

Three Consequent Pediatric Liver Transplant Deaths in the COVID-19 Era

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ABSTRACT

The effect of COVID-19 on the transplant recipients is not well-established. Many reports underestimate the effect of COVID-19 on the immunosuppressed population. Herein, we report on 3 pediatric liver transplant recipients who were transplanted at our center between February 11 and March 10, 2020—during the COVID-19 pandemic era. The 3 patients aged between 5 and 10 months, had a rapid and aggressive respiratory deterioration that necessitated mechanical ventilation and extracorporeal life support; and eventually died. The clinical and pathological pictures likely represent COVID-19 pneumonia. Chest x-rays showed progressive infiltrates. Lung autopsies showed diffuse alveolar damage in two cases. We concluded that COVID-19 is very likely to have catastrophic effects on transplant recipients.

KEYWORDS: Pediatric liver transplant, COVID-19, respiratory failure.

INTRODUCTION

Solid organ transplantation is the treatment of choice for end-stage organ failure. Recently, a pronounced progress in the organ transplantation field is being noticed due to the improvement in the surgical techniques, immunotherapy and antiviral therapy. However, infectious diseases may get in the way of the overall success of transplantation [1], since transplant recipients are usually more prone to infections as compared to healthy individuals. These infections may result in long-term effects on morbidity and mortality [2]. Recently, a new virus invaded the globe and caused panic worldwide, especially among immunocompromised individuals. The disease is named by Corona virus 2019 disease (COVID-19), which is caused by severe acute respiratory syndrome coronavirus type

2 (SARS-CoV-2) [3]. It first appeared in Wuhan, China [4]. Shortly thereafter, it spread to the Middle East, Europe, and then to the USA [5].

Although the COVID-19 disease is known to be very contagious and fatal, especially among elderly subgroups with comorbidities [6], the effect of COVID-19 on transplant recipients, especially liver recipients in pediatric age group is still conjectural for lack of quality evidence. However, most transplantation centers around the globe have suspended all transplantation activities except for extremely urgent cases, in order to avoid exposing those vulnerable patients to additional risks.

Herein, we present our devastating experience of three consecutive deaths of pediatric liver transplant recipients who were transplanted at our center between February 11 and March 10, 2020. They died of mysterious lung failure in the era of COVID-19.

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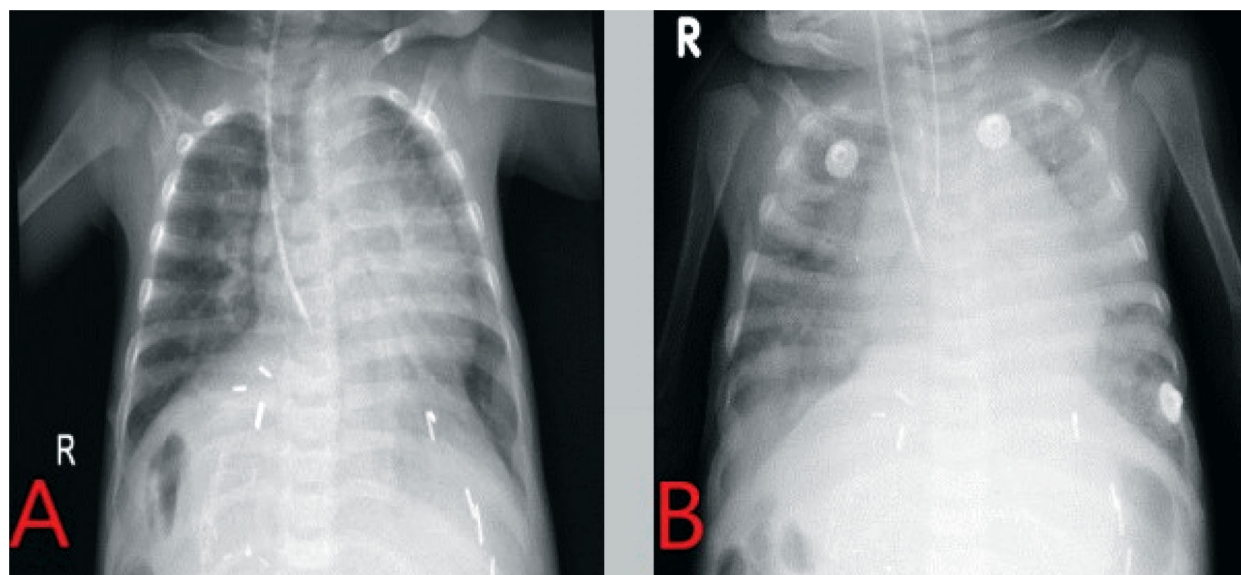


