Three rare presentations of High Altitude Pulmonary Edema at a high altitude clinic in the Everest region (4371 m): A Case Series

Sachin Subedi[1], Priyanka Regmi[1], Sanjeeb Bhandari[2], and Suvash Dawadi[3]

[1]Tribhuvan University Institute of Medicine
[2]Western Maryland Regional Medical Center
[3]CIWEC Hospital

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Abstract

Presentation of High Altitude Pulmonary Edema (HAPE) in accordance with its usual natural history is a diagnostic clue. In resource-limited settings, distinguishing HAPE from other respiratory illnesses is challenging; especially when the presentation deviates from the natural history. Here we have discussed those three rare presentations of HAPE at 4371m.

Introduction

The beauty of the mountains is 'breathtaking'. They astound us not only with their grandiosity but also by drowning us through uneven pulmonary vasoconstriction. [1] High Altitude Pulmonary Edema (HAPE) does not reveal itself immediately because the pathophysiological changes begin early but progress through clinically silent phases. [2] It usually takes 2 to 5 days and an altitude above 3000m to manifest into its fullest form. [3, 4, 5, 6]. The mountain Gods consider haste as a sign of disrespect. A careless attempt to compete against time makes it difficult to escape their wrath of acute mountain sickness and HAPE. Over-exertion and ascending with respiratory tract infection further increase the chances of suffering. [7, 8]

The clinical features of HAPE share a close resemblance with pneumonia: cough (mostly productive), shortness of breath, fatigue, tachypnea, tachycardia, mild fever, and crepitation. Unfortunately, the locations where HAPE is initially recognized are usually extremely resource-limited: where clues from history and clinical examination form the backbone for making an accurate diagnosis. HAPE and pneumonia are comparable to monozygotic twins, where one takes the blame for another's mischief. Diagnosis becomes more difficult when they both co-exist or are preceded by an upper respiratory tract infection. Ascent profile, duration of altitude exposure, and a previous history of HAPE provide major clues for a diagnosis favoring HAPE. However, in some rare cases of delayed onset HAPE, where the patient develops symptoms after staying at a particularly high altitude for more than 5 days, diagnosis of HAPE becomes a formidable task as alternative diagnoses must also be considered and ruled out.

Oxygenation is the cornerstone for the treatment of HAPE. This can be achieved either through increasing the pressure of inspired air (descent or Gamow bag) or through ventilation (preferably non-invasive). [8, 9, 10, 11] Temporary management with supplemental oxygen until the patient is stable enough to bear the exertion of descent by foot has been in practice in the Himalayan Rescue Association Aid Post. Over the years, this approach has been successful in the aid post. Here we present three unique cases of HAPE that do not show consistency with their usual natural history. We made the diagnosis based on clinical and ultrasonographic parameters using Point of Care Ultrasound (POCUS) (Butterfly iQ)

Clinical Case 1 (Delayed onset HAPE):

A 41 years male with a history of HAPE 13 years back had ascended from Lukla (2860m) to Everest Base Camp (5364 m) within a span of 4 days and had been residing in the Everest Base Camp. On the 11^{th} day at the base camp, he started having shortness of breath, which lasted for 2 days before presenting to HRA Aid Post, Pheriche. A day after the onset of shortness of breath; he started having a productive cough with no fever or chest pain. He had no hypertension or prior medical illness and was not under any medications. The COVID-19 vaccine doses were uptodate as per recommendation but previous vaccination history could not be recalled. On examination, the patient was able to walk into the clinic and was well oriented to time, place and person. There were no signs of respiratory distress. A faint "gurgling" sound from the chest was audible without a stethoscope. His peripheral oxygen saturation was 53%, heart rate was $108min^{-1}$ and axillary temperature was 98.4 degrees Fahrenheit. His blood pressure was 125/80 mm Hg. There was no parasternal heave, pedal edema, hepatomegaly or elevation of JVP. Vocal fremitus was normal bilaterally. A dull percussion note was observed from the 5th intercostal space onwards anteriorly on the right side and from the 4^{th} intercostal space onwards anteriorly on the left side. Auscultation revealed equal air entry along with inspiratory crackles and broncho-vesicular breath sounds in all the chest segments bilaterally. Heart sounds were normal. Ultrasonography of the lungs did not reveal any pleural collections, the lung sliding was normal. However, multiple B-lines with absent A-lines were seen in the anterior and lateral segments, most prominent in the anteroinferior and inferolateral segments. (Figure 1) The patient was given Nifedipine SR 20mg along with oxygen from an oxygen concentrator at 10 $Lmin^{-1}$ for 3 hours, following which he got evacuated to a well-facilitated center. During his stay, his oxygen saturation improved from 53% to 91%. The patient apparently improved with treatment in a hospital for 4 days but could not be contacted following descent.

