Coarctation of the Aorta and Other Late Sequelae of Administration of Thorium Dioxide (Thorotrast)

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SUMMARY

Coarctation of the aorta secondary to a cervicamediastinal thorotrastoma developed in a 30-year-old man 25 years after carotid arteriography. Other local manifestations of the thorotrastoma included occlusion of the left common carotid artery and partial occlusion of the left vertebral and left subclavian arteries, bilateral recurrent laryngeal nerve paresis, periesophageal adhesions, and multiple traction diverticula of the esophagus. There was no evidence of hepatic neoplasm or malignant transformation of the thorotrastoma. The major risk for this patient in the future, even though small, would be the development of a malignant hepatic neoplasm. Surgery may be indicated if local symptoms, enlarging tumor mass, or signs of increasing aortic obstruction develop.

Additional Indexing Words:
Carotid arteriography Aortography Hypertension

THOROTRAST, a 25% colloidal suspension of thorium dioxide, was introduced as a contrast medium for carotid angiography by Moniz1 and Löhr and Jacobi2 in 1933. Owing to lack of immediate signs of toxicity, it became a widely used contrast medium in the ensuing 15 years for hepatolienography, mammography, angiography (particularly carotid arteriography), and to a lesser extent for visualization of cerebral ventricles, paranasal sinuses, and the renal collecting system. Soon after the introduction of Thorotrast it was noted that accidental extravasation into tissues would often cause consecutive fibrosis and granuloma formation. With the advent of newer radiographic contrast media, Thorotrast was taken off the market in the early 1950's. However, by then Thorotrast had already been administered locally or parenterally to several thousand patients in medical centers throughout the world. It can be predicted that some of these patients may return with many of the late sequelae of Thorotrast administration.

There have been 82 documented cases of cervical thorotrastoma3-21 and a significant, but undetermined, number of the 81 cases of local granuloma reported by Horta and associates7 have been cases of cervical thorotrastoma (table 1). Partial or complete occlusion of one or both carotid arteries demonstrated arteriographically6,8-10 or in surgical specimens11-13,21 have been reported in eight patients. Apparently asymptomatic extensions of cervical thorotrastomas into the superior mediastinum have been previously noted in nine cases4,10,12,14,15 and around the arch of aorta, in four cases4,15 without arteriographic

