ARDS With Pneumothorax in a Young Adult

Jonah Rubin, MD; Michelle L. Chiu, MD; Mari Mino-Kenudson, MD; Amita Sharma, MBBS; Alison S. Witkin, MD; Peter P. Moschovis, MD, MPH; Yehuda Vogel; Kenneth Shelton, MD; Jerome Crowley, MD; and Yuval Raz, MD

CASE PRESENTATION: A 19-year-old, previously healthy man presented with 3 days of cough, high-grade fevers (40 °C), and dyspnea. Apart from a resolved history of seizures not requiring medications, he had no medical or surgical history. He had no known drug allergies. He took montelukast for allergies and trimethoprim-sulfamethoxazole (TMP-SMX) for 2 weeks before admission for acne, but no other medications, including over-the-counter medications and supplements. He had animal exposures to a new puppy and a friend’s bird. He had no history of smoking, vaping, or recreational drug use. His paternal grandmother had rheumatoid arthritis.

In the ED, a chest radiograph showed patchy, multifocal opacifications, pneumomediastinum, and a right pneumothorax. A right-sided chest tube was inserted. He then developed worsening hypoxemic respiratory failure requiring intubation on hospital day 3. He had an elevated ferritin and inflammatory markers, but a complete rheumatologic and infectious workup including a bronchoscopy with BAL was negative. CT of the chest showed subcutaneous emphysema, pneumomediastinum, bibasilar consolidations with air bronchograms, and diffuse ground-glass opacities (Fig 1). The differential diagnosis included infectious, autoimmune, inflammatory, and malignant etiologies. Supporting clinical and radiographic features for each potential diagnosis are reviewed in Table 1. Given this broad differential diagnosis, he was treated with antibiotics, steroids, anakinra, and hydroxychloroquine, but his condition failed to improve.

On hospital day 18, he underwent a bedside biopsy of the left lingula, which revealed diffuse alveolar damage, organizing to fibrotic phase, with alveolar denudation and prominent peribroncholar metaplasia, consistent with an advanced stage of diffuse alveolar injury with delayed epithelization (DAIDE) (Fig 2).

His condition deteriorated requiring cannulation to veno-venous extracorporeal membrane oxygenation (ECMO) on hospital day 25. CT of the chest on hospital day 47 showed persistent bilateral pneumothoraces, peripheral extensive ground glass with intra- and interlobular septal thickening, and airway dilation indicative of fibrosis (Fig 3). Given lack of recovery and evidence of fibrosis, his ECMO goal was transitioned from bridge-to-recovery to bridge-to-transplant.

AFFILIATIONS: From the Division of Pulmonary and Critical Care Medicine, Department of Medicine (J. Rubin, A. S. Witkin, and Y. Raz), the Division of Pediatric Pulmonary Medicine, Department of Pediatrics (M. L. Chiu and P. P. Moschovis), the Department of Pathology (M. Mino-Kenudson), the Department of Radiology (A. Sharma), Massachusetts General Hospital, Boston, MA; the Queens College (Y. Vogel), City University of New York, Flushing, NY; the Department of Anesthesia, Critical Care and Pain Medicine (K. Shelton and J. Crowley), Massachusetts General Hospital and Harvard Medical School, Boston, MA; and Harvard Medical School (J. Rubin, M. L. Chui, M. Mino-Kenudson, A. Sharma, A. S. Witkin, P. P. Moschovis, K. Shelton, J. Crowley, and Y. Raz), Boston, MA.

CORRESPONDENCE TO: Jonah Rubin, MD; email: jrubin5@mgh.harvard.edu

Copyright © 2021 American College of Chest Physicians. Published by Elsevier Inc. All rights reserved.

DOI: https://doi.org/10.1016/j.chest.2021.09.006
sedation was lightened, and the ventilator settings were liberalized. However, the patient’s native lungs recovered, and he was successfully decannulated from ECMO on hospital day 59. He was discharged to rehabilitation after 99 days, still dependent on mechanical ventilation but improving.

