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# Marked clinical improvement in patients with hepatocellular carcinoma by surgical removal of extended tumor mass in right atrium and pulmonary arteries

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**Abstract.** Two patients with advanced hepatocellular carcinoma presented severe exertional dyspnea because of extension of a tumor into the right side of the heart. Removable of the tumor thrombus by open-heart surgery ameliorated the symptoms in each case, but their subsequent courses differed considerably. One patient survived for as long as 8 months thanks to successive multidisciplinary treatments, whereas the other patient died suddenly 1 month after the surgery. The first patient's hepatocellular carcinoma was more differentiated, and the dyspnea was caused by a low cardiac output due to the intracardiac tumor mass, not by pulmonary embolism as in the second patient's case. We conclude that successive multidisciplinary treatments to control the growth of hepatocellular carcinoma is the most important approach and is indispensable for improving the prognosis.

## Introduction

Hepatocellular carcinoma has a tendency to invade the hepatic veins as well as the portal veins in its advanced stages, which usually causes changes in both the intestinal and systemic hemodynamics. In particular, extension of hepatocellular carcinoma through the hepatic veins into the right side of the heart can cause severe dyspnea followed inevitably by sudden death, even when the primary tumor is relatively localized [3]. Since antemortem diagnosis of right atrial thrombi was considered to be difficult [3], few patients had been successfully treated until quite recently. Dazai et al. [1] reported on a 42-year-old man with hepatocellular carcinoma complicated by a right atrial tumor thrombus, who survived for as long as 7 months after chemoembolization therapy with Lipiodol, doxorubicin, and mitomycin C. However, it is widely accepted that surgical treatment is the most effective way to resolve such an urgent situation. We report on two such cases in which marked clinical improvement was achieved by surgical removal of an extended tumor mass, and we also discuss strategies for improving the prognosis.

## Case presentation

*Case 1.* A 47-year-old male HBV carrier felt abdominal distension and pretibial pitting edema in November 1989. Angiography was performed on December 21 and showed a hypervascular liver tumor in

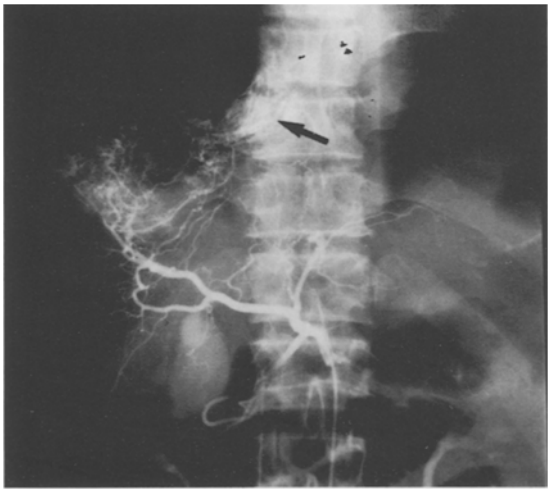

**Fig. 1.** Common hepatic arteriogram shows a hypervascular tumor in segment 8, with a tumor thrombus extending into the right atrium (*black arrow*) in case 1

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*Abbreviations:* HBV, hepatitis B virus; TAE, transarterial embolization; AFP, α-fetoprotein; PIVKA, protein induced by vitamin K absence; FDP, fibrinogen/fibrin degradation products; CT, computerized tomography; MRI, magnetic resonance imaging

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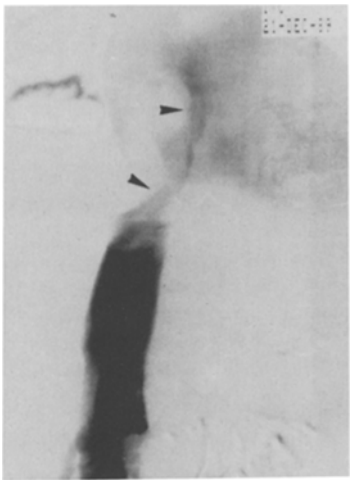

