Clinical Observations

Multiple malignant neoplasms 40 years after angiography with Thorotrast

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Thorotrast (colloidal thorium dioxide) has been known for 30 years to be a cause of malignant disease. Tumours have been reported in nasal sinuses, bones and liver, as well as other sites.[1-7] This communication reports the discovery of two histologically distinct types of malignant tumour of the liver (angiosarcoma and hepatocellular carcinoma), as well as carcinoma of the lung and tubular adenomas of the kidneys, in a man who had undergone angiography with Thorotrast 38 years previously.

Case report

Clinical course

A 74-year-old man was admitted to hospital because of increasing weakness, loss of appetite and progressive swelling of the abdomen for 3 months. Two weeks prior to admission he had begun to experience drowsiness and abdominal pain. His urine became darker, and an episode of diarrhea was reported.

Thirty-eight years earlier, while in hospital for investigation of progressive failure of vision in his right eye, he had undergone bilateral internal carotid arteriography, with Thorotrast (total dose 36 ml) as the contrast medium. This showed a calcified lesion interpreted as an aneurysm of the right internal carotid artery. Two-stage ligation of the artery was performed. He had been in hospital several times for various medical and surgical problems. Fifteen years before the current admission he had given up cigarettes after 20 years of smoking two packs a day. He denied excessive intake of alcohol.

He was icteric and lethargic. His blood pressure was 150/70 mm Hg, and his temperature and pulse rate were normal. His chest was dull to percussion; wheezes and rhonchi were detected at the base of both lungs. Ascites and hepatomegaly were present. Neurologic examination yielded no abnormalities except for blindness of his right eye.

The following abnormal laboratory findings were of note: blood erythrocyte count 2.9 $\times$ 10^{12}/l, hemoglobin level 11.5 g/dl, hematocrit 32.7% and glucose level 143 mg/dl (7.9 mmol/l), total serum bilirubin level 3.8 g/dl (65 μmol/l) and serum levels of lactate dehydrogenase, glutamic oxaloacetic transaminase and alkaline phosphatase 416, 133 and 624 IU/l respectively. Tests for antinuclear, antimitochondrial and anti-smooth-muscle antibodies, α-fetoprotein (AFP) and hepatitis B surface antigen (HB_sAg), the last by radioimmunoassay, gave negative results.

A chest roentgenogram demonstrated hyperinflation and an ill defined opacity in the lower lobe of the left lung that had not changed in appearance in 4 years.

A plain film of the abdomen (Fig. 1) showed fine metallic densities outlining an irregularly shaped liver and a small spleen. Similar speckles were present in the hilar nodes of the spleen and the para-aortic nodes.

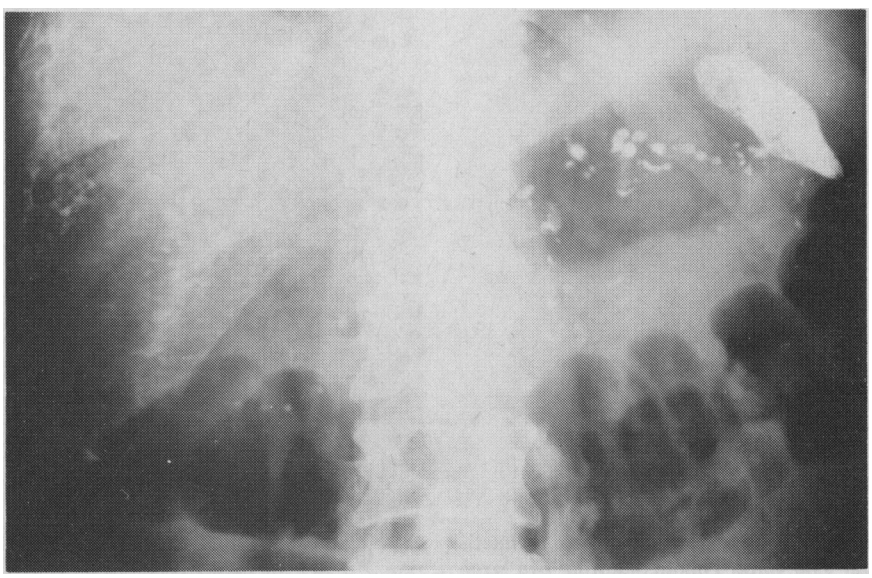

FIG. 1—Plain film of abdomen, showing fine metallic densities, characteristic of Thorotrast deposition, in irregularly shaped liver, small spleen and lymph nodes.

