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ORIGINAL ARTICLE

Liver pathology in collagen vascular disorders highlighting the vascular changes within portal tracts

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ABSTRACT

Background: Collagen vascular disorders (CVDs) are autoimmune disorders with multisystem involvement. Clinical liver involvement is not a characteristic feature though histological involvement could be frequent. Liver disease in CVDs could be the consequence of various factors. **Aim:** The aim was to analyze the histological spectrum of liver in collagen vascular disorders (CVDs) at autopsy. **Materials and Methods:** Thirty-six autopsy livers negative for hepatitis B or C virus were studied in CVD cases with no known association with chronic liver disease or vascular thrombosis or hematological disorder. Cirrhotic and normal livers were used as controls. The paired t-test, one-way ANOVA, and two-sided Dunnett t-test were used for comparison (< 0.05). None of the control cases showed any abnormal vessels. **Results:** There were 21 systemic lupus erythematosus (SLE), 7 rheumatoid arthritis (RA), 5 systemic sclerosis (SSc), and 3 polyarteritis nodosa (PAN) cases (M:F = 11:25, age range 23–60 years). Histology: Diffuse nodular regenerative hyperplasia of liver (NRHL) was seen in 10 cases, and 6 (5 SLE and 1 RA) had numerous abnormal thin-walled vessels in intermediate- and small-sized portal tracts with no vascular occlusion or inflammation. Moderate sized portal tracts showed more interface and lobular inflammation. The main portal vein and its major branches were normal. None of these six cases had increased transmainases (P>0.05). Most SLE cases had increased transaminases (P<0.05). No evidence of portal hypertension was seen in all except in one RA. Septicemia is known to be associated with raised transaminases. **Conclusion:** A rare pathology of conglomerate of abnormal vessels in intermediate- and small-sized portal system was observed co-existing with NRHL in CVDs. Raised liver enzyme with interface hepatitis in CVD may not necessarily warrant an overlap, as a similar feature could be observed in septicemia.

KEY WORDS: Autoimmune hepatitis, collagen vascular disorders, nodular regenerative hyperplasia of liver, portal hypertension, portal vein

INTRODUCTION

Collagen vascular disorders (CVDs) are autoimmune disorders with multisystem involvement. Clinical liver involvement is not a characteristic feature though histological involvement could be frequent.[1-3] Liver disease in CVDs could be the consequence of various factors such as fatty infiltration, drug toxicity, superadded infection by hepatotrophic viruses, vascular thrombosis, diabetes, or overlap with autoimmune hepatitis (AIH). Most CVD patients could develop a mild transient abnormal liver function test during the disease course.[1] Differentiating between liver involvement in CVDs and overlap syndrome with AIH could be difficult. Diagnosis of AIH could be suggested if the liver on histology shows dominant portal and periportal inflammation with less dominant lobular inflammation associated with marked hepatocyte rossetting.[4] CVD may coexist with primary biliary cirrhosis (PBC), AIH, and nodular regenerative hyperplasia of the liver (NRHL).[4-8] Medline search revealed one study in English where detail pathological analysis of liver in CVDs was carried out.[9] We retrospectively analyzed histological profiles of liver at autopsy in CVDs who terminally had pneumonia and succumbed to uncontrolled septicemia. Liver histology described in CVDs is mostly based on needle biopsy. We also observed histological changes in the intrahepatic portal vein which has not been described in CVDs before, though reported in idiopathic portal hypertension (IPH)[10] and noncirrhotic portal fibrosis (NCPF).[11]

MATERIALS AND METHODS

Autopsy cases diagnosed clinically as CVDs were retrieved from the departmental records over a period of 17 years. Cases with a history of any overt or chronic liver disease were excluded. Any case with one or more of the following were also excluded: (i) history of alcohol intake, (ii) documented infection by hepatotropic viruses based on the positive serological report or demonstration of viral particle

