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Mini Review

An Unusual Etiology for Adult Acute Respiratory Distress Syndrome: Botulinum Toxin Type A

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ABSTRACT

Acute Respiratory Distress Syndrome (ARDS), which is seen in adults and can also be referred to as noncardiogenic pulmonary edema, is a life-threatening complication that is treated with intubation and positive pressure ventilation. It usually occurs in association with various conditions such as pneumonia, aspiration, major trauma, and sepsis. There is a permanent hypoxemia that does not respond to support with an oxygen mask, and since there is an absolute need for intensive care, its main management in the acute period is done in intensive care. Possible etiologies include recent surgery, acute pancreatitis, transfusion with blood products, cases of drowning and smoke inhalation, neurogenic edema, and overdose to some drugs and chemicals. However, a recent case where a patient with Central Pontine Myelinolysis (CPM) developed ARDS after an adequate dose of Botulinum Neurotoxin Type A (BoNTA) application to the gastrocnemius muscle group for spasticity management, suggests a possible new factor in ARDS's etiological framework. The issue of osmotic imbalance is also noted in different organ regions that intersect the paths of CPM and ARDS through BonTA. BoNTA-associated pulmonary interstitial complication, which is first reported recently in the literature, deserves further examination.

Keywords: Pulmonary edema; Congestive heart failure; Central pontine myelinolysis; Osmotic balance; Capillary endothelial damage; White lung; Spasticity; Aesthetics; Onabotulinum toxin type A

INTRODUCTION

First described in 1967, Acute Respiratory Distress Syndrome (ARDS) is an acute disease that begins within hours of a triggering event and is characterized by bilateral pulmonary infiltration and severe progressive hypoxemia without any evidence of cardiogenic pulmonary edema [1]. ARDS, in which hypercapnia and tachypnea are also observed, is an acute, widespread, inflammatory form of lung damage and is life-threatening. At the microscopic level, the disease is associated with capillary endothelial damage and diffuse alveolar damage. The marked decrease in lung compliance seen in adults with ARDS is similar to that seen in preterm infants. It can often be diagnosed using ultrasound and pulse oximetry in limited-resource environments. Although ARDS has a somewhat different appearance than congestive heart failure in that the opacity is much more prominent in the typical x-ray image, hence being described as "white lung", the distinction is not easy and the main distinction is clinical [2]. Pathological samples from patients with ARDS often reveal widespread alveolar damage. Laboratory studies have shown that both alveolar epithelial and lung endothelial damage results in the accumulation of protein-rich inflammatory edema fluid in the alveolar space [3].

Using ultrasonography, a practical diagnostic device, when making differential diagnosis is frequently preferred by physicians today. As a result of echocardiography, especially if the ejection fraction is at a normal level, cardiac etiology can be more easily ruled out [2,4]. When sudden and permanent hypoxia develops especially in neurologically disabled patients with predisposing factors, it is also important to make differential diagnoses such as infective pneumonia and aspiration pneumonia by primary physicians and infection and chest diseases consultants. In this sense, possible predisposing factors that may lead to ARDS such

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as whether the patient has neurological and immunosuppressive diagnoses, or whether there may be uncontrolled use of drugs that may cause endothelial damage should be carefully examined. Treatment focuses on lung-protective ventilation and no specific pharmacotherapy has been identified. Diagnosis of ARDS depends solely on clinical criteria because it is impractical to obtain direct measurements of lung damage with pathological samples of lung tissue in most patients. Additionally, blood samples are insufficient to diagnose ARDS [5].

LITERATURE REVIEW

The LUNG-SAFE study in 2014, in which 30 thousand patients from different countries were cross sectionally analyzed, provided valuable epidemiological data. In this study, the prevalence of ARDS in intensive care patients was found to be 10%, and ARDS was detected in 23% of all ventilated patients [6]. A follow-up analysis of the same study determined that 21% of patients with ARDS in the study were immunocompromised and that hospital mortality in these patients was much higher than in non immunocompromised patients. It also revealed that clinicians' recognition of ARDS was low. That is, this study confirmed that ARDS is common in critically ill patients, yet it remains underrecognized and undertreated [7]. Various exposures and comorbidities, including alcohol, smoking, air pollution, hypoalbuminemia, and the presence of traumatic brain injury, have been associated with increased susceptibility to ARDS [5].

