



**Case Report**

# Consecutive Tumor Lysis Syndrome and Hepatic Failure after Transarterial Chemoembolization for Treatment of Hepatocellular Carcinoma: A Case Report and Literature Review

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## Abstract

**Introduction:** Acute tumor lysis syndrome (ATLS) and hepatic failure are fatal complications that can occur in patients with hepatocellular carcinoma (HCC) who undergo transarterial chemoembolization (TACE).

**Presentation of Case:** We report the case of a 78-year-old man with HCC who had successive ATLS and hepatic failure after the first course of TACE. He succumbed due to rapid deterioration of his condition.

**Conclusion:** We therefore concluded that awareness of the risks of ATLS and hepatic failure before administration of TACE is crucial in patients with HCC.

**Keywords:** Hepatic failure; Hepatocellular carcinoma; Transarterial chemoembolization; Tumor lysis syndrome

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## Introduction

Hepatocellular carcinoma (HCC) is one of the common human neoplasm worldwide. Currently, transarterial chemoembolization (TACE) is the most common approach for the management of HCC without curative option. Although TACE is an effective modality for unresectable HCC, there are several potential side effects such as hepatic failure, internal bleeding, liver abscess, biliary tract injury, renal failure, and rarely, acute tumor lysis syndrome (ATLS) [1].

ATLS is characterized by the release of intracellular components into the bloodstream due to massive lysis of malignant cells [2]. The condition is associated with a rapidly growing neoplasm. Infrequently, it can occur in patients with HCC [1, 3-7]. The incidence of post-TACE hepatic failure has varied from 2.1% to 60%. This variation may be due to different definitions of hepatic failure [8]. Most studies suggest that a poor liver reserve before TACE is the main determinant in development of hepatic failure after TACE.

Here, we present a case of HCC with successive ATLS and hepatic failure after the first course of TACE. We also review other reports of ATLS and hepatic failure in HCC that were retrieved from the MEDLINE database.

## Case Presentation

A 78-year-old retired businessman was admitted to our hospital after experiencing progressive abdominal fullness for one month. He had no past history of viral hepatitis B, C or alcohol consumption. He had a fair appetite but had lost 5 kilograms in the past 3 months. Initially, he went to a local clinic where he received abdominal sonography which revealed multiple liver tumors. Then he was referred to our hospital for further evaluation and management.

On physical examination after admission, the patient's body temperature was 36°C, heart rate was 80 beats per minute, blood pressure was 124/85 mm Hg, and respiratory rate was 14 breaths per minute under normal conditions. There were no icteric sclera, yellowish skin discoloration, gynecomastia, spider angiomas, palmar erythema or leg edema. Laboratory data demonstrated serum aspartate aminotransferase (AST) 92 U/L (normal: 8 to 38

U/L), alanine aminotransferase (ALT) 102 U/L (normal: 4 to 44 U/L), total bilirubin 0.6 (normal: 0.2 to 1.2 mg/dL), alkaline phosphatase (ALP) 236 U/L (normal: 50 to 190 U/L), blood urea nitrogen (BUN) 40 mg/dL (normal: 8 to 20 mg/dL), creatinine 1.6 mg/dL (normal: 0.6 to 1.5 mg/dL), potassium 4.4 (normal: 3.5 to 4.3 mEq/L), lactate dehydrogenase (LDH) 197 U/L (normal: 20 to 240 U/L), and prothrombin time (PT) 11.2 seconds (normal: 8.5 to 11.5 seconds). The chest X-ray film showed no active lung lesion. Computed tomography (CT) scan of the liver revealed liver cirrhosis and numerous tumors enhanced in the arterial phase and early wash-out in the portal phase, which were compatible with multiple HCC, as shown in Figure 1. Angiography also found multiple hypervascular tumors in bilateral lobes of liver. The tumor marker serum alpha-fetoprotein (AFP) was as high as 326 ng/mL (normal <12 ng/ml). Under the diagnosis of cirrhosis, Child-Turcotte-Pugh class A, and multiple HCC, BCLC stage B, TACE was suggested and administered with epirubicin 20mg and lipiodol 5ml. On the 2nd day after TACE, the patient complained of mild epigastria, but the laboratory data revealed rapid elevation of serum GOT (11320), GOT (2721), LDH (6069), creatinine (2.6), potassium (6.0), phosphate (10.5; normal: 2.5 to 4.5 mg/dl), uric acid (14.2; normal: 2.4 to 7.2 mg/dL), decreased calcium (6.5; normal: 8.4 to 10.2 mg/dL) and metabolic acidosis (pH 7.17, normal 7.35-7.45; HCO<sub>3</sub> 7.3, normal 22-26 L/mmol). Other serum markers, including serum hemoglobin, CK, bilirubin and PT, were all within normal limits. ATLS was diagnosed, and adequate hydration, allopurinol and intravenous sodium bicarbonate were given immediately. However, oliguria, dyspnea and drowsy consciousness occurred on the 3rd day after TACE, so emergent hemodialysis was performed and an endotracheal tube was inserted with ventilation support on the same day. The laboratory data revealed decreased serum GOT, LDH, uric acid and potassium, as shown in Figure 2. Unfortunately, the patient's serum bilirubin and PT levels got progressively worse in the next few days, and acute liver decompensation was considered. Refractory severe high anion-gap metabolic acidosis persisted in spite of hemodialysis, and he passed away on the 8th day after administration of TACE.

