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Thoughts and Progress

Extracorporeal Membrane Oxygenation for Refractory Severe Respiratory Failure in Acute Interstitial Pneumonia

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Abstract: Acute interstitial pneumonia (AIP) is a rare idiopathic interstitial lung disease with rapid progressive respiratory failure and high mortality. In the present report, three cases of AIP complicated by refractory respiratory failure supported with extracorporeal membrane oxygenation (ECMO) are presented. One male and two female patients (ages 27–59) were included. Venovenous ECMO support was provided using miniaturized systems, with two-site femoro-jugular circuit configuration. Despite lung protective ventilation, prone position and neuromuscular blockade, refractory respiratory failure of unknown etiology supervened (ratio of arterial oxygen partial pressure to fractional inspired oxygen 46–130) and ECMO was initiated after 3–7 days of mechanical ventilation. AIP diagnosis was established after exclusion of infectious and noninfectious acute respiratory distress syndrome on the basis of clinical and analytical data, bronchoalveolar lavage analysis and lung imaging, with a confirmatory surgical lung biopsy revealing diffuse alveolar damage of unknown etiology. Immunosuppressive treatment consisted in high-dose corticosteroids and cyclophosphamide in one case. Two patients survived to hospital discharge. ECMO allowed AIP diagnosis and treatment in the presence of refractory respiratory failure, therefore reducing ventilator-induced lung injury and bridging lung recovery in two patients. ECMO referral should be considered in refractory respiratory failure if AIP is suspected. **Key Words:** Acute interstitial pneumonia—Acute respiratory distress syndrome—Extracorporeal membrane oxygenation—Acute respiratory failure.

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Acute interstitial pneumonia (AIP) is a rare idiopathic interstitial lung disease, first described in 1965 by Hamman and Rich (1). It has a poor prognosis with a mortality >50% in the first 2 months after disease onset (2). It mostly occurs in previously healthy individuals without lung disease, has neither gender predominance nor association with smoking habits and can occur at any age with a mean age occurrence of 50 years (2). The onset of AIP is usually rapid, with a prodromal illness that typically lasts 7–14 days prior to presentation (3,4). The most common presenting signs and symptoms are fever, cough, and progressive severe shortness of breath, affecting 75, 79, and 90%, respectively (3,5,6). The majority will have hypoxemia at presentation and most will require intubation and mechanical ventilation within a few days. Patients may also report prodromal symptoms of myalgias, arthralgias, chills, and malaise (2). However, the clinical and radiological presentation of AIP is nonspecific, frequently mimicking acute respiratory distress syndrome (ARDS) and the term idiopathic ARDS appears to be quite appropriate (2). Therefore, diagnosis requires a confirmatory lung biopsy showing a diffuse alveolar damage (DAD) histologic pattern. Known causes of DAD such as infection, acute exacerbation of idiopathic pulmonary fibrosis, acute hypersensitivity pneumonitis, connective tissue disorders, drug toxicity, aspiration, inhalants toxins, and pancreatitis need to be excluded in order to establish the diagnosis of AIP (7).

Extracorporeal membrane oxygenation (ECMO), referring to an extracorporeal circuit that directly oxygenates and removes carbon dioxide from the blood, may be considered in refractory respiratory failure when positive-pressure ventilation alone is insufficient to maintain adequate gas exchange, or when adherence to lung-protective ventilation strategies, neuromuscular blockade, prone position, and conservative strategy of fluid management results in unacceptable levels of hypoxemia, hypercapnia, and acidemia (8). In most cases of ECMO for severe acute respiratory failure, venovenous ECMO is utilized, in which blood is withdrawn from and returned to a central vein (9). Recently, there has been increasing interest in ECMO as a result of

advances in extracorporeal technology, with more efficient oxygenators and lower rates of complications, along with multiple reports of improved survival with ECMO for severe ARDS (10–13).

