Case Report

Delayed-onset high-altitude pulmonary edema: A series of 8 patients

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Abstract

Clinical studies were performed in eight consecutive patients who developed high-altitude pulmonary edema (HAPE) after 6 days of stay (range: 8–121 days) at the same altitude who were admitted to our hospital. The findings of this series revealed respiratory infection with exertion and cold exposure as the predominant causes of delayed-onset HAPE. HAPE in its delayed-onset form is likely to be more severe based on mortality findings in our series and requires intense monitoring and preparation of contingencies for prompt evacuation in severe or nonresponsive cases.

Keywords: High altitude, hypoxia, pulmonary edema

INTRODUCTION

High-altitude pulmonary edema (HAPE) is a life-threatening medical condition of high altitude and usually occurs within 2–4 days of ascent to an altitude above 8000 ft. This period of occurrence enables prevention by taking precautions in the form of gradual ascent and drug prophylaxis.[1] The interest in high-altitude illness is primarily due to increased movement of sojourners to altitudes above 8000 ft for recreational, professional, military, and adventure activities. This series is based on the hospital data in the Ladakh region of Jammu and Kashmir State, India, at an altitude of 11,500 ft. In a population of predominantly lowlanders entering high altitude (~5–6 times a year) for professional reasons, intensive public health initiatives in the form of mandatory acclimatization and gradual ascent have resulted in fall in the incidence of HAPE. This scenario has also resulted in a variation in the presentation of this condition. Till now, only a few cases of HAPE after more than 6 days at the same altitude or HAPE in resident highlander (high-altitude resident pulmonary edema, HARPE) are reported.[2-7] Here, we report a series of 8 patients admitted for HAPE occurring after more than 6 days at the same altitude.

METHODOLOGY

During the 1-year study period, 147 patients (young soldier native of low altitude) were admitted with HAPE to our hospital located at an altitude of 11,500 ft, of them 8 (1.9%) patients developed HAPE after 6 days of stay (range: 8–121 days) at the same altitude. All patients were healthy young male soldiers (age range: 28–40 years), and the diagnosis of HAPE was suspected on the following criteria: cough, dyspnea on history, tachypnea, crepts on

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chest auscultation, resting room air hypoxemia (oxygen saturation: <90%) determined on pulse oximetry, and the presence of pulmonary infiltrates on chest radiograph. Grade of HAPE severity was assessed as per classification given in Table 1.[8] Detailed history and medical examination were carried out to find the risk factors contributing to the development of HAPE even after proper acclimatization. Treatment consisted of bed rest, fluid restriction, nifedipine, and oxygen inhalation in all patients and evacuation to a lower altitude in two patients who failed to maintain the oxygen saturation on high-flow oxygen inhalation. The findings of all patients were recorded including response to treatment, details of entry to high altitude, and height of stay prior to onset of symptoms.

RESULTS

The clinical details of the patients with delayed-onset HAPE are presented in Table 2. All patients were young male soldier (resident of low-altitude posted to high altitude) with a mean age of 34 years (range: 28–40 years), physically active (moderate-to-high-intensity physical activity for 1 h at least 4–5 times a week), and had no previous chronic medical comorbidities. All patients had previously entered high altitude and stayed at moderate high altitude after successful acclimatization [Table 2]. All patients had symptoms of cough, dyspnea, crepts on chest auscultation, and hypoxemia determined by pulse oximetry. All cases reported were admitted in winter and cold exposure (night temperature of −20°C–−30°C and daytime temperature of −2°C–−4°C) was a consistent finding in all patients. All patients had heating arrangement during sleep except no 3 patient who slept without proper heating arrangements. Evaluation of risks factor revealed that respiratory infection with exertion and cold exposure were the predominant causes of delayed-onset HAPE. In one patient, evaluation could not be done due to severe respiratory distress along with clouded consciousness (patient no 4). Mortality was much higher (4 deaths of 8 patients; 50%) in delayed-onset HAPE group as compared to classical HAPE (one death of 139 patients; 0.72%). In patients with delayed-onset HAPE, two deaths occurred despite air evacuation (done after 36 h of hospitalization – patient numbers 2 and 8) to lower altitude as compared to excellent recovery in classical HAPE despite being managed at the same altitude. Of four patients who deceased, two patients had concurrent respiratory infection (patient numbers 2 and 8), one reported late (5 days after development of HAPE – patient no 6), and one had severe HAPE at the time of presentation (patient no 4). One patient developed delayed-onset HAPE after 8 days of stay at extreme high altitude. More than 60% of patients were suffering from upper respiratory infections or influenza-like illness. Two patients gave a history of unaccustomed exertion: one associated with cold exposure and one with acute pharyngitis. Autopsy findings were consistent with the diagnosis of HAPE in all four deceased patients along with high-altitude cerebral edema in one (patient no 4).

