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CENTRAL VENULITIS IN THE ALLOGRAFT LIVER: A Clinicopathologic Study [1,2]

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Back to Top

Abstract

Background. Central venulitis denotes a histologic lesion of the allograft liver characterized by perivenular and subendothelial mononuclear inflammation of the terminal hepatic venules associated with varying degrees of perivenular hepatocyte dropout. Although this lesion had generally been considered a manifestation of acute rejection, some have suggested that it instead represents tacrolimus hepatotoxicity.

Methods. We therefore compared the clinicopathologic features of 30 episodes of isolated central venulitis with 22 episodes of combined central venulitis and typical portal acute rejection occurring in 27 patients. Nineteen of the patients received tacrolimus and eight

received cyclosporine as primary immunosuppression.

Results. No significant differences were found between the two groups, except that isolated central venulitis more often displayed a mild inflammatory component (P=0.007) with small lymphocytes as the predominant cell type (P=0.002). None of the patients had tacrolimus or cyclosporine levels that exceeded the therapeutic range, and none had other clinical evidence of drug toxicity. Usual antirejection therapy was instituted in all but two episodes; response was evident in 93% (28 of 30) of the isolated central venulitis and 86% (19 of 22) of the central venulitis-portal acute rejection group, with histologic regression documented in all follow-up specimens (four and five, respectively). Due to persistent central venulitis, two cyclosporine patients were switched to tacrolimus, with prompt resolution.

Conclusions. These findings are inconsistent with the concept that central venulitis represents drug toxicity and indicate instead that it is a form of acute allograft rejection.

The term “central venulitis” refers to perivenular and subendothelial mononuclear inflammation of the terminal hepatic venules associated with varying degrees of perivenular hepatocyte dropout. This lesion has been recognized as a feature of acute rejection from the inception of liver transplantation (1), and it exemplifies the role of the perivenular region as a primary site (in addition to the portal tracts) of immune stimulation in allograft rejection (2).

The possibility that central venulitis might constitute drug-induced hepatic injury was considered during the initial clinical trials with tacrolimus (FK506), but this suspicion was dismissed because similar changes were noted with rejection in patients treated with cyclosporine and, moreover, the temporal requirements for an adverse drug reaction

were not satisfied (3, 4). However, with more widespread use of this agent, two reports from one group of investigators have indicated that central venulitis instead represents tacrolimus-induced hepatotoxicity (5, 6). In these studies, tacrolimus was considered to represent a direct hepatotoxin, although idiosyncratic mechanisms could not be excluded, and affected over 10% of patients treated (6).

This debate over the nature of central venulitis has resulted in considerable confusion over its appropriate management, centering on whether increased or decreased immunosuppression is the proper therapy. To address this controversy, we compared the clinicopathologic features of 30 episodes of isolated central venulitis to 22 episodes of central venulitis that were accompanied by typical portal changes of acute rejection. If central venulitis indeed represents drug-induced injury, pertinent features such as blood drug levels, evidence of other drug-related toxicity, and response to anti-rejection therapy should differ considerably between the two groups. If, however, central venulitis instead represents a manifestation of acute rejection, the groups should demonstrate generally similar features.

Back to Top

MATERIALS AND METHODS

Case selection. We identified and reviewed cases with a diagnosis of central venulitis from the files of the Division of Transplantation Pathology and excluded those instances that occurred in allografts other than the first or in patients transplanted for chronic hepatitis B or C to obtain examples uncomplicated by potential confounding features such as hepatitis-associated perivenular inflammation. This review yielded a total of 52 cases, 30 with central venulitis alone (CVA * group) and 22 with central venulitis together with portal acute rejection (PAR-CV group), derived from 27 liver transplant recipients. These patients ranged from 19 to 44 years old (48±17 years old) and included 14 men and 13 women. Their original liver diseases included ethanol abuse (n=6), primary biliary cirrhosis (n=5), and primary sclerosing cholangitis

(n=5), with a variety of conditions accounting for the remaining 11 cases.