The use of ECMO for acute respiratory failure in interstitial lung disease is controversial (14), with reports of ECMO for refractory respiratory failure in AIP uncommon (15). To widen the knowledge in this field, a series of three cases of AIP complicated by refractory respiratory failure is presented in detail, with an emphasis on the role of ECMO as a bridge to definitive diagnosis and treatment initiation, as well as to eventual native lung recovery.

PATIENTS AND METHODS

The Ethics Committee of the Hospital S. João approved the study and waived the requirement for patient consent.

Case 1

A 27-year-old woman with a past medical history of obesity presented with 1-week of odynophagia, fever, and purulent cough that persisted despite antibiotic therapy with levofloxacin (Supporting Information Table S1). She evolved with prostration, asthenia, worsening dyspnea and went to the emergency department of a secondary hospital. On admission she was alert and had a respiratory rate of 30–40 breaths per minute, peripheral saturation of 56% breathing air, crackles in the right hemithorax, blood pressure 110/60 mm Hg, heartbeat of 110 pm, and a tympanic temperature of 39.5°C. Arterial blood gas analysis showed severe respiratory failure (pH 7.50, PaO_2 17 mm Hg, $PaCO_2$ 32 mm Hg, and HCO_3^- 26 mEq/L). Blood tests revealed an elevated C-reactive protein (129 mg/dL), normal white blood count and no renal, hepatic or hematological dysfunction. Chest X-ray showed consolidation of the right pulmonary base. A provisional diagnosis of severe community-acquired pneumonia (CAP) was made and antibiotic treatment with meropenem and oseltamivir started. The patient was then intubated and transferred to our hospital for ICU admission. Severe respiratory failure (pH 7.46, PaO_2 46 mm Hg, $PaCO_2$ 38 mm Hg, and HCO_3^- 24 mEq/L) persisted after adjustment of mechanical ventilation (fraction of inspired oxygen [FiO_2] of 100%, positive end-expiratory pressure [PEEP] of 15 cm H_2O, tidal volume of 380 mL, respiratory rate of 22 cpm, and plateau pressure of 29 cm H_2O). Chest X-ray showed an evolving consolidation of the right and of the inferior two-thirds of the left lungs (Fig. 1). Neuromuscular blockade and prone position were then initiated with no patient improvement (Supporting Information Table S2). Antibiotics were later changed to piperacillin/tazobactam, azithromycin, and oseltamivir was maintained. Cultural and noncultural microbiological results from BAL were negative, including virus and atypical agents. Oseltamivir was stopped and the antibiotics were kept for 8 and 5 days, respectively. The clinical status continued to worsen and a chest CT scan was performed, showing diffuse bilateral ground glass pattern and inferior lobar consolidation. At Day-6 of invasive mechanical ventilation, refractory hypoxemia under aggressive mechanical ventilation persisted and venovenous ECMO was then initiated (23-Fr. outflow cannula—from the patient—in the femoral vein and a 17-Fr. inflow cannula—to the patient—in the internal jugular vein) (Supporting Information Table S3). A surgical lung biopsy was performed on the ECMO Day-2 revealing DAD pattern in organizing phase (Fig. 2), with negative microbiological and cancer results (Supporting Information Table S4). Immunosuppressive therapy was started with methylprednisolone (1 g/day during 5 days and then 2 mg/kg/day) and intravenous cyclophosphamide (2 g/month), on ECMO Day-3. Right hemopneumothorax developed as a consequence of the lung biopsy and was managed with chest tubes (two) and hematologic support. After 15 days of progressive improvement on ECMO, decannulation was safely performed and the patient weaned from invasive mechanical ventilation in the next 5 days. She was then transferred to a level II-ICU on ICU Day-28, where she stayed for more than 11 days, recovering from critical illness myopathy and residual respiratory failure, and treating a recurrent pneumothorax and *Proteus mirabilis* acute pyelonephritis (5 days meropenem). Later she was transferred to the pulmonology ward where respiratory failure fully resolved, completing 51 days of hospital stay. Currently she remains without respiratory symptoms and without any immunosuppressive therapy, after a 2-year course of azathioprine.

