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LETTER TO THE EDITOR

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Severe COVID-19 evolving towards organizing pneumonia in a pediatric lung transplant recipient

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To the Editor,

Lung transplantation (LT) and rituximab represent two risk factors for severe COVID-19 in adults.[1] Conversely, pediatric solid organ recipients and children receiving rituximab did not appear to be at increased risk for severe COVID-19, which led some authors to suggest that children on immunosuppressive therapy should not be more strictly isolated than children who are not.[2]

1 | CASE

A 12-year-old girl developed a severe form of COVID-19 10 months after a bilateral LT indicated end-stage respiratory failure due to cystic fibrosis. The transplant course was marked by an Epstein–Barr virus + polymorphic posttransplant lymphoproliferative disorder treated with rituximab (four weekly infusions of 375 mg/m^2) between months 9 and 10 post-LT. Tacrolimus, mycophenolate mofetil, and prednisone composed the maintenance immunosuppressive regimen.

Between the third and fourth rituximab infusion, the patient developed a cough, fever, and respiratory distress requiring a maximal oxygen flow of 2.5 L/min due to severe acute respiratory syndrome coronavirus 2 (SARS-Cov2) D614G variant infection. Chest computed tomography (CT) scan showed bilateral ground-glass opacities (Figure 1A–C). COVID-19 convalescent plasma (CCP) was administered (two infusions of 400 ml over 2 days), and oxygen was weaned within 48 h. One month later, she developed a second similar episode (Figure 1D–F). SARS-Cov-2 polymerase chain reaction (PCR) was positive in the bronchoalveolar lavage (BAL) with moderate to high viral excretion (cycle threshold <33 according to the real-time reverse transcription-PCR assay from Institut Pasteur). Transbronchial biopsies showed a subacute interstitial inflammation with type II pneumocyte hypertrophy compatible with organizing pneumonia and

