatous Hepatitis

NRH is known to develop in the setting of sarcoidosis of the liver (Devaney et al. 1993), likely due to obliterative (granulomatous) microvascular alterations.

Hypogammaglobulinemia

NRH can occur in the setting of primary hypogammaglobulinemia, e.g., caused by common variable immunodeficiency (Ravindran et al. 1995; Smith et al. 1995; Arenillas Rocha et al. 2003; Carbone et al. 2005; Ward et al. 2008; Fuss et al. 2013), and has been described as the main liver disease in these disorders (Malamut et al. 2008). In a systematic study, NRH in primary hypogammaglobulinemia was histologically associated with lymphocytic intrasinusoidal infiltrate and was found in 87 % of the patients with a liver biopsy. As other patients without liver biopsy often showed cholestasis (52 %) and splenomegaly (46.5 %) it was expected that the prevalence of NRH in hypogammaglobulinemia is high throughout. An association with intrasinusoidal T cells, portal vein endophlebitis, autoimmune diseases, and peripheral lymphocytic abnormalities suggest an autoimmune mechanism for NRH in this setting (Malamut et al. 2008).

NRH in the Setting of Cell and Organ Transplantations

NRH can develop de novo in liver grafts (Gane et al. 1994; Devarbhavi et al. 2007). The development of NRH after orthotopic liver transplantation (OLT) has usually been ascribed to the use of azathioprine. However, there are also reports showing that NRH can emerge in OLT patients in the absence of azathioprine therapy. Fourteen patients of one study developed NRH 3 months to 11 years after OLT; a total of ten patients developed NRH within 4 years (early onset), and four other patients showed the alteration beyond 4 years of OLT (late onset). These patients may later develop portal hypertension. A total of seven symptomatic patients, all in the early-onset group, had features of portal hypertension with vascular abnormalities on Doppler ultrasonography that were preceded by the diagnosis of NRH (Devarbhavi et al. 2007). At a certain stage, NRH occurring in the context of liver grafts becomes an irreversible lesion (gane et al. 1994). NRH has been observed in the setting of bone marrow transplantation (Pezzullo et al. 2000) and following renal transplantation, whereby azathioprine may play a role in at least part of the patients (Bredfeldt and Havey 1981; Morales et al. 1987; Buffet et al. 1988).

Hematologic Disorders

NRH occurs in the setting of various hematologic disorders (review: Al-Mukhaizeem et al. 2004). It can occur in reactive disorders such as aplastic anemia (Gonzalez-Huezo et al. 2006), but more commonly it develops in the setting of hematologic malignancies, including acute lymphoblastic leukemia (Mesa Latorre et al. 1990), myelofibrosis, polycythemia rubra vera, and other myeloproliferative syndromes (Shorey et al. 1979; Wanless et al. 1990; Al-Mukhaizeem et al. 2004). NRH occurring in myeloproliferative disorders may be caused by obliterative portal venopathy following venous thrombosis (Wanless et al. 1980). In myelofibrosis with hepatic extramedullary hematopoiesis, obstruction of small hepatic vascular channels by hematopoietic cells is thought to the pathogenic mechanism of NRH. A vascular pathogenic role is suggested by the observation of NRH in the setting of light

chain deposition in the liver in a patient with Waldenström's macroglobulinemia (Voinchet et al. 1988). NRH is a known complication of mastocytosis and is thought to be related to portal venopathy and veno-occlusive disease occurring in this disorder (Mican et al. 1995). NRH was also observed in patients with several types of Non-Hodgkin lymphomas, including macroglobinemia Waldenström and T-cell lymphomas, or with Hodgkin's disease (Wanless et al. 1981; Zuber et al. 1989; Gonzalez-Alegre et al. 2004; Kataoka et al. 2006; Ciria-Bru et al. 2014; Lopez et al. 2014). NRH was also found in association with Castleman's disease, with a possible pathogenic role of IL-6 (Kiyuna et al. 2005).

Gastrointestinal Disorders

NRH has been observed in children and adult patients with celiac disease and portal hypertension (Riestra et al. 2001; Biecker et al. 2006). IgA anticardiolipin antibodies were reported in celiac patients with NRH, suggesting a pathogenic role of these antibodies in celiac disease (Cancado et al. 2006). NRH can occur in the setting of Crohn's disease (Petrovic et al. 2011).