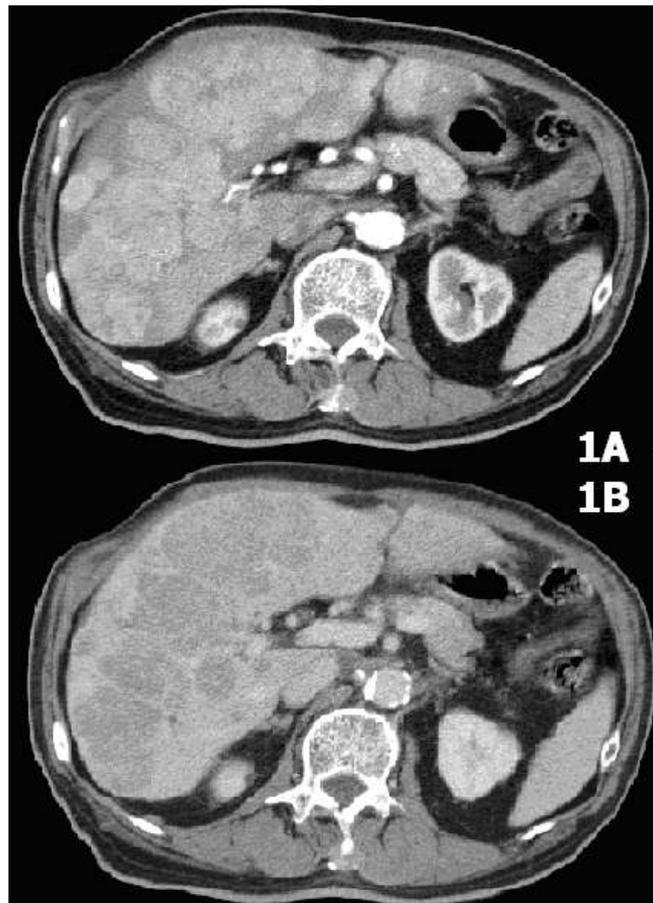


Figure 1 CT scan of the liver noted liver cirrhosis and multiple HCC

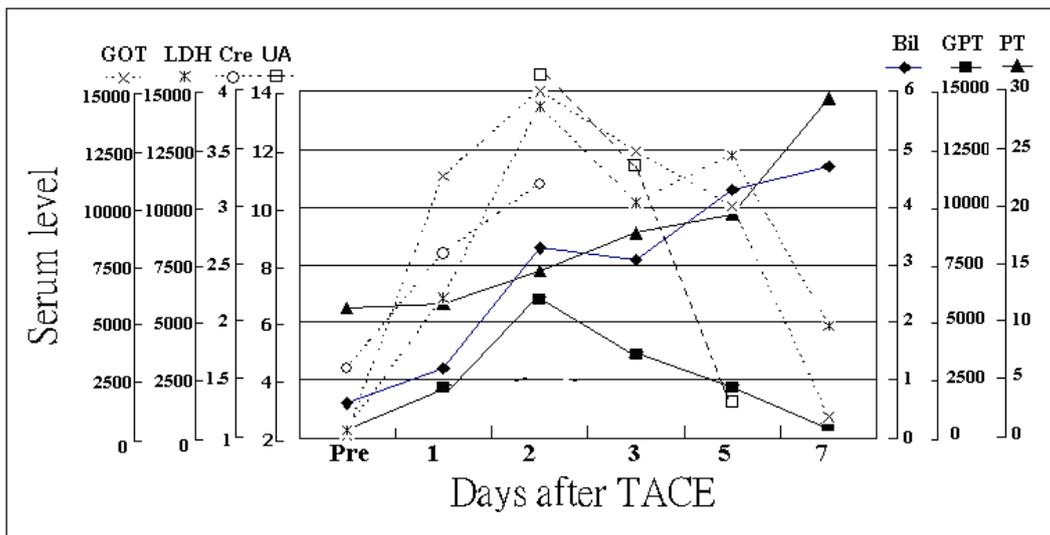


Figure 2 The laboratory data showed the markers of tumor lysis syndrome, including GOT, LDH and urine acid and potassium, declined after the 2nd day, but serum bilirubin and PT levels increased in the next few days.

## Discussion

TACE was first used to treat HCC in Japan in 1974, but broader application of TACE began only after lipiodol was introduced as a drug carrier and an embolic agent. TACE involves mixing cytotoxic agents such as doxorubicin, cisplatin, mitomycin C with lipiodol and administering it into the feeding artery of the tumor. It thus has both selective ischemic and therapeutic effects on HCC [9]. Major complications of TACE have been well documented, including liver dysfunction, severe post-embolization syndrome, hepatic infarction, biloma formation, liver abscess, tumor rupture, septicemia, gastrointestinal bleeding, gallbladder infarction, splenic infarction, pulmonary oil embolism, and spinal cord injury [5].

ATLS is characterized by the release of intracellular components into the bloodstream due to massive lysis of malignant cells. The condition is associated with rapidly growing neoplasms, such as Burkitt's leukemia and acute lymphoblastic leukemia, and usually occurs after treatment with chemotherapy, steroids or interferon [2]. ATLS is less likely to occur in patients with solid tumors, especially HCC, which are relatively insensitive to anti-neoplastic therapies. Only 7 HCC cases with ATLS after TACE have been reported in the literature and they are summarized in Table 1 [1, 3-6].

The pathogenesis of ATLS is related to rapid tumor cell destruction, which may result in the release of intracellular ions and metabolic byproducts into the systemic circulation. The risk factors for the development of ATLS in cancer patients include chemo-sensitive tumors, bulky tumors, large numbers of ischemic areas within the tumor, increased serum uric acid and impaired renal function prior to chemotherapy [4]. Clinically significant ATLS can occur spontaneously but most often is seen 48–72 h after initiation of cancer treatment [1, 4].

