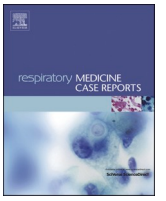
Respiratory Medicine Case Reports 41 (2023) 101791

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

High altitude pulmonary edema at 2640 m altitude associated with an acute Rhinovirus infection. First case in the literature

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ARTICLE INFO

Keywords:
Pulmonary edema of mountaineers
Rhinovirus
Respiratory distress syndrome
Respiratory tract infections
Pneumonia
Viral

ABSTRACT

High altitude pulmonary edema (HAPE) is a multifactorial condition that may occur after ascent of high altitudes, especially in genetic predisposed individuals. Diagnosis is challenging and could lead to potentially lethal complications such as acute respiratory distress syndrome (ARDS). We present one of the few reported cases of HAPE below 3000 m of altitude, and the first to our knowledge to present with a concomitant acute Rhinovirus infection, precipitating and complicating the diagnosis and clinical course. Clinical manifestations, treatment, and outcomes are shown below.

1. Introduction

HAPE is a potentially lethal condition that tends to occur two to five days after the ascent of heights greater than 2500–3000 m [1–3]. Many factors contribute to the development of this condition such as oxygen decrease, rate of ascent, strenuous exercise, cold weather, recent acute respiratory infections, and male sex [2–4]. Genetic factors have also been described, such as missense mutations in the Janus kinase 2 gen (jak2) and in the p1b1 cytochrome genes; and a deletion in the histidine rich glycoprotein (HRG), which increases the probability of presenting HAPE at young ages [5,6].

2. Case report

A previously healthy 25-year-old man presented to the emergency department in Bogotá, Colombia with complaints of three days of progressive dyspnea, orthopnea, nonproductive cough, asthenia, adynamia, general malaise, and fever. He arrived three days ago after a six-month trip from Connecticut, USA, where he had previously visited on three occasions without having presented any symptoms. He mentioned having a recent exposure to soil and organic material during excavation activities in a forestall area in Connecticut two days before the trip, with no use of personal protective equipment. His symptoms started right before the flight, with a mild fever and general malaise, but worsened progressively after having arrived in Bogotá.

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https://doi.org/10.1016/j.rmcr.2022.101791
Received 6 August 2022; Received in revised form 1 December 2022; Accepted 7 December 2022
Available online 9 December 2022

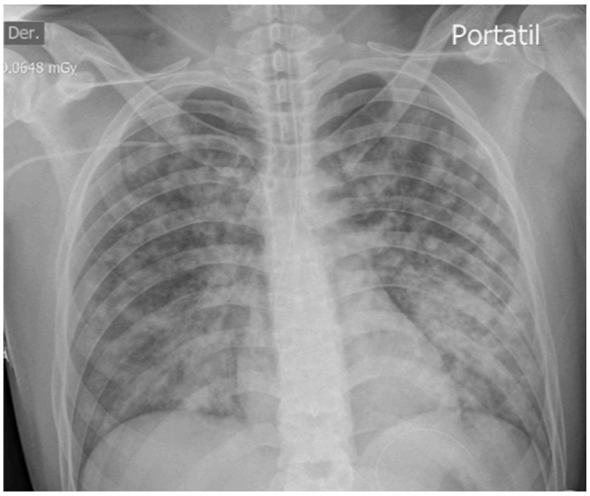

Fig. 1. Chest X-ray on admission showed symmetrical lung fields with multiple alveolar opacities of nodular appearance with a tendency to coalescence on both lung bases.

Upon physical examination, he was in poor general condition, with an arterial blood pressure of 120/78 mmHg, a body temperature of 36.4 °C, and a heart rate of 140 beats per minute. His blood oxygen saturation quantified by pulse oximetry was 50%, with signs of respiratory distress and use of accessory muscles of breathing. Auscultation revealed rhythmic heart sounds and generalized rales in both lung fields. His extremities were well perfused, with a bilateral grade I edema in the lower limbs. Following his admission, the patient required orotracheal intubation and invasive mechanical ventilation. Chest X-ray and admission laboratories are shown in Fig. 1 and Table 1, respectively.

