LOCOREGIONAL LATE EFFECTS OF PARAVASCULAR THOROTRAST DEPOSITS: RESULTS OF THE GERMAN THOROTRAST STUDY

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SUMMARY

Purpose: The aim of this study was to assess late effects of long-term exposure to alpha irradiation caused by paravascular Thorotrast deposits.

Subjects and methods: 899 patients, who had received the radioactive contrast medium Thorotrast for angiography in the 1930s and 1940s, and 662 controls were followed-up since 1968 every two years by standardized clinical and laboratory examinations. Initially, X-ray plain films of the thorax, upper abdomen and the former injection site were performed. In selected patients the sites of paravascular Thorotrast deposits were evaluated by ultrasonography, CT and MRI.

Results: Paravascular Thorotrast deposits were detected in 245 patients. Clinical symptoms related to deposits appeared 10 to 30 years after Thorotrast administration. The severity of symptoms depended on the location and extension of granulomas and were mainly caused by fibrosis, nerve paralysis and vascular changes. Four malignant tumors adjacent to granulomas were observed (one soft tissue sarcoma in the groin, two squamous cell carcinomas of the parotid gland and one lymphoepithelial carcinoma of the nasopharynx). MRI including MRA allowed an accurate determination of tissue damage, whereas the utility of US and CT was restricted due to strong sound attenuation and streak artefacts caused by the high X-ray absorption of Thorotrast.

Discussion and conclusion: Locoregional late effects of paravascular Thorotrast deposits mainly comprise radiation induced, fibrotic tissue destruction. The incidence of malignant tumors, in particular sarcomas, adjacent to deposits, however, is much lower than initially expected.

Key words: Thorotrast, thorium-232, contrast media, radiation, adverse effects.

RÉSUMÉ

Effets locaux tardifs des dépôts paravasculaires de Thorotrast : résultats de l'étude allemande de Thorotrast

But : Le but de cette étude a été d'évaluer les effets tardifs après une exposition de longue durée à des irradiations causées par des dépôts paravasculaires de Thorotrast.

Sujets et méthode : 899 patients ayant reçu l'agent de contraste Thorotrast pour angiographie dans les années 1930 et 1940. 662 contrôles ont été effectués depuis 1968 tous les deux ans avec des examens cliniques et de laboratoire standardisés. Initialement, les radiographies du thorax, du haut de l'abdomen et de l'ancien site d'injection ont été examinés. Chez les patients sélectionnés, les localisations des dépôts de Thorotrast ont été évalués par ultrasons, scanner et IRM.

Résultats : Des dépôts paravasculaires de Thorotrast ont été détectés chez 245 patients. Les symptômes cliniques liés aux dépôts de Thorotrast sont apparus 10 à 30 ans après l'administration de Thorotrast. La sévérité des symptômes dépendait de la localisation et de l'extension des granulomes qui ont été causés par fibrose, paralysie des nerfs et altérations vasculaires. 4 tumeurs malignes ont été observées à proximité des granulomes (dont un sarcome des tissus mous, deux carcinomes épidermoïdes de la glande parotide et un carcinome lymphoépithélial du nasopharynx). L'IRM, y compris l'IRM-angiographie, a permis de déterminer précisément les lésions tissulaires. En revanche, l'utilité de l'échographie et du scanner a été limitée par de forts artefacts causés par la réflexion des ultrasons et l'absorption marquée de rayons par le Thorotrast.

Discussion et conclusion : Les effets locaux tardifs des dépôts paravasculaires de Thorotrast consistent, avant tout en une destruction du tissu fibreux. L'incidence de tumeurs malignes, en particulier des sarcomes à proximité des dépôts, est pourtant moins élevée que l'incidence initialement attendue.

Mots-clés : Thorotrast, thorium-232, produit de contraste, irradiation, effets secondaires.

