Hereditary Angioedema with Normal C1 Esterase Inhibitor: A Case of Late Diagnosis in a 48-year-old Male

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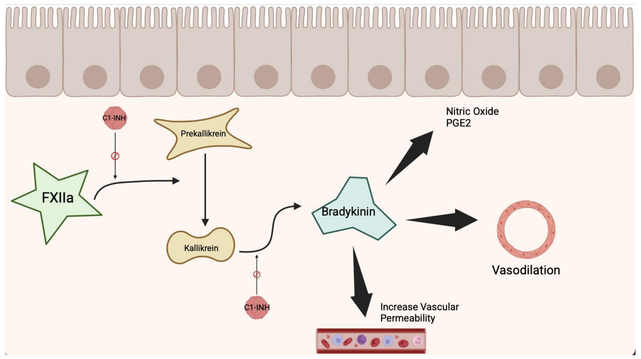

Figure 2: This figure depicts the bradykinin pathway involving activation of factor XII (FXIIa), which converts prekallikrein to kallikrein. C1 esterase inhibitor (C1-INH) regulates the pathway by inhibiting both this conversion and the subsequent formation of bradykinin. Bradykinin promotes vasodilation and increases vascular permeability through the release of nitric oxide and prostaglandin E2 (PGE2)
Figure created by © Natalie Elazar in BioRender [10] using information from [7].

Introduction

- Angioedema is characterized by asymmetrical non-pitting swelling—also referred to as edema—that affects the mucosal, submucosal, or subcutaneous tissues [1].
- In hereditary angioedema, the lack of C1-INH leads to increased activation of the kallikrein-kinin system through activation of Factor XII. This results in the excess release of bradykinin, a chemical that causes vasodilation and increases vascular permeability by triggering the release of substances like nitric oxide and prostacyclin, as shown in Figure 2.
- Hereditary angioedema (HAE) is considered a rare condition, affecting approximately 1 in 50,000 people worldwide [3].
- The average age of diagnosis is around 20 years old, with the first symptoms typically starting in adolescence [5].
- A rare subtype of HAE, known as hereditary angioedema with normal C1 esterase inhibitor, is diagnosed based on exclusion and has no specific blood markers available for diagnosis. A normal C1 esterase inhibitor, as well as a history of recurrent angioedema without resolution and with the presence of mast cell inhibitors and no urticaria, suggests this rare disease [4].

Discussion

- Patient B is a 34-year-old male brought into the emergency department for progressive facial swelling and acute dysphagia [3].
- Facial edema developed spontaneously 16 hours prior to presentation, and first-line therapies such as methylprednisolone and epinephrine were ineffective.
- This patient was found to have type I C1 esterase inhibitor deficiency. His family history revealed three generations of idiopathic edema, which is notable for this type of disease.
- While idiopathic edema is comparable to the case at present, Patient A and Patient B are both manifesting different types of this disease, with Patient A showing no signs of deficient C1-INH on lab results despite recurrent presentations of angioedema.
- A similar case of HAE involved patient C, a 75-year-old male patient who had significant breathing difficulty.
- Patient C presented to the emergency room with an acute onset of facial and throat swelling accompanied by shortness of breath for the past 10 hours, prior to presentation to the emergency room. The patient had an oxygen saturation of 80% and desaturated to 60% during his stay [8].
- The patient's symptoms improved once he was placed on a bradykinin inhibitor [8].
- Similar to our case with patient A, both patients A and C did not have a family history but did have a history of recurrent symptoms, which is pathologic for this disease. Unlike patient C, patient A's C1-INH levels remained within normal limits, despite recurrent symptoms.
- The lack of responsiveness to conventional antihistamine therapy-commonly employed as a first-line treatment for allergic-induced edema-in these patients is associated with an increased risk of adverse clinical outcomes.

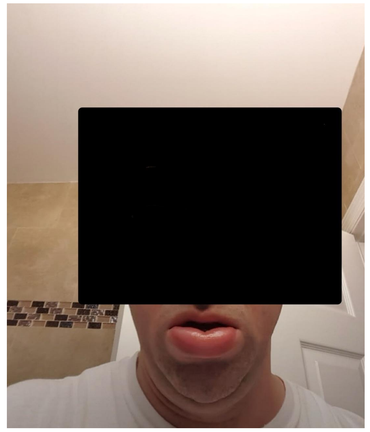

Figure 1: Patient A, lower lip swelling during acute angioedema flare.

Parameter	Patient Values	Reference Range
C1 Inhibitor (Protein)	26 mg/dL	21-39 mg/dL
C1 Inhibitor (Functional Activity)	93%	≥67%
Complement C1q	9.2	5.0-8.6
Rheumatoid Factor - IgG	7 U	<6 U
Rheumatoid Factor - IgM	28 U	<6 U
Rheumatoid Factor - IgA	10 U	<6 U
Total Complement (CH50)	>60 U/mL	31-60 U/mL
C-Reactive Protein (CRP)	11.5 mg/L	<8 mg/L

Table 1: The lab results of patient A with corresponding reference ranges.

Case Presentation

- Patient A is a 48-year-old male with a history of Epstein-Barr Virus, diagnosed in 2008, and hyperlipidemia, who presents with recurrent angioedema of his lower lip, face, throat, and extremities, including hands, feet, and genitals, as shown in Figure 1.
- Notable symptomatic episodes include significant digital swelling resulting in constriction around the patient's wedding ring, raising concerns for potential vascular compromise and possible ring removal.
- He reported frequent visits to the emergency department for acute symptom exacerbations of lip enlargement and denied any identifiable or consistent triggers.
- During his first flare, a comprehensive diagnostic workup was performed, including assessment of C1 esterase inhibitor levels, all of which yielded results within normal limits. Patient A was initiated on antihistamine therapy for symptom management; however, he continued to experience near-daily flare-ups.
- His lab results in 2022, after his first rheumatology encounter, also showed negative C1 INH results, with values of 26mg/dL for protein and 93% shown for the protein's functional activity, as shown in Table 1.
- The patient was prescribed icatibant 30 mg/3 mL, taken subcutaneously with an injector for acute hereditary angioedema flare-ups, as well as berotralstat 150 mg capsules taken once daily for the prevention of hereditary angioedema attacks.
- Although the patient continues to experience occasional flare-ups, their frequency and severity have decreased with improved control.

Conclusion

- This case study emphasizes the importance of understanding and spreading awareness of the different types of HAE.
- An earlier diagnosis may have been possible with further investigation following the initial negative C1-INH result, along with recognition that repeated ineffective treatment with corticosteroids and antihistamines warranted alternative therapeutic strategies.
- This represents a rare case of HAE with normal C1-INH that did not result in life-threatening, edema-induced hypoxia; however, numerous cases have demonstrated severe and potentially fatal outcomes.
- Greater clinical awareness of HAE with normal C1-INH will provide physicians and patients with a better understanding of this complex condition, facilitating earlier diagnosis and appropriate management.
- More investigational research into non-allergic pathways causing angioedema is needed.

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