An initial diagnosis of acute respiratory distress syndrome (ARDS) secondary to a respiratory infection was considered, and antibiotic and corticosteroid therapy were started with ampicillin-sulbactam and dexamethasone, suspecting typical bacteria versus SARS-CoV-2 infection. He was taken to the intensive care unit (ICU), and a high-resolution chest tomography was obtained, which is shown in Fig. 2A, revealing multilobar consolidation with centrilobular micronodules configuring a tree-in-bud pattern. Due to the recent exposure to soil in the Connecticut area, pulmonary mycosis versus infection by atypical mycobacteria was considered too, and coverage with liposomal amphotericin B and clarithromycin was added two days after admission. A fibrobronchoscopy with bronchoalveolar lavage was performed, with collection of samples for a transbronchial lung biopsy, and a molecular infectious panel; serum immunological and infectious studies were also collected, which are shown in Table 2.

The molecular panel revealed an acute infection by Rhinovirus/Enterovirus, but due to the severity of the clinical presentation and the radiological pattern, it was considered necessary to rule out other etiologies. Metastases and vasculitis were considered as low

Table 1
Laboratory findings during hospitalization.

Laboratory	Admission	Discharge
White blood cell count (x10^3/μL)	9.32	4.97
Neutrophils (x10^3/μL)	7.81 (83.7%)	1.45 (29.1%)
Lymphocytes (x10^3/μL)	0.74 (10.1%)	1.99 (40%)
Monocytes (x10^3/μL)	0.74 (6%)	0.44 (8.8%)
Eosinophils (x10^3/μL)	0.30 (4%)	1.04 (21.1%)
Hematocrit (%)	43.8	39.9
Hemoglobin (g/dL)	14.5	13.2
MCV (fL)	93.8	93.6
MCH (pg)	29.4	30.9
MCHC (g/dL)	32.7	33
RDW (%)	12.4	13
Platelets (x10^3/μL)	164	371
C-reactive protein (mg/L)	78.1	12.29
Blood urea nitrogen (mg/dL)	23.7	12.3
Creatinine (mg/dL)	0.96	2.02
pH	7.24	7.43
SaO2 (%)	96.9	94.2
PaO2 (mmHg)	125.3	76.4
PaCO2 (mmHg)	47.6	30.6
HCO3 (mmol/L)	20	20
Base excess (mmol/L)	−7.6	−3.3
FIO2	0.8	0.21

