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Beyond the Norm: Exploring the Management Dilemmas of Severe and Refractory Angioedema

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Abstract

Angioedema is a rare condition characterized by recurrent episodes of localized swelling, affecting various body parts. We present a challenging case of hereditary angioedema with recurrent exacerbations refractory to standard medical management. A 63-year-old female, diagnosed with type III hereditary angioedema on home C1 esterase inhibitor therapy, experienced acute facial edema and respiratory distress leading to four consecutive hospital admissions requiring intubation over a four-month period. Despite receiving conventional treatments such as epinephrine, tranexamic acid, and fresh frozen plasma, the patient's airway edema persisted, necessitating ongoing interventions including corticosteroids, antihistamines, and additional fresh frozen plasma units.

Extensive diagnostic evaluations for infectious, autoimmune, and malignancy-related causes yielded negative results. The patient was ultimately discharged with a tracheostomy and oral prednisone. This case highlights the need for increased awareness and consideration of alternative therapeutic approaches in managing recurrent and refractory hereditary angioedema exacerbations, emphasizing the complexity and variability of this rare condition.

Background

Angioedema is a condition characterized by sudden and pronounced swelling, typically affecting areas such as the face, lips, tongue, and extremities. Angioedema can manifest in two distinct forms: hereditary angioedema (HAE), which is genetically inherited and often linked to mutations in the C1 inhibitor gene, and acquired angioedema, which arises from secondary causes such as medications, autoimmune disorders, malignancies, or infections [1]. Diagnosis is primarily based on clinical evaluation, including a thorough assessment of medical history and physical examination. Allergy testing, including skin tests or blood tests, may be employed if an allergic trigger is suspected.

Laboratory tests measuring complement levels and C1 inhibitor function help differentiate between histamine-mediated and bradykinin-mediated angioedema [1]. In some cases, imaging studies like CT scans or MRI may be utilized to rule out other potential causes, such as malignancies. The diagnostic process aims to discern the underlying cause and guide appropriate treatment strategies tailored to the specific type of angioedema identified.

The treatment of angioedema involves addressing the underlying cause and managing symptoms, but the challenge arises when the condition proves difficult to manage or becomes refractory. Standard approaches include antihistamines, corticosteroids, and, in acute allergic cases, epinephrine [2]. For hereditary angioedema, replacement therapy with C1 inhibitor and bradykinin receptor blockers are traditionally employed [3]. However, some cases, pose a challenge as they are refractory to conventional therapies [4].

In such instances, a comprehensive diagnostic workup is crucial to identify potential triggers, ruling out secondary causes, and determining the specific mechanism of angioedema. Continuous monitoring, patient education, and psychological support become integral components of managing refractory cases. Future research exploring alternative therapies e.g., monoclonal antibodies, immune modulators, and increased awareness among healthcare providers are essential for advancing our understanding of angioedema and refining strategies for challenging and refractory cases.

A 63-year-old woman with a history of well-managed hereditary angioedema presented with a sudden exacerbation marked by acute facial edema and respiratory distress. Despite a history of well-managed angioedema with a C1 esterase inhibitor, this episode marked the fourth occurrence in just four months, without identifiable triggers. Standard interventions, including intramuscular epinephrine, tranexamic acid, and fresh frozen plasma (FFP), were insufficient in mitigating the acute respiratory distress, resulting in intubation. Intravenous (IV) methylprednisolone, IV famotidine, icatibant, berotral-

stat, and additional FFP were administered to alleviate symptoms. Unfortunately, these interventions proved ineffective, resulting in the escalation of symptoms and the onset of urticaria. In response to the urticaria, the patient was treated with IV diphenhydramine.

Despite these measures, the patient continued to experience advancing tongue and facial swelling, indicating a challenging and refractory course of hereditary angioedema. Extensive diagnostic investigations, including laboratory tests, imaging, malignancy workup, infectious and autoimmunity assessments, and allergen testing, yielded unremarkable results. Medication reconciliation revealed no recent changes in the patient's medication regimen. Notably, the patient's increased frequency of angioedema episodes remained unexplained. The culmination of unsuccessful interventions led to the patient's discharge with a tracheostomy and oral prednisone. This case underscores the perplexing nature of refractory angioedema, urging a deeper exploration of potential underlying causes and emphasizing the need for innovative therapeutic options in challenging situations.