Central Pontine Myelinolysis (CPM) is a neurological disorder resulting in loss of myelin in the pons and basal ganglia of the brain, its lateral geniculate bodies, external and internal capsules and cerebellum. CPM is known as the most common clinical presentation of osmotic demyelination syndrome seen after rapid correction of hyponatremia [8]. It has also been shown to rarely develop in hyperosmolar conditions and some electrolyte disorders, even without hyponatremia. Diagnosis is made by characteristic symptoms and cerebral magnetic resonance imaging, where hyperintense areas are seen on T2-weighted images. Outcome varies, mortality is high, and most survivors have some degree of neurological deficit [9,10].

In a recently published case study, a CPM patient who received 300 International Units (IU) of Botulinum Neurotoxin Type A (BoNTA) to the spastic muscles of the calf group to improve gait pattern, has been reported to develop ARDS on the 3rd day after the application of BoNTA [11]. BoNTA blocks the release of the neurotransmitter acetylcholine, preventing its transmission at the neuromuscular junction and resulting in partial and temporary paralysis of the target muscle. Therefore, BoNTA injection reduces unwanted muscle activities and muscle tension. It is a neurotoxin used frequently and safely by physiatrists and neurologists, especially in the management of spasticity and dystonia [12]. The fact that a possibly fatal complication, ARDS, has been encountered with BoNTA raises a serious concern, particularly considering that BoNTA has been widely used for also aesthetic applications including in many developing countries, presence of many under-the-counter products with non-original molecules, possible application of BoNTA by unqualified practitioners, and the fact that even when performed within the medico-legal framework it may lead to temporary and regional complications such as ptosis [11,13]. For this reason, in the etiology of ARDS, the use of BoNTA, whose use has increased tremendously in recent years for reasons such as aesthetic applications, spasticity, dystonia and painful muscle spasm management, should now be considered. The issue of osmotic imbalance in different organ regions that intersects the paths of CPM and ARDS through BonTA is noteworthy. BoNTA-associated pulmonary interstitial complication, which is the first in the literature, deserves further examination.

DISCUSSION

In ARDS, fluid and protein permeability increases along the lung endothelium, leading to edema in the lung interstitium. The edematous fluid then migrates towards the alveoli, which usually occurs as a result of damage to the normally tight barrier properties of the alveolar epithelium [2,3]. Increased alveolar-capillary permeability to fluid, proteins, neutrophils, and red blood cells is the hallmark of ARDS. Arterial hypoxemia in patients with ARDS is caused particularly by ventilation-perfusion mismatch. Additionally, impaired carbon dioxide excretion is an important component of respiratory failure [5]. Endothelial damage is the key to the source of pathology here. Endothelial disruption can be caused by a wide variety of pathogens and their toxins. This primary damage is inevitably exacerbated by a secondary wave of inflammatory damage. Epithelium can be directly damaged by mechanical forces, for example, bacterial products, viruses, acid, oxygen toxicity, hypoxia, and ventilator-associated lung damage. It may also be damaged by inflammatory cells or their products, as in sepsis and pancreatitis. The extent of epithelial damage is an important determinant of the severity of ARDS. In addition, epithelial cell death, either apoptotic or necrotic, is a characteristic feature of alveolar damage in ARDS. This may similarly be caused by lytic viral infections, bacterial toxins, acid, hypoxia, hyperoxia and mechanical stress [2-5].

When we look at the literature, it is possible to come across some data, albeit sporadic, regarding pulmonary complications due to BoNTA. First of all, in April 2009, the FDA mandated a warning stating "Warning: Distant Spread Of Toxin Effect" on all botulinum toxin products. The most frequently reported toxin-related adverse event is muscle weakness beyond the injection site [14]. However, specific toxin-associated risk factors remain unclear. In 2018, a refractory migraine patient with immunosuppressive predisposition has developed worsened lung function in the 6th month of a 150 IU BoNTA application to be administered every 3 months for 24 months. The patient's respiratory function has been documented to improve again within 6 months of discontinuing BoNTA [15]. Although this effect is not a direct pulmonary interstitial effect, it is important in that it is a systemic complication that causes deep respiratory weakness in the person by affecting the respiratory muscles with the spread of the toxin to the distant region. In animal experiments conducted in the 1990s, widespread endothelial weakening was observed in electron microscopic examination of rabbit lungs poisoned with botulinum toxin c2, and pulmonary