INTRODUCTION

The radiographic contrast medium Thorotrast is a colloidal suspension of thorium dioxide stabilized by dextran. After its introduction in 1928 it was predominantly used for carotid, axillary and femoral angiography for about 20 years. At that time, thorium dioxide met important specific criteria of an excellent contrast medium: it had a high X-ray absorption rate due to high atomic weight (better than lead), was nontoxic, chemically inert, and could be administered intra-arterially without pain and vasospasm. Although it was well known that the used isotope Thorium-232 is radioactive with a physical half-life time of $1.39 \times 10^{10}$ years and emits primarily alpha radiation, Thorotrast was not considered harmful to the patients health. The radiation effect was thought to be minimal, if usual doses were applied [5]. In the late 1940s, however, an increasing number of reports of severe side effects related to Thorotrast administration were published. In particular a high incidence of malignant neoplasias, mainly primary liver cancer and leukemia, was observed. Until these reports finally resulted in the worldwide proscription of Thorotrast in the 1950s more than 50,000 patients have received this contrast medium.

After intravascular injection thorium dioxide particles were stored in the organs of the reticuloendothelial system and caused a lifelong irradiation of the patients. When the top of the needle moved during injection, varying amounts of Thorotrast were injected paravascularly causing chronic irradiation to the tissue near the injection site. K.H. Bauer, one of those who early warned against administration of Thorotrast in Germany, predicted the development of liver cancer after intravascular injection and of sarcomas in case of paravascular deposits [2]. Accordingly, thorough epidemiological studies have been performed in several countries focusing on the development of liver cancer and leukemias [1, 10, 14-16, 22]. Regarding paravascular Thorotrast deposits (Thorotrast granulomas, Thorotrastomas or thorium dioxide granulomas), however, only case reports were published describing individual fibrous, inflammatory and malignant complications [11, 18-20, 24, 27, 30-32].

The German Thorotrast Study represents the worldwide largest study on Thorotrast patients including a systematical evaluation of late effects caused by paravascular Thorotrast deposits. This presentation details our experience with these patients.

SUBJECTS AND METHODS

The German Thorotrast-study started 1968 and comprised 2,326 patients, who received Thorotrast for angiography (70 % for carotid angiography and 30 % for arteriography of the upper and lower limbs) as well as 1890 age and sex matched control patients out of a pseudorandomized, non-“Thorotrast” group. A subgroup of 899 Thorotrast patients and 662 controls were subsequently followed-up every two years. Standardized examinations of each patient were performed and documented every 2 years on an out-patient basis including patient history, physical examination, abdominal ultrasonography as well as hematological and blood chemical values. Incorporated radioactivity was determined by whole-body-counting and measuring of the radioactivity in the breath due to the exhalation of Radium-220. The initial examination additionally included plain X-ray films of the chest, upper abdomen and the former injection site in two orthogonal planes to detect and to estimate the amount of retained thorium dioxide deposits. The extension of paravascular Thorotrast deposits were measured on plain X-ray films to roughly estimate the local tissue radiation dose at the site of the thorium dioxide deposit. Since 1976 the upper abdomen was also imaged by CT and since 1989 by multiplanar T1 and T2 weighted MRI to screen for liver malignancy.

In dedicated patients Thorium dioxide granulomas were examined by ultrasonography (XP 10 scanner, Acuson, Mountainview, CA, USA), CT (SOMATOM Plus 4, Siemens, Erlangen, Germany) and MRI (1.5-T MAGNETOM Vision, Siemens, Erlangen, Germany). The standard MRI study protocol included multiplanar T1- and T2- weighted MRI spin-echo sequences. When additionally contrast-enhanced MR angiography was performed (0.2 mmol/[kg body weight] Gd-DTPA, Magnevist®, Schering, Berlin, Germany), post-contrast spin-echo T1- weighted MRI with and without frequency selected fat suppression was added.

RESULTS

Most patients had received Thorotrast between 1937 and 1947, about two third of them for cerebral angiography and one third for angiography of the upper or lower limbs. At the time of Thorotrast administration the mean age of the patients was 26 years (range 2 to 54 years). On average 2 ampoules of Thorotrast had been injected according to 24 ml Thorotrast (range 5 ml to 100 ml depending on the vascular territory to be visualized). Abdominal

<table>
<thead>
<tr>
<th>Site of Thorotrast injection</th>
<th>Total</th>
<th>Paravascular deposit</th>
<th>%</th>
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<tbody>
<tr>
<td>Neck</td>
<td>659</td>
<td>157</td>
<td>24</td>
</tr>
<tr>
<td>Shoulder-arm</td>
<td>76</td>
<td>33</td>
<td>43</td>
</tr>
<tr>
<td>Pelvic-limb</td>
<td>164</td>
<td>55</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>899</td>
<td>245</td>
<td>27</td>
</tr>
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TABLE I. — Frequency of paravascular Thorotrast deposits in 899 patients, who had received Thorotrast for angiography.
X-ray films illustrated thorium dioxide deposits within the liver, spleen and abdominal lymph nodes (figure 1).

