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CASE REPORT

Misdiagnosed Hereditary Angioedema with Recurrent Abdominal Pain: A Novel *SERPING1* Frameshift Variant

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Background: Hereditary angioedema (HAE) is typically autosomal dominant, though recessive cases exist. It is characterized by recurrent episodes of swelling affecting the subcutaneous tissues, oropharyngeal mucosa, and gastrointestinal tract. This report describes a misdiagnosed case with a novel "SERPING1" variant.

Case Presentation: A 22-year-old Chinese male presented with recurrent acute abdominal pain since March 2018, initially misdiagnosed as gastroenteritis or intestinal obstruction at multiple hospitals. During current hospitalization, detailed history revealed non-pitting eyelid edema in July 2019 that progressed to facial edema within 24 hours after a cold. Over the subsequent three years, he experienced recurrent subcutaneous edema involving face and extremities, typically resolving spontaneously within one week. Family history showed his father had similar self-limiting episodes of abdominal pain and edema between ages 20–30, with no recurrence after age 40. Physical examination demonstrated upper abdominal tenderness without rebound pain. Low C4 levels prompted C1INH testing and genetic analysis, confirming HAE due to C1INH deficiency type 1 (HAE-C1INH-Type1) with a novel *SERPING1* variant. Since initiating lanadelumab (300mg biweekly) on April 26, 2023, the patient has completed 11 injections and remains in good condition.

Conclusion: HAE is a rare disease that is often misdiagnosed. Complement C4 remains a critical screening biomarker for patients with HAE. In addition, we reported a novel frameshift variant in the coding region of the *SERPING1* gene, and the specificity of the position offers a unique point of interest in the discussion of the disease's causative locus.

Keywords: hereditary angioedema, *SERPING1* gene, C1 inhibitor

Introduction

Hereditary angioedema (HAE) is a rare, life-threatening genetic disease with an approximate prevalence of 1 in 50,000.[1] It is characterized by recurrent episodes of non-pitting, asymmetric, and self-limiting edema of subcutaneous and/or submucosal tissues.[2] Unlike edema triggered by allergies, HAE edema does not respond to antihistamines, glucocorticoids, or epinephrine.[3] HAE due to C1INH deficiency type 1 (HAE-C1INH-Type1) accounts for about 85% of the cases, while HAE due to C1INH deficiency type 2 (HAE-C1INH-Type2) comprises about 15% of cases. Variants in the *SERPING1* gene lead to a reduction of C1 inhibitor (C1INH) levels or defects in C1INH function. Patients with HAE-C1INH generally demonstrate low C4 levels and impaired C1INH function. HAE-C1INH-Type1 is characterized by C1INH deficiency with serum C1INH levels below 50% of normal, while HAE-C1INH-Type2 presents with normal C1INH levels.[1] C1INH is encoded by the *SERPING1* gene, regulating various proteases involved in complement, the contact system, coagulation, and fibrinolysis.[2,4] Bradykinin has been identified as the biological mediator of swelling in HAE with C1INH deficiency.[5,6] The pathogenic variants of the *SERPING1* gene underlie HAE-C1INH-Type1 and HAE-

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C1INH-Type2. The *SERPING1* gene, located on chromosome 11 (11q12-q13.1), encodes the C1INH protein, with over 809 pathogenic/likely pathogenic variants documented.[7]

