JBR–BTR, 2014, 97: 254-258.

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

B. Coulier[1], F. Pierard[2], I. Gielen[3], Ph. Maldague[4]

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 (Th^{232}) 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 Th^{232} 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 Th^{232} related HAS ever published.

Key-words: Liver neoplasms – Thorium oxide.

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 (Th^{232}) exposure – known as the most known iatrogenic cause of HAS – were associated. The history of the problems associated to the use of Thorotrast (TH^{232}) 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 Th^{232} 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 < 5 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

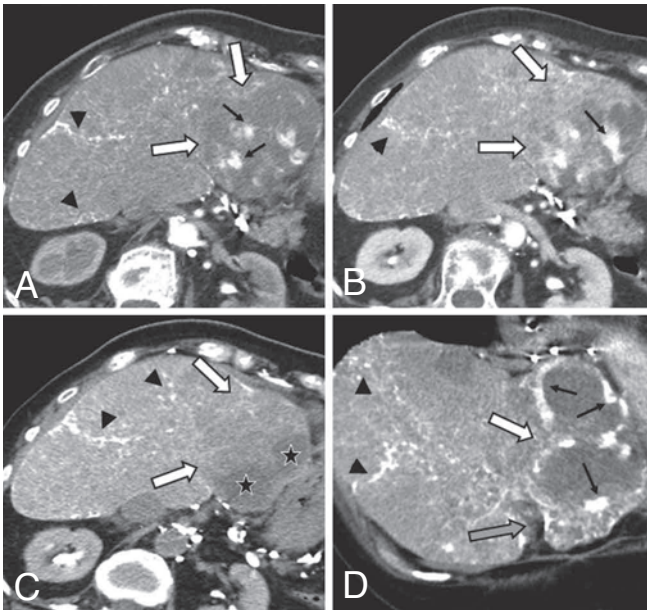

Fig. 1. — Hepatic MDCT axial views obtained during arterial phase (A) (= 30 sec after contrast injection), mixed arterio-portal semi-delayed phase (B) (= 120 sec after contrast injection) and delayed phase (C) (= 180 sec after injection). The liver appears diffusely heterogeneous with diffuse fine lace-like reticular bands of calcifications (small black arrows). An 8 cm hypodense heterogeneous mass if found in the S2 & S3 segments (white arrows) as clearly confirmed on the arterial coronal oblique view (D) where the umbilical fissure is clearly delineated (grey arrow). During the arterial phase (A, D) atypical and unusual diffuse irregular curvilinear peripheral and nodular central puddling of contrast enlightens the mass (small black arrows). Progressive filling produces during the intermediate time (B) and appears maximal on the delayed phase (C). Only two ovoid areas remain hypodense probably corresponding to cystic and/or necrotic foci (black stars).

From: Department of 1. Diagnostic Radiology, 2. Visceral Surgery, 4. Gastroenterology, Clinique St Luc, Bouge (Namur), 3. Institute of Pathology and Genetics, Loverval, Belgium.
Address for correspondence: Dr B. Coulier, M.D., Department of Diagnostic Radiology, Clinique St Luc, Rue St Luc 8, 5004 Bouge (Namur) Belgium.
E-mail: bcoulier@skynet.be

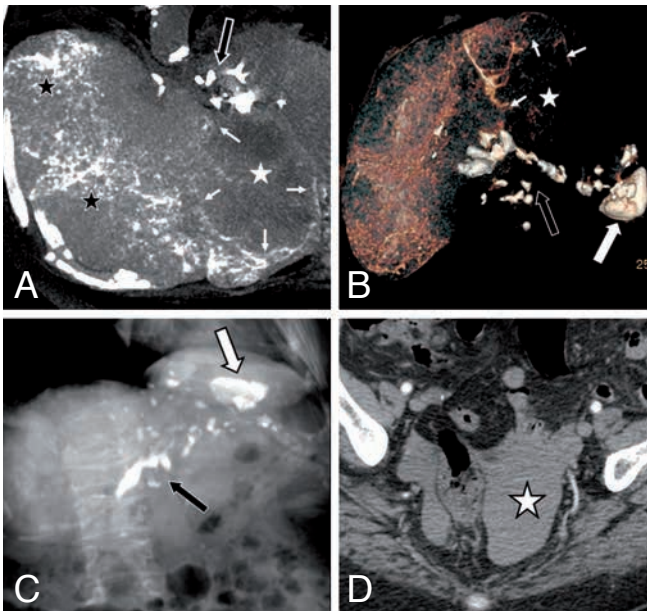

Fig. 2. — Thick coronal oblique maximal intensity projection (MIP) view (A), Volume Rendering (VR) view (B) and very thick average MPR view (C) illustrate very pathognomonic findings consistent with prior Thorotrast (Thorium dioxide or Th^{232}) exposure: lace-like reticular calcifications within the 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).

