Lethal acute liver failure in a 60 y/o female patient with AILD III (Ann Arbor) T-cell lymphoma in remission state – Case report

Maryla Kuczyńska¹, Ewelina Dziaduch¹, Anna Grzywa-Celińska², Patrycja Lachowska-Kotowska², Jerzy Mosiewicz²

¹ Scientific Society of Students at the Department of Internal Medicine, Medical University, Lublin, Poland
² Department of Internal Medicine, Medical University, Lublin, Poland

Abstract
Acute liver failure (ALF) is a rare condition in which liver function deteriorates suddenly, leading to encephalopathy and coagulopathy in patients previously unaffected with hepatic cirrhosis. The case is presented of a 60-year-old woman admitted to our Department with complaints of general malaise, excessive sweating and body temperature elevation. Her history was relevant in terms of T-cell lymphoma in remission, hypertension and paroxysmal atrial fibrillation. The patient only reported using methylprednisolone in 4–8 mg daily dosage. Liver function tests were abnormal, with considerably elevated ALT, AST and GGTP concentrations. Diagnostic imaging revealed non-dilated biliary ducts, hepatomegaly and a single enlarged lymph node between the inferior vena cava and hepatic portal vein. A needle biopsy of the liver was non-diagnostic due to protein masses blurring the specimen. Autoimmune markers and investigation for Wilson’s disease both presented no alterations. The patient presented hyperthyroidism with no signs of thyrotoxicosis, significant leukocytosis and thrombocytopenia. Her state deteriorated rapidly despite aggressive pharmacological treatment. The patient died before a needle core biopsy could be performed; no post-mortem examination was carried out at the request of the family.

ALF should be suspected in every patient who exhibits highly elevated hepatic enzymes and whose condition is deteriorating rapidly. In our investigation, we should primarily focus on histopathological examination and qualifying the patient for the liver transplantation.

Key words
acute liver failure, T-cell lymphoma, remission

INTRODUCTION
Acute liver failure (ALF) is a manifestation of sudden, severe and extensive necrosis of liver parenchyma cells or vast hepatocyte replacement with malignancies [1, 2, 3]. Both metabolic and detoxicative hepatic functions are compromised [2]. This medical emergency may be caused by numerous conditions, among which the most common are: drug-induced (esp. acetaminophen) toxicity and viral hepatic injury. Other factors include Wilson’s disease (3% of ALF), auto-immune disorders, sepsis, as well as states of compromised circulation (Budd-Chiari syndrome, shock liver) [1, 2, 4]. Among the less common causes of ALF neoplastic infiltration of the liver is also a possibility [4, 5, 6, 7]. ALF is associated with multi-organ failure leading to abrupt deterioration of the patient’s status. Although ALF is characterized by a high mortality rate, the outcomes have improved due to liver transplantation procedures (the survival rate formerly stated as 15%, nowadays exceeds 65%) [1, 2, 5, 8]. Qualification to this procedure requires prior screening for all the possible contraindications and stating accurate diagnosis, together with the primary cause, is essential in this situation [9]. However, the symptoms of ALF are non-specific, as presented by a number of dysfunctional systems, significantly hampering the diagnostic process.

CASE REPORT
A 60 y/o female was admitted to the Internal Medicine Department complaining of general malaise, muscle pains, headaches, vertigo, nausea, elevated body temperature and excessive sweating progressing for a month. Two months before admission she had laboratory tests performed that showed a slight elevation of total bilirubin (up to 1.8 mg/dl) and C-reactive protein (CRP) concentration reaching abnormal values of 60 mg/dl (normal range up to 5 mg/dl). She had a previous history of T-cell lymphoma (in remission for subsequent five years after receiving a total of 2 cycles of multi-agent chemotherapy), hypertension, paroxysmal AF. Prior surgeries included cholecystectomy. She was suspected of having some kind of systemic disease, but this was never definitely confirmed. She reported to using methylprednisolone in 4–8 mg daily dosage. The patient denied using acetaminophen or drugs other than the prescribed medications, herbs or supplements. There was no history of alcohol abuse or sexual risk factors. The family history was unremarkable.

On admission, the patient was somnolent, but oriented and febrile. On physical examination tremor was observed with the patient presenting a tender abdomen with shifting
nullness. There were no signs of lymphadenopathy and apart from being mildly icteric, the patient exhibited no further visible signs of liver dysfunction.

The laboratory data (Tab. 1.) revealed RBC count of 5.41 M/uL, Na – 133 mmol/l, Cl – 96 mmol/l, CRP – 50.9 mg/l. Chest X-ray revealed no relevant aberrations. Further tests indicated remarkably elevated levels of hepatic enzymes (AST over 410 U/l, ALT over 340 U/l, GGTP over 380 U/l), total bilirubin (T Bil in range 2.94–26.84 mg/dl) and direct bilirubin (D Bil in range 6.41–16.80 mg/dl), urea (in range 52.5–104.7 mg/l), LDH (in range 243–388 U/l). Further studies concerning serologies for HBV, HCV and toxoplasmosis were negative. Tests for CMV antibodies revealed IgM negative and IgG positive results. Immunoglobulins levels were IgG – 19.75 g/l (norm: 7–16) and IgM – 8.71 g/l (norm: 0.4–2.3) respectively.

