Abstract. Background: Malignancies rarely cause of acute liver failure, the presence of which have to be ruled-out during transplant evaluation. Tumor-related liver ruptures sporadically occur and might further complicate patient management. Case Report: We report the case of a previously healthy 56-year-old male with complaints of abdominal pain. Initially, levels of liver enzymes were elevated, however, comprehensive imaging examinations revealed no gross abnormalities. As acute liver failure developed, transplantation was evaluated. Sudden liver rupture and hemorrhage forced the performance of an emergency laparotomy. Hepatectomy was planned, until a donor organ was allocated. Intraoperatively, the liver unexpectedly revealed diffuse tumor infiltration. Without further therapeutical options, the patient died. Immunohistochemistry showed metastatic infiltration of a carcinoma of unknown primary. Conclusion: Even in previously healthy patients suffering from acute liver failure, exclusion of malignancies is mandatory before transplantation. As imaging might be misleading, a biopsy should be considered early in unresolved cases.

Acute liver failure (ALF) is a life-threatening emergency, where fast-track treatment is mandatory. In ALF, liver transplantation frequently represents the only rescue option. Nevertheless, prior to listing for transplant, a thorough evaluation, including screening for potential obstacles, is necessary. A case in point is the diagnosis of an advanced malignant process, representing a clear contraindication to transplantation. Although liver infiltration is commonly observed within the course of metastatic disease, tumor-related ALF, as a primary symptom of a malignant disorder, is very exceptional. Furthermore, the co-incidence of tumor-related ALF and spontaneous liver rupture is even more unusual. During expedited patient evaluation, diffuse hepatic infiltration as an underlying disease might thus be missed. To facilitate patient management in similar cases and to disclose possible pitfalls during patient evaluation, we herein report a case of acute liver failure due to hepatic de novo tumor manifestation, complicated by spontaneous liver rupture and fatal hemorrhagic shock.

Case Report

A 56-year-old Caucasian male, with uneventful past medical history, presented at his local hospital complaining of persistent and severe pain in the upper right field of his abdomen. Other symptoms, such as weight loss, fever or night sweat, were absent. Only very moderate alcohol consumption was stated. On the basis of elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin, ultrasound and endoscopic retrograde cholangiopancreatography (ERCP) were performed. However, besides a slightly enlarged liver, no gross abnormalities were detected and an explicit diagnosis was therefore lacking. On the basis of elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin, ultrasound and endoscopic retrograde cholangiopancreatography (ERCP) were performed. However, besides a slightly enlarged liver, no gross abnormalities were detected and an explicit diagnosis was therefore lacking. During the subsequent days, the patient’s symptoms did not resolve. Moreover, blood tests pointed to deteriorating liver function, associated with signs of increasing hepatocellular damage. Prothrombin time dropped to 40%, accompanied by continuously rising levels of liver enzymes (ALT=382 U/ml, AST=1650 U/ml) and bilirubin (11.7 mg/dl). In addition, lactate dehydrogenase (LDH; 6565 U/l) as well as uric acid...
(16.2 mg/dl) plasma concentrations were substantially increased. With the tentative diagnosis of acute liver failure of unknown origin, the patient was transferred to the Intensive Care Unit of our university hospital where, evaluation for liver transplantation started immediately. Virology screening demonstrated immunity to hepatitis A and B, but active viral infections were excluded. Within 12 h after admission, hemoglobin dropped from 14.3 mg/dl to 7.1 mg/dl. Ultrasound examination showed increasing intra-abdominal fluid collections, which corresponded to blood on exploratory puncture. A whole-body scan finally revealed spontaneous liver rupture with concomitant intra-abdominal hematoma (Figure 1). Additionally, diffuse parenchymal alterations were seen, which were assumed to be tissue abnormalities associated with hemorrhagic shock. However, circumscribed, tumor-suspicious, hepatic lesions were not detected. Besides the liver rupture, no other abnormalities of thoracic or abdominal organs were disclosed.

Subsequently, the patient underwent interventional angiography in an attempt to stop the bleeding via coiling of feeding arterioles. After insertion of a 4 French (Fr) sheath, a 4 Fr Cobra catheter (Terumo Glidcath; Terumo GmbH, Eschborn, Germany) was used for the selective intubation of the celiac axis, the superior mesenteric artery and the phrenic artery (Figure 2). A variant anatomy with a hepatomesenteric trunk was seen, which supplied liver segments 6/7. The catheter was placed in the common hepatic artery. All arterial vessels had a very small diameter, most likely related to vasoconstriction during hemorrhagic shock. However, during angiography there was no apparent active arterial bleeding from hepatic artery branches or from the phrenic artery. Progressive hemodynamic instability forced cessation of further radiological interventions. Therefore, superselective intubation of smaller hepatic arteries in the periphery was not performed.

