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Roentgenologic Appearance of a Thorotrast-Induced Small Cholangiocarcinoma in a Case of Thorotrastosis

An Autopsy Case of Massive Gastrointestinal Bleeding of Esophageal Varices

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トロトラスト症に合併した小胆管細胞癌の1症例

—食道静脈瘤破裂による突然死の剖検症例—

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食道静脈瘤の破裂による突然死したトロトラスト（以下「ト」）症の72歳男性の剖検ではじめて発見された直径1cm大の小胆管細胞癌のX線像を報告する．死亡前の1年間に腫瘍マーカーCA19-9の急激な増加がみられ，肝胆道系の悪性腫瘍の存在が疑われた．このためCT，肝生検および血管造影が施行されたが，いずれも悪性腫瘍を示唆する所見が得られなかった．剖検肝割面をみると，萎縮した右葉S^7に境界の不明瞭な径1cmの灰白色腫瘤がみられ，胆管細胞癌と診断された．1cm厚のスライス片の軟線撮影では萎縮した右葉内の「ト」沈着が多くみられ，特に肝内胆管癌の中心部に放射状により高密度の「ト」粒子沈着領域がみられた．この症例では胆管細胞癌が小さな時期から「ト」粒子へ強い親和性をもつということが考えられる．従って，「ト」症の経過観察時にCA19-9などの腫瘍マーカーが上昇があり，CTで肝内「ト」粒子による高密度領域がみられるときには初期の胆管細胞癌が存在する可能性が高いことが示唆される．将来，CTの空間分解能が改善されれば，適当なウインドウ幅の設定により肝内「ト」粒子の不均一分布を経時的に分析が可能であり，肝悪性腫瘍の早期検出に有用な手段となるかもしれない．

Abstract

A small cholangiocarcinoma was detected at autopsy in a patient with thorotrastosis who died from the rupture of esophageal varices at the esophagogastric junction. Prior to the advent of recent diagnostic imaging technique, a correct antemortem diagnosis could only be obtained from tumor markers. However, the tendency for the opacity of the liver to decrease slowly with time and develop uneven trabeculation suggests that small tumors may be difficult to detect against such a non-homogeneous background.

Introduction

Thorotrast was first utilized as a contrast medium in diagnostic radiology in 1928. Since it has no

acute side effects and was an excellent contrast agent, it rapidly came into use all over the world[1]. However, thorotrast radiates alpha-rays and its biological and physiological half-life is very long. MacMahon et al, first reported the occurrence of an endothelial cell sarcoma as a late effect of Thorotrast administration[2]. The etiological associations between thorotrastosis and hepatic malignant neoplasms are well-known, the predominant lesion being cholangiocarcinoma, angiosarcoma and hepatocellular carcinoma[3][4][5].

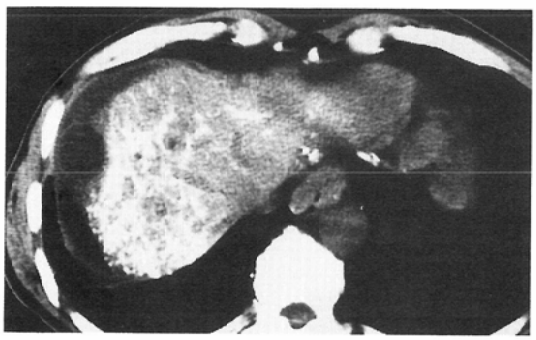
In this paper, a case of thorotrastosis with a small cholangiocarcinoma detected at autopsy is presented and the roentgenographic appearance of small cholangiocarcinoma is discussed.

Case Presentation

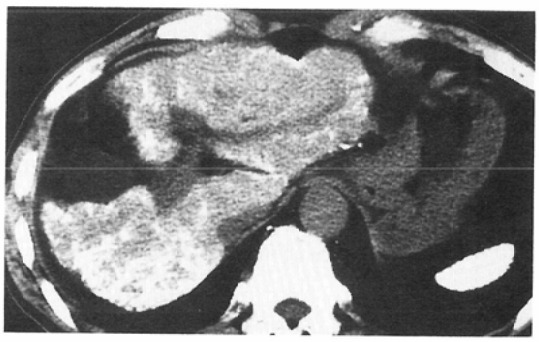
A 72-year-old man had a 5-year history of liver dysfunction from hepatic fibrosis. In 1941, he received a