Case

The proband, a 22-year-old man from China, first experienced symptoms in March 2018, including nausea, vomiting, abdominal pain, and melena, following fatigue. He was diagnosed with acute hemorrhagic necrotizing enteritis by the general surgery department at a local hospital and experienced relief through symptomatic supportive therapy within approximately one week. Subsequently, he experienced recurrent episodes of abdominal pain without melena, leading to four hospitalizations at various hospitals, including three visits to the gastroenterology department and one to the emergency department. His primary diagnoses during these episodes were acute gastroenteritis, chronic gastritis, and pseudo-intestinal obstruction, with symptom resolution following supportive treatment. During a previous episode accompanied by prolonged facial swelling, the proband was almost admitted to the intensive care unit of the emergency department for a proposed tracheotomy due to dyspnea. However, his symptoms improved after supportive treatment, and he was discharged without a tracheotomy. In December 2022, the patient was hospitalized for the second time in our Digestive system department due to upper abdominal paroxysmal colic. Upon detailed inquiry, it was revealed that in July 2019, he experienced eyelid edema that gradually progressed to the forehead, cheeks, nose, and mouth within one day following a cold. This progression eventually impaired his ability to speak, eat, and open his eyes (Figure 1). Since then, he has reported recurrent episodes of edema affecting the face, buttocks, genitals, and extremities. Each episode lasted approximately a week, occurring two to three times annually. Moreover, the patient noted a disfiguring change in the face, and involvement of the extremities resulted in limited movement of his hands and feet. Despite treatment with dexamethasone injections and loratadine, the outcomes were unsatisfactory. Besides, the proband's father had experienced similar episodes of abdominal pain and edema between the ages of 20 and 30, which resolved spontaneously without recurrence after the age of 40. During the current abdominal episode, a physical examination revealed marked abdominal tenderness without rebound pain, facial or limb edema. During hospitalization, laboratory tests demonstrated an elevated white blood cell count of 13.49×10^9/L (normal range: 3.50×10^9/L–9.50×10^9/L) and a neutrophil count of 10.06×10^{12}/L (normal range: 1.80×10^{12}/L–6.30×10^{12}/L), while hemoglobin concentration and platelet count were within normal range. The tests for anti-extractable nuclear antigen (anti-ENA) autoantibody profiles and anti-neutrophil cytoplasmic antibodies were negative. Complement C4 levels (0.032 g/L) were reduced, and C-reactive protein (17.1 mg/L) was elevated. Additional details of laboratory findings are provided in Table 1. Enhanced chest and abdominal computed tomography (CT) demonstrated thickening of the small intestine and edema in the right lower abdomen with incomplete intestinal obstruction accompanied by abdominal cavity and pelvic effusion

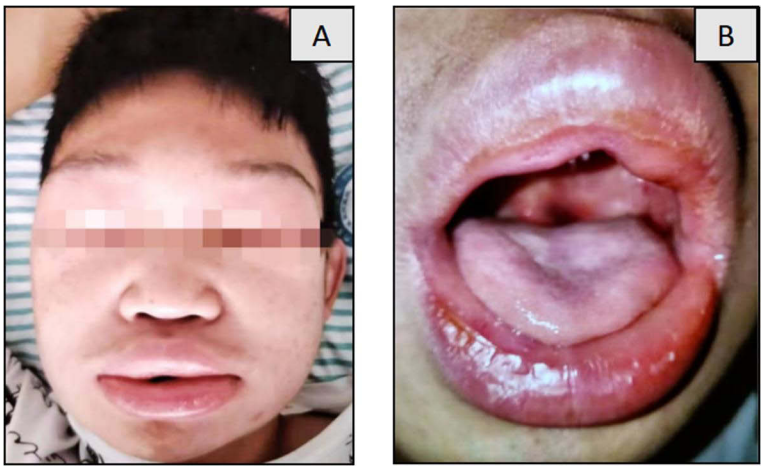

Figure 1 The patient's face, tongue and throat are swollen.
Notes: (**A**) Shows facial swelling. (**B**) Demonstrates swelling of the lips and epiglottis.