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## Table 1

**Cervical Thorotomomas Following Carotid Arteriography**

<table>
<thead>
<tr>
<th>Senior author &amp; reference No.</th>
<th>Thorotomomas (cases)</th>
<th>Latent period before symptomatic(yr)</th>
<th>Symptoms</th>
<th>Malignant transformations</th>
<th>Mediastinal extension</th>
<th>Diagnostic arteriography</th>
<th>Surgical procedure</th>
<th>Results of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dahlgren²</td>
<td>1</td>
<td>19</td>
<td>Mass</td>
<td>Recurrent neurofibrosarcoma-tous tumors</td>
<td>None</td>
<td>ND</td>
<td>Local excision several times</td>
<td>No change</td>
</tr>
<tr>
<td>Looney⁴</td>
<td>5</td>
<td>9-18</td>
<td>Pain, dysphagia, RLN paralysis</td>
<td>None</td>
<td>2 cases</td>
<td>ND</td>
<td>None</td>
<td>—</td>
</tr>
<tr>
<td>Blomberg⁵</td>
<td>7</td>
<td>10-20</td>
<td>NA</td>
<td>Neurofibrosarcomas in 2 cases</td>
<td>None</td>
<td>ND</td>
<td>None</td>
<td>—</td>
</tr>
<tr>
<td>Novik⁶</td>
<td>4</td>
<td>17-23</td>
<td>CN palsy, local masses &amp; ulcers, brachial plexus compression</td>
<td>Neurofibrosarcoma &amp; malignant mesothelioma in 1 case each</td>
<td>None</td>
<td>Left CA occlusion in 1 case</td>
<td>Local neck resection &amp; resection per os in 1 case each</td>
<td>Excellent improvement in 1 case</td>
</tr>
<tr>
<td>Horta⁷</td>
<td>81*</td>
<td>2-25</td>
<td>Local destruction &amp; compression</td>
<td>3 cases</td>
<td>None</td>
<td>ND</td>
<td>None</td>
<td>—</td>
</tr>
<tr>
<td>Barry⁸</td>
<td>2</td>
<td>3-20</td>
<td>Mass, local symptoms</td>
<td>None</td>
<td>None</td>
<td>Right CA occlusion in 1 case</td>
<td>Local resection in 1 case</td>
<td>Some improvement</td>
</tr>
<tr>
<td>Kuisk⁹</td>
<td>1</td>
<td>27</td>
<td>IX to XII CN palsy, Horner's syndrome, RLN paralysis</td>
<td>None</td>
<td>None</td>
<td>Right CA occlusion</td>
<td>Fistulae after 1st exploration then local resection</td>
<td>No change</td>
</tr>
<tr>
<td>Chalet¹⁰</td>
<td>1</td>
<td>11</td>
<td>Mass, progressive hoarseness</td>
<td>None</td>
<td>Into SM</td>
<td>Left CA occlusion</td>
<td>Radical neck dissection</td>
<td>Left RLN palsy, Horner's syndrome</td>
</tr>
<tr>
<td>Levowitz¹¹</td>
<td>1</td>
<td>20</td>
<td>Stridor, dysphagia, weight loss</td>
<td>None</td>
<td>None</td>
<td>ND</td>
<td>Radical neck dissection</td>
<td>Symptomatic improvement</td>
</tr>
<tr>
<td>Brady¹²</td>
<td>1</td>
<td>10</td>
<td>Mass, left RLN &amp; XII CN palsy, Horner's syndrome</td>
<td>None</td>
<td>Into SM</td>
<td>ND</td>
<td>Radical neck dissection</td>
<td>Symptomatic improvement</td>
</tr>
<tr>
<td>Winter(^{14})</td>
<td>1</td>
<td>7-25</td>
<td>Mass, X to XII CN &amp; right RLN palsy</td>
<td>None</td>
<td>None</td>
<td>ND</td>
<td>Radical neck dissection</td>
<td>Symptomatic improvement</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Levy(^{14})</td>
<td>2</td>
<td>1-12</td>
<td>Right RLN palsy &amp; increasing mass</td>
<td>None</td>
<td>To apex of right lung in 1 case</td>
<td>ND</td>
<td>None</td>
<td>—</td>
</tr>
<tr>
<td>Amory(^{15})</td>
<td>6</td>
<td>NA</td>
<td>Pain &amp; dysphagia in 2 cases</td>
<td>None</td>
<td>Into SM &amp; partially around aortic arch in 3 cases</td>
<td>ND</td>
<td>Local resection in 2 cases</td>
<td>Improvement in 1 case</td>
</tr>
<tr>
<td>Backer(^{14})</td>
<td>25</td>
<td>7-18</td>
<td>No symptoms in 9 cases</td>
<td>None</td>
<td>None</td>
<td>ND</td>
<td>Local resection in 3 cases</td>
<td>Partial success in 2 cases</td>
</tr>
<tr>
<td>Berrett(^{17})</td>
<td>20</td>
<td>5-22</td>
<td>RLN palsy in 2 cases</td>
<td>None</td>
<td>None</td>
<td>ND</td>
<td>Local resection in 1 case</td>
<td>No improvement</td>
</tr>
<tr>
<td>Jones(^{18})</td>
<td>1</td>
<td>2</td>
<td>Dysphagia, local pain, left CA not palpable</td>
<td>None</td>
<td>None</td>
<td>ND</td>
<td>Biopsy without resection</td>
<td>—</td>
</tr>
<tr>
<td>Baker(^{19})</td>
<td>1</td>
<td>6</td>
<td>Dysphagia, pain, mass</td>
<td>None</td>
<td>None</td>
<td>ND</td>
<td>Biopsy without resection</td>
<td>—</td>
</tr>
<tr>
<td>Plenge(^{20})</td>
<td>1</td>
<td>5</td>
<td>Dysphagia, dyspnea, hoarseness, local mass</td>
<td>Fibroblastoma</td>
<td>None</td>
<td>ND</td>
<td>Local resection</td>
<td>NA</td>
</tr>
<tr>
<td>Wachsmuth(^{21})</td>
<td>1</td>
<td>6</td>
<td>Partial compression left CA, local mass</td>
<td>None</td>
<td>None</td>
<td>ND</td>
<td>Biopsy &amp; local resection</td>
<td>Uncontrolled hemorrhage from CA; relieved by ligation of CA</td>
</tr>
<tr>
<td>Thind (present report)</td>
<td>1</td>
<td>5</td>
<td>Hoarseness</td>
<td>None</td>
<td>Into SM MM, &amp; PM</td>
<td>Coarctation of aorta, occlusion of left CCA &amp; left subclavian artery</td>
<td>None</td>
<td>—</td>
</tr>
</tbody>
</table>

\*Local thorotrastomas.