Table 1 Change in level of tumor markers during 4-year period

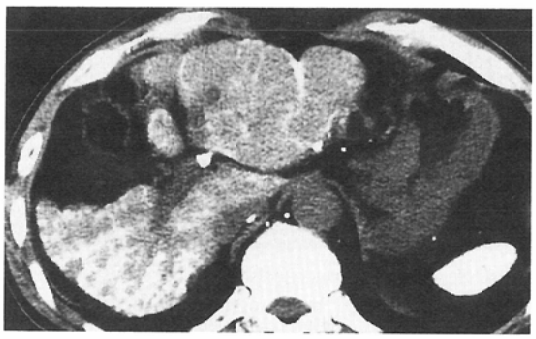
	'84 4/27	'85 10/17	'86 5/1	'87 4/15	'87 6/20	'88 4/20
AFP (20mg/ml)	3.3	3.0	4.8	4.5	3.4	2.1
CEA (5ng/ml)	15.7	8.9	12.6	12.4	11.4	12.4
CA19-9 (35U/ml)	26.0	45.0	42.0	55.0	58.0	104.0



1A



1B

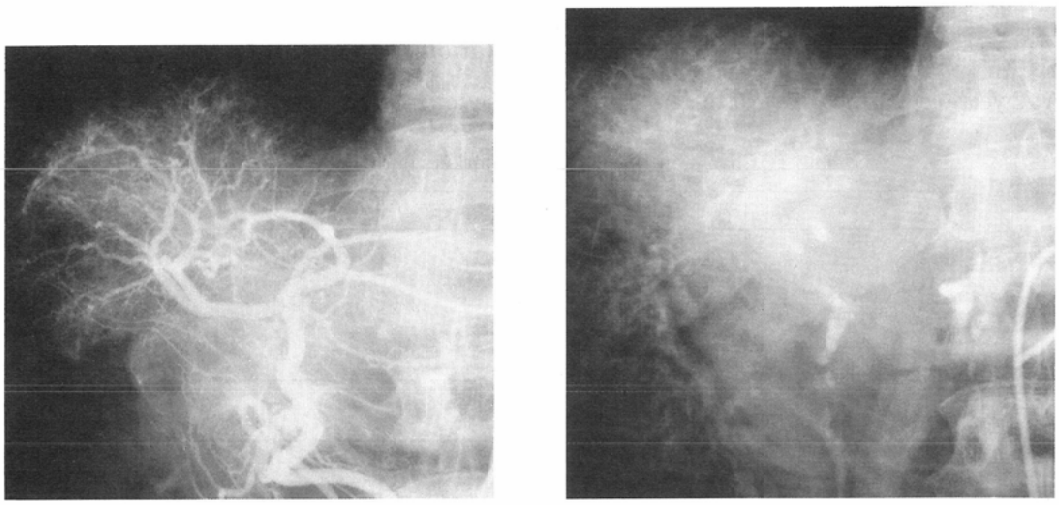


1C

Fig. 1A-C Plain computed tomography
Due to a long-term exposure to Thorotrast, fibrotic scarring and shrinkage condenses intrahepatic Thorotrast deposits, creating uneven high-density areas in the right hepatic lobe.

bullet wound in the right anterior chest wall, and was examined by angiography with Thorotrast, and treated. He had been monitored for thorotrastosis at Aichi Cancer Center Hospital since January 1976. A plain abdominal X-ray film disclosed opacification characteristic of Thorotrast deposition. The patient was well-nourished, and a physical examination revealed no abnormal findings. No liver tumor was found by abdominal ultrasonography and computed tomography in January 1981. In January 1984, laboratory findings showed abnormal liver function. The next year, endoscopy revealed esophageal varices.

Laboratory examinations from April 1984 to April 1988 showed that levels of tumor markers such as



2A 2B

Fig. 2 Celiac angiograms
A: Early arterial phase. Hepatic artery and its branches are markedly dilated and extremely tortuous.
B: Venous phase. Density of the hepatogram phase is increased. The liver is small, but there are no focal lesions.