Pathologic design. Two hematoxylin and eosin-stained slides from each of the 52 biopsy specimens were independently reviewed by two pathologists (A.C.T. and R.G.L) blinded to the clinical and therapeutic profile, and a variety of specific histopathologic features were evaluated. These features included the adequacy of the specimen; the total number of central veins (terminal hepatic venules), and the number and percentage of central veins involved by central venulitis; the degree of associated perivenular inflammation (absent, mild, moderate, or severe), its predominant cell type (small lymphocytes, blastic [activated] lymphocytes, plasma cells, eosinophils, neutrophils, or macrophages), and whether the subendothelial regions were involved ("endotheliitis") or the midzonal areas (acinar zone 2) were affected; and the presence and extent of hepatocyte dropout, sinusoidal dilation and congestion, central vein fibrosis, and cholestasis. The portal tract changes of acute (cellular) rejection were recognized by the well-established international criteria of a mixed but predominantly mononuclear portal infiltrate, bile duct inflammation or damage, and subendothelial inflammation of portal veins (7). A diagnosis of chronic (ductopenic) rejection was similarly based on international criteria of convincing evidence of duct loss (>50% of portal tracts) or obliterative arteriopathy (7). Other coexistent pathologic alterations, including the presence of viral inclusions, were additionally noted when present.

Disagreements in the independent assessments were reconciled by joint review, and a consensus conclusion then made. All available preceding (n=14) and subsequent (n=25) biopsy specimens from the patients were also examined to determine the histologic antecedents and outcome of the CVA and PAR-CV episodes.

Clinical correlation. Of the 27 patients, 19 had received tacrolimus and 8 had cyclosporine as primary immunosuppression. The patients were routinely monitored for the development of allograft dysfunction by serum liver tests consisting of alanine aminotransferase, aspartate

aminotransferase, alkaline phosphatase, [gamma]-glutamyltranspeptidase, and total bilirubin. Cholangiography, ultrasonography, angiography, serologic assays, and microbial cultures were performed whenever indicated to confirm the diagnosis in suspected vascular or biliary problems, microbial infections, or other posttransplant complications. Acute rejection was treated according to previous protocols (8) by augmentation of tacrolimus or cyclosporine doses, steroid bolus/taper, or OKT3 antilymphocyte preparation depending on the severity of the episode.

The liver test profile, serum creatinine, and tacrolimus or cyclosporine levels at the time of each of the 52 study biopsies were reviewed and correlated with the pathologic findings and the response to treatment. The therapeutic response and clinical follow-up were determined for each case from the medical and clinical records, flow-sheets, and discussion with the attending surgeons. Patients were followed-up until the close of the study on August 31, 1995, and complete follow-up was available to that day.

Statistical analysis. All the 52 specimens were deemed adequate for evaluation and included in the study. The statistical evaluation employed the Mann-Whitney rank-sum test and the Fisher Exact Test as appropriate, with the significance level set at 0.05.

Back to Top

RESULTS

Histopathology. Central venulitis, whether occurring in the CVA or PAR-CV groups, displayed the same general range of morphologic changes. The lesion was characterized by a well-defined but variably sized zone of hepatocyte dropout surrounding the central vein (Figs. 1 and 2). The associated inflammatory component, usually of mild degree, was predominantly mononuclear in nature and was composed of small lymphocytes, blastic lymphocytes, plasma cells, and pigmented macrophages in varying combination. The inflammatory cells were typically concentrated at the interface between the zone of dropout and


Figure 1


Figure 2

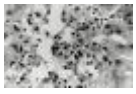
Figure 3

adjacent intact hepatocytes. Subendothelial inflammation was sometimes noted, but was not an invariable finding (Fig. 3). Accompanying these alterations were sinusoidal dilation and congestion, sometimes with localized hemorrhage, together with perivenular fibrosis in occasional cases. Central venulitis primarily affected the perivenular region (acinar zone 3), but more severe lesions could extend into the midzonal region (acinar zone 2) or even bridge between perivenular zones (Fig. 2).

As summarized in Table 1, only a few differences were noted between the CVA and PAR-CV groups. There was a tendency for CVA to occur later in the posttransplant course, although the difference was not statistically significant (P=0.06). Central venulitis in the CVA group more often demonstrated mild inflammation (P=0.007) and was dominated by small lymphocytes (P=0.002). Otherwise the groups were generally indistinguishable. Although bile duct loss of 40% (6 of 15 portal tracts) and 17% (1 of 6 portal tracts) was noted in two specimens (one CVA and one PAR-CV), this was a transient and nonprogressive finding not noted in subsequent biopsies.