Table 1 The Proband's Laboratory Data

Laboratory Data	Measured Value	Reference Value	Result
White-cell count (10^9/L)	13.49	3.50–9.50	H
Red-cell count (10^{12}/L)	5.70	4.30–5.80	
Platelet count (10^9/L)	275	125–350	
ANC (10^9/L)	10.06	1.80–6.30	H
Hemoglobin (g/l)	158	130–350	
BASO (10^9/L)	0.08	0–0.06	H
MON (10^9/L)	0.94	0.10–0.60	H
Total protein (g/l)	59	65–85	L
Albumin (g/l)	37	40–55	L
Alanine transaminase (U/l)	16	9–50	
Aspartate transaminase (U/l)	14	15–40	L
Urea (umol/l)	4.78	3.10–8.00	
Creatinine (umol/l)	76	57–97	
Uric acid (umol/l)	523	208–428	H
PCT (ng/mL)	<0.05	<0.05	
ESR (mm/h)	1	0–15	
C-reactive protein (mg/L)	17.10	<8.00	H
Potassium (mmol/l)	4.30	3.50–5.30	
Sodium (mmol/l)	138	137–147	
Chloride (mmol/l)	101	99–110	
Calcium (mmol/l)	2.12	2.11–2.52	
Total cholesterol (mmol/l)	4.55	3.40–1.70	
HDL-C	1.55	0.78–2.00	
LDL-C	2.62		
Triglyceride	1.73	0.55–1.70	H
Fasting blood glucose (mmol/L)	4.92	3.89–6.11	
LDH (U/L)	156	120–250	
CK (U/L)	70	50–310	
CK-MB (U/L)	13	<25	
MYO (ug/L)	32	<90	
PT (sce)	10.20	9.00–14.00	
INR	0.90	0.70–1.50	
PTA%	131.70	70.00–130.00	H
APTT (s)	25.60	24.3–32.7	
TT (sce)	17	14–21	
FN	1.80	1.80–3.50	
Amylase (U/L)	46	35–135	
Lipase (U/L)	15	1–60	
Immunoglobulin G (g/l)	8.42	7.00–16.00	
Immunoglobulin A (g/l)	1.61	0.70–4.00	
Immunoglobulin M (g/l)	0.44	0.40–2.30	
Immunoglobulin E (g/l)	479	0–358	H
Complement 3 (g/l)	0.864	0.900–1.800	L
Complement 4 (g/l)	0.032	0.100–0.400	L
Complement 4 (g/l)	0.051	0.100–0.400	L
TSH (mIU/L)	0.475	0.350–4.940	
ANCA (c-ANCA p-ANCA atypia-ANCA)	Negative	Negative	
ANCA (MPO-IgG PR3-IgG) (RU/mL)	1.88	<20	
dsDNA. ANA.SSA. SSB. RNP. Sm. Jo-1. SCL70.	Negative	Negative	

(*Continued*)

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Table 1 (Continued).

Laboratory Data	Measured Value	Reference Value	Result
Urine analysis	Normal	Normal	
Stool routine	Normal	Normal	
Fecal occult blood test	Positive	Positive	

Abbreviations: ANC, absolute neutrophil count7; BASO, Baso absolute count; MON, Monocytes absolute count; PCT, Procalcitonin; ESR, Erythrocyte Sedimentation Rate; HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; LDH, Lactate dehydrogenase; CK, Creatine kinase; CK-MB, creatine kinase-MB; MYO, myoglobin; PT, prothrombin time; INR, international normalized ratio; PTA, plasma thromboplastin antecedent; APTT, Activated Partial Thromboplastin Time; TT, thrombin time; FN, Fibronectin; TSH, Thyroid Stimulating Hormone; ANCA, anti-neutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PR3-IgG, Anti-proteinase 3 antibody IgG; dsDNA, double-stranded DNA, anti-dsDNA antibody; ANA, anti-nuclear antibodies; SSA, Sjögren's syndrome type A, anti-SSA antibody; SSB, Sjögren's syndrome type B, anti-SSB antibody; RNP, anti-ribonuclear protein antibody; Sm, anti-Smith antibody; Jo-1, anti-Jo-1 antibody; SCL70, anti Scl70 antibody; H, high; L, low.

(Figure 2). Gastroscopy identified chronic gastritis and duodenitis, while no abnormality was observed in colonoscopy (Figure 3). Following consultation with the nephrology department, HAE was suspected based on decreased complement C4 levels, recurrent subcutaneous edema, and abdominal pain. This prompted further testing of C1INH concentration and genetic analysis conducted at Goeld-field Medical Laboratory. C1 esterase inhibitor concentration was found to be 0.08 g/L (normal range: 0.21–0.39). Next-generation sequencing (NGS) identified a variant in the *SERPING1* gene (NM_000062.3: c.1436_1437dup, p. Val480SerfsTer97; GRCh37: chr11:57,381,988–57,381,989) in the proband (Figure 4 and Table 2). This variant results from a non-triad nucleotide repeat duplication in exon 8 of the *SERPING1* coding region, creating a frameshift variant that is predicted to cause premature termination of protein translation. Subsequently, analysis of Sanger sequencing from the subject's family revealed an inheritance of the variant from the

