Pathomorphological Characteristics of Thorotrast-Related Cholangiocarcinoma

YUJI ITO

Department of Pathology, Kurume University School of Medicine, Kurume, 830 Japan

Received for publicaion April 25, 1988

Summary: The pathomorphologic characteristics of 44 autopsy cases of thorotrast (Th)-related hepatic malignancies are described and compared to the features of non-Th cases. Grossly, the majority (91.4%) of Th hepatic malignancies were located in the middle-peripheral portion of the liver. In contrast, 77.8% of the non-Th cases were located in the hilar portion. The basic histologic pattern of the tumor of the Th cases was not different from the pattern for non-Th cases. In non-cancerous areas, papillary proliferation of the epithelium of relatively large bile ducts was seen in 11 (25.0%) patients, and proliferation of ductules around the portal area was seen in 9 (20.5%) patients. However, in the non-Th cases, the same histologic features were seen in non-cancerous areas.

Key words: thorotrast (Th) — thorium dioxide — cholangiocarcinoma — pathomorphologic study — autopsy case

Introduction

A 25% colloidal solution of thorium dioxide (Thorotrast) was first introduced for radiocontrast studies in 1928 (Oka, 1928; Radt, 1929) and achieved worldwide use in the 1930s and 1940s. The injected Thorotrast (Th) is retained within the reticuloendothelial system throughout life. The biological half-life of Th is 200-400 years and it emits most of its energy in the form of alpha particles (Janower et al. 1972). These facts led Bauer (Bauer, 1943) to warn that long term late effects of alpha particle emission might develop in patients who had received Th injections. Since MacMahon et al. (1947) first reported the occurrence of Th angiosarcoma (AGS) of the liver in 1947, there have been many reports of the development of hepatic neoplasms, especially cholangiocellular carcinoma (CHC), in patients who had received Th injections (Baserga et al. 1960; Hiraoka et al. 1981; Kojiro et al. 1982;

Sakai et al. 1984; Dippold et al. 1985).

In the present study, the pathomorphologic characteristics of 44 autopsy cases of Th CHC are described, and compared these to the features of non-Th CHC cases.

Materials and Methods

This study consists of an analysis of 44 CHC cases among 157 autopsy cases of individuals who had been injected with Th. The autopsy cases were collected from various institutions throughout Japan, as part of an epidemiologic study of the late effects of Th during the 28 years from 1960 to 1987. The Th CHC cases were compared with 45 cases of non-Th CHC which were autopsied at the Pathology Department of Kurume University Hospital during the last 20 years.

The livers were fixed in 10% formalin. In 25 of the 44 Th cases and all the non-

Th cases, the livers were cut in their entirety into 0.5-1.0 cm slices to facilitate careful gross and histological examinations. The liver slices were divided into 25-30 blocks and all of the blocks were embedded in paraffin. If the liver slices were not available, several blocks of the tumor and the non-tumorous areas were examined. All sections were stained with hematoxylin-eosin (H. E) and selected sections were also examined with periodic acid-Schiff (PAS) and Mayer's mucicarmin stains. The tissue localization of carcinoembryonic antigen (CEA) was examined in selected cases using an immunoperoxidase method (DAKO peroxidase-antiperoxidase kit, Copenhagen, Denmark). Clinical information concerning the patients was obtained from the clinical charts.

Results

Clinicopathologic Features

1. Frequency

Among the 157 Th autopsy cases, there were 102 cases of Th hepatic malignancy. The frequency of each malignancy is shown in Table 1 and compared to the frequencies for of non-Th cases.

2. Latent period

The latent period for the Th CHCs had a range of 23-45 years with a mean of 35 ± 7 years ($\pm$ SD). The latent periods for the other Th hepatic malignancies were: AGS, 27-49 years with a mean of 37 ± 6 years ($\pm$ SD); HCC, 23-45 years with a mean of 36 ± 7 years ($\pm$ SD).

3. Age and Sex

The ages of patients with Th CHCs had a range of 37-73 years with a mean of 57 ± 8 years ($\pm$ SD). The male-female ratio for Th CHC was 37:3. The ages of non-Th patients had a range of 41-81 years with a mean of 63 ± 11 years ($\pm$ SD). The male-female ratio of the non-Th cases was 28:17.

4. Initial symptoms, Survival time, and Cause of Death

In the Th CHC cases, upper abdominal pain was the most frequent initial symptom (44.0%). Other initial symptoms were jaundice, abdominal fullness, ascitis, and generalized malaise. In the non-Th cases, the most frequent initial symptom was a jaundice (40.0%).

The survival times of the Th CHC patients after the initial diagnosis had a range of 2-18 months with a mean of 6 ± 4 months ($\pm$ SD). Liver failure was the most frequent cause of death.

TABLE 1
Frequencies of Th-related and non-Th hepatic malignancies.

