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CASE REPORT

Platypnea-Orthodeoxia Syndrome in Coronavirus Disease 2019 Pneumonia: A Case Report and Literature Review

Takahiko Tanimoto[1,2], Yoshihiro Eriguchi[1], Tomonori Sato[1], Akiko Yonekawa[1], Noriko Miyake[1], Koichi Akashi[1], Nobuyuki Shimono[3]

[1]Department of Clinical Immunology and Rheumatology / Infectious Disease, Kyushu University Hospital, Fukuoka, Japan; [2]Department of Infectious Diseases, Kagoshima Seikyo Hospital, Kagoshima, Japan; [3]Center for the Study of Global Infection, Kyushu University Hospital, Fukuoka, Japan

Correspondence: Yoshihiro Eriguchi, Department of Clinical Immunology and Rheumatology / Infectious Disease, Kyushu University Hospital, 3-1-1, Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan, Tel +81 92-801-1011, Fax +81 92-862-8200, Email eriguchi.yoshihiro.145@m.kyushu-u.ac.jp

Abstract: Platypnea-orthodeoxia syndrome (POS) is a rare disorder associated with coronavirus disease 2019 (COVID-19) pneumonia. However, POS may be underdiagnosed. We report the case of a 59-year-old female patient with POS complicated by pulmonary embolism in COVID-19. Imaging revealed ground-glass opacities predominantly in the lower lobes and a pulmonary embolus in the right upper lobe. She was diagnosed with POS due to marked postural discrepancies between supine and upright oxygen saturations and blood oxygenation. Intracardiac shunt, one of the etiologies of POS, was not detected by bubble contrast echocardiography, and postural de-saturation gradually improved with methylprednisolone and edoxaban administration. In our literature review, only 3 of the 16 patients with POS associated with COVID-19 had cardiac shunting, suggesting that moderate to severe COVID-19 causes POS without cardiac shunts. COVID-19-associated vasculopathy and lower lung lesion predominance in COVID-19 pneumonia may cause ventilation-perfusion mismatch due to gravitational shunting of blood into the poorly ventilated lower lungs in the upright position, which may ultimately cause POS. Hypoxemia impedes rehabilitation, whereas early initiation of supine positioning in bed, with knowledge of the pathophysiology of POS, may have a positive effect.

Keywords: platypnea, orthodeoxia, COVID-19, ventilation-perfusion mismatch

Introduction

Platypnea-orthodeoxia syndrome (POS) is a rare clinical condition characterized by positional dyspnea (platypnea) and arterial de-saturation (orthodeoxia) while in the upright position. The hypoxia in POS has been attributed to the mixing of arterial and venous blood through a shunt. The most prevalent etiology of POS is cardiac disease,[1] whereas pulmonary disease etiology is relatively rare.[2]

The clinical conditions of hypoxia in patients with coronavirus disease 2019 (COVID-19) have been previously elucidated. One characteristic is significant arterial hypoxemia without signs of respiratory distress, which is referred to as "Happy hypoxemia".[3] However, this may hinder the diagnosis of POS. In this report, we presented a case of POS associated with COVID-19 pneumonia and reviewed the previously reported cases in the literature.

Case Report

In the middle of the first Omicron variant pandemic wave, a 59-year-old female patient presented with fatigue, fever, and oliguria with a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test. She was admitted to a local hospital 6 days after symptom onset. Her past medical history included type 2 diabetes treated since the age of 43, hypertension, kidney transplant at the age of 57 due to end-stage renal failure, myocardial infarction, peripheral artery disease, and brain infarction. She had been prescribed 1500 mg of mycophenolate mofetil, 4 mg of tacrolimus, and 2 mg of