At that time, the patient was listed for liver transplantation and prepared for emergency laparotomy, since there were no apparent contraindications for such a procedure. Total hepatectomy and temporary creation of a portocaval shunt were planned to control the bleeding and bridge the time to transplant, until a suitable organ was allocated. Upon laparotomy, massive blood collections emptied. Subsequent exploration of the liver revealed a rupture of the capsule in the area of segment 6/7 with diffuse hemorrhage. Liver parenchyma was strongly indurated, with widespread, fine-nodular alterations, macroscopically suspicious of malignant tumor.
Biopsies were taken from various sites of the liver and sent for immediate frozen-section analysis (Figure 3). Microscopic analysis confirmed diffuse metastatic infiltration of the hepatic tissue with a poorly differentiated carcinoma, however, further morphological classifications were not possible. Based on the intraoperative initial diagnosis of advanced malignant disease, the patient had to be withdrawn from the liver transplant list immediately. Because local hemostatic measures were unable to control the bleeding, the abdomen was packed with towels and closed. Within the following hours, the patient died from the consequences of hemorrhagic shock, since further therapeutical options were lacking. Besides moderately increased carcino-embryonal antigen (CEA) and carbohydrate-antigen 19-9 (CA 19-9) levels, post mortem serum tumor marker analysis showed strongly elevated pro-gastrin releasing-peptide (ProGRP) and neurone-specific enolase (NSE) levels, primarily suggestive of a small cell carcinoma of the lung, less likely of a tumor of the gastrointestinal (GI)-tract (Table I). However, review of the CT scan disclosed no lung, GI-tract or any other malignancy.

Immunohistochemistry showed a strong positive staining for cytokeratin 20 (CK20), chromogranin A, CD56 and a weak antibody reaction for CK7, not typical for lung malignancies. However, it was not possible to obtain a more lineage-specific immunohistochemical profile; results were negative for prostate-specific antigen, thyroid transcription factor-1 (TTF-1), human melanoma black 45 and caudal type homeobox transcription factor 2 (CDX-2). The final histopathological diagnosis therefore was high-grade carcinoma with neuroendocrine differentiation. Based on the histomorphological analysis the primary tumor potentially might have been located in the GI-or in the urogenital tract. The presence of a Merkel cell carcinoma also had to be taken into account. Postmortem examination was refused by the next of kin.

**Discussion**

ALF is characterized by its rapid and often detrimental progress, which is associated with a high mortality rate. Hence, the therapeutic window is small and strict time management concerning diagnostic work-up and initiation of life-saving measures is essential for patient survival (1). Liver transplantation frequently represents the sole treatment option in ALF. Listing for liver transplantation should therefore be achieved as fast as possible. However, thorough evaluation is
needed to exclude contraindications to liver transplantation. For example, patients with malignancies and concomitant hepatic metastasis clearly should not undergo transplantation.

Although the liver is prone to metastatic disease, ALF is rarely the result of rapid tumor progression. ALF due to diffuse hepatic infiltration as primary manifestation of a malignant disease has been described sporadically. In these cases, a variety of different tumor entities was present. The vast majority of patients suffered from a previously unknown small–cell carcinoma of the lungs (2–7), but diffuse lymphomatous (3), pancreatic and GItract– (5), urogenital– and melanoma– (8,9) related infiltrations of the liver have also been described. To our knowledge, ALF on the basis of a de novo non-hepatocellular carcinoma (HCC) tumor manifestation with concomitant spontaneous liver rupture has not been reported so far.

Interestingly, in many of these patients, radiological findings were inconclusive and neither detected the tumor manifestation within the liver, nor the site of the primary tumor, similar to the presented case. Indeed, diffuse tumor infiltration may remain undetected by multidetector CT. In this scenario, magnetic resonance imaging (MRI), using liver-specific contrast agents, could help to establish a diagnosis and to reveal the tumor extent (10). However, MRI examination of patients, depending on intensive care treatment, is still difficult or – as in our patient – impossible, due to hemodynamic instability following rupture of the diseased liver.