Figure 1: Antero-posterior chest x-rays (A) shows minimal bilateral infiltrates, ground-glass opacities; (B) three hours later, progression of infiltration and increased shadowing in both lungs is seen.

CASE 1

A 10-month-old male weighing 5.1 kg had been suffering from a cholestatic liver disease. He was also known to have hepatopulmonary syndrome. After performing the routine pre-operative evaluation and finding that he was eligible for transplantation, he underwent a left lateral segment liver transplantation from his father on February 11, 2020. The procedure was unremarkable with no intra-operative complications; routine intra-operative ultrasound showed normal arterial and venous flow. In the first post-operative day, he was extubated; his chest x-ray was normal; the remaining post-operative course was uneventful until the 8th post-operative day when he started to suffer from shortness of breath and fever that deteriorated progressively. Despite the mechanical ventilation and extracorporeal life support (ECMO), the patient died on February 20. Two successive chest x-rays with 3 hours gap were done and showed progressive diffuse bilateral opacities (Fig 1). His blood test results and routine Doppler ultrasound (US) were normal.

Histopathologic examination of post-mortem lung biopsy showed mild interstitial edema and focal inflammatory infiltration with many microvascular thrombi. Neither intra-alveolar exudate nor hyaline membranes was pres-

ent. Microvascular thrombi did not contain any adipose tissue or bone-marrow elements; bone-marrow embolism and a possible septic embolism were excluded. An early stage of diffuse alveolar damage was suggested (Fig 2A).

CASE 2

A 10-month-old male weighing 9.2 kg suffered from cryptogenic cirrhosis. Pre-operative routine evaluation confirmed his eligibility for transplantation. A left lateral segment liver transplantation was performed from his aunt, on February 20, 2020. The patient was admitted to the same ward the previously reported patient (Case 1) had been stayed. The surgery was unremarkable with no intra-operative complications. Routine intra-operative US showed normal arterial and venous flow. On the post-operative day six, he developed high-grade fever with neutropenia and elevated liver enzymes. A liver biopsy showed signs of inflammation and suspected rejection. Serial chest x-ray showed a deteriorating infiltration in the bilateral lobe (Fig 3). On the 9th post-operative day, a severe neutropenia occurred with increasing in the severity of the respiratory failure. ECMO was started. The patient died on March 2, 2020. Post-mortem biopsy could not be done.

