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SUDDEN-ONSET PLATYPNEA-ORTHODEOXIA SYNDROME IN A PATIENT WITH LUNG ADENOCARCINOMA AND COVID-19 WITHOUT A PATENT FORAMEN OVALE

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ABSTRACT

Background: Platypnea-orthodeoxia syndrome is a rare but important cause of positional hypoxemia, typically resulting from a right-to-left shunt that may be intracardiac or intrapulmonary in origin.

Case report: We present the case of a 78-year-old woman with metastatic lung adenocarcinoma and recent mild coronavirus disease 2019 (COVID-19) who developed acute-onset platypnea-orthodeoxia syndrome during hospitalization. Diagnostic workup revealed intrapulmonary shunting in the absence of pulmonary embolism or significant parenchymal lung disease. High-resolution chest computed tomography scan showed hypervascular consolidations, while bubble contrast transthoracic echocardiography confirmed delayed appearance of microbubbles in the left heart, consistent with an intrapulmonary shunt.

Conclusion: This case highlights the complex interplay between tumour-induced intrapulmonary vascular abnormalities and possible COVID-19-related endothelial dysfunction in the development of platypnea-orthodeoxia syndrome. It emphasizes the need for heightened clinical suspicion and a multimodal diagnostic approach in patients with unexplained positional hypoxemia, especially in the setting of malignancy or recent viral infections. Diagnostic confirmation relies on imaging and shunt detection techniques, and management should be guided by the patient's overall prognosis and goals of care.

KEYWORDS

Platypnea-orthodeoxia, intrapulmonary shunt, respiratory medicine, advanced lung cancer, COVID-19

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LEARNING POINTS

- Platypnea-orthodeoxia syndrome should be considered in patients with unexplained positional hypoxemia and/or dyspnoea, especially in the context of malignancy or recent viral infection.
- Contrast-enhanced echocardiography is key to identifying right-to-left shunts and distinguishing between intracardiac and intrapulmonary causes.
- Pulmonary malignancies and coronavirus disease 2019 (COVID-19) can independently or synergistically contribute to the development of platypnea-orthodeoxia syndrome through vascular remodelling and angiogenesis.

INTRODUCTION

Platypnea-orthodeoxia syndrome (POS) is a rare clinical condition defined by positional dyspnoea and arterial hypoxemia that worsen in upright posture and improve when supine. It is caused by positional shunting of deoxygenated blood into the arterial circulation. It can be caused by an anatomical or functional shunt and may be due to intracardiac defects such as a patent foramen ovale but may also be of extracardiac origin. Recognition is crucial, as treatment may vary depending on the shunt's origin. In the era of coronavirus disease 2019 (COVID-19), the syndrome has gained renewed attention, as pulmonary vascular remodelling can exacerbate its pathophysiology.

CASE DESCRIPTION

The patient, a 78-year-old woman, had stage IVa lung adenocarcinoma with osseous, pulmonary, and adrenal metastases, hypertensive and valvular heart disease, a prior transient ischemic attack, and recent COVID-19 infection. She had no history of tobacco use or alcohol abuse. She was undergoing palliative cancer treatment with alectinib, later switched to lorlatinib (respectively 2nd and 3rd generation of tyrosine kinase inhibitors used to treat anaplastic lymphoma kinase positive metastatic non-small cell lung cancer), which was discontinued due to her deteriorating general condition. She was referred to our hospital due to nausea, vomiting, and opioid-induced constipation, as well as exacerbated back pain due to bone metastases. Imaging revealed tumour progression. Her gastrointestinal symptoms were attributed to constipation from opioids and tumour progression, with no infectious focus identified. She was hospitalized for pain management and monitoring of bowel function.

There was no history of dyspnoea, cough, expectoration, haemoptysis, or chest pain. Examination of the respiratory system revealed a symmetrical vesicular murmur, with no additional sound.

Due to elevated inflammatory markers and reduced SpO_2 (86%) on ambient air, a nasopharyngeal swab was obtained, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) reverse transcription polymerase chain reaction testing returned positive. The chest X-ray showed no pneumonic infiltrate, no larger pleural effusion, and no pulmonary venous congestion. Examination of other systems including the cardiovascular system was also within normal limits. No treatment for the COVID-19 infection was initiated and low-flow oxygen therapy (1 l/min) achieved >90% oxygen saturation. On day 6 of admission, the oxygen therapy could be stopped due to sufficient oxygen saturation on room air.

