CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 77 (2020) 80–85

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

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

Alessandro Palleschi[a,b,*], Lorenzo Rosso[a,b], Letizia Corinna Morlacchi[c], Alessandro Del Gobbo[d], Miriam Ramondetta[e], Andrea Gori[b,f], Francesco Blasi[b,c], Mario Nosotti[a,b]

[a] Thoracic Surgery and Lung Transplantation Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico of Milan, Italy
[b] University of Milan, Italy
[c] Internal Medicine Department, Respiratory Unit and Adult Cystic Fibrosis Center, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico of Milan, Italy
[d] Pathology Unit, Center - Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico of Milan, Italy
[e] North Italy Transplant Program (NITp), Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico of Milan, Italy
[f] Infectious Diseases Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico of Milan, Italy

ARTICLE INFO

Article history:
Received 26 September 2020
Received in revised form 22 October 2020
Accepted 22 October 2020
Available online 28 October 2020

Keywords:
SARS-CoV-2
COVID-19
Lung transplantation
Donation after circulatory death donor
Acute antibody-mediated rejection
Case report

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.

© 2020 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

The first certified Coronavirus COVID-19 case in Italy was diagnosed on February 18th, 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-

Abbreviations: DSA, donor-specific antibodies; NIV, non-invasive ventilation; DCD, donation after circulatory death; PaO_2, partial arterial oxygen pressure; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; POD, post-operative day; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction; CT, computed tomography; AMR, antibody-mediated rejection.

* Corresponding author at: Thoracic Surgery and Lung Transplantation Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via F. Sforza 35, 20122, Milan, Italy.
E-mail address: alessandro.palleschi@unimi.it (A. Palleschi).

https://doi.org/10.1016/j.ijscr.2020.10.105
2210-2612/© 2020 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

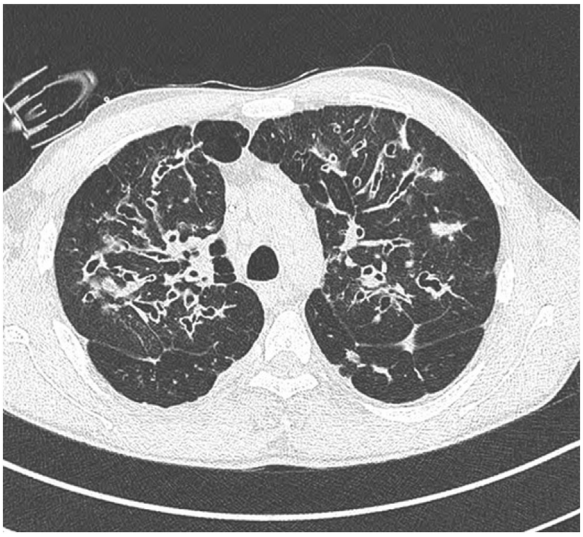

Fig. 1. Recipient's chest CT scan pre-transplantation.

icking viral pneumonia. Our article is drawn up in line with the SCARE 2018 criteria [2].

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 PaO_2/FiO_2 ratio: 489), the grafts were deemed suitable for transplantation. No extracorporeal support was needed during