(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

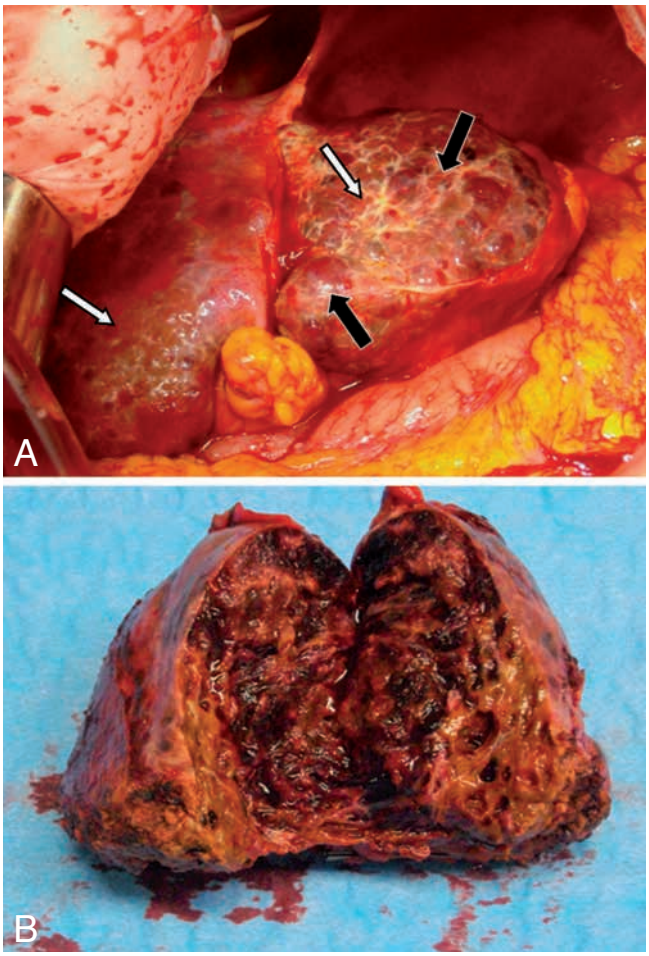

Fig. 3. — Intra-operative view (A): diffuse intraperitoneal free hemorrhage is visible and more than one liter of fresh blood was aspired. The entire surface of the liver has a pale tan reticulated pattern where the Thorotrast accumulated and caused fibrosis (white arrows). The S2 and S3 tumorous segments 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.

