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LETTER TO THE EDITOR

WILEY

Negative pressure flash pulmonary edema in a child with hereditary angioedema

To The Editor:

Negative pressure pulmonary edema (NPPE) is an uncommon, however, potentially fatal complication due to rapid-onset upper respiratory tract obstruction.[1] NPPE is usually observed in critical care and perioperative settings. Common causes include infections and tumors of the glottis and sub-glottis and laryngospasm.[1] Laryngeal edema due to hereditary angioedema (HAE) is another potential cause of upper respiratory tract obstruction. Most patients die because of asphyxiation caused by obstruction of larynx.[2] However, NPPE because of laryngeal edema has not been reported in patients with HAE. We herein report one such case.

A 14-year-old boy was diagnosed to have HAE at the age of 11. He was identified to have a splice site defect in *SERPING1* gene (intron 6 c.1030-1G>C). He was initiated on long-term prophylaxis (stanozolol 2 mg per day). However, he had poor compliance with therapy and continued to have episodes of laryngeal edema (once per year). These episodes were managed in a nearby healthcare facility using fresh-frozen plasma.

In November 2021, he presented to emergency room with respiratory failure. He started complaining of double chin in the morning (09:00 h) on that day, and by evening (17:00 h), he started developing hoarseness of voice. Three hours later (20:00 h), he developed respiratory distress and he was taken to a nearby healthcare facility. He was initiated on oxygen support and referred to our hospital. At presentation, he was found to be in respiratory failure and auscultation revealed crepitations in bilateral chest fields. A possibility of laryngeal edema was considered and he was immediately intubated. During the procedure of intubation, it was noted that he had pink frothy secretions with evidence of laryngeal edema. Fresh-frozen plasma (FFP) infusion was initiated. However, despite securing the airway, he remained hypoxic with requirement of very high positive inspiratory pressure and high positive end-expiratory pressure. Chest X-ray showed diffuse air space opacification with air bronchogram suggestive of pulmonary edema (Figure 1A). Laboratory investigations showed no evidence of infections. A clinical possibility of flash pulmonary edema was considered and he was initiated on furosemide. Following the use of furosemide, requirements for ventilator support improved substantially. He was continued on FFP infusions. Repeat chest X-ray after 24 h of hospital stay was normal (Figure 1B). An attempt was made to extubate in operation theater (OT) at 36 h of hospital stay. However, in view of the presence of laryngeal edema (on direct video laryngoscopy), extubation was deferred and he was initiated on T-piece ventilation along with continuation of FFP infusions. Twenty-four hours later, he was taken to OT again, and direct video laryngoscopy showed no laryngeal edema. He was extubated and FFP infusions were continued for 24 h after extubation. He was given 20 units of FFP over 84 h (at 20 ml/kg/day for 3 days). He was initiated on stanozolol (2 mg per day) and tranexamic acid (1500 mg per day) and discharged. He remains well on follow-up.

Hereditary angioedema is an uncommon disorder characterized by recurrent episodes of subcutaneous and/or submucosal edema predominantly affecting distal extremities, face, gastrointestinal tract, and upper respiratory tract.[3] Edema of larynx is a potentially life-threatening complication and may affect approximately 50% of all patients.[4]

Acute attacks of life-threatening laryngeal edema in patients with HAE are usually managed using plasma-derived or recombinant C1-inhibitor (C1-INH) concentrate, kallikrein inhibitor (Ecallantide), or bradykinin B2 receptor antagonist (Icatibant).[5] However, these drugs are not available in India, and as such, FFP is used in managing acute HAE attacks.[6] Although there are no controlled trials on dosage of FFP in acute attacks of HAE, authors have suggested a dose of 20 ml/kg.[7] It has been reported that up to 4 units of FFP in adults may lead to improvement within 90 min to 4 h.[7] Doses may be repeated if there is no clinical improvement. Index case had persistence of laryngeal edema even at 48 h. Hence, FFP transfusion was continued till complete clinical recovery.

Attenuated androgens are not recommended as the treatment of choice for long-term prophylaxis. However, they constitute second-line therapy for long-term prophylaxis when first-line medications are not available as is the situation in most developing countries including India.[8] Because of nonavailability of all first-line medications for management of HAE in India, we often have to use attenuated androgens as long-term prophylaxis even in young children. Our published experience suggests that growth retardation is not common in these patients while virilization and side effects related to puberty are often seen.[7] It is important to monitor following parameters in these patients once every 6 months: growth (weight, height, and body mass index), blood pressure, lipid profile, liver function tests, and ultrasonography of liver.[8]

Index patient presented with laryngeal edema and respiratory failure. He was promptly intubated. However, he continued to remain hypoxic, and hence, a clinical possibility of flash pulmonary