Clinical Case 2 (Early onset HAPE):

A 29 years lowlander male had been working as a porter in Namche for 2months, shifting loads up and down from Namche(3400m) to Pangboche(3800m). During a particular trip from

Namche, while he was carrying a heavy load from Pangboche (where he stayed a night on the way) to Thukla; at around 4500m, he started having persistent cough and shortness of breath that persisted on rest. He had no fever. His cough was frequently productive with "watery-bubbly sputum". As he was severely short of breath, he spent the night inside a cave. He descended to the clinic after no improvement of symptoms the next morning. Upon arrival, the patient was well oriented but was having labored breathing and using accessory muscles. There was fatigue without headache, nausea or dizziness. No symptoms suggestive of pneumonia or upper respiratory tract infection were present prior to decompensation. 3years ago, he suffered from HAPE at Amolapcha base (5000 m) and was treated in Lukla for a week. He had no hypertension or any other medical conditions. The COVID-19 vaccine doses were uptodate as per recommendation but previous vaccination history could not be recalled. His heart rate was 105 min^{-1}, blood pressure was 122/86 mm Hg, respiratory rate was 32 min^{-1}, oxygen saturation at room air was 67% and the oral temperature was 99.1 degrees Fahrenheit. There was no pedal edema, parasternal heave or hepatomegaly. Vocal fremitus was normal. Auscultation revealed inspiratory crepitations in the infra-axillary regions bilaterally. USG revealed multiple comet tail signs on the inferior axillary regions bilaterally, which were more prominent on the right side. (Figure 2) The B-lines in other segments were not as prominent. There was no consolidation. Oral Nifedipine SR 20mg three times a day was started along with O_2 from an oxygen concentrator at 10L min^{-1} via facemask. The treatment improved SpO_2 to 98% within 15 minutes. His oxygen saturation was maintained at 93% from oxygen at 3L min^{-1}. Cough remitted and shortness of breath resolved the next morning. His saturation in room air was 91% at rest and 88% following a short walk. He was advised to descend while continuing Nifedipine for 3 days. However, his descent happened only after he somehow managed to deliver the goods up to Thukla.

Clinical Case 3 (Unilateral HAPE):

A 32 years female presented to the clinic with a cough for 8 days. The productive cough started at 2800m in Phakding and was associated with fever. Initial symptoms got resolved after 7 days of Amoxicillin. However, there was some remnant intermittent dry cough. At Lobuche (4800m) she started having persistent coughs