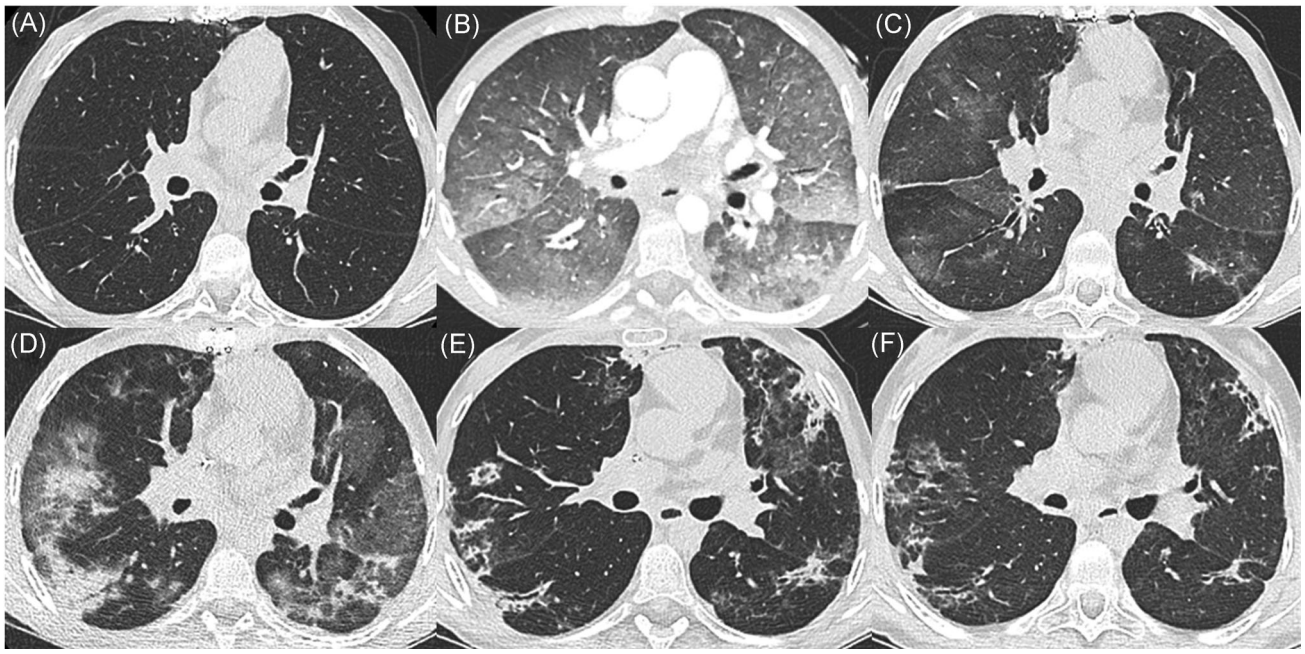

FIGURE 1 Evolution of chest CT-scans over time. (A) Month 9 (M9) postlung-transplantation: normal aspect of the control CT scan. (B) M10, SARS-Cov2 infection: onset of diffuse ground-glass opacities predominantly in the posterior subpleural regions. (C) M10, 3 weeks after diagnosis of SARS-Cov-2 infection: partial regression of the anomalies with some scattered ground glass areas of lower density remaining. (D) M11, recurrence of the disease: new increase of ground glass opacities and development of bilateral subpleural consolidation areas. (E) M12, 1 month after the recurrence: progression of the consolidations towards retractile opacities associated with traction bronchiectasis and subpleural reticular images in favor of an evolution towards fibrosis. (F) M16, 4 months after the recurrence: improvement but persistence of subpleural reticular opacities and traction bronchiectasis. CT, computed tomography; SARS-Cov2, severe acute respiratory syndrome coronavirus 2

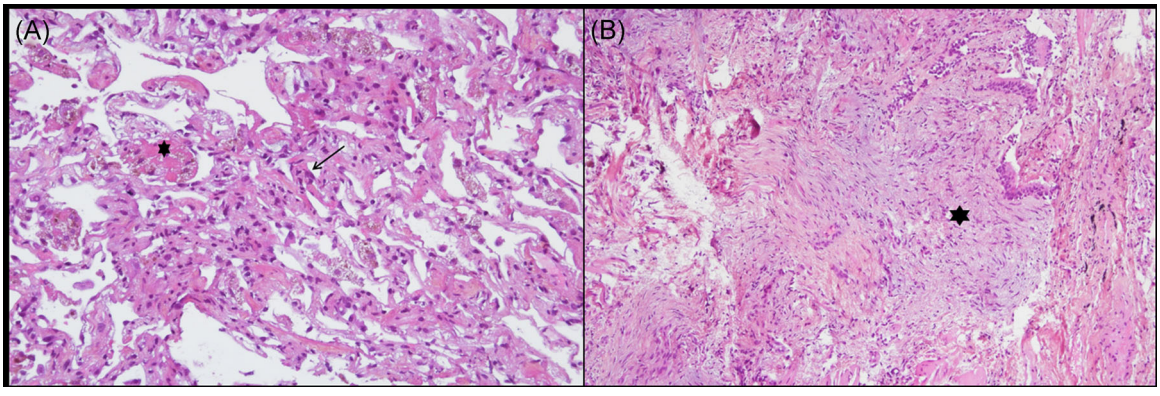

FIGURE 2 Evolution of histopathology on transbronchial biopsies. (A) Month 11 (M11), recurrence of the disease: acute lung injury with fibrin deposits (star), interstitial inflammation, and pneumocytes hypertrophy in favor of organizing pneumonia (arrow) (*hematoxylin eosin saffron stain, ×200 magnification)*. (B) M16, 4 months after the recurrence: fibrotic evolution with fibrotic plugs in alveoli (star) (*hematoxylin eosin saffron stain, ×100 magnification)* [Color figure can be viewed at wileyonlinelibrary.com]

no acute cellular rejection (Figure 2). CCP was administered again and prednisone increased to 2 mg/kg/day. After 6 days, oxygen could be weaned; prednisone was slowly tapered to 0.3 mg/kg/day over 4 months. SARS-Cov2 PCR remained positive in three consecutive BALs for 4 months, and there was no evidence of SARS-Cov2 new variant.

The patient developed a restrictive syndrome and the forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) dropped from 2.52 (106%) and 1.94 L (90%) before SARS-Cov2 infection, to 2.29 (96%) and 1.63 L (76%) after the first episode, and 1.43 (60%) and 1.34 L (62%) after the second, respectively. Over the next 4 months, FVC and FEV1 increased and stabilized at 1.86 L (78%) and 1.7 L (79%), respectively, with concomitant improvement and stabilization of CT-scan findings suggesting organizing pneumonia and fibrosis. This was confirmed by aspects of buds of endoalveolar connective tissue at histopathology (Figure 2).