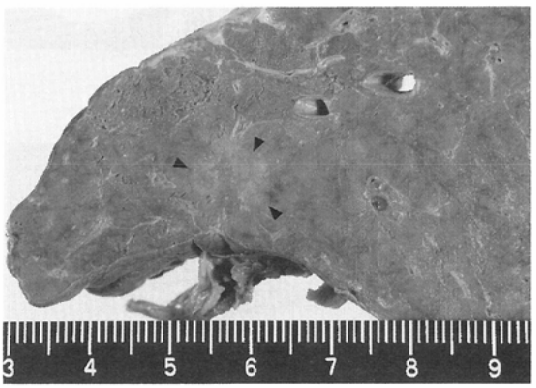
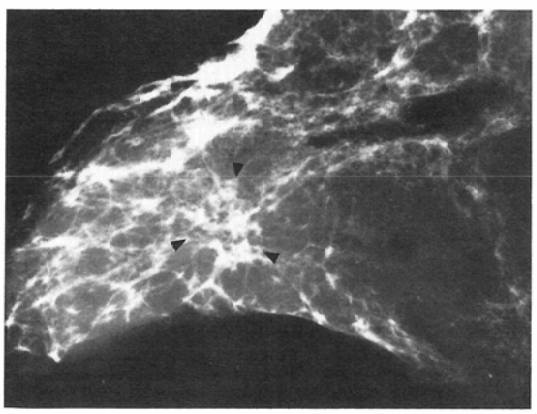


Fig. 3 Autopsy gross section of liver shows markedly spiculated mass of cholangiocarcinoma measuring 1 × 1 × 1 cm in the posterior inferior segment of the shrunken right hepatic lobe (arrowheads). In contrast, multiple regenerating hyperplasia of hepatocytes was observed in the left lobe.

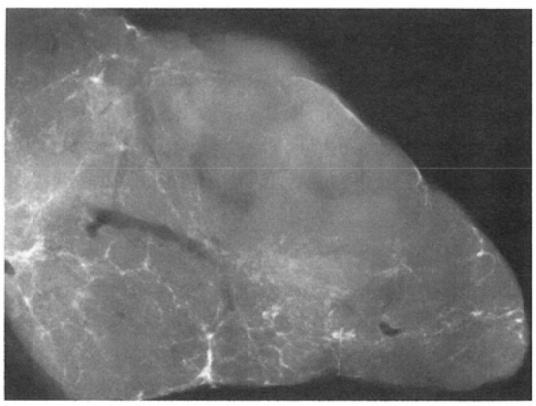
CEA and CA19-9 had been increasing (Tab. 1). Abdominal computed tomography was carried out in December 1987 to rule out the possibility of hepatobiliary malignant neoplasm, but did not reveal any lesion. Hepatic fibrotic scars and shirinkage, probably due to long-term exposure to the Thorotrast deposits were seen as uneven high-density areas in the right lobe of the liver (Fig. 1A-C). Radionuclide liver-spleen scan also showed shrinkage of the right lobe, enlargement of the left hepatic lobe, and widening of the interlobar fissure, but decreased tracer uptake from liver tumor was not seen. Hepatic angiography showed only fibrotic changes with contraction of liver volume and widespread corkscrewing arteries, but not any abnormal mass in the liver (Fig. 2A-B).

In spite of the regular follow ups, the patient died from rupture of the esophageal varices at the esophagogastric junction on May 31, 1988. At autopsy, esophageal varices with a large rupture at the esophagogastric junction and a massive gastrointestinal hematoma were found. The cause of death was thought to be the massive gastrointestinal bleeding. The gross specimen showed a small cholangiocarcinoma nodule measuring $1 \times 1 \times 1$ cm in the posterior inferior segment (S^7 in Coulnaud's subdivision) of the liver with Thorotrast deposits (Fig. 3). Hepatic fibrosis and atrophy were remarkable in both posterior and anterior segments of the right lobe, where Thorotrast deposition was greater than in the rest of the liver. On the other hand, multiple nodular lesions compatible with regenerating hyperplasia of hepatocytes were prominent in both lateral and medial segments.

