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Case report

Platypnea-orthodeoxia syndrome in SARS-CoV-2 related ARDS: a case report

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Abstract. Platypnea-Orthodeoxia Syndrome (POS) is an often misdiagnosed clinical condition characterized by dyspnea and hypoxia in sitting or semi-sitting position, reversible in supine position. Although POS is typically associated with intracardiac shunts, it seems frequent also in SARS-CoV-2 related Acute Respiratory Distress Syndrome (ARDS). In fact, the prevalent involvement of the lung bases due to interstitial pneumonia can determine refractory positional hypoxemia, with marked desaturation in the sitting position and regression or improvement in the supine position, configuring the clinical picture of the POS. We present a clinical case of POS associated with acute respiratory distress from SARS-CoV-2 pneumonia in which refractory hypoxia would have required support by invasive mechanical ventilation if the syndrome had not been identified. (www.actabiomedica.it)

Key words: COVID-19, SARS-CoV-2, Platypnea-Orthodeoxia Syndrome, ARDS

Running Title: Platypnea-Orthodeoxia Syndrome in COVID-19

Introduction

Acute Respiratory Distress Syndrome (ARDS) is one of the most frightening complications of SARS-CoV-2 interstitial pneumonia (1). Patients with acute respiratory distress require respiratory support, ranging from low-flow oxygen supplementation to continuous positive airway pressure (CPAP), to orotracheal intubation (OTI) and invasive mechanical ventilation (IMV), according to clinical needs. Some patients with SARS-CoV-2 pneumonia related ARDS show refractory positional hypoxemia, which can benefit from the acquisition of a prone (more often) or a supine position (2). The latter case configures the picture of the Platypnea-Orthodeoxia Syndrome (POS), a rare clinical condition characterized by hypoxemia in a sitting or semi-sitting position, which is reversible in supine position (3). This syndrome is more frequently related to the presence of intracardiac shunts. However, pulmonary diseases with predominantly lung bases involvement (typical features of SARS-CoV-2 interstitial pneumonia) may result in POS because of a right-to-left intrapulmonary shunt with mixture of venous and arterial flow and consequent refractory hypoxia. In the setting of ARDS related to SARS-CoV-2 pneumonia, identifying POS correctly would allow to perform appropriate management (supine position, tailored rehabilitation path) and avoid unnecessary IMV.

For this purpose, we describe the clinical case of a 82-year-old woman with SARS-CoV-2 pneumonia-related POS in which early identification of the syndrome allowed to avoid OTI and guarantee a non-invasive treatment and suitable respiratory rehabilitation path.

Case report

A 82-year-old woman with SARS-CoV-2 interstitial pneumonia was admitted to our ward for the appearance of fever, cough and dyspnea in the last few days. In the medical history, the patient suffered from arterial hypertension. No smoking history was reported.

On physical examination there was hypoxemia (84% peripheral oxygen saturation, SpO_2) and a mild tachypnea (respiratory rate, RR: 22 acts/min). The blood gas analysis showed type 1 respiratory failure, with PaO_2 (partial pressure of oxygen) of 41 mmHg and PaO_2/FiO_2 ratio (P/F; FiO_2: fraction of inspired oxygen) $<$ 200. Lung ultrasound and Computed Tomography (CT) scan showed moderate to severe interstitial lung involvement greater at the lung bases, with lower-upper increasing gradient (Lung Ultrasound Score equal to 18/36; CT scan severity score 11/20) (**Figure 1**) (4, 5).

Blood tests showed an increase in the indices of inflammation (C-Reactive Protein - CRP: 7.8 mg/dl) and lymphopenia (470 cells/mmc). The electrocardiogram showed sinus tachycardia.

The patient was quickly treated with cycles of CPAP in a semi-sitting supine position, alternating with high flow nasal cannulae (HFNC) oxygen therapy to allow oral feeding. Initial PEEP was set at 7 cmH_20, with titration upwards until 9 cmH_20 according to clinical response and patient's tolerance. Therapy with low molecular weight heparin at prophylactic dosage and dexamethasone (6 mg/day) was also set up. Despite the therapy, the patient showed no significant improvement in the first two days after admission.

