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Platypnea-orthodeoxia syndrome as a consequence of SARS-CoV-2 pneumonia: an uncommon case of dyspnea

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ABSTRACT:

— ***Introduction:*** Platypnea-orthodeoxia syndrome (POS) is a rare syndrome characterized by dyspnea and arterial oxyhemoglobin desaturation induced by moving to the upright position and relieved by recumbency. Different pathogenic processes can lead to POS including cardiopulmonary and hepatopulmonary disorders.

— ***Case presentation:*** We here present an unusual case of POS triggered by a previous severe SARS-CoV-2 pneumonia in a 66-year-old man admitted to our Emergency Department with worsening dyspnea and chest pain.

— ***Conclusions:*** SARS-CoV-2 pneumonia should be considered an emerging cause of POS because of its pulmonary and cardiac/intravascular pathological implications.

— ***Keywords:*** Platypnea-orthodeoxia syndrome, SARS-CoV-2, Dyspnea, Interstitial lung disease, Patent foramen ovale (PFO).

INTRODUCTION

Platypnea-orthodeoxia syndrome (POS) is a rare clinical entity characterized by positional dyspnea (platypnea) and arterial desaturation in the upright position (orthodeoxia). Different pathogenic processes can lead to POS including cardiopulmonary and hepatopulmonary disorders[1]. The decrease in oxygen saturation is considered significant when PaO_2 falls greater than 4 mmHg or SpO_2 greater than 5% from supine to upright position[2]. Its true prevalence is unknown[2]. The first case of POS was reported in 1949, in a patient with post-traumatic intrathoracic arteriovenous shunt[3]. „Platypnea" and „orthodeoxia" are terms that were later coined by Altman et al[4] (1969) and Robin et al[5] (1978) reporting patients with POS resulting from liver and lung disease. The first description of a patient with POS from intracardiac shunt dates back to 1984: the orthostatic accentuation of hypoxemia in the absence of hepatopulmonary dysfunction or elevated right heart pressure has been described by Seward et al[6]. Causes of POS are classified into intracardiac abnormalities, extracardiac abnormalities, and various etiologies. Intracardiac communication between the two atria is the most common cause of POS, accounting for nearly 87% of all patients[2]. A PFO was the most common reported site followed by interatrial septal defect (ASD) and atrial septal aneurysm (ASA). Extracardiac causes of POS include interstitial lung disease (ILD) (4%) and intrapulmonary arteriovenous malformations (9%). The latter are found in the hepatopulmonary syndrome where acquired pulmonary arteriovenous fistulas arise from liver disease allowing the necessary right-left shunting[7]. Association of POS with ILD has rarely been reported[8,9]. Parenchymal lung disease with preferential involvement of the lung bases may present as POS through severe ventilation/perfusion (V/Q) mismatch. The upright position determines orthodeoxia as deoxygenated blood corresponds to fibrotic areas of the lung bringing to a physiological shunt. We here present an unusual case of POS triggered by a previous severe SARS-CoV-2 pneumonia with a fibrotic evolution.

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CASE PRESENTATION

A 66-year-old man was admitted to our Emergency Department with worsening dyspnea and chest pain. His medical history included stage IV renal failure (GFR 20 ml/min according to Cockroft-Gault equation), kidney lithiasis, arterial hypertension and cigarette smoking (20 pack-years). Six months earlier, he developed SARS-CoV-2 infection complicated by interstitial pneumonia with acute respiratory distress syndrome (ARDS) requiring oro-tracheal intubation and best evidence based therapy. The original hospitalization from SARS-CoV-2 infection was complicated by worsening renal function, requiring hemodialysis treatment, pericardial effusion, multiple septic episodes caused by multidrug-resistant *Staphylococcus epidermidis*, *Candida parapsilosis*, *Pseudomonas aeruginosa*, and *multifactorial anemia*.