Hepatic Microcirculatory Disorders Caused by Tumors

Multiple hepatic metastases can compromise the microcirculation of the liver and induced NRH (Minato and Nakanuma 1992). NRH has been observed in a patient with an advanced carcinoid tumor, thought to be caused by vasoactive hormones secreted by the tumor followed by intrahepatic microcirculatory disturbances (Al-Hamoudi et al. 2009). In other situations, NRH associated with liver tumors, including hepatocellular carcinoma, may be caused by tumor treatment, in particular hepatic arterial infusion chemotherapy followed by vascular damage (Kobayashi et al. 1993).

Thorotrastosis

Thorotrast, following injection as contrast medium can damage portal vein radicles (Isner et al. 1978) and induce NRH (Dachman et al. 1987; Beer et al. 1998).

Infections

NRH was observed in association with subacute infectious endocarditis (Knowles et al. 1975) and following liver tuberculosis (Rougier et al. 1978; Boursier et al. 2005).

Congenital Metabolic Disorders

NRH can develop in patients with chronic granulomatous disease. In a study of 194 patients, NRH was seen in nine patients, including 6 of 12 autopsy specimens (Hussain et al. 2007). As venopathy of the portal vein was found in 80 % and venopathy of the central veins in 63 %, a vascular etiology of NRH has to be considered. Patients with cystinosis can develop noncirrhotic portal hypertension, mainly due to a sinusoidal block caused by accumulation of crystal-laden Kupffer cells in the sinusoids and deposition of collagens in Disse space (Klenn and Rubin 1994; DiDomenico et al. 2004; Rossi et al. 2005). But also NRH is a are late complication of cystinosis, with an undefined mechanism (O'Brien et al. 2006). NRH has been found in hyperhomocysteinemia associated with portal vein thrombosis and pronounced vascular lesions both in portal venules and in arterioles (Buchel et al. 2005).

Other Congenital Disorders

There are rare observations of NRH in the fetal liver, associated with severe malformations (Galdeano and Drut 1991). NRH can occur in patients with Turner syndrome, the pathogenesis being unknown (de Lédighen et al. 1994; Thevenot et al. 1998; Roulot 2013). There are

very rare instances of familial NRH (Albuquerque et al. 2013).

Pathogenic Pathways

Why Nodules

The pathogenesis of nodules in NRH has been discussed in detail (Reshamwala et al. 2006). For many cases of NRH, a common pathogenic pathway seems to involve hepatic obliterative vascular damage inducing a post-ischemic regenerative response of hepatocytes, although such vascular changes are lacking in other cases (Ibarrola and Colina 2003), rendering the definition of a common pathogenic pathway difficult. A blood vessel-based mechanism is rather well established for the microvascular vasculitis which often accompanies rheumatoid arthritis, Felty's syndrome, SLE, and other collagen vascular/immune-complex-mediated autoimmune diseases. But why should stenosing arterial lesions promote hepatocyte regeneration, as the hepatocyte parenchyma depends on portal blood flow, and not on hepatic arterial blood flow? Based on a morphometric study of the liver of a patient with rheumatoid vasculitis it was proposed that the arterial lesions caused secondary portal venous obliteration and portal hypertension followed by NRH (Reynolds and Wanless 1984).

Partial Nodular Transformation of the Liver

Introduction

Partial nodular transformation of the liver (PNTL) is a rare hepatic condition of still unknown pathogenesis, characterized by hepatocyte nodules that replace certain regions of the otherwise noncirrhotic liver. The perihilar region of the liver is predominantly affected, a but a subcapsular localization or a restriction to certain liver segments are also known. Many patients with PNTL have noncirrhotic portal hypertension and portal vein thrombosis.

