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HEPATIC ATROPHY DUE TO INTRA-ARTERIAL CHEMOTHERAPY FOR LIVER METASTASIS

Shingo KAMEOKA, Akiyoshi SESHIMO and **Kyoichi HAMANO**
Department of Surgery II, Tokyo Women's Medical College

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Intra-arterial chemotherapy is often administered for hepatic metastasis from colorectal cancer. Among its side-effects, hepatic dysfunction has been observed but reports on the pathological findings are few. Herein, we report a case in which marked atrophy of the liver developed due to intra-arterial chemotherapy. The pathological findings are also described. The patient was a 61-year-old male. Intra-arterial chemotherapy was started for a metachronous metastatic lesion of the right lobe at the request of the patient. With a catheter retained in the right hepatic artery, leucovolin 30 mg and 5-fluorouracil 1,250 mg were administered through a port once a week. The treatment was transiently effective, but the lesion expanded, necessitating right lobectomy a year later. On CT, the right lobe regressed markedly with a compensatory hypertrophy of the left lobe. The removed right lobe was small, weighing only 250 g. The pathological findings included a collapsed liver with marked thickening of the Glisson system and fatty degeneration. These changes, unlike evidence of biliary sclerosis, were considered attributable to chronic hepatocytic damage due to medication and circulatory disturbances.

Introduction

Hepatectomy is the treatment of choice for hepatic metastasis from colorectal cancer in terms of achieving the best prognosis, but the proportion of cases eligible for hepatectomy is about 20% to 40%[1)2)]. For the remaining non-operative cases, intra-arterial chemotherapy is aggressively administered as the second best method.

No conclusion has been reached as to whether or not the intra-arterial chemotherapy improves the prognosis, but its therapeutic effects on metastatic lesions of the liver are good and this therapy has been shown to be effective in 40% to 70% of cases[3)~7)]. Recently, whether or not intra-arterial chemotherapy is effective for preventing recurrence in the remaining liver after hepatectomy has been studied. However, complications accompanying this therapy are numerous. Complications such as arterial obstruction, infections and extravascular deviation of the catheter, in addition to the side-effects of anti-cancer drugs, have been noted in about 30% of cases. Liver diseases including chemical hepatitis and sclerotic cholangitis[8)9)], also occur but reports on their pathological findings are few. We encountered a case, for whom right lobectomy of the liver was performed about one year after intra-arterial chemotherapy. Pathological findings including marked atrophy of the right lobe, were observed. This report details our findings.

Case Report

The patient was a 61-year-old male. In September, 1991, he underwent sigmoidectomy because of sigmoid colon cancer. Pathological findings were well differentiated adenocarcinoma, with invasion reached into muscular layer without metastatic lymph nodes; Dukes A, stage 1 according to the classification sys-

tem of the Japanese Research Society for Cancer of the Colon and Rectum. Carcinoembryonic antigen (CEA) on discharge was 3.5 ng/ml. In August, 1992, CEA rose to 35 ng/ml and three metastatic lesions developed in the right lobe. We recommended surgery but failed to obtain the patient's consent. Intra-arterial hepatic chemotherapy was therefore started.

A catheter was retained in the right hepatic artery and connected to a port embedded under the skin. Intra-arterial chemotherapy was administered repeatedly at our out-patient clinic. Thirty mg of Leucovolin® and 1,250 mg 5-fluorouracil were administered for about one hour on a weekly basis. CEA decreased to 10 ng/ml in January 1993 after a total of consecutive 17 administrations and, on CT as well, the tumor regressed by about 52%. A total of 38 times of intra-arterial injections were done. Thereafter, however, CEA increased gradually reaching 143 ng/ml in August and the diameter of the tumor also increased. We persuaded the patient to undergo a right lobectomy which was done in September. Postoperatively, CEA returned to the normal level and the patient followed a satisfactory postoperative course, but died of recurrence in the remaining liver and metastasis to the lung in January, 1995.

CT scans of the liver during the clinical course are shown in Fig. 1. Fig. 1-A represents CT at the inception of the intra-arterial injection; a metastatic lesion 4 cm in diameter was noted in the posterior segment of the right lobe and the image on the cranial side showed two metastatic lesions each 2 cm in diameter. Fig. 1-B represents CT after the intra-arterial chemotherapy which had been administered for 4 months; the metastatic lesion had regressed, while a mild hypertrophy of the left lobe was seen. Fig. 1-C represents CT before hepatectomy after 1 year of chemotherapy; atrophy of the right lobe and hypertrophy of the left lobe were prominent; the posterior segment showed low density, poorly discriminated metastatic lesion which had expanded more than before. Angiograms recorded from the

