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Refractory Hypoxic Respiratory Failure in a Pseudo Cyanotic COVID-19 Patient with Argyria Due to Chronic Colloidal Silver Supplement.

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Abstract

***Objective**: Unusual clinical course*

***MeSH Keywords**: Argyria, hypoxemia, endotracheal intubation, Silver, ARDS, Melanin, COVID-19, Human, dietary supplement, cyanosis, hypoxemia, Pseudocyanosis, Heavy metal poisoning, blue man.*

Background:

Argyria is rare skin disease caused by cutaneous deposition of silver granules on the skin, due to chronic consumption or contact with silver salts. It is characterized by a blue – gray discoloring that can occur on the skin and mucous membranes. Skin biopsy confirms the diagnosis by demonstrating tiny brownish granules in connective tissue surrounding sebaceous glands, in perineural tissue and in arteriolar walls. Pigmentation is permanent but benign, causing only an aesthetic concern. This is a very rare condition as use of silver compounds and work exposure in the manufacturing process of silver has increased regulations to protect workers. The discoloration can become permanent due to the changes in melanin, the grey blue discoloration becomes permanent and predominates on sun exposed areas. This passive photosensitivity reaction leads to silver tattooing of the light-exposed skin. It is believed that silver compounds form complexes with proteins in the skin which reduce to elemental silver when exposed to light, similar to the process of photo imaging. There is no definite therapy for this condition. Chelating agents have no role in removing the silver, although laser therapy seems to be an emerging treatment option with limited improvement.

This bluish coloration of the nail beds and skin can be the same presentation as cyanosis. Fortunately, this condition is becoming rare as medications containing silver are not widely used and when used it is for short period of time. The cases keep decreasing and the number of patients with this form of pseudocyanosis continues to decline worldwide. Other conditions that can cause pseudocyanosis include methemoglobinemia, medication induced such as Amiodarone, Minocycline and antimalarial medications, hemosiderosis, Wilson disease, heavy metal ingestion of mercury and gold.

When these patients present with COVID-19 and have profound hypoxemia due to reduced oxygen transport. The bluish coloration in combination with the deposits of silver in the tissues can affect oxygen transport and cause severe hypoxemia and low saturations.

We report a case of a COVID-19 patient's presentation with Acute Hypoxemic respiratory failure and refractive hypoxemia argyria. We treated the patient with, Remdesivir and dexamethasone standard COVID therapy at the time this case was written. We intubated the patient, used ARDS Net protocol of low tidal volume and high peep with sedation protocol, roto prone and paralytics due to ventilator desynchrony with plateau pressures of equal or less than 30 mmHg. Patient was noticed to have a bluish discoloration of the skin as noted in figure 1. He was blue prior to intubation and had low saturations in the 75%. Despite, mechanical resuscitation, peep, prone ventilation and paralytics the oxygenation did not improved and after 48 hours of refractory hypoxemia the family decided the patient be let go.

Results

54-year-old male presented to the emergency room after practicing social distancing due to COVID-19. The patient complaints, of cough, fever, and progressive SOB for the past one week. Patient did not get vaccinated. Patient was living in an endemic area with high numbers of COVID-19 Delta variant. Patient was seen in the Emergency Room, increased oxygen requirements and low saturations of 85% that corrected with supplemental oxygen 5 liters to 75%. PCR confirmed the diagnoses of COVID-19. Chest Radiograph reveals bilateral ground glass opacities, Figure 2. Despite initiation of steroids, remdesivir and antibiotics. His overall condition continued to get worse. A chest tomography Angiogram of the chest was ordered that showed ground grass opacifies with no evidence of pulmonary embolism. The WBC was 12 x10 3. , Beta Natriuretic Peptide of 75pg./ML, ferritin of 3214 ng/L and a D dimer > 4.0 the rest of the chemistries and liver functions were initially normal. Patient was tachycardic and despite further fluids and oxygen he required mechanical intubation. Patient was placed on the ventilator to assist with respiratory needs, he was in shock, hypotensive and hypoxic. His initial mechanical ventilation settings were Assist control mode 16 with a peep of 10 and 100% of oxygen. His arterial blood gas was 7.13, pCO2 53 po2 37 %. Saturation of 75% The peep was titrated to 20, patient was paralyzed with rocuronium and subsequently prone on a roto prone high PEEP low tidal volume and plateau or 30 his PO2 improved to 139. Patient also required norepinephrine at 30 mcg/min and vasopressin infusion. Overnight saturation did not improve and over the next 48 hours, his chest radiograph remained with bilateral alveolar patched areas of consolidation. Saturations never improved above 75% , due to lack of clinical improvement the family decided on compassionate extubation and palliative care was best.

MeSH Keywords: Argyria, hypoxemia, endotracheal intubation, Silver, ARDS, COVID-19 Cyanosis, hypoxemia, Pseudocyanosis, blue man, heavy metal toxicity.

Figure 1. Chest Radiograph demonstrated bilateral opacities with bilateral infiltrates significant for acute respiratory syndrome (ARDS) due to Corona virus 2019 Disease.