**Fig. 2.** Digital subtraction venogram of the inferior vena cava shows almost complete obstruction by an extended tumor thrombus (*arrow head*) and remarkable dilatation of the inferior vena cava in case 1

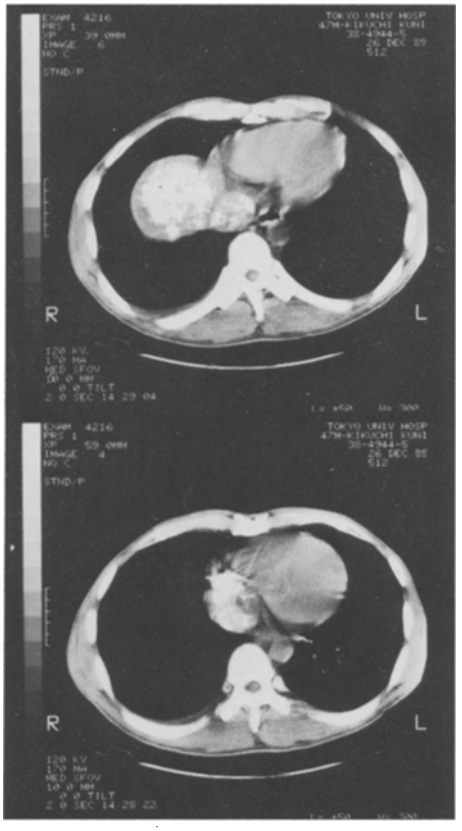


**Fig. 3.** CT scan performed 5 days after the first TAE, demonstrating sufficient deposition of Lipiodol in the liver tumor (*upper panel*) and tumor thrombus (*lower panel*)

segment 8 (Fig. 1), and venography of the inferior vena cava revealed almost complete obstruction by an extended tumor thrombus (Fig. 2). Accordingly, the symptoms seemed to fit secondary Budd-Chiari syndrome. The first TAE was successfully performed as evidenced by sufficient deposition of Lipiodol in the tumor thrombus as well as in the primary tumor (Fig. 3). However, 2 months later the patient experienced severe exertional dyspnea and was admitted to our hospital.

**Table 1.** Laboratory data of case 1 on admission

| | | | |
|---|---|---|---|
| Hematology | | Coagulation system | |
| RBC | 485×10⁴/μl | PT | 14.6 s |
| Hb | 15.4 g/dl | | (49.1%) |
| Ht | 47.6% | APTT | 42.6 s |
| WBC | 6200/μl | HPT | 51.0% |
| Plt | 7.2×10⁴/μl | Fbg | 224 mg/dl |
| Biochemistry | | Serological tests | |
| TP | 6.3 g/dl | HBsAg | (+) |
| Alb | 3.3 g/dl | Anti-HBs | (−) |
| AST | 112 u/l | HBeAg | (−) |
| ALT | 74 u/l | Anti-HBe | (+) |
| LDH | 362 u/l | | |
| γ-GTP | 58 u/l | Tumor markers | |
| ALP | 7.7 KAU | AFP | 58 ng/ml |
| T. Bil | 1.4 mg/dl | PIVKA-II | 3.8 AU/ml |
| T. Chol | 187 mg/dl | | |
| BUN | 18 mg/dl | Arterial blood gas | |
| Cr | 1.1 mg/dl | pH | 7.510 |
| CRP | 1.6 mg/dl | $pO_2$ | 71.8 mmHg |
| | | $pCO_2$ | 28.4 mmHg |
| | | $HCO_3$ | 22.7 mEq/l |

PT, Prothrombin time; APTT, activated partial thromboplastin time; HPT, hepaplastin test; Fbg, fibrinogen