Epidemiology and Clinical Features

In 1966, Sherlock and colleagues described four cases of a liver disease showing multiple hepatocyte nodules in the perihilar area of the liver associated with bleeding from oesophageal varices, the latter being caused by portal hypertension. The authors termed this constellation, partial nodular transformation of the liver/PNTL (Sherlock et al. 1966). In the following years, several other cases were reported (Maillard et al. 1967; Classen et al. 1970; Dick and Gresham 1972; Variend 1978; Donoso 1980; Fletcher and Wight 1980; Shedlofsky et al. 1980; Sansonno et al. 1981; Pedinelli et al. 1983; Terayama et al. 1995; Hoso et al. 1996; Takahata et al. 1997; Hytiroglou and Theise 1998; Simizu et al. 2006). PNTL is a rare disorder and an uncommon cause of noncirrhotic portal hypertension. In a study of 107 livers of patients with noncirrhotic, long-standing portal hypertension (92 wedge biopsies and 15 autopsy specimens), PNTL was found in only two cases and was much less common than NRH (Nakanuma et al. 1996). PNTL is often diagnosed at an early age and seem to be more common in females of childbearing age. In one review of the literature, the mean age at presentation was 35 years (Pedinelli et al. 1983), i.e., later then many types of liver cirrhosis. PNTL also develops in the pediatric liver (Tsui and So 1993). PNTL has been found in a patient with persistent ductus venosus and hypoplasia of the major intrahepatic portal veins (Wanless et al. 1985).

Pathology

Macroscopy

Patients with PNTL often show a grossly nodular region occupying the perihilar area, while more peripheral parts do not show nodular change. The diameter of the nodules ranges from a few millimeters to 4 cm. On cut surfaces of the liver, dilated vessels in the center of polygonal nodules may be seen, the adjacent parenchyma protruding above the periphery of the nodules (Classen et al. 1970). Typically, the parenchyma outside the nodular area does not show any nodular changes. Larger

nodules of the perihilar liver area may compress portal vein branches (Dick and Gresham 1972). However, other hepatic regions may also be involved, often with marked enlargement of the affected area, e.g., the caudate lobe (Fletcher and Wight 1980), and in some patients, nodules are mainly found in otherwise atrophic subcapsular parts of the liver. In PNTL, the extrahepatic portal vein usually exhibits evidence of old thrombosis, and distortions and stenosis of intrahepatic portal vein branches are often found. The extrahepatic portal vein can show wall thickening and calcifications, residual changes after organized thrombosis.

Histopathology

The regenerative nodules are composed of in part enlarged hepatocytes with irregular nuclei, liver cell plates often being thicker than two liver cells. Similar to NRH, the reticulin network may be compressed or condensed between nodules. The nodularity of the parenchyma causes an irregular arrangement of portal tracts, with abnormal portal tract spacing. Portal vein branches in nodular areas or in the vicinity of nodules may show intimal fibro-elastic thickening (Dick and Gresham 1972). Portal tracts with some fibrous extensions and abnormal vessels are often located in the centers of nodules, with a radiating arrangement of hepatocyte plates. Within the nodules, the number of branches of the hepatic vein are considerably reduced (Classen et al. 1970). Portal tracts situated in the perinodular tissue show minor degrees of ductular proliferation, caused either by compression of intrahepatic bile ducts by nodules, or by a progenitor cell reaction. In part of the cases, perihilar nodule formation is associated with portal tract fibrosis and septal fibrosis, causing interlaced "calloused" strands associated with some lymphocytic infiltration (Classen et al. 1970).

Differential Diagnosis

PNTL may histologically resemble nodular regenerative hyperplasia with a focal expression pattern, but nodules in PNTL are often larger than those in NRH and show a distinct spatial distribution pattern in the liver, e.g., with a perihilar predominance, or involvement of a segment or a lobe. Patients with noncirrhotic portal hypertension may, in the absence of clear-cut NRH or PNTL, show a vague nodular hyperplasia of hepatocytes not surrounded by fibrous septa, mainly in stages with subcapsular parenchymal atrophy (Nakanuma et al. 2001).

Is PNTL the Same Alteration as Incomplete Septal Cirrhosis of the Liver?

Incomplete septal cirrhosis (ISC) is an enigmatic disorder characterized by macronodular liver change and the development of fine, thin and incomplete septa taking their origin in portal tracts (review: Schinoni et al. 2004). Definition of ISC and the elucidation of its pathogenesis pose difficulties, because (1) ISC may be associated with other nodular liver lesions, including NRH, PNTL and some forms of true cirrhosis; (2) at least some ISCs may represent nonactive macronodular cirrhosis with signs of reversion of the cirrhotic process and vanishing of complete septa; and (3) different criteria and interpretations as to what ISC is have been formulated. In fact, it has been proposed that ICS is not a disease as such, but rather a stage of progression and regression of liver fibrosis (Schinoni et al. 2004).