ATLS is a constellation of hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia, which typically develops after administration of aggressive combination chemotherapy for a rapidly proliferating neoplasm. L. Baeksgaard reported the biochemical characteristics of ATLS in solid tumors; the most common findings were hyperuricemia (98%) and increased LDH (96%). Less common findings were azotemia (93%), hyperphosphatemia

(89%), hypocalcemia (89%), metabolic acidosis (83%) and hyperkalemia (73%) [10]. According to the Cairo-Bishop classification, ATLS is defined as a 25% change or a level above or below normal for any two or more serum values of uric acid, potassium, phosphate, and calcium within 7 days after cancer therapy [11]. In our patient, all the laboratory parameters matched these findings.

Paye et al. examined HCC liver resection specimens after TACE and found that post-chemoembolization cytolysis was more common in patients with large tumors [12]. Therefore, the large tumor burden is a potential risk factor for ATLS. Tumor necrosis, rather than damage to normal hepatic parenchyma, was strongly suggested by hyperuricemia and elevation of serum LDH levels. Thus, all patients with HCC undergoing TACE, particularly those with huge tumors, a rich blood supply and complete embolization, should be monitored closely for ATLS [3].

The standard preventive approach consists of aggressive rehydration, allopurinol, and urinary alkalization following chemotherapy or other treatment in patients with a large tumor and complete embolization [4, 7]. As for the outcome of ATLS in solid tumors, the results have generally been poor, and the mortality rate is higher than that for hematologic malignancies [13]. However, the prognosis is relatively good if there is recovery of renal function after the uric acid level is lowered [4]. Although ATLS was diagnosed and treated immediately in our patient, he still died due to consecutive hepatic failure.