Table 1

Clinicopathologic correlation and outcome. Of the 52 episodes, 11 (5 CVA and 6 PAR-CV) occurred under cyclosporine immunosuppression, and the remaining 41 episodes (25 CVA and 16 PAR-CV) developed under tacrolimus immunosuppression. Seven patients (one cyclosporine-treated and six tacrolimus-treated) developed both CVA and PAR-CV, and in each case, PAR-CV developed earlier. Of the 14 specimens obtained before central venulitis was identified, 1 showed prior portal acute rejection, and the others lacked notable pathologic features.

Following the general practice at our institution, 50 of the 52 episodes of central venulitis were treated as allograft rejection with increased immunosuppression. The only exceptions were two


Table 2

episodes (one CV and one PAR-CV) occurring in a 74-year-old woman who was being treated for bacterial sepsis and subsequently died. Clinical improvement was noted in 93% (27 of 29) of the treated CV and 86% (19 of 21) of the treated PAR-CV cases, with a prompt and persistent reversal of liver test abnormalities within a week after treatment was instituted (Table 2).

Three of the five nonresponsive episodes were subsequently treated with an additional course of enhanced immunosuppression. This enhancement entailed a repeat steroid bolus and recycle in two cyclosporine-treated patients and a repeat steroid bolus and increased tacrolimus dosage in one tacrolimus-treated individual, and resulted in a clinical response and improved liver tests within 10 days in all instances. There was no correlation between the number of the CVA and PAR-CV episodes per patient and the response to treatment. The other two nonresponsive episodes occurred in two patients who were noted at cholangiography to have biliary tract abnormalities (T-tube dysfunction and duct stricture) that were then treated surgically with subsequent improvement in liver test abnormalities.

Follow-up biopsy specimens were obtained within 14 days after treatment in nine cases, four from the CVA group and five from the PAR-CV group; histologic resolution was noted in each instance. One follow-up specimen obtained 67 days after a posttransplant day 13 episode of PAR-CV demonstrated bile duct loss in 4 of 12 portal tracts (33%). However, this finding was not present in four interval specimens obtained between day 13 and 80, and was not noted in subsequent specimens from the patient. No clinical or histopathologic evidence of chronic rejection was identified in any of the 27 patients.

Because of recurrent central venulitis, two cyclosporine-treated

patients were switched to tacrolimus on posttransplant days 912 and 2395, and a rapid clinical response was recorded. In another case from the cyclosporine group, an attempt to wean immunosuppression at 1664 days posttransplant was soon followed by PAR-CV. This quickly responded, however, to reinstitution of cyclosporine. In conclusion, through the close of the study, 26 patients were alive between 30 and 3384 days (median, 1584 days) after transplantation with well-functioning grafts.

Immunosuppressive drug levels and toxic manifestations. At the time of CVA or PAR-CV, none of the patients displayed evidence of drug-induced nephrotoxicity or neurotoxicity, and none of the concurrent tacrolimus or cyclosporine levels exceeded the therapeutic range. The tacrolimus level data are summarized in Table 3. Cyclosporine levels ranged from 250 to 800 ng/dl (median, 652 ng/dl) at the time of the biopsy and from 325 to 930 ng/dl (median, 703 ng/dl) at 7 days after treatment; therapeutic values are considered to be between 800 and 1000 ng/dl.

Table 3

Mean serum creatinine values at the time of biopsy and 7 days after treatment were 1.5±0.7 mg/dl and 1.5±0.8 mg/dl in the CVA group compared with 1.6±0.9 mg/dl and 1.7±1.5 mg/dl in the PAR-CAV group. Similarly, blood urea nitrogen levels were 35±26 mg/dl and 42±31 mg/dl in the CV group and 38±20 and 54±36 mg/dl in the PAR-CV groups. Three patients (two receiving tacrolimus and one cyclosporine) required dialysis because of renal failure that developed 13, 26, and 265 days after transplantation, but this did not correspond to episodes of either CV or PAR-CV at follow-up. No renal biopsies were performed in any patient. In addition, at 510 days after transplant, one patient developed polyneuropathy attributed to tacrolimus toxicity with concurrent drug plasma levels of 1.3 ng/dl. Renal dysfunction was not present. The patient later developed pneumonia, and when immunosuppression was lowered, liver

dysfunction ensured. A liver biopsy demonstrated CVA, which responded to tacrolimus augmentation, and the patient was doing well at the close of the study.