On the third day the patient showed a sudden clinical worsening, with severe hypoxia ($SpO_2 < 80\%$) and tachypnea (RR $>$ 35 acts/min), despite a progressive increase in oxygen supplementation, the shift of CPAP to Pressure Support Ventilation (PSV) through the application of a pressure support (PS) and the progressive increase of the same ventilation pressures. At the bed-side lung ultrasound control, there were no signs of pneumothorax and pleural effusion. In addition, there were no signs of hypokinesia or right heart overload on echocardiography. Respiratory distress rapidly worsened until reaching P/F values of about 46 in less than an hour with a preserved hemodynamics

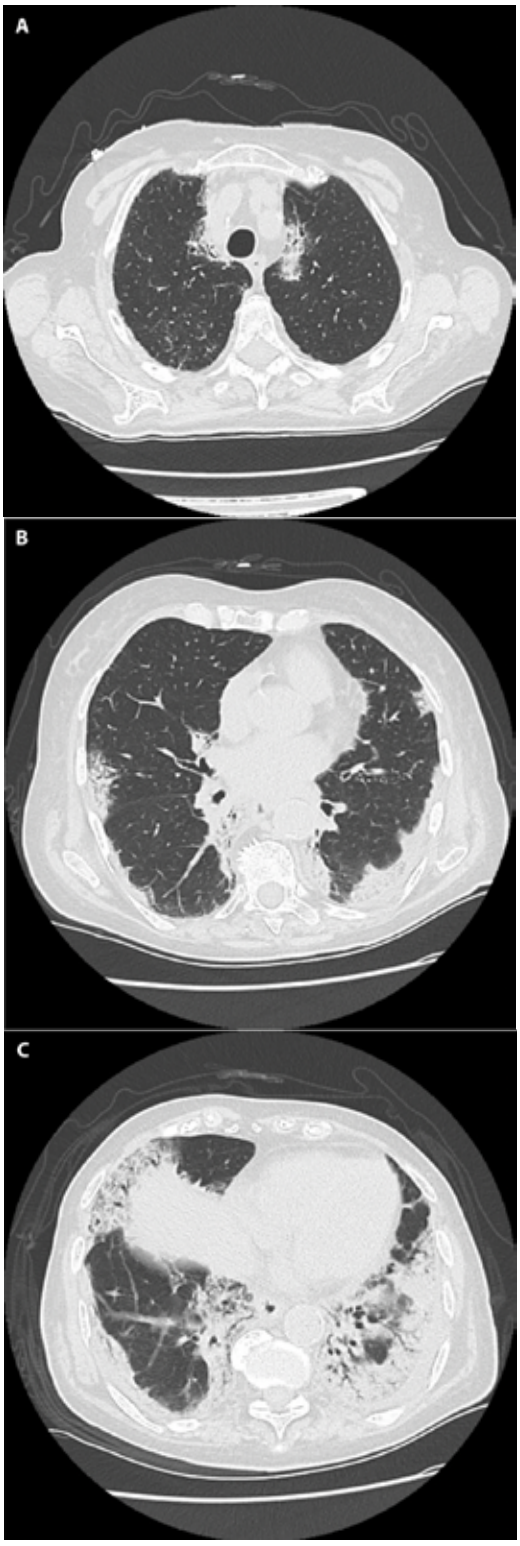

Figure 1. CT scan on admission with details of the apical (A), middle (B) and basal (C) regions and evidence of pulmonary involvement with increasing cranio-caudal gradient.

(arterial pressure, capillary refill, state of consciousness). Given the sudden deterioration and lack of responsiveness to the therapy, OTI was needed and the patient was placed in the supine position in the preparatory maneuvers. Soon after a rapid and spontaneous improvement in peripheral oxygenation was observed at pulse oximetry (> 30%) and confirmed by blood gas analysis, which showed a recovery of the P/F value up to 150 in Venturi Mask (FiO_2 40%). The changed clinical picture in relaxed supine position made it possible to first defer and then avoid the OTI and to use non-invasive methods of respiratory support (particularly low flow nasal cannulas). On chest CT performed after stabilization, almost total involvement of the pulmonary bases was confirmed with increasing apico-basal gradient and further complications (e.g. pulmonary embolism, pneumothorax) or anatomical shunt (eg: arteriovenous malformations) were excluded.

Therefore, on the basis of the clinical-radiological picture, the diagnosis of the platipnea-orthodeoxia syndrome related to SARS-CoV-2 interstitial pneumonia was made. Exclusion of intra-cardiac shunts (e.g. patent foramen ovale) by bubble-contrast echocardiography and complete reversal of the clinical picture after resolution of SARS-CoV-2 interstitial pneumonia confirmed the diagnosis.

The patient continued the treatment with dexamethasone and low molecular weight heparin, in accordance with the Italian and International guidelines (6, 7), and the respiratory support with low flow oxygen in supine position. The patient was gradually adapted to assume the semi-sitting position first and then sitting. She was discharged on the eighteenth day and sent for rehabilitation.

Discussion

Platypnea-Orthodeoxia syndrome (POS) is a rare clinical disorder characterized by positional dyspnea (platypnea) and arterial desaturation (orthodeoxia) when the patient is in a sitting or semi-sitting position, with improvement or regression of symptoms in the supine position (3). Desaturation in POS is defined as a drop in $PaO_2 > 4$ mmHg or $SpO_2 > 5\%$ from supine to an upright position, reversible by recovering the original position. POS associated hypoxemia requires mixing deoxygenated venous blood into oxygenated arterial blood by an arteriovenous shunt. Although more frequently related to right-to-left intracardiac shunting, POS can have a variety of etiologies (Table 1) (3).