with "watery" sputum. Persistent cough brought her to the high-altitude clinic at 4200m. She had shortness of breath during descent but no shortness of breath at rest or lying down. She had no fever, chest pain or palpitation. She had a mild generalized headache at Lobuche, which resolved following descent. Her appetite was normal; she had no nausea, vomiting or dizziness. She had been taking acetazolamide along with chlorpheniramine-bromhexine cough syrup prior to her arrival at the clinic. She had no significant medical history. Vaccination status was up-to-date. There was no history of altitude-related illness in her only altitude trip to 4200m. The patient was able to walk comfortably to the clinic. Her heart rate was 115, oxygen saturation was 77%, respiratory rate was 16 min^{-1}, blood pressure was 126/82 and oral temperature was 98.8 degrees Fahrenheit. There were no signs of respiratory distress or pedal edema. The apex beat was palpable on the 5^{th} intercostal space in the midclavicular line. There was no parasternal heave. Vocal fremitus was normal in all segments. Heart sounds were normal. There was equal air entry with broncho-vesicular sounds in all segments of both lungs except the right inferior regions that had late coarse inspiratory crackles, which persisted until the early expiratory phase. Chest ultrasonography revealed no pericardial or pleural collection. Lung sliding was normal bilaterally. Left-sided chest ultrasonography revealed multiple A-lines with no signs of consolidation. However, Right-sided chest ultrasonography revealed A-lines along with multiple moderately interspaced B-lines (7-8) on the inferior segment, but no signs of consolidation. The superior segments revealed A-lines with few B-lines (5-6) (Figure 3). Dexamethasone 8mg was given immediately; followed by Nifedipine SR 20 mg, three times a day and tablet Dexamethasone 4mg four times a day. The oxygen concentrator provided oxygen at 6L min^{-1} via a simple facemask. Within 30 minutes of treatment, her oxygen saturation improved to 93% and her heart rate to 102 min^{-1}. Her cough was relieved 2 hours after starting the treatment. She received treatment in the clinic for 12 hours. Following overnight treatment, her cough remitted while saturation improved to 85% on room air. However, there were persistent late inspiratory crackles, albeit of lesser duration and intensity. On repeat ultrasonography, there were 2 B-lines in the left inferior chest fields. (Figure 4) There was no immediate rescue available, so she had to stay for another day at the same altitude without oxygen. She was then discharged on 2 more doses of Dexamethasone and Nifedipine 20 mg three times per day until descent and was asked to stay very close to the treatment facility. She descended the day after the discharge. Upon further contact, she stated that had no cough or difficulty breathing and had a sound sleep on the night after her discharge.

Discussion

Due to resource limitations, other differential diagnosis like pneumonia could not be ruled out with a guarantee in any of the cases. However, many symptoms, examination findings, young age, absence of significant past medical history more importantly, ultrasonography findings suggesting pulmonary edema along with rapid improvement in symptoms and oxygen saturation within a very short period of oxygen in all three patients make a strong case favoring the diagnosis of HAPE.

Certain preventive measures can be applied to minimize the modifiable risks of HAPE: gradual ascent (via vascular remodeling) [2, 8, 9] and Nifedipine (via reduction in pulmonary artery pressure) [2, 7, 8, 9] and with moderated exertion. However, certain non-modifiable risk factors, especially those attributable to higher pulmonary artery pressure [12], stronger hypoxic pulmonary vasoconstriction [12], reduced nitric oxide [13], inappropriate sympathetic response [13], congenital heart defects (e.g. patent foramen ovale) have their own share of hidden role in causing HAPE. Hypoxic pulmonary vasoconstriction response primarily functions to reduce the ventilation-perfusion mismatch created by a diseased lung segment. It, however, also works as the main pathophysiological phenomenon behind HAPE. In the background of individual risk factors, regional variability in response to pan-hypoxia [14, 15, 16], and stress failure of capillaries [1] makes some individuals more susceptible to this non-inflammatory, non-cardiogenic exudative edema.[17]