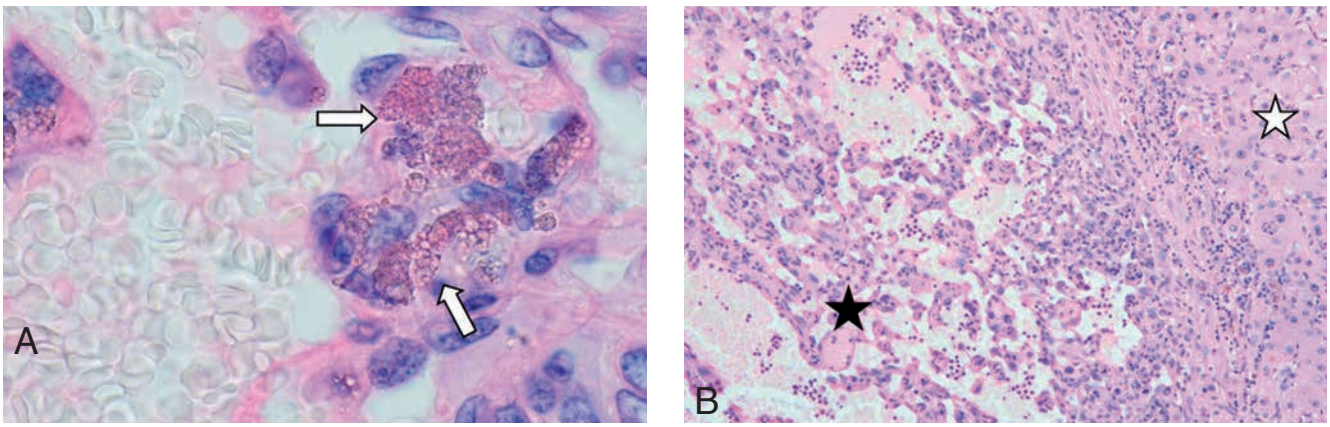

Fig. 4. — Histopathology (A): accumulation of a birefrengent Thorotrastic granular material (white arrows) is seen within endothelial neoplastic cells (hematoxylin and eosin staining; magnification of 100x). B. The typical angiosarcomatous aspect (black star) is constituted by a network of immature anastomotic 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 puddling 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 intrahepatic 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 being exposed to Thorotrast (Th^{232}). 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 recrudescence 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 cavities.

Histopathology (Fig. 4) revealed accumulation of birefrengent thorotrastic granular material within neoplastic endothelial cells. The typical angiosarcomatous aspect was confirmed and constituted by a network of immature anastomotic vascular spaces boarded by very 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, hepato-spleno-portography, pyelography, urethrography, hysterosalpingography and instillation of anatomic cavities comprising paranasal sinuses. It consisted of a 25% colloidal solution of thorium dioxide (Th^{232}). After intravascular injection Th^{232} aggregates were stored lifelong in the reticulo endothelial system (4-7).

Approximately 70% 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 Th^{232} increased, because of the lack of acute toxicity and excellent radiological results compared with other contrast media. With time, the carcinogenic effects of Th^{232} became increasingly clear and numerous cases of Th^{232}-related malignancies were reported, especially malignant hepatic tumours, such as hepatocellular carcinoma, cholangiocarcinoma and hemangiosarcoma (HAS) (2-7). Th^{232} 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 Th^{232} 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 mesothelimas (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 Th^{232} 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 Th^{232} as a cause of neoplasia: the Th^{232} must be present in vicinity of the tumor, the latent period must be sufficiently long (average 20 years) and the dose must have been sufficiently high (6).

CT findings of Th^{232} 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 occuring more frequently than fibrosarcoma, malignant fibrohistyocytoma 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^{th}-7^{th} decade) and in males (ratio 4:1).

Etiological factors in HAS may be environmental or occupational exposure to carcinogens comprising thorium dioxide (Th^{232}), polyvinyl chloride, arsenic, inorganic copper and anabolic steroids (1). In all cases of environmental exposure, a prolonged latency period has been

established of 20-30 years on average (6).

Th^{232} is the most known iatrogenic cause of HAS the liver, 7-10% of HAS being Th^{232} 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 Th^{232} the tumor grows in an infiltrating pattern and contains some Th^{232} 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). Additionnally in cases exposed to Th^{232} the entire surface of the liver – as also typically observed in our case (figure 3) – has a pale tan reticulated pattern where the Th^{232} accumulated and produced secondary fibrosis.

In the absence of Th^{232} 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 that 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 prolongated peripheral enhancement may appears 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 show 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 flecked enhancements – as present in the reported case (Fig. 1) – on early contrast-enhanced CT (11).

When not related to Th^{232} 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 vascular tumors comprising hemangioma, epithelioid hemangioendothelima, cholangiocarcinoma and hepatoblastoma (13).

When Th^{222} exposure is recognized other types of Th^{232} related neoplasms have to be considered comprising hepatocarcinoma (HCC) but also intrahepatic-cholangiocarcinoma (2). The presence of splenic metastases and/or hemoperitoneum are suggestive of HAS. On the contrary an elevated alpha fetoprotein level is rather suggestive of HCC. In general HCC show a rapid global arterial phase enhancement depending on its vascularity, which rapidly decreases to the attenuation value of normal liver (8). In contrast to non-Th^{232} related cases which are preponderantly located in the hepatic hilum, Th^{232} related cholangiocarcinoma are preponderantly of the peripheral-middle type, in which the tumor is located in the periphery to middle portion of the liver (14). Peripheral cholangiocarcinoma classically manifests as a large, well-defined hepatic mass with lobulated margins and peripheral rim enhancement (15). Moreover cholangiocarcinoma frequently demonstrates intrahepatic ductal dilatation (2, 7).

