Hepatic Angiosarcoma (HAS) is the more common mesenchymatous liver tumor. Nevertheless it remains rather rare and accounts for less than 2% of primary hepatic tumors (1, 2). Clinical diagnosis is usually difficult because symptoms and signs are non specific (2, 3). Moreover HAS is also difficult to differentiate from other hepatic tumors even with modern imaging techniques. As a rule the tumor progresses rapidly and has a poor prognosis (4). We present a rare case of HAS fortuitously diagnosed in an 85-year-old woman. The diagnosis was prompt for several reasons: the patient presented with spontaneous hemoperitoneum – a classical complication of HAS precipitating emergency imaging and surgery –, the MDCT findings were rather typical of a vascular tumor and finally pathognomonic CT signs related to previous Thorotrast (Th²³²) exposure – known as the most known iatrogenic cause of HAS – were associated. The history of the problems associated to the use of Thorotrast (TH²³²) and the imaging features of HAS are briefly remembered (4-7). With a delay of 65 years after Thorotrast exposure, this “historical” case probably represents, to our knowledge, the most delayed presentation of Th²³² related HAS ever published.

Key-words: Liver neoplasms – Thorium oxide.

HEPATIC ANGIOSARCOMA OCCURRING 65 YEARS AFTER THORIUM DIOXIDE (THOROTRAST) EXPOSURE: IMAGING, SURGICAL AND HISTOPATHOLOGIC FINDINGS OF A HISTORICAL CASE

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We report the CT, surgical and histopathologic findings of a rare case of Hepatic Angiosarcoma (HAS) diagnosed in a 85-year-old women 65 years after Thorotrast (Th²³²) exposure for angiography. At the early arterial phase of dynamic MDCT, peripheral curvilinear and central nodular puddling of contrast produced in the 8 cm tumor. Then progressive contrast filling of the tumor was observed on the delayed scans. Associated pathognomonic signs related to previous Th²³² exposure were also found comprising diffuse intrahepatic reticular bands of calcifications, numerous calcified epigastric lymph nodes and a calcified shrunken spleen. Emergency laparotomy was performed because of associated hemoperitoneum. With a delay of 65 years after Thorotrast exposure, this historical case probably represents, to our knowledge, the most delayed presentation of Th²³² related HAS ever published.

Case report

A 85-year-old woman was admitted in the department of gastroenterology for alteration of the general state, macrocytic anemia and left subcostal and epigastric pain exacerbated by meals. Laboratory tests at admission confirmed the anemia with hemoglobin level at 81 g/L (normal range 120-160 g/L), a mild inflammatory syndrome with C-reactive protein level at 45 mg/L (normal value < 6 mg/L) and alteration of the hepatic function with SGOT at 36 U/L (normal value < 35 U/L), SGPT at 17 U/L (normal value < 31 U/L), GGT at 121 U/L (normal value < 36 U/L), LDH at 368 U/L.

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(normal value < 250 U/L), and ALP at 246 U/L (normal range 35-105 U/L). Gastroscopy was normal but abdominal ultrasound (not illustrated) revealed an 8 cm solid mass in the left hepatic lobe.

Multiphasic contrast enhanced abdominal MDCT was performed (Fig. 1). An 8 cm hypodense tumoral mass was confirmed in the S2 & S3

![Image](image1.png)

Fig. 2. — Thick coronal oblique maximal intensity projection (MIP) view (A), Volume Rendering (VR) view (B) and very thick average MPR view (C) illustrate very pathognomonic findings consistent with prior Thorotrast (Thorium dioxide or Th²³²) exposure: lace-like reticular calcifications within the hepatic parenchyma (black stars), multiple extremely dense calcified epigastric lymph nodes (black arrow) and a calcified shrunken spleen (white arrow). Thorotrast is displaced circumferentially by the tumor (small white stars) and is concentrated in its periphery in a capsule like fashion (little white stars). Axial view of the pelvic area (D) shows hyperdense hemorrhagic ascitic fluid (white star).

![Image](image2.png)

Fig. 3. — Intra-operative view (A): diffuse intraperitoneal free hemorrhage is visible and more than one liter of fresh blood was aspirated. The entire surface of the liver has a pale tan reticulated pattern where the Thorotrast accumulated and caused fibrosis (white arrows). The S2 and S3 tumorous segments appear extremely nodular, congestive (black arrow) and numerous superficial erosions are spontaneously bleeding. Gross anatomy (B): at opening the degenerated left lobe has an extremely irregular spongious appearance constituted by an anarchic network of numerous irregular necrotic and hemorrhagic cavities.

