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Airway bleeding during extracorporeal membrane oxygenation treatment of covid-19 pneumonia: A case report

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Abstract

COVID-19 virus disseminates throughout the body but the host response to this infection is variable. Inflammation and coagulation are essential host defense mechanisms that protect from infection. When unregulated these processes can lead to profound end organ injury. Anticoagulation remains a standard for Extracorporeal Membrane Oxygenation (ECMO) support. However, bleeding complications are highly comorbid in ECMO patients. For ECMO-supported COVID-19 patients, invasive procedures like tracheostomy may also be required. Invasive procedures can compound ongoing bleeding complications during ECMO treatment like airway bleeding. Although the etiology of airway bleeding is broad, major life-threatening complications may go unrecognized.

Keywords: ECMO; ARDS; Mechanical intubation; Tracheostomy; Coagulopathy; Anticoagulation.

Abbreviations: ACE-2R: Angiotensin-Converting Enzyme 2 Receptor; ARDS: Acute Respiratory Distress Syndrome; BMI: Body Mass Index; BSA: Body Surface Area; COC: COVID-19 Coagulopathy; COVID-19: Severe, Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2); CT: Computed Tomography; ECMO: Extracorporeal Membrane Oxygenation; ELSO: The Extracorporeal Life Support Organization; HIT: Heparin-Induced Thrombocytopenia; ICU: Intensive Care Unit; MAPK: Mitogen Activated Protein Kinase; TIF: Tracheoinnominate Fistula.

Introduction

When respiratory demands are no longer met with mechanical ventilation, ECMO represents a last line of defense to prevent multisystem organ dysfunction. Early in the COVID-19 pandemic, utilization of ECMO support to treat medically refractory respiratory failure was associated with dismal outcomes [1]. Pooled analysis of all Chinese centers utilizing ECMO to treat medically refractory COVID-19 pneumonia demonstrated 94% mortality in March 2020, even greater than medical therapy alone. Despite early failures, by October 2020, ECMO had been utilized to treat more than 2708 cases of COVID-related ARDS, with greatest use in North America (1749 cases, 64.6%) and Europe (594 cases, 21.9%). Mean duration of ECMO support was 14.4 days. Frequent ECMO complications included renal failure (27%), intracranial hemorrhage (6%), and stroke (1%). Survival to hospital discharge was 53% (ELSO).

Inherent in ECMO therapy are the risks of bleeding and thrombosis. Patient-specific anticoagulation tactics must be weighted with pre-ECMO coagulation status of the patient, anticoagulant type, organ/drug metabolic deficits of the patient, frequency of anticoagulation monitoring, velocity of ECMO circuit flow, and the state of platelet inhibition/activation. These challenges are even greater in critically ill, COVID-19 patients requiring frequent invasive procedures. Bleeding, especially in-

volving the airway, during routine procedures like tracheostomy can be profound and difficult to manage. Written HIPAA authorization has been attained to report this unique case of airway bleeding.

Case description

Our 44 year old (30 kg/m^2 BMI, 1.9 m^2 BSA), male patient presented to the emergency department with 2 weeks of fever, sore throat, and body aches. He was admitted to the hospital, tested positive for COVID-19 virus, received oral steroids, full dose anticoagulation, empiric broad spectrum antibiotics, convalescent plasma, zinc with ascorbic acid, and Remdesevir. Despite this treatment, his respiratory status worsened, requiring ICU admission. On ICU day 7, he was intubated for hypoxia. Despite maximum ventilator settings, paralysis, and prone positioning, by day 5 of mechanical ventilation, the patient developed worsening hypercarbia (pCO_2 80s), hypoxemia (pO_2 50s), and acidosis. Therefore, we initiated Peripheral Venovenous (VV) Extracorporeal Membrane Oxygenation (ECMO). On day 5 of ECMO support, he experienced a precipitous decline in platelet count concerning for heparin induced thrombocytopenia. We transitioned his anticoagulation to Bivalrudin. This was well tolerated, with minimal interruptions in anticoagulation secondary to oozing around the mouth and cannulation sites. On ECMO day 17, after negative COVID-19 testing, the patient underwent uneventful percutaneous tracheostomy. Thereafter, intermittent bleeding from around the tracheostomy responded well to temporary discontinuation of anticoagulation. Unfortunately, eight days after tracheostomy placement, the patient developed sudden and massive hemorrhage from his tracheostomy. Rupture of a Tracheoinnominate Fistula (TIF) was evident. He rapidly exsanguinated and expired.