Results

N/A

Discussion

Treating angioedema can be challenging due to the condition's diverse etiologies and variability in presentation. Angioedema can result from allergic reactions, hereditary factors, or other systemic conditions, each requiring a tailored approach. The unpredictable nature of angioedema attacks also makes it challenging to implement proactive preventive measures. Most commonly, angioedema can be attributed to factors such as medication use, including acetylcholine esterase inhibitors, or an underlying condition such as malignancy or systemic lupus erythematosus [3]. The treatment of angioedema in these cases is to address the underlying issue. In cases refractory to standard medical management, documented cases in the past have observed improvement with FFP as it provides additional functional C1 esterase inhibitor [4].

However, complications arise when angioedema cases are not only refractory but also idiopathic, presenting a challenge in identifying the underlying cause and exacerbating the difficulty in devising effective treatment strategies. The complexity in managing angioedema is also compounded by individual variations in treatment responses and the need for a comprehensive diagnostic evaluation to identify contributing factors. Addressing these challenges calls for a multidisciplinary approach, collaboration between specialists, and future research to refine treatment strategies for this often-perplexing condition. This study presents a unique and notable contribution to medical literature, introducing the first documented case of refractory idiopathic angioedema.

This case of recurrent and refractory angioedema imparts several valuable lessons. It underscores the complexity of angioedema management, emphasizing the importance of a thorough diagnostic evaluation to identify the specific underlying cause and mechanism. In this case study, the patient was on a maintenance C1 esterase inhibitor therapy for angioedema and continued to have breakthrough episodes. This may be attributed to the possibility of an underlying bradykinin-mediated mechanism, as seen in hereditary angioedema, which may not be effectively addressed by C1 esterase inhibitor targeting the classical complement pathway [2]. The patient was also trialed on antihistamines which did not improve patient symptoms, further suggesting that the underlying mechanism might be bradykinin-mediated rather than histamine-mediated, as antihistamines primarily target the histamine pathway in allergic reactions [3].

Although, administration of bradykinin receptor antagonist icatibant also did not improve patient symptoms, neither did berotralstat, a plasma kallikrein inhibitor. The patient's angioedema was also refractory corticosteroids, indicating the potential involvement of a non-inflammatory mechanism rather than an inflammatory pathway that steroids typically address [2,3]. The case highlights the diverse etiologies of angioedema, including hereditary factors, and the need for clinicians to consider both histamine-mediated and bradykinin-mediated pathways in treatment decisions.

Furthermore, the lack of improvement in the patient's symptoms with FFP suggests a potential non-complement-mediated or non-plasma factor-related mechanism in the pathogenesis of this patient's angioedema [4]. The challenges in managing refractory cases highlight the current limitations in therapeutic approaches and the necessity for continued research to develop more effective interventions. This case serves as a reminder of the ongoing complexity and variability in angioedema cases, contributito our understanding of the condition and guiding future advancements in diagnosis and treatment strategies.

Conclusion

In conclusion, the presented case of recurrent and refractory angioedema provides valuable insights into the intricacies of managing this complex condition. The challenges encountered underscore the necessity for a meticulous diagnostic approach to delineate the underlying causes and mechanisms, considering both histamine-mediated and bradykinin-mediated pathways. The refractory nature of the case emphasizes the limitations of current therapeutic strategies and the imperative for ongoing research to develop more targeted and efficacious interventions. This case also highlights the importance of collaboration among healthcare specialists in managing complex and elusive conditions such as angioedema. As we navigate the complexities of angioedema, this case serves as a catalyst for advancing our understanding of the condition, refining diagnostic protocols, and fostering the development of innovative treatment modalities for improved patient outcomes in the future.

References

1. Kesh S, Bernstein JA (2022) Isolated angioedema: A review of classification and update on management. Ann Allergy Asthma Immunol 129(6): 692-702.

2. Irwin TM, Irwin TM, Longanecker A, Bodenhamer WS, Carla C Keirns (2023) A Case of Refractory Angioedema. J Intensive Care Med 38(3): 313-320.

3. Habibagahi Z, Ruzbeh J, Yarmohammadi V, Kamali M, Rastegar MH (2015) Refractory Angioedema in a Patient with Systemic Lupus Erythematosus. Iran J Med Sci 40(4): 372-375.

4. Hassen GW, Kalantari H, Parraga M, Chirurgi R, Meletiche C, et al. (2013) Fresh frozen plasma for progressive and refractory angiotensin-converting enzyme inhibitor-induced angioedema. J Emerg Med 44(4): 764-772.