CASE REPORT

Extracorporeal membrane oxygenation rescue in adolescent with bronchiolitis obliterans-organizing pneumonia like Wegener’s granulomatosis

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Key Clinical Message
We report a 17-year-old woman with bronchiolitis obliterans-organizing pneumonia (BOOP)-like granulomatosis with polyangiitis developing severe airway obliterations. Pending age, phase and grade of autoimmune treatment, and offering ECMO treatment may be crucial for survival but occasionally preface futility. ECMO-treated patient with BOOP-like GPA has never been described before.

Keywords
Extracorporeal membrane oxygenation, granulomatosis with polyangiitis, Wegener’s granulomatosis.

Introduction
Wegener’s granulomatosis (granulomatosis with polyangiitis, GPA) is an uncommon disorder (1–3/100,000 per year) causing multisystem systemic necrotizing granulomatous vasculitis affecting small- to medium-sized arteries, capillaries, and veins [1–3]. The inflammation involves blood vessels in nose, sinuses, throat, lungs, and kidneys. The tracheobronchial tree is involved in more than half of the patients displaying symptoms from airway narrowing, wheezing, dyspnea, cough, and hemoptysis. Early recognition and treatment of GPA may lead to full recovery. Without treatment, GPA can be fatal [1]. Symptoms vary from mild to life-threatening and treatment is part symptomatic, part curative including pharmacologic treatment, interventional bronchoscopy, or surgery [4]. In about 1% of the patients, the inflammation turns bronchiocentric [5] developing another entity of lung disease, bronchiolitis obliterans-organizing pneumonia (BOOP)-like GPA. This report describes one such case and its implications on ECMO treatment. The damage from vasculitis is much less and bleeding is uncommon. This type has been described in a few case reports [6, 7], and concerning histopathology [8].

Venovenous extracorporeal membrane oxygenation (V-V ECMO) is a life-sustaining salvage therapy in severe refractory respiratory failure supporting respiratory gas exchange [9, 10] superior to conventional ventilator therapy [11, 12]. To oxygenate the blood and clear carbon dioxide by an artificial lung (oxygenator) outside the body, the blood has to be drained from the patient, pumped through the oxygenator, and re-introduced to the patient. Either one dual-lumen cannula (DLC) or two single-lumen cannulas (SLCs) are used. In the SLC approach, one cannula is placed via the right internal jugular vein (IJV) or a femoral vein (FV) with the tip in the right atrium (RA). The other cannula is placed via the other FV. Femoroatrial or atriofemoral flow direction could be used. Placement of a DLC is performed via the right jugular vein with tip in proximity to the RA according to the cannula-specific algorithm. Heparin infusion is used for anticoagulation.
GPA patients with lung bleeding (angiocentric GPA) have been salvaged repeatedly by ECMO [2, 13–16]. However, ECMO has to our knowledge not been used in BOOP-like GPA before.

Case

This case reflects a 17-year-old, 55-kg former athletic girl. Her first healthcare contact was in early February 2015, and shortly she was diagnosed with GPA exhibiting involvement from nose, sinuses, and lower airways. Histology showed necrotizing granulomas with inflammation. Widespread necrotic areas predominantly in the right lower lung lobe were revealed at a CT scan, with further progression at follow-up. The cANCA (PR3-ANCA) was 23 U/mL (ref: ≥1.0 = positive) but anti-MPO negative. cANCA was reduced to 5.3 U/mL by four treatments of plasmapheresis. Pharmacological therapy consisted of high-dose steroids and rituximab since only minor response to cyclophosphamide (cANCA 20 U/mL). The patient’s daily problems were loss of stamina (200 m walking distance) and obstructive symptoms, demonstrated using a spirometry performed in mid-May (Table 1). She was admitted to hospital later the same month due to respiratory problems. A CT scan showed pneumomediastinum, pneumothorax, and subcutaneous emphysema. cANCA was 7.6 U/mL. A transfer to the regional University Hospital was undertaken and she was further investigated; the mediastinal emphysema was increased, and the right heart and larger vessels were compressed. A multi-disciplinary conference was decided for the conservative treatment; ECMO was considered futile. The patient’s oncologist contacted us for “second opinion.” She was accepted for ECMO if deteriorating, a decision based on her age, and our earlier experience from GPA with lung bleeding, a group with a good prognosis. BOOP-like GPA was not reported at this time.

The patient was on noninvasive ventilation for another 2 days. Due to combined hypoxic and hypercarbic respiratory failure, intubation was inevitable. After intubation, a peak inspiratory pressure (PIP) of 70 cm H2O was needed to maintain reasonable tidal volumes. Inhalations did not improve her obstructive problems; hence, intravenous infusions of terbutaline, theophylline, and MgSO4 were given. After a few hours, PIP was 50 cm H2O, positive-end expiratory pressure (PEEP) +2–4 cmH2O, and tidal volume (TV) 280 mL.