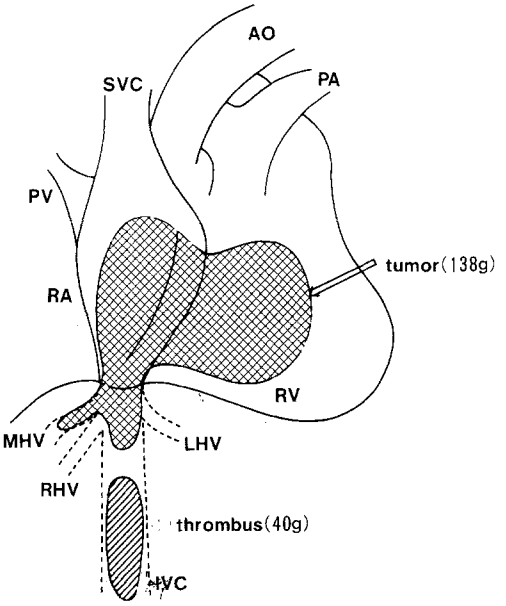


**Fig. 4.** Diagram of operational findings in case 1. The tumor thrombus, extending into the right ventricle, was removed through an incision in the right atrium. Blood clots in the inferior vena cava were also successfully aspirated

As shown in Table 1, the laboratory data on admission disclosed moderate elevation of liver enzymes and remarkable coagulopathy. The serum AFP level was slightly elevated, and the plasma concentration of PIVKA-II was significantly increased. Arterial blood-gas analysis revealed respiratory alkalosis with mild hypoxemia. Chest roentgenograms on admission showed no abnormality in either lung, but an ultracardiogram detected a huge tumor mass in the right atrium and ventricle (image not shown). These lines of evidence suggested that the dyspnea was caused by a low cardiac output due to the presence of the tumor thrombus in the inferior vena cava and the right side of the heart.

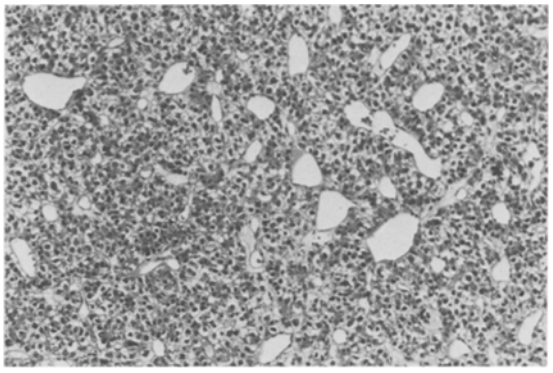

**Fig. 5.** Histologic findings of the excised tumor thrombus. The tumor is diagnosed as an Edmondson's grade II hepatocellular carcinoma arranged in a trabecular pattern (hematoxylin-eosin stain; original magnification, ×66)