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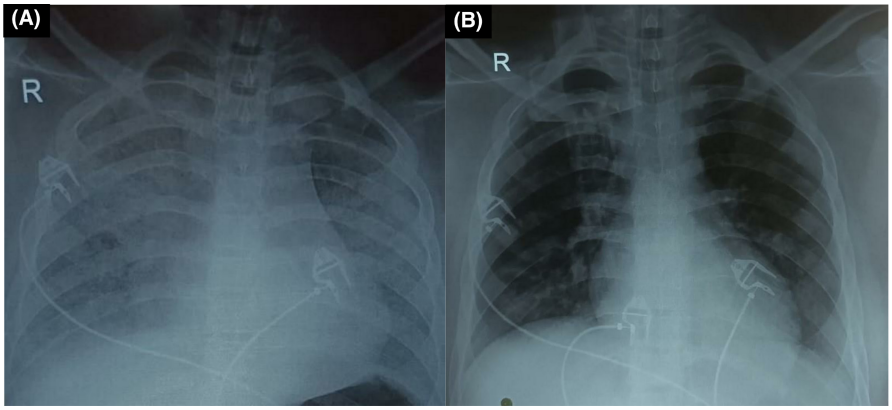

FIGURE 1 (A) Antero-posterior view of chest radiograph at hospital admission showed evidence of pulmonary edema. (B) Antero-posterior view of chest radiograph after 24 h of hospital admission showed no pulmonary edema