**TABLE 1 | Differential Diagnosis of ARDS in This Otherwise Healthy Young Adult**

<table>
<thead>
<tr>
<th>Category</th>
<th>Specific Processes</th>
<th>Supportive History and Findings</th>
<th>Nonsupportive History and Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>• Bacterial</td>
<td>• Acuity of presentation, diffuse process</td>
<td>• Negative cultures including sputum and BAL, legionella culture, CMV viral load, EBV IgM and IgG, mycoplasma IgM, respiratory viral panel</td>
</tr>
<tr>
<td></td>
<td>• Viral</td>
<td></td>
<td>• No improvement with antibiotics</td>
</tr>
<tr>
<td></td>
<td>• Fungal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune</td>
<td>• Inflammatory myopathies</td>
<td>• Acuity of presentation, diffuse process</td>
<td>• No joint or muscle pains, no rashes</td>
</tr>
<tr>
<td></td>
<td>• Vasculitis (GPA, EGPA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td>• Hypersensitivity pneumonia</td>
<td>• Acuity of presentation, diffuse process</td>
<td>• Negative ANA, ANCA, RF, CCP, dsDNA, U1RNP, Smith, SSA, SSB, and myositis antibodies</td>
</tr>
<tr>
<td></td>
<td>• Drug-induced pneumonia</td>
<td>• Family history of RA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Acute eosinophilic pneumonia</td>
<td>• Bird, dog exposure</td>
<td>• Atypical CT imaging</td>
</tr>
<tr>
<td></td>
<td>• Acute fibrinous organizing pneumonia</td>
<td>• Newly on TMP-SMX</td>
<td>• No response to steroids</td>
</tr>
<tr>
<td>Malignancy</td>
<td>• Lymphoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANA = antinuclear antibodies; ANCA = anti-neutrophil cytoplasmic antibody; CCP = cyclic citrullinated peptide; CMV = cytomegalovirus; dsDNA = double-stranded DNA; EBV = Epstein-Barr virus; EGPA = eosinophilic granulomatosis with polyangiitis; GPA = granulomatosis with polyangiitis; RA = rheumatoid arthritis; RF = rheumatoid factor; SSA = Sjogren syndrome A; SSB = Sjogren syndrome B; TMP-SMX = trimethoprim-sulfamethoxazole; U1RNP = U1 small nuclear ribonucleoprotein
Figure 2 – Histopathology from left lung lingula biopsy. A, Predominantly organizing fibrosis replaced normal lung parenchyma with B, prominent peribronchiolar metaplasia. C, Scattered foci of residual airspaces lack epithelial lining. D, A keratin AE1.3/ CAM5.2 immunostain highlights the prominent peribronchiolar metaplasia and small patches of regenerative pneumocytes, and E, confirms the absence of epithelial lining of residual airspaces. F, Macrophages line the airspaces in some areas instead, highlighted by a CD163 immunostain (arrows); no significant hyaline membranes are seen. G, Elastic and trichrome stains reveal relatively preserved alveolar architecture with (H) prominent organizing fibrosis and patchy collagen fibrosis.
What is the diagnosis?
Discussion

Clinical Discussion

TMP-SMX is an uncommon, case-reported cause of drug-induced lung diseases, including hypersensitivity pneumonitis,1 drug-induced pneumonitis,2 and acute fibrinous organizing pneumonia.3 In one series of 10 patients (60-84 years of age) taking TMP-SMX for 4 to 32 days during treatment of various underlying interstitial lung diseases, prospective CT imaging to assess for new, asymptomatic lung injury revealed various, otherwise unexplained, pulmonary abnormalities.7 Lesions were most commonly patchy, unilateral, upper lobe, ground-glass or other interstitial infiltration, with a dose-disease relationship. In 70% of cases, the lesions resolved despite continued therapy (prophylactic dosing), and in 20%, after discontinuation. Only one patient had radiographic evidence of permanent scarring. Pathologic specimens were not obtained.

However, a recent case series of 14 children and young adults (10-37 years of age) described a much more severe, fulminant respiratory failure in response to TMP-SMX, strikingly similar to this patient,5,6 with unique, shared, histopathologic findings (DAIDE, discussed later). These patients had been on TMP-SMX for a median of 21 days for acne or minor infections. All patients presented with dyspnea, and 57% presented with fevers. Laboratory results on admission were typically unremarkable. Eighty-six percent of patients required ECMO, and the median hospital length of stay was 102 days. Thirty-six percent of patients did not survive; 21% underwent transplantation. All surviving patients not lost to follow-up at 1 year had weaned off supplemental oxygen.

Drug-induced pulmonary toxicity is a diagnosis of exclusion, but all patients in the series, and this patient, scored “probable” on the Naranjo adverse drug reaction probability scale.7 Whether this severe response preferentially affects children and young adults, or whether this population simply has fewer potential confounding etiologies, yielding the diagnosis more frequently, is unknown. Unlike many other drug-induced pulmonary toxicities, this unique clinical entity does not appear to rapidly improve with offending agent discontinuation or steroids. Patients require supportive care as a bridge to recovery or transplantation. There is no known therapeutic agent at this time.