Back to Top

DISCUSSION

In this study, we found that the clinicopathologic features of isolated central venulitis did not differ substantially from those of central venulitis associated with typical portal tract changes of acute rejection. Isolated central venulitis did, however, tend to occur later after transplantation, and its predominant inflammation cell was more likely to be small lymphocytes rather than blastic lymphocytes. In either setting, though, the process uniformly responded both biochemically and histologically to antirejection therapy. Although these results, in the absence of an untreated control group, do not prove that central venulitis represents a manifestation of acute rejection, they nonetheless provide strong support for that concept.

Central venulitis forms a morphologic continuum with subendothelial inflammatory infiltration of the terminal hepatic veins, which is a principal feature of acute rejection, (7) and it can be pathogenetically considered as an advanced, localized advanced form of that process. The lesion presumably evolves from this initial subendothelial involvement (“endotheliitis”), possibly with a contribution by outflow blockage at the sinusoidal-venous junction (9), to produce local hepatocyte injury and loss with sinusoidal dilation and congestion. In due time, the inflammatory component spreads to a perivenular (as opposed to strictly subendothelial) distribution, and associated perivenular fibrosis can eventually develop (10).

Although recognized previously as a feature of acute rejection, central venulitis has often been neglected in the literature. In part, this probably reflects the emphasis that has been placed on the strict presence of subendothelial inflammation as a diagnostic criterion. Nevertheless, the same lesion referred to as central venulitis has been described in three studies under the broader and more inclusive label of “centrilobular necrosis” (9, 11, 12).

The conclusions of these three studies are generally similar and broadly correspond to those reached in our investigation. They all suggest some relationship with acute rejection based on the concurrence, simultaneously or metachronously, of central venulitis and terminal hepatic venular endotheliitis or portal-based acute rejection (9, 11, 12). Often central venulitis tended to persist or recur in these studies, and a response to additional immunosuppression was noted in some cases. These reports additionally raised the possibility that centrilobular necrosis serves as a harbinger of poor prognosis, because 18% (12) to 75% (9) of the 100 reported cases subsequently progressed to chronic rejection. In contrast, none of the patients in our study developed this complication. Although this study did not examine the natural history of untreated central venulitis and cannot address the issue of spontaneous resolution, we suggest that its prompt treatment as acute rejection in our patients accounts for this difference in outcome.

The results of our study do not support the concept proffered by two recent reports from Mt. Sinai Medical Center (5, 6) that central venulitis is a feature of tacrolimus hepatotoxicity. For example, we identified the lesion in both cyclosporine-treated and tacrolimus-treated patients, in agreement with previous studies (4, 9, 11, 12). None of our 52 cases concurrently demonstrated other manifestations of drug toxicity or had drug levels that exceeded the therapeutic

range. In addition, central venulitis responded both clinically and histologically to augmented tacrolimus, and in two cases, resolved after the patients were switched from cyclosporine to tacrolimus. If, as suggested, tacrolimus were a significant hepatotoxin, the opposite result would have been expected.

The hepatotoxicity hypothesis was initially based on identifying central venulitis in tacrolimus-treated patients and associating this finding with a higher frequency of HLA-DR expression in the perivenular region of patients receiving tacrolimus as opposed to cyclosporine (5). It should be noted, however, that central venulitis was actually more common among cyclosporine-treated (6 of 17) than tacrolimus-treated patients (3 of 14) in that report. Moreover, all nine of the patients with central venulitis had other features of acute rejection including concomitant portal tract changes and terminal hepatic venular endotheliitis (5).