Discussion

Thrombotic and bleeding complications of COVID-19 infection are now well recognized [2-4]. Postmortem studies by Ackermann found a 9-fold higher incidence of alveolar capillary microthrombi in COVID-19 compared to Influenza deaths [2]. Al-Samkari and colleagues reviewed the rates of bleeding and thrombosis in 400 hospitalized COVID-19 patients, 144 admitted with critical illness [5]. Thrombotic complications were 9.5% and 18.1% respectively. Major bleeding occurred in 2.3% of hospitalized and 5.6% of critically ill patients. Risk factors included an elevated D-dimer >2500 ng/mL, platelet count >450 x 10^9/L, c-reactive protein >100 mg/L, and erythrocyte sedimentation rate >40 mm/h [5].

Hematopoietic derangements caused by COVID-19 are similar to, but also unique from known pathogenic causes of bleeding and thrombosis. COVID-19 Coagulopathy (COC) presents with laboratory values similar to other infection-induced inflammation [3]. Thromboembolism however is more frequent than sepsis-induced and disseminated intravascular coagulation [4]. Iba and colleagues have proposed one mechanism for COC may be through binding and inactivation of the Angiotensin-Converting Enzyme 2 Receptor (ACE-2R). Inactivation of ACE-2R, can lead to excessive levels of angiotensin II, reduced nitric oxide production, increased platelet aggregation, and subsequent vasoconstriction [4]. Manne et al suggest that platelet hyperreactivity, via to heightened MAPK pathway activation and thromboxane generation, is a second mechanisms of COVID-19 associated hypercoagulability. Platelets from COVID-19 patients more frequently aggregated with other inflammatory cells, aggregated faster, and had faster motility on fibrinogen and collagen matrices [6].

Early tracheostomy has been lauded for improved management of airway secretions, ventilator synchrony, and decreased sedation requirements [7]. During the COVID-19 pandemic however, concerns regarding staff exposure, patient isolation, and poor outcomes with mechanical ventilation caused the timing and performance of tracheostomy in critically ill COVID-19 patients to become obscure. Due to early reports of dismal survival for critically ill COVID-19 patients requiring tracheostomy, Chao et al. aimed to avoid tracheostomy in most patients intubated <21 days. Survival (30%) and ventilator liberation (56.6%) were consistent with other academic centers. Average time to decannulation was 16.6 +/- 5.0 days with 35.8% of patients requiring ongoing ventilatory support. Authors proposed that earlier tracheostomy correlated with faster ventilator liberation ($R2 = 0.138$; $p = 0.04$) [7]. Kon and colleagues have been more aggressive with early tracheostomy, particularly in those requiring ECMO support. This group studied 27 critically ill patients suffering from COVID-19 pneumonia supported with VV-ECMO [8]. Their patients spent ≤3 days mechanically ventilated prior to ECMO cannulation and underwent tracheostomy within 3 days of ECMO initiation. Time requiring mechanical ventilation post ECMO decannulation for survivors was 6 days. At the time of their report, their survival utilizing this approach was 96.3%, and no participating healthcare workers contracted the virus [8].

