Dengue virus induced hepatitis with chronic calcific changes

History—A 15 year old patient from Guadeloupe (French Indies) was assessed for liver transplantation, having developed acute liver insufficiency after a week of flu-like illness and jaundice.

Investigations—Viral hepatitis serology (hepatitis A, B, non A-non B), herpes virus simplex, Ebstein-Barr virus, cytomegalovirus, and sequential tests for haemorrhagic fever viruses (dengue, chikungunya, yellow fever, Japanese encephalitis, and West Nile) were negative. Ultrasonography showed a heterogeneous liver with multiple large hyperechogenic zones disseminated to all hepatic segments. Transjugular liver biopsy showed preserved liver architecture, numerous and diffuse foci of hepatocyte necrosis, affecting all zones randomly, in association with few Councilman bodies. These foci of non-zonal necrosis contained minor inflammatory changes with only rare lymphocytes and histiocytes. Subsequently, all four dengue serotypes 1–4 rose dramatically, revealing an acute dengue virus infection.

Outcome—The patient did not require transplantation and improved with conservative management. Ten years later follow up tests revealed a positive hepatitis C serology by ELISA and radioimmunoblot assay, probably contracted after blood transfusion. Human immunodeficency virus and hepatitis B virus serology were negative. Liver computerised tomography showed hepatomegaly, with diffuse hyperdense areas distributed throughout the liver, without mass effect, suggestive of calcifications (fig 1A, B). Percutaneous liver biopsy confirmed the presence of diffuse non-zonal calcified areas (fig 1C) which paralleled areas of previous hepatic necrosis found on the biopsy 10 years earlier. Chronic hepatitis C changes (portal and lobular inflammation and fibrosis) were not observed (fig 1D).

Discussion—Dengue fever is an endemic arthropod borne viral disease transmitted by the mosquito *Aedes aegypti*.[1] All four dengue serotypes cause a variety of clinical manifestations ranging from a flu-like illness to severe haemorrhagic fever with shock. Biological and clinical hepatitis is a well known feature of this infection[1 2] but is almost never documented on histology. Severe hepatocellular insufficiency is usually associated with confluent necrosis, intense portal and lobular inflammation, and periportal hepatocyte necrosis. However, histological features observed in our case resembled those of less common diseases such as yellow fever and were similar to those reported previously from postmortem liver sections with dengue infection.[2] Evidence of direct hepatocyte infection has been demonstrated in vivo by the presence of dengue viral antigens in these cells and by immunohistochemistry on paraffin liver sections.[3] Molecular biology has shown that apoptotic hepatocytes were found to be colocalised with dengue virus infected hepatocytes.[3] Calcification has not been reported previously secondary to fulminant or subfulminant

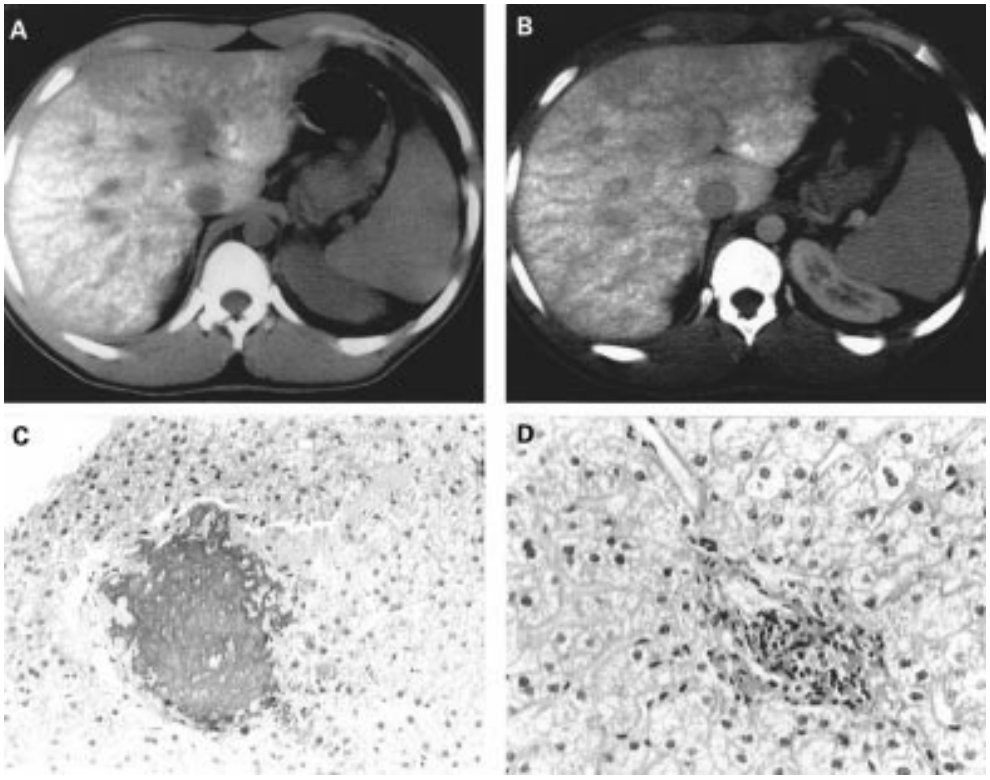

Figure 1 Tomodensitometry 10 years after the initial infection without (A) and with (B) intravenous contrast, revealing diffuse hepatic calcifications. Corresponding histology from liver biopsy showing the focus of calcification surrounded by a fine rim of fibrosis (C). Note the absence of portal inflammation and fibrosis (D). Haematoxylin-eosin stain, ×180 (C), ×250 (D) .

classical viral hepatitis, which gives rise to mutilating post-inflammatory fibrosis or cirrhosis.[4] Previous studies have hypothesised a link between the occurrence of calcifications and apoptosis[5] and this may explain the findings observed in this patient. This case demonstrates that dengue virus induced liver injury should be included in the differential diagnosis of fulminant hepatitis in endemic areas; it may be responsible for asymptomatic calcified long term sequelae. Lack of reports of subsequent calcification in cases of hepatic dengue involvement may result from the limited number of patients surviving such an acute liver insult.

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