Abbreviations: ND indicates not done; RLN, recurrent laryngeal nerve; NA, data not available; CN, cranial nerves; CA, carotid artery; SM, superior mediastinum; MM, middle mediastinum; and PM, posterior mediastinum.
studies. The purpose of this paper is to describe an unusual case in which coarctation of the aorta was yet another unrecognized late complication of Thorotrast carotid arteriography.

Report of Case

A 30-year-old white man was admitted to the Graduate Hospital of the University of Pennsylvania on October 23, 1968, for surgical correction of flexion contracture deformities of the left elbow and wrist. The patient was well until age 5 years when he was admitted to the Children’s Hospital of Philadelphia because of the sudden onset of left hemiplegia. General physical examination, including blood pressure of 112/66 mm Hg, was normal. Severe left hemiparesis included the lower part of the face. Initially the left-sided weakness improved greatly but 3 days later a second episode occurred and lasted 24 hours. Reappearance of left hemiparesis for the third time resulted in transfer of the patient to the Hospital of the University of Pennsylvania. An electroencephalogram showed diminished alpha activity on the right suggesting a lesion of the right temporoparietal region and a pneumoecephalogram on January 5, 1943, 17 days after the first symptoms, showed slight dilatation of the ventricular system.

An open right carotid arteriogram was performed on January 14, 1943, with single intraarterial injection of 12 cc of Thorotrast. Right internal carotid and anterior cerebral arteries were visualized, but the right middle cerebral artery did not fill. Four days later an open left carotid arteriogram was attempted. Following injection of 12 cc of Thorotrast there was no arterial visualization. After a second injection of the same amount, there was again no vascular filling, but Thorotrast was seen oozing out into the wound and no further injections were made. The patient was discharged 5 days later with a diagnosis of left hemiparesis secondary to occlusion of the right middle cerebral artery. At the age of 10 years, the patient developed hoarseness and was told that he had vocal cord paralysis.

Physical examination at the time of the most recent admission revealed a moderately developed and nourished male with skin and mucous membrane pallor. The supine blood pressure in the right arm was 120/90 mm Hg, in the left arm 0/0 (50 to 60 mm Hg systolic by palpation), in the right leg 115/80, and in the left leg 100/60. Neither lymphadenopathy nor thyroid enlargement was present. Firm diffuse thickening and fibrosis were present in the left sternomelenas-toid muscle and the skin of the left side of the neck, but no tumor was palpable. There was a palpable systolic thrill in the suprasternal notch. The left carotid and left subclavian arteries were not palpable. Pulsations were normal in the right carotid and right subclavian arteries. The left axillary, brachial, and radial arteries were palpable, but the force and volume of pulsation were considerably decreased in comparison to the right side. Arterial pulses were present in both legs without audible bruits. There was no peripheral edema or vascular insufficiency.

Examination of the cardiovascular system revealed no cardiomegaly. Cardiac rhythm was regular, and the rate was 76 beats per minute. There was a palpable systolic thrill, and a grade III to IV/V ejection systolic murmur was heard in the precordium with maximum intensity at the base to the left of the midline. The murmur extended into both carotid arteries and anteriorly toward the left shoulder. The murmur was also loudly audible in the upper left side of the thorax posteriorly. The first and second heart sounds were of normal intensity; no diastolic murmur or gallop rhythm was audible. The chest was normal on examination. No hepatic or splenic enlargement was detected.

Neurologic examination revealed left ptosis and miosis. The voice was husky and phonation was performed on inspiration. Indirect laryngoscopy showed bilateral midline paralysis and prominence of the left arytenoid muscle suggesting left posterior cricoarytenoid cartilage weakness. Motor power was nearly equal in all four extremities, even though there was an obvious muscular atrophy on the left side. The muscular tone was increased, and deep tendon reflexes were hyperactive in the left arm and leg with an extensor plantar response on the left. The sensory system and cerebellar and higher functions were normal. The skeletomuscular system revealed torticollis to the left, secondary to the cervical thorotrastoma. Except for flexion, all other movements of the cervical spine were limited. There was a 90° flexion posture of the left elbow and wrist joints with nearly normal range of passive movements. Bilateral mild pes cavus deformities were the only skeletal deformities of the lower extremities.