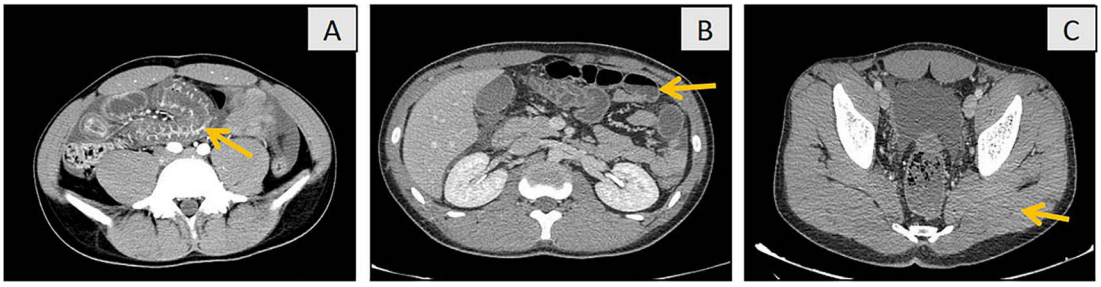

Figure 2 Abdominal cavity + pelvic CT.
Notes: Thickening of the small intestinal edema in the right lower abdomen with incomplete intestinal obstruction is accompanied with abdominal cavity and pelvic effusion. Arrows: (**A**) small intestinal wall edema in the right lower abdomen (**B**) transverse colon edema (**C**) peritoneal effusion.

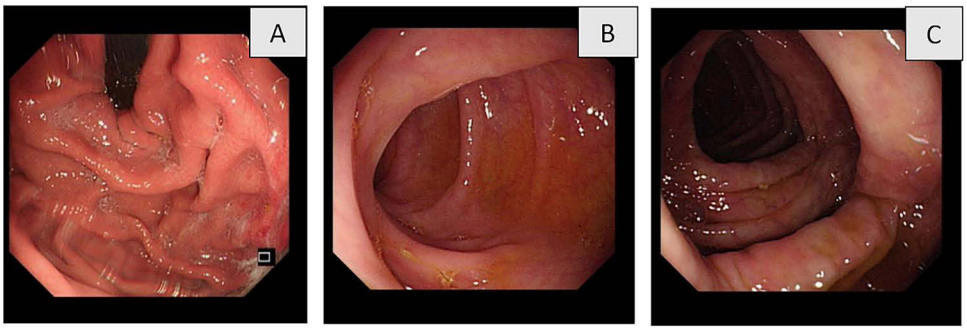

Figure 3 The result of gastroscope and colonoscopy.
Notes: Chronic gastritis, duodenitis, no abnormality in colonoscopy. (**A**) Fundus of stomach (**B**) Small intestine (**C**) Large intestine.

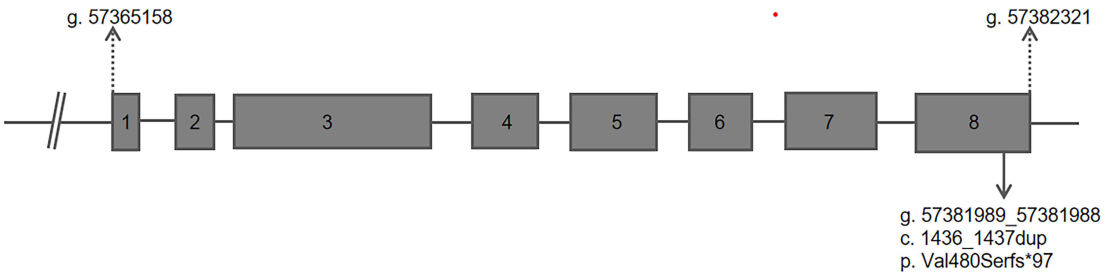

Figure 4 Genetic variant diagram.
Notes: The genomic coordinates chr11: 57,365,158–57,382,321 (GRCh37/hg13 assembly) represent the canonical transcript region of the *SERPING1* gene (OMIM no. 606860; GenBank NM_000062.2): eight blue boxes represent exons. Seven lines connecting boxes represent introns. 57,365,158: Transcription start site. 57,382,321: Termination site. p. Val480Serfs*97 (protein-level variant): Val480Ser: Missense variant (The valine (Val) at position 480 is replaced by serine (Ser). fs*97: Frameshift causing a new stop codon after 97 aberrant amino acids. *: terminal. The variant (c.1436_1437dup) falls within this region at chr11:57,381,988–57,381,989 (Exon 8).