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by polymerase chain reaction (both HCV and HBV) and also by immunohistochemistry on paraffin sections using HBsAg and HBcAg, (iii) overt obesity or malnutrition, (iv) diabetes, (v) history of drug-related liver injury or hypersensitivity reaction established by the temporal relationship between the drug intake and onset of clinical symptom, (vi) history or presentation with a thrombotic episode including hepatic outflow tract obstruction or any primary hematological disorder, (vii) previous history of overt liver disease or abnormal liver enzymes to suggest an underlying chronic liver disease or autoimmune hepatitis (AIH),[4] or (viii) any malignancy. Diagnosis of each collagen vascular disease was established according to the criteria of American College of Rheumatology for systemic lupus erythematosus (SLE),[12] rheumatoid arthritis (RA),[13] polyarteritis nodosa (PAN),[14] and systemic sclerosis (SSc)[15] and Alarcon-Segovia diagnostic criteria for mixed connective tissue disease (MCTD).[16] Of 106 cases of CVDs at autopsy, 36 could be included in the study. Disease duration in these 36 cases ranged from 76 to 120 months. Terminally, all had hospital admission for pneumonia leading onto septicemia and death.

In each case, eight tissue blocks were sampled from different areas of liver so that any patchy morphological changes could be identified on histological examination. Sampling of blocks were as follows: one from hilum, one each from left and right lobes near hilum, three further down from the right lobe, and two from the left lobe. H and E, reticulin, elastic Van Gieson (EVG), and Masson's trichrome (MT) stains for connective tissue were used for baseline evaluation. Histochemistry for iron, PAS with diastase for any resistant material, Shikata orcein for copper-binding protein, and immunohistochemistry by the peroxidase–antiperoxidase (PAP) method for HBV surface and core antigens and CD34 (Dako, Denmark) were carried out. Histological parameters evaluated were as follows: (i) liver architecture, (ii) portal tract fibrosis and inflammation graded subjectively, (iii) lobular inflammation, (iv) changes in the hepatic artery, bile duct, and portal vein, (v) hepatocytes, Kupffer cells, and sinusoids, (vi) amount of iron, copper-binding protein, any diastase-resistant PAS-positive materials, (vii) hepatitis B surface and core antigens, and (viii) CD34-highlighting endothelial cells of abnormal vasculatures. Cases which showed abnormal vasculature in portal tracts were further subjected to serial sections to study the interrelationship between abnormal vasculatures and portal vein. The classification of the portal vein was done according to Nakanuma *et al.*:[17] (i) small portal vein refers to up to 300 μm, (ii) large portal vein refers to more than 2-mm-sized third or fourth branch of right and left portal veins in the normal liver, and (iii) medium size portal vein refers to an intermediate size vein between small and large ones. Parameters used to assess liver function were ALT, AST, conjugated and unconjugated bilirubin, and alkaline phosphatase (AP). To compare the abnormal vessels observed, two control groups were selected: (i) 20 cases of HBV-related liver cirrhosis with portal hypertension with no obstruction or thrombosis of portal or hepatic veins and (ii) 20 cases of the morphologically normal liver at autopsy. A minimum of five blocks were studied from cirrhotics and three blocks from the normal liver. All control slides for baseline histological analysis were stained with H and E and reticulin.

As the study has been done using postmortem liver tissue, getting an informed consent is not applicable to this study.

Statistical Analysis

Values were expressed as means ± SD. Different groups were compared by the *t*-test, one-way ANOVA and two-sided Dunnett's *t*-test. A *P*-value less than 0.05 was considered statistically significant.

RESULTS

Of the 36 cases studied, there were 21 (58%) with SLE, 7 (19%) with RA, 5 (14%) with SSc, and 3 (8%) with PAN. Eight (22%) cases had mild jaundice toward the end of their terminal illness and liver became just palpable in 7 (19%) of them. One RA case had evidence of portal hypertension at hospital presentation indicated by palpable spleen, ascites, and grade II esophageal varices. In 36 cases, investigations revealed elevated hepatic transaminases in 22 (61%), and 13 (36%) had more than twice the normal level of ALT (normal < 40 U/L) and AST (normal < 30 U/L). AP was elevated in 16 (44%, normal < 9.9 KA), and was more than twice the normal level in 8 (22%) cases. Bilirubin was elevated in 16 (44%), with half of them having mild clinical jaundice [Table 1].