![Image](image3.png)

Fig. 4. — Histopathology (A): accumulation of a birefringent Thorotrastic granular material (white arrows) is seen within endothelial neoplastic cells (hematoxylin and eosin staining; magnification of 1000x). B. The typical angiosarcomatous aspect (black star) is constituted by a network of immature anastomotic vascular spaces boarded by very atypical hyperchromatic endothelial cells. The spaces contain red and hematopoietic cells. White star = normal liver.
segments. Diffuse irregular curvilinear peripheral and nodular central pilling of contrast enlightened the mass during the arterial phase. Then progressive filling produced during the portal phase and appeared maximal on a delayed phase. Only two ovoid areas remained hypodense probably corresponding to cystic and/or necrotic foci. These characteristics were considered compatible with a vascular tumor. Associated but fundamental findings in terms of specific diagnosis were simultaneously found in the epigastric area comprising diffuse intraperitoneal fine lace-like reticular bands of calcifications, the presence of multiple extremely dense calcified epigastric lymph nodes and finally a calcified shrunken spleen. These pathognomonic findings were extremely similar to those reported in the literature in patients having previously been exposed to Thorotrast (Th²³²). Further interrogation of the old woman revealed a previous history of cerebral arteriography performed in 1948 at the age of 20 years. This arteriography had been performed with Thorotrast to investigate tinnitus. The decisive CT finding justifying an emergency laparotomy was the presence fresh hemorrhagic ascites in the pelvic cavity (Fig. 2). The final preoperative radiologic diagnosis was that of a bleeding hepatic angiosarcoma (HAS) that had developed 65 years after Thorotrast exposure.

The clinical state of the old woman suddenly deteriorated with discomfort, hypotension and an acute recrendescence of epigastric pain. Emergency laparotomy found more than one liter of fresh blood in the peritoneum. The entire surface of the liver – where Thorotrast had accumulated and had induced fibrosis – had a pale tan reticulated pattern (Fig. 3). The S2 and S3 tumorous segments were diffusely nodular and congestive with numerous spontaneously bleeding superficial erosions. At opening the tumor had an extremely irregular spongious appearance constituted by an anarchic network of numerous irregular necrotic and hemorrhagic caviets.

Histopathology (Fig. 4) revealed accumulation of birefringent thorotrastic granular material within neoplastic endothelial cells. The typical angiosarcomatous aspect was confirmed and constituted by a network of anastomotic vascular spaces boarded by atypical hyperchromatic endothelial cells. The immediate postoperative period was uneventful but unfortunately the general state of the old women altered rapidly. She experienced recurrent episodes of ischemic strokes and died one month later.

Discussion

Thorotrast was the trade name of an X-ray contrast medium used worldwide from about 1928 to 1955 (4–7). The preponderant form of administration was intra-arterial injection mostly for cerebral angiography, but this contrast medium was also used for ventriculography, hepatospleno-portography, pyelography, urethrography, hysterosalpingography and instillation of anatomic cavities comprising paraanal sinuses. It consisted of a 25% colloidal solution of thorium dioxide (Th²³²). After intravascular injection Th²³² aggregates were stored lifelong in the reticulo endothelial system (4–7).

Approximately 100% of the medium was taken by the liver, 20% by the spleen and the remainder by the bone marrow and lymph nodes causing a chronic exposure to alpha (90%), beta- (9%) and gamma (1%) rays especially in these organs. The biological half-time was of 400 years (4–7).

Approximately ten years after its introduction, first reports of possible carcinogenic effects, especially tumors formation in the liver, were published in the international literature. Despite these publications, the use of Th²³² increased, because of the lack of acute toxicity and excellent radiological results compared with other contrast media. With time, the carcinogenic effects of Th²³² became increasingly clear and numerous cases of Th²³²-related malignancies were reported, especially malignant hepatic tumors, such as hepatocellular carcinoma, cholangiocarcinoma and hemangiosarcoma (HAS) (2-7). Th²³² was abandoned following a report by MacMahon et al. (8) of HAS attributed to Thorotrast exposure in 1947 (6–8).

Since about 1950, various national epidemiologic studies, sometimes extending over very long periods, undertook observation of large series of exposed patients and compared them with cohorts of control patients. The purpose was the study of the long term effect of Th²³² in the depository organs (5, 9). The main related reported diseases and causes of death were malignant primary liver tumors (HAS, hepatoma, cholangiocarcinoma), cirrhosis of the liver, blood diseases comprising anaplastic anemia, thrombocytopenic anemia, hemolytic anemia, myelofibrosis and other neoplastic diseases comprising cancers of the extrahepatic bile duct, pancreas, oesophagus, larynx, non-hodgkin's lymphoma, bone sarcomas, plasmocytomas and mesothelias (5-7).

Various rare cases of transitional cell carcinoma or squamous cell carcinoma due to suburothelial thorium deposition – thorotrast kidney – have been described in patient who had undergone retrograde pyelography with Thorotrast (10).

Statistical analysis showed that the incidences of these disorders were significantly higher in the exposed patients than in the controls. The lifespan of Thorotrast administered persons decreased with the amount of Th²³² injected. A clear mean dose rate effect relationship exists: the tumor frequency depends on the time of exposure or the cumulative dose to the liver respectively and not on the age at injection (4–5).

Three criteria must be met before implicating Th²³² as a cause of neoplasia: the Th²³² must be present in vicinity of the tumor, the latent period must be sufficiently long (average 20 years) and the dose must be sufficiently high (6).

