Case Report

Erythroleukemia and Gastric Cancer Following Thorotrast Injection

Yuko HIROSE, Susumu KONDA, Keiko SASAKI*,
Fumio KONISHI* and Eisuke TAKAZAKURA**

A 63-year-old male, who had undergone angiography using thorium dioxide (Thorotrast) at the age of 15 for investigation of a giant hemangioma on his left thigh, developed anemia in September 1986 (47 yrs after the angiography). A diagnosis of erythroleukemia was made from a bone marrow study which showed 56.4% megaloblastoid erythroblasts and 12.8% myeloblasts. Autopsy revealed Thorotrast deposition in the liver, spleen, bone marrow, and lymph nodes, and monotonous proliferation of myeloblasts in the bone marrow. He also had differentiated tubular adenocarcinoma of the posterior wall of the stomach.

Key words: Hematological malignancy, Thorium dioxide, Angiography, Giant hemangioma, Autoradiograph

Thorium dioxide (Thorotrast) was developed in 1930 in Germany as a contrast medium for roentgenography. Thorium (^{232}Th) is the principal ingredient of Thorotrast. Thorium is known to have a very long half-life of 1.39×10^{10} yrs. As Thorotrast is insoluble in body fluids, it is readily deposited in the reticuloendothelial system where it remains for a long period. Because of these characteristics, the incidence of malignancy due to in vivo irradiation by α rays is very high following the injection of this contrast medium; in Japan, more than 10 cases of this type of leukemia have been reported. In this paper, we report a case of erythroleukemia which developed 47 yrs after intravenous Thorotrast injection for the angiographic investigation of a hemangioma of the left thigh.

CASE REPORT

A 63-year-old male had a giant hemangioma on his left thigh and left buttock which was present

from birth. In 1939, at the age of 15, prior to the hemangioma surgery, he underwent angiography and Thorotrast was used as the contrast medium. He remained well until September 1986 (47 yrs after the infusion of Thorotrast), when he was first found to have anemia at a routine medical examination. In December 1986, he developed palpitations, fever, and cough and was admitted to Kurobe City Hospital. Laboratory investigations revealed the following: RBC, 1.94 million/ μl ; hemoglobin, 7.2 gm/dl; Ht, 21.6%; reticulocytes, 1.3%; WBC 10,900/ μl ; and platelet count, 42,000/ μl . The bone marrow showed normocellular marrow with 56.4% megaloblastoid erythroblasts, and 12.8% myeloblasts. Some erythroblasts were periodic acid Schiff (PAS)-positive and the myeloblasts showed Auer bodies. From these findings, a diagnosis of erythroleukemia was made. He was given low-dose cytosine arabinoside therapy but thrombocytopenia progressed.

As he had a giant hemangioma on his left buttock

From Division of Hematology and Immunology, Department of Internal Medicine, *First Department of Pathology, Kanazawa Medical University, Ishikawa and **Division of Internal Medicine, Kurobe City Hospital, Kurobe

Received for publication December 27, 1989; Accepted for publication August 30, 1990

Reprint requests should be addressed to Yuko Hirose, MD, Division of Hematology and Immunology,

Department of Internal Medicine, Kanazawa Medical University, 1-1 Daigaku, Uchinada-machi, Kahoku-gun, Ishikawa 920-02, Japan

Fig. 1. Large cavernous hemangioma on the left buttock and left thigh.