In 245 out of 899 patients (27 %) paravascular Thorotrast deposits were detected (table I). At the time of the first examination the patients were on average 54 years old (range 26 to 78 years). The mean interval between the time of Thorotrast injection and the first clinical examination was 28 years (range 22 to 45 years). In patients with large granulomas, the clinical examinations revealed callous, tumor-like lesions along the neurovascular bundles (figure 2). On plain X-ray films of the former injection site Thorotrast granulomas were detected as inhomogeneous opacification in the perivascular soft tissue (figure 3). On CT Thorotrast deposits appeared as mass lesion composed out of regions with metallic density and calcification, whereas on MRI the deposits presented with signal void or at least strong hypointense signal intensity (figure 4). Histologically, granulomas were composed out of retained thorium dioxide particles within areas of dense fibrosis and calcification (figure 5).

More than 50 % of the patients with paravascular thorium dioxide deposits were symptomatic 10 to 25 years (on average 19 years) after Thorotrast extravasation. Clinical symptoms most frequently appeared in patients who had neck and shoulder-arm deposits compared to patients who had pelvic-limb deposits. For each region of Thorotrast extravasation deposits were larger in symptomatic patients. The extensions of the deposits were quantified planimetrically on conventional X-ray films (figure 3b) and measured 2 up to 140 cm². 50 % of all deposits were larger than 10 cm². Table II summarizes the sites and the mean sizes of Thorotrast deposits in symptomatic and asymptomatic patients.

Most frequent clinical symptoms were related to neck deposits, because Thorotrast was most frequently used for carotid angiography, and deposits in the neck region caused more serious symptoms than deposits in the shoulder-arm or pelvic-limb region. The symptomatology included most frequently pain, restriction of movement, paresis/paralysis of cervical sympathetic, or caudal cranial nerves resulting in dyspnoea, dysphagia, asphyxia, and hoarseness (figure 6). Furthermore cerebrovascular insufficiency or hemorrhage due to vascular stenosis or erosion of the carotid artery (figure 7), pharyngeal ulceration and soft tissue fistula (figure 2) were observed. Compression or obstruction of larynx/trachea or pharynx/esophagus (figure 8) could result in life threatening effects including severe dyspnea, aspiration pneumonia and dysphagia. Five patients needed a tracheostoma. In three patients the carotid artery spontaneously ruptured. Local chronic inflammation lead to formation of fistulas in 8 and abscesses in 7 patients. Symptoms related to Thorotrast deposits in the shoulder-arm region included pain, restriction of movement, paralysis of the brachial plexus, stenosis or occlusion of the subclavian or axillary arteries and veins and soft tissue fistulas. Deposits in the pelvic-limb region caused most frequently stenosis or occlusion of the femoral artery, vein and lymphatic vessels, as well as paralysis of the femoral nerve or lumbosacral plexus and soft tissue fistulas. A nephrectomy had to be performed in three patients due to ureter obstruction. In another patient an obstructed sigmoid colon had to be resected. An occlusion of the ductus deferens was found in 1 patient. Detailed data of late effects are given in table III.

Up to now 6 patients died from radiation induced, fibrotic tissue destruction caused by Thorotrast deposits: three patients from rupture of the carotid artery, one patient from rupture of the aortic arch, one patient from recurrent aspiration pneumonia due to cranial nerve paralysis, one patient from cachexia due to esophageal obstruction. Malignant tumors arising from the edges of Thorotrast granulomas were observed in four patients. In two patients a squamous cell carcinoma of the parotid gland developed 40 and 50 years after Thorotrast administration (figure 9), and both patients died from local recurrence 3 and 1 year later, respectively. Another patient developed a lymphoepithelial