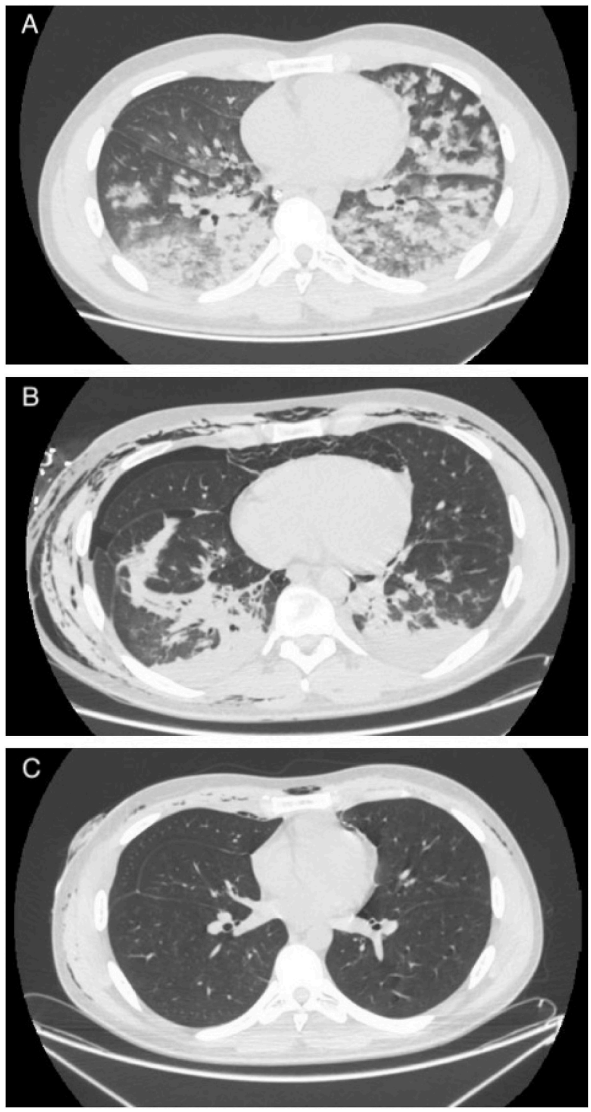

Fig. 2. Progression of chest computed tomography. **Panel A:** Computed tomography on admission showed multiple patchy and coalescent areas corresponding to centrilobular micronodules in a tree-in-bud pattern, and discrete areas of ground glass opacities with compromise of both lung fields, especially in the inferior lobes. **Panel B:** Computed tomography five days from admission showed a significant decrease in multinodular opacities in comparison to the previous study, with persistence of centrilobular micronodules in a tree-in-bud pattern in the superior lobes and lingula. Residual anterior pneumothorax in the right hemithorax and extensive pneumomediastinum and subcutaneous emphysema. **Panel C:** Computed tomography thirteen days from admission showed complete resolution of ground glass opacities and centrilobular micronodules in comparison to previous studies, resolution of right pneumothorax, and significant decrease of pneumomediastinum and subcutaneous emphysema.

probability due to the rapid clinical progression and the negative immunological panel, respectively. During ICU stay, the patient presented an acute right pneumothorax secondary to a central venous catheter procedure, with requirement of a thoracostomy tube, after which, he also presented a pneumomediastinum and subcutaneous emphysema in relation to the procedure. Evolution afterwards was favorable, allowing extubation four days after admission. A control computed tomography of the chest was performed to check on the pneumomediastinum (Fig. 2B), which revealed a marked improvement in the parenchymal lesions only five days apart from the initial tomography. This finding strongly suggested a hydrostatic etiology probably due to HAPE.

As evolution continued to improve, a negative report of procalcitonin, fungal, and mycobacterial studies ruled out bacterial pneumonia and pulmonary mycosis. Since radiological and clinical improvements were highly suggestive of HAPE, the antibiotics and antifungal therapy were discontinued a week after their initiation. A complete resolution of tomographic lesions was achieved in less than two weeks after admission, with an almost complete resolution of the pneumomediastinum and subcutaneous emphysema (Fig. 2C). The patient was considered to have an acute case of HAPE, possibly precipitated and complicated by an acute Rhinovirus infection, and was discharged from the hospital without supplemental oxygen requirements, with the indication of pharmacological prophylaxis therapy in case of new heights ascending.

Table 2
Summary of immunological, infectious, and pathological data.

Laboratory	Specimen	Results
Anti-nuclear antibodies	Blood	Negative
Anti-neutrophil cytoplasmic antibodies	Blood	Negative
Histoplasma Capsulatum antigen	Blood	Negative
Histoplasma Capsulatum antibodies	Blood	Negative
Cryptococcus antigen latex agglutination test	Blood	Negative
Galactomannan antigen test	Blood	Negative
Procalcitonin	Blood	Negative
Histoplasma Capsulatum antigen	Urine	Negative
Culture for common microorganisms	Bronchoalveolar lavage	Negative
Baciloscopy	Bronchoalveolar lavage	Negative
KOH test	Bronchoalveolar lavage	Negative
Galactomannan antigen	Bronchoalveolar lavage	Negative
BioFire ® FilmArray ® Pneumonia Panel	Bronchoalveolar lavage	Positive for Human Rhinovirus/Enterovirus
Transbronchial lung biopsy	Right lower lobe	Pulmonary parenchyma consisting of broken alveoli with spaces occupied by recent bleeding, accompanied by neutrophils and pigmented histiocytes. No granulomas, microorganisms, or malignancy were observed

3. Discussion

HAPE is a multifactorial condition that may occur after ascent of heights greater than 2500–3000 m [1,3]. Its pathophysiology is not completely understood, a decrease in barometric pressure leads to a certain degree of hypobaric alveolar hypoxia, which in healthy individuals are compensated by the activation of adaptive mechanisms that favor oxygenation, such as an increase in ventilatory response and sympathetic tone. However, in individuals with a genetic predisposition or poor adaptation to hypoxic states, the physiological response manifests with exaggerated pulmonary vasoconstriction that eventually increases alveolar capillary and microvascular pressure. At this point, asymmetric regional pulmonary perfusion and increased capillary permeability occur, favoring extravasation of the plasma content into the interstitial and alveolar spaces, which disturbs the ventilation/perfusion ratio and diffusion leading to hypoxemia [2,5].

