

Dear Editor

Hereditary Angioedema as the Cause of Death from Asphyxia: Postmortem Computed Tomography Study

Hereditary angioedema (HAE) is an autosomal dominant disorder. Type I and type II HAE result from a deficiency of the C1-esterase inhibitor (C1-INH) due to a deletion or mutation(s) of C1INH. It may cause episodic and transient swellings of deep cutaneous and/or mucosal tissues. Symptoms usually last for a few days and may resolve spontaneously. However, airway edema may cause asphyxia and lead to death if not properly treated.^{1,2} Although the asphyxia is generally due to laryngeal edema,³ “upper airway obstruction” is more characteristic than “laryngeal edema” to depict symptoms of HAE. Here, we report a case of HAE which led to the patient’s death and revealed fatal pharyngeal edema on postmortem CT.

A 23-year-old man visited Niigata City General Hospital because of severe facial edema. He had had three similar episodes since he was 19-years-old. At this time, he did not complain of breathlessness. Laboratory examination showed reduced levels of CH50, 12 U/ml (normal 30-40 U/ml) and C4, 4 mg/dl (normal 13-34 mg/dl). Serum C1INH concentration was also decreased to 6 mg/dl (normal 10-25 mg/dl) and its enzymatic activity was <25% (normal 80-125%). On the other hand, the level of his serum C1q was normal, 10.1 mg/dl (normal 8.8-15.3 mg/dl). Upon the administration of 1000 units of C1INH concentrate (Berinerf™), all symptoms remarkably improved within one day.

His mother, until her menopause, had had a his-

tory of recurrent ileus and episodes of swelling of extremities and face. Her serum C1-INH protein concentration and its enzymatic activity were low (9 mg/dl, and <25%). According to these clinical and laboratory observations, we diagnosed him as Type I HAE. We prophylactically administered danazol (400 mg/day), but could not completely prevent recurrent occurrences of edema.

When he was 24-years-old, he also experienced an episode of severe abdominal pain, and was diagnosed as ileus, based on significant bowel swelling revealed by CT scans.

On one occasion at the age of 25-years, he noticed swelling of his face, and several hours later, he felt dyspnea. When emergency crews arrived at his house by ambulance, his face and throat were extremely edematous and his pulse was weak. He then died, although he was conducted to our hospital and received cardiopulmonary resuscitation.

His family declined the traditional autopsy, but granted postmortem imaging, which was performed 67 minutes later after his arrival at our hospital. Examinations were performed with a 6-row detector multislice CT scanner (SOMATOM Emotion 6, Siemens, Munich, Germany). Images were obtained using the spiral mode from the neck to the diaphragm for the routine body studies. The neck CT showed a diffuse increased density in the fat layer, which represents tissue edema. Severe mucosal thickness was presented in the oropharynx (Fig. 1a) and the hypopharynx (Fig. 1b). The airway in the oropharynx and the hypopharynx had almost disappeared. Although submucosal density was also increased in the larynx, the edema was milder than that observed in the pharynx and the glottis remained opened (Fig. 1c). We therefore concluded that the cause of his death was

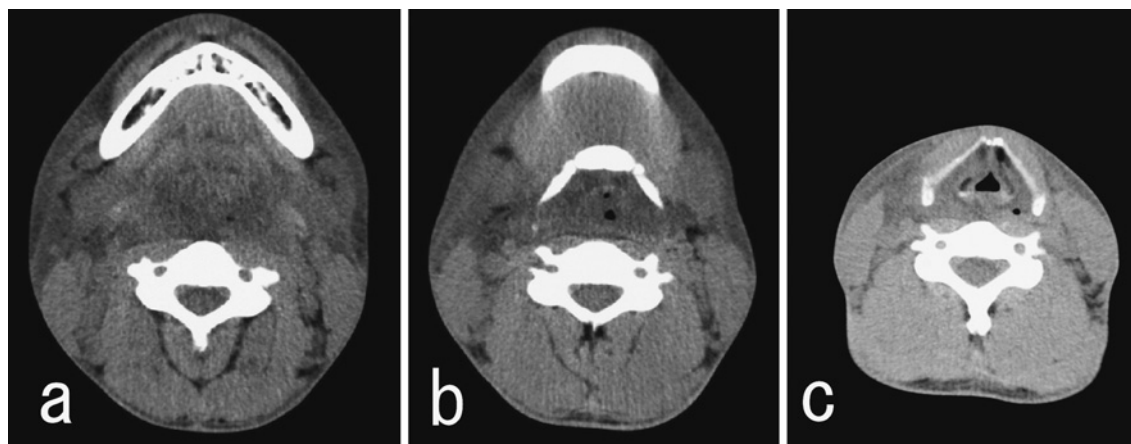


Fig. 1 The postmortem neck CT showed diffusely increased density of the fat layer. Severe mucosal thickness with the effacement of the airway in the oropharynx (a) and the hypopharynx (b) was presented. The piriform recess (b) (c) and the laryngeal vallecula disappeared (b). Although, the fat density increased in the larynx, the glottis remained open (c).

asphyxia due to pharyngeal edema.