In livers with ICS, abnormal spacing between portal tracts and veins, crowding of reticulin fibers between adjacent zones of hyperplastic parenchyma, and hepatocyte hyperplasia have been noted (Sciot et al. 1988), alterations known for nodular regenerative hyperplasia/NRH. Noncirrhotic nodular change with increased fibrosis of portal areas with the penetration of a few thin strands of connective tissue into the parenchyma and isolation of single nodules just under the liver capsule has been described in idiopathic portal hypertension (see below; Ziarkiewicz-Wroblewska et al. 2004). Such a nodular pattern resembles that of PNTL, which may also be associated with minor degrees of portal tract fibrosis. One may therefore consider that ICS, PNTL and

NRH share common pathogenic pathways, in particular hepatic vascular damage, and represent different manifestations of the same pathologic process.

Pathogenic Pathways

PNTL as a Disorder Caused by Vascular Abnormalities

It has been suggested that the pathogenesis of PNTL is similar to that of nodular regenerative hyperplasia (NRH) and focal nodular hyperplasia (FNH), i.e., a regenerative hepatocyte response in the vicinity of hypoperfused atrophic parenchyma (Wanless et al. 1985; Kondo 2001; Kondo et al. 2004). This suggestion is supported by the observation of portal vein thrombosis in the immediate vicinity of coalescent nodules at the liver hilus (Terayama et al. 1995) and by rare situations where PNTL and NRH synchronously develop in the same liver (Shedlofsky et al. 1980). Kondo (2001) developed the concept that congenital vascular anomalies are the origin of benign nodular hepatic lesions (the anomalous portal tract syndrome, APTS). It has later been proposed that the concept of APTS may be helpful in understanding the clinicopathological and radiological features of various hyperplastic liver lesions (Ueda et al. 2011). Irrespective of the concept of APTS, which implies a congenital base of vascular change, several acquired forms of obstructive vascular alterations, mainly of the portal vein system, have been implicated as a cause of nodular hyperplastic lesions of the liver. Slowly developing parenchymal ischemia not leading to acute mass necrosis or liver infarction is thought to be the driving force for the regenerative hepatocyte response. This is typically expected for obliterative portal venopathy. A postischemic pathogenic pathway may also be assumed for cases where PNTL emerges around intrahepatic portal venous emboli of tumors, e.g., hepatocellular carcinoma (Hoso et al. 1996). PNTL has also been observed in the setting of extrahepatic portal obstruction (Simizu et al. 2006). Why differ nodules in nodular regenerative hyperplasia/NRH from those in PNTL? It has been proposed that in NRH obliteration of small portal vein branches leads to uniform small hepatocyte nodules, whereas in most cases of PNTL portal vein thrombosis with irregular recanalization causes larger nodules often near large portal vein branches (Wanless et al. 1985).

One unresolved question is to explain why this hyperplasic response is nodular instead of diffuse or other patterns. As, in contrast to liver cirrhosis, the nodules developing in NRH, PNTL and FNH are not surrounded by fibrotic tissue, a scaffold effect exerted by extracellular matrix does not seem to be a likely pathway. A nodular hyperplastic response may, therefore, have several causes or combinations thereof, e.g., an effect reflecting the geometry of the damaged vascular network and its finest ramifications; the creation of an abortive, not well regulated liver lobule; or the outgrowth of clonal cells in the form of a nodular hepatocyte colony.

