Thorotrast associated nodular regenerative hyperplasia of the liver

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Abstract
A case of nodular regenerative hyperplasia (NRH) of the liver is described in association with exposure to the radiographic contrast medium Thorotrast. This is the first case in which the pathological findings have been fully documented. It is suggested that NRH may have developed through Thorotrast induced damage to portal vein radicles.

Keywords: Thorotrast; nodular regenerative hyperplasia; liver

Case report
A 64 year old man presented with a short history of ascites and a general decline in health. An ultrasound scan suggested hepatic cirrhosis but computed tomography, using intravenous contrast, revealed high density material in a reticular pattern throughout the liver (fig 1). The spleen was also of high density. Liver function tests were deranged, with a raised \( \gamma \)-glutamyltransferase (1184 IU/litre, normal range 8–78) and alkaline phosphatase (393 IU/litre, normal range 38–126), but normal bilirubin (12.5 µmol/litre, normal range 3–22). The patient died before a definitive diagnosis could be made.

Three years previously he had a Duke's stage C colonic adenocarcinoma resected and had been well in the interim, taking no drugs. Forty five years before, in 1951, he had a spontaneous subarachnoid haemorrhage owing to rupture of an aneurysm on the right cerebral artery identified on cerebral angiography.

At necropsy there was extensive ascites and the liver was nodular throughout, weighing 1580 g. A tumour nodule 40 mm diameter was present at the anterior surface of the right lobe of the liver and there was generalised peritoneal thickening. Ischaemic heart disease caused by coronary artery atheroma was present, and there were also multiple small pulmonary thromboemboli. No splenic enlargement or varices were seen to suggest portal hypertension.

Liver histology showed nodular regenerative hyperplasia characterised by diffusely distributed nodules of regenerating hepatocytes throughout the liver, with compression of reticulin around the nodules but without associated fibrous tissue. There was also conspicuous brown pigment in portal tracts (fig 2). Microanalysis of the pigment by \( x \)-ray showed it to be thorium-rich (fig 3), consistent with Thorotrast. Although the majority of portal tracts contained normal portal vein branches, there appeared to be loss of the veins in some. The hepatic arteries and veins were otherwise normal. There was carcinomatosis peritonei and the liver tumour was an area of metastatic colonic adenocarcinoma.

Discussion
Nodular regenerative hyperplasia of the liver has been recognised since at least the early 1950s under a variety of synonyms, occurring in up to 0.6% of necropsies. Many clinicopathological processes predispose to its development but the most frequent associations are with immune complex, lymphoproliferative, and myeloproliferative diseases. A spectrum of drugs and toxins has also been implicated, most notably steroids and cytotoxic agents. Hepatic irradiation has been associated with...
nodular regenerative hyperplasia in a patient with Hodgkin’s disease.\(^4\)

Thorotrast was widely used between 1928 and 1955 as an x-ray contrast medium. It contains thorium dioxide with a radioactive half life of approximately 400 years. After intravenous injection it is deposited in the reticuloendothelial system, the majority being stored in the liver. Virtually none is eliminated. Various liver neoplasms have been reported after Thorotrast administration, most notably angiosarcoma and cholangiocarcinoma. There is also an increased incidence of hepatocellular carcinoma and possibly an increased risk of cancers in non-hepatic sites.\(^5\)

Cirrhosis of the liver has been reported, and a 20-fold increase in risk calculated.\(^6\) Further non-neoplastic liver changes described include veno-occlusive disease,\(^7\) hepatoportal sclerosis, focal nodular hyperplasia,\(^8\) and ill defined liver nodularity.\(^9\)

There are two previous reviews alluding to the role of Thorotrast in the development of nodular regenerative hyperplasia,\(^10\) but this case is the first in which the pathological findings are fully documented.

Nodular regenerative hyperplasia is thought to be a regenerative phenomenon following ischaemia of the hepatic acinus which may follow damage to small hepatic arteries or portal veins.\(^7\) There is evidence that Thorotrast may produce vascular damage which in some cases has led to infarction from vessel occlusion.\(^11\) Damage to carotid arteries has been fatal in some cases.\(^12\) In our case, nodular regenerative hyperplasia was associated with a reduction in portal vein branches, possibly caused by chronic alpha irradiation from Thorotrast.

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Figure 3  X Ray microanalysis of the liver pigment showing multiple peaks corresponding to isotopes of thorium (Th). Copper peaks (Cu) are from the specimen support grid.