We carried out a DNA analysis of his mother. The analysis was approved by the institutional review board of Niigata City General Hospital. After informed consent was obtained, genomic DNA was extracted from her peripheral blood and polymerase chain reaction was carried out to amplify 8 exons. DNA sequencing was performed using an Applied Biosystems 3100-Avant DNA Analyzer (Applied Biosystems, Warrington, UK).

A deletion of 9587G in exon 5 of C1-INH was identified. It had caused a frameshift mutation and made 9653-9655 the premature termination codon of TAG.

There is no doubt that autopsy remains the gold standard to determine cause of death. Nevertheless, the number of autopsies performed has declined dramatically in recent years. Relatives feel that the deceased has been through enough and an autopsy will be of additional no benefit.⁴ Due to advances in medical imaging technologies, postmortem CT has been introduced into autopsies and forensic investigations.⁵⁻¹⁰ The concept of introducing autopsy imaging has been proposed in Japan.⁶ Although families decline to have a traditional autopsy performed on a relative, they may not refuse an imaging examination.⁵⁻⁷

In this case, while the relatives of the patient declined the traditional autopsy, postmortem imaging was an acceptable substitute for an autopsy. Postmortem CT clarified that the airway in the pharynx was effaced. We diagnosed that the patient had died from asphyxia caused by mucosal and fat layer edema of pharynx, based on postmortem CT findings. Thus, postmortem CT provided important information about the judgment of the cause of death.

In angioedema, airway obstruction is usually referred to as "laryngeal edema".² However, the postmortem CT of this patient revealed pharyngeal edema rather than laryngeal edema as a cause of airway obstruction and death. In HAE, "upper airway obstruction" is more appropriate than "laryngeal edema" to represent lethal airway obstruction.

Michiko Shibuya^{1,2}, Naoya Takahashi^{3,4}, Masahiro Yabe⁵, Kazumasa Iwamoto⁶ and Michihiro Hide⁶

¹Department of Dermatology, ³Department of Radiology, ⁵Department of General Internal Medicine, Niigata

City General Hospital, ⁴Present address: Department of Radiological Technology, Graduate School of Health Sciences, Niigata University, Niigata, ²Present address: Department of Dermatology, Asoka Hospital, Tokyo and ⁶Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

Email: michikos@asokakai.or.jp

Conflict of interest: No potential conflict of interest was disclosed.

REFERENCES

1. Bowen T, Cicardi M, Farkas H *et al.* 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 2010;**6**:24.
2. Farkas H. Management of upper airway edema caused by hereditary angioedema. *Allergy Asthma Clin Immunol* 2010;**6**:19.
3. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med* 2006;**119**:267-74.
4. Shojania KG, Burton EC, McDonald KM, Goldman L. Changes in rates of autopsy-detected diagnostic errors over time. A systemic review. *JAMA* 2003;**289**:2849-56.
5. Mitka M. CT, MRI scans offer new tools for autopsy. *JAMA* 2007;**298**:392-3.
6. Ezawa H, Yoneyama R, Kandatsu S, Yoshikawa K, Tsuji H, Harigaya K. Introduction of autopsy imaging redefines the concept of autopsy: 37 cases of clinical experience. *Pathol Int* 2003;**53**:865-73.
7. Takahashi N, Higuchi T, Shiotani M, Maeda H, Sasaki O. Multiple lung tumors as the cause of death in a patient with subarachnoid hemorrhage: postmortem computed tomography study. *Jpn J Radiol* 2009;**27**:316-9.
8. Arai A, Shiotani S, Yamazaki K *et al.* Postmortem computed tomographic (PMCT) and postmortem magnetic resonance imaging (PMMRI) demonstration of fatal massive retroperitoneal hemorrhage caused by abdominal aortic aneurysm (AAA) rupture. *Radiat Med* 2006;**24**:147-9.
9. Ikeda G, Yamamoto R, Suzuki M, Ishiwaka H, Kikuchi K, Shiotani S. Postmortem computed tomography and magnetic resonance imaging in a case of terminal-stage small cell lung cancer: an experience of autopsy imaging in tumor-related death. *Radiat Med* 2007;**25**:84-7.
10. Aghayev E, Sonnenschein M, Jackowski C *et al.* Postmortem radiology of fatal hemorrhage: measurements of cross-sectional areas of major blood vessels and volumes of aorta and spleen on MDCT, and volumes of heart chambers on MRI. *AJR* 2006;**187**:209-15.