<table>
<thead>
<tr>
<th>Site of paravascular Thorotrast deposit</th>
<th>Symptomatic patients (mean size of Thorotrast deposits)</th>
<th>Asymptomatic patients (mean size of Thorotrast deposits)</th>
<th>Frequency of symptomatic patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>95</td>
<td>62</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>(24.3 cm²)</td>
<td>(7.2 cm²)</td>
<td></td>
</tr>
<tr>
<td>Shoulder-arm</td>
<td>19</td>
<td>14</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>(69 cm²)</td>
<td>(10.0 cm²)</td>
<td></td>
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<tr>
<td>Pelvic-limb</td>
<td>28</td>
<td>27</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>(66.6 cm²)</td>
<td>(14.5 cm²)</td>
<td></td>
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</table>
### Clinical symptoms | Injured anatomical structure | Frequency
--- | --- | ---
1. Neck granulomas (n = 95) | Pain | neck | 40
| Paralysis | sympathetic plexus | 89
| | recurrent nerve | 76
| | glossopharyngeal nerve | 46
| | hypoglossal nerve | 42
| | accessorius nerve | 9
| Chronic inflammation | soft tissue (fistula, abscess) | 15
| Arterial compression / occlusion | carotid artery | 14
| | aortic arch | 1
| | carotid artery | 3
| Severe dysphagia | obstruction of esophagus | 2
| Severe dyspnoea | obstruction of trachea | 5
| Recurrent aspiration pneumonia | larynx | 4
| Malignancy | parotid gland | 2
| | epipharynx | 1
2. Shoulder-arm granulomas (n = 19) | Pain | shoulder, back pain | 10
| Paralysis | brachial plexus | 6
| | phrenic nerve | 3
| Chronic inflammation | soft tissue (fistula, abscess) | 4
| Arterial compression / occlusion | subclavian / axillary artery | 6
| Recurrent aspiration | larynx | 4
3. Pelvic-limb granulomas (n = 28) | Paralysis | lumbosacral plexus | 3
| | femoral nerve | 3
| Chronic inflammation | soft tissue (fistula, abscess) | 7
| Arterial compression / occlusion | femoral artery | 10
| Hydronephrosis | obstruction of ureter | 3
| Infertility | obstruction of ductus deferens | 1
| Mechanical bowel obstruction | obstruction of sigmoid colon (scar tissue) | 1
| Malignancy | soft tissue | 1

**Fig. 1.** — Abdominal X-ray of a patient 30 years after intravascular administration of Thorotrast for angiography, demonstrating inhomogeneously scattered opacifications within liver, spleen and abdominal lymph nodes. The opacifications represent thorium dioxide particles retained in the reticuloendothelial system (Reprinted with permission of [15]).

**Fig. 2.** — Callous thickening along the cervical neurovascular bundle on the left neck side representing a paravascular Thorotrast deposit in a patient after Thorotrast administration for cerebral angiography. A pharyngocutaneous fistula developed at the cranial portion of the deposit (arrow).

**Fig. 3.** — Plain X-ray films showing radiopaque paravascular Thorotrast deposits around different intravascular injection sites (a) in the neck, (b) axilla, (c) hollow of the knee, (d) and groin. (b) Margins of deposits were marked on plain X-ray films to quantify their extensions.

**Fig. 3.** — Radiographie standard montrant les dépôts radio-opaques paravasculaires de Thorotrast autour des sites d’injection intravasculaires au niveau (a) du cou, (b) de l’aisselle, (c) du creux du genou, (d) de l’aine. (b) Les marges des dépôts sont marquées sur les radiographies standards pour quantifier l’extension.
LATE EFFECTS OF PARAVASCULAR THOROTRAST DEPOSITS

1

2

3a

3b

3c

3d
carcinoma of the nasopharynx 25 years after Thorotrast administration and died 2 years later from metastatic disease. Another patient developed a soft tissue sarcoma in the groin 27 years after Thorotrast administration and died 3 years later from metastatic disease. Regarding all examined patients 851/899 of the follow-up patients (623 without and 228 with paravascular Thorotrast deposits) died up to now. There was no statistical significant difference between the mean age at death for patients without (65.8 +/- 10.2 years) and with (63.5 +/- 8.4 years) paravascular Thorotrast deposits.