DISCUSSION

HAPE is one of the most common causes of mortality in regions with heights above 8000 ft. In this case series, we describe the occurrence of HAPE beyond 6 days of stay at high altitude. The severity, risk of complications, and mortality observed in this form of HAPE are much higher compared to HAPE in its classical form despite similar initial clinical and radiological presentation in both the HAPEs. In addition, two patients in the series showed an inadequate response to regular management including descent and expired despite evacuation to near sea level.

The exact mechanism leading to the development of delayed-onset HAPE after prolonged stay at high altitude is not clear. Most of our patients had a history of previous (<1 week) or concomitant respiratory tract infection and unaccustomed exertion. Since all the cases were admitted in winter, cold exposure cannot be ruled out during daily activities. Hence, it is likely that cold exposure was underreported in our study, as central heating facilities were not available to the population under study prior to admission. It is likely that respiratory infections and unaccustomed exertion in the background of cold exposure could have resulted in delayed-onset HAPE similar to cases of HARPE in children who develop pulmonary edema at

Table 1: Severity classification of high-altitude pulmonary edema

Grade	Clinical symptoms	Heart rate/min	Respiratory rate/min	Chest radiograph
Mild	Minor symptoms with dyspnea on moderate exertion	<110	<20	Minor opacities involving <1/4 of one lung field
Moderate	Symptoms of dyspnea, weakness, fatigue on slight effort, and headache with cough	110-120	20-30	Opacities involving ½ of one lung field
Serious	Severe dyspnea, headache, weakness, nausea at rest, and recurrent productive cough	121-140	31-40	Opacities involving at least ½ of each lung field or unilateral exudates involving whole one lung field
Severe	Clouded consciousness, unable to stand or walk, severe cyanosis, copious sputum, usually bloody Severe respiratory distress	>140	>40	Bilateral opacities involving >½ of each lung field

Table 2: Summary of patients with delayed-onset high-altitude pulmonary edema

Height of occurrence (ft)	Onset (days)	Severity	Number of times entry to high altitude over lifetime	Risk factors	Treatment	Outcome
18,000	8	Serious	4	Extreme high altitude	Oxygen, rest, descent to an altitude of 11,500 ft	Recovered after 1 day
11,500	30	Serious	4	Concomitant acute tonsillitis	Oxygen, rest, antibiotics, nifedipine, evacuation, and invasive ventilation	Deceased within 12 h of air evacuation
14,000	44	Serious	7	Exertion in day and slept in extreme cold	Oxygen, rest, descent to altitude of 11,500 ft	Recovered after 5 days
11,500	47	Severe	4	Evaluation could not be done	Oxygen, rest, antibiotics, nifedipine, dexamethasone, evacuation, and invasive ventilation	Deceased within 24 h
11,500	62	Moderate	7	history of influenza-like illness 7 days back and exertion	Oxygen, rest, nifedipine, and fexofenadine	Recovered after 4 days
11,500	92	Serious	3	history of pharyngitis 5 days back	Oxygen, rest, antibiotics, nifedipine, evacuation, and invasive ventilation	Deceased after 2 days
11,500	120	Serious	5	Pharyngitis 6 days back, exertion	Oxygen, rest, and nifedipine	Recovered within 5 days
11,500	121	Serious	3	Concomitant influenza-like illness	Oxygen, rest, antibiotics, nifedipine, evacuation, and invasive ventilation	Deceased within 12 h of air evacuation

high altitude without any change in altitude triggered by upper respiratory tract illnesses.[6,7]