2 | DISCUSSION

The case of this young girl was notable for a severe SARS-Cov2 pneumonia with persistent viral shedding, and its progression towards organizing pneumonia and pulmonary fibrosis.

We speculate that this severe form of COVID-19 resulted from both her high level of immunosuppression following her recent LT and the use of anti-CD20 monoclonal antibody. LT and rituximab are two established risk factors for severe forms of COVID-19 in adults. A multicenter nationwide cohort study conducted in France in 2020 identified 35 cases of COVID-19 in adult LT recipients. Thirty-one (88.6%) required hospitalization, 13 (37%) were critically ill, and 5 (14%) died.[1] Similarly, adults treated by anti-CD20 depleting therapy are at risk of prolonged and severe SARS-Cov2 pneumonia.[3]

Because children are demonstrated to be protected from developing severe forms of COVID-19 by an age effect, it remained unclear whether LT and rituximab were still risk factors in this population. Indeed, children seem to have a distinct infection course than adults, possibly explained by a lower expression of the viral receptor (angiotensin-converting enzyme 2) on the nasal epithelia or a more robust innate immune response. A study conducted in 2020 among five transplant centers in the United States found 26 pediatric patients with solid organ transplantation (10 liver recipients, 8 kidney, 6 heat, and 2 lung) infected by SARS-Cov2.[4] All these children presented mild or asymptomatic diseases, including the two children with LT. However, both these children had undergone LT more than 3 years before the infection, and their level of immunosuppression was probably much lower than in our patient.

Similarly, rituximab was initially not associated with worse outcomes in children infected by SARS-Cov2. In a study involving 113 children with kidney diseases taking immunosuppressive therapies, Marlais et al.[2] concluded that because most children had mild diseases with SARS-Cov2 infection, they should not be more strictly isolated than other children. However, looking closely at the data, of the 12 children who received anti-CD20 therapy, 3 children received supplemental oxygen, and 1 required noninvasive ventilation.[2] Thus, we speculate that the high level of immunosuppression including combined B- and T-cell deficiency due to the association of rituximab, tacrolimus, mycophenolate mofetil, and prednisone prevented the elicitation of a specific SARS-Cov2 immune response in our patient.

Despite the early and repeated use of CCP, our patient developed organizing pneumonia. Organizing pneumonia is a nonspecific pulmonary response pattern associated with a variety of clinical contexts including connective tissue diseases, drug reactions, and viral infection. Classically, peribronchovascular/peripheral ground glass opacities or consolidations which can be migratory are observed on chest CT scans, and a prolonged course of corticosteroids allow remission in most cases. Organized pneumonia had been reported in adults with COVID-19 but never before in a pediatric patient.[5] The increase in prednisone to 2 mg/kg/day improved the pulmonary status of our patient, but did not prevent the emergence of sequela under the form of areas of pulmonary fibrosis.

3 | CONCLUSION

Pediatricians need to be aware that adolescents with high level of immunosuppression including rituximab may develop severe forms of COVID-19. These cases may be complicated by organizing pneumonia and long term sequelae.

CONFLICT OF INTERESTS

Pierre Frange is a consultant for and has received travel support from MSD France. Other authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

David Drummond: investigation (equal); writing – original draft (lead); writing – review and editing (equal). **Caroline Thumerelle**: investigation (equal); writing – review and editing (equal). **Antoine Roux**: investigation (equal); writing – review and editing (equal). **Clémence Mordacq**: investigation (equal); writing – review and editing (equal). **Pierre Frange**: investigation (equal); writing – review and editing (equal). **Marianne Leruez**: investigation (equal); writing – review and editing (equal). **Laure Gibault**: investigation (equal); writing – review & editing (equal). **Laureline Berteloot**: investigation (equal); writing – review and editing (equal). **Charlotte Roy**: investigation (equal); writing – review and editing (equal). **Margaux Pontailler**: investigation (equal); writing – review and editing (equal). **Vanessa Lopez**: investigation (equal); writing – review and editing (equal). **Mehdi Oualha**: investigation (equal); writing – review and editing (equal). **Marion Grimaud**: investigation (equal); writing – review and editing (equal). **Laure de Saint Blanquat**: investigation (equal); writing – review and editing (equal). **François Parquin**: investigation (equal); writing – review and editing (equal).

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