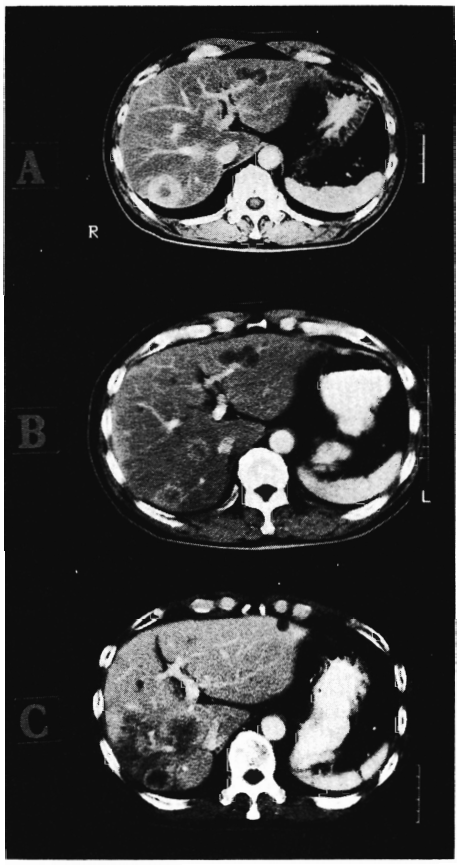


Fig 1 CT scans of liver during the clinical course A; Before treatment, B; After 4 months of intra-arterial chemotherapy, C; Before hepatectomy.

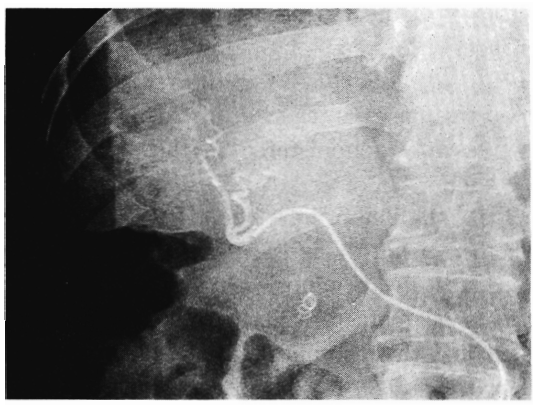


Fig. 2 Angiogram recorded from the port

port before hepatectomy are shown in Fig. 2. The branches of A5 and A6 were not visualized

and encasement was noted in the peripheral vessels. On the ultrasonographic examination performed before hepatectomy, the anterior segment of the right lobe became hyperechoic, while the posterior segment became spotty and hypoechoic; the metastatic lesion was poorly demarcated from the surrounding tissue. The serum level of ALP and LDH were elevated and increased very gradually during the clinical course.

The removed right lobe was markedly atrophied, weighing only 250 g. The liver as a whole was found to be collapsed presenting a dark red color. When the cut surface was examined, a grayish yellow localized metastatic lesion was seen in the center and yellow hepatic tissues with severe fatty degeneration were scattered like islands around the lesion (Fig. 3). According to the pathological findings, the metastatic lesion was considered to be a highly differentiated adenocarcinoma, with necrosis and degeneration being present throughout. When the hepatic tissue around the lesion was examined (Fig. 4), fatty degeneration was seen advancing diffusely in the insular region, and

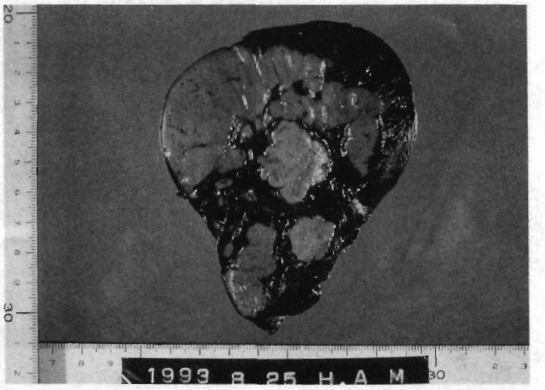
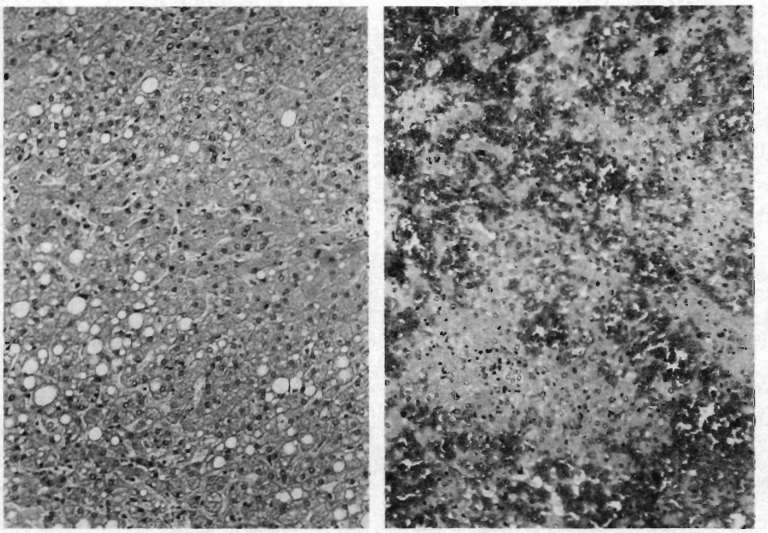


Fig. 3 The cut surface of the removed righ lobe

was particularly severe at the margin of the lobule. The collapsed region was in a state of severe hemorrhagic necrosis, leaving only a hepatocytic streak. The Glisson system in that region was surrounded by thick connective tissues. Particularly, the wall of the bile duct and hepatic artery had been 5 to 6 times as thick as the normal size, and resembled on onion (Fig. 5). The mucosa of the bile duct did not show a pattern of marked degeneration and necrosis as observed in chemical impairment of



(A) (B)

Fig. 4 Microscopic section of the removed liver
A; The insular lesion of the hepatic tissue around the metastatic region, B; The collapsed region.

