Peliosis hepatis in recipients of renal transplants

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SUMMARY Peliosis hepatis, an uncommon liver lesion characterised by blood-filled cavities bordered by hepatocytic plates, was found in 12 patients three to 17 months after renal transplantation. Hepatomegaly and portal hypertension were present in five of the six patients with major peliosis hepatis, and were absent in the other six with minor hepatic lesions. Alterations of centrilobular vein walls in some of these patients suggest that peliosis hepatis could be the result of a blockade of liver blood outflow at the junctions of sinusoids and centrilobular veins. The cause of these alterations might be azathioprine.

Peliosis hepatis, from the Greek πελιόσ (which means livid), is an uncommon liver lesion consisting of blood-filled cavities distributed at random in the hepatic parenchyma. This liver lesion has been reported in patients suffering from various diseases (Zak, 1950; Hamilton and Lubit, 1952; Trites, 1957; Kent and Thompson, 1961; Caroli et al., 1964; Orandi and Pirozynski, 1967) or receiving various drugs (Yanoff and Rawson, 1964; Bernstein et al., 1971; Delage and Lagacé, 1973; Naeim et al., 1973; Bagheri and Boyer, 1974; Kühböck et al., 1975); the mechanism whereby these diseases and drugs induce peliosis hepatis is unknown. The purpose of this paper is (1) to demonstrate that the frequency of the disorder is relatively high in renal transplant recipients, and (2) to offer a hypothesis for the mechanism of this liver lesion.

Methods

Patients
The present investigation was based on a series of 500 patients, 328 men and 172 women, aged from 16 to 56 years, suffering from chronic renal failure, who were treated by renal transplantation between 1965 and 1975. In 138 of them, a liver specimen was taken intraoperatively during renal transplantation. All the renal transplant recipients received azathioprine and corticosteroids. Among these 500 patients, 55 were referred to the Liver Unit because they had one or several disorders suggesting liver alteration: liver enlargement, ascites, oesophageal varices, increased level of serum transaminases, hepatitis B surface antigen (HBsAg) present in serum. A liver specimen was taken three to 17 months after renal transplantation by surgical biopsy in five of the patients, by percutaneous needle biopsy in 45, and by transjugular needle biopsy in five; the last method can be used in those patients with bleeding tendency in whom percutaneous needle biopsy is contraindicated (Lebrec et al., 1978). In six of the patients with peliosis hepatis peritoneoscopy was performed. In eight of the patients with this lesion, a second liver specimen was obtained three to 32 months after the first histological examination either by one of the methods of biopsy mentioned above or at necropsy.

Results
No liver lesions suggesting peliosis hepatis were found in any of the 138 patients submitted to biopsy during renal transplantation. Lesions of peliosis hepatis were demonstrated in 12 of the 55 patients submitted to biopsy after renal transplantation. The ages of these 12 patients ranged from 24 to 56 years. There were 11 men and one woman. None of them took anabolic, androgenic, or oestrogenic steroids. According to the size and extent of the liver lesions, we distinguished a minor and a major form of
Peliosis hepatis: in the former, the size of the blood-filled cavities was small, and the lesions affected only a part of the hepatic lobules (Fig. 1); in the latter, the blood-filled cavities were large and often confluent, and the lesions affected a large portion of the hepatic lobules (Fig. 2); the hepatocytic plates lining the small cavities were normal, but those lining the large cavities were thin and often interrupted. The minor form of peliosis hepatis was found in six of the 12 patients, and the major form in the other six.

In four of the six cases of the major form of the disorder, the walls of some centrilobular veins were oedematous and fibrous; these alterations affected either the whole or only a part of the circumference of the vessels and were not associated with thrombosis (Fig. 3); the lesions of the centrilobular veins were not spatially related to the areas of peliosis hepatis. In the other two cases of the major form of the lesion and in all six cases of the minor form, these venous alterations were not seen.

Peritoneoscopy showed multiple purplish areas, more or less circular, with a diameter ranging from 0.5 to 2 mm, disseminated at the surface of the liver, in two of the three patients with the minor form of the lesion and in all the three patients with the major form in whom this examination was performed.

Peliosis hepatis was associated with chronic persistent hepatitis or chronic active hepatitis (as defined according to the histological criteria of De Groote et al. (1968)) in three and four, respectively, of the 12 patients. HBsAg, tested for by radioimmunoassay, was present in the sera of six out of those seven patients with peliosis hepatis and chronic hepatitis; HBsAg was absent in the sera of the other five patients with the disorder and without chronic hepatitis.