His arterial blood gas (ABG) analysis in ambient air showed PaO_2 35 mmHg, $PaCO_2$ 25 mmHg, and pH 7.53. The lactate level was 1.4 mmol/l. Electrocardiogram (ECG) showed a sinus rhythm (90 bpm), first degree atrioventricular block (PR 0.24 sec) with nonspecific repolarization abnormalities. Blood tests confirmed a chronic kidney disease (CKD) (creatinine 3 mg/dl) with an increase of D-Dimer (1,379 ng/ml, range 0-500), NT-proBNP (6,725 pg/ml, range 0-125) and troponin (502 pg/ml, range 0-57). The latter showed substantial stability among the following controls (316 pg/ml-342 pg/ml-361 pg/ml). White blood cells (WBC) and C-reactive protein (CRP) values were unremarkable (7,250 WBC/cc with 68% neutrophils, 18% lymphocytes; CRP 0.4 mg/dl-normal value <0.5 mg/dl). Procalcitonin was in normal range (0.04 ng/ml-normal value <0.05 ng/ml). SARS-CoV-2 swab resulted negative. Transthoracic echocardiography showed a left ventricle normal both in dimensions and ejection fraction (EF 50%) with overt septal dyskinesia. The right heart ultrasound window pointed out a global hypokinesia involving the distal septum. Enlargement of the aortic root and ascending aorta (54 mm and 47 mm, respectively) was noted with an organized pericardial effusion around the right sections (20 mm maximum, unchanged from the previous examination).

A chest contrast-enhanced computed tomography (CT) scan excluded pulmonary embolism, highlighting a peripheral ground-glass disease of both lungs with a moderate amount of pleural effusion of the left lung with focal consolidations in the lower and upper lobe of the right lung (Figure 1).

Chest ultrasound was also carried out, displaying diaphragmatic hypofunction (end-expiratory thickness values of 0.16 cm left and 0.18 cm right) secondary to prolonged hospitalization, corticosteroid therapy, intercurrent infections, and protein-calorie malnutrition (PCM).

Our patient was treated with oxygen therapy combined with noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC). Parenteral nutritional support was initiated. Twelve days after admission, the patient's condition showed improvement requiring lower-flow oxygen