In a subsequent brief communication from the same group, five patients were selected with central venulitis and clinical evidence of drug toxicity, including nephrotoxicity, neurotoxicity, and gastrointestinal manifestations, from among 50 liver transplant recipients receiving tacrolimus (6). None of the patients had elevated plasma or blood levels of tacrolimus, but all had elevated alanine aminotransferase and/or alkaline phosphatase levels that decreased after a reduction or discontinuation of tacrolimus. In only two cases, however, did improvement occur within 7 days after the change in dosage; in other cases, the liver tests decreased by 30 days, although they did not completely normalize.

Although a biochemical response to a lessened exposure to the agent is consistent with drug-induced liver injury, several considerations make this conclusion less tenable. First, the onset of the process

among the five cases ranged from 6 to 24 weeks after beginning treatment; a latency period of this duration is incompatible with a direct, dose-dependent hepatotoxin (13). On the other hand, the relatively high prevalence of the process (overall, 12% of the 50 patients) is inconsistent with an indirect or idiosyncratic hepatotoxin, which, even with the most notorious culprits, seldom provokes hepatic injury in more than 1% of treated individuals (13). As an alternative explanation, the biochemical response observed when tacrolimus was decreased might represent the result of changes in other immunosuppressive agents, particularly steroid doses. Such changes were not specifically addressed by the Mt. Sinai report, but we have previously recognized that the frequency of central venulitis may be affected by alterations in steroid dosages (4). This observation may also account for the anecdotal experience that isolated central venulitis is more common among tacrolimus-treated, who typically receive less steroids, than cyclosporine-treated patients. In addition, central venulitis was not identified in a review of liver biopsy specimens from patients receiving tacrolimus for allografts other than liver. (unpublished observations)

Central venulitis is one of several centrilobular necroinflammatory conditions that can be encountered in liver allografts. The chief differential diagnostic considerations are delineated in Table 4; generally these can be distinguished by close attention to the histologic details in conjunction with clinical correlation.

 Table 4

Back to Top

Footnotes

This work was supported in part by the Pathology Education and Research Foundation. [Context Link]

This work was presented in part at the 75th Annual Meeting of the United States and Canadian Academy of Pathology, Washington, DC, March 23-29, 1996 (Modern Pathol 1996; 9: 138A). [Context Link]
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Back to Top

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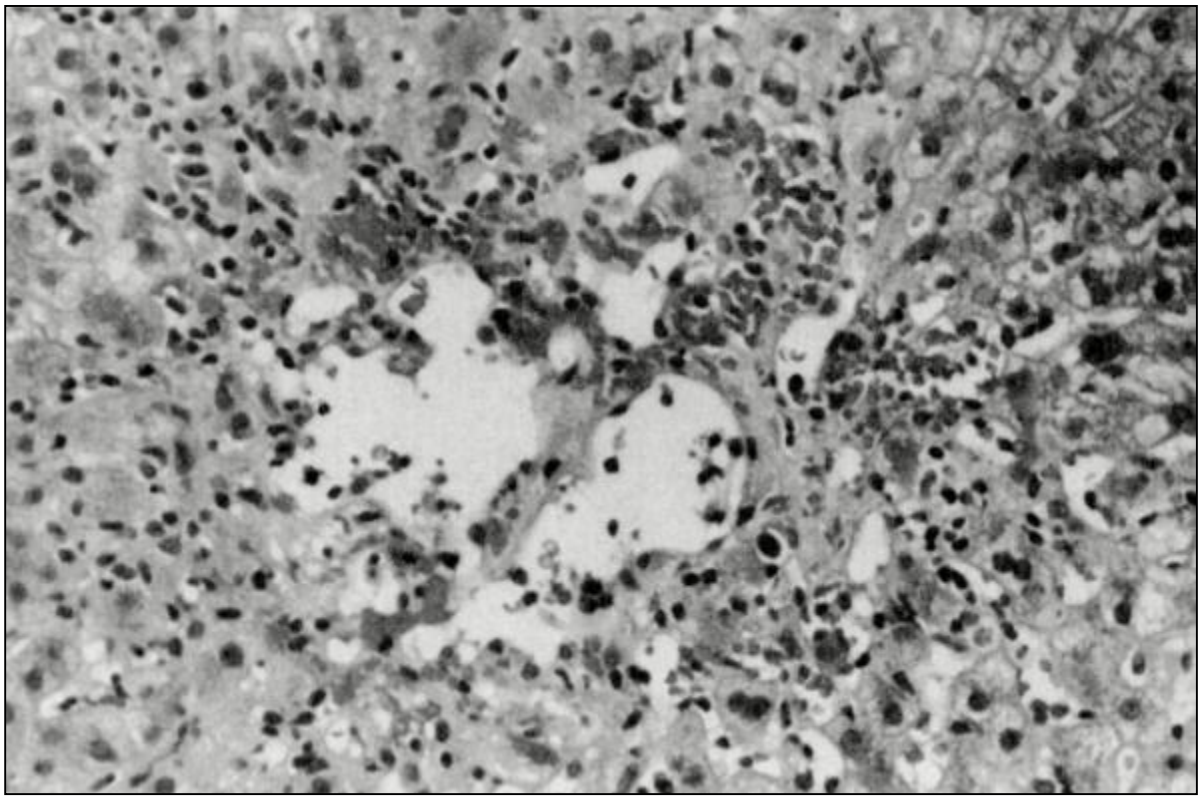