The gross liver weight ranged from 1170 to 1450 g (mean = 1290 g); in females it ranged from 1170 to 1320 g with a mean of 1210 g and in males it ranged from 1230 to 1450 g with a mean of 1350 g. Ill-formed nodules with incomplete fibrous septation were observed in SSc and 7 of the 36 (19%) cases showed exaggerated mottling. The liver appeared pale and fatty in 17 (47%) cases. A large scar was noted along the major portal tract in PAN cases, one with fibrin thrombus and extensive hepatocyte necrosis. RA with portal hypertension had mildly dilated portal vein. A variable degree of lobular disarray was present in all 36 cases. There were 10 (28%) cases with diffuse NRHL comprising 9 SLE and 1 RA (with portal hypertension). The liver showed micronodules measuring 2–4 mm with no fibrous septation. They were well visualized under low power in H and E- and reticulin-stained sections [Figure 1a and b]. Some portal tracts had mild-to-moderate chronic inflammatory cell infiltration with occasional bridging fibrosis. A total of 6 of 10 cases (60%) with NRHL comprising 5 SLE and 1 RA had portal tract expansion by numerous abnormal thin-walled vascular channels. These vascular channels were seen involving about 40% of intermediate- and small-sized portal tracts entrapping bile ducts and hepatic arteries with a variable amount of collagen in between [Figures 2a]. These vessels had no or just a thin layer of smooth muscle cells, occasional ones with early intimal plaque [Figure 2b]. The EVG section revealed a thin rim of elastic fiber at the periphery of the vessels and intervening stroma displaying abundant elastic tissue. Larger ones could be seen under low power and

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Table 1: Distribution of cases in the four groups highlighting number of cases with increased ALT, AST, alkaline phosphates, and bilirubin levels

	*SLE (21)**	*PAN (3)**	*SSc (5)**	*RA (7)**	*Total (36)**
Sex					
Male	4	3	1	3	11
Female	17	–	4	4	25
Age range (years)					
Male	26–44 (mean = 35.25)	30–39 (mean = 35.33)	40	44–60 (mean = 52.67)	24–60 (mean = 39)
Female	23–45 (mean = 32.8)	–	31–59 (mean = 42.25)	45–58 (mean = 51.25)	23–59 (mean = 37.26)
ALT					
Increased level	17	3	1	1	22
>2 times normal	11	1	–	1	13
AST					
Increased level	16	2	1	1	20
>2 times normal	11	1	–	1	13
AP					
Increased level	11	2	2	1	16
>2 times normal	4	2	2	–	8
Increased level of total bilirubin	11	2	2	1	16
Clinical jaundice	6	1	–	1	8

*Figures within parentheses indicate the number of cases for each group. >2 times normal = more than twice the normal level. PAN - Polyarteritis nodosa, SLE - Systemic lupus erythematosus, SSc - Systemic sclerosis, RA - Rheumatoid arthritis

Table 2: Distribution of NRHL, abnormal portal vasculature, other histological parameters, and liver enzyme levels in the four groups

	*SLE (21)**	*PAN (03)**	*SSc (05)**	*RA (07)**	*Total (36)**
NRHL	9	–	–	1	10
Abnormal vessels in portal tracts	5	–	–	1	6
Portal tract inflammation	14	2		2	18
Mild	6	1	–	1	8
Moderate	8	1		1	10
Lobular inflammation	6	1	–	–	7
Interface hepatitis	9	1	–	1	11
Periductal fibrosis	3	–	1	1	5
Portal tract fibrosis	16	1	5	5	27
Bridging fibrosis	9	–	5 (1 with incomplete biliary cirrhosis)	3	17
Number of cases with >2 ALT/AST levels	7	–	–	1	8

*Figures within parentheses indicate the total number of cases studied. NRHL = nodular regenerative hyperplasia of liver. PAN - Polyarteritis nodosa, SLE - Systemic lupus erythematosus, SSc - Systemic sclerosis, RA - Rheumatoid arthritis

smaller ones could only be seen under high power. Some portal tracts had hundreds of these abnormal vasculatures. They were well within the lamina limitant except a very occasional one extending just beyond the lamina limitant into the adjacent hepatic lobule. Lining endothelial cells were positive for CD34 on immunohistochemistry. Involved portal tracts were scattered in many foci, contiguous in a small area and were well away from the hilum. Large portal tracts did not have these abnormal vessels. The main portal vein and its right and left branches were normal except in RA with portal hypertension. LFT in these six cases did not show any significant difference from the rest (*t*-test, $P > 0.05$) [Table 2].