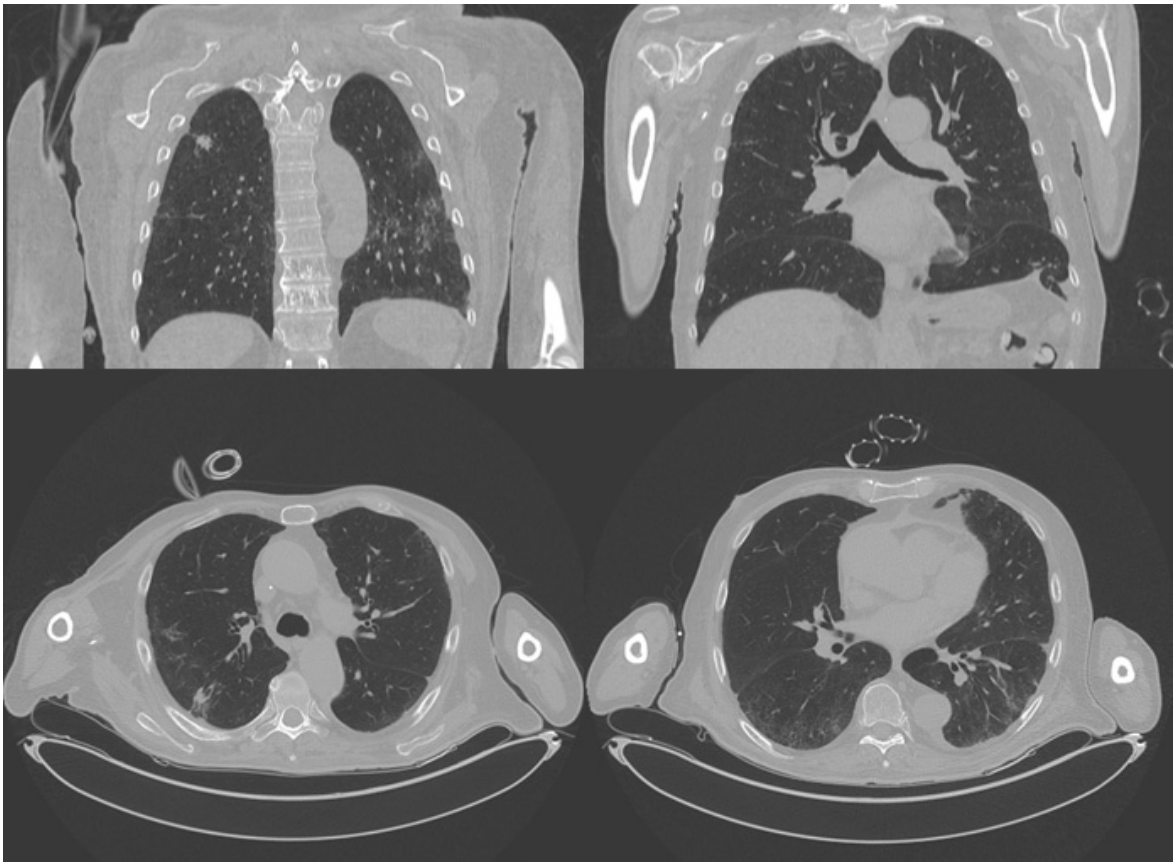

Figure 1. HRCT scan images (axial and coronal): peripheral ground-glass disease of both lungs with moderate amount of pleural effusion of the left lung with focal consolidations in the lower and upper lobe of the right lung.

therapy. ABG analysis showed: PaO_2 75 mmHg, $PaCO_2$ 27 mmHg, pH 7.43, SpO_2 96% (FiO_2 0.31 with standard nasal cannula). Over the next few days, while attempting to acquire a sitting position, the patient developed dyspnea with SpO_2 of 82% (FiO_2 0.31) and transient hyposthenia of the left hemisome, which progressively normalized over the next 3 hours. He underwent an urgent CT scan of the brain that excluded acute neurological events.

Similar events occurred on subsequent days trying to change from supine to sitting position, with improvement in SpO_2 after recumbency. A color-Doppler ultrasound (CDUS) of the epiaortic vessels excluded carotid stenosis confirming a regular orthodromic vertebral flow. A high resolution lung CT scan (HRCT) showed stability of the previous findings as probable fibrotic evolution following SARS-CoV-2 pneumonia. A POS was therefore suspected and investigated with agitated saline contrast echocardiography that detected a patent foramen ovale (PFO) responsible for the right-to-left intracardiac shunt (Figure 2).

The patient thus underwent endovascular closure of the PFO resulting in remarkable improvement of the respiratory situation. As a matter of fact, no further episodes of dyspnea and desaturation occurred, and one week after the procedure, he was able to maintain a SpO_2 of 97% on room air. The patient was then transferred to a rehabilitation ward to complete his course, at the end of which he was discharged home without further complications.

DISCUSSION

Different pathogenic processes can lead to POS, including cardiac, pulmonary and hepatic disorders. SARS-CoV-2 infection may be an emergent cause of POS. Several cases of POS triggered by COVID-19 are reported in literature, the majority characterized by pulmonary fibrosis as the "culprit" of the syndrome, with intrapulmonary arteriovenous shunt and new-onset intracardiac defects being far less common[10]. In our patient the remarkable clinical improvement after endovascular closure of the PFO indicates the intracardiac disturbance as the main cause of POS, although he developed, as well, an interstitial-fibrotic lung in the sub-mantle areas. Mechanical ventilation, especially in ARDS, may determine a stretch of the pulmonary vascular system and the right ventricle, reversing the interatrial pressure gradient, leading to the opening of the foramen ovale and a right-to-left shunt[11,12].

The prevalence of PFO ranges between 16% to 19% in ARDS patients[13-15]. A PFO shunt is associated with a decreased effectiveness of positive end-expiratory pressure (PEEP) titration in improving oxygenation, a greater use of adjunctive interventions, weaning difficulties from mechanical ventilation and longer permanence in the intensive care unit[15].