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The distribution and appearance were typical of Thorotrast deposition. A liver–spleen scan with technetium 99m sulfur colloid showed two large defects, one in the right lobe and the second in the left lobe of the liver (Fig. 2). A radionuclide scintiangiogram demonstrated that the left-lobe lesion was hypervascular but there was no perfusion to the right-lobe lesion. The features of the left-lobe lesion were considered consistent with a hepatocellular carcinoma or a very vascular tumour such as a hemangiosarcoma, while those of the right-lobe lesion were considered consistent with a necrotic tumour or an avascular tumour such as a cholangiocarcinoma (known to be associated with Thorotrast). Cytologic study of the ascitic fluid did not reveal malignant cells.

Since it was apparent that the patient was in hepatic failure and in the terminal stage of his illness, no further invasive investigation was considered. He became progressively more lethargic, then confused, and finally comatose. He died 10 days after admission.

Autopsy findings

The abdomen was markedly distended by 2000 ml of serosanguineous fluid. The liver was enlarged and firm, and weighed 1800 g. The capsular surface was irregular, with prominent small and large nodules. There were multiple small hemorrhagic and necrotic foci on the surface of the right lobe, which represented the sites of bleeding. Sections of the surface of the left lobe revealed multiple pale tan, well defined, firm nodules of hepatocellular carcinoma ranging in diameter from a few millimetres to 3 or 4 cm; between the nodules were areas of fibrosis (Fig. 3). The right lobe contained several areas of ill defined reddish, hemorrhagic and necrotic

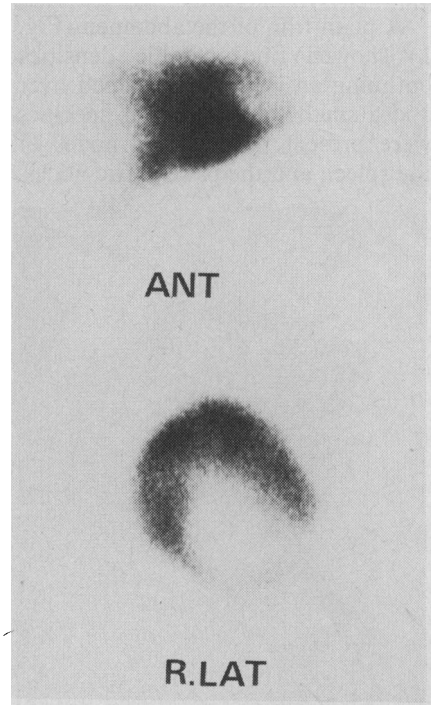

FIG. 2—Liver–spleen scan with technetium 99m sulfur colloid, showing two large defects, one in right lobe and second in left lobe of liver.

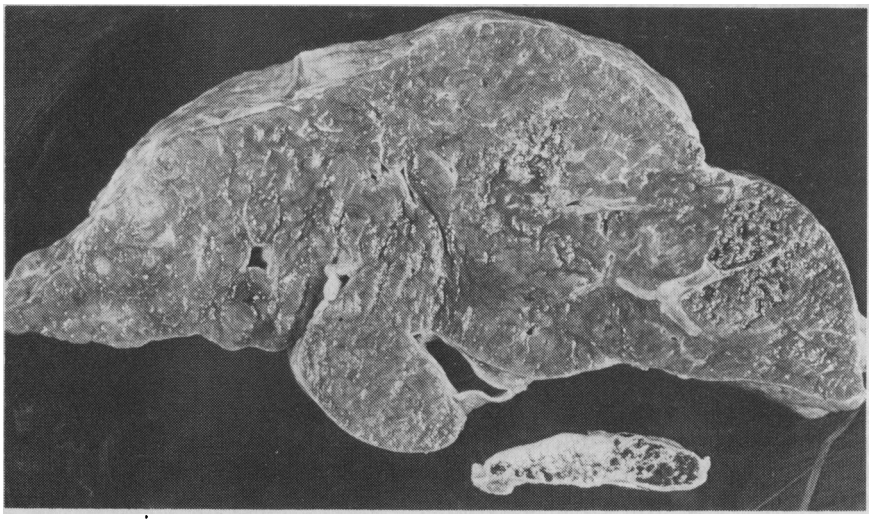

FIG. 3—Coronal section of liver and spleen. Liver is hypertrophic and firm, and contains multiple nodules of hepatocellular carcinoma and angiosarcoma (darker areas). Spleen is small and atrophic, with normal architecture replaced by fibrosis.