Case 2

A 59-year-old man with a past medical history of ulcerative colitis managed with mesalazine and prednisolone, came to our Emergency Department with a 3-day history of progressive worsening dyspnea, asthenia, and dry cough (Supporting Information Table S1). On admission, he presented a respiratory rate of 30–40 breaths per minute,

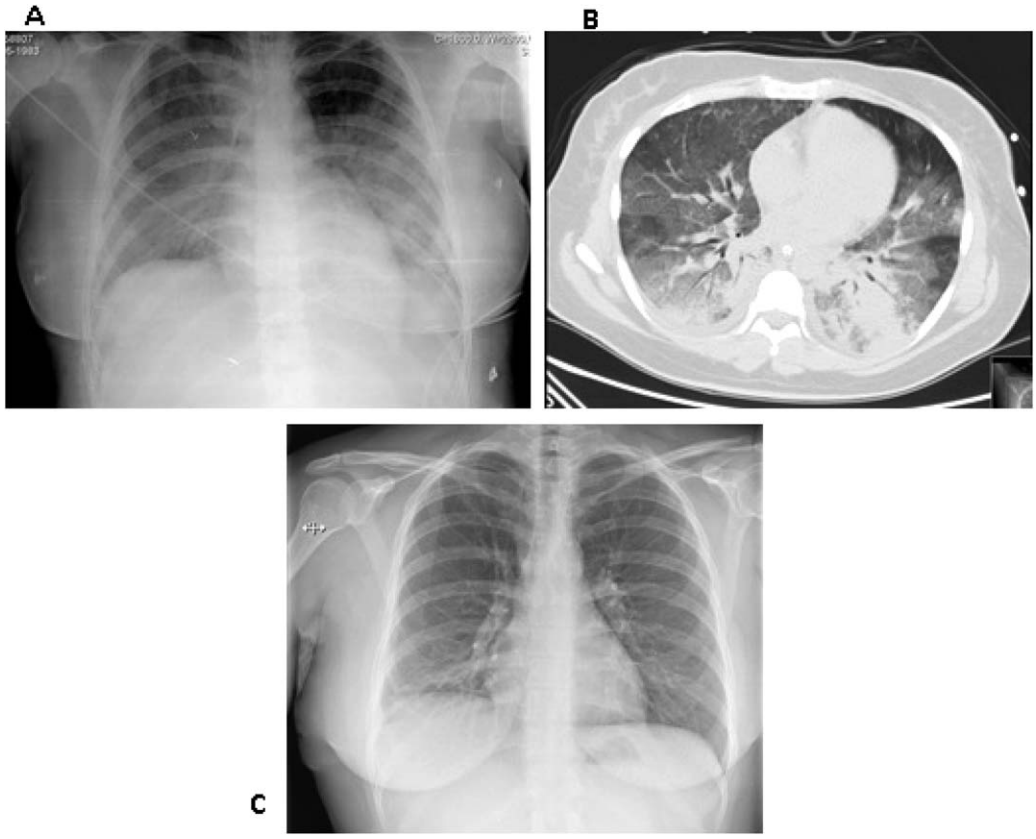

FIG. 1. Chest X-ray (A) and thoracic computed tomography (B) at admission and chest X-ray of the last pulmonology consultation of Patient 1. (A) Consolidation of the right and of the inferior two-thirds of the left lungs. (B) Diffuse bilateral ground glass pattern and inferior lobar consolidation. (C) Complete resolution of bilateral infiltrates.

