Netherlands
The Journal of Medicine

REVIEW

Thorium dioxide-related haemangiosarcoma of the liver

R.J.W. van Kampen*, F.L.G. Erdkamp, F.P.J. Peters

Department of Internal Medicine, Maasland Hospital, Sittard, the Netherlands, *corresponding author (currently: Department of Internal Medicine, Maastricht University Hospital, Maastricht, the Netherlands): e-mail: rjw.vankampen@gmail.com

ABSTRACT

Rare tumours of the liver are occasionally seen; thorium dioxide-related haemangiosarcoma of the liver, with an estimated frequency of 0.14 to 0.25 per million in the normal population, is one of these. Causes, epidemiology and pathobiology are described related to a clinical case of angiosarcoma. A differentiation of hepatic tumours with imaging techniques is presented. Last, a short review on up-to-date treatment of haemangiosarcoma is discussed. Lessons can always be learned from history: will the contrast agent gadolinium be the Th^{232} of this era?

KEYWORDS

Hepatic haemangiosarcoma, postradiation cancer, thorium dioxide

INTRODUCTION

Liver carcinoma, especially primary hepatocellular carcinoma, is quite a common tumour in the world, accounting for 1 to 2% of malignant tumours at autopsy in Western Europe and the United States.[1] Beside these more common liver carcinomas, rare tumours of the liver are occasionally seen in daily clinical practice. Angiosarcoma of the liver, with an estimated frequency of 0.14 to 0.25 per million,[2] is one of these rare tumours. Aetiological factors in angiosarcoma are exposure to thorium dioxide (Th^{232}), polyvinyl chloride, arsenic, inorganic copper and anabolic steroids. Th^{232} is the most known iatrogenic cause of angiosarcoma of the liver. Pathobiology, radiological signs and epidemiology will be presented related to a recent illustrative case in our hospital.

CASE REPORT

Patient A, a 67-year-old man with a history of osteomyelitis of the right femoral bone, left parietal cerebral infarction and a Whartonian tumour of the parotid gland, was sent to our emergency room for severe malaise of several weeks' duration. A weight gain of 6 kilos within a week was accompanied by progressive dyspnoea and oedema of the lower extremities. The patient smoked five to six cigarettes a day; he was not taking any medication at presentation. Physical examination showed a slightly icteric man with normal blood pressure, pulse and temperature. No pathological lymph nodes were found. Heart and lungs revealed no abnormalities, the abdomen was spherical and tense with minimal peristalsis. Signs of shifting dullness were present; the liver and spleen could not be evaluated because of the ascites. The lower extremities showed pitting oedema. Laboratory tests revealed a haemoglobin level of 6.5 mmol/l, with normal leucocytes and platelets. Creatinine measured 74 μmol/l, and there were abnormalities in the liver function tests: bilirubin 38.3 μmol/l, alkaline phosphatase 365 U/l, aspartate aminotransferase and alanine transaminase 73 and 93 U/l, respectively. The lactate dehydrogenase (LDH) was 494 U/l and albumin 32 g/l. Alpha-fetoprotein level was 2.6 IU/ml. Paracentesis produced 5.5 litres and was a transudate (total protein <20 g/l, LDH 188 U/l). Cytology showed reactive mesothelial cells. No abnormalities were seen on the chest X-ray; abdominal X-ray showed calcifications in the upper left abdominal quadrant (*figure 1*). An ultrasound revealed multiple echo-dense lesions in the liver, which was followed by abdominal computed tomography (CT) scanning. An enlarged liver with capsular and subcapsular densities and a very small spleen, filled with contrast-like agent, were noticed (*figure 2*). The native CT scan also spotted contrast-like agent in the large visceral vasculature.