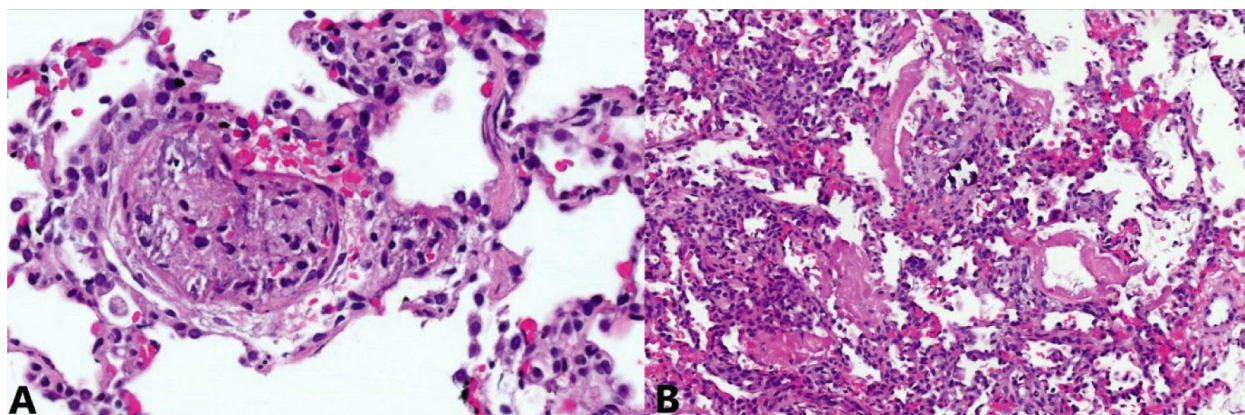


Figure 2: H&E staining of lung tissue of (A) the first case showing mild interstitial edema and focal inflammatory infiltration with numerous micro-vascular thrombi, no hyaline membranes are seen; (B) the third case: intra-alveolar fibrin exudates, hyaline membranes, mild interstitial inflammation of mixed cellular type and micro-vascular thrombi are observed.

CASE 3

A 5-month-old male weighing 6.3 kg with a history of biliary cirrhosis was admitted to hospital for several days; he was intubated 5 days prior to the transplantation due to signs of encephalopathy. On March 12, he had a left lateral segment liver transplantation from his mother. The surgery was uneventful with no reported complications. On post-operative day 3, he was extubated. About 12 hours after extubation, he developed progressive respiratory deterioration; ECMO was started on March 16, but it did not last too long; the patient died on the same day. Repetitive chest x-rays showed progressive pulmonary infiltration (Fig 4). Post-mortem lung biopsy showed exu-

date phase of diffuse alveolar damage characterized by intra-alveolar fibrin exudates and hyaline membranes, mild interstitial inflammation, and microvascular thrombi (Fig 2B).

DISCUSSION

COVID-19 has recently risked the lives of many susceptible people. In the present study, we reported on the hazard that is particularly imposed on liver transplant recipients whose immune system is considerably suppressed by long-term immunosuppressive drugs. The above-mentioned cases were treated with tacrolimus and steroids.

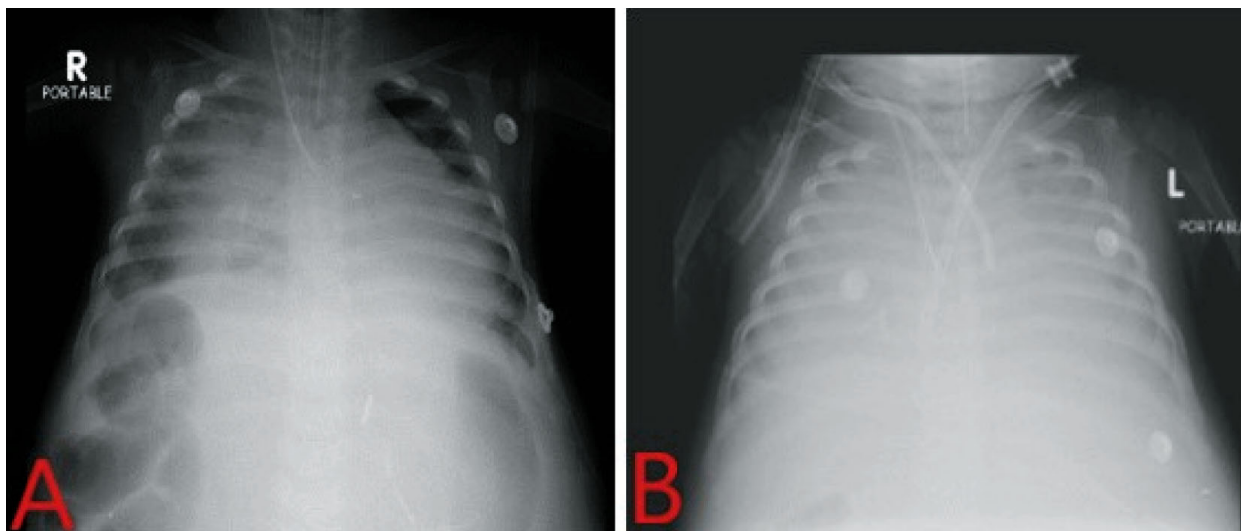


Figure 3: Antero-posterior chest x-rays showing (A) bilateral consolidation that is more pronounced on the right side; and (B) diffuse haziness and ill-defined cardiac shadow, one day later.

