

CASE REPORT

Three rare presentations of high-altitude pulmonary edema at a high-altitude clinic in the Everest region (4371 m): A case series

Sachin Subedi^{1,2}  | Priyanka Regmi² | Sanjeeb S. Bhandari^{2,3} | Suvash Dawadi^{2,4}¹Institute of Medicine, Tribhuvan University, Maharajgunj, Nepal²Himalayan Rescue Association of Nepal, Kathmandu, Nepal³Department of Emergency Medicine, Western Maryland Medical Center, Cumberland, Maryland, USA⁴CIWEC Hospital, Kathmandu, Nepal**Correspondence**

Sachin Subedi, Institute of Medicine, Tribhuvan University, Maharajgunj, Nepal.

Email: imsachinsubedi@gmail.com**Key Clinical Message**

Diagnosis of HAPE can be challenging when the presentation deviates from usual natural history. Point of care ultrasonography serves as a great diagnostic tool in such settings. An umbrella treatment could be beneficial during such scenarios.

KEYWORDS

case series, delayed onset HAPE, early-onset HAPE, resource-limited settings, unilateral HAPE

1 | INTRODUCTION

The pathophysiological changes of high-altitude pulmonary edema (HAPE) begin early with uneven pulmonary vasoconstriction and progress through clinically silent phases.^{1,2} It takes 2–5 days and an altitude above 3000 m for its complete manifestation.^{3–6} While rapid ascent is an important risk factor, overexertion and ascending with respiratory tract infection further increases the risk.^{7,8}

The diagnosis becomes challenging when both HAPE and pneumonia coexist or if a recent respiratory tract infection has occurred. The initial diagnosis often happens in extremely resource-limited settings, where clues from history and clinical examination form the backbone for making a provisional diagnosis. Major indicators for a diagnosis that favors HAPE include the ascent profile, duration of altitude exposure, and a prior history of HAPE. However, misdiagnosis is likely

to occur in instances where the presentation deviates from the usual natural history, such as in rare cases of late-onset HAPE (symptoms appearing after 5 days at a particular high altitude), early-onset HAPE (symptoms appearing before 2 days at a particular altitude), or unilateral HAPE.

Oxygenation is the mainstay treatment for HAPE. Over the past many years, different clinicians working for the Himalayan Rescue Association (HRA) Aid Post, Pheriche (4240 m) have been managing HAPE with supplemental oxygen until the patient is stable enough to bear the exertion of descent by foot.^{8–11} This approach has yielded positive results in the aid post over the years.

Here we present three unique cases of HAPE that do not run parallel to the natural history. Clinical parameters, point of care ultrasound (POCUS) (Butterfly iQ) and response to treatment helped us diagnose HAPE in these unusual cases.

Abbreviations: ENaC, epithelial sodium channel; HAPE, high-altitude pulmonary edema; HRA, Himalayan Rescue Association; JVP, jugular venous pressure; POCUS, point of care ultrasonography.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2023 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

1.1 | Clinical case 1 (delayed onset HAPE)

A 41-year-old male with a history of HAPE 13 years back had ascended from Lukla (2860 m) to Everest Base Camp (5364 m) within a span of 4 days and had been residing in the Everest Base Camp. On the 11th 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 up-to-date 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 108 min^{-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 fifth intercostal space onwards anteriorly on the right side and from the fourth 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 antero-inferior and inferolateral segments. (Figure 1) The patient was given Nifedipine SR 20 mg along with oxygen from an oxygen concentrator at 10 Lmin^{-1} for 3 h, 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.

1.2 | Clinical case 2 (early-onset HAPE)

A 29-year-old lowlander male had been working as a porter in Namche for 2 months, shifting loads up and down from Namche (3400 m) to Pangboche (3800 m). 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 4500 m, 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. Three years 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 up-to-date 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 20 mg three times a day was started along with O_2 from an oxygen concentrator at 10 Lmin^{-1} via face mask. The treatment improved SpO_2 to 98% within 15 min. His oxygen saturation was maintained at 93% from oxygen at 3 Lmin^{-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.



FIGURE 1 Lung ultrasonography showing multiple B-lines with absent A-lines.