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methylprednisolone daily as immunosuppressants post-kidney transplant. On the day of initial admission, a chest radiograph revealed pneumonia. However, due to serum creatinine levels of 2.94 mg/dL, sotrovimab was administered instead of remdesivir. Oxygen therapy at 1 L/min and a 10-day course of dexamethasone 6.6 mg intravenous infusion were initiated the next day. Simultaneously, oxygen saturation improved with treatment, and renal function worsened, with serum creatinine levels increasing to 7.33 mg/dL and blood urea nitrogen levels increasing to 138.3 mg/dL. Subsequently, the patient was transferred to our hospital on day 12 after symptom onset. At the time of transfer, the patient was afebrile, but tachypneic at 28 breaths/min with an oxygen saturation of 95% on ambient air. Physical examination revealed late inspiratory crackles in the bilateral lower lungs, and arterial blood gas analyses showed metabolic acidosis of pH 7.32, partial pressure of carbon dioxide 19 mmHg, bicarbonate 9.5 mmol/L, base excess −14.7 mmol/L with normal lactate, and mild hypoxemia with partial pressure of oxygen (PO_2) 70.5 mmHg. Her white blood cell count was 5580 cells/μL, and laboratory analyses were remarkable for renal dysfunction, with serum creatinine levels of 6.52 mg/dL and BUN levels of 129 mg/dL. Liver function test showed no remarkable abnormality with total bilirubin 0.5 mg/dL, aspartate aminotransferase 16 IU/L, alanine aminotransferase 8 IU/L, alkaline phosphatase 55 IU/L, gamma-glutamyl transferase 13 IU/L, albumin 3.3 mg/dL, and prothrombin time 81%. Inflammatory markers were slightly elevated, including C-reactive protein of 0.31 mg/dL, ferritin of 537.4 ng/dL, and procalcitonin of 0.56 ng/mL. Additionally, the D-dimer level was elevated at 4.1 μg/mL. Pyuria was detected in the urine analysis, and a urine smear revealed gram-negative rods, which was consistent with a history of recurrent urinary tract infections caused by extended-spectrum β-lactamase-producing *Escherichia coli*. Subsequently, the patient was given meropenem intravenously. Renal function gradually improved over the next days with adequate rehydration. However, on the second day after transfer, dyspnea and desaturation occurred while the patient was sitting on a portable toilet, and high-flow oxygen therapy was initiated. Computed tomography (CT) revealed deteriorating bilateral peripheral and patchy ground-glass opacities (Figure 1). Methylprednisolone 125 mg was administered for 5 days, and mycophenolate mofetil was discontinued until the viral infection could be controlled. Eighteen days after symptom onset, we observed that her oxygen saturation was considerably lower in an upright position in bed compared with a supine position (95% and 85%, respectively). Due to an elevated plasma D-dimer level of 22.0 μg/mL and a pulmonary embolus in the right upper lobe on contrast CT (Figure 2), edoxaban 30 mg was started on day 19 after symptom onset. CT also showed new ground-glass opacities in the lung fields. Positional de-saturation continued even when the patient was asymptomatic or complained only of mild dyspnea. On day 30, a comparison of arterial blood gas analyses in supine and seated positions, with O_2 at 3 L/min by Oxymizer P-244 (Nihon Rufuto, Tokyo, Japan), showed PO_2 of 90.6 mmHg and 67.2 mmHg, respectively,