Chest X-ray revealed no relevant aberrations. The abdominal ultrasonography exhibited signs of biliary tree dilation. As biliary tract inflammation was suspected, the patient was placed on ciprofloxacin to effect normalizing of body temperature and lowering the CRP concentration. MRI of the abdominal cavity, however, excluded the primary diagnosis. The patient was consulted by the gastroenterologist who proposed performing an abdominal CT which showed that the common biliary duct as well as intrahepatic bile ducts were non-dilated. The CT scan also showed hepatomegaly, with the liver presenting as homogenous without evident nodular alterations. A single enlarged lymph node (size 27 x 9 mm) was visible between the hepatic portal vein and inferior vena cava. A needle aspiration liver biopsy was performed giving a non-diagnostic outcome owing to protein masses blurring the specimen.

Autoimmune markers were within normal ranges. Investigation for Wilson’s disease presented reduced serum ceruloplasmin levels (12.1 mg/dl – norm: 16–45); however, ALP:T Bil ratio exceeded 4 and AST:ALT ratio was below 1.8. The following laboratory results concerning thyroid gland capacity showed thyroxine serum concentration of 33.07 pmol/l (norm: 9.0–20.0), with TSH level below 0.005, indicating hyperthyroidism, with no signs of clinical thyrotoxicosis. Therapy with thiamazole was initiated.

The patient developed significant leukocytosis with granulocytosis, thrombocytopenia (requiring blood platelet concentrate transfusion), the APTT exceeded normal ranges; there was also present hypokalemia resistant to treatment, slight hypoproteinaemia with significant hypoalbuminemia (2.5 g/dl – norm: 3.50–5.20 g/dl)). There were signs of opportunistic fungal and bacterial infection of the oral cavity and urinary tract; however, blood culturing showed no bacteremia.

Liver function deteriorated rapidly and progressively, despite aggressive pharmacological treatment. The patient’s clinical status reached critical level and a liver transplantation procedure was considered. However, because of the lack of evidence excluding neoplastic infiltration of the organ, the patient was not qualified this particular form of treatment.

Due to progressing symptoms of hepatic encephalopathy (which is a key symptom of ALF), as well as increasing lactic acidosis, the patient was transferred to ICU, where she died. The needle core biopsy that could cancel out possibility of lymphoma recurrence or primary hepatic infiltration was scheduled on the day of patient’s death. There was no post mortem examination performed on family request.

**DISCUSSION**

Acute liver failure is a rare medical emergency requiring immediate actions, both in the diagnostic and therapeutic fields; setting proper diagnosis decides on further treatment, predetermining transplantation procedure or conversely – rejecting it as a therapeutic option [1, 2, 5, 9]. The number of symptoms presented by a patient blurs the image of ALF, misleading the diagnostician. In addition, numerous conditions resulting in ALF demand thorough investigation and step-by-step confirmation or rejection.

Presently, the majority of ALF cases in the USA as well as highly developed European countries arise as a result of drug-induced liver injury, mainly because of prolonged use of...
high doses of acetaminophen [1, 2]. This cause of ALF, unlike others, is also the most characteristic for older patients, especially those aged over 60 [1]. However, the patient described in the presented case denied using any medications, drugs or herbal preparations other than methylprednisolone prescribed by the specialist; laboratory tests did not show any characteristics indicating drug influence on the patient. On that basis, drug-induced ALF was rejected.

The very possible etiology of lethal ALF is the HBV infection – novel or due to seroconversion and reactivation in immunocompromised patients previously infected with the virus (with the immunosuppression resulting in particular from malignances or treatment, among other causes), similar to the patient described in this case. In such a case, the overall mortality incidence is much higher than for other viral causes [1, 8]. The tests for viral antibodies led to the exclusion of viral-induced ALF, as the markers were negative for HBV, HCV, CMV IgM, even though it is estimated that nearly 50% of the patients tested for HBV may develop the seronegative form of ALF [1, 2]. Antibodies against toxoplasmosis were not detected. The patients was also screened for autoimmune disorders, with negative outcome.

Medical imaging showed no signs of compromised hepatic circulation, biliary tract disorders or signs of malignant infiltration of the liver or surrounding tissue. The patient exhibited no symptoms of shock, and bacteremia was absent.

There was no sign of any active neoplastic hemopoietic process in laboratory tests. However, the patient developed leukocytosis with granulocytosis, which together with thrombocytopenia and anemia may resemble the myeloproliferative disease. On the contrary, such an image may be caused by prolonged use of methylprednisolone, as steroids cause marginalization of the white blood cells, leading to higher numbers of them being detected in blood morphology tests [10, 11, 12]. Anaemia, in turn, may be caused by pathologic bleeding which occurred due to liver insufficiency in clotting factors production and/or thrombocytopenia.

Wilson’s disease, which accounts for approximately 5% of the ALF worldwide, was also taken under consideration [13]. Patient’s ceruloplasmin level was decreased (12.1 mg/dl – norm: 16–45). However, it was reported in numerous publications that the ceruloplasmin level alone is a non-diagnostic marker of Wilson’s disease, especially in the case of fulminant liver failure [13, 14]. There were indicators of specificity and sensitivity even exceeding 90%, namely ALP:T Bil ratio below 4 and AST:ALT ratio over 2.2 [13, 15]. Both of these ratios were negative markers of Wilson’s disease in this case study. The patient also did not present Kayser-Fleischer ring.

This case demonstrates the complexity and ambiguity of clinical images in patients suffering from ALF that create a diagnostic maze which, in turn, delays the onset of adequate treatment options. In spite of lacking histopathological confirmation of the proposed hypotheses which left the diagnosis unresolved, this medical case should be presented in order to depict the scheme of proceedings leading to a life-saving treatment in ALF patients. There is also a need to emphasize the obligatory verification of each of the prevailing causes of ALF described in the literature, including both primary and secondary liver infiltration by malignancies. There is also a necessity for the diagnosis to be confirmed through histopathological investigation, as its outcome will decide on introducing or rejecting liver transplantation procedure.

REFERENCES