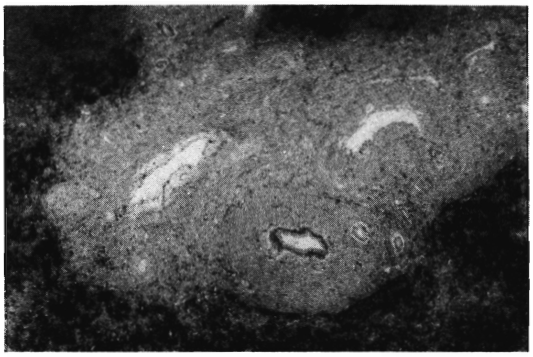


Fig. 5 Microscopic section of the Glisson system in the collapsed region

the bile duct. These changes in the Glisson system were considered changes incidental to marked degeneration of hepatic parenchyma, in contrast to hyaline changes or fibrosis as observed in sclerotic cholangitis.

Discussion

Intra-arterial chemotherapy for hepatic metastasis from colorectal cancer produces satisfactory local effects. According to our results[3] as well, this treatment is effective in 50% of cases and the same results were obtained in other reports. However, opinion is still divided as to its life-prolonging effect as compared with the systemic administration of anti-cancer drugs. The life-prolonging effect of intra-arterial chemotherapy was reported to be negative in controled studies in the U.S. in the 1980s, but more favolable opinions have been expressed recently[4)~7)]. On the other hand, it produces many side-effects, one of which is hepatic dysfunction. It has been reported that chemical hepatitis occurs in many cases[9)], but few histological studies have been conducted. Hohn et al[8)] have reported biliary sclerosis as the most common complication and maintained that it could account for chemical hepatitis. Mohamed et al[10)] operated on 1 case of biliary sclerosis, conducted a histological study and reported that the long-term administration of floxuridine would account for this disorder and that it was improved by steroid administration. Reports on biliary sclerosis are few in Japan where floxuridine is not commercially available[11)]. Thus, biliary sclerosis may be a complication that is specific to the administration of floxuridine. Our case also manifested global degeneration of hepatocytes and liver atrophy. Thickening of the Glisson system including the peripheral bile duct was considered an incidental change, different from biliary sclerosis. Hepatic toxicity of 5-fluorouracil was considered its most likely cause. Because the catheter was retained selectively in the right hepatic artery, the dose of anticancer drugs was relatively too much, which was considered contributory. These changes could not be predicted from the findings of biochemical examinations during the clinical course, and the liver atrophy revealed by CT was characteristic.

Fifty percent of cases with hepatic metastasis die of liver failure attendant upon expansion of the metastatic lesion. It is possible that intra-arterial chemotherapy is contributory. Any biochemical examinations are unable to measure the reserve functional mass of the liver, such that the decrease in this reserve capacity is sometimes overlooked. Recently, therefore, we have conducted the ICG loading test periodically and performed intra-arterial chemotherapy while evaluating the reserve capacity of the liver. Intra-arterial chemotherapy to prevent recurrence in the remaining liver after hepatectomy is beginning to be studied, but careful consideration of the doses and the duration of administration is essential.

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肝動注療法による肝萎縮

東京女子医科大学　第二外科学
亀岡（カメオカ）　信悟（シンゴ）・瀬下（セシモ）　明良（アキヨシ）・浜野（ハマノ）　恭一（キョウイチ）

大腸癌肝転移に対して肝動注化学療法はしばしば行われている．その副作用の一つとして肝機能障害を認めるが，その病理所見の報告は少ない．我々は動注化学療法により著しい肝萎縮を生じた1例を経験したので，病理所見を含めて報告する．61歳の男性で，肝右葉の異時性転移巣に対して，患者の希望にて動注療法を開始した．カテーテルを右肝動脈に留置し，皮下に埋没したリザーバーに接続し，外来通院にて Leucovolin® 30mg，5-fluorouracil 1,250mg を毎週1回で計38回動注した．一時効果を認め，4カ月後には画像上では PR となり，CEA も35ng/ml から10ng/ml まで低下したが，その後に増大したため，動注開始の1年後に肝右葉切除を行った．CT では1年間に肝右葉は著しく縮小し，左葉の代償性肥大を伴った．摘出した右葉は250g と小さく，病理所見では Glisson 系の著しい肥厚を伴う肝虚脱と脂肪変性を認めた．動注療法の合併症としては，硬化性胆管炎が欧米ではしばしば報告されている．自験例はそれらの所見と異なり，慢性の薬物による肝細胞障害と，循環障害が原因と考えられた．