At arrival of the ECMO team, the patient was deep sedated, muscle-relaxed, manually ventilated (FiO2 1.0); PO2 49 kPa [368 torr]; PCO2 11.4 kPa [86 torr]; pH 7.16; sinus rhythm 100/min; BP 120/65 mmHg; and no vasoactive support. A plain chest X-ray indicated hyperinflation/air entrapment. Extracorporeal carbon dioxide removal was not an option due to severity and complexity of illness. V-V ECMO using dual SLC technique was decided due to the compression of the SVC (risk of draining problems). A 25-F/38-cm Maquet HLS® cannula (Maquet Nordic AB, Solna, Sweden) was placed via the right IJV with the tip approximately 40 mm above the diaphragm. Re-introduction of oxygenated blood was performed via a 19-F/18-cm Biomedicus® (Medtronic, Minneapolis, MN, USA) inserted percutaneously via left FV using Seldinger technique. From experience, atrio-femoral, “the Stockholm,” flow direction was used for safety in case of emergency conversion to veno-arterial (V-A) ECMO for cardiopulmonary support.

The ECMO circuit was composed of a CentriMag® centrifugal pump (Thoratec Europe Ltd., Cambridgeshire, U.K.), a hollow fiber oxygenator (HILITE® LT700, Medos Medizintechnik AG, Stolberg, Germany). After commencement of ECMO, PIP was reduced for lung protection. Unfortunate loss of TV and cephalad motion of the diaphragm increased recirculation during V-V ECMO. Indication came from equilibration of blood color between the venous and arterial ECMO tubes, as confirmed by blood gas assessments. The increase in recirculation was augmented by a decrease in cardiac function shown by a trans-esophageal echocardiogram. The decrease in ECMO efficiency became a concern for a safe transport; hence, the right femoral artery was cannulated with a 19-F/18-cm Biomedicus (Medtronic) for cardiopulmonary support. The ECMO configuration was now dual venous drainages (jugular and femoral), with re-introduction of oxygenated blood via the femoral artery (VV-A ECMO). At an ECMO flow of 2.5 L/min carbon dioxide normalized, and a satisfactory oxygenation achieved. A 650-km combined ground/air transfer to ECMO Centre Karolinska was then conducted.

ECMO ICU day 1: A bronchoscopy showed widespread general bronchial abnormalities such as mucosal edema,
cobblestone mucosa, millimeter-sized yellowish granulomas, luminal narrowing of the bronchial tree, and almost complete stenotic parts on the right side (Fig. 1). No bleeding was observed. cANCA and MPO were negative. A CT scan showed ground glass opacities in both lungs, interpreted as signs of bleeding or inflammation. Airway obliterations/narrowings seen during bronchoscopy were confirmed (Fig. 2). The soft tissue emphysema seemed to have decreased in size.

Antimicrobials were continued/commenced (meropenem, vancomycin, fluconazole and Bactrim), and samples for culturing were obtained accordingly.

Due to sedation problems, she was made awake and extubated day after arrival. Her cough was weak, and she talked in a weak voice managing 25 L/min in peak expiratory flow (PEF, see also May 15th, Table 1). She was struggling during both inspiration and expiration. The National center for lung transplant was informed about the case. The rheumatologists, however, deferred the transplant concern at this point as rituximab needed more time before final effect assessment.

Respiratory stress and panicking led to sedation and re-intubation on day 5. Her lungs were stiff and exhibited no tidal volumes. The bronchoscopy showed obstructions of all visible segments. She was now totally ECMO dependent. Airway samples showed growth of Saccharomyces cerevisiae, Candida DNA, and high titers of Epstein-Barr virus (66,000 DNA copies/mL).

Intravenous amphotericin-B (Ambisome) and aciclovir were introduced. The patient was accepted for discussions at following Grand Round at the National transplant centre. Figure 3 shows the chest X-ray from day after.

The situation in mediastinum resolved slowly and at ECMO day 9 the venous femoral cannula was removed, changing the ECMO mode from VV-A to V-A (atrio-femoral). Concerning the lung function, no improvement was seen and the rheumatologist regarded her GPA inactive and refractory to treatment.

From now on, the tidal volumes increased from approximately 80 to >400 mL with a parallel...
improvement in lung function. At day 14, she was
converted from V-A to V-V ECMO, that is, lung support.
The following day she managed 10 min at the time with¬
out ECMO support (ECMO sweep gas turned off).
Within the week (day 21), she was weaned off from
ECMO, supported by a conventional ventilator with mod¬
erate settings (FiO2 0.4; pressure support 15 cmH2O/+) PEEP).

Improvement continued. After 29 days, she was trans¬
ferred back to the hospital where she was admitted and
was spontaneously breathing with 2 L/min O2 over the
tracheal cannula. All major chest radiology findings were
of reversed, but for the right side basal necrotic mass
(Fig. 4). Prophylaxis against Pneumocystis and EBV (0
DNA copies) was continued. Amphotericin-B was chan¬
ged for posaconazole.