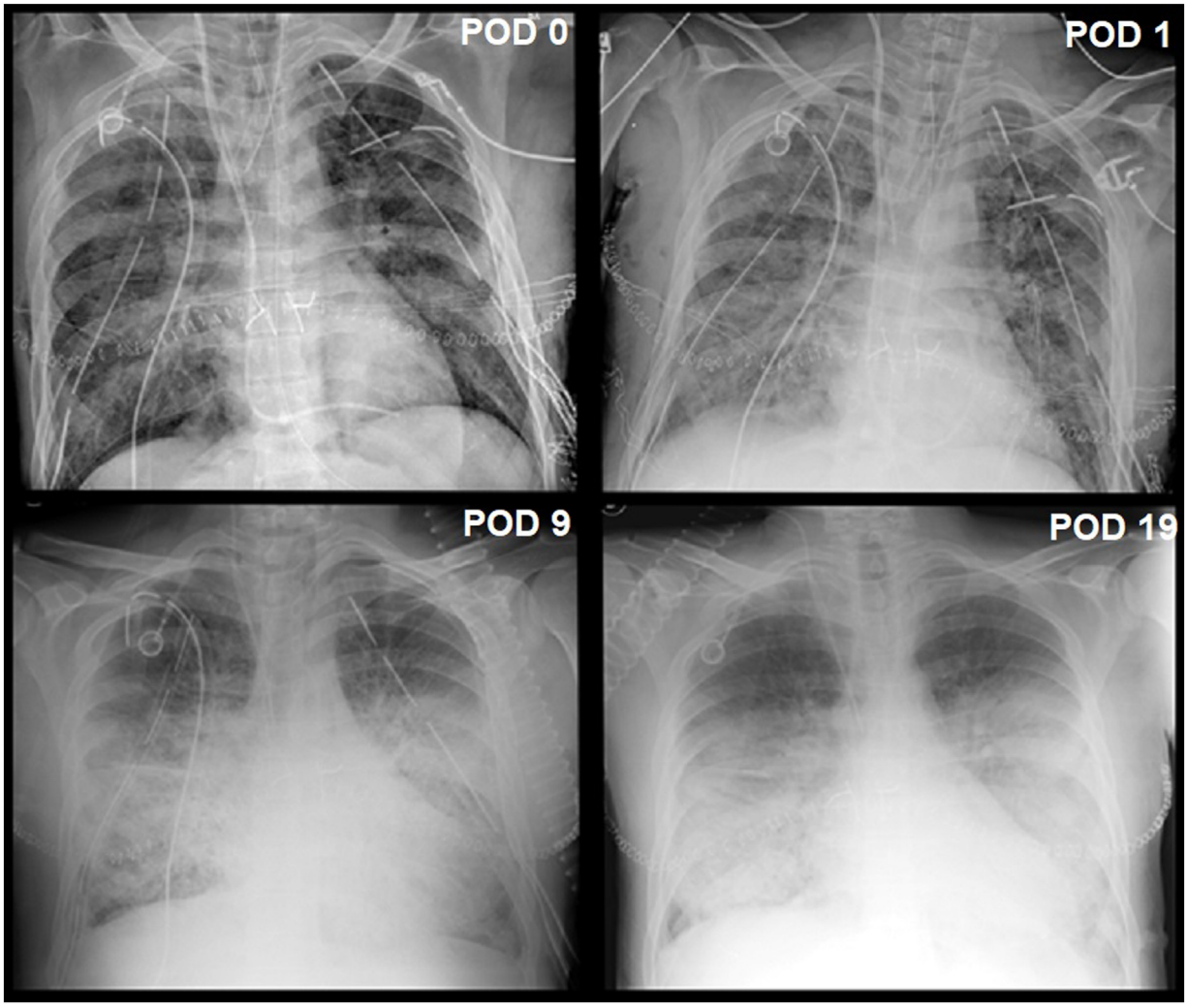

Fig. 2. Post-transplantation chest x-rays. POD: postoperative day.