father, consistent with the father's history of similar symptoms (Figures 5 and 6). After investigation and analysis by the researchers, this variant was classified as likely pathogenic according to the ACMG-AMP criteria.[8,9] Based on diagnostic criteria, the proband was diagnosed with HAE-C1INH-Type1. Treatment with subcutaneous Lanadelumab injections (300 mg every two weeks) was initiated on April 26, 2023, and to date, the patient has received 11 injections without relapse, indicating the safety and efficacy of this regimen. Intermittent monitoring of creatinine and liver function has indicated normal results. Moreover, on January 11, 2024, the patient's C1INH concentration returned to normal (Table 3). Although the patient's sister and brother did not exhibit symptoms of HAE, they underwent evaluation due to the hereditary nature of the disease. The proband's 25-year-old sister exhibits a specific C1INH function defect, and the 9-year-old brother displays low C4 and C1INH levels, along with impaired C1INH function (Table 4 and Figure 6).

Discussion

HAE commonly affects various body regions, including the face, limbs, trunk, genitals, upper respiratory tract, and gastrointestinal tract. Symptoms exhibit considerable variability between attacks and among patients. In this case, the patient exhibited prominent manifestations of abdominal attacks and skin edema. The abdominal CT scan revealed thickened edema in the small bowel along with abdominal and pelvic effusion, which are characteristic imaging findings associated with HAE.[10] Abdominal attacks are prevalent in patients with HAE, constituting approximately 93% of cases.[11] Abdominal pain results from mucosal edema affecting various segments of the gastrointestinal tract. These attacks induce severe pain, often accompanied by nausea, vomiting, or diarrhea and frequently necessitating bed rest. Moreover, severe edema can cause disfigurement and significant inconvenience.[2]

Given its simplicity and rapidity, complement C4 levels can serve as an initial screening index for HAE.[12] For patients suspected of having HAE, the evaluation of complement C4 levels, C1INH concentration and function is crucial

Table 2 Whole Genome Sequencing for Rare Diseases

Single Nucleotide Variants and Small Insertion/Deletion Variants (SNV/indel)							
gene	**Location of the Chromosome**	**Information of Variation**	**Type of Zygote**	**Name of Disease**	**Patterns of Inheritance**	**Sources of Variation**	**Classification of Variation**
SERPING1	chr11:57381989_57381988	NM 000062.3: c.1436_1437 dup (p. Val480Serfs*97)	Heterozygote	HAE type- I	AD/AR	The father	Suspected therapeutic variation

Notes: the asterisk (*) denotes a termination codon (stop codon) resulting from the variant.