Within days the tracheal cannula was removed, she was
discharged from hospital. The assessment concerning lung
transplantation continued, and in November 2015, she
was listed. Her situation today is a struggle, but she is a
fighter. Actually, she has managed to move into her own
apartment.

Discussion

We report a 17-year-old woman with the rare BOOP-like
GPA [5, 8]. Her diagnosis was set months before from
histology and PR3-ANCA. After about 3½ months, the
dominant and increasing features from her inflammatory
processes were from her airways; rapid onset of dyspnea,
obstructive symptoms with air trapping. At first presenta¬
tion, involvement of lung bleeding, the common indica¬
tion for ECMO, was expected [2, 13–17]. However, in the
acute situation to commence ECMO, there was no time
to reflect, but at bronchoscopy and closer examination of
the X-ray, examinations differed in appearance from the
expected. A literature search was executed, and BOOP¬
like variant of GPA was identified. The incidence for
BOOP-like GPA is one to three in 10 million per year
[1–3, 5]. Two case reports were found, none of the
patients of which had been submitted to ECMO. Our
experience from GPA is positive, as is published data
from ANCA vasculitis patients (GPA, Goodpasture’s, and
systemic lupus erythematosus) with diffuse alveolar hem¬
orrhage (DAH) [13–18]. From case reports, case series,
and reviews on DAH, the chances for hospital and long¬
time survival are good in both the young [17] and adult
[16, 18]. Anticoagulation from start or delayed has been
used, and in most cases, the bleeding ceases within the
first or second day [18].
Physiology

As the systemic disease slowly progressed, the diaphragm worked harder and harder due to increased subsequent demand for more negative trans-pulmonary pressures to overcome the airway resistance. The tissue tearing led to air leakage leading to the decompartmentalization of air at time of admission. Trapped air may exert tissue compression on the distal airways upstream the bronchial obliterations augmenting flow resistance and obstructive physiology, exacerbating air trapping. Applying a positive pressure (PEEP) to the “ambient” side of the obliterations will reduce differential pressure over the obstruction, subsequently decreasing flow resistance, and a maneuver used is known as the waterfall phenomenon in ventilation of the obstructive patient [19].

The peak pressure of 70–50 cmH\textsubscript{2}O was far above the 30 cmH\textsubscript{2}O in plateau pressure commonly used as an ECMO indicator to minimize barotrauma. Such high pressures may lead to hemodynamic problems. In this case, ECMO was primarily a life-saving rescue, and secondary became lung and heart support until the patient was weaned off from ECMO to conventional ventilation support. Activation of a viral infection or opportunistic fungal infection due to immunosuppression cannot be ruled out as potentiating the problem.

In the present case, all conventional treatments had been tried including last resort pharmacotherapy rituximab. The argument to accept for ECMO treatment is a reversible cause, that is, come off ECMO alive, or bridge to transplant. Time for diagnosis may be considered in select cases. No hesitation exists concerning acceptance of GPA with lung bleeding, and this patient was believed to be “just another Wegener’s patient”. Day after diagnosis of BOOP-like GPA, the National lung transplant center was engaged not to lose time in such evaluation. Published results after lung transplant in GPA are scarce. There are doubts concerning transplantation in this patient group [20, 21], for example, mostly concerning healing capability of the anastomoses. From young age and human decency, the patient was not rejected by the transplant surgeon. However, the rheumatologist regarded the initial contact far too early from his experience that rituximab needed more time for evaluation, which showed to be true. If the ECMO question had been evoked later in course of disease, the risk of futility would have increased.

This patient is the only one receiving ECMO and the youngest BOOP-like GPA to be published. It is likely that future patients will be 40–60 years of age [8]. Considering such patient not responding to best treatment available, the poor transplant results, and age, chances for lung transplant are low. Thus, to avoid futile treatment, it is of great importance to discriminate the bleeding GPA of angiocentric type from the nonbleeding bronchiocentric type. In BOOP-like GPA refractory to treatment, albeit immunosuppressive therapy has been at its optimum for 4–5 months or more, lung transplant is probably the only way out, at least if the disease has progressed to need for ECMO.

Conclusions

ECMO has since decades been used for rescue treatment of GPA in case of lung bleeding as published in small numbers but repeatedly. Concerning the rare form BOOP-like GPA, no experience exists. The current case report illustrates that ECMO support may be beneficial in BOOP-like GPA, buying time for immunomodulation treatments to gain full effect. If reversibility of the airway component is not expected, or does not occur, lung transplant is probably the only option to avoid futility.

Unless the patient, already before the ECMO question arises, is accepted for bridge to transplant, it is very important to engage the lung transplant competence early in the course of illness to avoid futile ECMO treatment and unnecessary patient suffering.

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Disclosures

LMB is a member of the Advisory board of Eurosets Srl, Medolla, Italy.

Conflict of interest

None declared.

Authorship

LF: collected, analyzed, and interpreted the data, cowrote and critically revised the manuscript, and approved the final version for submission; LMB: designed the concept of the manuscript, collected, analyzed and interpreted the data, drafted the manuscript, and approved the final version for submission.

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