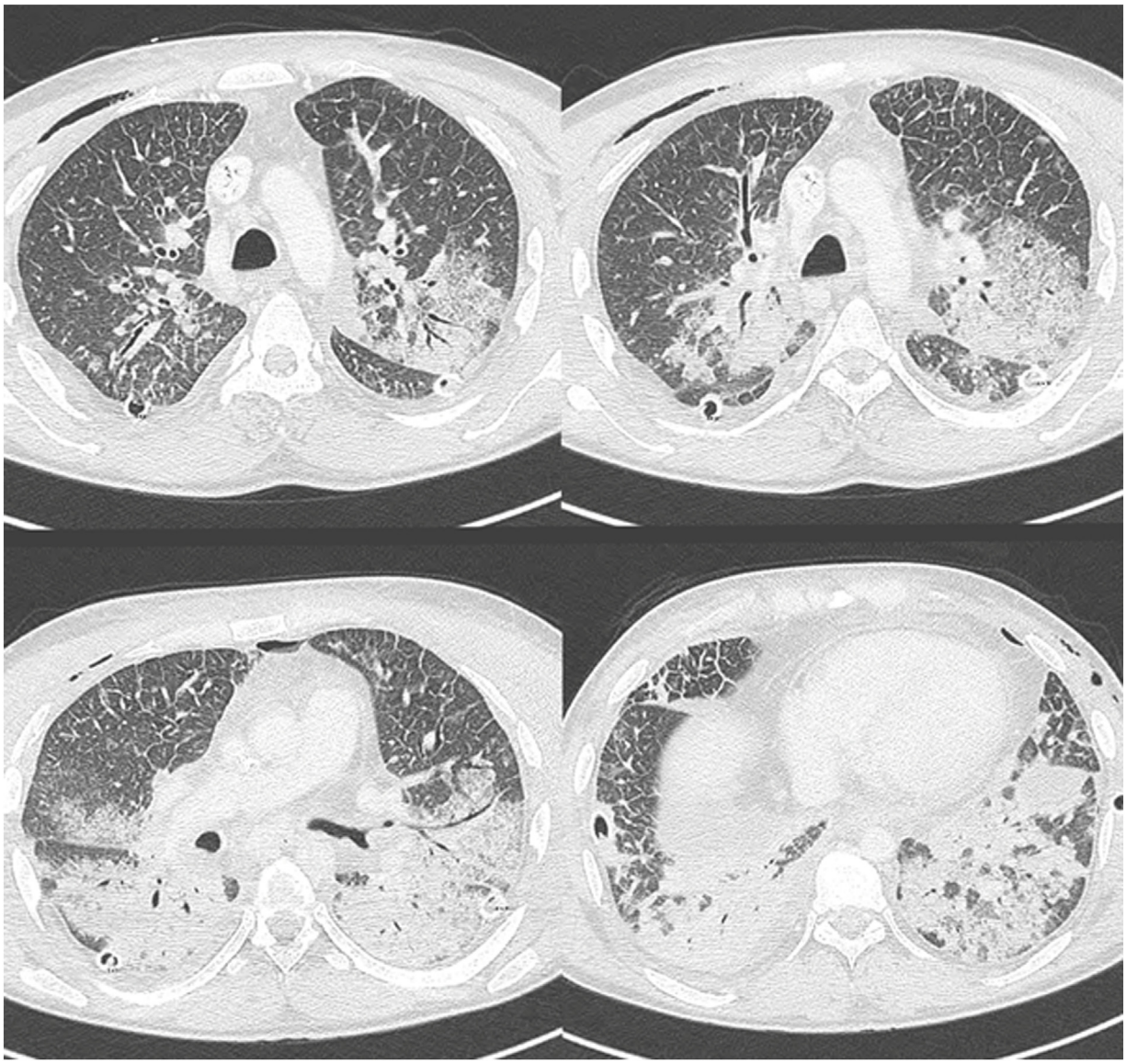

Fig. 3. Chest CT scan on POD10.

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 (PaO_2/FiO_2 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