PNTL and Related Hepatic Hyperplastic Lesions as a Cause of Noncirrhotic Portal Hypertension

Banti, in 1889, published his research on splenomegaly and anemia, probably including a variety of disorders that we now classify as forms of cirrhosis with portal hypertension, and noncirrhotic portal hypertension (Banti 1889). Guido Banti (born 1852 in Montebicchieri; deceased 1925 in Florence, Italy) is considered to be the most eminent Italian pathologist of the early twentieth century who, in addition to histological works, published the first Italian textbook of bacteriological technique. From 1882 to 1904, Banti studied various forms of spleen enlargement, then called primitive splenomegalies (noninfectious splenomegalies). During these investigations, he found the intricate relationship between splenomegaly, anemia, and chronic liver disease, a constellation later termed Banti's disease or Banti's syndrome. These findings paved the way for the later understanding of portal hypertension, congestive splenic disease, and splenogenic hematological disorders, although Banti thought that this constellation was a primary splenic disorder, a view refuted by William Osler already in 1900 (Ravenna 1940; Costa 1958; Grannis 1975). In the sixties of the last century,

Indian investigators described a distinct group of adult patients having portal hypertension in the absence of liver cirrhosis (Ramalingaswami et al. 1962; Wig et al. 1966). In the same time period it was reported that patients with portal hypertension without cirrhosis can show concentric thickening or sclerosis of the portal vein and its radicles, a condition termed "hepatoportal sclerosis" (Mikkelsen et al. 1965). Boyer and coworkers identified patients having portal hypertension in the absence of liver cirrhosis and proposed the term "idiopathic portal hypertension" (Boyer et al. 1967). The authors compared patients with "idopathic portal hypertension" with those having cirrhosis or extrahepatic portal vein obstruction and found that patients with portal hypertension associated with hepatoportal sclerosis had a better prognosis. As suggested by the term "hepatoportal sclerosis," many cases of noncirrhotic portal hypertension were attributed to stenosing lesions of the portal vein and its large branches, but it later emerged that stenosing lesions in the hepatic microcirculation can cause, or be associated with, the same type of blood flow disorder, including the entire spectrum of hyperplastic lesions of the liver.

Serum Amyloid A-positive Hepatocellular Neoplasms/Nodules

Introduction

In patients with alcoholic liver cirrhosis, distinct hypervascular hepatocellular nodules or neoplasms resembling inflammatory hepatocellular adenoma (IHCA) were detected. These atypical nodules occurred more often in males than females, were multiple (more than 3 lesions) in all patients, and were serum amyloid A positive and in part CRP positive, thus resembling the phenotype of IHCA, but with certain differences (Sasaki et al. 2012, 2013, 2014). These nodules may coexist with focal nodular hyperplasia-like nodules in alcoholic cirrhosis, but these FNH-like lesions showed focal or no immunoreactivity for serum amyloid A (Sasaki et al. 2013). In small fraction (11.8 %) of serum amyloid A-positive nodules, STAT3 mutations were identified (Sasaki et al. 2014). These nodules developing in livers with alcoholic cirrhosis may represent a novel form of inflammatory hepatocellular neoplasm.

Pathology

Histologically, the nodules displayed a hepatocellular cell lineage, increased cellular density, inflammatory infiltrates, sinusoidal dilatation, arteries with abnormally thickened walls, variable ductular reaction, and positivity for serum amyloid A. In contrast to other hepatocellular neoplasms these nodules were negative for glutamine synthetase and glypican-3 (Sasaki et al. 2012). One serum amyloid A-positive abnormal nodule was CRP positive (Kim et al. 2004b).

Hypervascular FNH-Like Nodules in Alcoholic Liver Disease (ALD)

In patients with chronic alcoholic liver disease (ALD) and subsequent liver cirrhosis, distinct hypervascular nodules may develop, lesions that may be confounded with small hepatocellular carcinomas. In one type of such nodules, randomly distributed lesions measuring 9–21 mm in diameter were detected by ultrasonography during follow-up of cirrhosis as hypoechoic or isoechoic nodules, were high attenuated in early phase CT and iso attenuated in delayed phase (without wash-out in the venous phase), showed hypervascularity on angiography, and histologically shared features with focal nodular hyperplasia (Nakashima et al. 2004). Other types of hypervascular hepatic lesions occurring in ALD ("type 2") were described by Kim and coworkers (2004b). The authors found hypoechoic nodules measuring 2–4 cm in diameter that were isodense in early CT images, hypointense in T1-and T2-weighted MR images, and markedly hypervascular in angiograms. The differential diagnosis included HCC, FNH, and angiomatous tumors.