Findings of the series suggest that pathophysiological processes triggered by the above-described risk factors could overcome the protection from HAPE provided by successful acclimatization. Although nonuniform pulmonary vasoconstriction and shear stress have been proposed as pathophysiological mechanisms resulting in HAPE, inflammation may trigger, potentiate, or exacerbate the formation of edema.[9-12] Hence, the release of vasoactive, inflammatory mediators during infection could have resulted in priming of pulmonary endothelium manifesting as HAPE in response to exertion (as in 2 of 8 cases). Animal experiments have demonstrated a rise in oxygen consumption and ventilation with an increase in nor-epinephrine turnover in hypoxic conditions on cold exposure.[13-15] Similar processes in humans during cold exposure in hypoxia could be a possible contributing factor leading to delayed-onset HAPE during cold exposure in association with respiratory infections and exertion.

A study on HAPE at extreme altitude has demonstrated that HAPE cannot be prevented at an extreme altitude beyond 18,000 ft by preinduction acclimatization, mountain training, or prolonged stay at such altitude.[4,16] An isolated case report of a native highlander suffering from HAPE on accustomed exertion raises the possibility of pathophysiological processes overcoming protective effects of acclimatization leading to HAPE.[16] The rare likelihood of delayed-onset HAPE after successful acclimatization could result from a similar phenomenon in susceptible individuals due to interaction of vasoactive inflammatory mediators released due to infection with the endothelium in the background of cold exposure or due to unaccustomed exertion.

The condition of HAPE is managed predominantly by descent to a lower altitude with a recommendation of minimum 1000 m (~3280 ft) descent or till symptoms resolve.[1] In the present series, two patients were evacuated to heights of 1073 ft and 1150 ft from an altitude of 11,500 ft. The decrease in altitude did not result in improvement of symptoms raising the possibility of infection associated pathophysiological mechanisms in addition to the effect of hypobaric hypoxia contributing to the occurrence of delayed-onset HAPE. In the hospital setting, treatment with bed rest and oxygen may be sufficient and evacuation to lower altitude may be unnecessary.[1] Similar management of HAPE at moderate altitude with supplemental oxygen without descent has been successfully carried out in a smaller number in another study.[12] This is in concurrence with our experience in the management of HAPE with oxygen alone at the same altitude. Among other management modalities, continuous positive airway pressure may also improve oxygenation, although the effect on outcomes has only been evaluated in smaller numbers in studies.[14,15] Nifedipine (potent pulmonary vasodilator) at a dose of 60 mg daily in divided doses can be added in patients who worsen or fails to improve with oxygen and bed rest.[14] There is a lack of systematic studies to suggest effectiveness beta-agonists and phosphodiesterases in patients of HAPE.[11] Diuretics are not recommended in the management of HAPE due to possible worsening of volume depletion in patients of HAPE.[11] HAPE being refractory and not responding to oxygen and descent has been observed in another study where all patients were recent inductees to high altitude and diagnosed to have acute respiratory distress syndrome along with HAPE.[17] This possibility could also have resulted in higher mortality than conventional HAPE in the present series. However, in our cases, autopsy findings were consistent with the diagnosis of HAPE.

CONCLUSION

The findings of this series suggest a high index of suspicion for HAPE even after successful acclimatization at high altitude. The likelihood of HAPE rises in association with unaccustomed exercise, concomitant respiratory infections, and cold exposure. HAPE in its delayed-onset form is likely to be more severe based on mortality findings in our series. This requires intense monitoring and preparation of contingencies for prompt evacuation in severe or nonresponsive cases. Furthermore, the interaction of respiratory infections with HAPE should be studied further to enable better prognosis prediction of this life-threatening condition.

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Conflicts of interest
There are no conflicts of interest.

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