Figure 1 . Mild central venulitis with localized loss of centrilobular hepatocytes, sinusoidal dilatation, and mild inflammatory infiltration.

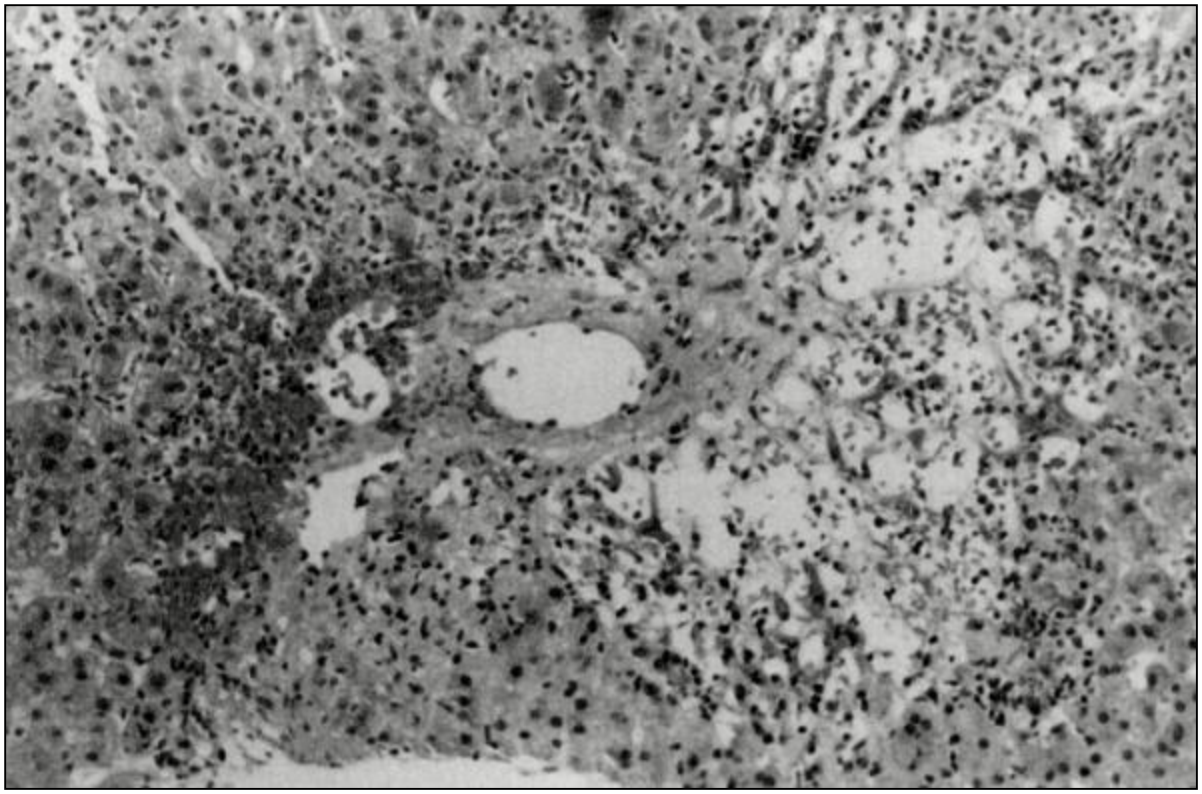

Figure 2 . Severe central venulitis with substantial hepatocyte dropout involving the midzonal region, pronounced sinusoidal dilatation, and focal hemorrhage together with a patchy inflammatory infiltrate. Note also the thin cuff of perivenular fibrosis outlining the central vein.