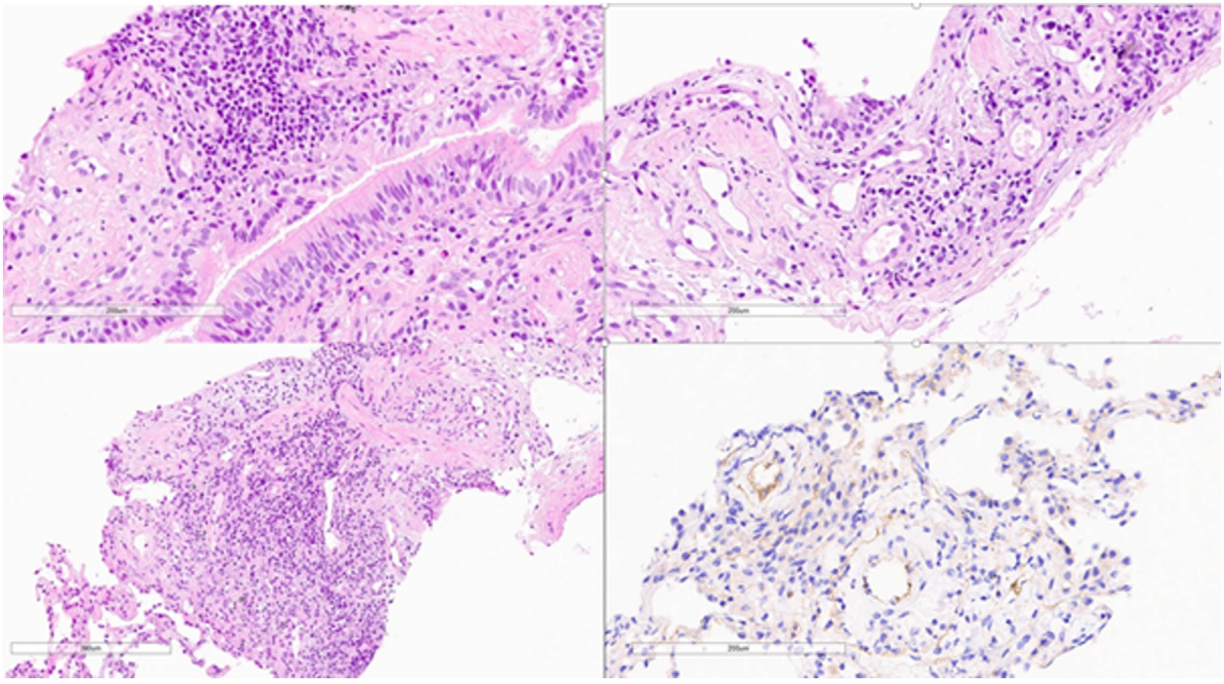

Fig. 4. Lung core-biopsy stained glass slides.
Acute alveolar damage with hyaline membrane deposition in the alveolar lumina, associated with patchy interstitial acute e chronic infiltrate, showing plurifocal infiltration of the bronchiolar wall and epithelium and plurifocal venulitis. C4d immunohistochemical staining showed a diffuse, weak staining of the capillary walls.

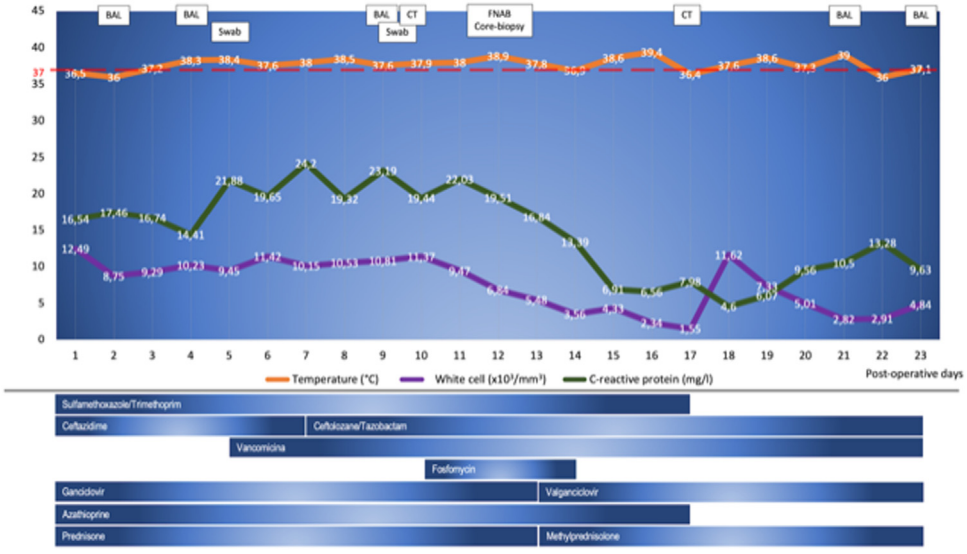

Fig. 5. Clinical course of the patient. BAL: bronchoalveolar lavage; CT: computed tomography; FNAB: fine needle aspiration biopsy.

dyspnoea. Bronchoscopy with BAL was repeated and resulted negative for bacteria and viruses except for the previously known *Pseudomonas aeruginosa* strain. A new total-body CT showed an unchanged picture. We repeated a cycle of high-dose steroids while preparing the patient for plasmapheresis. On POD 22, the clinical condition of the patient deteriorated, requiring intubation. Therefore, the patient was tested again for COVID-19 on BAL. The result read negative once again. On POD 23, the patient underwent plasmapheresis in the ICU, but he died the following night due to multiorgan failure. Fig. 5 summarizes the clinical course of the patient.