Radiologic Discussion

No known specific radiographic findings correlate with the pathologic finding of DAIDE5,6 or TMP-SMX-associated lung disease. In the reported case series, radiographic imaging early in the disease course revealed extensive ground-glass opacities and consolidations in all patients, and pneumomediastinum, pneumothorax, or both, in 57%. This patient’s radiographic findings at diagnosis are consistent with these reports. Previous case reports do not include a description of late-stage radiographic findings, which we present for this patient in Figure 3. There was diffuse, lower lobe predominant, peripheral, extensive ground-glass opacities with intralobular lines and septal thickening and traction bronchiectasis. This extensive involvement of the disease process with fibrosis was thought to be irrecoverable, prompting a transition in the goals of care from bridging to recovery to a bridge to transplantation. However, despite the degree of fibrotic lung disease, which persisted on follow-up imaging months later, the patient nevertheless remarkably proved capable of recovering with his remaining, nonfibrotic native lungs during ventilator liberalization, sedation lifting, and physical therapy. This case reflects the possibility of recovery for patients with diffuse alveolar damage changes on CT imaging. It may further reflect the resilience of otherwise young, healthy patients, or the natural history of this unique pathophysiologic entity.

Pathologic Discussion

Histopathology of this patient indicated diffuse alveolar damage with alveolar denudation and prominent peribronchiolar metaplasia, consistent with DAIDE (Fig 2). The predominance of an organizing phase may demonstrate an advanced stage of DAIDE not previously reported, although further review of such staging is required. Most of the lung parenchyma was replaced by predominantly organizing fibrosis (Fig 2A), with prominent peribronchiolar metaplasia (Fig 2B). Scattered foci of residual airspaces completely lacked lining epithelial cells (Fig 2C). A keratin AE1.3/CAM5.2 immunostain highlighted prominent peribronchiolar metaplasia and small patches of regenerative pneumocytes (Fig 2D) and confirmed the absence of epithelial lining of residual airspaces (Fig 2E). Alveoli were instead lined by macrophages in some areas, highlighted by a CD163 immunostain (arrows in Fig 2F); no significant hyaline membranes were seen. Elastic
and trichrome stains revealed relatively preserved alveolar architecture (arrows in Fig 2G) with prominent organizing fibrosis and patchy collagen fibrosis (Fig 2H). Cytomegalovirus, herpes simplex virus, adenovirus, and varicella-zoster virus immunostains were all negative for viral microorganisms.

DAIDE was first described in 2018, discovered on wedge biopsy specimens of two young adults who had been taking TMP-SMX and developed fulminant respiratory failure requiring ECMO; one patient had native lung recovery, and the other required a transplant. These biopsy specimens revealed diffuse alveolar injury, edematous and mildly fibrotic alveolar walls, rare hyaline membranes, near-complete absence of regenerative type 2 alveolar epithelial cells (AEC2), and squamous metaplasia. Pathologic evaluation of the explanted lungs of the patient who underwent transplantation showed diffuse interstitial fibrosis with prominent reepithelialization by AEC2s. The near-complete absence of AEC2s in the presence of squamous metaplasia was a heretofore undescribed phenomenon, not consistent with typical diffuse alveolar damage processes, and was termed DAIDE.

In 2019, after a nationally broadcast news story of an otherwise healthy adolescent who developed fulminant respiratory failure after taking TMP-SMX, a case series of five similar patients was collected and published. This was the first series to connect and describe the association between TMP-SMX and these patient presentations. No pathologic findings were reported in this series.

By 2021, a total of 14 such patients had been described, and the pathologic findings of seven were obtained and described. All demonstrated the unique DAIDE pattern. Explanted lung tissue was also available from three patients, including the patient described here, which revealed reepithelialization, advanced fibrosis, architectural remodeling, and prominent bronchiolization.

This patient’s case adds to the existing literature describing this unique clinical entity, and further supports the association between TMP-SMX-induced fulminant respiratory failure and the pathologic findings of DAIDE.

Conclusion

- Fulminant respiratory failure is a rare complication of TMP-SMX administration, thus far primarily described in otherwise healthy children and young adults taking TMP-SMX for 3-4 weeks, that can occur as early as 7 days after first drug initiation, with a median time to presentation of 21 days.
- There are currently no known CT findings to specifically correlate with this disease. Furthermore, even a significant degree of fibrosis should be considered cautiously when being used to guide prognosis and goals of care in this patient population.
- Diffuse alveolar injury with delayed epithelialization is a unique pathological finding seen in these patients.
- This condition has significant morbidity and mortality, including the potential need for ECMO and transplantation.
- A comprehensive medication history may play a critical role in the evaluation of the acutely ill.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to CHEST the following: M. M.-K. has served as a compensated consultant for H3 Biomedicine and AstraZeneca and has received research (institutional) funding from Novartis and loyalty from Elsevier, all of which are also not related to this report. A. S. has received research (institutional) funding from Hummingbird Diagnostics not related to this report. A. S. W. serves on an advisory board for United Therapeutics and receives research funding from Johnson & Johnson, which are not related to this report. None declared (J. R., M. L. C., P. P. M., K. S., J. C., Y. R., Y. V.).

Other contributions: CHEST worked with the authors to ensure that the Journal policies on patient consent to report information were met.

References