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Acute liver failure associated with influenza A virus infection: an autopsy case report

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**Summary**

An 84-year-old man with chronic renal failure, anemia, and diabetes was admitted for hemodialysis initiation. His vital signs were stable until the eighteenth hospital day, before having an influenza A virus infection. Three days later, he died of septic shock with severe liver impairment. His leukocyte count, prothrombin time (PT-INR), and liver enzymes, such as AST and ALT, were significantly increased. Hypercytokinemia was also observed. Autopsy revealed bilateral diffuse pneumonia with neutrophil infiltration. The liver showed extensive centrilobular hepatocyte necrosis. Immunohistochemistry for influenza A nucleoprotein was positive in the ciliated columnar epithelium of the bronchi and negative in the trachea, lungs, and liver. Hypoxic hepatitis is characterized by an abrupt and massive increase in aminotransferase levels (more than 20 times of the upper normal limit) due to the anoxic centrilobular hepatocyte necrosis. The occurrence of hypoxic hepatitis requires a pre-existing, chronic condition, such as anemia, causing less oxygen supply to the liver, followed by an acute drop in hepatic oxygen supply, such as septic shock. Therefore, this report suggests that hypoxic hepatitis can be an important causative factor for acute liver failure associated with influenza virus infection.
Acute liver failure (ALF) associated with influenza virus infection is uncommon. On rare occasions, cases of influenza virus infection related to ALF have been reported (1-3), but its pathogenesis or histopathological features have not been fully understood. Herein, we report an autopsy case of ALF associated with influenza A virus infection.

An 84-year-old man with chronic renal failure was admitted for hemodialysis initiation. He complained of general fatigue. His past medical history was significant for hypertension and diabetes including diabetic retinopathy. There was no history of liver disease or any allergies. He used to smoke and also drank 500 mL of liquor and water a day. He had not received an influenza vaccination for a year. On examination, conjunctival anemia and pedal edema were observed. The rest of the examination was normal. Creatinine (4.75 mg/dL) and blood urea nitrogen (66 mg/dL) levels were increased, AST (45 IU/L) level was slightly increased, but hemoglobin (7.2 g/dL) level was decreased. All the other values were within the normal range, including blood sugar and hemoglobin A1c. Tests of the blood for hepatitis B virus surface antigen and hepatitis C virus antibody were negative. An echocardiogram revealed normal ventricular function and absence of valvular calcifications. On day 2, hemodialysis was started with no complications. His vital signs were stable until day 18. Afterward, he developed high fever (38.3°C), and the nasopharyngeal swab specimens were positive.
for influenza virus type A antigen, as detected by rapid diagnostic test (QuickNavi™-Flu2 Influenza A&B Kit; Denka Seiken, Japan). Oseltamivir (75 mg) was orally administered once. A few days before, one of the visitors was reportedly diagnosed with seasonal influenza A virus infection. On day 21, our patient became afebrile but complained of dyspnea. An hour later, he became stuporous, and the oxygen saturation was 55% (15 L/min through a face mask). His blood pressure was 64/39 mmHg; respiratory rate, 35/min; temperature, 36°C; and heart rate, 78 bpm. His limbs were cold. Leukocyte count (17,250/μL, eosinophils 0%), prothrombin time, and liver enzyme levels, including AST and ALT, were significantly increased (Fig. 1). Platelet count (126,000/μL) and other laboratory data did not indicate disseminated intravascular coagulation. Serum cytokine levels, including TNF-α, IL-2R, and IL-6, were significantly increased to 10.5 pg/mL (normal, < 1.79 pg/mL), 1,280 U/mL (121–613 ng/mL), and 21.9 pg/mL (< 2.41 pg/mL), respectively. The blood culture did not reveal any causative organism. Chest X-ray revealed bilateral pulmonary infiltrates, suggesting pulmonary edema and/or pneumonia. The occurrence of influenza virus infection, a quick Sequential Organ Failure Assessment score of 3, and severe hypotension enabled us to conclude that he suffered from septic shock. His family denied aggressive therapy and cardiopulmonary resuscitation, and he died shortly after.
Autopsy revealed macroscopically moderate pulmonary edema with irregular, reddish patches in the lungs (left, 470 g; right, 410 g) (Fig. 2a and b). There was no pulmonary infarction or embolism. The bilateral main bronchi were hemorrhagic without prominent mucus. The heart (404 g) showed mild left ventricular hypertrophy. In the liver (833 g), irregular-shaped whitish patches were diffusely observed (Fig. 2c). Microscopically, the lungs revealed bilateral diffuse pneumonia with neutrophil infiltration (Fig. 3a). Microabscess was occasionally observed. The bronchi were hemorrhagic with mild inflammation. There was no diffuse alveolar damage. Gram and Grocott stains did not reveal any bacterial and fungal components. The liver exhibited extensive centrilobular hepatocyte necrosis with less prominent inflammatory cells (Fig. 3b). Microvesicular lipid droplets in the non-necrotic hepatocyte areas were scattered. There was no cholestasis. Portal areas did not show any significant changes. Epstein-Barr encoding region in situ hybridization and cytomegalovirus immunohistochemistry did not detect positive cells in the liver. Hemophagocytosis was observed in the bone marrow and spleen. There were no myocardial infarction or necrosis and any findings that suggested myocarditis such as lymphocytic infiltrates. The kidneys showed diffuse and global mesangial proliferative glomeruli with arteriolar hyalinization, which were compatible with diabetic glomerulosclerosis.
Sections from the lungs, bronchi, trachea, and liver were immunostained with a mouse monoclonal antibody against influenza A nucleoprotein (InfA-NP) antigen. Specific antigen-antibody reactions were visualized by 3, 3’-diaminobenzidine tetrahydrochloride staining using Dako Envision System (Dako Cytomation, Copenhagen, Denmark). Positive signals for InfA-NP were detected only in the ciliated columnar epithelium of the bronchi (Fig. 3c and d). The influenza A virus genomic RNA and messenger RNA in each formalin-fixed paraffin-embedded tissue sample were below measurable limits, as observed using real-time RT-PCR. Therefore, the subtype of the influenza A virus was not determined.