Hypoxic vasoconstriction of some arteries shifts the pressure to other arteries. Adaptation involves remodeling of such arteries over the period of hours to days so that the downstream capillaries are protected from damage due to redirected pressure. This remodeling usually gets completed within 5 days. [5, 6, 18] However, few case reports, including a case series of eight patients have described delayed onset HAPE where symptoms began after 5 days. [19] While there is no clear explanation for such a phenomenon, few hypotheses attribute

the triggers to risk factors related to individual physiological differences, infection [20] and overexertion [21], which overcome the protection provided by proper acclimatization. [19, 22] It can also be hypothesized that individuals susceptible to delayed onset HAPE might either have a slower pulmonary vascular remodeling process at high altitude or have underlying congenital defects that could create a physiological base where a single 'push factor' in the form of infection, overexertion, etc. could trigger HAPE. The high recurrence rate of HAPE in individuals with a history of HAPE further supports the interplay of underlying individual risk factors. [23] Re-entry HAPE among highlanders shows that the previously obtained adaptive features can reverse upon migration away from the hypoxic high-altitude environment. [24]

In our series, even though the first and the second case patients had no evident features suggestive of respiratory infection; in the background of their probable physiological susceptibility, overexertion led to a rise in cardiac output and pulmonary artery pressure. The increase in these two parameters probably served as a trigger for HAPE. [25] Impairment of their alveolar ENaC channels in response to hypoxia and hypothermia could have played a role as well. [26]

In our third case, preceding pulmonary injury due to infection probably predisposed the affected lung towards HAPE. Pre-existing ventilation-perfusion mismatch along with endothelial stress leading to impaired fluid clearance must have played a significant role in the development of HAPE isolated to a single lung.

In all three cases, POCUS has played an important part in the diagnosis. It can provide an objective measure of a patient's response to treatment as in our third case. However, the correlation between clinical and ultrasonography findings during the course of treatment needs to be studied.

Conclusion :

Diagnosis of HAPE can get challenging when it deviates from the course of its natural history. Association to over-exertion or respiratory illness can contribute to such a phenomenon. The threshold for diagnosis and treatment should be lowered in a resource-limited setting, especially in young adults presenting with a dubious picture, who have minimal risk factors for other acute lung diseases. POCUS is a great asset for early diagnosis of HAPE in resource-limited settings. Its role in HAPE monitoring needs to be explored further.

Abbreviations:

HAPE: High Altitude Pulmonary Edema

HRA: Himalayan Rescue Association

JVP: Jugular Venous Pressure

ENaC: Epithelial Sodium Channel

POCUS: Point of Care Ultrasonography

Consent for publication : Written informed consent was obtained from all three patients. A copy of written consent is available for review by Editor-in-Chief of this journal on request.

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Author's contribution :

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References

1. West JB, Tsukimoto K, Mathieu-Costello O, Prediletto R. Stress failure in pulmonary capillaries. J Appl Physiol. 1991;70(4):1731-42.

2. Swenson ER. Early hours in the development of high-altitude pulmonary edema: time course and mechanisms. J Appl Physiol (1985). 2020;128(6):1539-46.

3. Bärtsch P, Swenson ER. Clinical practice: Acute high-altitude illnesses. N Engl J Med. 2013;368(24):2294-302.

4. Saibal A, Menon AK, Bhatnagar S, Singh Sanjeev. Clinico-epidemiological profile of high altitude pulmonary edema. International Journal Of Community Medicine And Public Health, 2021;8(1):196-200.

5. Stenmark KR, Frid M, Nemenoff R, Dempsey EC, Das M. Hypoxia induces cell-specific changes in gene expression in vascular wall cells: implications for pulmonary hypertension. In: Roach RC, Wagner PD, Hackett PH (eds). Hypoxia: into the next millennium. Advances in experimental medicine and biology. PA: Springer, Boston, MA; 1999:474: 231–58.

6. West JB, Mathieu-Costello O. Structure, strength, failure, and remodeling of the pulmonary blood gas barrier. Annu Rev Physiol. 1999;61:543-72.

7. Bärtsch P, Maggiorini M, Ritter M, Noti C, Vock P, Oelz O. Prevention of high altitude pulmonary edema by nifedipine. N Engl J Med 1991;325(18):1284–9.