	Th-related cases	Non-Th cases
Cholangiocarcinoma (CHC)	44 (43.1%)	45 (9.1%)
Angiosarcoma (AGS)	39 (38.3%)	2 (0.4%)
Hepatocellular carcinoma (HCC)	16 (15.7%)	439 (88.3%)
Double cancer	3 (2.9%)	11 (2.2%)
CHC+HCC+AGS	1	0
CHC+HCC	2	11
Total	102 cases	497 cases

Th: Thorotorast

Pathomorphologic Features

1. Gross findings

The weights of the livers ranged from 640 to 2380 g, with a mean of 1485 ± 529 g. Depending on the location of the tumor, they were classified as the hilar type or the middle-peripheral type. In the hilar type, the tumor was located in the hepatic hilum (Fig. 1a). In the middle-peripheral type, the tumor was located in the middle or peripheral portion of the liver (Fig. 1b). In the 21 cases of Th CHC in which gross findings were available, there were only 2 cases (9.6%) of the hilar type. By contrast, for the non-Th cases, 35 (77.8%) were of the hilar type and 10 cases (22.2%) were of the middle-peripheral type. Grossly, they were classified into three subtypes: nodular (2 cases), diffuse (1 cases), and massive (18 cases). This distribution is similar to that for the middle-peripheral type of the non-Th cases. All of the Th cases exhibited varying degrees of hepatic fibrosis related to Th deposition in the noncancerous areas. Cryptogenic cirrhosis (mixed macro- and micronodular type) was observed in one case.

2. Histologic features

Th CHCs were classified into four histologic types: tubular adenocarcinoma, papillary adenocarcinoma, poorly differentiated adenocarcinoma and adenosquamous carcinoma. Poorly differentiated adenocarcinoma exhibited a solid pattern without tubular or papillary structures. Occasional cells in poorly differentiated adenocarcinomas were mucin- and/or CEA-positive. The majority of the cases were well-differentiated tubular adenocarcinomas with abundant fibrous stroma (Fig. 2). The basic histological patterns were not different from those of non-Th cases.

In non-cancerous areas, papillary proliferation of the epithelium of relatively large bile ducts was seen in 11 (25%) of the 44 cases, and proliferation of ductules around the portal area was seen in 9 (21%) of 44 cases (Fig. 3). In the non-Th cases, papillary proliferation of the epithelium of large bile ducts, and proliferation of bile ductules around the portal area were seen in 4 (22%) and in 6 (33%) of the 18 cases without bilestasis, respectively. In the Th cases, sinusoidal dilatation of varying degrees was seen in 8 cases (18.2%) (Fig. 4), but was not observed in the non-Th cases.

Fig. 1. Th cholangiocarcinoma a: Hilar type. A massive and infiltrative tumor is located in the hilum. b: Peripheral type. An infiltrative tumor is located in the periphery of the right lobe, and metastatic lesions are scattered throughout the liver.

Fig. 2. Histology of a Th-related cholangiocarcinoma. This is a tubular adenocarcinoma with abundant fibrous stroma. Th deposits are seen in the fibrous stroma. (HE stain, $\times 50$)

Fig. 3. Papillary proliferation of bile duct epithelium in a non-tumorous area of Th cholangiocarcinoma. (HE stain, $\times 50$)

Fig. 4. Marked sinusoidal dilatation with hyperplastic changes of the sinusoidal lining cells associated with Th cholangiocarcinoma. (HE stain, $\times 20$)

Discussion

The occurrence of a variety of malignant tumors, especially hepatic malignancies, is well known as a late effect of Th-injection. A comparison of the frequency of hepatic malignancies, either related to Th or not related to Th, revealed some interesting differences. In Th cases, CHC was most frequent (43%) and AGS was next (40%). In contrast, approximately 90% of the non-Th cases were HCC. The differences in the frequency of CHC, HCC and AGS among Th and non-Th groups were statistically significant ($P < 0.01$ X^2 test). In 1967, Miyagawa et al. (1967) reported that Th hepatic malignancies in Japan involved more CHC and fewer AGS than the early series from Europe. But the recent data reported from West Germany revealed CHC in 36.8%, AGS in 25.0%, HCC in 16.4%, hepatic carcinoma (type not specified) in 22.3% and double cancer in 3.2% of the cases (van Kaick and Kaul,

1984). These results are very similar to those of the present study.

The average age for the Th CHC was significantly lower than that for CHC in the non-Th series and those for the Th AGS and HCC. Rubel and Ishak (1982) also noticed similar differences in their study of 14 cases of Th CHC. In 1960, Baserga et al. (1960) found that the longer the latent period of the Th-related tumors was, the more frequently liver epithelial tumors occurred. In our study, however, the latent periods of the hepatic malignancies were not significantly different.

Comparison of the gross features of Th and non-Th CHC cases revealed a striking difference in the location of the tumors in the liver. The tumors were located in the hepatic hilum in the majority (77.8%) of non-Th cases, but in only 2 (8.3%) of the Th cases.