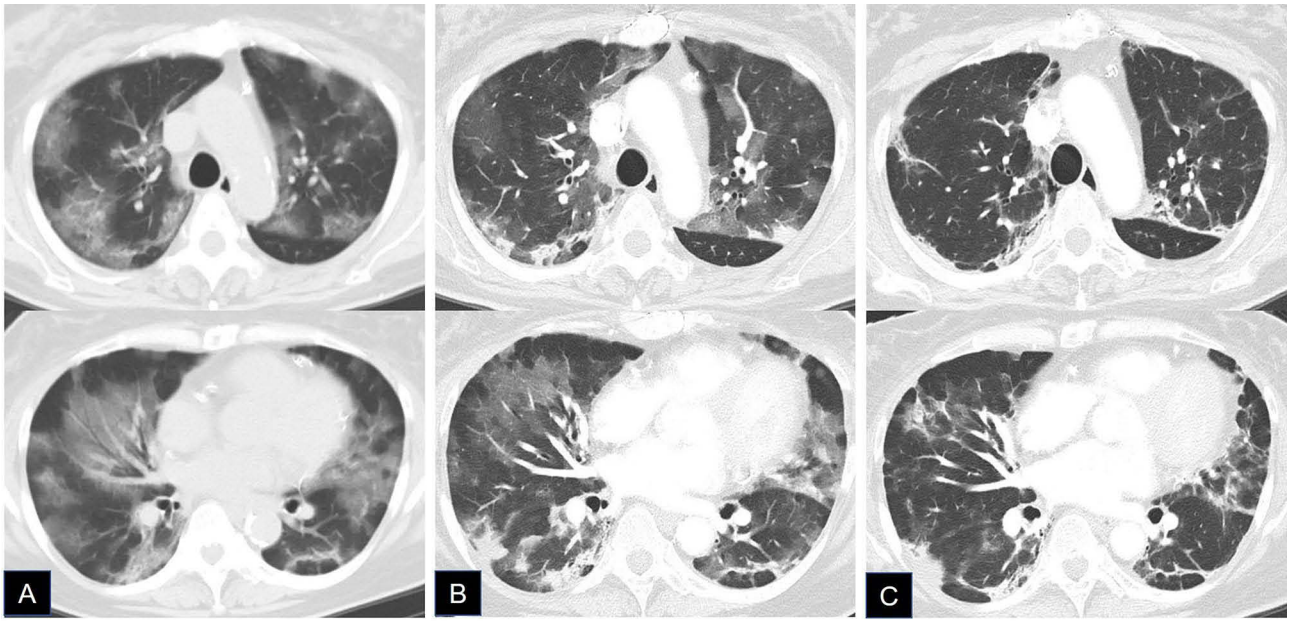

Figure 1 Computed tomography. (**A**) day 13; (**B**) day 19; and (**C**) day 37, after symptom onset. Upper images show upper lobes, and lower images show lung bases where ground glass opacities and consolidations appeared predominant.

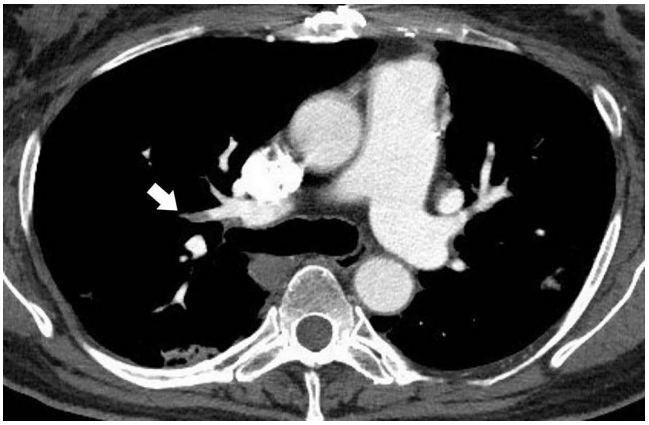

Figure 2 Computed tomography. Day 19 after symptom onset. The arrow shows a pulmonary embolus in the right upper lobe on contrast CT.

which was consistent with the POS diagnosis. Orthodeoxia and oxygen dependence gradually improved with methylprednisolone dose reduction every 3 days. Chest CT showed diminished opacification and augmentation of consolidation, particularly predominant at the lung bases (Figure 1). Additionally, the pulmonary embolism resolved on day 37. The patient's SARS-CoV-2 PCR examination resulted in a negative on day 47, and dyspnea resolved without oxygen administration. Moreover, postural desaturation in the supine and sitting positions improved to 97% and 94%, respectively, and oxygen therapy was subsequently discontinued. However, PO_2 in the supine and sitting positions remained abnormal at 77.5 mmHg and 61.7 mmHg, respectively. We performed an agitated saline contrast bubble echocardiography to evaluate intracardiac shunting as the possible etiology of POS; however, no shunt was noted. The patient was ultimately discharged home on day 56 after symptom onset.