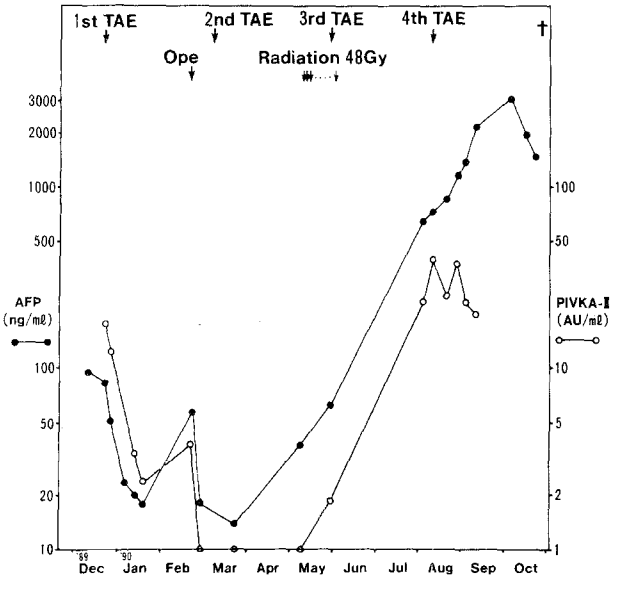


**Fig. 6.** Serial changes in AFP (*filled circles*) and PIVKA-II (*open circles*) levels in case 1

Emergency open-heart surgery was performed on the day after admission. A tumor thrombus weighing 138 g, which extended into the right ventricle, and 40 g of blood clots in the inferior vena cava were successfully removed (Fig. 4). Microscopic examination of the excised specimens showed a trabecular pattern of hepatocellular carcinoma with bile production and abundant cytoplasmic glycogen, corresponding to Edmondson's grade II hepatocellular carcinoma (Fig. 5). Postoperative venography showed the absence of any tumor thrombus in the right side of the heart and inferior vena cava (image not shown). Figure 6 shows the time course of the AFP and PIVKA-II levels. The second TAE was performed immediately after the operation, and this suppressed the tumor progression for at least 3 months. The patient was discharged and could return to work for a while. He was capable of staying home with his family for 124 days in total, corresponding to half of the rest of his life after the operation. However, the tumor expanded so rapidly that two subsequent TAEs and radiation therapy resulted in failure. The patient died of respiratory distress due to multiple lung metastases at 8 months after the open-heart surgery.

At autopsy, the primary tumor measuring 3×2.5×2 cm in size was completely necrotic, whereas numerous green nodules measuring up to 1 cm in diameter occupied the entire liver. Direct invasion to the inferior vena cava with lymphogenous metastasis to the bilateral pulmonary hilar nodes and para-pancreatic nodes were found. Hematogenous metastasis to the lungs, pericardium, bilateral adrenal glands, and fourth lumbar vertebra were also found.

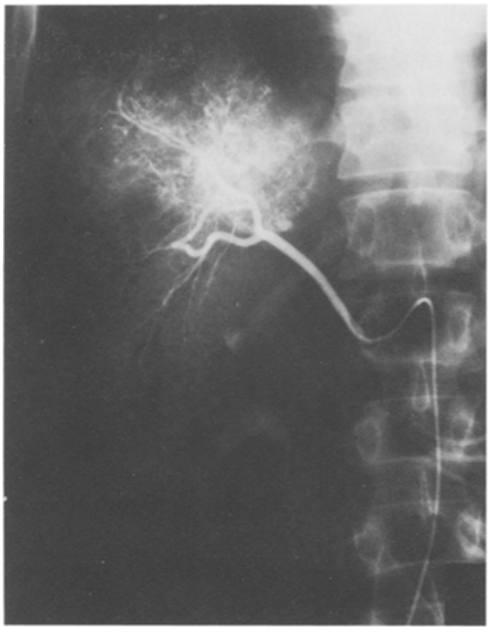

**Fig. 7.** Right hepatic arteriogram shows a hypervascular tumor in segment 7 of case 2

**Table 2.** Laboratory data of case 2 on admission

| | | | |
|---|---|---|---|
| Hematology | | Coagulation system | |
| RBC | 429×10⁴/μl | PT | 12.6 s |
| Hb | 14.4 g/dl | | (93.0%) |
| Ht | 41.8% | APTT | 31.6 s |
| WBC | 8500/μl | Fbg | 337 mg/dl |
| Plt | 9.2×10⁴/μl | FDP | 60.4μg/dl |
| Biochemistray | | Serological tests | |
| TP | 6.3 g/dl | HBsAg | (+) |
| Alb | 3.6 g/dl | Anti-HBs | (−) |
| AST | 109 u/l | HBeAg | (±) |
| ALT | 69 u/l | Anti-HBe | (±) |
| LDH | 567 u/l | Anti-HCV | (−) |
| γ-GTP | 421 u/l | | |
| ALP | 193 u/l | Tumor markers | |
| T. BiL | 0.5 mg/dl | AFP | 59.5 ng/ml |
| T. Chol | 144 mg/dl | PIVKA-II | <0.06 AU/ml |
| BUN | 10 mg/dl | | |
| Cr | 1.0 mg/dl | Arterial blood gas | |
| CRP | 3.9 mg/dl | pH | 7.435 |
| | | $pO_2$ | 54.9 mmHg |
| | | $pCO_2$ | 34.7 mmHg |
| | | $HCO_3$ | 23.6 mEq/l |

PT, Prothrombin time; APTT, activated partial thromboplastin time; Fbg, fibrinogen

*Case 2.* A 48-year-old male HBV carrier was diagnosed as having a liver tumor during a regular check-up examination by ultrasonography in August 1991. Angiography was performed on October 22 and showed a hypervascular liver tumor in segment 7 (Fig. 7), and the first TAE was performed. However, 4 months later the patient started to feel exertional dyspnea and was admitted to our hospital. His mother was also an HBV carrier and had died of hepatocellular carcinoma.