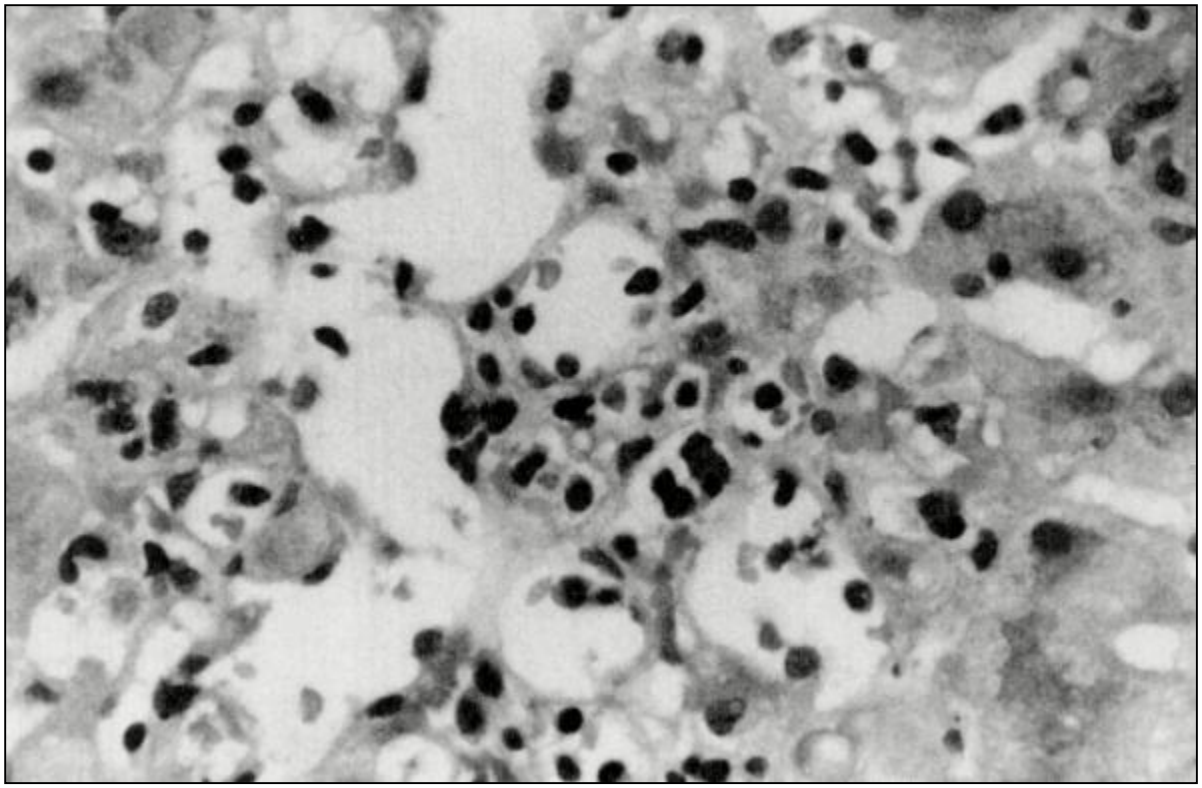

Figure 3 . Mononuclear cells collect beneath the endothelium in a mild example of central venulitis.