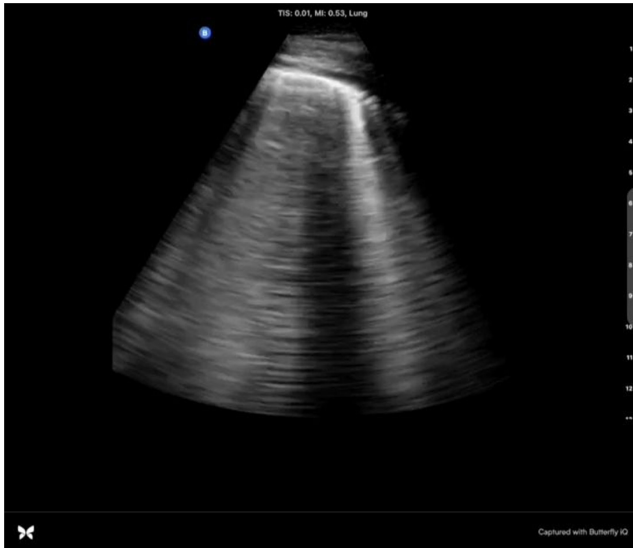


FIGURE 2 Lung ultrasonography showing multiple B-lines with absent A-lines.

1.3 | Clinical case 3 (unilateral HAPE)

A 32-year-old female presented to the clinic with a cough for 8 days. The productive cough started at 2800 m 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 (4800 m) she started having persistent coughs with “watery” sputum. Persistent cough brought her to the high-altitude clinic at 4200 m. 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 4200 m. 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 fifth 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,

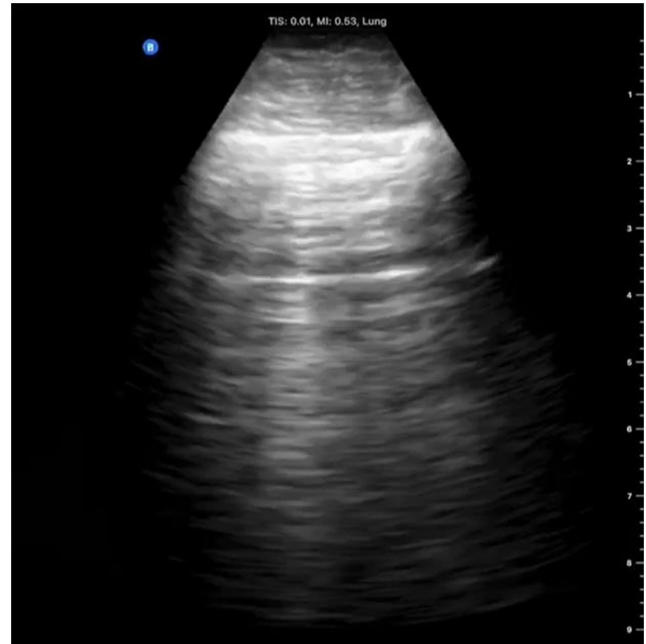


FIGURE 3 Ultrasound of the right lung showing A-lines along with multiple superimposed B-lines.

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 8 mg was given immediately; followed by Nifedipine SR 20 mg, three times a day and tablet Dexamethasone 4 mg four times a day. The oxygen concentrator provided oxygen at 6 L min⁻¹ via a simple face mask. Within 30 min of treatment, her oxygen saturation improved to 93% and her heart rate to 102 min⁻¹. Her cough was relieved 2 h after starting the treatment. She received treatment in the clinic for 12 h. 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 two 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.

2 | DISCUSSION

In the background of limited resources, complete ruling out other differential diagnoses was not possible.

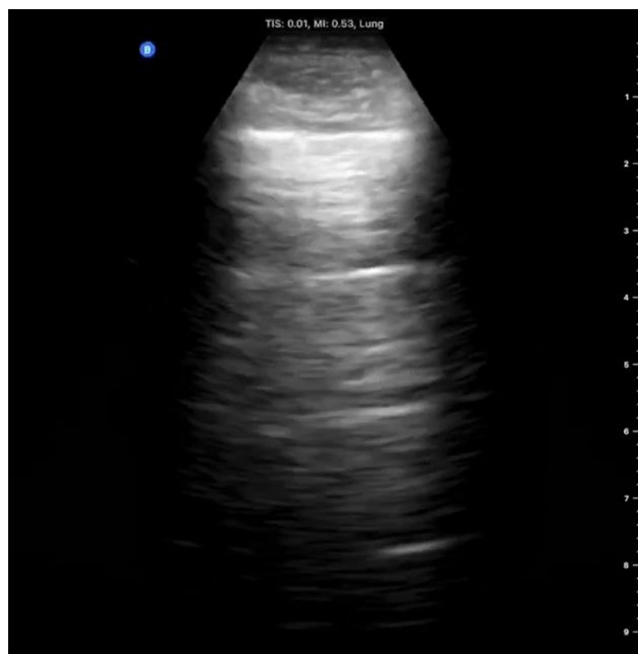


FIGURE 4 Ultrasound image of right lung showing improvement with reduced numbers of B lines (2).