Laboratory Data

Routine blood examination revealed persistent anemia with a hemoglobin of 8.6 to 9.1 g/100 ml, hematocrit of 28 to 30%, moderate polikilocytosis, anisocytosis, hypochromia, target-cell formation, and 3.3 million red blood cells /mm³. Reticulocyte counts varied from 0.3 to 1.4%, and platelets numbered from 530 to 615 × 10³ /mm³. Initially several total leukocyte counts were 4,000 to 5,100/mm³ with 37 to 51% neutrophils, 45 to 53% lymphocytes, 2 to 7% monocytes, and 2 to 5%
COARCTATION OF THE AORTA

Figure 1
Multiple traction diverticula in upper part of esophagus secondary to periesophageal adhesions.

eosinophils. Subsequently, the leukocyte count rose to 5,800-7,900/mm³ with a normal differential count. A detailed investigation of the renal and hepatic systems was normal. Collagen disease work-up was also negative. The electrocardiogram was normal as was an electroencephalogram. Bone marrow aspirate and sections revealed low normal cellularity, increased normoblastic erythropoiesis, normal granulopoiesis, numerous megakaryocytes, and increased stainable iron stores. The hematologic studies suggested strongly that this patient had anemia probably secondary to Thorotrast administration. Barium study of the esophagus showed considerable irregularity, narrowing, and maximal dilatation at the level of the aortic arch due to periesophageal adhesions and fibrosis and small traction diverticula were present (fig. 1). A progress meal study showed a normal stomach, duodenum, and small bowel except for lymphoid hyperplasia in the distal 15 cm of the terminal ileum. X-rays of the skull, pelvis, long bones, and spine failed to provide evidence of thorium dioxide deposition. A liver scan revealed no hepatic enlargement or non-uniform uptake of the nucleotide. A brain scan showed no abnormal intracranial uptake of the nucleotide. External counting of thorium dioxide decay products over the liver was 3,691 counts/min, spleen 3,380 counts/min, right side of neck and upper part of chest 1,633 counts/min, and left side of neck and upper part of chest 3,937 counts/min. Even though no thorium dioxide deposits could be detected in the liver and skeletal system by ordinary x-ray examinations, there is obviously considerable thorium dioxide in these tissues.

A selective right carotid arteriogram using the Seldinger technic was performed. The parietal, angular, and posterior temporal branches of the right middle cerebral artery were completely occluded. The contrast material filled the anterior cerebral artery directly, and the posterior cerebral

Figure 2
Plain roentgenogram of chest shows mediastinal extension of thorotrastoma to level of seventh dorsal vertebra. Thorotrast granuloma of the spleen is also present.
Thoracic aortography shows the coarctation with marked tenting of inferior aspect of the arch by Thorotrust granuloma (A & B). There was a 15-mm Hg pressure gradient across the isthmus. Complete occlusion of the left carotid artery and partial occlusion of the left subclavian and vertebral arteries (arrows) are best seen by photographic subtraction (B). The subtraction film also demarcates the extension of the thorotrustoma around the arch and descending thoracic artery.

Thoracic aortography was performed by the Seldinger technic and serial roentgenograms in the lateral, 10° and 80° LAO projections were obtained. The inferior aspect of the arch of the aorta was elevated for at least 5 cm and sharply notched inferiorly by the mediastinal extension of the thorotrustoma (fig. 3). The caliber of the aorta at this point was diminished by at least 50%, but a sharply localized pressure gradient of 15 mm Hg was obtained across the narrowed segment. The pulse contour in the thoracic aorta distal to the stenosis was not significantly changed. Although femoral artery pulsations were decreased bilaterally, no direct pressure recording was obtained in the abdominal aorta. The mere presence of the pressure gradient implied a significant degree of stenosis of the distal arch. The findings of a clinically significant coarctation also suggested that the angiographic assessment was most likely an underestimate of the actual

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Figure 3

Thoracic aortography shows the coarctation with marked tenting of inferior aspect of the arch by Thorotrust granuloma (A & B). There was a 15-mm Hg pressure gradient across the isthmus. Complete occlusion of the left carotid artery and partial occlusion of the left subclavian and vertebral arteries (arrows) are best seen by photographic subtraction (B). The subtraction film also demarcates the extension of the thorotrustoma around the arch and descending thoracic artery.

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severity of the narrowing. The root and ascending aorta, aortic valve, and coronary arteries were well visualized and were normal. The left carotid was visualized only near its origin from the aorta. Filling of the left vertebral and left subclavian arteries was delayed. There was no rib notching or collateral circulation around the stenotic aorta.