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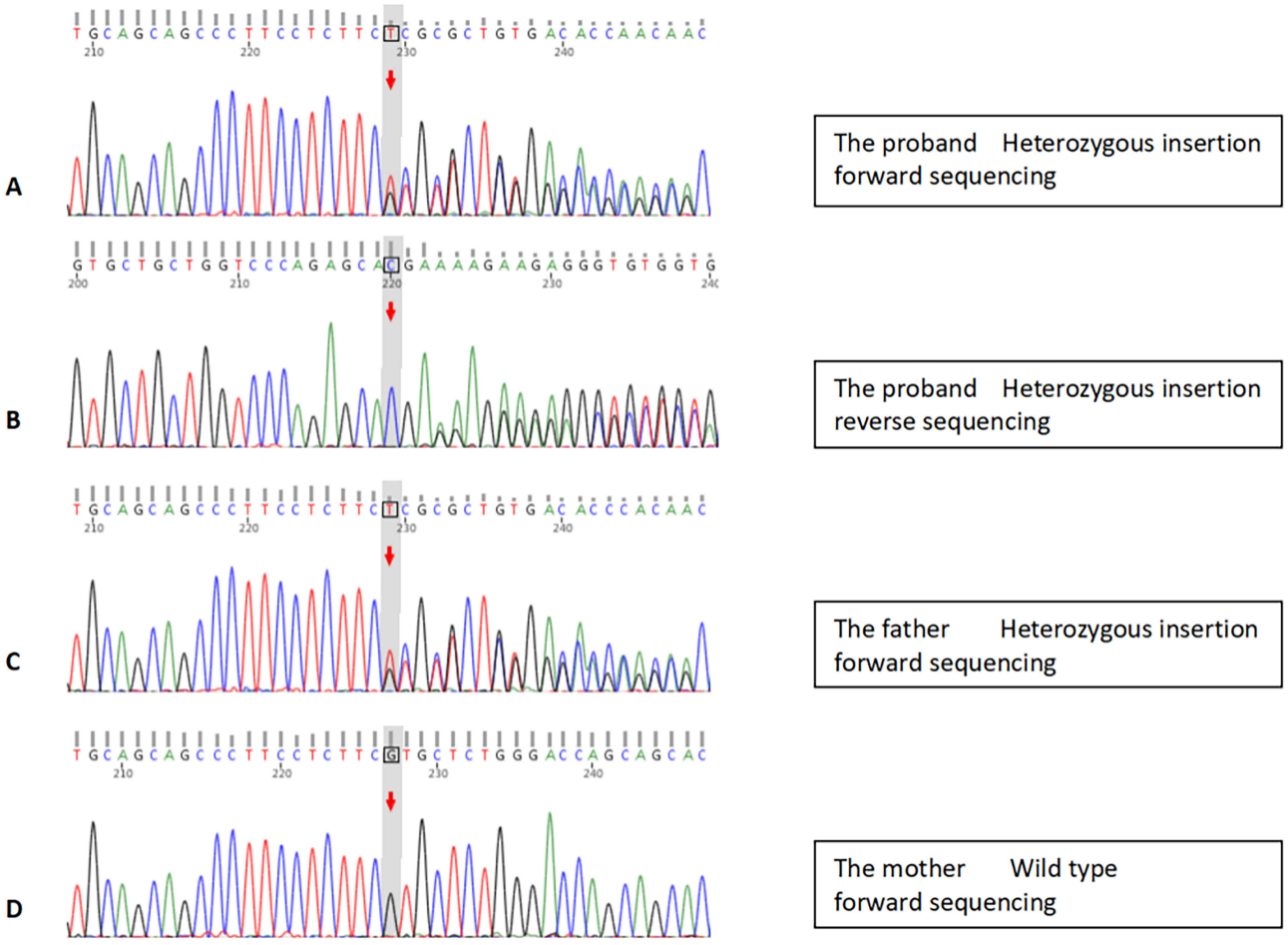

Figure 5 Sanger sequencing plots and electropherograms of *SERPING* variants.
Notes: (**A**) The proband (**B**) The proband (**C**) The father (**D**) The mother.