Discussion

POS is a rare clinical condition characterized by positional dyspnea and arterial de-saturation while in the upright position, which has been attributed to arteriovenous shunting. A meta-analysis by Agrawal et al reported that 87% of POS was of cardiac origin, with a patent ovale foramen being the most common cause.[1] POS may also be less frequently caused by extracardiac shunts, related to a ventilation-perfusion mismatch, and has been reported in interstitial lung disease, interstitial *Pneumocystis jirovecii* pneumonia, cytomegalovirus pneumonia, and drug-induced lung injury.[2] Hepatopulmonary syndrome can also cause POS by dilatation of pulmonary capillaries leading to ventilation-perfusion mismatch, reduced alveolar-arterial oxygen diffusion, and arteriovenous shunting.[1] Recently, cases of POS associated with COVID-19 pneumonia have been reported. Therefore, to review the characteristics of patients with COVID-19 with concomitant POS, including our case, we reviewed the literature in PubMed using following keywords: "Platypnea-orthodeoxia" and "COVID-19". We excluded literature in languages other than English. A retrospective analysis conducted in India[4] was also excluded, as the profiles of each case were not elaborated.

Ultimately, we found 17 reports on 22 patients with POS associated with COVID-19 (Table 1). Regarding the presence of cardiac shunting, foramen ovale patency was found in three cases[5–7] and absent in 13 cases,[8–18] while no echocardiographic results were mentioned in the remaining three reports.[19–21] Most cases required respiratory support with high-volume oxygen, noninvasive ventilation, or invasive mechanical ventilation. Many of the cases reported CT findings of ground-glass opacities and consolidations predominantly in bilateral lower lobes and lung bases. The lower lung predominant lesion in COVID-19 pneumonia causes ventilation-perfusion mismatch due to the occurrence of gravitational shunting of blood into the poorly ventilated lower lungs when in the upright position.[21] Moreover, pulmonary embolism was found in 3 of the 23 cases,[8,17] including our case. However, pulmonary micro-thrombosis and vasculopathy undetectable using CT may also be an etiology of POS in COVID-19.[21] The time to POS diagnosis ranged from 4 to 28 days after COVID-19 onset or hospitalization (Table 1). Notably, POS was more likely determined after rehabilitation following acute-phase treatment.[10,17,19] Furthermore, the prognosis for POS associated with COVID-19 was generally good, with most patients recovering within 4 to 65 days; however, three patients required long-term

Table 1 POS Caused by COVID-19 Pneumonia

References	Age	Gender	Oxygen Therapy	Radiographic Findings	Diagnosis of POS	Duration of POS	Cardiac Shunt	Outcome
Our case	59	Female	HFNC	Bilateral GGO and consolidation predominant in lower lobes and pulmonary embolism	Day 18 from onset	38 days	Negative	Discharged
Dodson et al[5]	85	Male	HFNC	Bilateral GGO and consolidation	Day 28 from diagnosis	50 days	PFO and ASA	Discharged
Vanhomwegen et al[6]	55	Male	NIV	Bilateral GGO and consolidation predominant at lung bases	–	About 3 weeks	PFO	Discharged with LTOT
Jenab et al[7]	50	Female	–	Peripheral GGO	–	–	Right coronary cusp rupture and PFO	Discharged
Longo et al,[8] Zanoni et al[22]	76	Female	NIV	Bilateral patchy GGO and pulmonary embolism	Day 14 from admission	Longer than 2 months	Negative	Dead
Singh et al[9]	66	Male	–	Bilateral GGO mainly in lower zones	Day 8 from admission	7 days	Negative	Discharged
Tham et al[10]	69	Male	IMV	Bilateral diffuse patchy GGO	Day 18 from onset	65 days	Negative	Discharged
	63	Male	HFNC		Day 26 from onset	22 days	Negative	Discharged
Ismail et al[11]	89	Female	Venturi mask	Bilateral GGO at lung bases	–	–	Negative	Discharged
Hoshi et al[12]	73	Female	HFNC	Bilateral peripheral consolidation	Day 11 from admission	Longer than 28 days	Negative	Discharged with LTOT
Salvotti et al[13]	84	Female	NIV	Bilateral GGO mainly in lower lobes	Day 24 from admission	22 days	Negative	Transferred
Aprea et al[14]	82	Female	NIV	Interstitial involvement greater in lung bases	Day 3 from admission	18 days	Negative	Discharged
Asami-Noyama et al[15]	83	Male	HFNC	Bilateral GGO	Day 27 from infection	Longer than 2 weeks	Negative	Transferred
Bhushan et al[16]	55	Male	Face mask	Bilateral fibrosis in upper and lower lobes	-	-	Negative	-