Portal tract fibrosis with bridging was observed in 75% (27 of 36) including cases with NRHL. It was not a dominant feature and appeared similarly distributed between NRHL and none NRHL. The inflammation of the portal tracts was seen in 50% (18 of 36), mild in 8 and moderate in 10 cases. Mild interface hepatitis was seen in 31% (11 of 36) with small foci of lobular inflammation in 20% (7 of 36) with moderate portal tract inflammation. Inflammatory cells were mainly lymphocytes and plasma cells admixed with neutrophils and few eosinophils. None had lymphoid follicle, bile duct epithelial cell injury, plasma cell dominant infiltration, or hepatocyte rosette formation. There was Kupffer cell hyperplasia, sinusoidal neutrophil infiltration, a variable degree of micro- and macro-vesicular fatty changes and perivenular sinusoidal congestion. Mild intracytoplasmic and occasional intracanalicular cholestasis was present in zone 2 and 3. Terminal portal tracts were fibrotic with no or mild chronic inflammation suggesting an obliterative fibroinflammation. There was mild excess of iron in hepatocytes and Kupffer cells, with no increase in the copper-binding protein or PAS-positive hepatocytic granules. PAN showed ecstatic recanalized thrombosed vessels with perivascular collagenization, with one case showing marked centrizonal hepatocytic necrosis [Figure 3].

ALT and AST (*t*-test, $P<0.05$) and AP (*t*-test, $P > 0.05$) were higher in cases with portal tract fibrosis than without. Mean

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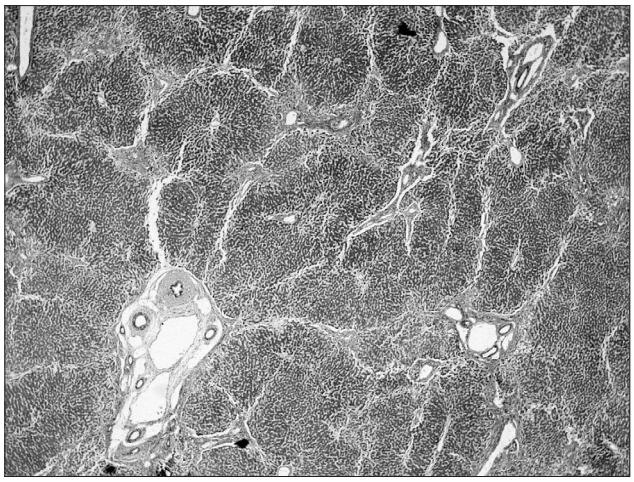

Figure 1a: Low power photomicrograph of liver to show multiple small uniform sized regenerative nodules with no fibrous septa and expanded portal tracts with obviously dilated portal veins. (H and E, ×50).

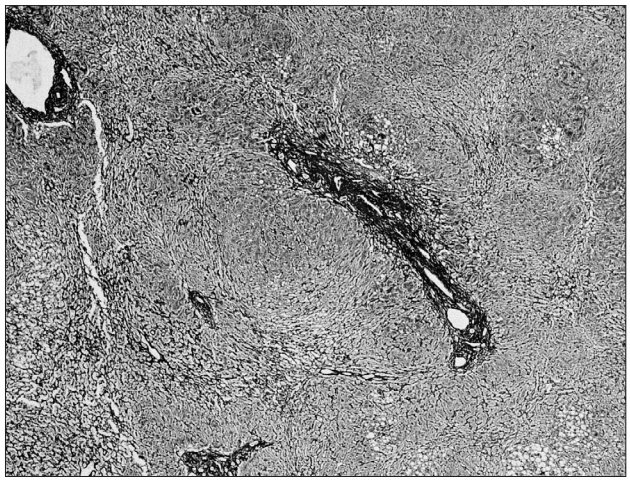

Figure 1b: Low power photomicrograph of liver to show multiple small uniform sized regenerative nodules with obviously absent fibrous septation. (Reticulin, ×140).