On day 9 of admission, routine vital parameter monitoring revealed asymptomatic oxygen saturation of 66% on room air in the sitting position, whereas 3 hours earlier, it was 94%. Arterial blood gas analysis in sitting position demonstrated marked hypoxemia, with a partial pressure of oxygen of 36 mmHg (4.8 kPa) *(Table 1)*. Oxygen via a non-rebreathing mask at 12 l/min achieved an SpO_2 of 82% in the sitting position. When in supine position, the SpO_2 was 100% with the non-rebreathing mask at 12 l/min. These findings were consistent with a diagnosis of POS.

Considering the abrupt and position-dependent desaturation, and given the patient's risk profile (malignancy, recent COVID-19 infection, hypercoagulability), a contrast-enhanced high-resolution chest computed tomography (CT) scan was performed to rule out pulmonary embolism and other parenchymal causes of hypoxemia. The CT scan excluded embolism, infiltrates, or pulmonary congestion, but revealed patchy to confluent consolidations in the posterior pleural angles bilaterally, with features

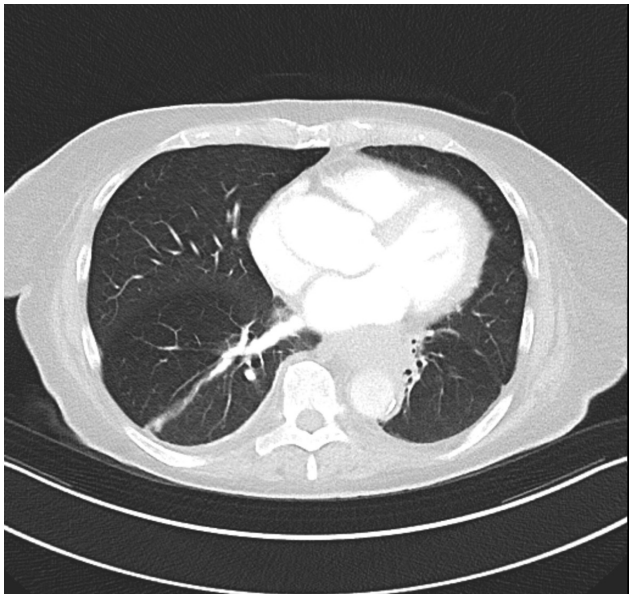
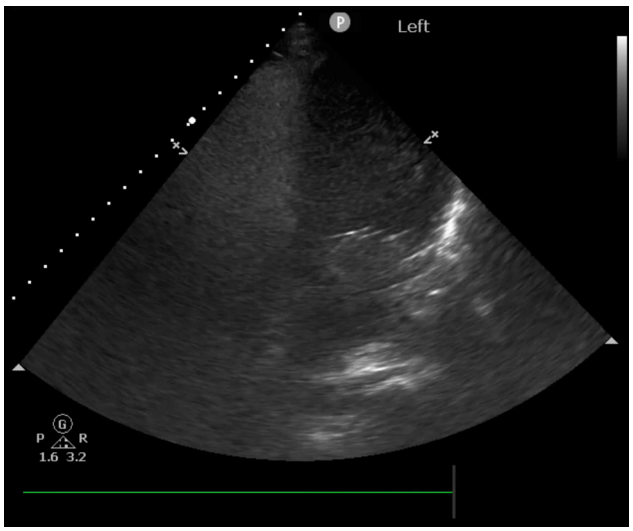


Figure 1. High-resolution contrast-enhanced computed tomography scan of the chest showing confluent consolidations in the posterior pleural angles bilaterally, with features suggestive of hypervascularization.



Video 1. Positive bubble-contrast echocardiography (apical 4 chamber view).
https://youtu.be/0jE1nvBXlZY

suggestive of abnormal hypervascularization. These findings were interpreted as macroscopic intrapulmonary vascular structures, possibly representing tumour-related neoangiogenesis or dilated capillaries contributing to a right-to-left shunt *(Fig. 1)*.

To confirm the presence and nature of the suspected shunt, a transthoracic echocardiogram with bubble contrast was performed. The transthoracic echocardiogram demonstrated preserved left and right ventricular function, with no evidence of pulmonary embolism or pericardial effusion. Mild, stable aortic and mitral valve insufficiency was noted. In the bubble-contrast echocardiography, bubbles were observed in the left ventricle after approximately 5-6 cardiac cycles, indicating a positive test *(Video 1)*. This suggests the presence of an intrapulmonary shunt rather than an intracardiac defect.