CT findings of Th²³² deposition are extremely pathognomonic. Typically high-density deposits are seen in the liver, spleen and lymph nodes and the atrophy of the spleen due to fibrosis is also a typical sign (2-4). Deposition in bone marrow is also described (4). Beside the common hepatocellular carcinoma, more rare malignant tumours of the liver are occasionally seen in daily clinical practice. Although benign vascular tumors of the liver are extremely common (hemangioma being the most familiar) malignant vascular tumors (HAS, epithelioid hemangioendothelioma and Kaposi sarcoma) are very rare (2). Although it is the more common mesenchymatous liver tumor occurring more frequently than fibrosarcoma, malignant fibrohistiocytoma and leiomyosarcoma, HAS accounts for less than 2% of primary hepatic tumors, with an estimated frequency of 0.14 to 0.25 per million (1-4). It is more common in late adulthood (6°7° decade) and in males (ratio 4:1).

Etiologic factors in HAS may be environmental or occupational exposure to carcinogens comprising thorium dioxide (Th²³²), polychloro- vinyl chloride, arsenic, inorganic copper and anabolic steroids (1). In all cases of environmental exposure, a prolonged latency period has been
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established of 20-30 years on average (6). TH²³² is the most known iatrogenic cause of HAS the liver, 7-10% of HAS being Th²³² related (2, 4). HAS is also associated with hemochromatosis and von Recklinghausen disease (1, 3). However, most of HAS (75%) occur either in the absence of know risk factors or with cirrhosis of the liver (1, 2).

The diagnosis of HAS is often performed too late due to nonspecific symptoms comprising abdominal pain, weakness, alteration of the general state (2, 3). Ascites and jaundice may be seen. Hemorrhagic ascitis is common and spontaneous hemoperitoneum and splenic metastases also occur (2, 3).

In HAS vessels are lined with malignant endothelial cells (2). The tumor cells also grow along preformed vascular channels, particularly the sinusoids, and may form solid nodules consisting of malignant spindle cells or cavitary spaces lined with tumor cells. In cases related with Th²³² the tumor grows in an infiltrating pattern and contains some Th²³² but the majority of the product however is displaced circumferentially by the tumor and is concentrated in the periphery of the HAS in a capsule like fashion (2, 3). This situation was found in the reported case (Fig. 1). Additionally in case exposed to Th²³² the entire surface of the liver – as also typically observed in our case (figure 3) – has a pale tan reticulated pattern where the Th²³² accumulated and produced secondary fibrosis.

In the absence of Th²³² exposure, the CT appearance of HAS is consistent with a vascular tumour, in which two predominant growth patterns can be seen: multinodular lesions or a predominantly large solitary mass (1, 2, 4). These masses generally appear spontaneously hypoattenuating on native CT (2, 11). Hyperattenuating areas or areas of very low attenuation near that of fluid may also be found respectively corresponding to fresh hemorrhage or old hemorrhage or necrosis (2). On the dynamic contrast-enhanced CT images and when it appears as a large mass, HAS may show heterogeneous enhancement during the arterial phase. At delayed imaging, there is progressive diffuse enhancement of the lesion compared with the rest of the early phase images. This enhancement pattern on dynamic contrast enhanced images merely mimics that of a cavernous hemangioma, a benign tumor which is finally 10,000 times more common than HAS. Histopathologically multiple vascular channels that are separated by fibrous septa are similar in both tumors (1, 2, 11, 12). During the hepatic parenchymal phase or delayed post-contrast scans, the entire mass or at least some of its areas become isodense with normal liver (11). When typical central necrosis or hemorrhage is present substantial and prolonged peripheral enhancement may appear and may mimic a very large benign angioma in which incomplete contrast filling is a rule (2, 7).

Recent reports have demonstrated some distinctive aspects of HAS at biphasic imaging when compared with classical hemangioma (3, 11): HAS shows more heterogeneous and persistent enhancement that may be less than that of the aorta or hepatic artery, while typical hemangioma shows progressive centripetal nodular enhancement that is of similar density of the contrast opacified blood in the aorta or the hepatic artery during all phases of imaging (3). Moreover some cases show not only peripheral curvilinear puddles of contrast but also multiple irregular central felleck enhancements – as present in the reported case (Fig. 1) – on early contrast-enhanced CT (11). When not related to Th²³² exposure, HAS, whatever presenting as multiple nodules or as a single mass, often cannot be readily distinguished from hypervascular metastases (such as from neuroendocrine tumors) and hepatocellular carcinoma (3). All of these tumors may demonstrate internal hemorrhage and heterogeneity, in addition to early and heterogeneous enhancement. In contrast to hepatocellular carcinoma, however, HAS demonstrates continuing, progressive enhancement on delayed-phase images. Splenic metastases, associated hematologic abnormalities and the lack of cirrhosis or elevated alpha-fetoprotein may also suggest HAS rather than of hepatocellular carcinoma. The differential diagnosis also concerns other tumors comprising hemangioma, epithelioid hemangioendothelium, cholangiocarcinoma and hepatoblastoma (13). When Th²³² exposure is recog-
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