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# Rare Case of Hereditary Angioedema Presenting as Recurrent Ascites – A Case Report

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***Abstract:***
***Background:*** *Hereditary angioedema is an autosomal dominant genetic disorder with a prevalence of 1 in 50,000. It arises from gene mutations encoding for an important protease known as C1 inhibitor. These lead to an overshooting local production of bradykinin and a primarily vascular reaction. This rare disease forms a serious health problem for those affected patients and their families and is usually preceded by a delay in the diagnosis due its rarity and the way it mimics other disorders. A rare presentation of hereditary angioedema in the form of debilitating gastrointestinal symptoms makes this case unique.*
***Case Summary:*** *In this case report, we have described a 30-year-old male who presented with recurrent abdominal pain for 6 years. Diagnostic workup could not point to a specific diagnosis. As a result, he underwent symptomatic treatment for the recurrent episodes. The development of edema of extremities helped initiate workup of angioedema. Correlating family history of recurrent edema along with the patient's C1-INH deficiency on laboratory workup helped conclude a diagnosis of Type 1 HAE*. Initiation of danazol and patient counseling helped manage the disease.
***Keywords:*** *Hereditary angioedema, Danazol, C1- INH deficiency*

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## I. Introduction

Hereditary angioedema (ICD-10: D84.1) is an autosomal dominant inherited condition characterized by vascular reaction of deep dermal and subcutaneous tissues or mucosal and submucosal tissues with localized increased permeability of blood vessels resulting in tissue swelling.

There are 2 main types of HAE that are inherited in an autosomal dominant manner with mutations in SERPING1 gene. Type 1 HAE is a quantitative deficiency of C1-INH while Type 2 HAE is due to a dysfunctional C1-INH. Type 1 accounts for 85 percent of cases while Type 2, 15 percent. A third form associated with a gain of function mutation of F12 gene with factor XII changes lead to the identification of a rare Type 3 HAE. This is characterized by normal quantitative and functional studies of C1-INH.

The disease has a classical presentation of recurrent episodes of non-pitting, subcutaneous and submucosal swelling characterised by absence of pruritus. This affects limbs, face especially lips, intestinal tract and airway and manifests as acute abdomen and ascites and breathing difficulty. The onset of disease is typically from childhood and persists throughout life. It is triggered by dental, surgical procedures and physical trauma and drugs like ACE inhibitors, OCPs and NSAIDs. Other triggers are psychological stress, *Helicobacter pylori* infection and menstruation. The case being presented showed predominant gastrointestinal symptoms and was later correlated with the limb and facial swelling leading to the conclusion of Type 1 HAE.

## II. Case Report

30-year-old manual labourer was apparently asymptomatic 6 years back when he developed episodic severe colicky generalized abdominal pain. Abdominal pain was of acute onset, associated with nausea and vomiting. The episodes recurred every two months initially and became more frequent for the past 6 months. Each episode lasted 4-6 hours. It was not associated with fever, jaundice or abdominal distension. Episodes were not related to food intake or alcohol intake. He was totally asymptomatic between the episodes. He presented at the outpatient department with these past complaints and is currently asymptomatic. There was no history of altered bowel habits, blood or mucus in stools, fever, weight loss, oral ulcers, photosensitivity, arthritis, non-

healing skin lesions, skin pigmentation or digital gangrene. There was no history of diabetes mellitus, psychiatric illness or migraine.

On clinical examination, patient was conscious and oriented. Vitals: Pulse-90/min, BP-110/70 mm Hg and respiratory rate-18/min. General examination was normal. On systemic examination, abdomen was soft non tender with normal bowel sounds and no organomegaly. Chest was clear on auscultation with no added sounds. Cardiovascular examination was normal. He had intact higher mental function with no deficits in the nervous system examination.

Laboratory testing revealed Hb: 13g%, (normal: 12.0-15.5g%), WBC: 8400cells/$mm^3$ (normal: 4500-11000 cells/$mm^3$), Platelets: $247\times10^9$/L (normal:$150\text{-}450\times10^9$/L), ESR: 17mm/hr (normal: 20mm/hr), Urea: 20mg/dL (normal: 5-20mg/dL), Serum creatinine: 1.1mg/dL (normal: 0.6-1.2mg/dL), Bilirubin total: 0.7mg/dL (normal: 0.1-1.2mg/dL), Bilirubin direct: 0.2mg/dL (normal:<0.3mg/dL), Total protein: 6.5g/dL (normal:6-8.3g/dL), Albumin: 3.9g/dL (normal: 3.4-5.4g/dL), SGOT: 20IU/L (normal: 5-40IU/L), SGPT: 13IU/L (normal: 7-56IU/L), ALP: 46IU/L (normal: 44-147IU/L). Serum amylase and lipase were normal. His USG abdomen taken in the past during episodes of abdominal pain revealed mild ascites. But USG abdomen during current admission was normal. CECT abdomen done in the current admission also was normal. Serum fasting cortisol was 18mcg/dL and urine porphobilinogen and stool occult blood tested negative.