This result contrasts with those of most investigators who find that peripheral CHC was more common (Mori and Nagasato,

1976). This finding suggests that Th CHC is more likely to develop in relatively small bile ducts in the peripheral or middle portion of the liver, rather than in the larger bile ducts of the hilar region. It is also possible that some of the non-Th cases actually represent extrahepatic bile duct carcinomas which had extended into the hilar region of the liver.

Tateno et al. (1984) reported atypical hyperplasia of the bile duct epithelium and proliferation of periportal bile ductules in Th cases. Rubel and Ishak et al. (1982) observed similar changes of the bile duct in 3 (21%) of their 14 cases. They considered that such proliferative changes of the bile duct were related to Th injection. Similar atypical hyperplasia of the bile duct epithelium and bile ductules around the portal area were observed in the present study in about one third of the Th cases. However, these proliferative changes of the bile duct were also observed in fifty percent of the non-Th cases. Furthermore, they were also observed sporadically in cases with AGS and HCC, therefore these hyperplastic changes of the bile ducts are probably not specific for Th cases, but may be secondary changes from the CHC. Edmondson also considered that such proliferation were reactive changes to the carcinoma (Edmondson, 1958).

Although CHC was the most frequent of the Th-related hepatic malignancies, there were no significant differences in the histological features of either the tumors or the non-cancerous areas of Th and non-Th CHC cases.

Acknowledgment: This study was supported in part by a grant-in-aid for scientific research from the Ministry of Education, Science and Culture of Japan and a grant from the Japanese Ministry of Health and Welfare. The author gratefully acknowledges Professor M. Kojiro of the Kurume University School of Medicine for his helpful comments. The author also are grateful to the hospitals and universities for their

permission to use the materials and wish to thank Mr. Kazuo Takashima for photomicrographs.

References

- BASERGA, R., YOKOO, H. and HENENGAR, G.C. (1960). Thorotrast-induced cancer in man. *Cancer*, **13**, 10 21-1031.
- BAUER, K.H. (1943). Thorotrast und Krebsgefahr. *Chirurg*, **15**, 204.
- DIPPOLD, W.G., DIENES, H.P. and KNUTH, A. et al. (1985). Hepatocellular carcinoma after Thorotrast expose: Establishment of a new cell line. *Hepatology*, **5**, 1112-1119.
- EDMONDSON, H.A. (1958). Tumors of the liver and intrahepatic bile ducts. Fascicle 25, Armed Forces Institute of Pathology, Washington, D.C.
- HIRAOKA, T., KAMBARA, T., MORINAGA, T. and NAKAGAWA, S. (1981). Hemangioendothelial sarcoma of the liver after Thorotrast injection. *Acta Pathol. Jpn.* **31**, 853-861.
- JANOWER, M.L., MIETTINEN, O.S. and FLYNN, M.J. (1972). Effects of Long-term Thorotrast exposure. *Radiology*, **103**, 13-20.
- van KAICK, G. and KAUL, H.M.A. (1984). Follow-up study. In *Radiation Protection*. ed. van Kaick, G. and Kaul, H.M.A. The German Thorotrast study. Luxenbururg, Comission of the European Communities
- KOJIRO, M., KAWANO, Y., KAWASAKI, H., NAKASHIMA, T. and IKEZAKE, H. (1982). Thorotrast-induced hepatic angiosarcoma, and combined hepatocellular and cholangiocarcinoma in a single patient. *Cancer*, **49**, 2161-2164.
- MACMAHON, H.E., MURPHY, A.S. and BATE, M.I. (1947). Endothelial-cell sarcoma of liver following Thorotrast injections. *Am. J. Pathol.* **33**, 585-613.
- MIYAGAWA, W. and SHIBATA, H. (1967). Hepatoma due to Thorotrast. *Jpn. J. Clin. Med.* **25**, 2255-2264. (In Japanese)
- MORI, W. and NAGASATO, K. (1976). Cholangiocarcinoma and related lesions. In *Hepatocellular Carcinoma*. ed. Okuda, K. and Peters, R., pp. 227-246. New York: Wiely.
- OKA, M. (1928). Eine neue Methode zur roentgenologischen Darstellung der Milz (Lienographie). *Fortschr. Roentgenstr.* **40**, 497-501.

- RADT, P. (1929). Eine Methode zur roentgenologischen Darstellung von Milz und Leber, *Klin. Wschr.* **46**, 2128-2129.
- RUBEL, L. R. and ISHAK, K. G. (1982). Thorotrast-associated cholangiocarcinoma: An epidemiologic and clinicopathologic study. *Cancer*, **50**, 1408-1415.
- SAKAI, K., SHIINA, M., ISHIHARA, N. and KATO, Y. (1984). Thorotrast-induced multiple primary malignant tumor of the liver. Cholangiocarcinoma and malignant hemangioendothelioma. *Jpn. J. Clin. Oncol.* **14**, 411-416.
- TATENO, H., HOSODA, S., YMADA, Y. and KIDO, C. (1984). Pathological study on the Thorotrast-deposited liver. *Jpn. J. Cancer. Clin.* **30**, 23-34. (In Japanese)