peripheral saturation of 70% breathing air, and diminished breath sounds and crackles in both lung bases on auscultation. He was alert and hemodynamically stable, with a tympanic temperature of 38.4°C. Arterial blood gas analysis showed severe respiratory failure (pH 7.45, PaO_2 35 mm Hg, $PaCO_2$ 33 mm Hg, and HCO_3^- 25 mEq/L). Blood tests revealed leukopenia (WBC 3000/mm^3), elevated C-reactive protein (91 mg/dL) and no renal, hepatic or hematologic dysfunction. Chest X-ray showed heterogeneous infiltrates in both inferior halves of the lungs (Supporting Information Fig. S1). A provisional diagnosis of CAP was made and treatment with ceftriaxone, azithromycin, and oseltamivir started, together with ICU admission for noninvasive mechanical ventilation support. Due to negative cultural and noncultural microbiological results and confirmation of recent exposure to prednisolone, antibiotics were changed to piperacillin/tazobactam plus azithromycin. The patient evolved with worsening respiratory failure despite invasive mechanical ventilation, neuromuscular blockade, prone position, negative fluid balance, and an attempt of protective ventilator strategy with permissive hypercapnia. On ICU Day-5, ECMO was started (Supporting Information Table S3). A flexible bronchoscopy showed no signs of

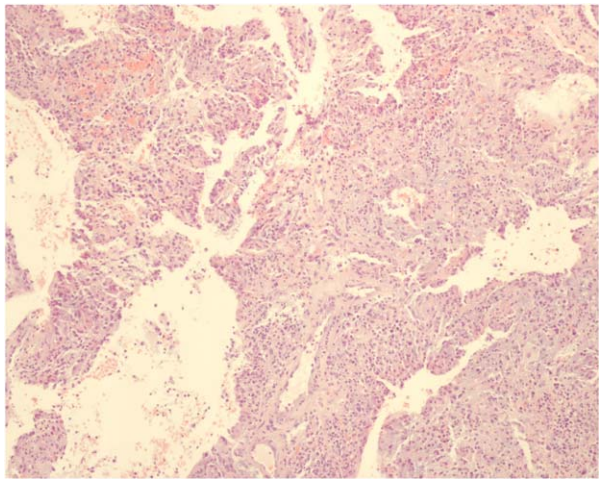

FIG. 2. Lung biopsy of Patient 1: Diffuse alveolar damage with uniform-appearing widening of alveolar septa by fibrosis and pneumocytes hyperplasia (hematoxylin and eosin-stained section; ×100). [Color figure can be viewed at wileyonlinelibrary.com]

typical and atypical infections and the microbiological (cultural and noncultural) and histologic results were unrevealing. Bronchoalveolar lavage fluid showed neutrophil predominance with mild eosinophilia (11%) and no lymphocytosis. A right pneumothorax subsequent to bronchoscopy led to pleural drain insertion. A thoracic CT-scan performed on ECMO Day-3 showed right pneumothorax with well-placed drain, minor bilateral pleural effusion, inferior and superior lobes consolidation with a ground glass pattern in the remaining parenchyma (Supporting Information Fig. S1). A surgical lung biopsy was performed on ECMO Day-9 showing pulmonary parenchyma with DAD pattern in organizing phase (Supporting Information Fig. S2), with negative microbiological, and cancer results. Methylprednisolone was then started (2 mg/kg/day) and the patient evolved favorably in the next days, being successfully decannulated on ECMO Day-15. He stayed for more 16 days in the ICU due to difficult mechanical ventilation weaning associated with a bronchopleural fistula and ICU-acquired weakness. He was transferred to a level II-ICU on ICU Day-37, where he stayed for 22 days and was transferred to an internal medicine ward on Hospital Day-59, and 7 days later he was transferred to a rehabilitation center. Currently he remains on hospital follow-up as a rheumatology and gastroenterology outpatient, with no respiratory symptoms.