Soft X-ray films of the excised liver of the posterior inferior segment of the atrophic right lobe demonstrated a 1×1 cm irregularly opacified lesion with condensed Thorotrast deposits, which was diagnosed as Thorotrast-induced cholangiocarcinoma with scirrhotic elements (Fig. 4A). The left lobe, on the other hand, had regenerating hyperplasia of hepatocytes and contained many radiolucent areas (Fig. 4B), because regenerating hyperplasia has no affinity for Thorotrast particles and displaces the Thorotrast opacified tissue. The tumor nodule consisted of well-differentiate dadenocarcinoma which was cholangiole-like, and similar to the tubular type with small, narrow, anastomosing tubules. Neither distant nor intrahepatic metastases were found.



4A



4B

Fig. 4 Soft X-ray films

A: Radiograph of a liver slice showing intensely opacified area corresponding to the cholangiocarcinoma nodule in the right lobe (arrow heads).

B: In the left hepatic lobe, however, unevenly distributed thorotrast deposits, are observed as low density areas in regenerative nodules.

Discussion

Thorotrast accumulates in the reticuloendothelial system, especially in the liver (60—70%) and spleen (20%), and also in the bone marrow and lymph nodes[6]. Many authors ahve advocated the usefulness of abdominal computed tomography for the evaluation of hepatic neoplasms in patients with thorotrastosis, as it delineates hepatic neoplasms clearly as low density areas[7][8]. However it is difficult to detect a Thorotrast-induced cholangiocarcinoma in an early stage, because these neoplasms have an affinity for Thorotrast particles and consequently concentrate these particles at the tumor, mimicking a Thorotrast granulation. In spite of periodic biochemical surveillance and imaging every 6 months, when such tumors with thorotrastosis were diagnosed as a cholangiocarcinoma, these tumors were often too big to remove surgically[9]. Hepatic distribution of the Thorotrast in early stages is dense subdiaphragmatically, and in the later stages is generally in the right lobe. After long exposure to Thorotrast, fibrotic change and shrinkage may increase the density of the intrahepatic Thorotrast and create the high-density area in the right lobe. In the left lobe, which contained regenerative nodules, an uneven distribution of Thorotrast was observed as low density areas. If there is a risk of hemorrhage, sclerotherapy is recommended, because thorotrastosis is often associated with hepatic fibrosis and esophageal varices[10][11].

Cholangiocarcinoma, and mixed hepatocellular and cholangiocelular carcinoma may have a strong affinity for Thorotrast particles, with concentration of Thorotrast particles in the tumor. The neoplastic high-density distribution resembles Thorotrast granulations, so it is difficult to find a Thorotrast-induced cholangiocarcinoma at an early stage. The presence of a high-density area in the Thorotrast-opacified liver does not directly indicate the existence of a Thorotrast-induced cholangiocarcinoma. However, even if angiographic findings and specimens obtained by aspiration biopsy are negative, malignancy in particular cholangiocarcinoma, cannot be totally excluded, when condensed Thorotrast deposit areas exist, as our case shows. On the other hand, it is easy to detect other Thorotrast-induced hepatic malignancies, because hepatocellular carcinoma and angiosarcoma have no affinity for Thorotrast particles and displace the Thorotrast-opacified liver[8][9].

In the present study, there were high positive rates of CEA and CA19-9, which are well known to elevate in various bile ductal disorders, and are also useful for predicting hepatic malignant neoplasms at an early stage[9]. However, a gradual elevation of tumor markers is more suggestive of the presence of the latter in cases accompanied by thorotrastosis. In addition, computed tomography is useful for analyzing the uneven Throtrast distribution due to the presence of a liver tumor[9]. However, the tendency for the homogeneous opacity of the liver to decrease slowly with time and result in uneven trabeculation suggests that small tumors may be difficult to detect against such a non-hemogeneous background on computed tomography.

Conclusion

A Thorotrast-induced small cholangiocarcinoma appeared as an irregular opacified lesion with condensed Thorotrast deposits on soft X-ray film of autopsy specimen. However, antemortem imaging diagnosis of small cholangicarcinoma is difficult against a non-homogeneous background of liver with Thorotrast deposits. If both CEA and CA19-9 levels are high, and if a high density area with a non-homogeneous Thorotrast deposit is observed by computed tomography, the possible existence of a small cholangiocarcinoma should be considered.

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