Based on the site of the shunt, the mechanisms of hypoxemia in POS can be classified into intracardiac (e.g.: patent foramen ovale), extracardiac (e.g.: pulmonary, as in case of arteriovenous malformations) and miscellaneous.

Table 1. Main causes of platypnea-orthodeoxia syndrome - synthesis from Agrawal et al [3].

Intracardiac shunt
Patent Foramen Ovale
Atrial Septal Defect
Atrial Septal Aneurysm
Pulmonary Venous Connection
Fontan procedure
Transposition of great vessels
Unroofed coronary sinus
Extracardiac Shunt
- *Intrapulmonary shunt:*
Pulmonary arterio-venous malformation
Hepato-pulmonary syndrome
Acute respiratory distress syndrome
Massive Pleural effusion
- *Ventilation perfusion mismatch:*
Chronic obstructive pulmonary disease
Interstitial lung disease
Pneumonectomy
Pulmonary embolism
Miscellaneous mechanisms:
Amiodarone lung toxicity
Parkinson's disease
Diabetic autonomic neuropathy
Organophosphorus poisoning
Radiation-induced bronchial stenosis
Traumatic bronchial rupture
Bronchogenic carcinoma
Ileus
Fat embolism

Pneumopathies with prevalent involvement of the lung bases can be responsible for POS (3, 8). In particular, SARS-CoV-2 determines a pulmonary involvement with an increasing apico-basal gradient and not infrequently an almost total lung bases involvement. Indeed, other cases of POS in COVID-19 disease are described in the literature, with (9-11) or without (8, 12-16) evidence of intracardiac shunt. Moreover, recent data highlight that POS in COVID-19 may be underestimated since almost one third of patients with moderate-stage of ARDS due to SARS-CoV-2 pneumonia seems to show it (17). The pathophysiological mechanism of POS due to SARS-CoV-2 pneumonia is likely related to right-to-left intrapulmonary shunt leading to hypoxaemia due to the high ventilation/perfusion (V/Q) mismatch in the alveoli of the lung bases. In severe COVID-19 disease with predominant lung bases involvement the gravitational redistribution of pulmonary blood flow in a sitting position results in high perfusion of unventilated lung basal alveoli and in a shunt mechanism with severe hypoxia, while the apical regions act as dead space, resulting in POS (3, 8, 18). Moreover, compensatory mechanisms of hypoxic vasoconstriction (Euler-Lilijestrand mechanism) are less efficient in SARS-CoV-2-related ARDS, resulting in normal perfusion of poorly ventilated alveoli and severe hypoxemia (19). Furthermore, the presence of thrombosis and microangiopathy of the pulmonary capillaries, frequently associated to COVID-19, can also worsen the high V/Q mismatch (20). In the supine position the redistribution of blood flow towards the lung apexes (better ventilated) reduces the V/Q mismatch and attenuates the degree of hypoxia. Longo et al. (12) have recently confirmed these physio-pathological hypotheses by V/Q scan in supine and sitting position in setting of SARS-CoV-2 related ARDS. Authors confirm that the genesis of positional hypoxemia depends on the V/Q mismatch. Despite a consensual reduction in both ventilation and perfusion in the sitting position in the alveoli of lung bases, alveolar ventilation is significantly more reduced than perfusion, resulting in severe hypoxia (12).

In any case, differential diagnostics between the various aetiologies of POS is mandatory. CT scan should be done to rule out arteriovenous malformations and/or pulmonary embolism. Furthermore, in this context an intracardiac shunt must also be excluded by bubble contrast echocardiography, since elevated right-sided filling pressures due to severe lung involvement may worsen or lead to right-to-left flow, otherwise not present or not significant (9, 21). Indeed, pulmonary embolism and intracardiac shunts may cause first or be cofactors of POS even in ARDS related to SARS-CoV-2 infection. Moreover, the coexistence of an atrial defect, high right-sided pressures and a thrombophilic state such as that induced by SARS-CoV-2 determines a significant increase in the risk of paradoxical embolism. Other etiologies must also be excluded in each case (eg hepato-pulmonary syndrome in patients with liver cirrhosis) (22).

Conclusions

Although sporadically identified, Platypnea-Orthodeoxia syndrome due to SARS-CoV-2 related pneumonia seems to be more frequent and likely underestimated, particularly in patient with moderate-to severe ARDS. Recognising POS can reduce morbidity and unnecessary warnings, improve patient safety and allow to properly manage the respiratory supports and rehabilitation processes. POS should be suspected and evaluated in all cases of moderate or severe ARDS with prevalent involvement of the lung bases and refractory hypoxemia in sitting or semi-sitting position. In this context, intracardiac shunts must be always ruled out.