Figure 1. *Calcifications in the upper abdomen with a spotty appearance of the skeleton, indicating Thorotrast deposition in lymph nodes and skeleton in patient A*

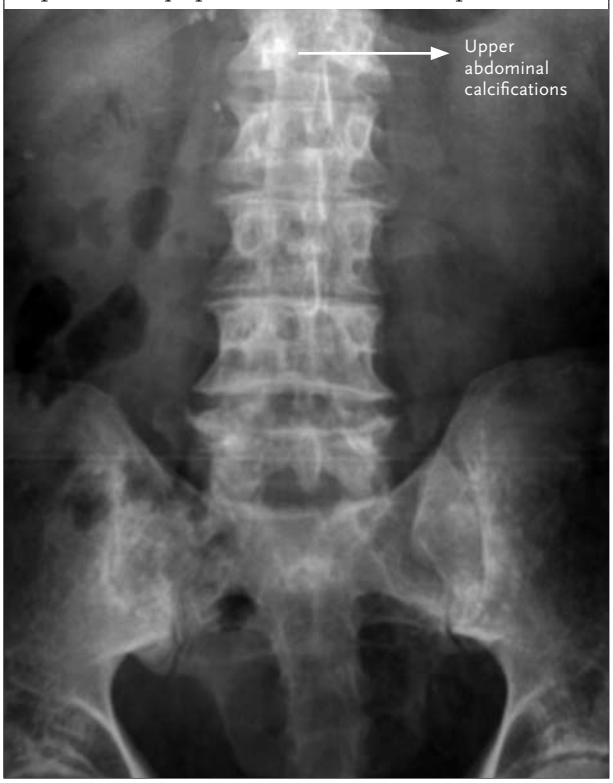
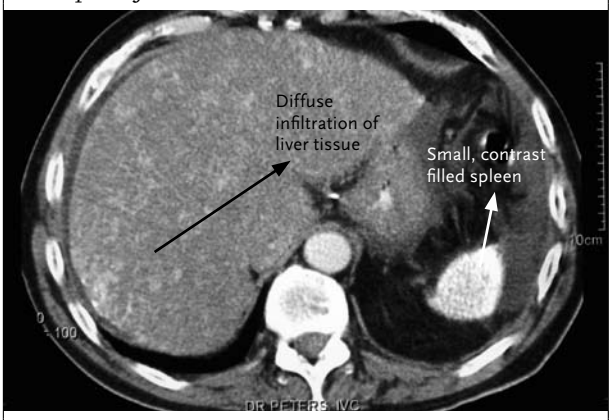


Figure 2. *Abdominal CT scan of patient A showing multiple defects*



Small, high-density spleen. Multiple lucent defects in the liver resembling thorium deposition and defects resembling metastases. Again lucent deposition was noticed in the spine.

Repeated anamnesis resolved the phenomenon: a cerebral angiography was performed when the patient was 17 years (1954) because of an unexplained coma, pointing in the direction of exposure to Th^{232}. The patient denied exposure to polyvinyl chloride.

In the diagnostic procedure a liver biopsy was performed, which revealed a hepatic haemangiosarcoma. Three weeks after diagnosis our patient died due to progressive hepatic failure. Post-mortem section revealed a very small, contrast-filled spleen and a large liver diffusely infiltrated with tumour. Microscopically, the diagnosis of hepatic haemangiosarcoma was confirmed and large quantities of Th^{232} agent were seen in the liver, spleen and bone tissue.

Thorium dioxide and its effects

Thorotrast was a 25% thorium dioxide (Th^{232}) colloidal solution, used worldwide between 1928 and 1955 as a contrast medium for various roentgenographic examinations. Th^{232} was developed for specific imaging of liver and spleen but it was mostly used in cerebral angiographies. Approximately ten years after its introduction, reports of possible carcinogenic effects, especially tumour 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 haemangiosarcoma.[3,4] Other Th^{232}-related neoplasms such as granuloma, bone sarcoma, plasmacytoma and malignant peritoneal or pleural mesothelioma were also reported. Coexistent Th^{232}-related neoplasms were seen in one patient.[5]

Th^{232} is a radioactive isotope that naturally emits α-, and β-particles and γ rays. Ninety percent are α-particles and Th^{232} has a half-life of 14 billion years.[6] After intravascular injection Th^{232} is stored for life in the reticulo-endothelial system, particularly the liver, spleen and bone marrow. Chronic irradiation with an estimated radiation dose of approximately 0.250 grays a year results.[7] Higher amounts of injected Th^{232} seem to account for a higher incidence of liver tumours.[6] Although cholangiocarcinoma is most frequently seen, thorium-related angiosarcoma is characteristic for chronic α-radiation.[8] Characterisation of genetic changes in Th^{232}-induced liver tumours revealed that large deletions were not frequently seen. Typically most mutations were transitions, as is also seen in neoplasms in the general population. This suggests that the changes in thorium-induced carcinomas are not the direct effect of radiation, but mainly of delayed mutations.[9] The effects of these delayed mutations lie around 40 years after exposure, but cases up till 60 years after exposure have been published.