Figure 2. Cyanotic patient in Respiratory failure, noticed color go the skin, and cyanosis despite 100 percent oxygen and PEEP therapy with Mechanical Ventilation.

Discussion

COVI-19 causes severe hypoxemia due to severe VQ mismatches patients with argyria may have pseudocyanosis and because the condition is rare, identified by history it is important not to be confused with true cyanosis from medications, other toxins and true hypoxia.

Hypoxia is defined as a drop in partial pressure of oxygen in the arterial blood. This occurred when PaO2 is less than 80 mmHG breathing air at sea level. The value of PaO2 falls with age according to the following equation PaO2 = 103.5 – (.42 x age). This measurement will vary according to elevation and mixture of gases. Tissue oxygen depends on the interaction of three factors; the blood oxygen content, determined by PaO2 and Hemoglobin. Blood flood to the tissues and consumption of tissue oxygen which depends on metabolic activity. Patients with COVID-19, have poor extraction of oxygen which lower PaO2 content and may also have increased metabolic consumption from secondary infections and sepsis. In this case this patient also had ARDS and chronic skin discoloration from chronic silver deposition given a cyanotic presentation which is not a direct cause of demise but definitely a unique presentation of Hypoxic respiratory failure due to COVID-19.

			PaO_2	
Mechanism	**Most frequent causes**	**$PaCO_2$**	**Exercise**	**FIO_2 100%**
FIO_2 decrease	• Altitude	Low	No significant changes	Correction (> 500mm Hg)
Alveolar hypoventilation	• Depression of the respiratory center • Spinal cord injury • Neuromuscular Disease • Obstructive lung diseases	High	Variable	Correction (> 500 mm Hg) with risk of PaO_2 increase
Disruption of diffusion	• Interstitial diseases • Pulmonary edema	Normal or low	Sharp decrease	Correction (> 500mm Hg)

Right-left short circuit (shunt)	• Anatomical
	  ○ Congenital heart disease
	  ○ Pulmonary AV fistulas
	• Functional
	  ○ Atelectasia
	  ○ Consolidation
		Normal or low	Generally decreases	Partial improvement (<500 mm Hg)

Ventilation-perfusion irregularities	• All kinds of bronchopulmonary disease	Normal or low	Generally decreases	Correction (> 500mm Hg)
PvO_2 decrease	• Low minute volume • Increased tissue consumption • Coexistence with lung disease	According to existing lung pathology	Decrease	Correction (> 500 mm Hg) according to lung pathology

The mechanisms of hypoxemia production under various clinical conditions and the means of differentiating them are summarized in **Table 1**

1) Decrease in inspired oxygen pressure.

2) Alveolar hypoventilation.

3) Alterations in diffusion

4) Short circuit from right to left ("shunt").

5) Irregularities of ventilation-perfusion.

6) Decreased O2 content in venous blood.

Clinical signs of hypoxemia and hypoxia. Cyanosis vs Pseudocyanosis.

Cyanosis has been considered for many years as the classic semiological sign that indicates the decrease in the level of O2 in the blood and /or tissues. The term cyanosis (from "kyanos" = blue) defines the bluish coloration of the skin and mucosa and is seen earlier in those places where the skin is thinner or where there is an abundant capillary network, such as the tongue, lips, nails, pinnae, cheeks, and nose. Cyanosis responds to the presence of reduced hemoglobin in the blood, the color of which is purple red in contrast to the bright red of oxyhemoglobin.

Cyanosis is evident when the blood flowing through the capillaries contains more than 5 g of reduced Hb per 100 ml (normally there are 0.70 - 0.75 g reduced Hb in 100 ml of arterial blood). However, the presence of cyanosis is not an early sign of hypoxemia or hypoxia. The possibility of appreciating it is influenced by the subjective impression of the observer, as well as by the pigmentation and thickness of the skin, the state of the capillary bed and even by ambient light. The existence of anemia masks its presence (there is not enough Hb to reach 5 g of reduced Hb), while the capillary plethora associated with polycythemia can simulate cyanosis.

Unfortunately, cyanosis can only be clearly recognized when O2 saturation in arterial blood is less than 75%, that is, a Pa02 of approximately 50 mm Hg, which implies marked hypoxemia. Therefore, it can be affirmed that cyanosis is not an early indicator of the provision of 02 to the tissues and that its detection is a rather late sign of a hypoxemia whose magnitude is severe, with milder degrees previously that go unnoticed. That is why the absence of cyanosis should not be interpreted in any case as a sign of adequate blood oxygenation.

Conclusion

Argyria is a unique form of pseudocyanosis. In case of an emergency the bluish discoloration alone without history in the presence of COVID-19 may not be the direct cause of hypoxemia. Fortunately, the use of colloidal silver substances have been banned in the United States but the presentation of the skin in this patient with Acute hypoxic respiratory failure is a reminder that in the world of a pandemia evolving into an endemia we need to be aware of argyria as form of pseudocyesis which may not be the direct cause of death but a concomitant presentation of and old chronic condition with a new viral infection.

As intensivist and respirology's is important to keep in mind the differential diagnoses of hypoxemia and a confirm clinical presentation and the skin examination in content with laboratory data and the patient's personal and work history.

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