Discussion

Our patient presented with many of the late complications of Thorotrast administration and local extravasation. It is generally believed that granuloma formation is a pure foreign-body reaction to the interstitially deposited fine particles of thorium dioxide and that the radiation has an aggravating effect at most. It is possible that the chemicals used in suspending and stabilizing the colloidal particles of thorium dioxide are local irritants and contribute to the fibrosis. The incidence of extravasation of the contrast medium following carotid arteriography and subsequent development of thorotrastoma is difficult to assess. However, Blomberg and co-workers reported at least a 3% chance of perivascular extravasation, and of such patients nearly 50% developed granulomas. Horta and associates reported a 7.4% occurrence of local Thorotrast granulomas in 1,107 cases of angiography.

The musculofascial structures affected are replaced by contracting fibroplastic connective tissue giving rise to a fixed, firm to hard cervical mass in 60% of 45 cases of symptomatic granulomas. Symptoms depend upon the amount of extravasation and the degree to which neighboring structures are involved. There may be no symptoms, but frequently seventh, ninth, tenth, eleventh, and twelfth cranial nerves and the sympathetic chain become involved in the constrictive fibrotic process. Patients with recurrent laryngeal paralysis, particularly if it is bilateral, may develop respiratory distress. This may necessitate tracheotomy, especially in the presence of a respiratory infection. The skin overlying these granulomas is usually well preserved since alpha particles penetrate so poorly. However, pharyngo-esophageal lesions (ulcers and fistulae) do occur secondary to impairment of the blood supply and extensive cicatrical reaction. Diagnosis of thorotrastoma is easily made from plain roentgenograms of neck and chest. This may be confirmed by gamma-ray activity over the granuloma. Histologic examination of an occasional biopsy or surgical specimen shows thorium dioxide particles in macrophages, fibroplastic reaction, and occasionally calcium particles. Autoradiograms obtained from the tissue are positive for thorium dioxide.

Surgical excision of cervical thorotrastomas has usually been reserved for troublesome complications, such as a rapidly growing, painful tumor, pharyngo-esophageal fistula, or tracheal dysfunction. Severe desmoplastic involvement of the carotid vessels, trachea, esophagus, and cranial nerves accounts for the incomplete removal of the mass after attempted partial or radical resection. Local resection of cervical thorotrastomas was performed in 13 patients with partial or transitory improvement in seven patients. More recently, radical dissection in the neck has been carried out in four patients with reported symptomatic improvement of local pain, tumor, and dysphagia (table 1).

Other important late sequelae of thorium dioxide are radiation-induced malignant neoplasms of the liver and hematopoietic system. The latency period before the diagnosis of hepatic malignancy is made, has been generally 12 to 35 years (mean of about 18 years). Ku and co-workers reviewed the literature to 1967 and found 41 cases of hepatic sarcomas (the majority were reported as hemangioendotheliomas) and 24 cases of hepatic carcinomas (eight cases of hepatoma, 11 of carcinoma of biliary duct, and five of unspecified type). Looney collected nine reported cases of tumors in the maxillary sinus, breast, neck, kidney, bronchus, and eyelid occurring 6 to 35 years after local injection of Thorotrast. In reviewing the literature on malignant transformations in or near cervical thorotrastomas (table 1), we found only five cases of sarcoma occurring 10 to 25 years after carotid arteriography. Even though there is a potential risk of
malignant change in cervical thorotrastomas, the reported incidence is extremely low. According to most investigations, the reported change of malignant hematologic abnormalities were reported by Looney, Berrett and McRae and Blomberg and associates. Horta and co-workers, however, found a statistically significant and gross excess of leukemias (acute in six and chronic in two patients) and other fatal blood dyscrasias (aplastic anemia in six and purpura in two patients) in 1,107 patients after previous administration of thorium.

The patient whose case is presented herein had left Horner's syndrome, bilateral recurrent laryngeal nerve paralysis, complete left carotid artery, and partial occlusion of the left vertebral and left subclavian artery, periesophageal adhesions with formation of multiple diverticula and coarctation of the aorta. To our knowledge, coarctation of the aorta has not been previously reported as a complication of thorium granuloma. It is possible that this clinically and angiographically demonstrated coarctation will become more extensive or more hemodynamically significant in the future. Some of the other future hazards of Thorotrast administration include: (1) symptomatic constriction of trachea and esophagus, (2) superimposition of bacterial endocarditis on the coarctation, (3) radiation effects on the hematopoietic system and, (4) development of malignant neoplasm in the liver.

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