Epidemiology

The effects of chronic low-dose α-particle radiation have been investigated in cohorts of patients previously injected with Th^{232} in several countries. In a Swedish

cohort of 432 patients injected with Th^{232} with a follow-up period of 40 years, 170 cases of cancer were diagnosed. According to the standardised incidence ratio, 57 cases were expected.[10] In a Portuguese cohort study (1931 exposed patients, 2258 non-exposed patients) overall mortality was increased in the Th^{232} group, peaking 30 years after administration. This rise in overall mortality was essentially due to liver cancer (RR 70.8; 95% CI 19.9-251.3) and nonmalignant liver disorders (RR 5.67; 95% CI 3.13-10.3) such as liver cirrhosis. As mentioned before, a strong and consistent gradient with cumulative α-particle radiation dose was seen.[11,12] In a large international study, a cohort of 3143 patients were followed for up to 40 years. A significantly increased mortality among patients exposed to Th^{232} was detected (RR 1.7; 95% CI 1.5-1.8).[7,13]

Radiographic and pathological signs

CT findings of Th^{232} deposition are pathognomonic. Typically, high-density deposits within the liver, spleen and lymph nodes are seen (*figures 1* and *2*). Atrophy of the spleen because of fibrosis is also a typical sign of previous Th^{232} exposure. Deposition of Th^{232} in bone marrow is also described, which can cause anaemia, thrombocytopenia and leucopenia in patients. CT and magnetic resonance imaging (MRI) of the liver provide a useful means of early detection of Th^{232}-related tumours, but can be notoriously nonspecific.[14] The CT appearance of hepatic haemangiosarcoma is consistent with a vascular tumour, in which two growth patterns can be seen: multifocal and an, often large, solitary mass. Shapes can vary from ring-shaped to irregular shapes. Most of the time nodules are hypoattenuating, but isoattanuation or hyperattanuation are also seen. This seems to be a reflection of the varied pathological features of hepatic haemangiosarcoma.

Addition of angiography and/or MRI might improve differentiation between haemangiosarcoma and several other hepatic tumours. Presence of Bud-Chiari syndrome or veno-occlusive disease and the absence of cirrhosis make the presence of primary hepatic haemangiosarcoma more plausible.[15]

Shortly after exposure to Th^{232}, depositions are present in Kupffer cells located within sinusoids and uniformly distributed throughout the liver parenchyma from portal tract to central veins. At that time extracellular deposits are not usually seen. With time, mononuclear cells containing Th^{232} may form and extracellular deposits may be seen. Collagen deposition and areas of fibrosis are seen.

Haemangiosarcoma is characterised by spindle-shaped cells, demonstrating vascular formation in different patterns. Substantial areas of necrosis and haemorrhage are present most of the time (>80%). Immunochemically factor VIII stains are positive.

Treatment

The prognosis of hepatic haemangiosarcoma is very poor, almost every patient dying within one year of diagnosis. Several sarcoma studies with angiosarcoma included as a subgroup show rather disappointing results. Schedules containing doxorubicin and cyclophosphamide, which are considered the first-line therapy, reveal response rates of 20% in the entire group of advanced sarcomas. In approximately 5% of the entire group an improvement in overall survival is seen. A number of phase II and III trials with several agents, e.g. docetaxel, gemcitabine and the combination of ifosfamide and liposomal daunorubicin in first- and second-line therapy, result in almost the same response rates. Some small nonrandomised trials with high-dose chemotherapy and autologous stem cell rescue showed a five-year survival rate of up to 50% in a diverse sarcoma patient group. Whether this only reflects selection of patients needs to be tested in a prospective randomised trial.[16]

Attempted radical resection in case of localised disease, even in R0 resections, seems very disappointing with fast relapses of the haemangiosarcoma. In case of liver transplantation where a haemangiosarcoma was unexpectedly found in the resected liver, relapse-free and overall survival did not last longer than one year. Liver transplantation does not seem feasible in this disease.[17]

CONCLUSIONS

Angiosarcoma of the liver is a neoplasm very rarely seen in the general population, certainly in the case of prior Th^{232} exposure. This is partially due to the relatively small number of patients living today who were exposed to Th^{232}. But nowadays exposure to polyvinyl chloride, a major component in the production of PVC, remains a major cause of angiosarcoma. This is mainly in non-Western countries with inappropriate facilities to prevent exposure in factory workers.

