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Hereditary Angioedema Type III Estrogen-Sensitive: A Case Report and Literature Review

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Abstract **Case Report**

Hereditary angioedema (HAE) is a rare autosomal dominant disorder caused by excessive bradykinin production, leading to recurrent episodes of subcutaneous or submucosal edema. Type III HAE, primarily affecting women, is associated with hormonal factors such as estrogen, which exacerbate the frequency and severity of attacks. Unlike types I and II, this form lacks C1-inhibitor deficiency, making diagnosis challenging. We report the case of a 33-year-old pregnant woman (16 weeks of gestation) admitted with progressive upper lip edema. Her medical history revealed recurrent facial and neck edema triggered by oral estrogen-containing contraception, with no symptoms after its discontinuation. Genetic testing confirmed a heterozygous mutation in the F12 gene. The patient was treated with tranexamic acid, resulting in rapid symptom resolution. Type III HAE often requires targeted therapies such as icatibant or C1-inhibitor concentrates for acute attacks and tranexamic acid for prophylaxis, particularly in pregnancy. Patient education on self-administration of emergency treatments and family screening are essential to reduce morbidity. This case underscores the importance of recognizing estrogen-sensitive type III HAE, implementing tailored management strategies, and ensuring preventive measures to improve patient outcomes.

Keywords: Hereditary Angioedema, type III HAE, Estrogen-Sensitive, Bradykinin, Pregnancy, F12 Mutation, Tranexamic Acid, Icatibant, C1-Inhibitor, Therapeutic Education.

INTRODUCTION

Hereditary angioedema (HAE) is a rare disease caused by excessive production of bradykinin, an inflammatory mediator resulting from an autosomal dominant genetic mutation. Accounting for less than 1% of all angioedemas, this condition is characterized by recurrent episodes of subcutaneous or submucosal edema without associated urticaria. Type III HAE, more recently described, is often triggered by hormonal factors, particularly estrogens, and predominantly affects women. The clinical presentation can be severe, posing a life-threatening risk in cases of laryngeal involvement, warranting prompt recognition and appropriate management.

CASE REPORT

We report the case of a 33-year-old woman, pregnant at 16 weeks of gestation, admitted for progressive and painful edema of the upper lip, which appeared three hours prior to admission. Her medical history revealed recurrent episodes of facial and neck edema since 2010. These episodes, resistant to corticosteroids and antihistamines, led to several hospitalizations, including one for vocal cord involvement in 2011.

A diagnosis of type III estrogen-sensitive HAE was made based on a heterozygous mutation in the F12 gene, associated with a gain of function. The episodes began after starting oral estrogen-based contraception in 2010 and ceased following its discontinuation. Upon admission, the patient showed no signs of severity. She received tranexamic acid (Exacyl®), which led to rapid improvement and a significant reduction in edema within a few hours.

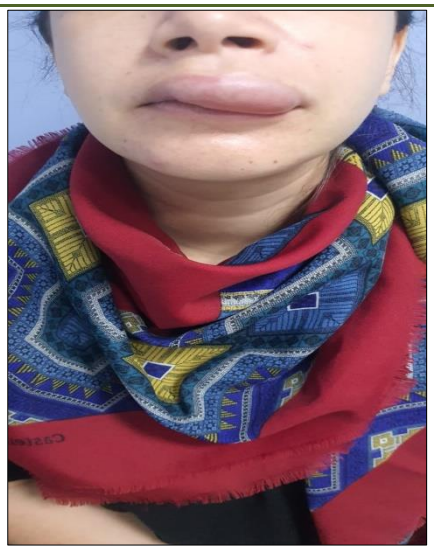

Figure 1: Odema of the upper lip

Discussion and Literature Review

Type III HAE is a rare condition characterized by excessive bradykinin production, typically due to an F12 gene mutation, although this mutation is only found in 15% of cases [1, 2]. Unlike types I and II HAE, which involve quantitative or qualitative C1-inhibitor deficiency, type III HAE primarily affects women and is closely linked to hormonal fluctuations, particularly estrogen [3, 4]. Estrogens increase the expression of factor XII and bradykinin production, exacerbating the frequency and severity of episodes [5]. Clinical manifestations include recurrent, localized edema without associated urticaria, primarily affecting the extremities, gastrointestinal tract (mimicking obstruction), and the oropharyngeal region, the latter posing a life-threatening risk due to asphyxiation [6, 7].

Diagnosis is based on clinical features and the exclusion of types I and II HAE through C1-inhibitor and C4 complement assays. In type III HAE, biological abnormalities are absent, making diagnosis more challenging [8, 9]. Estrogen-containing contraceptives, identified as a major triggering factor, should be replaced with progestin-only alternatives [10.]

Therapeutic management focuses on targeted medications such as icatibant, a bradykinin B2 receptor antagonist, and plasma-derived or recombinant C1-inhibitor concentrates, which are effective within 30 minutes for severe episodes [11, 12]. Tranexamic acid, used prophylactically, is particularly recommended during pregnancy to reduce recurrence risks [13, 14]. Androgens, although reserved for specific cases, remain an option for refractory episodes in men or postmenopausal women [15.]

The literature emphasizes the importance of therapeutic education, enabling patients to self-administer emergency treatments, significantly reducing complications and improving quality of life [16, 17]. Additionally, family screening is essential due to the autosomal dominant inheritance pattern, allowing early diagnosis and prophylactic management of at-risk relatives [18, 19].

Conclusion

Estrogen-sensitive type III HAE is a rare but potentially severe condition. This case highlights the importance of prompt recognition and appropriate management. Patient education, prevention of triggering factors, and access to targeted therapies are essential to improve prognosis and quality of life.

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