In four patients with the major form of peliosis hepatis, a second liver specimen was obtained; in two of them, lesions of peliosis hepatis almost similar to those observed previously were demonstrated one and 15 months, respectively, after the first histological examination; in the other two patients in whom the lesion was not associated with chronic hepatitis, cirrhosis with marked fibrosis and small-sized regenerative nodules was demonstrated three and 12 months, respectively, after the first histological examination. In four patients with the minor form of peliosis hepatis, a second liver specimen was obtained; in one of them, lesions almost similar to those demonstrated previously were observed 15 months after the first histological examination; in the other three patients in whom peliosis hepatis was associated with chronic active hepatitis, cirrhosis was demonstrated three, 17, and 32 months, respectively, after the first histological examination.

There was a relationship between some clinical manifestations and the degree of peliosis hepatis. Liver enlargement was present in all, and manifestations suggesting portal hypertension—that is, oesophageal varices and/or ascites—were present in five of the six patients with the major form of peliosis hepatis. The liver size was normal, and manifestations suggesting portal hypertension were

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Fig. 1  Minor form of peliosis hepatis. The blood-filled cavities (some are indicated by arrows) are small; they are bordered by normal hepatocyte plates. Haematoxylin and eosin stain × 225.
absent in all the six patients with the minor form of peliosis hepatis. Rejection episodes occurred at the time of, or before recognition of the disorder in all the 12 patients.

Discussion

The histological pattern of the liver lesions observed in our 12 patients is that attributed to peliosis hepatis. The random distribution of the lesions throughout the hepatic lobules distinguishes peliosis hepatis from congestive liver, Budd-Chiari syndrome, and veno-occlusive disease of the liver (Bras et al., 1954; Stein and Isaacson, 1962; Putzke et al., 1972) in which sinusoidal dilatation predominates in the centrilobular areas. According to Yanoff and Rawson (1964), there are two varieties of peliosis hepatis: (1) phlebectatic, in which the blood-filled spaces are lined with endothelium, and (2) parenchymal, in which the blood-filled spaces possess no endothelial lining; the liver lesions observed in our patients belong to the latter variety.

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our patients—that is, small purplish areas at the surface of the liver—are similar to the macroscopic lesions described at necropsy of patients with peliosis hepatitis (Zak, 1950). This finding reinforces the view that the liver lesions observed in our patients correspond to peliosis hepatitis and confirm the value of peritoneoscopy for the diagnosis of the disorder (Caroli et al., 1964).

The clinical manifestations of peliosis hepatitis have been poorly defined, probably because, in most of the cases reported, the liver lesions have been recognised only at necropsy, and have been associated with a severe disease, the signs and symptoms of which have been intermingled with those of peliosis hepatitis. However, it has been established that the disorder can induce hepatomegaly (Naeim et al., 1973), liver failure (Bernstein et al., 1971), and intraperitoneal bleeding (Bagheri and Boyer, 1974). In our experience, the minor form of peliosis hepatitis was clinically latent and the major form was associated with hepatomegaly and portal hypertension. In two of our patients in whom peliosis hepatitis was not accompanied by chronic active hepatitis, cirrhosis was found at a subsequent histological examination: this finding is compatible with the view that peliosis hepatitis per se can induce the development of cirrhosis.

Peliosis hepatitis or similar lesions have been reported in patients suffering from malignancy (Zak, 1950; Caroli et al., 1964; Yanoff and Rawson, 1964; Delage and Lagacé, 1973), tuberculosis (Hamilton and Lubitz, 1952), or diabetes (Hamilton and Lubitz, 1952) and in patients receiving anabolic, androgenic, or oestrogenic steroids (Yanoff and Rawson, 1964; Bernstein et al., 1971; Naeim et al., 1973; Bagheri and Boyer, 1974; Kühlbök et al., 1975; Winkler and Poulsen, 1975; Westaby et al., 1977); none of these recognised aetiological factors is implicated in the aetiology of peliosis hepatitis in our patients. Peliosis hepatitis has also been reported in a patient suffering from chronic renal disease (Trites, 1957); however, in our patients, peliosis hepatitis is likely to be related, not to chronic renal disease, but to renal transplantation, since this liver lesion has been detected in none of our patients submitted to biopsy during renal transplantation, and only in patients after renal transplantation. The association of the disorder with renal transplantation has not been hitherto described, although the liver lesions have been extensively investigated in large series of renal transplant recipients (Hill et al., 1966; Evans et al., 1968; Gault et al., 1971; Torisu et al., 1971; Berne et al., 1975; Nielsen et al., 1975; Ware et al., 1975); we have no explanation for this discrepancy between our findings and the apparent absence of peliosis hepatitis in the other series; the selection of the patients, the technique of renal transplantation, and the nature and dosage of immunosuppressing drugs seem to be no different in our series and in the other series.