	Isolated central venulitis (n=30)	Central venulitis-portal acute rejection (n=22)	P[a]
Time of biopsy (days after Tx)	17–3337 (median 525)	4–3323 (median 157)	NS
Lobular changes			
% of central veins involved	17–81% (median 51%)	14–88% (median 49%)	NS
Extension to midzonal region	1 (3%)	5 (23%)	NS
Location of inflammation			
Subendothelial	5 (17%)	6 (27%)	NS
Perivascular	25 (83%)	16 (73%)	
Degree of inflammation			
Mild	29 (97%)	15 (68%)	0.007
Moderate	1 (3%)	7 (32%)	
Predominant inflammatory cell			
Blastic lymphocytes	5 (17%)	12 (55%)	0.002
Small lymphocytes	23 (77%)	7 (32%)	
Hepatocyte dropout	30 (100%)	22 (100%)	
Mild	20	10	NS
Moderate	10	12	
Sinusoidal dilatation	30 (100%)	22 (100%)	
Mild	28	16	NS
Moderate	2	6	
Central vein fibrosis	16 (53%)	6 (27%)	
Mild	12	5	NS
Moderate	4	1	
Cholestasis	3 (10%)	2 (9%)	NS
Portal changes			
Acute rejection	0	22 (100%)	
Bile duct loss	1 (3%)	1 (5%)	NS

[a] NS, not statistically significant.

Table 1 . Comparative clinicopathologic features of 52 cases of central venulitis

	Isolated central venulitis			Central venulitis-portal acute rejection		
	7 days before	Day of biopsy	7 days after	7 days before	Day of biopsy	7 days after
ALT (IU/ml)	86 (10–599)	281 (91–1787)	104 (28–785)	67 (20–319)	362 (93–672)	92 (30–544)
AST (IU/ml)	47 (12–152)	114 (27–511)	40 (10–270)	44 (18–124)	185 (24–746)	44 (6–252)
γ-GTP (IU/ml)	169 (22–989)	330 (43–1265)	204 (36–970)	150 (29–918)	331 (52–1184)	220 (29–989)
ALP (IU/ml)	98 (60–232)	152 (85–362)	94 (60–266)	84 (35–465)	123 (75–757)	95 (62–465)
Total bilirubin (mg/dl)	0.8 (0.4–8)	1.2 (0.5–12)	0.8 (0.4–9)	1.0 (0.3–9.3)	2.5 (0.5–12.5)	0.4 (0.3–6.6)

[a] Values expressed as median (range). ALT, alanine aminotransferase (<40 IU/ml); AST, asparate aminotransferase (<40 IU/ml); γ-GTP, γ-glutamyl transpeptidase (<120 IU/ml); ALP, alkaline phosphatase (<130 IU/ml).

Table 2 . Serum liver tests preceeding, at the time of, and after treatment of central venulitisa

	Isolated central venulitis		Central venulitis-portal acute rejection	
	Day of biopsy	7 days later	Day of biopsy	7 days later
Plasma (ng/dl)	0.4±0.2 (0.1–0.9)	0.9±0.5 (0.2–1.7)	0.5±0.3 (0.1–1.3)	0.7±0.3 (0.3–1.3)
Whole blood (ng/dl)	11±6 (5–19)	14±7 (5–28)	8±2 (5–10)	11±5 (6–21)

[a] Values expressed as mean±SD (range). Plasma levels, 0.5–2 ng/dl; whole blood levels, 5–20 ng/dl.

Table 3 . Tacrolimus levels at the time of and after treatment of central venulitisa

	Distinguishing histologic features	Clinical history
Central venulitis	Perivenular inflammation; hepatocyte dropout; sinusoidal congestion +/− subendothelial inflammation	Variable time of onset; inadequate immunosuppression
Ischemia	Hepatocyte dropout; coagulative necrosis; sparse neutrophil inflammation	Onset early with harvesting ischemia, later with vascular compromise
Chronic rejection	Bile duct loss and pyknosis, obliterative arteriopathy, perivenular sclerosis; hepatocyte ballooning and dropout	Progressive increase in cholestatic markers; inadequate immunosuppression
Azathioprine hepatotoxicity (*10, 14*)	Sinusoidal congestion; centrilobular hepatocyte necrosis; veno-occlusive lesions	Uncommon side effect; onset usually within 2 months after administration; jaundice at presentation
Venous outflow obstruction	Sinusoidal congestion and hemorrhage; hepatocyte dropout; space of Disse hemorrhage; perivenular and sinusoidal fibrosis	Infrequent allograft problem, although minor changes can be transient finding
Viral hepatitis	Confluent necrosis associated with lobular hepatitis	Uncommon complication; confirm diagnosis with viral serology and polymerase chain reaction

Table 4 . Centrilobular necroinflammatory lesions of the allograft liver