Early acute rejection after lung transplantation mimicking viral pneumonia in the middle of COVID-19 pandemic: A case report

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ABSTRACT

INTRODUCTION: In addition to morbidity and mortality rate per se, COVID-19 outbreak leads to potential ‘side effects’, which are difficult to evaluate and predict. Lung transplantation is a consolidated treatment for end-stage chronic lung disease requiring significantly demanding management. Deciding whether to keep transplant programmes open during an epidemic of this size is not easy, as immunosuppressed subjects face the risk of infection and related mortality. Additionally, there is a chance for the patient's standard care process to be compromised.

PRESENTATION OF CASE: We report the case of a patient undergoing bilateral lung transplantation during the explosion of COVID-19 epidemic in Lombardy; he died from definite early acute antibody-mediated rejection, clinically (persistent high fever, unresponsive to treatment) and radiologically mimicking viral pneumonia but persistently negative for SARS-CoV-2.

DISCUSSION: The diagnosis was difficult given this atypical presentation, confounded by global scenario. Grafts were procured from a donation after circulatory death donor in an uncontrolled setting and a donor-recipient transmission was possible. Our institute became a COVID-Hospital right during the first post-transplantation days. Radiological imaging had the same features of SARS-CoV-2 pneumonia.

CONCLUSIONS: This is the first report of lung transplantation of the COVID-19 era in Europe. Our extremely fragile patient was COVID-19 free up to the end. Donor-recipient transmission is conceivable, but the risk should be assessed with respect to waiting list mortality. Ultimately, treating COVID-19 patients can be a resource-consuming activity but we decided to keep our centre open.

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1. Introduction

The first certified Coronavirus COVID-19 case in Italy was diagnosed on February 21st, 2020 [1]. The initial epicentre was Lombardy, from where the virus has spread rapidly throughout the country. On March 19th, Italy became the country with the highest number of confirmed deaths from SARS-CoV-2 in the world. In addition to the morbidity and mortality rate per se, an epidemic of this magnitude leads to potential ‘side effects’, which are more difficult to evaluate and predict. Lung transplantation is a consolidated treatment for end-stage chronic lung disease and requires significantly demanding management. Deciding whether to close or keep transplant programmes open during an outbreak of this size is not easy, as immunosuppressed subjects face the risk of infection and related mortality. Additionally, there is a chance for the standard care process of the patient to be significantly compromised. We hereby report the challenging case of a patient who underwent bilateral lung transplantation during the explosion of COVID-19 epidemic in Lombardy and died from early acute rejection mim...
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2. Presentation of case

We present the case of a 31-year-old man with end-stage respiratory disease secondary to cystic fibrosis (CF), who underwent bilateral lung transplantation. The patient had been listed one year earlier: blood group was 0 and latest lung allocation score was 40.32. No pretransplant donor-specific antibodies (DSA) were identified. The patient suffered from Pseudomonas aeruginosa and Mycobacterium kansasii chronic colonization that caused frequent acute exacerbations (Fig. 1). He also required oxygen therapy during exercise and non-invasive ventilation (NIV). The lungs were procured on February 21st, 2020 from an uncontrolled donation after circulatory death (DCD) donor, following the technical protocol previously reported [3]. The donor was a 64-year-old non-smoker man with hypertension. The chest x-rays and bronchoscopy were negative for opacity and secretions. The ABO group was identical to the recipient’s and pre-transplant crossmatch test was negative. Lungs were flushed 225 min after the witnessed cardiac arrest. After the usual ex-vivo lung perfusion assessment (final PaO2/FiO2 ratio: 489), the grafts were deemed suitable for transplantation. No extracorporeal support was needed during

Fig. 1. Recipient’s chest CT scan pre-transplantation.

Fig. 2. Post-transplantation chest x-rays. POD: postoperative day.

icking viral pneumonia. Our article is drawn up in line with the SCARE 2018 criteria [2].
surgery, but bilateral bronchorrhea occurred shortly after the closure of the clamshell incision. Invasive mechanical ventilation lasted 24 h postoperatively. The patient was then supported with NIV. Primary graft dysfunction was graded at level 2, 1 and 1 after 24, 48 and 72 h, respectively. In addition to usual immunosuppressive (tacrolimus, steroids, azathioprine) and prophylactic (voriconazole, ganciclovir) protocols, ceftazidime and colistin were administered according to the patient’s latest sputum culture, and antibiotics sensitivity. Specific therapy for *Mycobacterium* (ethambutol, rifampin, azithromycin) was continued. The recipient was transferred from the intensive care unit (ICU) to the ward on postoperative day (POD) 3. On the same night, he developed high fever without chills. Since the microbiological analyses of the donor were negative, a bronchoalveolar lavage (BAL) on POD 4 and a nasopharyngeal swab on the following day were performed to rule out COVID-19. As the SARS-CoV-2 PCR test was negative, vancomycin was added to target potential Gram-positive pathogens. In addition, due to the confirmation of bronchial recolonization from the previous *Pseudomonas* strain, we switched from ceftazidime to ceftolozane/tazobactam. Despite the adjustment of antibiotic therapy, no clinical improvement was observed, with persistent hyperpyrexia (38–39 °C) and mild respiratory failure (PaO2/FiO2 ratio: 200–250). The daily chest radiographs showed unchanged findings: ill-defined bilateral confluent diffuse airspace opacities were initially interpreted as ischemia-reperfusion damage, but the progressive increase proved otherwise (Fig. 2). These assessments together with the general uncontrolled spread of SARS-CoV-2 cases in Lombardy and, specifically, in our institute, fuelled the suspicion about COVID-19, despite the negative SARS-CoV-2 PCR test on BAL. This hypothesis was reinforced by the results of the total-body computed tomography (CT) performed on POD 10 (Fig. 3). BAL and swab were immediately repeated but results were still negative for SARS-CoV-2. Therefore, on POD 11 a trans-thoracic pulmonary fine-needle aspiration for microbiological tests and a core-biopsy under ultrasound guidance were performed to the bedside for histological characterization. The pathology revealed a moderate/severe acute rejection as well as the presence of C4d staining (Fig. 4). The diagnosis was confirmed by blood tests that showed elevated anti HLA-DQ7 donor specific antibodies. Pulsed-dose methylprednisolone was administered for 3 days, followed by steroid tapering. After a moderate clinical improvement, which lasted for less than 48 h, the patient’s conditions worsened again, with high fever and
Fig. 4. Lung core-biopsy stained glass slides. Acute alveolar damage with hyaline membrane deposition in the alveolar lumina, associated with patchy interstitial acute e chronic infiltrate, showing plurifocal infiltration of the bronchiolar wall and epithelium and plurifocal venulitis. C4d immunohistochemical staining showed a diffuse, weak staining of the capillary walls.