Case 3

A 56-year-old woman with a past medical history of unilateral renal agenesis and major depressive disorder treated with quetiapine, sertraline, clomipramine, and lorazepam, went to the emergency department of a secondary hospital with a 3-day history of fever, dry cough, dizziness, and respiratory difficulty (Supporting Information Table S1). On admission she was alert with a respiratory rate of 30–40 breaths per minute, presented a peripheral saturation of 81% with a nonrebreathing facemask with reservoir (FiO_2 ~85%), crackles on the right hemithorax and presented hemodynamic stability. Arterial blood gas analysis showed severe respiratory failure (pH 7.41, PaO_2 48 mm Hg, $PaCO_2$ 41 mm Hg, and HCO_3^- 26 mEq/L). Blood tests revealed normal white blood count (with neutrophilia), elevated C-reactive protein (350 mg/dL), and no renal, hepatic, or hematological dysfunction. Chest X-ray showed diffuse bilateral infiltration (Supporting Information Fig. S3). A provisional diagnosis of severe CAP was made and ceftriaxone, azithromycin, and invasive mechanical ventilation initiated with the following parameters: FiO_2 of 100%, PEEP of 14 cm H_2O, tidal volume of 420 mL, respiratory rate of 24 cpm and plateau pressure of 32 cm H_2O. Cultural and noncultural microbiological results were negative. She evolved with persistent hypoxemia refractory to prone position, neuromuscular blockade, recruitment maneuvers, and negative fluid balance. ECMO was started (Supporting Information Table S3) in loco on ICU Day-7, followed by patient transport to our hospital. Rest ventilation was initiated and antibiotic sustained for a total of 8 days, according to negative microbiological results. She persisted on ECMO with multiorgan dysfunction and with an increasing inflammatory syndrome. Vesicles and ulcers developed on the oral mucosa and acyclovir initiated after a blood positive molecular result to Herpes simplex virus 1. The patient showed no signs of improvement and a thoracic and abdominal CT scan showed extended areas of consolidation and ground glass pattern more exuberant in the inferior pulmonary lobes. A surgical lung biopsy (access by minithoracotomy, with chest tube insertion under direct visualization) was held, revealing a morphologic picture of DAD in organizing phase (Supporting Information Fig. S4), without evidence of infection or cancer. Methylprednisolone (1 g/day in the first 5 days, then 2 mg/kg/day) was started. The patient developed signs of intubation associated pulmonary infection and imipenem plus vancomycin were initiated. Multiresistant *Acinetobacter baumannii* (only susceptible to imipenem and aminoglycosides) was isolated in bronchial lavage, and combined therapy with meropenem plus sulbactam initiated. A bronchopleural fistula with a persistent pneumothorax developed, despite multiple chest tube placements. A massive hemothorax emerged and the patient was disconnected from the ventilator during 3 days, remaining on ECMO, in a conservative attempt to solve the hemopneumothorax, without success. A surgery (access by right lateral thoracotomy) was tried for closure of the fistula and clot removal, but during the procedure tissues were very friable and marked blood loss was seen, forcing massive blood transfusion. After surgery the patient was admitted in the ICU in circulatory shock and progressive multiple organ failure. Withdrawal of ECMO in anticipation of death was then performed on ECMO Day-73.

DISCUSSION

In the present report, we describe three patients with AIP complicated by refractory respiratory failure and rescued with venovenous ECMO. ECMO allowed minimization of further ventilator-

induced lung injury and the prosecution of a diagnostic work-up that included a surgical lung biopsy, bridging the patient to a definitive diagnosis, immunosuppressive treatment, and lung recovery in two patients.

All three patients had no previous lung disease, did not smoke and had an acute onset of disease, although with shorter median times for dyspnea development than those usually presented in the literature (2). The evaluation on hospital admission highlights severe acute respiratory failure with an accompanying inflammatory syndrome, without hemodynamic instability or other concomitant major organ dysfunction. The chest X-rays showed alterations consistent with pneumonia, and this diagnosis was erroneously made, leading to an inadvertent use of antibiotics and delaying definitive diagnosis. The diagnostic work-up for AIP is very laborious, requiring the exclusion of other diseases, and requiring a confirmatory lung biopsy revealing DAD of unknown etiology (7).