The prevalence of peliosis hepatitis in our series of renal transplant recipients is 2.4%: this is a minimal figure as only those patients with manifestations suggesting liver alteration have been subjected to biopsy, and most of our patients have been observed for only a part of their lifetime. The male-to-female ratio is much higher in our patients with peliosis hepatitis than in the entire group of renal transplant recipients, being 1:0:1 and 1:0:5, respectively; we have no explanation for this male predominance. Hepatitis B virus is not the causal factor of peliosis hepatitis, as only six of our 12 patients with the disorder are chronic HBsAg carriers. Rejection episodes have occurred in all our patients; however, rejection being a common complication of renal transplantation, a fortuitous association with peliosis hepatitis cannot be excluded. All our patients have received corticosteroids and azathioprine; peliosis hepatitis has not been reported in patients receiving these drugs; however, veno-occlusive disease of the liver or sinusoidal dilatation, both hepatic lesions probably closely related to peliosis hepatitis (as discussed below), have been reported in patients treated with azathioprine (Marubbio and Danielson, 1975), or 6-mercaptopurine (Clark et al., 1960), a metabolite of azathioprine, or 6-thioguanine (Griner et al., 1976), a compound chemically close to 6-mercaptopurine; sinusoidal dilatation has also been described in dogs receiving azathioprine (Stuart et al., 1967).

The hypothesis we offer for the mechanism of peliosis hepatitis is based on an assumption and an observation: (1) sinusoidal dilatation, the basic lesion of peliosis hepatitis, would result from congestion due to a blockade of liver blood outflow; (2) alterations of the walls of some centrilobular veins are present in some of our patients and, interestingly, have likewise been observed in patients with peliosis hepatitis after long-term administration of methyltesterone (Paradinas et al., 1977). From this assumption and this observation, we hypothesise that sinusoidal dilatation in peliosis hepatitis might be the consequence of a blockade of liver blood outflow located at the junctions of sinusoids and centrilobular veins; the absence of vascular lesions in some of our patients and in most cases reported previously might be only apparent and be due to their patchy distribution. In other words, peliosis hepatitis would be a variant of the syndromes resulting from a blockade of liver blood outflow, the other variants being veno-occlusive disease of the liver and Budd-Chiari syndrome in which the blockade is located on
the centrilobular veins and on the main hepatic veins, respectively.

Our hypothesis fits in with, and is reinforced by, the following observations and considerations: (1) the lesions of centrilobular veins are more frequent in our patients with the major form of peliosis hepatis than in those with the minor form; a similar parallelism between the degree of peliosis hepatis and the severity of the vascular lesions has been noted in patients with the disorder after long-term administration of methyloxysterone (Paradinas et al., 1977); (2) sinusoidal dilatation is the basic lesion in peliosis hepatis as well as in veno-occlusive disease of the liver and Budd-Chiari syndrome; the random distribution of sinusoidal dilatation in the former and the centrilobular predominance in the latter conditions might be related to the different locations of the blockade of liver blood outflow; (3) some aetiological factors are common to peliosis hepatis and thrombosis of the hepatic veins or veno-occlusive disease of the liver; this is the case for oestrogenic steroids and azathioprine; the former have been recognised as a cause of both peliosis hepatis and similar lesions (Winkler and Poulsen, 1975) and thrombosis of the hepatic veins (Hoyumpa et al., 1971); the latter has been mentioned as a cause of veno-occlusive disease of the liver (Marubbio and Danielsson, 1975), and could be the aetiological factor of peliosis hepatis in our patients; (4) portal hypertension, a common complication of the major form of peliosis hepatis in our patients, might be another consequence of the presumed blockade of liver blood outflow.

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