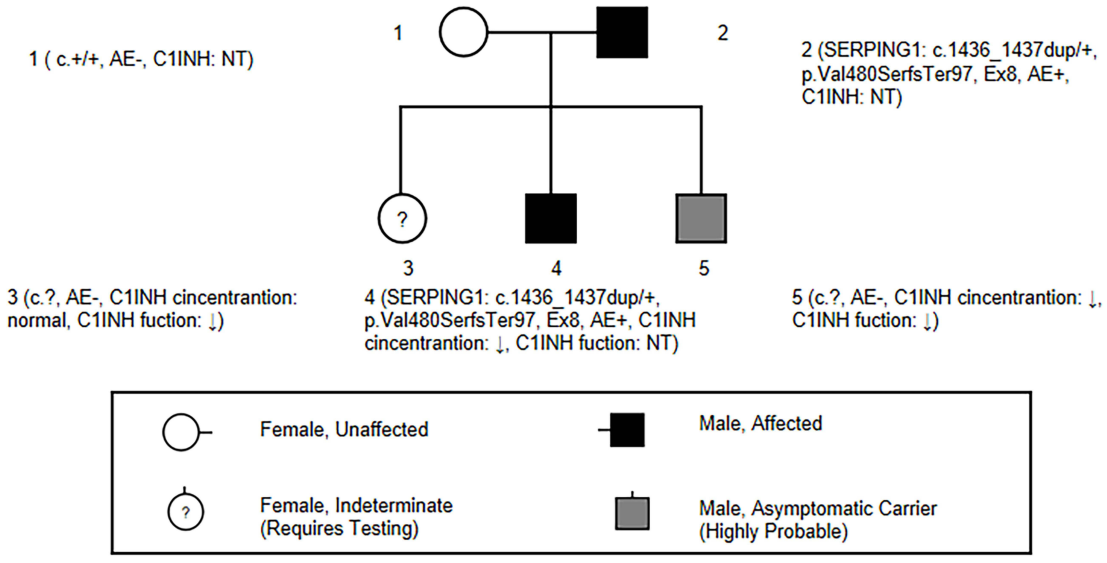

Figure 6 Disease Genealogy of HAE.
Notes: 1. The proband's mother 2. The proband's father 3. The proband's sister 4. The proband 5. The proband's brother. Wild type: c.+/+; Heterozygous: c.[variant]/+; c.: cDNA-level notation; ↓: Below normal range.
Abbreviations: AE, Angioedema; NT, Not tested; dup, Duplication variant.

Table 3 Trend Chart of C3, C4 and C1 INH Concentration. The Proband Received Treatment with Lanadelumab Starting April 26, 2023

	Supplement C3 (g/L)	Supplement C4 (g/L)	C1INH Concentration (g/L)
2022.12.03	0.084	0.032	0.08
2023.04.20	0.940	0.052	
2023.05.12	1.020	0.050	0.05
2023.06.05	1.230	0.059	
2023.06.27	1.050	0.048	
2023.08.04	1.080	0.040	
2024.01.11	1.020	0.060	0.240
Reference range	0.900~1.800	0.100~0.400	0.21–0.39

Table 4 Family Data Table for Hereditary Angioedema

Family Member	Age/Sex	*SERPING1* Genotype	AE History	Supplement C4 (ug/mL)	C1INH Concentration (g/L)	C1INH Function (%)
Father	? / M	c.1436_1437dup/+	AE+	NT	NT	NT
Mother	? / F	c. +/+	AE-	NT	NT	NT
Proband	22/M	c.1436_1437dup/+	AE+	0.32	0.08↓	NT
Sister	25/F	c.? (Not tested)	AE-	217.79	107.39	<41.34↓
Brother	9/M	c.? (Not tested)	AE-	39.84	9.74↓	<7 ↓

Notes: Wild type: c.+/+; Heterozygous: c.[variant]/+; c.: cDNA-level notation; ↓: Below normal range. Reference range: Supplement C4 (72.85–372.95 ug/mL) C1INH concentration (81.46–291.29 g/L), C1INH Function (>58.9%).
Abbreviations: AE, Angioedema; NT, Not tested; dup, Duplication variant; M, Male; F, Female.

for understanding the disease pathogenesis and establishing diagnosis.[13] The diagnosis of HAE was suspected based on the proband's clinical presentation of recurrent abdominal attacks accompanied by characteristic imaging findings (bowel wall edema/ascites), recurrent mucocutaneous angioedema, and a positive family history of similar edema symptoms. The observation of persistently reduced C4 levels prompted confirmatory testing of C1 inhibitor (C1INH) concentration and functional activity. Subsequent genetic analysis through next-generation sequencing (NGS) identified a likely pathogenic variant in the *SERPING1* gene. Sanger sequencing revealed paternal inheritance of this variant, consistent with the father's symptomatic history, thereby completing the diagnostic workup from clinical suspicion to molecular confirmation. However, due to the absence of relevant literature or frequency data in large-scale population-based databases such as gnomAD, further research and observation are required to ascertain the precise nature and impact of this variant.[14] Regarding such unidentified variants, experts must make evidence-based assessments while pursuing comprehensive research and analysis. The proband's father is affected with HAE, as confirmed by both the presence of the likely pathogenic *SERPING1* variant and a history of edema attacks, while the mother remains unaffected with no variant detected. The proband himself is definitively affected, exhibiting both the familial variant and characteristic clinical manifestations. Current laboratory assessments of C4 and C1INH levels/function indicate that the proband's younger brother is considered a suspected patient of HAE-C1INH-Type1, which typically manifests between 8–12 years of age, worsening during adolescence.[4] In contrast, the classification of the proband's sister remains uncertain, as current test results cannot definitively differentiate between HAE-C1INH and Acquired Angioedema due to C1INH deficiency (AAE-C1INH) (Figure 6).[4] Although both the sister and brother remain asymptomatic, we recommend repeated measurements of complement C4, C1INH levels/function, and *SERPING1* gene sequencing during the asymptomatic phase. This comprehensive assessment underscores the importance of serial evaluations for at-risk family members, particularly those with discordant or borderline laboratory results. These clinical findings have significantly improved the family's understanding of acute HAE risks. However, due to financial constraints and geographical barriers, these follow-up tests have not yet been completed. Accordingly, our medical team has provided comprehensive disease management

education, including emergency response protocols and guidance on timely medical intervention, along with recommendations for regular clinical follow-ups to ensure proper health monitoring.