In line with the current literature, we strongly believe that the combination of pulmonary SARS-CoV-2 infection associated with increased pulmonary artery pressure, activation of coagulation, and supine or prone positioning during mechanical ventilation, may explain the increased right atrial pressure, leading to refractory hypoxemia with a paradoxical embolism due to intracardiac shunting[16-18]. In our case, the prompt recognition of a PFO and it's surgical correction led to a definite, stabile clinical improvement. Considering that endovascular treatments are curative in the majority of intracardiac abnormalities (i.e., PFO), clinicians should always consider, in their diagnostic and therapeutic algorithm, an eventual contrast-enhanced echocardiography associated to the standard pulmonary imaging, especially when oxyhemoglobin desaturation is detected with postural changes.

CONCLUSIONS

COVID-19 pneumonia should be considered an emerging cause of POS because of its pulmonary (frequent) and cardiac/intravascular (uncommon, but notable) pathological implications. Cardiovascular *sequelae*

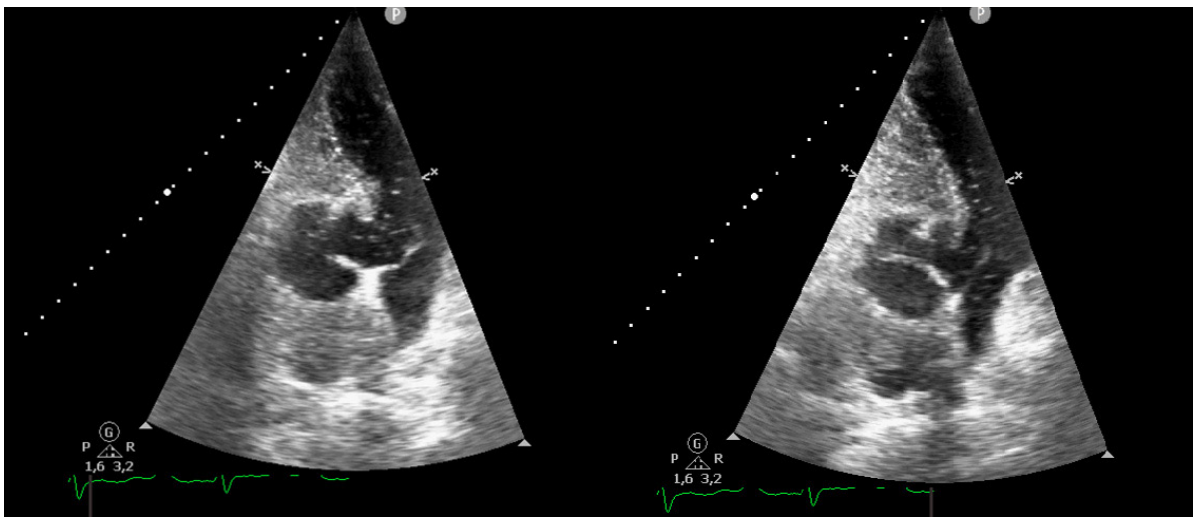

Figure 2. Agitated saline-contrast echocardiography showing a patent foramen ovale (PFO) responsible for the right-to-left intracardiac shunt.

emerged with the global pandemic of the last two years are diverging from the data reported in the literature of the past decades: Agrawal et al[2], reviewing the scientific data from 1949 to 2016 found only 31 cases of pulmonary POS (9 with parenchymal disease and 22 with pulmonary arteriovenous malformations) out of a total of 239 subjects. Nevertheless, since the pandemic, we found 11 cases of pulmonary POS secondary to SARS-CoV-2 complications with limited cases of POS related to intracardiac defects[10]. Although the ultimate etiologic mechanisms are not yet fully understood, it is possible that both pulmonary interstitial changes and vascular involvement are physiopathologically active in COVID-19 pneumonia, with the latter probably being the most important trigger of the syndrome[19].

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Obtained.

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