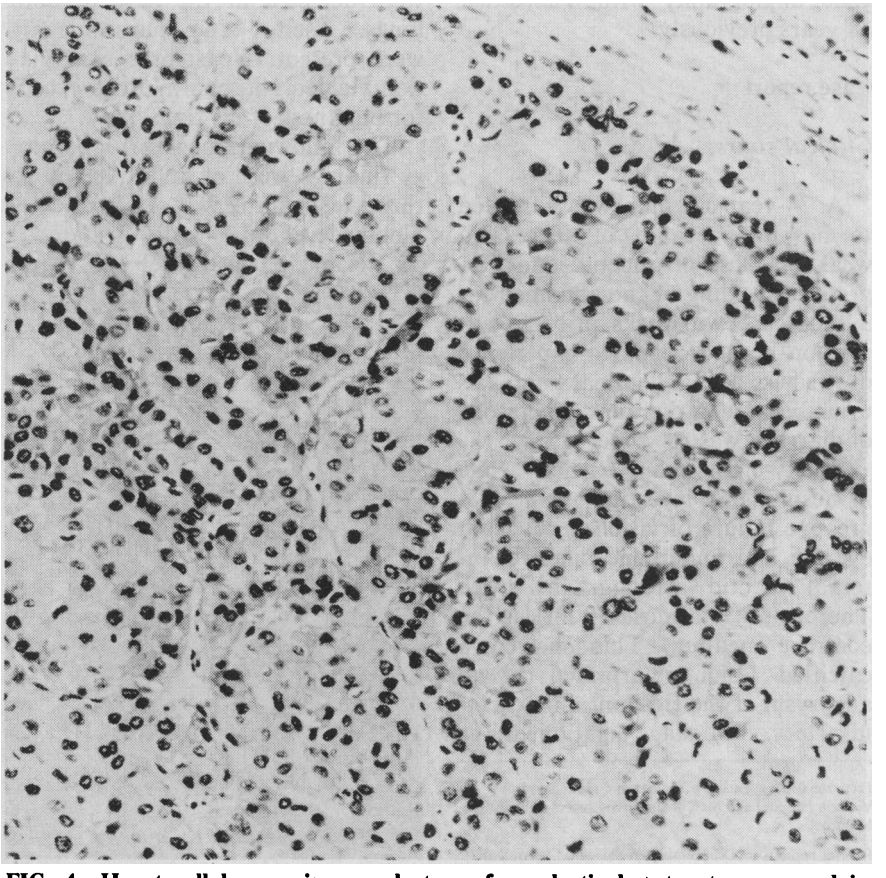

FIG. 4—Hepatocellular carcinoma: clusters of neoplastic hepatocytes arranged in well defined nodules and in trabeculae (hematoxylin–eosin [H–E]; ×190).

lesions, the largest measuring 10 cm in its greatest dimension. There was focal involvement of capsular surfaces by the vascular, friable and necrotic tumour. There was no evidence of portal vein thrombosis. The other abdominal organs were free of tumour.

Microscopy of the sectioned liver showed a mixture of well differentiated to poorly differentiated hepatocellular carcinoma in the left lobe (Fig. 4). Bile formation was present in the tumour cells. Portal fibrosis and bile duct proliferation were prominent throughout the lobe. The right lobe showed a spectrum of morphologic changes characteristic of angiosarcoma. In some areas there were minimal changes, such as hyperplasia and hypertrophy of hepatocytes, sinusoidal dilatation and compression atrophy of adjacent parenchyma. In other areas the hepatic plates were more than one cell thick and showed proliferation of abnormal endothelial cells (Fig. 5); these cells were pleomorphic and had large irregular nuclei and prominent nucleoli, with conspicuous mitoses. The fully developed lesions consisted of peliotic areas (blood-filled lacunae) containing numerous sarcomatous cells and reactive hepatocytes. Hemorrhage and necrosis were prominent. Throughout the parenchyma of both lobes abundant Thorotrast aggregates of various sizes were identified. They were more numerous in portal tracts and areas proximal to the tumours.