Fig. 5. Clinical course of the patient. BAL: bronchoalveolar lavage; CT: computed tomography; FNAB: fine needle aspiration biopsy.

3. Discussion

The patient suffered from clinical definite acute antibody-mediated rejection (AMR) no responsive to treatment [4]. The clinical presentation consisted in persistent, drug-resistant high fever. To the best of the authors’ knowledge, such severe hyperthermia associated to AMR has not being reported so far [5]. The diagnosis of lung AMR was especially difficult given both the atypical picture and the complexity of the global scenario. The phenomenon of graft re-colonization after transplantation is well known. In patients suffering from CF, airway-colonizing bacteria and their antibiotic sensitivity are perfectly known prior to
transplantation, resulting usually in an effective and comfortable therapeutic management. On the other hand, the re-colonization can be particularly alarming, considering that the very isolation of *Pseudomonas aeruginosa* is considered an independent factor associated with an increased risk of developing DSA [6]. More importantly, we had to deal with the COVID-19 outbreak, which escalated in this time frame, considering how it presents high unresponsive fever and lung involvement as the most frequent symptoms. Grafts were procured from a DCD donor in an uncontrolled setting. Up to his decease, the donor had displayed no fever nor dyspnoea. In this scenario, one must take into account that COVID-19 might be asymptomatic, especially in its early stages and the possibility of a donor-recipient transmission could not be excluded. Our institute was converted into a COVID-Hospital during the early post-transplant period. Despite the implementation of additional protective measures for transplant patients, the risk of contagion was substantial. Ultimately, radiological imaging requires special awareness. Initial chest x-rays showed diffuse opacities, the typical pattern of pulmonary oedema. The subsequent daily chest radiographs revealed diffuse bilateral pulmonary infiltrates with progressive consolidation, with the exception of upper areas. The CT at POD 10 confirmed an extensive bilateral pulmonary involvement, consisting of limited ground glass opacities (with or without intralobular septal thickening combined) with extended parenchymal consolidation with air bronchogram. The apical regions, the lingula and the middle lobe were relatively spared. There was no mediastinal lymphadenopathy, no cavitation and no pleural effusion. Those findings were consistent with advanced cases of SARS-CoV-2 pneumonia, as reported in literature [7]. Clearly, a complete CT-sequence history could have helped, in relation to the presence of multiple peripheral ground-glass images, typical of the earliest stages of the infection. To this date, there are limited reports regarding the radiological findings of AMR: data regarding management are also insufficient. Diagnostic criteria for definite AMR include histopathologic features, presence of DSA and positive C4d staining, exclusion of other causes [4]. Notably, we successfully performed the biopsy by trans-thoracic approach instead of the customary trans-bronchial one, given the patient’s condition.

4. Conclusions

To the best of the authors’ knowledge, this is the first report of lung transplantation in the COVID-19 era in Europe. Caution is required when assessing whether to perform transplants in the context of the current COVID-19 pandemic. Transplant recipients are not necessarily at higher risk of SARS-CoV-2 infection. D’Antiga suggests that immunosuppression could even have protective effects, as the majority of Coronavirus-related injuries are caused by the host’s own immune response [8]. One must bear in mind that our patient, while being extremely fragile, tested COVID-19 free up to his death. Donor-recipient transmission has not been reported yet; nevertheless, such a risk should be assessed in consideration of the waiting list mortality rate. Treating COVID-19 patients can be a resource-consuming activity for centres and their staff, as an outbreak reduces hospital capacity and the healthcare manpower available for transplantation. Closing transplant centres may seem the only viable option [9]. We strongly believe that it is not the right way and we decided to preserve our activity. One must take into account that COVID-19 targets lungs, resulting in a restrictive alteration both in early and middle phases; the first transplants for this disease have already been carried out in China [10]. Health authorities should seek proper balance between the massive commitment to the pandemic and the identification of pathways reserved for the treatment of the most critical patients in need of a transplant.

Conflicts of interest

None.

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Ethical approval

The study was approved by Ethics committee of Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico Milano. Mortality risk factors in patients waiting and submitted to lung transplant. Ref. n° 181 (24/01/2017).

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Registration of research studies

N/A.

Guarantor

Alessandro Palleschi, Mario Nosotti.

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CRediT authorship contribution statement

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