We also think that the story of Th^{232}-related malignancy should remind us of the possible dramatic effects of (formerly) prescribed medications in patients. For example, in the last decades, the accrual of gadolinium as a contrast agent in MRI studies has been welcomed as an almost ideal and nontoxic agent, compared with the known toxicities of conventional iodine-containing contrast agents. But several recent reports have associated intravenous gadolinium with a rare, relatively new, and as yet idiopathic disorder called nephrogenic systemic fibrosis.[18]

ACKNOWLEDGEMENT

The authors would like to thank C.A. Kamps, radiologist, for reviewing the radiographic images.

REFERENCES

1. De Bac C. Pathogenic factors in cirrhosis with and without hepatocellular carcinoma: A multicenter Italian study. Hepatology 1994;20:1225.
2. Mani H, van Thiel DH. Mesenchymal tumours of the liver. Clin Liver Disease 2001;5:219-57.
3. MacMahon E, Murphy AS, Bates MI. Endothelial cell sarcoma of the liver following Thorotrast injection. Am J Pathol 1947:585-613.
4. Leitner ZA. Sequelae of Thorotrast. BMJ 1965;2:1062-3.
5. Jansen TL, Meijer JW, Kesseliring FO, Mulder CJ. A surprising double tumour of the liver 60 years following Thorotrast diagnosis. Ned Tijdschr Geneeskd 1992;136:1413-7.
6. Goto A, Takebayashi Y, Liu D, et al. Microdistribution of alpha particles in pathological sections of tissues from Thorotrast patients detected by imaging plate autoradiography. Radiat Res 2002;158:54-60.
7. Sharp GB. The relationship between internally deposited alpha-particle radiation and subsite-specific liver cancer and liver cirrhosis: an analysis of published data. J. Radiat Res 2002:371-80.
8. Harrison JD, Muirhead CR. Quantitative comparisons of cancer induction in humans by internally deposited radionuclides and external radiation. Int J Radiat Biol 2003;79:1-13.
9. Ishikawa Y, Wada I, Fukumoto M. Alpha-particle carcinogenesis in Thorotrast patients: epidemiology, dosimetry, pathology and molecular analysis. J Environ Pathol Toxicol Oncol 2001;20:311-5.
10. Nyberg U, Nilsson B, Travis LB, Holm LE, Hall P. Cancer incidence among Swedish patients exposed to radioactive Thorotrast: a forty year follow-up survey. Radiat Res 2002;157:419-25.
11. dos Santos Silva I, Jones ME, Malveiro F, Swerdlow AJ. Mortality in the Portuguese Thorotrast study. Radiat Res 1999;152:S88-92.
12. Dos Santos Silva I, Malveiro F, Jones ME, Swerdlow AJ. Mortality after radiological investigation with radioactive Thorotrast: a follow-up study of up to fifty years in Portugal. Radiat Res 2003;159:521-34.
13. Travis LB, Land CE, Andersson M, et al. Mortality after cerebral angiography with or without radioactive Thorotrast: an international cohort of 3,143 two-year survivors. Radiat Res 2001;156:136-50.
14. Koyama T, Fletcher JG, Johnson CD, Kuo, MS, Notohara K, Burgart L. Primary hepatic angiosarcoma: findings at CT and MR imaging. Radiology 2002;222:667-73.
15. Rademaker J, Widjaja A, Galanski M. Hepatic hemangiosarcoma: imaging findings and differential diagnosis. Eur Radiol. 2000;10:129-33.
16. Blay J-Y, van Glabbeke M, Verweij J, et al. Advanced soft-tissue sarcoma: a disease that is potentially curable for a subset of patients treated with chemotherapy. Eur J Cancer 2003;39:64-9.
17. Weitz J, Klimstra DS, Cymes K, et al. Management of primary liver sarcomas. Cancer 2007;109:1391-6.
18. Lin S-P, Brown JJ. MR contrast agents: physical and pharmacologic basics. J Magn Reson Imaging 2007;25(5):884-99.