Abreu et al[17]	62	Male	NIV	Pulmonary embolism and bilateral fibrosis in lower lobes	Day 24 from admission	15 days	Negative	Discharged
Talwar et al[18]	32	Male	NIV	Bilateral GGO predominant in lower lobes	Day 9 from admission	15 days	Negative	Discharged
Tan et al[19]	71	Male	IMV	Bilateral GGO and consolidation predominantin posterior segments and lower lobes	Day 10 from onset	23 days	-	-
	64	Male	IMV		Day 16 from onset	17 days	-	-
	54	Male	IMV		Day 18 from onset	6 days	-	-
	69	Male	IMV		Day 18 from onset	39 days	-	-
	61	Male	IMV		Day 24 from onset	17 days	-	-
Oldani et al[20]	80	Male	NIV	Bilateral GGO predominant in lower lobes	-	-	-	-
Aayilliath et al[21]	46	Male	HFNC	Bilateral GGO and consolidation predominant in lower zones	Day 4 from admission	4 days	-	Discharged

Notes: Boxes with "-" are no data in the original article. Radiographic findings are predominant distribution in bilateral lower lobes and lung bases in many of the reported cases. Pulmonary embolism was found in 3 of 24 cases including our case. The time to POS diagnosis ranged from 4 to 28 days after COVID-19 onset or hospitalization and the majority of patients recovered except one case who died from pulmonary fibrosis, pneumonia, and pneumomediastinum.
Abbreviations: HFNC, high flow nasal cannula; NIV, noninvasive ventilation; IMV, invasive mechanical ventilation; GGO, ground glass opacities; LTOT, long term oxygen therapy; PFO, patent foramen ovale; ASA, atrial septal aneurysm.

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oxygen therapy (LTOT) after discharge.[6,8,12] One patient was re-hospitalized for worsening respiratory status 2 months after discharge home on LTOT and subsequently died from pulmonary fibrosis, pneumonia, and pneumomediastinum.[8,22]

POS may impede the rehabilitation and lead to disuse related to prolonged bed rest. The resulting lower extremity muscle weakness may subsequently exacerbate POS by decreasing venous return and cardiac output in the upright position.[10] Rehabilitation in bed with supplemental oxygen support may be beneficial to maintain muscle activity and joint range of motion until the patients can adapt to an upright position.[10] In a retrospective analysis conducted in India, 15 of the 53 (28%) patients with moderate COVID-19 were diagnosed with POS,[4] suggesting that POS associated with COVID-19 is more common than previously believed. Therefore, physicians and health-care providers should recognize POS as a cause of dyspnea and hypoxemia in patients with COVID-19, investigate possible etiologies, and avoid excessive bed rest, while providing appropriate treatments.

Conclusion

POS may be an under-recognized cause of dyspnea and hypoxemia in patients with moderate to severe COVID-19. Although most POS associated with COVID-19 were reversible and had good outcomes, hypoxemia may ultimately interfere with rehabilitation. The search for treatable arteriovenous shunting and early on-bed rehabilitation with appropriate treatments may lead to good outcomes.

Ethics Approval and Consent to Participate

No institutional approval was required to publish the case details.

Informed Consent

Informed consent for the publication of clinical details and clinical images was obtained from the patient.

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Disclosure

The authors report no conflicts of interest in this work.

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