The American Academy of Otorhinolaryngology-Head and Neck Surgery published the first societal recommendations for tracheostomy during the COVID-19 pandemic. They proposed tracheostomy be performed as an open technique, >14 days from the time of intubation. The focus was to reduce infectious particle aerosolization and subsequent health care worker infection [9]. Months later, The American College of Chest Physicians, published their recommendations advocating for tracheostomy in patients in which long term mechanical support was expected. However, they confessed that it was "impossible" to provide specific guidance regarding the timing of tracheostomy in COVID-19 patients due to the lack of available COVID-19 tracheostomy evidence, conflicting data concerning early versus late tracheostomy in medical ICUs, and unique health care worker risks specific to COVID-19 [10].

The etiology of airway bleeding in critically ill patients can be multifactorial. Critically ill patients undergo serial orogastric and airway interventions that can lead to soft tissue trauma and subsequent bleeding. Seemingly insignificant mechanical trauma can lead to frank bleeding in patients who are already anticoagulated and/or coagulopathic due to their critical illness. Aside from trauma, the differential diagnosis for airway bleeding in these patients is broad; including pneumonia, lung cancer, mycotic infections like tuberculosis, and bronchiectasis. For critically ill patients, who receive tracheostomies to support chronic respiratory failure there is a high risk (40-50%) of complications [11]. These complications include bleeding, infection, extratracheal air, tracheal stenosis, decannulation/malposition, and fistula formation. Only ~1% of tracheostomies lead to a catastrophic events like TIF, as experienced in our patient, but half

of these events result in death [11].

Major bleeding incidence during VV-ECMO support is variable [12]. Sklar and colleagues performed a large meta-analysis of 18 studies including 646 patients receiving VV-ECMO support for acute respiratory failure. Major bleeding rates varied from 8-56% (average 16%). Authors acknowledged that the incidence of bleeding and strategy of anticoagulation must be weighed against thrombosis risk, which averaged 53% in their review [12]. While unfractionated heparin is the mainstay of antithrombic therapy during ECMO, risks of developing HIT are high, and other anticoagulants including Bivalrudin yield similar outcomes in bleeding and thrombosis.

TIFs are rare, life threatening emergencies. The incidence of TIF after percutaneous tracheostomy is 0.1-1.0% with peak incidence between 3-42 days. Sentinel bleeding occurs in more than 50% of cases [13]. Flexible bronchoscopy and/or CT angiographic imaging are key first steps in investigating hemoptysis or bleeding around a tracheostomy site. Temporizing maneuvers during massive airway bleeding include over inflating the tracheostomy cuff or digital compression through the stoma with subsequent endotracheal intubation [14]. Surgically, once proximal and distal control of the innominate artery is attained, the injury can be primarily repaired, patched, or the innominate artery can be ligated with subsequent right carotid-subclavian by pass. The arterial wall of the TIF is left in situ on the anterior wall of the trachea to assist with primary tracheal repair.Surgical repair provides a 25-50% survival rate during an otherwise fatal event [15].

Endovascular repair represents a valuable alternative for TIF repair. Recently, Taechariyakul et al. performed a pooled cohort analysis of 261 patients from 137 published case reports comparing surgical versus endovascular repair of TIF. They found only 12.6% of cases were treated endovascularly, all cases reportedafter the year 2000. However, their data show that a percutaneous approach was associated with lower procedural complications (30 v 50%) and 30-day mortality (9 v 23%) [15]. Complications of endovascular were few, but included endograft infection, stent graft failure leading to rebleeding, and tracheal erosion by the stent graft.

Conclusion

In conclusion, an overactive host response and virally mediated coagulopathy are key elements in COVID-19 pathology. These aberrant host defense mechanisms are poorly understood and represent an emerging area of research interest. Airway bleeding in ECMO-supported COVID-19 patients can be multifactorial. Etiologies of airway bleeding should always be investigated, because, for patients like ours, the window for management can be limited.

Declarations

Conflicts of interest/disclosures: None.

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HIPPA: Written HIPPA authorization has been obtained.

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