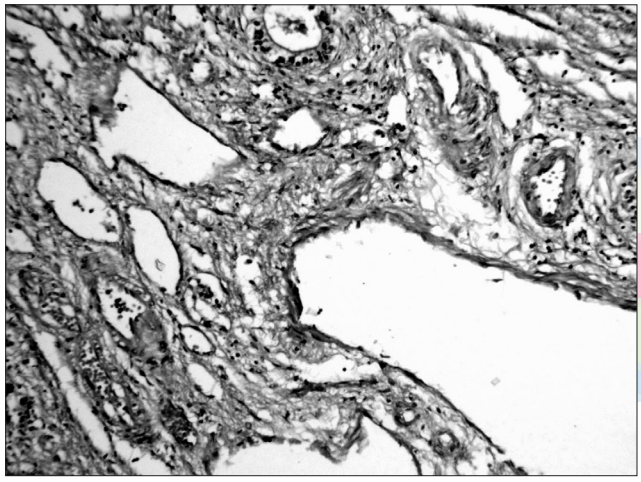

Figure 2a: Medium power view of an expanded intermediate sized portal tracts with innumerous thin walled portal veins. (H and E, ×440).

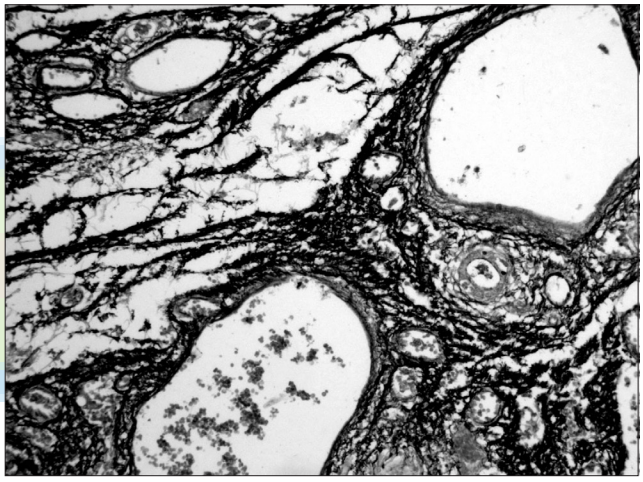

Figure 2b: Another view of portal vessels to highlight the early intimal plaque formation in some of the portal veins and sparse inflammatory cells. (EVG, ×440).

ALT, AST, and AP levels were higher with interface hepatitis and lobular inflammation than only interface hepatitis or lobular inflammation (*t*-test, $P < 0.05$). Of the 10 cases with NRHL, ALT, AST, and bilirubin were elevated in 7 (19%) and AP in 9 (25%). Comparing the age factor, RA had a higher mean than SLE and PAN (ANOVA, $P < 0.005$). SLE had a lower mean with female dominant (*t*-test, $P < 0.001$). ALT and AST were higher in SLE and PAN than RA and SSc but not between SLE and PAN or PSS and RA (ANOVA). AP did not differ significantly in any of the groups. In group statistics, sex did not have any influence on age, ALT, AST, bilirubin, or AP (*t*-test, $P > 0.05$).

Control cirrhotics showed gross disorganization of the normal lobular architecture and variable thickness of fibrous septa. None showed any abnormally proliferating vascular structures as observed in the study group. The normal liver did not show any abnormality in the portal tract.