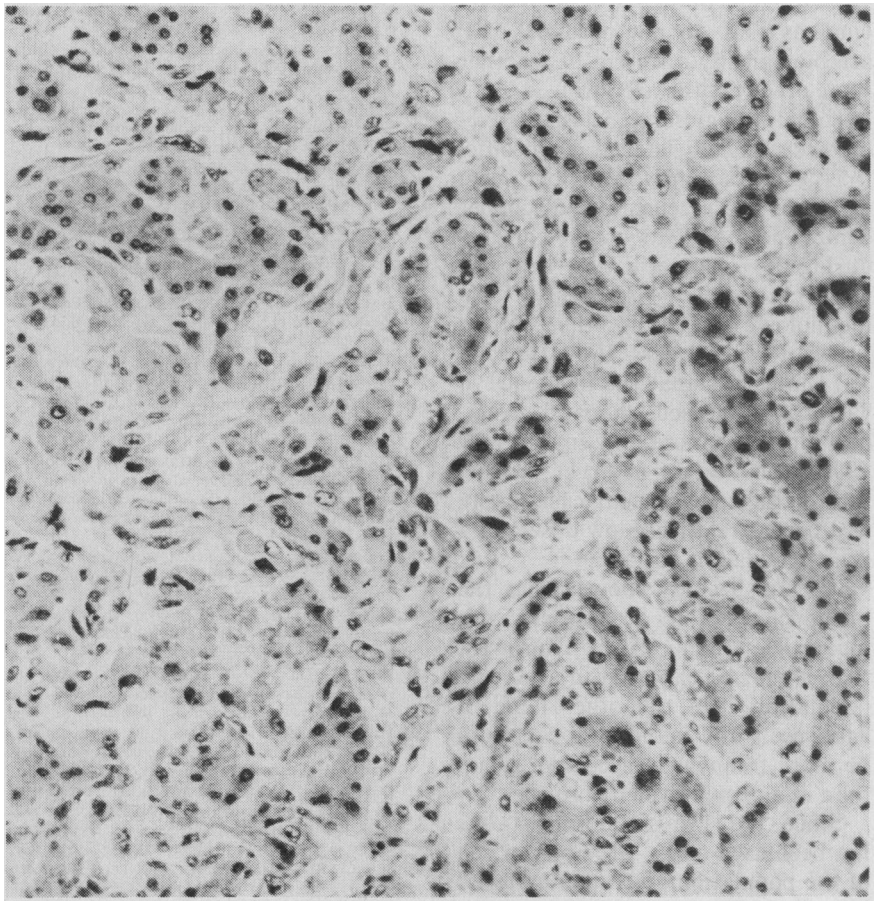

FIG. 5—Angiosarcoma: dilated sinusoids lined by increased number of hyperchromatic endothelial cells; clusters of hepatocytes and erythrocytes within lesion (H–E; ×40).

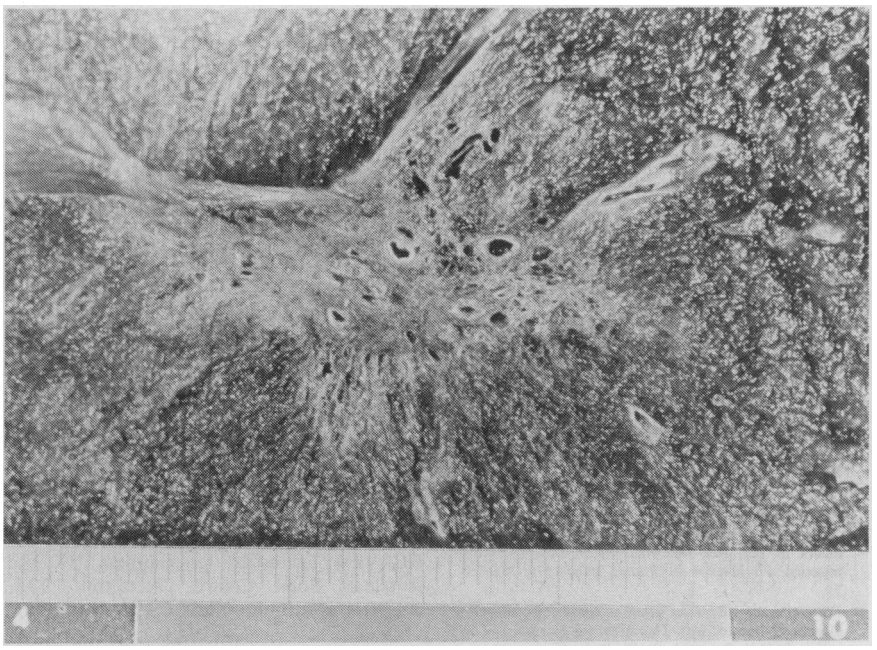

FIG. 6—Small, ill defined adenocarcinoma of left lung. Scale in centimetres.

The spleen was markedly atrophic and weighed only 20 g. Its normal architecture was completely obliterated by fibrosis (Fig. 3). Microscopy showed numerous aggregates of Thorotrast particles in all parts of the parenchyma.