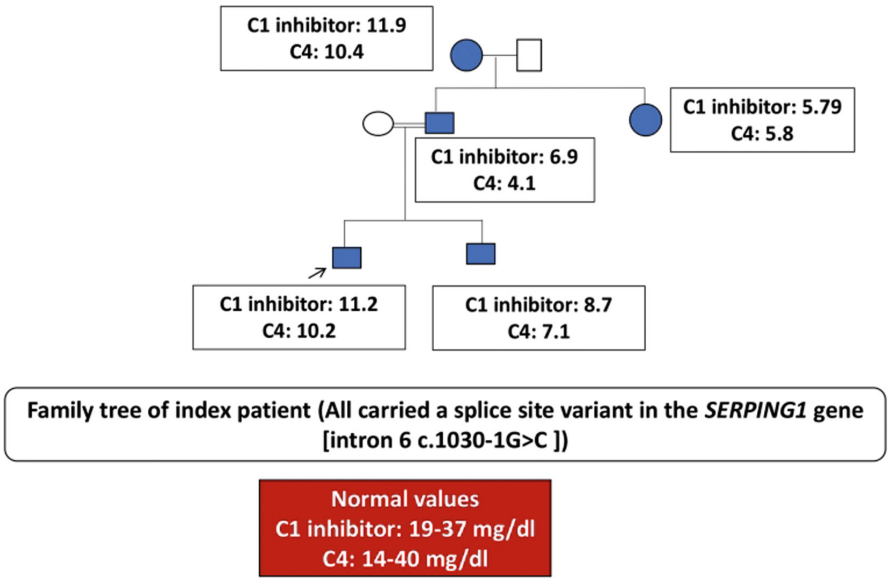

FIGURE 2 Family tree of index patient

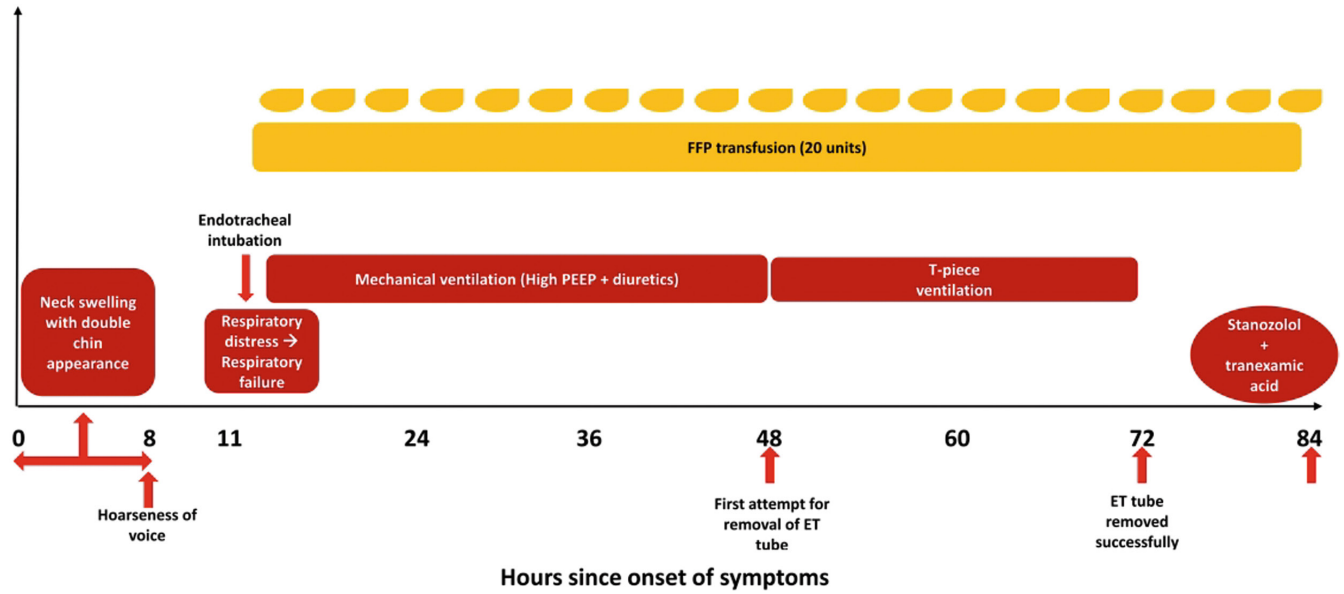

FIGURE 3 Course and management of index patient. Abbreviations: ET, Endotracheal tube, FFP, Fresh-frozen plasma; PEEP, Positive end-expiratory pressure

edema because of sudden glottic closure was considered. He responded to furosemide infusion and FFP infusions.

Negative pressure pulmonary edema has several causes and mortality may range from 11% to 40%.[9] Pathophysiology of NPPE remains enigmatic. It has been postulated that intense inspiratory efforts against an obstruction lead to negative intrapleural and alveolar pressures thereby leading to leakage of fluid from pulmonary capillaries into the alveolar spaces.[1] Immediate release of upper airway obstruction with positive pressure ventilation and use of diuretics may lead to resolution of NPPE within 24–48 h.[1] This was also seen in the index case (Figures 2 and 3).

Negative pressure pulmonary edema as a complication of laryngeal edema in patients with HAE has never been reported. However, one should consider this complication in patients with HAE in the context of sudden laryngeal obstruction. Prompt release of obstruction (either by endotracheal intubation or by tracheostomy) and use of diuretics may lead to rapid recovery. This case also highlights the difficulties in the management of acute attacks of angioedema in patients with HAE in resource-constrained settings where all first-line medications are not available. Prompt recognition of laryngeal edema in patients with HAE and use of FFP may be lifesaving in these situations.

AUTHOR CONTRIBUTIONS

Prabal Barman: Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); resources (lead); software (lead); supervision (lead); validation (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead). **Suprit Basu:** Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); resources (lead); software (lead); supervision (lead); validation (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead). **Ishita Thakur:** Investigation (equal); methodology (equal); visualization (equal); writing – original draft (equal). **Sanchi Chawla:** Investigation (equal); resources (equal); software (equal). **Anit Kaur:** Investigation (equal); resources (equal); software (equal). **Anudeep Jafra:** Conceptualization (equal); supervision (equal); validation (equal); writing – review and editing (equal). **Ankur Kumar Jindal:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); resources (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Surjit Singh:** Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); resources (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).

CONSENT

Informed consent was obtained from patient for publication purposes.

PEER REVIEW

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REFERENCES

1. Bhattacharya M, Kallet RH, Ware LB, Matthay MA. Negative-pressure pulmonary edema. *Chest*. 2016;150(4):927-933.
2. Cancian M, Perego F, Senter R, et al. Pediatric angioedema: essential features and preliminary results from the hereditary angioedema global registry in Italy. *Pediatr Allergy Immunol*. 2020;31(S24):22-24.
3. Wahn V, Aberer W, Aygören-Pürsün E, et al. Hereditary angioedema in children and adolescents – a consensus update on therapeutic strategies for German-speaking countries. *Pediatr Allergy Immunol*. 2020;31(8):974-989.
4. Betschel S, Avilla E, Kanani A, et al. Development of the hereditary angioedema rapid triage tool. *J Allergy Clin Immunol Pract*. 2020;8(1):310-317.e3.
5. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA medical advisory board 2020 guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
6. Saeb A, Hagglund KH, Cigolle CT. Using fresh frozen plasma for acute airway angioedema to prevent intubation in the emergency department: a retrospective cohort study. *Emerg Med Int*. 2016;2016:1-6.
7. Jindal AK, Reshef A, Longhurst H. GEHM workgroup (global equity in HAE management). Mitigating disparity in health-care resources between countries for Management of Hereditary Angioedema. *Clin Rev Allergy Immunol*. 2021;61(1):84-97.
8. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-the 2021 revision and update. *Allergy*. 2022. doi:10.1111/all.15214
9. Bhaskar B, Fraser J. Negative pressure pulmonary edema revisited: pathophysiology and review of management. *Saudi J Anaesth*. 2011;5(3):308.