This case is considered a nosocomial influenza A virus infection. The patient was immunocompromised due to chronic renal failure, diabetes, and advanced age. Additionally, he did not receive an influenza vaccination, suggesting that he was highly susceptible to influenza viral infection. A previous randomized controlled trial reported that the long-term use of oseltamivir as an influenza prophylaxis was effective in reducing the incidence of influenza for transplant patients (4). Furthermore, early administration of neuraminidase inhibitors, such as oseltamivir, reportedly reduced the duration and severity of symptoms (5-7). This suggests that prophylaxis with anti-influenza drugs may be useful to control hypercytokinemia and septic shock during
influenza virus infections.

ALF shown in this patient may be due to hypoxic hepatitis, which is characterized by an abrupt and massive increase in aminotransferase activity secondary to an anoxic centrilobular hepatocyte necrosis (8). The diagnostic criteria of hypoxic hepatitis include all of the following conditions: (i) a sharp increase in serum aminotransferase levels (more than 20 times of the upper normal range); (ii) the presence of respiratory, cardiac, or circulatory failure; and (iii) exclusion of other causes of acute liver injury (8). The former two were met in this case. Regarding the third condition, although uncommon, drug-induced liver injuries should be excluded. However, drug involvement was less likely in this case, as the percent of eosinophils was not elevated and no typical histologic findings of a drug-induced liver injury, such as cholestasis, were observed.

The typical histological characteristic of hypoxic hepatitis is centrilobular hepatocyte necrosis without prominent inflammation (3, 8), which is consistent with the findings of this case.

The occurrence of hypoxic hepatitis requires a pre-existing, chronic condition that reduces oxygen supply to the liver, followed by an acute event that further decreases hepatic oxygen supply (9, 10). In this case, chronic anemia due to chronic renal failure was an underlying condition supplying less oxygen to the liver. Additionally, septic
shock probably caused an acute drop in hepatic oxygen supply. Therefore, this report suggests that hypoxic hepatitis can be an important causative factor for ALF associated with influenza virus infection. Further studies are warranted to elucidate the exact pathogenesis.

Acknowledgments

None.

Ethical considerations

Ethical approval for this study was obtained from the Ethics Committee at the Tokyo Metropolitan Geriatric Hospital. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki, and written informed consent for the use of tissues was obtained from the families of the patient.

Conflict of interest

None.

References


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**Fig. 1. Clinical course.**

After the diagnosis of influenza A virus infection (day 18), levels of AST, ALT, and prothrombin time (PT-INR) were rapidly increased.


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Fig. 2. Macroscopic findings of the lungs and liver.

(a and b) Moderate pulmonary edema (a, right; b, left) and hemorrhagic main bronchi (arrow) were observed. (c) Cut surface of the liver showed irregular-shaped whitish patches.
Fig. 3. Microscopic findings of the lungs and liver.

(a) The lungs revealed pneumonia with massive neutrophil infiltration. (b) The liver showed centrilobular hepatocyte necrosis (arrowhead). (c) The ciliated columnar epithelium of the bronchi showed slightly enlarged nuclei. (d) Immunohistochemistry for influenza A nucleoprotein was positive in the ciliated columnar epithelium of the bronchi. Inset: higher magnification of the positive signal. Hematoxylin & eosin staining (a, b, and c). Original magnification, ×200 (a, b), ×400 (c, d).