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Patients consent statements: Informed consent was obtained from the patient included in the study.

References

1. Montenegro F, Unigarro L, Paredes G, et al. Acute respiratory distress syndrome (ARDS) caused by the novel coronavirus disease (COVID-19): a practical comprehensive literature review. Expert Rev Respir Med 2021; 15: 183-195.
2. Guérin C, Albert RK, Beitler J, et al. Prone position in ARDS patients: why, when, how and for whom. Intensive Care Med 2020; 46: 2385-2396.
3. Agrawal A, Palkar A, Talwar A. The multiple dimensions of Platypnea-Orthodeoxia syndrome: A review. Respir Med 2017; 129: 31-38.
4. Lugara M, Oliva G, Pafundi PC, et al. Clinical application of lung ultrasound score on COVID-19 setting: a regional experience in Southern Italy. Eur Rev Med Pharmacol Sci 2021; 25: 3623-3631.
5. Chang YC, Yu CJ, Chang SC, et al. Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation with thin-section CT. Radiology 2005; 236: 1067-75.
6. National Istitutes of Health (NIH). COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/ Date last updated: October 27, 2021. Date last accessed: November 29, 2021.
7. Agenzia Italiana del Farmaco (AIFA). https://www.aifa.gov.it/en/web/guest/home. Date last updated: October 21, 2021. Date last accessed: November 29, 2021.
8. Tan GP, Ho S, Fan BE, et al. Reversible platypnea-orthodeoxia in COVID-19 acute respiratory distress syndrome survivors. Respir Physiol Neurobiol 2020; 282:103515.
9. Vanhomwegen C, Taton O, Selvais N, Vanhove O, Leduc D. Patent foramen ovale revealed by COVID-19 pneumonia. BMC Pulm Med 2021; 21: 126.
10. Dodson BK, Major CK, Grant M, Yoo BS, Goodman BM. Platypnea Orthodeoxia Due to a Patent Foramen Ovale and Intrapulmonary Shunting After Severe COVID-19 Pneumonia. Am J Case Rep 2021; 22: e933975.
11. Jenab Y, Hosseinsabet A, Vaskelyte L, Hosseini K. Platypnoea-orthodeoxia syndrome after percutaneous treatment of ruptured sinus Valsalva complicated by SARS-Cov-2 pneumonia: a case report. Eur Heart J Case Rep 2021; 5: ytab176.
12. Longo C, Ruffini L, Zanoni N, et al. Platypnea-orthodeoxia after fibrotic evolution of SARS-CoV-2 interstitial pneumonia. A case report. Acta Biomed 2020; 91: ahead of print.
13. Singh K, Kadnur H, Ray A, et al. Platypnea-orthodeoxia in a patient with severe COVID-19 pneumonia. Monaldi Arch Chest Dis 2020; 90.
14. Tham SL, Ong PL, Lee AJY, Tay MRJ. Rehabilitation of Patients with Platypnea-Orthodeoxia Syndrome in COVID-19 Pneumonia: Two Case Reports. J Rehabil Med Clin Commun 2020; 3: 1000044.
15. Hoshi T, Tadokoro Y, Nemoto M, Honda J, Matsukura S. Platypnea-orthodeoxia syndrome associated with COVID-19 pneumonia: a case report. JA Clin Rep 2021; 7: 67.
16. Salvotti F, Poiatti F, Bressa S, Montani G, Nardin M, Rizzoni D. Platypnoea-Orthodeoxia Syndrome in COVID-19. Eur J Case Rep Intern Med 2021;8: 002849.
17. Athavale T, Athavale A, Khatri V, et al. Platypnea-orthodeoxia Syndrome (POS) in Moderate COVID-19: An Uncommonly Common Bedside Sign? J Assoc Physicians India 2021; 69: 11-12.
18. Herrmann J, Mori V, Bates JHT, Suki B. Modeling lung perfusion abnormalities to explain early COVID-19 hypoxemia. Nat Commun 2020; 11: 4883.
19. Pfeifer M, Ewig S, Voshaar T, et al. Position Paper for the State-of-the-Art Application of Respiratory Support in Patients with COVID-19. Respiration 2020; 99: 521-542.
20. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med 2020; 8: 681-686.
21. Rajendram R, Kharal GA, Puri R. COVID-19 May Be Exacerbated by Right-to-Left Interatrial Shunt. Ann Thorac Surg 2021; 111: 376.
22. Torres-Valencia J, Quevedo-Mori A, Untiveros-Mayorga F. Hypoxemia, high alveolar-arterial gradient, and bubbles in both sides of heart: A case of hepatopulmonary syndrome in the setting of COVID-19 pandemic. Clin Case Rep 2021; 9: e04204.

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