Fig. 2. Giant erythroblast with multiple megaloblastoid nuclei. $\times 1250$

Fig. 3. PAS-positive erythroblasts. The erythroblast in the center contains multiple nuclei. $\times 1250$

and thigh, it was suspected that the thrombocytopenia might be a symptom of the Kasabach-Merritt syndrome. To investigate the possibility of irradiation of the giant hemangioma to improve his

thrombocytopenia, he was referred to Kanazawa Medical University on March 9, 1987. On admission, his temperature was 37.6°C , B.P. 120/40 mmHg, and his pulse rate was 90/min. He had anemia but no jaundice. The lungs were clear to auscultation. The heart was not enlarged and no murmurs were audible. His liver was palpable 3cm in the midline but the spleen was not palpable. He had a huge cavernous hemangioma on his left buttock and thigh (Fig. 1). The following were the laboratory data on admission: erythrocyte sedimentation rate, 150 mm/h; RBC, 1.55 million/ μl ; hemoglobin, 4.6 g/dl; hematocrit, 14.3%, and WBC, 3,610/ μl (2.0% myeloblasts, 69.0% neutrophils, 22.0% lymphocytes, 0.5% monocytes, 4.0% eosinophils, 1.0% basophils). Nucleated red blood cells were seen in the peripheral blood. The platelet count was 51,000/ μl .

In the bone marrow, the nucleated cell count was 24,000/ μl , with 6.4% erythroblasts, 55.4% myeloblasts, and 2.0% promyelocytes. The erythroblasts had megaloblastoid features (Fig. 2) and were PAS-positive (Fig. 3). The myeloblasts had Auer bodies (Fig. 4), and they were peroxidase-positive but negative for α -naphthyl butyrate esterase stain. The prothrombin time was 13.1 s, the activated partial thromboplastin time was 30.2 s, the Thrombo-test was 47.7%, and the hepaplastin test was 61.8%. His fibrinogen level was 225 mg/dl, and fibrin degradation products were less than 10 $\mu\text{g/ml}$. The following clotting factor activities were noted: antithrombin III, 66%; factor II, 58%; factor V, 104%; factor VII, 30%; factor VIII, 148%; factor

Fig. 4. Myeloblasts in the bone marrow; each cell has Auer bodies (arrows). $\times 1250$

Fig. 5. Plain abdominal X-ray revealed radio-opaque material (arrows) in the left hypochondrium, the left side of the abdomen, and the pelvic cavity, representing Thorotrast aggregates in the lymph nodes and spleen.

IX, 80%; and factor X, 48%. His total protein level was 7.8 g/dl, albumin 3.5 g/dl, SGOT 21 U/l, SGPT 48 U/l, LDH 252 U/l, and alkaline phosphatase 87 U/l. TTT was 4.9 U and ZTT was 17.1 U. A plain abdominal X-ray revealed radio-opaque material in the left hypochondrium and in the pelvic cavity (Fig. 5).

In the clinical course, in attempt to improve his thrombocytopenia, irradiation was used to treat the giant hemangioma (48 Gys over 29 days). However, the thrombocytopenia did not improve and epistaxis and gastrointestinal bleeding developed. He died due to gastrointestinal hemorrhage and *Pseudomonas aeruginosa* septicemia on April 30, 1987.

In the autopsy findings, the bone marrow showed monotonous proliferation of myeloblasts with a marked decrease in erythroblasts and megakaryocytes. Infiltrations of leukemic cells were seen in the liver, spleen, both lungs, and the kidneys. Deposition of Thorotrast was noted in the liver, spleen (Fig. 6), bone marrow, and lymph nodes. The Thorotrast dosimetric study of autopsy materials is presently under examination at the National Institute of Radiological Sciences. He also had a well-

Fig. 6. Thorotrast aggregates in the spleen. $\times 312$

Fig. 7. Well-differentiated tubular adenocarcinoma of the posterior wall of the stomach. $\times 312$

Fig. 8. Autoradiograph of liver section showing α tracks from clumps of Thorotrast. Exposure, 70 days.

differentiated tubular adenocarcinoma of the posterior wall of the stomach (Fig. 7). But a histologically recognizable deposit of Thorotrast was not present in the stomach. Autoradiographs of the liver and stomach tissue were performed, and alpha ray tracks were detected in the liver tissue (Fig. 8) but not in the stomach tissue at 70 days exposure.