DISCUSSION

CVDs have frequent subclinical liver disease with variedly raised liver enzymes.[1-3] Reported incidences of palpable liver in CVDs range from 12% to 55%[18-20] with an incidence of 19% (7 of 36) in the present study. We had more cases with elevated transaminases than in reported series.[1-3] This could be due to difference in the patient population where we had terminally ill patients with septicemia, and in quoted series, the presenting problem was either arthritis or unexplained prolonged fever. Many studies have attributed septicemia to deranged liver function.[21-25] Septicemia though could explain abnormal LFT, interface hepatitis, and lobular inflammation observed in our cases cannot be explainable only by septicemia. Clinically, inactive CVDs have frequently been observed to have subclinical liver involvement.[1-3] More recently, liver involvement in SLE is considered to have more clinical significance.[20] Elevated liver enzymes were observed

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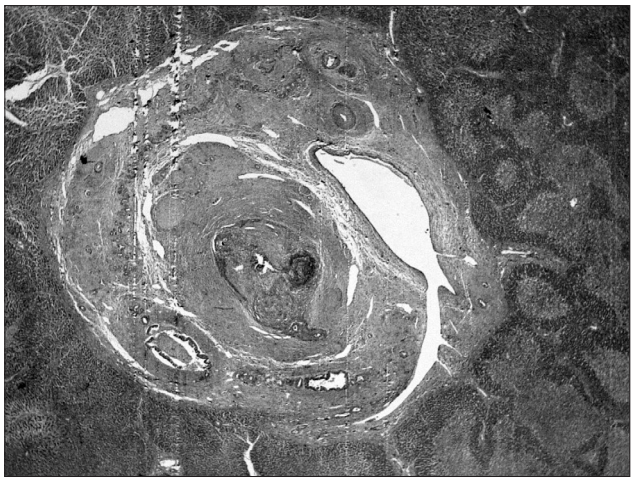

Figure 3: Low power photomicrograph showing a grossly expanded and fibrotic portal tract with a thrombosed hepatic artery and centrizonal necrosis. (H and E, ×140)

81% (17 of 21) and palpable liver was observed in 33% (11 of 21) in our SLE cases compared to reported 55%[26-30] and 35%,[20,27,30] respectively. The subclinical overlap cannot be ruled out in our cases based on serology alone, as many markers are common for both. Histology is an important feature in the diagnosis of AIH. Differentiating features for AIH from SLE-related liver disease are heavy portal and periportal lymphoid inflammation, hepatocyte pseudorosette, and dominant portal tract plasma cell infiltration in AIH and heavier lobular inflammation in SLE.[27] None of our cases had all these features to suggest AIH though autoantibody-negative clinically silent AIH with interface hepatitis has been reported.[28-30] Though the possibility of the overlap cannot be excluded, none of our cases had history of chronic liver disease.

NRHL is a well-known feature in CVDs with a hypothetical etiopathogenesis. Number of SLE cases with NRHL in our cases were higher than the reported series.[31,32] Increasingly, NRHL is reported with CVDs, many with portal vein occlusion,[33] which was not the situation in our cases. Etiopathogenesis for NRHL in SLE is an immune complex deposit in small vessels resulting in obliterative venopathy.[34,35] Obliterative fibroinflammation of the terminal portal tract was observed in all our NRHL cases. Similar cases to our one RA, portal hypertension and NRHL have been reported in Felty's syndrome.[31,32] Noncirrhotic portal hypertension (NCPH) has been reportedly more common in the Indian subcontinent.[36] Except one RA case, our cases with NRHL did not have portal hypertension. Nakanuma *et al.*[17] analyzed livers from IPH patients and described the presence of a dilated single vessel adjacent to the portal tract and fibrous septa. He described it as either a dilated portal vein herniating into the hepatic lobule or dilated parenchymal veins clustering within the hepatic lobule. These histological features were different from our cases with numerous abnormal vessels within portal tracts. Focal or diffuse regenerative liver nodules in IPH are described as the effect of either thrombosis or vasculitis in the portal vein and its major branches.[37-39] The high incidence of IPH associated with CVDs has been documented by Japanese groups.[10,36,37,39] NCPH is an Indian counterpart of Japanese IPH. Indian series on NCPH have not indicated CVDs as an associated condition.[40,41] The hypothesized pathogenesis of NRHL is the end-result of small vessel vasculitis producing hepatocytic atrophy associated with compensatory hyperplasia[31-35] and has also been observed with recurrent portal vein thrombosis.[35,38,42] Focal nodular hyperplasia is described with hemangioma and vascular dysplasia of liver.[43,44] CD34 has been described to stain vascular endothelial cells, negative to week positivity for endothelial cells of lymphatic origin.[45,46] CD34 was expressed by endothelial cells of all the abnormal vasculature in our cases thereby favoring vasculature more likely to be capillaries or venules. The abnormal vessels observed in the present six cases could have a direct bearing in the development of NRHL as they were seen in more than half of the cases and could be the after effect of segmental vasculitis resulting in the development of short collateral channels.