HAE episodes are highly unpredictable, with potential triggers including surgery, trauma, emotional stress, or infection. Guidelines recommend that a comprehensive understanding of these triggers is important for both patients with HAE and their families. In China, involvement of the upper respiratory tract mucosa can lead to rapidly progressing laryngeal edema, affecting over 50% of patients with HAE. This condition can potentially result in death by asphyxiation if prompt resuscitation measures are not undertaken, with a reported lifetime mortality rate as high as 40%.[8] Fortunately, in this case, the proband experiencing dyspnea sought timely medical attention, avoiding irreversible consequences. The patient first developed severe abdominal pain in March 2018 when initial medical evaluation was performed. However, the diagnosis remained elusive at that time due to the non-specific nature of the presentation and lack of definitive laboratory testing. The patient experienced recurrent symptoms and sought medical attention on multiple occasions over the course of several years. Following a comprehensive diagnostic workup, a definitive diagnosis of HAE-C1INH-Type1 was ultimately established in February 2023. The 5-year interval between symptom onset and definitive diagnosis reflects both the clinical challenges in recognizing HAE and the importance of maintaining a high index of suspicion for this condition in patients with recurrent angioedema.

The HAE-C1INH management primarily involves on-demand treatment of HAE attacks (intravenous C1INH, ecallantide, and icatibant), short-term prophylactic treatment (intravenous C1INH, fresh frozen plasma), and prophylactic treatment (Lanadelumad). Given the unpredictable nature of HAE attacks, guidelines strongly recommend that all patients keep sufficient on-demand medication on hand for two acute attacks.[13] Icatibant, the primary drug for targeted treatment of HAE acute attacks in China, is typically administered within 6 h of onset, with earlier administration correlating to improved drug efficacy. Skin and abdominal symptoms of the attack can be significantly relieved within 2–2.5 h post-injection.[15,16] Advancements in drug development and disease management aim to achieve the ultimate goal of "zero attacks" in HAE treatment. Long-term preventive treatment is crucial for attaining this objective. Lanadelumab, the first fully human monoclonal antibody approved for HAE attack prevention, is prescribed at a dose of 300 mg Q2W for patients with HAE aged > 12 years in the United States.[17] The average attack rate among patients was reduced by 87% after treatment with 300 mg Q2W of Lanadelumab for 26 weeks, according to the results of the HELP trial. Besides, 76.9% of patients in the stable phase experienced zero attacks.[18] These findings underscore Lanadelumab's potential to alleviate the disease burden by effectively reducing HAE attack rates.

Conclusion

This case highlights the challenge posed by the rarity of HAE and the heterogeneity of its clinical manifestations. Patients frequently struggle to confirm the diagnosis after multiple doctor visits, leading to delays that significantly heighten the risk of asphyxiation from laryngeal edema. Hence, efforts should be made to raise awareness of HAE. This case demonstrates how doctors across various departments, including dermatology, the gastroenterology department, and emergency medicine, can broaden their examination of suspicious cases, facilitating timely treatment for more patients with HAE. Moreover, the discovery of a new frameshift variant is broadening the spectrum of variants. Further data and studies are required to fully understand the impact and significance of this variant, which will subsequently play a more significant role in disease pathogenesis and targeted therapy.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Ethics Statement

This study, including the publication of anonymized case details, was reviewed and approved by the Medical Ethics Committee of Changsha Central Hospital, University of South China (Approval No: 1755527088055). In accordance with institutional policy, although the retrospective nature of the study qualified for a waiver of written informed consent

for the research, formal approval for publication was granted by the committee. Furthermore, explicit verbal consent for publication was obtained from the patient's family members.

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Disclosure

No potential conflicts of interest were disclosed by the authors.

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