DISCUSSION

The clinical use of Thorotrast began in Japan in 1927 and continued until about 1954. For the most part, it was used between 1937 and 1945 at various military hospitals for the diagnosis of war injuries (1). An increased incidence of hemangioendothelioma and cholangiocarcinoma have been reported as a late complication of Thorotrast administration (2). A high incidence of hematological malignancies has also been reported. Nakao et al (3) reported a case of erythroleukemia which developed 20 yrs after the intravascular administration of Thorotrast. Ikezaki et al (4) reported a case of erythroleukemia induced by Thorotrast given 30 yrs earlier. Ogura et al (5) and Kinoshita et al (6) also reported cases of erythroleukemia following Thorotrast administration. Cases of acute myeloblastic leukemia, multiple myeloma (7), and myelodysplastic syndrome (8) have also been reported. In the Japanese cases of hematological malignancy, the latent period has ranged from 16 to 36 yrs (2). The incidence of erythroleukemia is high among the cases of acute leukemia (2, 8), and this may be due to damage to stem cells. The α rays from $^{232}\text{ThO}_2$ aggregates trapped in the reticulo-endothelial cells of the liver, spleen, bone marrow, and lymph nodes can only penetrate less than 100 μm , so they only cause irradiation damage to the immediately adjacent tissue (9).

Carcinoma of stomach is rather rare among Thorotrast-induced malignancies. Among 103 deaths in a group of patients given Thorotrast intravascularly, 5 cases of carcinoma of the stomach were reported compared to 18 hepatic tumors (1). Six cases of gastric cancer were reported compared to 50 cases of hepatic tumor among 151 cases of

malignant Thorotrast-induced tumors in a Danish study (10). As we could not find a histologically recognizable deposit of Thorotrast in the stomach, the direct relationship between the carcinoma of the stomach and Thorotrast in the present case is not clear.

REFERENCES

- 1) Mori T, Maruyama T, Kato Y, et al. Epidemiological follow-up study of Japanese Thorotrast cases. *Environ Res* **18**: 44, 1979.
- 2) Mori T, Kato Y, Shimamine T, et al. Statistical analysis of Japanese Thorotrast-administered autopsy cases. *Environ Res* **18**: 231, 1979.
- 3) Nakao K, Sato S, Uchimura H, et al. A case of erythroleukemia developed after Thorotrast injection. *J Jpn Soc Int Med (Tokyo) (Nippon Naika Gakkai Zasshi)* **57**: 246, 1968.
- 4) Ikezaki H, Urakawa S, Honda M. An autopsy case of acute erythroleukemia induced by Thorotrast. *Jpn J Clin Hematol (Tokyo) (Rinsho Ketsueki)* **12**: 450, 1971.
- 5) Ogura Y, et al. A case of erythroleukemia developed 29 years after Thorotrast injection. *J Jpn Soc Int Med (Tokyo) (Nippon Naika Gakkai Zasshi)* **32**: 776, 1969.
- 6) Kinoshita Y, et al. A case of erythroleukemia developed after Thorotrast injection. *J Jpn Soc Int Med (Tokyo) (Nippon Naika Gakkai Zasshi)* **69**: 404, 1980.
- 7) Morita S, Nakata K, Muro T, et al. A case of Thorotrast-associated multiple myeloma. *J Jpn Soc Int Med (Tokyo) (Nippon Naika Gakkai Zasshi)* **72**: 1068, 1983.
- 8) Sadamori N, Shima M, Yano M, et al. An autopsy case of dysmyelopoietic syndrome with marked chromosomal abnormalities by Thorotrast. *Jpn J Clin Hematol (Tokyo) (Rinsho Ketsueki)* **26**: 1641, 1985.
- 9) Mori T. The history and present status of Thorotrast late effects in Japan. *J Clin Exp Med (Igakunoayumi)* **124**: 248, 1983.
- 10) Farber M. Twenty-eight years of continuous follow-up of patients injected with Thorotrast for cerebral angiography. *Environ Res* **18**: 37, 1979.