However, the symptoms, examination findings, young age, lack of significant past medical history, ultrasonography findings suggestive of pulmonary edema along with early improvement in symptoms and oxygen saturation within a short period of supplemental oxygen in all three patients strongly favor the diagnosis of HAPE.

Gradual ascent (via vascular remodeling),^{2,8,9} Nifedipine (via reduction in pulmonary artery pressure)^{2,7-9} and moderated exertion can reduce the risk of HAPE. However, there are nonmodifiable risk factors attributable to individual differences, such as higher pulmonary artery pressure,¹² stronger hypoxic pulmonary vasoconstriction,¹² reduced nitric oxide,¹³ congenital heart defects, and inappropriate sympathetic response,¹³ which contribute toward HAPE. Hypoxic pulmonary vasoconstriction response, which is supposed to reduce the ventilation-perfusion mismatch created by a diseased lung segment, is also an important pathophysiological process behind HAPE. In the background of individual risk factors; regional variability in response to pan-hypoxia,¹⁴⁻¹⁶ and stress failure of capillaries¹ make some individuals more susceptible to this noninflammatory, noncardiogenic exudative edema.¹⁷

Hypoxic vasoconstriction of some arteries shifts the pressure to other arteries. In order to protect the downstream capillaries from redirected pressure, such arteries undergo remodeling over the period of hours to 5 days.^{5,6,18} HAPE typically does not manifest after the success of remodeling. However, few case reports, including a case series of eight patients have described delayed onset HAPE, where symptoms had begun after 5 days.¹⁹ While the mechanism

remains unclear, few hypotheses attribute the triggers to infection,²⁰ overexertion²¹ and individual physiological differences in risk factors. The pathological changes attributable to these differences potentially override the protection provided by proper acclimatization.^{19,22} A hypothesis can be formed, wherein, individuals susceptible to delayed onset HAPE might either have a slower pulmonary vascular remodeling process at high altitude or might have underlying congenital defects, where a single “push” in the form of infection, overexertion, etc. could trigger HAPE. High recurrence rate of HAPE in individuals with prior history of it further supports the role of underlying individual risk factors.²³ Even native highlanders are susceptible to “de-adaptation” as suggested by incidences of re-entry HAPE.²⁴

In our first and second cases, there were no evident features suggestive of a prior respiratory infection. We believe that, in the background of probable individual physiological susceptibilities, overexertion might have resulted in an increase in cardiac output and pulmonary artery pressure, which served as triggers for HAPE.²⁵ Impairment of alveolar ENaC channels in response to hypoxia and hypothermia could have played a role as well.²⁶

In our third patient, a preceding pulmonary injury due to infection likely predisposed the affected left lung to HAPE. Endothelial stress from the preceding injury probably led to impaired fluid clearance and could have provided the grounds for developing HAPE isolated to a single lung.

Each patient exhibited high number of B-lines. Our confidence in HAPE as the diagnosis was increased by the absence of additional abnormalities like an air bronchogram, pleural effusion, or irregular lung sliding. As in our third case, POCUS also helped us evaluate the patient's response to treatment. However, further studies are required to determine the relationship between clinical improvement and ultrasound findings over the course of treatment.

3 | CONCLUSION

Diagnosis of HAPE can get challenging when the presentation deviates from the course of its natural history. Association to overexertion or respiratory illness can contribute to such phenomenon. The threshold for diagnosis and treatment should be lower for young adults presenting with no specific history and minimal risk factors for any other respiratory illness. POCUS is a great asset for early diagnosis of HAPE in resource-limited settings. Its role in HAPE monitoring requires further studies.

AUTHOR CONTRIBUTIONS

Sachin Subedi: Conceptualization; data curation; writing – original draft; writing – review and editing. **Priyanka Regmi:** Conceptualization; data curation; writing

– original draft; writing – review and editing. **Sanjeeb Sudarshan Bhandari**: Data curation; writing – review and editing. **Suvash Dawadi**: Data curation; writing – review and editing.

ACKNOWLEDGMENTS

We thank Himalayan Rescue Association for providing assistance and a platform for service.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

None.