edema formation was detected in pulmonary capillaries due to severely increased permeability [16,17]. In a mice study evaluating intranasally administered BoNTA-related pulmonary effects, some histopathological changes were detected in their lungs, even though the animals were protected against neurotoxic effects. Although this effect is not direct toxin poisoning, it has been interpreted as a cytokine-mediated inflammatory reaction triggered by the toxin. Due to pulmonary capillary endothelial damage, which is likely a result of this reaction, blood cell and protein migration into the alveolar area occurred, resulting in interstitial edema [18]. Just like this, the acute phase of ARDS is associated with widespread alveolar damage and lung capillary endothelial damage. White blood cells stick to the pulmonary capillaries and poke holes through the basal membrane. Thus, large plasma proteins such as albumin escape into the interstitial fluid, disrupting the osmotic balance in the Starling hypothesis. The disrupted balance triggers widespread pulmonary edema extending to the alveoli, reducing both gas exchange and lung compliance. Ground glass densities observed in patients' x-ray and thorax computed tomography images are the clear results of this pathophysiology that can be observed on radiography. However, the sequential mechanism of metabolic and immunological events that encourage cells to attack lung capillary and epithelial regions is still not adequately explained [2].

Considering the case report highlighted in this article, in cases where patients develop unexplained ARDS, one should also now bring to mind whether the patient has any recent history of interventional BoNTA [11]. The issue of treatment is still far from going beyond supportive treatments. According to an article published in the journal Nature Reviews Disease Primers in 2019, neuromuscular blockade can reduce mechanical lung damage in patients who develop ARDS [5]. In a multicenter study in patients with severe ARDS, 48-hour infusion of the neuromuscular blocking drug cisatracurium increased survival and ventilator-free days compared with isolated deep sedation without cisatracurium [5,19]. Because of the high respiratory drive, patients with ARDS on respiratory support often exhibit strong respiratory effort even while receiving high doses of sedatives. This respiratory effort may lead to serious patient-ventilator asynchrony and increased mechanical lung damage due to high transpulmonary pressures and/or cyclic atelectasis. If one speculates about the positive contribution of neuromuscular blockade to the treatment of ARDS mentioned in this review, some supporting examples from the case report highlighted in this article can be provided. In the case report [11], the patient who developed ARDS on the 3rd day after BoNTA and very quickly (within hours) required intubation, has also recovered very quickly and fully with the need for ventilation decreasing within days. We can potentially interpret this as BoNTA contributing to rapid treatment by compensating its direct pulmonary interstitial catastrophic effect with its neuromuscular blockade effect on the respiratory muscles. This, of course, is an unexpected and somewhat speculative inference. However, it was also unexpected that such a therapeutic drug, which has been proven all over the world for years and is considered very safe, despite being toxin-based, would lead to ARDS. Meanwhile, rapid improvement and quick recovery of the patient and her ventilation need might also be due to milder damaging effect of BonTA on the pulmonary capillary endothelium compared to other ARDS triggers in this vulnerable CPM patient. After all, despite being the most potent toxin, BonTA has been used safely for years and has been further developed over time, and has also reduced the protein-containing allergenic substances in its content, making it possible for BonTA to be applied in highly purified and crystalline form [20].

It is important to underline that the case highlighted in this article involves a patient with neurological disorder (CPM) who had a history of being intubated due to respiratory difficulty, who in turn could be considered more prone to ARDS compared to other individuals [11]. It is interesting to note that the osmotic balance disorder developed in CPM leading to catastrophic effects in the central nervous system is akin to the deterioration in osmotic balance seen in the pulmonary capillary and interstitial area in ARDS, although the affected areas are in different locations in different organs. This brings the two syndromes, whose paths intersect through BonTA, to a more interesting point [2-5,8-10]. While we cannot provide conclusive evidence, we also note, with our many years of clinical experience, that no complications have been observed in the BonTA applications we performed for spasticity management on patients diagnosed with traumatic brain injury who have a history of intubation and stayed in intensive care for very long periods of time, but did not have a CPM-like etiology.

CONCLUSION

When determining patient groups to be avoided for BoNTA applications, individuals with tracheostomy, respiratory muscle weakness or difficulty in breathing, those with allergic predispositions and immunosuppression have usually been considered. A particular concern is distant muscle involvement as a result of systemic retrograde spreads. However, one of the toxin's potential unknown implications could be possible pulmonary capillary endothelial damage resulting in ARDS, a fatal complication. This presentation of noncardiogenic pulmonary edema should be taken into account at least as much as other etiologies, especially in vulnerable patients such as CPM.

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