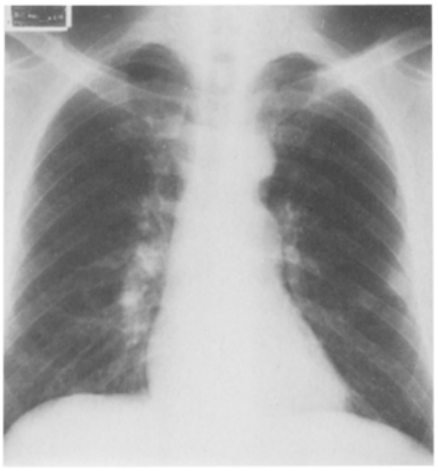

**Fig. 8.** Chest roentgenogram on admission reveals scattered metastatic lesions in both lungs of case 2

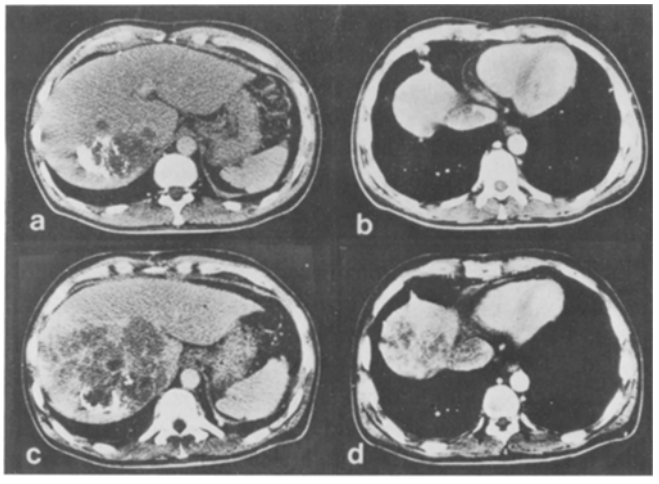


**Fig. 9a–d.** CT images obtained **a, b** just prior to open-heart surgery and **c, d** 1 month later in case 2. **a** A large hypodense nodule with daughter nodules is located in segment 7. Significant disappearance of deposited Lipiodol is noted. **b** Tumor thrombus in the inferior vena cava is clearly shown as a hypodense mass. **c** Rapid expansion of the liver tumor during 1 month is evidenced by this CT image in comparison with **a. d** Tumor thrombus almost completely occludes the inferior vena cava, and expanding liver tumors invade segment 8

As shown in Table 2, the laboratory data on admission disclosed moderate elevation of liver enzymes and FDP. The serum AFP level was slightly elevated. Arterial blood-gas analysis revealed severe hypoxemia. Chest roentgenograms showed several small metastatic lesions in both lungs (Fig. 8). As shown in Fig. 9a, a CT scan demonstrated a hypodense nodule in segment 7 with significant disappearance of deposited Lipiodol. In Fig. 9b the presence of a tumor thrombus in the inferior vena cava is clearly shown. In addition, as shown in the upper panel of Fig. 10, a CT scan demonstrated complete obstruction of the left pulmonary artery by the tumor thrombus, which was also confirmed by MRI (lower panel). These findings suggested that the dyspnea was caused by a mismatch of ventilation and perfusion due to the presence of the tumor thrombus in the left pulmonary artery.