CONSENT

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.

ORCID

Sachin Subedi  <https://orcid.org/0000-0002-7503-8041>

REFERENCES

- West JB, Tsukimoto K, Mathieu-Costello O, Prediletto R. Stress failure in pulmonary capillaries. *J Appl Physiol*. 1991;70(4):1731-1742.
- Swenson ER. Early hours in the development of high-altitude pulmonary edema: time course and mechanisms. *J Appl Physiol*. 2020;128(6):1539-1546.
- Bärtsch P, Swenson ER. Clinical practice: acute high-altitude illnesses. *N Engl J Med*. 2013;368(24):2294-2302.
- Saibal A, Menon AK, Bhatnagar S, Sanjeev S. Clinico-epidemiological profile of high altitude pulmonary edema. *Int J community med and Public Health*. 2021;8(1):196-200.
- 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*. Vol 474. PA: Springer; 1999:231-258.
- West JB, Mathieu-Costello O. Structure, strength, failure, and remodeling of the pulmonary blood gas barrier. *Annu Rev Physiol*. 1999;61:543-572.
- 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):1284-1289.
- Stream JO, Grissom CK. Update on high-altitude pulmonary edema: pathogenesis, prevention, and treatment. *Wilderness Environ Med*. 2008;19(4):293-303.
- McIntosh SE, Freer L, Grissom CK, 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.
- 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. *J Assoc Chest Physicians*. 2017;5(1):31-34.
- Gallagher SA, Hackett PH. High-altitude illness. *Emerg Med Clin North Am*. 2004;22(2):329-355.
- Maggiorini M, Mélot C, Pierre S, et al. High-altitude pulmonary edema is initially caused by an increase in capillary pressure. *Circulation*. 2001;103(16):2078-2083.
- Li Y, Zhang Y, Zhang Y. Research advances in pathogenesis and prophylactic measures of acute high altitude illness. *Respir Med*. 2018;145:145-152.
- West JB. The physiologic basis of high-altitude diseases. *Ann Intern Med*. 2004;141(10):789-800.
- Dehnert C, Risse F, Ley S, et al. Magnetic resonance imaging of uneven pulmonary perfusion in hypoxia in humans. *Am J Respir Crit Care Med*. 2006;174(10):1132-1138.
- 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.
- Swenson ER, Maggiorini M, Mongovin S, et al. Pathogenesis of high-altitude pulmonary edema: inflammation is not an etiologic factor. *JAMA*. 2002;287(17):2228-2235. Erratum in: *JAMA* 2002 Sep 4;288(9):1064.
- West JB, Mathieu-Costello O. Strength of the pulmonary blood-gas barrier. *Respir Physiol*. 1992;88(1-2):141-148.
- Singhal S, Srinivasa AB. Delayed-onset high-altitude pulmonary edema: a series of 8 patients. *Environmental Disease*. 2020;5(2):52-55.
- Murdoch DR. Symptoms of infection and altitude illness among hikers in the Mount Everest region of Nepal. *Aviat Space Environ Med*. 1995;66(2):148-151.
- Roach RC, Maes D, Sandoval D, et al. Exercise exacerbates acute mountain sickness at simulated high altitude. *J Appl Physiol*. 2000;88(2):581-585.
- Zafren K, Reeves JT, Schoene R. Treatment of high-altitude pulmonary edema by bed rest and supplemental oxygen. *Wilderness Environ Med*. 1996;7(2):127-132.
- Eichstaedt CA, Mairbäurl H, Song J, et al. Genetic predisposition to high-altitude pulmonary edema. *High Alt Med Biol*. 2020;21(1):28-36.
- Baniya S, Holden C, Basnyat B. Reentry high altitude pulmonary edema in the Himalayas. *High Alt Med Biol*. 2017;18:425-427.
- Basnyat B. High altitude cerebral and pulmonary edema. *Travel Med Infect Dis*. 2005;3(4):199-211.
- Sartori C, Allemann Y, Duplain H, et al. Salmeterol for the prevention of high-altitude pulmonary edema. *N Engl J Med*. 2002;346(21):1631-1636.

How to cite this article: Subedi S, Regmi P, Bhandari SS, Dawadi S. Three rare presentations of high-altitude pulmonary edema at a high-altitude clinic in the Everest region (4371 m): A case series. *Clin Case Rep*. 2023;11:e7236. doi:[10.1002/ccr3.7236](https://doi.org/10.1002/ccr3.7236)