For visualizing the location and extension of Thorotrast granulomas as well as the amount of destruction of adjacent anatomical structures nine patients were examined by CT and/or MRI (7/9 patients with neck granulomas, 1/9 with a popliteal and 1/9 with an inguinal granuloma). Neck granulomas were imaged in six patients by MRI including contrast enhanced MRA in 3 patients, in 3 patients additionally by CT and in one patient exclusively by CT. One patient with an inguinal granuloma was examined by CT and MRI, one patient with a popliteal granuloma exclusively by MRI. Figures 4 and 6-9 demonstrate the most significant imaging findings in different patients. MRI was superior than CT in particular for the assessment of soft tissue adjacent to Thorotrast granulomas (figure 4). With MRA in 2/4 patients severe morphologic alterations of common, internal and external carotid arteries adjacent to Thorotrast granulomas were found (figure 7). In all patients with neck granulomas the internal jugular vein was occluded.
**Fig. 6.** — (a) Coronal T2 weighted MRI demonstrates a large hypointense Thorotrast granuloma extending along the right neurovascular bundle from the skull base to the upper mediastinum. (b) Axial T1-weighted MR images show fatty degeneration of the right sternocleidoid (arrow), trapezius (open arrow) and intrinsic laryngeal muscles (curved arrow) as well as (c) of the tongue (arrow), which can be attributed to accessory, hypoglossal and recurrent nerve palsy, respectively. (b) Note that pulsatile artefacts from internal and external carotid arteries are visible only on the contralateral side (arrowhead) indicating carotid artery stenosis within the granuloma.

**Fig. 6.** — (a) IRM coronale pondérée T2. Une grande zone hypointense correspondant à un granulome de Thorotrast le long du faisceau neurovasculaire droit, de la base du crâne jusqu’au médiastin supérieur. (b) IRM axiale pondérée T1. Dégénérescence graisseuse du sternoclidomastoïdien droit (flèche) et (c) de la langue (flèche) que l’on peut attribuer respectivement à une paralysie de l’hypoglosse accessoire et du récurrent. (b) Notez les artefacts pulsatiles des carotides interne et externe visibles uniquement du côté controlatéral (tête de flèche) indiquant une sténose carotidienne au sein du granulome.

**Fig. 7.** — (a) Axial, contrast enhanced T1-weighted MRI with fat suppression demonstrates a Thorotrast granuloma in the right parapharyngeal space (arrow) of a patient, who was suffering from increasing episodes of syncopes. On the contralateral side contrast enhancement can be seen within the vertebral, internal and external carotid arteries as well as jugular veins. On the side of the granuloma, however, neither the internal and external carotid artery nor the internal jugular vein are visualized. (b) MRA confirms on the right side a long range, irregular narrowing of the common carotid artery beginning at the brachiocephalic trunk, a severe stenosis of the carotid bulb (arrow) as well as a lack of visibility of the internal carotid artery. The right internal jugular vein is completely occluded. On the contralateral side a stenosis of proximal segment of the external carotid artery (curved arrow) is due to atherosclerosis. Normal perfusion can be seen in both vertebral arteries.

**Fig. 7.** — (a) IRM axiale pondérée en T1 après injection de contraste avec une suppression de graisse. Granulome de Thorotrast dans l’espace parapharyngé droit (flèche) chez un patient ayant des épisodes de syncopes répétés. Le côté controlatéral montre un rehaussement au niveau vertébral, des carotides interne et externe et des veines jugulaires. Du côté du granulome, ni les carotides interne et externe ni la veine jugulaire interne ne sont visualisées. (b) L’IRM confirme un long rétrécissement irrégulier de la partie droite de l’artère carotide commune à partir du tronc brachiocephalique, une sténose serrée du bulbe (flèche) et un manque de visibilité de l’artère carotide interne. Occlusion complète de la veine jugulaire interne droite. La sténose du segment proximal de l’artère carotide externe du côté controlatéral (flèche courbe) est due à une athérosclérose. Perfusion normale des deux artères vertébrales.
DISCUSSION

After intravascular administration of Thorotrast thorium dioxide is cleared from the blood and retained by the reticuloendothelial system (RES). Since there is virtually no clearance, the biological half-time of thorium dioxide is approximately 400 years [8]. It is accumulated from RES as well as permanently deposited mainly in the liver (59 %), spleen (29 %), red bone marrow (9 %) and skeleton (2 %) [17]. Thorium-232 decays to 10 intermediate, radioactive daughter nuclides and finally to the stable lead isotop lead-208. Including the contribution of all radioactive daughter nuclides, retained thorium dioxide deposits emit 95 % alpha, 3 % beta and 2 % gamma irradiation. Alpha radiation has high linear energy transfer (LET) and accordingly high biological effectiveness.