Trudzinski et al. (15) recently published a retrospective analysis of 40 patients with interstitial lung disease and acute respiratory failure, of which 21 received ECMO support. Given the high mortality of patients treated with ECMO that did not undergo lung transplantation (93.3%), the authors concluded that ECMO is a lifesaving option for patients with interstitial lung disease and acute respiratory failure provided they are candidates for lung transplantation. However, in this relevant case series, only two patients that received ECMO support had AIP. In our case series, two patients survived without respiratory insufficiency suggesting that in the specific case of AIP complicated by acute respiratory failure, ECMO support should also be considered a bridge-to-recovery. In fact, interstitial lung diseases are a broad category of lung diseases of varied causation, treatment, and prognosis.

Controversies exist regarding the need and safety of lung biopsy in ICU patients, in an era of better laboratory expertise and techniques that can contribute to a more accurate diagnosis in the majority of pulmonary diseases. However, lung biopsies are still highlighted as the only way to establish a definitive diagnosis in some patients, namely those with persistent ARDS with negative blood and BAL results, with potential impact on treatment decisions and outcome (16). The most frequent complications of lung biopsies are pneumothorax, low-grade air leak, and hemothorax (16). This is particularly relevant during ECMO support, given the higher risk of these patients for bleeding complications. That was the case of Patient 3 in which lung biopsy complicated with bronchopleural fistula, persistent pneumothorax, and massive hemothorax, with a direct negative impact in clinical outcome. In this context, and given the absence of relevant findings after a very thorough diagnostic workup in our patients, a valid alternative clinical strategy could eventually have been one of immunosupressants without performing a lung biopsy.

There is no proven effective treatment for AIP (2). In patients requiring invasive mechanical ventilation a lung-protective strategy consisting of tidal volumes less than 6 mL/kg predicted body weight and a plateau pressure below 30 cm H_2O is recommended in order to minimize ventilator-induced lung injury, as in ARDS (17). Regarding the pharmacological treatment, the use of glucocorticoids remains controversial (2). The use of high dose steroids in the treatment of AIP is based on a lower mortality described in lupus pneumonitis (6) and ARDS (7). However, some authors have not found benefits of glucocorticoid therapy in the treatment of AIP (18). In this regard, high-dose steroids were used in all three patients, with steroid pulse therapy given only in patients 1 and 3. Some authors advocate the addition of immunosuppressive therapy, such as cyclophosphamide or vincristine in AIP (3). In our study, additional immunosuppressive therapy with cyclophosphamide was performed on Patient 1. Of note, patients 1 and 2 improved under high-dose steroids. This favorable clinical response to immunosuppressive treatment could be particularly relevant, given that AIP is a type of idiopathic interstitial pneumonia without clinical, serologic, and morphologic autoimmune features, such as those observed in interstitial pneumonia with autoimmune features (IPAF) (19).

CONCLUSIONS

Our report highlights the potential role of ECMO support in the diagnosis and management of suspected acute interstitial pneumonia complicated by refractory respiratory failure. ECMO allowed minimization of ventilator-induced lung injury and establishment of AIP diagnosis, bridging the patients to definitive diagnosis, immunosuppressive treatment, and eventual native lung recovery. Therefore, our results suggest a role for ECMO support in patients with acute and potentially reversible interstitial lung diseases complicated by refractory respiratory failure as a bridge to native lung recovery, in addition to its use as a bridge to lung transplantation in progressive interstitial lung diseases.

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Author Contributions: GGV, data collection/analysis and drafting article. NLP, concept/design, data analysis/interpretation, and critical revision of article. RRA, concept/design and critical revision of article. JAP, critical revision and approval of article.

Conflict of Interest: All authors have no conflicts of interest to declare.