Hepatic failure is considered as a more common cause of mortality in patients with HCC treated with TACE. Based on pathological studies, Paye et al. found that fever and hepatic dysfunction after TACE are mainly due to injury to the non-tumorous liver instead of tumor necrosis [12]. According to a previous study, Child-Turcotte-Pugh (CTP) class B, post-TACE syndrome and gastrointestinal bleeding, but not tumor size, were independent risk factors associated with liver failure in a multivariate analysis [14]. Another study reported the a pre-TACE ICG test, PT, the CTP class and lipiodol dosage are the most important indices to predict the liver damage of a patient after TACE [15]. Therefore, strict selection of candidates for TACE may prevent hepatic failure and make this treatment more feasible.

Table 1

Reference	Sex/ Age	Tumor size (cm)	Underline	TACE times	TACE drugs	ATLS (hours)	onset	Laboratory Data						Outcome
								Cre (mg/dL)	UA (mg/dL)	K (mg/dL)	Ca (mg/dL)	P (mg/dL)	LDH (U/L)	
urney. <sup>3</sup>	M/44	>5	n	3	DDP 60 mg/m2	8	-	10.7	7.7	10.1	11.8	2423	Death	
Burney. <sup>3</sup>	M/46	14x12	HBV,alcohol	1	n	60	-	-	-	-	-	1300	Recovery	
Sharma et al. <sup>4</sup>	M/63	14x12	HBV	1	5FU 1 g, DDP 80 mg, MMC 20 mg, LP 10 ml	74	5.9	13.2	4.4	7.6	6.9	-	Recovery	
Sakamoto et al. <sup>5</sup>	M/55	17x13	HBV	2	EPB 50 mg, LP 15 ml,	84	4.9	10	6.6	7.3	n	1241	Death	
iroaki et al., <sup>6</sup>	M/77	>10	n	1	EPB 70 mg +LP 20 ml,	72	5.2	16.3	5.7	7.7	10.3	2668	Recovery	
Hsieh et al. <sup>1</sup>	F/76	>10	n	1	ADM 20 mg	48	-	16.6	5.7	6.8	-	-	Death	
Hsieh et al. <sup>1</sup>	M/56	>5	HBV	1	ADM 20 mg	24	-	15.1	-	6.6	4.7	-	Recovery	
Our patient	M/78	12x10	HBV	1	EPB 20mg + LP 5ml	24	2.6	14.2	6.0	6.5	10.5	6069	Death	

## Abbreviations:

ATLS, acute tumor lysis syndrome; HCC, hepatocellular carcinoma; HBV/HCV, hepatitis B/C virus; TACE, transarterial chemoembolization; M, male; F, female; 5-FU, 5-fluorouracil; ADM, adriamycin; DDP, cisplatin; EPB, epidoxorubicin; GS, gelatin sponge; LP, lipiodol; MMC, mitomycin C; Cre, creatinine; Ca, Calcium; K: Potassium; LDH, lactate dehydrogenase; P, Phosphorus; UA: Uric acid

However, even among HCC patients classified as CTP class A or B who were candidates for TACE therapy, a small proportion (3%) had irreversible liver failure [16]. Although our patient was classified as having CTP class A cirrhosis, acute hepatic failure still occurred.

In summary, TACE may cause potentially fatal complications, including ATLS and hepatic failure, in HCC patients. Both of these conditions contribute directly to cytotoxic therapy and ischemic embolization necrosis. However, ATLS and hepatic failure have different presentations and mechanisms. Firstly, ATLS usually occurs between 48-72 hours after initial TACE, but hepatic failure often happens later. Secondly, the most important risk factor of ATLS after TACE in patients with HCC was the tumor size, but that of hepatic failure was the CTS class of these patients. Thirdly, the major pathologic damage of ATLS was at tumorous sites, whereas non-tumorous liver injury was found in hepatic failure cases.

In conclusion, we reported an unusual case of a patient with multiple HCC who underwent TACE and had fatal complications associated with consecutive ATLS and hepatic failure. Recognition of risks and prevention are the most important steps in the management of these syndromes.

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