The most frequent, severe late effects of systemic Thorotrast administration were malignant liver tumors (carcinomas and hemangiosarcomas) and myeloid leukemias including myelo-dysplastic syndroms. The incidence of liver malignancies was found to be correlated to the accumulated radiation dose [12, 15, 16]. In addition fibrosis of liver, spleen and abdominal lymph nodes were described by pathologists [34].

Paravascular Thorotrast deposits are the result of an accidental paravascular injection of Thorotrast. Considerable variations in the shape and extension of Thorotrast deposits were observed, since the spread of the contrast medium within the surrounding soft tissue depends on the amount of administered Thorotrast, the pressure of the injection and local anatomical structures. Thorium dioxide particles are retained locally either free or incorporated in histiocytes and cause radiation induced dense fibrosis, chronic inflammation, necrosis and calcification [33].

Radiographically, paravascular Thorotrast deposits show inhomogeneous hyperdensity in the perivascular soft tissue, which is caused by aggregates of thorium dioxide particles compounded by calcification (figures 3 and 4a). Conventional radiographs
were necessary for the detection of thorium dioxide granulomas and for the determination of their size (figure 3). Conventional X-ray follow-up of granulomas examinations after 2 to 4 years showed no substantial changes in the radiographic morphology and were therefore neglected for the majority of patients.

Cross sectional imaging was used for an accurate definition of topographic details, i.e. for a delineation of Thorotrast granulomas in relation to adjacent soft tissue structures and for the assessment of tissue destruction. Although ultrasonography is usually applied for the primary evaluation of superficial soft tissue masses, it was unsuitable for the examination of Thorotrast granulomas, since fibrosis, calcification and thorium dioxide particles cause complete sound reflection. Accordingly, the assessment of adjacent anatomical structures was restricted due to dorsal shadowing, and flow investigations within blood vessels could not be performed. The CT evaluation of Thorotrast granulomas and in particular surrounding soft tissue structures were often restricted due to streak artefacts caused by the high X-ray absorption rate of thorium dioxide.

MRI was superior to CT due to the absence of these artefacts, the excellent soft tissue contrast and the ability of multiplanar imaging. It was very helpful to determine the extension of large granulomas and their relationship to surrounding soft tissue structures, i.e. major vessels and nerves, in particular in the anatomical complex head and neck region. Since 70% of the patients received Thorotrast for cerebral arteriography, paravascular deposits are most frequently located along the neurovascular bundle of the neck. This anatomical region comprises the internal and external carotid artery, the internal jugular vein, the cranial nerves IX-XII and the sympathetic chain. Consequential damage of these structures are clearly visualized by MRI and MRA (figures 6 and 7). In particular MRA was helpful for the examination of Thorotrast patients, who tended to deny conventional angiography. But the question, whether susceptibility artefacts due to thorium dioxide cause an overestimation of vascular stenoses on MRA, could not be addressed, since both, MRA and invasive conventional angiography were not performed.

The diagnostic evaluation of the pharyngeal and laryngeal mucosa is based primarily on direct inspection or endoscopic procedures. In patients with Thorotrast granulomas, however, a pharyngolaryngeal examination could be complicated, if patients were unable to open their mouth sufficiently. MRI was very helpful to evaluate the pharyngeal wall and paralaryngeal space and to evaluate the spatial relationship to Thorotrast granulomas (figure 4b).

Depending on the site of the paravascular thorotrast deposits, a close relationship between the extension of the deposit and the seriousness of the symptomatology was observed. In the neck region already small deposits resulted in more serious symptoms as compared to deposits in the shoulder-arm and pelvic-limb region. The main clinical manifestation of cervical Thorotrast granulomas were hoarseness, dyspnea and dysphagia due to nerve paralysis as well as mass effect of the tumor-like granulomas. A progression into devasting and fatal complications like rupture of carotid artery or aortic arch, pharyngeal necrosis, and mediastinitis were reported [21, 29, 32].