REFERENCES

1. Hamman L, Rich AR. Fulminating diffuse interstitial fibrosis of the lungs. *Trans Am Clin Climatol Assoc* 1935;51:154–63.
2. Travis WD, King TE, Bateman ED, et al. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002; 165:277–304.
3. Olson J, Colby TV, Elliott CG. Hamman-Rich syndrome revisited. *Mayo Clin Proc* 1990;65:1538–48.
4. Vourlekis JS. Acute interstitial pneumonia. *Clin Chest Med* 2004;25:739–47, vii.
5. Vourlekis JS, Brown KK, Cool CD, et al. Acute interstitial pneumonitis. Case series and review of the literature. *Medicine* 2000;79:369–78.
6. Suh GY, Kang EH, Chung MP, et al. Early intervention can improve clinical outcome of acute interstitial pneumonia. *Chest* 2006;129:753–61.
7. Mukhopadhyay S, Parambil JG. Acute interstitial pneumonia (AIP): relationship to Hamman-Rich syndrome, diffuse alveolar damage (DAD), and acute respiratory distress syndrome (ARDS). *Semin Respir Crit Care Med* 2012;33:476–85.
8. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med* 2011;365:1905–14.
9. Del Sorbo L, Cypel M, Fan E. Extracorporeal life support for adults with severe acute respiratory failure. *Lancet Respir Med* 2014;2:154–64.
10. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009;374:1351–63.
11. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA* 2009;302:1888–95.
12. Patroniti N, Zangrillo A, Pappalardo F, et al. The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: preparation for severe respiratory emergency outbreaks. *Intensive Care Med* 2011;37:1447–57.
13. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA* 2011;306:1659–68.
14. Moerer O, Quintel M. Bridge or abyss: extracorporeal membrane oxygenation for acute respiratory failure in interstitial lung disease. *Am J Respir Crit Care Med* 2016; 193:474–6.
15. Trudzinski FC, Kaestner F, Schafers HJ, et al. Outcome of patients with interstitial lung disease treated with extracorporeal membrane oxygenation for acute respiratory failure. *Am J Respir Crit Care Med* 2016;193:527–33.
16. Papazian L, Doddoli C, Chetaille B, et al. A contributive result of open-lung biopsy improves survival in acute respiratory distress syndrome patients. *Crit Care Med* 2007;35: 755–62.
17. Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159–68.
18. Avnon LS, Pikovsky O, Sion-Vardy N, Almog Y. Acute interstitial pneumonia-Hamman-Rich syndrome: clinical characteristics and diagnostic and therapeutic considerations. *Anesth Analg* 2009;108:232–7.
19. Fischer A, Antoniou KM, Brown KK, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. *Eur Respir J* 2015;46:976–87.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

FIG. S1. Chest X-ray (A) at admission at the emergency room, thoracic computed tomography (B) pre-ECMO, and chest X-ray of the last rheumatology consultation of Patient 2. (A) Heterogeneous infiltrates in both inferior halves of the lungs. (B) Diffuse bilateral ground glass pattern with lobar consolidation and right pneumothorax. (C) Complete resolution of bilateral infiltrates.

FIG. S2. Lung biopsy of Patient 2: Diffuse alveolar damage with alveolar collapse with interstitial fibroblast proliferation (hematoxylin and eosin-stained section; ×40).

FIG. S3. Chest X-ray (A) at Centro Hospitalar São João admission, first (B) and fourth (C) day after admission. Thoracic computed tomography and last chest X-ray of Patient 3. (A) Diffuse bilateral infiltration. (B) Extended areas of consolidation and ground glass pattern more 20 exuberant in the in the inferior pulmonary lobes. (C) Persistent pneumothorax with hemothorax and persistent consolidation. (D) Diffuse bilateral infiltration.

FIG. S4. Lung biopsy of Patient 3: Diffuse alveolar damage with extensive interstitial fibroblast proliferation along with alveolar collapse and scant inflammatory cells (hematoxylin and eosin-stained section; ×100).

Table S1. Clinical presentation, diagnosis, and outcome of patients with AIP.

Table S2. ICU admission and treatment.

Table S3. Venovenous ECMO specifications.

Table S4. Diagnostic work-up for acute interstitial pneumonia.