In the presented case, high levels of plasma LDH and uric acid were found initially. This combination has been described for patients with a small–cell carcinoma of the lungs, manifesting primarily as ALF (11). Subsequent

Figure 3. Morphological findings. Light microscopic images reveal the infiltration of the liver [a; ×400] (b; area shown in (a) ×800] by poorly differentiated tumor cells (arrowhead), with only few residual hepatocytes (arrow), but widespread lymph and hemangiosis carcinomatosa (asterix) (hematoxylin/eosin staining). The massive diffuse infiltration pattern (c; ×200) is even more striking after pan-cytokeratin immunohistochemistry (arrow; few regular hepatocytes). The high proliferative capacity of the tumor cells is highlighted in Ki-67 immunohistochemistry (d; ×800), with nuclear signals being found only in tumor cells (arrowhead), surrounding non-staining hepatocytes (arrow).
determination of a tumor marker panel may help to substantiate the suspicion of malignant disease, however, positive markers do not guarantee identification of the tumor entity. Indeed, post-mortem analysis of blood and tissue samples revealed a clear discrepancy between the plasma tumor marker profile and immunohistochemically detected characteristics. Although levels of NSE and ProGRP were highly elevated, and thus suggestive of small-cell carcinoma of the lungs, tissue antigens practically excluded the presence of pulmonary malignancy. In contrast, strong positive staining for CK20 and a lack of staining for CK7 and TTF-1 more likely pointed to the presence of a primary tumor located in the gastrointestinal (supported by moderately increased CEA and CA 19-9 levels) or urogenital tract, or a Merkel-cell carcinoma. However, in the absence of an autopsy, we were not able to provide the final diagnosis, definitively. Nevertheless, a needle biopsy, performed at an early stage, when abdominal pain and laboratory results pointed to severe hepatic disorder, would have readily provided the diagnosis of a malignant disease. Thus, further patient management would have been facilitated, decisively.

Liver ruptures are rare events and are mainly due to pre-existing, chronic hepatic alterations (12). HCC-related ruptures have been described several times, occurring with an incidence between 4.8-26% (13). Most of these patients had a known history of cirrhosis and HCC diagnosis had already been noted (14-16). In contrast, spontaneous liver ruptures in previously healthy patients, without a longer history of hepatic disease, are even more extraordinary. In the presented case, abnormally rapid expansion of infiltrating tumor cells was responsible for the rapid disease progression and finally for liver rupture. Indeed, we found a massive, diffuse infiltration by poorly differentiated cells, only few residual hepatocytes, but widespread lymph- and hemangiosis carcinomatosa, as highlighted by CK and Ki-67 immunohistochemistry.

Sometimes spontaneous liver ruptures are associated with the “hemolysis, elevated liver enzymes and low platelet count” (HELLP) syndrome during pregnancy (17), or hepatocellular adenomas, mostly in females (18, 19), but casually also in male patients (20). Very few cases have been reported, where the underlying etiology remained occult (21). Consequently, comprehensive recommendations about the treatment options for spontaneous hepatic ruptures are as yet lacking.

Bleeding associated with a ruptured HCC remains an indication for surgery, provided that liver function is well preserved and the tumor appears locally resectable. Interventional angiography and tumor embolization should only be attempted in patients with multifocal HCC, poor liver function or reduced general condition. Direct hemostatic measures, packing with towels or hepatic artery ligation should only be tried in cases of relapse or uncontrollable bleeding (13).

Liver transplantation, as the ultimate treatment option for severe hepatic hemorrhage, where all other conservative, interventional or surgical therapies have failed or are not applicable, has been described for hepatic rupture associated with pre-eclampsia (22) and blunt liver trauma (23). Here, total hepatectomy represents the ultimate salvage measure to control bleeding. Since donor organs will not be available immediately, a two-stage surgical approach is necessary (24, 25). Firstly, total hepatectomy is performed to stabilize the patient hemodynamically. To avoid intestinal congestion and bacterial translocation during the subsequent anhepatic period, hepatectomy should be combined with the creation of a temporary portocaval shunt. As soon as a donor organ is allocated, transplantation can be accomplished in a second procedure. Interestingly, successful transplantations have been reported after mean anhepatic periods of approximately 20 h (25).

For the management of ALF of unknown cause, where liver transplantation is the remaining treatment option, we conclude that comprehensive exclusion of contraindications, such as advanced malignant disease, is mandatory, even in previously healthy individuals. Spontaneous liver ruptures in the disease course of ALF are rare complications, which per se do not exclude transplantation. Evaluation should include LDH and uric acid measurements, potentially followed by tumor marker analysis. Diffuse metastatic affection of the liver should be considered in unresolved cases of ALF associated with hepatomegaly, substantially increased LDH and uric acid levels, even if CT imaging studies cannot disclose a hepatic lesion. In these patients, MRI diagnostic should be also considered, assuming a clinically stable condition. A liver biopsy, performed early during the hospital course and prior to the development of clotting disorders, may facilitate a more rapid diagnosis and avoid further time-consuming procedures, thus alleviating patient management.

Conflicts of Interest

The Authors have no conflicts of interest or funding to disclose.

References


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