A peripheral scar carcinoma 2 cm in diameter was found in the lower lobe of the left lung near the interlobular septum (Fig. 6). The pleura overlying the lesion was thickened and indented. Microscopy revealed moderate to poorly differentiated adenocarcinoma. Small aggregates of Thorotrast were present near the tumour, though they were less abundant here than in the liver and spleen; they were also noted in the hilar lymph nodes.

Small cortical adenomas were identified in both kidneys. Other changes in the kidneys were compatible with hypertension and diabetes.

Discussion

Thorotrast was first used as a contrast medium for diagnostic radiology in 1928. It could be administered intravenously or intra-arterially and was used in cerebral angi-

ography, hepatosplenography, retrograde pyelography, hysterosalpingography and paranasal sinus cavity visualization.[1-8] Because of the excellent contrast it provided, it was employed in many parts of the world. Doses varied according to the diagnostic procedures.

Thorotrast contains a radioactive isotope, ^{232}Th, which is predominantly an α-particle emitter. It has a biologic half-life of 400 years. After intravenous injection 70% is taken up by Kupffer cells in the liver. Its distribution is inhomogeneous, aggregates of various sizes being formed. It has been estimated that with a 25-ml intravascular dose of Thorotrast the liver receives a mean radiation dose of 25 rad/yr.[8,9]

Dahlgren[10] has suggested that three criteria be met before Thorotrast is implicated as a cause of neoplasia: first, thorium dioxide particles must be present in the immediate vicinity of the tumour; second, the latent period must have been sufficiently long (average 20 years); and, third, the dose must have been sufficiently high. The case we have presented conforms to these criteria.

The long-term side effects of Thorotrast include a granulomatous reaction at the site of injection, most frequently occurring 4 to 6 years after administration. The most important late effect is the development of malignant tumours, usually in the liver. Hepatocellular carcinoma, cholangiocarcinoma and angiosarcoma have all been described.[2,3,11-16] In addition, there have been individual case reports of mesotheliomas of pleura and peritoneum, sarcoma of the soft tissues of the neck and of bone, and blood dyscrasias.[5] The latent period for the development of any Thorotrast-associated tumour averages 29 years.

Hepatocellular carcinoma usually produces no symptoms or signs until in its late stage, but in Western countries this stage is often preceded by cirrhosis. A rapid and unexplained deterioration in the condition of a patient with cirrhosis, along with a rapid increase in liver enzyme levels in the serum, suggests a hepatocarcinoma. Serum AFP levels exceeding 500 (usually 1000 to 1 million) ng/ml are common in cases of hepatocellular carcinoma.[17] The production of AFP tends to be associated with lower age, male sex, poor differentiation of the tumour and the presence of HB_sAg in the serum.[17,18] It is not clear whether the 10% to 15% of hepatocellular carcinomas that do not produce AFP are biologically different or whether some other factors are involved.

Hepatic angiosarcoma is relatively rare and not Thorotrast-specific: it is also associated with long-term exposure to arsenical and copper compounds and to vinyl chloride during its polymerization to polyvinyl chloride.[17,19] However, an epidemiologic study in the United States for the years 1964 through 1974 indicated that the incidence of Thorotrast-induced hepatic angiosarcoma was increasing in the early 1970s and that in a larger proportion of the more recent cases there had been a relatively low dose and a prolonged latent period.[20]

A Danish study showed that the incidence of lung carcinoma was higher in patients given Thorotrast than would be expected in a normal population.[5] On the other hand, a Japanese study found lung cancer to be more frequent in a control group than in a group given Thorotrast.[21]

Since the 1950s Thorotrast has not been used and a large proportion of the population given this material has died. There remain, however, patients who by virtue of the long period since the administration of Thorotrast are at high risk of not only a single malignant disease but two or three kinds of neoplasms in the liver, as has recently been documented.[4,11,22,23] In addition, as our case shows, neoplasms may develop at other sites too.

We thank Dr. Jonathan F. Meakins for helpful discussions about his patient.

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BOOKS

This list is an acknowledgement of books received. It does not preclude review at a later date.

AMERICAN PSYCHOLOGY SINCE WORLD WAR II. A Profile of the Discipline. Albert R. Gilgen. 273 pp. Greenwood Press, Westport, Connecticut, 1982. $29.95 (US). ISBN 0-313-23027-7

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CARE FOR THE DYING AND THE BEREAVED. Edited by Ian Gentles. 160 pp. Anglican Book Centre, Toronto, 1982. $9.50, paperbound. ISBN 0-999030-85-8

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