The patient was managed with high-flow oxygen therapy. Given her frailty status (Rockwood's clinical frailty scale: 7) and the advanced malignancy, invasive correction of the shunt was not pursued. The focus remained on optimizing comfort and symptom relief under palliative care guidelines. Over the subsequent days, low-flow oxygen therapy at 2 l/min achieved good oxygen saturation in the supine position. However, the patient's positional desaturation persisted. Due to severe metastatic disease and her overall prognosis, the care team and family elected to forego further investigations or interventions. The patient was transferred to a palliative care facility.

Parameter	Day 0	Day 9
FiO_2 (%)	21	21
pH	7.39	7.51
pCO_2 (mmHg)	32	34
pO_2 (mmHg)	63	36
HCO_3 (mmol/l)	20	27
$tcCO_2$ (mmol/l)	20	28
BE (mmol/l)	-4.7	4.3
SBE (mmol/l)	-5.3	4.2
sO_2 (%)	91	67

Abbreviations: FiO_2, fraction of inspired oxygen; pH, Potential hydrogen; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; HCO_3, bicarbonate concentration; $tcCO_2$, total carbon dioxide; BE, base excess; SBE, standard base excess; sO_2, oxygen saturation.

Table 1. Arterial blood gas analysis at admission (day 0) and on day 9 both in a sitting position.

DISCUSSION

POS is a rare clinical condition characterized by dyspnoea (platypnea) and/or hypoxemia (orthodeoxia) that worsens in an upright position and improves in the supine position. It is often associated with anatomical or functional right-to-left shunting, typically due to intracardiac or intrapulmonary shunts. The present case demonstrates a sudden onset of POS in a patient with advanced pulmonary malignancy and recent COVID-19, highlighting the complexity of its aetiology and management.

Intrapulmonary arteriovenous shunting can occur in the context of pulmonary malignancies due to tumour-related vascular remodelling, hypervascularization, or angiogenesis[1]. In this case, the patient had patchy consolidations suggestive of macroscopic intrapulmonary capillary structures, as seen on high-resolution CT scan. Reports have documented POS in lung cancer patients due to similar mechanisms, though it remains rare[2]. For example, a case of POS in a patient with advanced lung adenocarcinoma attributed to tumour-induced arteriovenous malformations was described[3]. This mechanism is consistent with the findings in our patient, whose bubble-contrast echocardiography confirmed an intrapulmonary shunt.

COVID-19, especially in severe cases, can induce vascular endothelial dysfunction, microvascular inflammation, and dysregulated angiogenesis, potentially contributing to intrapulmonary shunting[4]. Although our patient's COVID-19 was mild, it may have acted as a cofactor in the sudden onset of POS by exacerbating vascular remodelling or predisposing to shunt formation. A similar phenomenon has been described in other cases of COVID-19-related POS. For instance, instances of POS in COVID-19 patients with no prior cardiac or pulmonary anomalies, emphasizing the virus's role in altering pulmonary vascular dynamics, were highlighted[5].

However, the most common cause of this rare clinical entity remains the reopening of a patent foramen ovale[6]. Anatomical alterations of the interatrial septum, such as

septal aneurysms, have also been associated with patent foramen ovale-related shunting[7]. Additionally, POS has been described in the setting of hepatopulmonary syndrome, in which hypoxemia may result from intrapulmonary vascular dilatations, impaired hypoxic vasoconstriction, or ventilation-perfusion mismatch—often secondary to pleural effusions or diaphragmatic limitation caused by ascites[8]. Of note, our review of the literature did not identify any reported associations between tyrosine kinase inhibitors, including lorlatinib, and the occurrence of POS. However, tyrosine kinase inhibitors can be associated with pulmonary arterial hypertension, a condition that can worsen the symptoms of POS[9].

Given its rarity, POS should be considered in the differential diagnosis of patients presenting with positional dyspnoea and/or hypoxemia. Confirmation of a right-to-left shunt is critical for establishing the diagnosis. Although transthoracic contrast echocardiography may suggest the presence of a shunt, transoesophageal echocardiography is often required for accurate localization and characterization[10]. Alternatively, diagnostic approaches may include hyperoxia testing, ventilation-perfusion scintigraphy, or assessment of an elevated alveolar-arterial oxygen gradient[11]. As demonstrated in the present case, multiple pathophysiologic mechanisms may coexist, and intrapulmonary shunting should be carefully considered as a potential aetiology.

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