8. Stream JO, Grissom CK. Update on high-altitude pulmonary edema: pathogenesis, prevention, and treatment. Wilderness Environ Med. 2008;19(4):293–303.

9. McIntosh SE, Freer L, Grissom CK, Auerbach PS, Rodway GW, Cochran A, et al. Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Frostbite: 2019 Update. Wilderness Environ Med. 2019;30(4S):S19-S32.

10. Singhal S, Bhattachar AS, Rungta S. Management of HAPE with bed rest and supplemental oxygen in hospital setting at high altitude (11,500 ft): A Review of 43 Cases. The Journal of Association of Chest Physicians.2017;5(1):31-34.

11. Gallagher SA, Hackett PH. High-altitude illness. *Emerg Med Clin North Am* . 2004;22(2):329-55.

12. Maggiorini M, Mélot C, Pierre S, Pfeiffer F, Greve I, Sartori C, et al. High-altitude pulmonary edema is initially caused by an increase in capillary pressure. Circulation. 2001;103(16):2078-83.

13. Li Y, Zhang Y, Zhang Y. Research advances in pathogenesis and prophylactic measures of acute high altitude illness. Respir Med. 2018;145:145-152.

14. West JB. The physiologic basis of high-altitude diseases. Ann Intern Med. 2004;141(10):789–800.

15. Dehnert C, Risse F, Ley S, Kuder TA, Buhmann R, Puderbach M, et al. Magnetic resonance imaging of uneven pulmonary perfusion in hypoxia in humans. *Am J Respir Crit Care Med* . 2006;174(10):1132-8.

16. Hopkins SR, Garg J, Bolar DS, Balouch J, Levin DL. Pulmonary blood flow heterogeneity during hypoxia and high-altitude pulmonary edema. Am J Respir Crit Care Med. 2005;171(1): 83–87.

17. Swenson ER, Maggiorini M, Mongovin S, Gibbs JS, Greve I, Mairbäurl H, et al. Pathogenesis of high-altitude pulmonary edema: inflammation is not an etiologic factor. JAMA. 2002;287(17):2228 –35. Erratum in: JAMA 2002 Sep 4;288(9):1064.

18. West JB, Mathieu-Costello O. Strength of the pulmonary blood-gas barrier. Respir Physiol. 1992;88(1-2):141-8.

19. Singhal S, Srinivasa AB, Delayed-onset high-altitude pulmonary edema: A series of 8 patients. Environmental Disease.2020;5(2):52-55.

20. Murdoch DR. Symptoms of infection and altitude illness among hikers in the Mount Everest region of Nepal. Aviat Space Environ Med. 1995;66(2):148-51.

21. Roach RC, Maes D, Sandoval D, Robergs RA, Icenogle M, Hinghofer-Szalkay H, Lium D, Loeppky JA. Exercise exacerbates acute mountain sickness at simulated high altitude. J Appl Physiol (1985). 2000;88(2):581-5.

22. Zafren K, Reeves JT, Schoene R. Treatment of high-altitude pulmonary edema by bed rest and supplemental oxygen. Wilderness Environ Med. 1996;7(2):127-32.

23. Eichstaedt CA, Mairbaurl H, Song J, Benjamin N, Fischer C, Dehnert C, et al. Genetic Predisposition to High-Altitude Pulmonary Edema. High Alt Med Biol. 2020;21(1):28-36.

24. Santosh Baniya, Christopher Holden, and Buddha Basnyat.Reentry High Altitude Pulmonary Edema in the Himalayas.High Altitude Medicine & Biology.Dec 2017.425-427

25. Basnyat B. High altitude cerebral and pulmonary edema. Travel Med Infect Dis. 2005;3(4):199-211

26. Sartori C, Allemann Y, Duplain H, Lepori M, Egli M, Lipp E, et al. Salmeterol for the prevention of high-altitude pulmonary edema. N Engl J Med. 2002;346(21):1631–6.