The nodular lesions described by Nakashima et al. (2004) were macroscopically encapsulated in part of the cases and showed scar-like fibrosis in

more than half of cases (one nodule with central stellate fibrosis). Histologically, the nodules were devoid of portal tracts but contained scar-like fibrotic tracts containing artery-like and vein-like anomalous vessels, and inflammatory cell infiltrate, and a ductular reaction along the interface of fibrotic tracts. Hepatocytes in the nodules showed iron overload, mainly in encapsulated nodules. Fatty change of Mallory-Denk bodies were not found. The lesions were interpreted as FNH-like nodules which are found in several types of liver cirrhosis (Nakashima et al. 2004). The lesions described by Kim and coworkers (2004b) either showed the histology of large hyperplastic hepatocyte nodules with hypercellularity and a trabecular pattern, or nodules showing fibrosis in the absence of hepatocyte hyperplasia, in part with stellate scar-like fibrosis, i.e., resembling FNH. It follows that larger hypervascular liver nodules developing in chronic ALD cover a spectrum of lesions ranging from hyperplastic nodules with increased vascularity to FNH-like lesions.

Regenerative Nodules in Alagille Syndrome

Introduction

Alagille syndrome (synonyms: arteriohepatic syndrome, arteriohepatic dysplasia, syndromatic hepatic ductular hypoplasia, Alagille-Watson syndrome) is a congenital mostly autosomal dominant disorder that manifests as cholestasis in infancy, related to progressive intrahepatic bile duct paucity. The syndrome is also characterized by a characteristic facies, vertebral malformations (butterfly vertebra), eye abnormalities (posterior embryotoxon), retarded physical, mental, and sexual development, and a mesosystolic murmur caused by pulmonary stenosis (Alagille et al. 1975). About 39 % of patients also have renal involvement, mainly renal dysplasia. Histologically, intrahepatic bile duct paucity and associated fibrosis increase with age and may result in secondary biliary cirrhosis (Emerick et al. 1999). Alagille syndrome is known to complicated by hepatocellular carcinoma (Rabinovitz et al. 1989; Le Bail et al. 1990; Perez Becerra et al. 1991), but also benign hyperplastic nodular lesions develop in this condition.

Alagille syndrome type 1 (ALGS1; OMIM 118450) is caused by mutations (haploinsufficiency) of the Jagged1/JAG1 gene located on chromosome 20p12.2. The JAG1 gene product is the ligand for the Notch receptor. Mutations in JAG1 can be found in more than 90 % of Alagille syndrome patients. ALGS2 (OMIM 600275) is caused by mutations in the NOTCH2 gene. Notch2 receptor mutations account for less than 1 % of Alagille syndrome patients. A very rare autosomal recessive variant of Alagille-like syndrome not related to a mutation of the JAG1 has also been reported (Dyack et al. 2007).

Regenerative Liver Nodules in Alagille Syndrome

A patient with Alagille syndrome died at age 17 years, autopsy showed liver cirrhosis and large hyperplastic liver nodule interpreted as a hamartoma resembling focal nodular hyperplasia/FNH (Nishikawa et al. 1987). A 6-year-old boy with liver cirrhosis caused by Alagille syndrome showed, on CT images, a high-density nodular lesion in the right liver lobe. In the liver explant of OLT, the nodular region was large and lobulated, clearly distinguished from the surrounding hepatic tissue. Histologically, the lesion consisted of hyperplastic hepatocytes (Torizuka et al. 1996). In a boy with ALGS1, pre-transplantation CT and MRI examinations revealed a large hepatic lesion associated with multiple small nodular lesions, representing hepatic nodular hyperplasia (Tajima et al. 2001). Hepatic hyperplastic changes were also observed in adults with ALGS1. Pseudotumorous hyperplasia of the caudate lobe has been found in an 31-year-old female patient with Alagille syndrome. The caudate lobe was increased in size (Tuset et al. 1995). Syed and coworkers (2008) reported the multimodality imaging features of two patients with Alagille syndrome and hepatic regenerative nodules. One patient had a lesion

with a diameter of 3.8 cm, while the second patient showed a mass of 10.5 cm diameter, illustrating that nodular regenerative lesions in Alagille syndrome can grow to large size and may be confounded with HCC.

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