Krasinskas *et al.*[47] and Ohbu *et al.*,[48] in the studies on native and allograft liver biopsies, have described the presence of an aberrant vessel adjacent to the portal tract, with or without communication to a normal or dilated portal vein, that was distinctly different from the one observed by us. Similar histological features to our cases were described by Oikawa *et al.*[10] and Krasinskas *et al.*[11] in IPH and intrahepatic NCPF, respectively. Oikawa *et al.*[10] further characterized the abnormal vasculature into veins and lymphatic vessels based on positive staining for alpha smooth muscle actin, which probably was not the best way to characterize. They did not mention the associated liver parenchyma histology. Krasinskas *et al.*[11] observed the coexisting NRHL in their 15 (of 16, 94%) patients. It is important to emphasize on the presence of portal hypertension in all the patients of the two quoted studies in contrast to our cases who did not have that except in one case. We like to hypothesize that our six cases of NRHL with abnormal vasculature could be in the process of developing NCPH/IPH, as has been reported to be frequently associated with CVDs.[10,36,37,39] Wanless[8] and Matsumoto *et al.*,[9] in their series of NRHL had not mentioned similar vascular changes in the portal tract. Besides a hypothetical localization of intermediate or small-sized portal vein segmental vasculitis, the effect of a focal or localized obstruction by regenerative nodules cannot be totally ignored in our cases.

The pathophysiology of a liver injury in sepsis is multifactorial and involves infection, drugs, metabolic disturbances, and a spectrum of inflammatory mediators.[22-25] Canalicular cholestasis usually most severe in zone 3, and portal tract inflammation and lobular neutrophil infiltration have been described to be associated with the toxic shock syndrome. Intrahepatic cholestasis in septicemia could be attributed to many factors such as circulating endotoxin causing functional disorders in bile secretion, disturbances in bile canalicular contraction, and ischemia.[49]

The association of SSc with primary biliary cirrhosis is well known.[31,50] SSc cases in the present study had mildly deranged liver enzymes with bridging fibrosis resulting in a vaguely nodular liver due to incomplete nodule formation. A similar histological

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feature and biochemical parameter in SSc cases had also been observed by others.[51,52] The hepatic artery pathology observed in the three PAN cases has been well described.[53] Similar vascular changes in PAN had been reported in SLE[54] which was not seen in our cases. Our cases had a variable degree of hepatocytic micro- and macro-vesicular steatosis and centrizonal sinusoidal congestion. In a retrospective analysis of SLE at autopsy, liver congestion was found to be the commonest histological changes followed by a fatty liver.[26,27,30] Hepatocytic steatosis is usually attributed to steroid therapy in CVDs which has been contradicted by some recent studies as it was observed only in a small percentage of patients who were on steroids.[16,31] None of our cases were on steroids at the time of hospital admission. Steatosis is well described with septicemia.[23,25] The mean gross liver weight in our study was mild to borderline increased and seven had just palpable liver clinically. In a Japanese and Chinese series of cases, the mean liver weights had been reported as 1200 g and 1400 g in females and males, respectively,[55,56] comparable to our cases.

To conclude, we describe a novel finding of the presence of innumerous abnormal thin-walled vessels in intermediate- and small-sized portal tracts with a normal hepatic artery and bile duct in CVDs with NRHL in the absence of portal hypertension (except in one case) or overt vascular thrombosis, or abnormal hematological disorder. We also observed a high incidence of NRHL especially in SLE cases. Raised liver enzymes with interface hepatitis in CVDs may not necessarily warrant an overlap, as a similar feature could be observed in septicemia.

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