Attempts were once made to at least partially remove Thorotrast deposits surgically. In our study group, surgery was performed in 55 patients, but often severe postoperative side effects like delayed wound healing, formation of fistulas and abscesses were obtained. Three patients even died from uncontrollable, postoperative bleeding. Similar results with poor surgical outcomes or even fatal complications such as carotid rupture or mediastinitis were reported in the literature [11, 21, 27, 30]. In addition, the invasive nature of granulomas with involvement of vessels, nerves, trachea or esophagus often resulted in incomplete removal, which correspondingly implied a high risk of granuloma recurrence [30]. Our past experience has shown, that surgery should only be performed in case of life-threatening complications.

In animal experiments soft tissue sarcomas adjacent to thorium dioxide deposits were frequently found [3, 13, 26, 35]. It was surprising, however, that in Thorotrast patients the observed incidence of radiation induced sarcomas was much lower that initially expected. In our study with a follow-up period of more than 50 years after Thorotrast administration in 245 patients only in one patient a soft tissue sarcoma developed in the groin 27 years after femoral angiography. In other follow-up studies analogous small numbers of malignant soft tissue tumors were reported, although the exact number of patients with Thorotrast deposits is not documented: Two fibroblastic sarcomas in 1,052 Thorotrast patients in the Portugese [23] and two fibrosarcomas in 908 Thorotrast patients in the Sweden study [4]. Case reports concern one soft tissue sarcoma in the cervical region [9] and one malignant fibrous histiocytoma in the proximal thigh [7].

The low incidence of sarcomas at the site of Thorotrast granulomas in our study may be explained by the assumption that within the granulomas the dose rate of alpha irradiation is very high leading to a predominating cytolethal effect. Scharfstaedt et al. estimated the mean dose rate in the region of the paravascular Thorotrast deposit to be about 500 cGy per year by using data from X-ray films of the deposits, CT-based calculations of volume and density of liver and spleen, Radon-220 measurements in the ex-
haled breath and whole body counting [Scharfstaedt A et al., presented at the International Workshop on Health Effects of Thorotrast, Radium, Radon and other Alpha Emitters, Japan 1999, January 19-23].

Paravascular Thorotrast granulomas could have a malignant potential also for adjacent parenchymal or mucosal tissue. This consideration reminds on the final fate of the US female radium dial workers. The luminous paints used until the late 1920s in the dial factories contained various amounts of Radium-226 and Radium-228. The major deposition site for swallowed Radium entering the blood was the skeleton. Several studies concerning US women dial workers [25, 28] have shown that not only bone sarcomas but also carcinomas originating from the mucosa lining the cavities of paranasal sinuses and the mastoid air cells had developed due to radiation exposure originating from the underlying bone. In our study we found two cases of squamous cell carcinoma of the parotid gland (figure 9) and one case of a lymphoepithelial carcinoma of the nasopharynx adjacent to the area of Thorotrast extravasation. In the control group neither parotid gland tumors nor lymphoepithelial carcinomas nor sarcomas were observed. In the literature one anaplastic, large cell carcinoma in the tonsil [6] and one adenocarcinoma of the common hepatic duct adjacent to a granuloma caused by an attempted portography [23] were described.

In summary, best information on effects of radiation in humans comes from follow-up examinations of patients exposed to radiation. The final fate of Thorotrast patients is attributed to late effects of long-term exposure to alpha-radiation and is mainly caused by malignant liver tumors, liver cirrhosis and myeloid leukemias including myelo-dysplastic syndroms. Locoregional late effects of chronic radiation from paravascular Thorotrast deposits mainly comprised fibrous destruction of adjacent soft tissue, which could be fatal in some cases. Remarkably, the incidence of malignant tumors especially sarcomas at the sites of Thorotrast granulomas was much lower than initially expected. MRI including contrast enhanced MR angiography proved to be an excellent, noninvasive method for the examination of patients with Thorotrast granulomas in order to assess the extent of tissue destruction, the consequential damage due to e.g. nerve paralysis and vascular erosion, and to exclude the development of local malignancy.

REFERENCES