Open-heart surgery was performed 15 days after admission. In all, 25 g of tumor thrombus was removed from the left pulmonary artery and 19 g of tumor thrombus was removed from the inferior vena cava (Fig. 11). Microscopic examination of the excised specimens showed a pavement-like arrangement of malignant cells with a partially pseu-

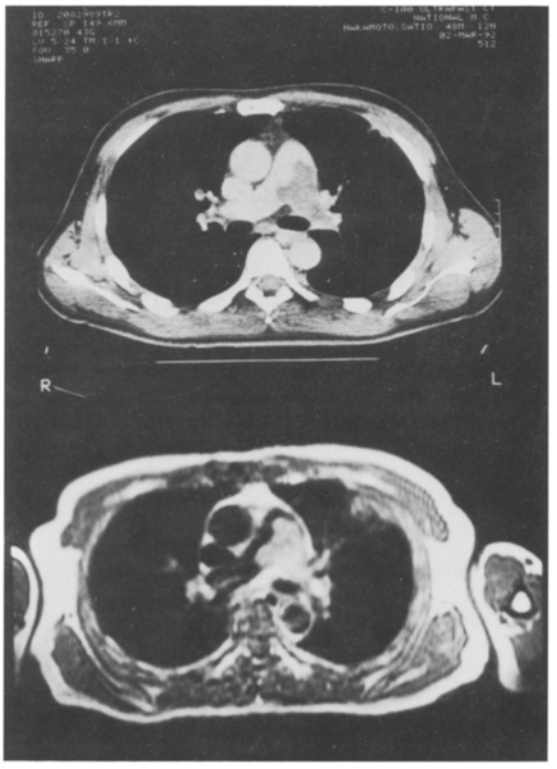


**Fig. 10.** CT (*upper panel*) and MRI (*lower panel*) images of pulmonary arteries obtained just prior to open-heart surgery. The tumor thrombus in the left pulmonary artery is clearly demonstrated as a hypointense mass (*upper panel*) or a hyperintense mass on the T1-weighted image (*lower panel*)

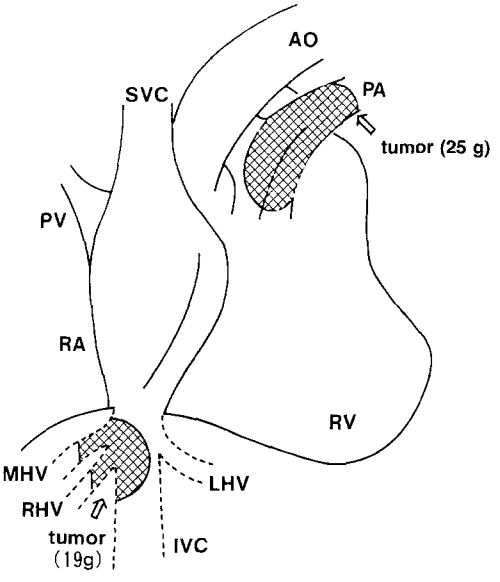


**Fig. 11.** Diagram of operational findings in case 2. The tumor thrombus, located in the left pulmonary artery, was removed through an incision in the main trunk of the pulmonary artery, and peripheral emboli were aspirated. Tumor thrombi in the inferior vena cava and in the branches of the hepatic veins were also removed through an incision in the right atrium

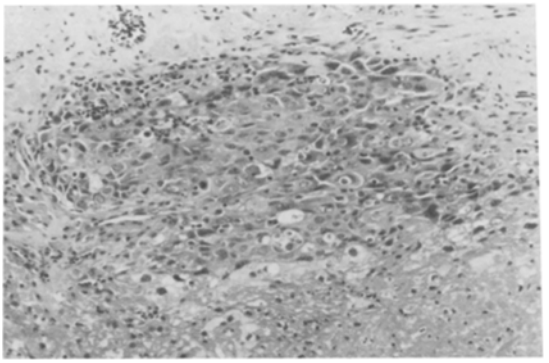

**Fig. 12.** Histologic findings of the excised tumor thrombus. The tumor is diagnosed as an Edmondson's grade III hepatocellular carcinoma arranged in a partially pseudoglandular pattern (hematoxylin-eosin stain; original magnification, ×50)