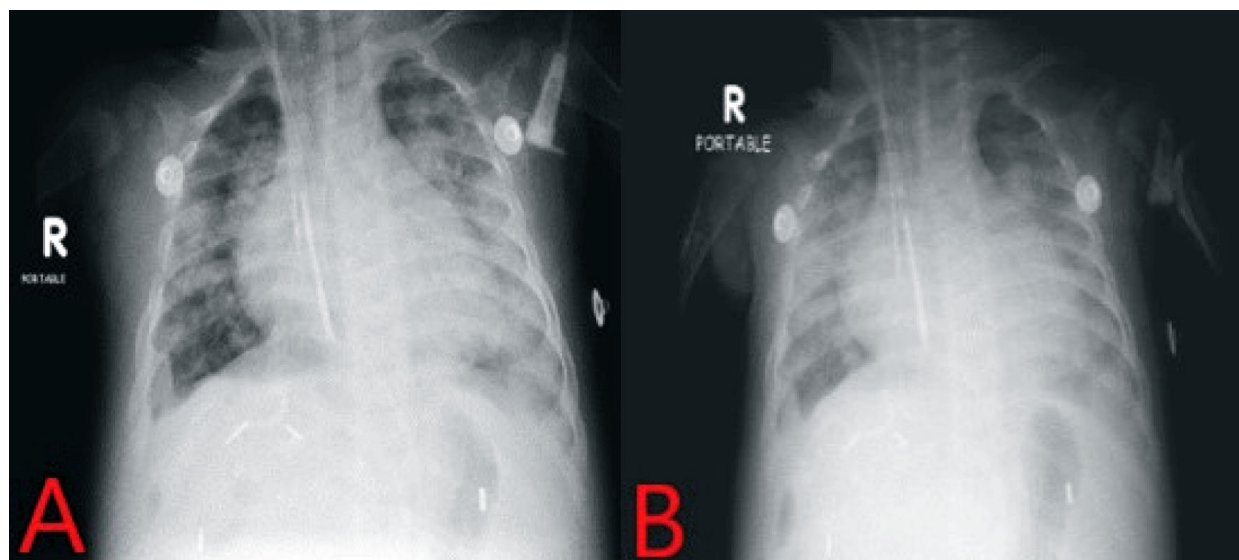


Figure 4: Antero-posterior chest x-rays showing (A) pulmonary nodules and ground-glass opacities; and (B) increased bilateral shadows, one day later.

The number of COVID-19 cases recorded in Iran and Greece, which share borders with Turkey, peaked to 13,938 and 331, respectively, by mid-March [10, 11]. Turkey astonishingly reported no cases until March 10 [12]. Shortly before this period of enormous reported cases worldwide, we noticed three consecutive unexplained deaths of recently live-transplanted patients that did not complain of any transplant-related problems. They suddenly developed respiratory failure, which necessitated ECMO. Unfortunately, all of them died.

The third case died six days after the first announcement of COVID-19 outbreak in Turkey [12]. The virus was transmitted rapidly so that the number of infected people in Turkey peaked to more than 38,000 patients with more than 800 deaths in less than one month [12]. These facts suggest that these cases share similarity in the underlying cause of mortality and turning back to the clinical picture of COVID-19 infection [13]. All three patients had complaints perfectly matched with the clinical pictures including fever, desaturation, dyspnea, hemoptysis, neutropenia, and x-ray findings suggestive of pneumonia.

The exact causes of the patients' sudden deaths were not clear, although they were presumably had COVID-19. To solve this mystery, post-mortem Tru-Cut® biopsies were taken from

two out of the three mentioned cases. The first case had mild parenchymal edema with some crowding and interstitial inflammation, and multiple microvascular thrombi. Although typical hyaline membranes were not seen, these findings suggest an early phase of diffuse alveolar damage. The third case showed characteristic features of diffuse alveolar damage in exudative phase characterized by intra-alveolar fibrin exudates and hyaline membranes. These findings matched with previous autopsies that were done for coronavirus infection [14]. Moreover, an x-ray for every patient was performed, all of which showed ground-glass opacities suggestive of pulmonary infection (Figs 1, 3, and 4). Serology for COVID-19 could not be completed since patients' problems progressed rapidly to respiratory failure and death, and at that time, COVID-19 serologies were still not available at the local level.

CONFLICTS OF INTEREST: None declared.

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