During admission and while undergoing diagnostic workup, he developed swelling of left hand which subsided on itself and on further enquiry, he had occasional transient episodes of swelling of hands, face and lips not associated with pruritis. Family history of father presenting with recurrent swelling of face was elicited. Recurrent episodes of abdominal pain associated with previous history of facial swelling and similar family history raised the suspicion of hereditary angioedema. Serum C1 esterase inhibitor and Serum C4 level testing was done. Serum C4 was 4.5(10-50) and Serum C1 esterase inhibitor: below 0.02(0.21-0.39). The final diagnosis of hereditary angioedema was made. He was started on danazol 100 mg daily as prophylaxis. Patient counselling was done and the need for avoiding triggers was explained. He is on follow up for the past 1 year and did not have any acute attacks of abdominal pain.

## III. Discussion

The identification and treatment of hereditary angioedema has evolved since its initial description in 1876 by J.L Milton and in 1888 by William Osler to the recent introduction of monoclonal antibodies for the treatment of the disease.

The main affected systems are skin, gastrointestinal tract and upper airway. While 80-99% people showed features of non pitting edema of limbs; only 5-29% presented with abdominal pain, ascites and intestinal edema. Our patient had multiple episodes of abdominal pain that recurred every 4-8 weeks and was the main complaint and elicitation of the history of edema of limbs and face was needed. Laryngeal edema was experienced by 49.6% of patients with HAE at some point in their life and had an occurrence of 1 case of laryngeal edema for every 54 cases of abdominal manifestations and 70 cases of skin swellings. Laryngeal involvement can be life threatening and was found as the cause of death in 25-30 percent of cases with deaths higher in undiagnosed cases of HAE compared to diagnosed HAE cases. So it is essential to identify the triggers and explain the prodromal symptoms and the need for precautions before dental and surgical procedures and timely emergency department visits.

The C1 esterase inhibitor C1-INH, a type of serine protease inhibitor acts as a major inhibitor of complement proteases and contact system proteases such as plasma kallikrein and coagulation factor XIIa. In the absence of C1-INH, plasma kallikrein cleaves high molecular kininogen producing bradykinin. Bradykinin is the primary mediator of swelling in HAE making it resistant to antihistamines and steroids that affect histamine pathway which mediates the usual allergic and anaphylactic reactions. The presence of prodromal signs like sensation of tingling accompanied by rash and angioedema with absence of urticaria and failure to respond to antihistamines, glucocorticoid, adrenaline with positive family history helps to reach a diagnosis of HAE. The confirmation is made with detection of low levels of C4, C1 inhibitor and/or C1 inhibitor function at baseline or during an acute attack.

Triggers were present in more than 79% cases and food was considered to be one among them but definitive food items were not identified and might differ from person to person. The acute presentation might lead to unnecessary interventions and diagnostic procedures but it is imperative to rule out the differential diagnoses like recurrent pancreatitis, Irritable Bowel Syndrome, Addison's disease, Acute Intermittent Porphyria and Inflammatory Bowel Disease.

Treatment of acute attack revolves around the use of C1-INH concentrates, Ecallantide (Kallikrein inhibitor) or Icatibant (Bradykinin Receptor antagonist). The alternatives like SDP Solvent Detergent treated Plasma and Fresh Frozen Plasma can be used in the absence of these modalities. The long term prophylaxis is maintained by subcutaneous twice weekly administration of plasma derived C1-INH or attenuated androgens like Danazol. Antifibrinolytics are not recommended for long term prophylaxis. Lanadelumab is a newer FDA

approved drug which is a fully human IgG1 monoclonal antibody acting as a plasma kallikrein inhibitor. It is given orphan drug and breakthrough therapy designation. The initiation of treatment has provided normal life span to most individuals and underlines the need for identification of atypical presentations of HAE and family screening of those identified.

## IV. Conclusion

Gastrointestinal manifestations of hereditary angioedema can be a debilitating condition that is often misdiagnosed due to its rarity. Although rare, physicians must always consider the possibility of such a disease in cases presenting with recurrent abdominal pain. Once diagnosed, patients must be counseled about the complications and family members must be alerted about the occurrence of the disease.

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