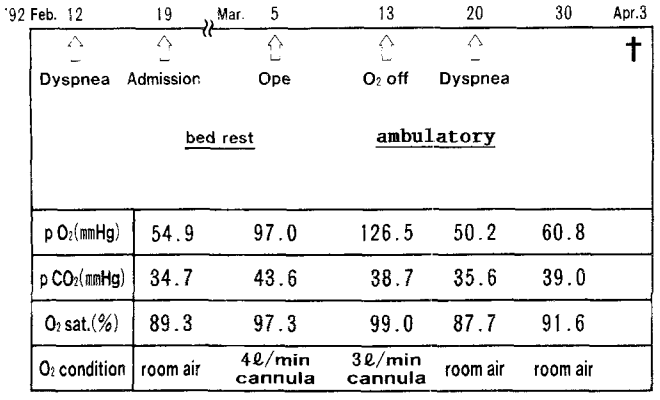


**Fig. 13.** Clinical course and serial changes in arterial blood-gas analysis in case 2. The blood-gas condition gradually improved after the operation, but it deteriorated again 15 days later, probably due to recurrence of the peripheral pulmonary embolism

doglandular pattern, bizarre nuclei, and active mitotic figures, corresponding to Edmondson's grade III hepatocellular carcinoma (Fig. 12). After the operation, the patient's blood-gas condition gradually improved, and he could walk without oxygen supplementation (Fig. 13). However, 15 days after the operation he again complained of dyspnea, and hypoxemia was noted. As shown in Fig. 9c, the liver tumor rapidly expanded, and the inferior vena cava was almost completely occluded by a tumor thrombus (Fig. 9d). However, tumor emboli were detected only in the peripheral pulmonary arteries. He was found dead in the hospital restroom at 29 days after the open-heart surgery. An autopsy was not permitted.

## Discussion

We experienced two patients with hepatocellular carcinoma who complained of severe dyspnea due to extension of the tumor into the right side of the heart. Tumor resection by open-heart surgery was capable of improving their symptoms. However, there was a significant difference in the quality of the postoperative course of the two patients. Case 1 could return to work and survived for as long as 8 months, whereas case 2 submitted to unsatisfactory recovery and died suddenly at 1 month after the operation.

What factors might account for such a great difference between these two cases (Table 3)? First, the histological

**Table 3.** Comparison of prognostic factors in the two patients with hepatocellular carcinoma

| Factor | Case 1 | Case 2 |
|---|---|---|
| Histological grade of HCC | Edmondson II | Edmondson III |
| Cause of dyspnea | Low cardiac output | Pulmonary embolism |
| Lung metastasis | – | + |
| Multidisciplinary treatment | + | – |

HCC, Hepatocellular carcinoma

grade of the hepatocellular carcinoma was less differentiated in case 2 than in case 1 (Figs. 5, 12). This was clearly evidenced by the observation that the liver tumor showed surprisingly rapid growth after the operation in case 2 (Fig. 9). Second, the dyspnea was caused by quite different pathophysiological mechanisms in the two cases: in case 1, by a low cardiac output due to the intracardiac tumor mass; and in case 2, by a mismatch of perfusion and ventilation due to the pulmonary tumor embolism. In addition, hematogenous metastases to both lungs were present at open-heart surgery only in case 2 (Fig. 8). Therefore, it was impossible to remove the tumor thrombi completely from the peripheral pulmonary arteries. By contrast, the respiratory condition of case 1 could be restored to normal by removal of the intracardiac tumor mass. Finally, only case 1 received multidisciplinary treatments such as TAE and radiation therapy after the operation to control tumor progression (Fig. 6). Unless new extension of the tumor thrombus is prevented by successive treatments for the primary liver tumor, the effects of the open-heart surgery will be transient and limited. Fujisaki et al. [2] recently reported the similar case of a woman who was treated by hepatic resection with removal of a tumor thrombus using a cardiopulmonary bypass, and she survived for 26 months after the surgery. Accordingly, even such a drastic treatment should be considered for selected cases.

In conclusion, tumor resection by open-heart surgery can be a useful therapeutic modality, even in cases with extension of hepatocellular carcinoma into the right side of the heart. The subsequent course will be determined by whether or not growth of the residual tumor can be controlled by successive multidisciplinary treatments.

## References

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