The global incidence of HAPE has been reported from less than 0.01–31% [7]. The clinical presentation usually consists of ARDS, dry cough, headache, pulmonary rales, tachypnea, and tachycardia, among other signs and symptoms [2,8]; with a radiological pattern of bilateral and multilobar ground glass opacities in a "butterfly wing" shape, suggesting partial alveolar occupation of hydrostatic etiology. Its diagnosis is challenging since the lack of a gold standard test, but usually responds well to the initiation of positive pressure ventilation [9,10]. The present case describes the occurrence of HAPE in a previously healthy patient who traveled from Connecticut, USA (mean elevation of 152 m above sea level) to Bogotá, Colombia (mean elevation of 2640 m above sea level). This would be among the first cases reported to our knowledge of HAPE presenting below 3000 m, with an absolute elevation of 2488 m. Walker C. et al. [11] describe a case of HAPE in a patient in Ohio, USA, with a recent elevation of approximately 2926 m after a trip to Breckenridge, USA; while, other reported cases worldwide are described in heights above 3000 m [4,8,11–14].

There were certain aspects in this case that initially did not favor the diagnosis of HAPE. The presence of inflammatory response syndrome and the tomographic findings of centrilobular micronodules organized in a "tree-in-bud" pattern, suggested an infectious etiology with an inflammatory compromise of the small airways. The recent history of exposure to soil in an area epidemiologically associated with *Aspergillus* spp. suggested a pulmonary mycosis, and since the case presented in 2020 during the COVID pandemic, a SARS-CoV-2 pneumonia was also considered amongst the differential diagnosis. The findings of the fibrobronchoscopy and the bronchoalveolar lavage were inconclusive but suggestive of an inflammatory process, and the microbiological studies were all negative except for a Rhinovirus/Enterovirus infection which, alone, didn't explain the whole clinical picture.

A rapid clinical and radiological improvement was presented soon after the initiation of mechanical ventilation. The diagnosis of pulmonary mycosis was ruled out after the negative result of fungal studies and the rapid tomographic resolution, which allowed early antifungal therapy discontinuation considering a diagnosis of HAPE. To date, such a rapid radiological improvement has not been described in cases of pulmonary mycosis, which usually takes from 6 to 12 months, with some reports ranging from 4 to 36 months [15–17]. Our case describes a marked radiological improvement in only 5 days from admission and a complete resolution of tomographic lesions in less than two weeks, which is in accordance with the median time of radiological resolution reported in cases of HAPE, of approximately 3 days [8,12,14,18,19]. Regarding the molecular detection of Rhinovirus, acute viral infections along with genetic predispositions have been described to play an important role precipitating HAPE events [2,3]. Acute viral respiratory infections and the local inflammatory response of the airways lead to an increase in pulmonary capillary permeability, increasing the risk of edema formation and possibly increasing the risk of presenting HAPE, even in lower heights and under slower rates of ascends [3]. In fact, observational reports describe that a high proportion of children presenting HAPE at relatively low altitudes had a pre-existing infection of the upper respiratory tract or middle ear [20]. Similar observational reports in adults have also been described to a lesser proportion [3]. The clinical presentation in this case suggests that the acute Rhinovirus infection presented early in the development of the disease, even before the flight, for which we think could both precipitate and complicate the course of HAPE. Some confounding factors, such as the inflammatory response syndrome and the tomographic findings suggestive of inflammatory compromise of the small airways, could also be explained by the Rhinovirus infection. This association of HAPE and Rhinovirus infection leading to severe ARDS had not been described previously.

4. Conclusions

- The diagnosis of HAPE is challenging and is usually an exclusion diagnosis. Treatment consists of supplementary oxygen, supportive therapy, diuretics, and, in some cases, high flow oxygen and positive airway pressure delivering systems. In case of new trips, pharmacological prophylaxis aimed at reducing pulmonary artery pressure is suggested to avoid new episodes of pulmonary edema.
- Many factors could contribute to the development of HAPE. Acute viral respiratory infections have been principally described as a risk factor in children, but it could also trigger an episode of HAPE in genetically predisposed adults. These respiratory tract infections could lead to a worse prognosis and difficult the process of diagnosis.
- The present case highlights the importance of considering the hydrostatic etiology as a cause of hypoxemia in patients who have traveled to high-altitude places. There are few reports of this condition below 3000 m of altitude.

Declaration of competing interest

We have no conflicts of interest to disclose.

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