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.

Funding

None.

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.

Provenance and peer review

Not commissioned, externally peer-reviewed.

CRediT authorship contribution statement

Alessandro Palleschi: Conceptualization, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Lorenzo Rosso:** Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision. **Letizia Corinna Morlacchi:** Resources, Data curation, Writing - review & editing. **Alessandro Del Gobbo:** Resources, Data curation, Writing - review & editing. **Miriam Ramondetta:** Resources, Writing - review & editing. **Andrea Gori:** Writing - original draft, Writing - review & editing. **Francesco Blasi:** Writing - original draft, Writing - review & editing. **Mario Nosotti:** Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration.

Acknowledgment

Not applicable.

References

[1] Ministero della Salute d'Italia, Covid 19. La situazione in Italia, 2000, http://www.salute.gov.it/portale/nuovocoronavirus/dettaglioContenutiNuovoCoronavirus.jsp?lingua=italiano&id=5351&area=nuovoCoronavirus&menu=vuoto. Accessed 8 May 2020.

[2] R.A. Agha, M.R. Borrelli, R. Farwana, K. Koshy, A.J. Fowler, D.P. Orgill, et al., The SCARE 2018 statement: updating consensus surgical CAse REport (SCARE) guidelines, Int. J. Surg. 60 (2018) 132–136.

[3] F. Valenza, G. Citerio, A. Palleschi, et al., Successful transplantation of lungs from an uncontrolled donor after circulatory death preserved in situ by

alveolar recruitment maneuvers and assessed by ex vivo lung perfusion, Am. J. Transplant. 16 (4) (2016) 1312–1318, http://dx.doi.org/10.1111/ajt.13612.
[4] D.J. Levine, A.R. Glanville, C. Aboyoun, et al., Antibody-mediated rejection of the lung: a consensus report of the International Society for Heart and Lung Transplantation, J. Heart Lung Transplant. 35 (4) (2016) 397–406, http://dx.doi.org/10.1016/j.healun.2016.01.1223.
[5] A.D. Parulekar, C.C. Kao, Detection, classification, and management of rejection after lung transplantation, J. Thorac. Dis. 11 (Suppl 14) (2019) 1732–1739, http://dx.doi.org/10.21037/jtd.2019.03.83.
[6] H.S. Kulkarni, K. Tsui, S. Sunder, et al., Pseudomonas aeruginosa and acute rejection independently increase the risk of donor-specific antibodies after lung transplantation, Am. J. Transplant. 20 (4) (2020) 1028–1038, http://dx.doi.org/10.1111/ajt.15687.
[7] S. Salehi, A. Abedi, S. Balakrishnan, et al., Coronavirus Disease 2019 (COVID-19): a systematic review of imaging findings in 919 patients, Am. J. Roentgenol. 14 (2020) 1–7, http://dx.doi.org/10.2214/AJR.20.23034 [Epub ahead of print].
[8] L. D'Antiga, Coronaviruses and immunosuppressed patients. The facts during the third epidemic, Liver Transplant. (2020), http://dx.doi.org/10.1002/lt.25756 [Epub ahead of print].
[9] A.K. Chui, A.R. Rao, H.L. Chan, et al., Impact of severe acute respiratory syndrome on liver transplantation service, Transplant. Proc. 36 (October (8)) (2004) 2302–2303, http://dx.doi.org/10.1016/j.transproceed.2004.08.018.
[10] J.Y. Chen, K. Qiao, F. Liu, et al., Lung transplantation as therapeutic option in acute respiratory distress syndrome for COVID-19-related pulmonary fibrosis, Chin. Med. J. (Engl.) (2020), http://dx.doi.org/10.1097/CM9.0000000000000839, 1 Apr. [Epub ahead of print].

Open Access
This article is published Open Access at sciencedirect.com. It is distributed under the IJSCR Supplemental terms and conditions, which permits unrestricted non commercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.