The prognosis of HAS is very poor, almost every patient dying within one year of diagnosis whatever the protocol of chemotherapy used. Attempted radical resections in case of localized disease are also very disappointing with fast relapses of the tumor. Even liver transplantation does not seem feasible in this disease (4).

Conclusion

Rare cases of Thorotrast-related HAS will continue to occur more and more sporadically and the disease will disappear in a few years. The reason is the convergence between a sometimes very long latency after exposure and the fact that the patients are today extremely old – if not already died from various diseases or simply from old age. The use of Thorotrast having been prohibited since 1950, even patients aged 20 to 30 years old at that time are in fact now aged of 83 to 93 years. Nevertheless the reported case remains didactic for young radiologists to be aware of the history of Thorotrast-related hepatic neoplasms. Moreover the MDCT findings of HAS reported in this report are also typical and are independent of a Thorotrast exposure.

References

1. Heo S.H., Jeong Y.Y., Shin S.S., Chung T.W., Kang H.K.: Solitary small hepatic angiosarcoma: initial and follow-up imaging findings. *Korean J Radiol*, 2007, 8: 180-183.
2. Buetow P.C., Buck J.L., Ros P.R., Goodman Z.D.: Malignant vascular tumors of the liver: radiologic-pathologic correlation. *Radiographics*, 1994, 14: 153-166.
3. Koyama T., Fletcher J.G., Johnson C.D., Kuo M.S., Notohara K., Burgart L.J.:

Primary hepatic angiosarcoma: findings at CT and MR imaging. *Radiology*, 2002, 222: 667-673.
4. van Kampen R.J., Erdkamp F.L., Peters F.P.: Thorium dioxide-related haemangiosarcoma of the liver. *Neth J Med*, 2007, 65: 279-282.
5. van Kaick G., Wesch H., Lührs H., Liebermann D., Kaul A.: Neoplastic diseases induced by chronic alpha-irradiation -epidemiological, biophysical and clinical results of the German Thorotrast Study. *J Radiat Res*, 1991, 32: 20-33.
6. Weber E., Laarbaui F,. Michel L., Donckier J.: Abdominal pain: do not forget Thorotrast! *Postgrad Med J*, 1995, 71: 367-368.
7. Azodo M.V., Gutierrez O.H., Greer T.: Thorotrast-induced ruptured hepatic angiosarcoma. *Abdom Imaging*, 1993, 18: 78-81.
8. Macmahon H.E., Murphy A.S., Bates M.I.: Endothelial-Cell Sarcoma of Liver Following Thorotrast Injections. *Am J Pathol*, 1947, 23: 585-611.
9. Mori T., Kato Y.: Epidemiological, pathological and dosimetric status of Japanese thorotrast patients. *J Radiat Res*, 1991, 32: 34-45.
10. Oyen R.H., Gielen J.L., Van Poppel H.P. et al.: Renal thorium deposition associated with transitional cell carcinoma: radiologic demonstration in two patients. *Radiology*, 1988, 169: 705-707.
11. Yu R., Zhang S., Hua J.: Hepatic angiosarcoma: CT findings. *Chin Med J (Engl)*, 2003, 116: 318-320.
12. Peterson M.S., Baron R.L., Rankin S.C.: Hepatic angiosarcoma: findings on multiphasic contrast-enhanced helical CT do not mimic hepatic hemangioma. *AJR*, 2000, 175: 165-170.
13. Rademaker J., Widjaja A., Galanski M.: Hepatic hemangiosarcoma: imaging findings and differential diagnosis. *Eur Radiol*, 2000, 10(1): 129-133.
14. Kojiro M., Sugihara S., Ito Y. et al.: Pathomorphological study of thorotrast-related intrahepatic cholangiocarcinoma – a comparison with non-thorotrast cases. *Gan No Rinsho. Japan Journal of Cancer Clinics*, 1986, 32: 349-355.
15. Han J.K., Choi B.I., Kim A.Y. et al.: Cholangiocarcinoma: pictorial essay of CT and cholangiographic findings. *Radiographics*, 2002, 22: 173-187.