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NOT JUST AN EDEMA: THE ROLE OF ANGIOEDEMA IN EARLY CANCER DETECTION

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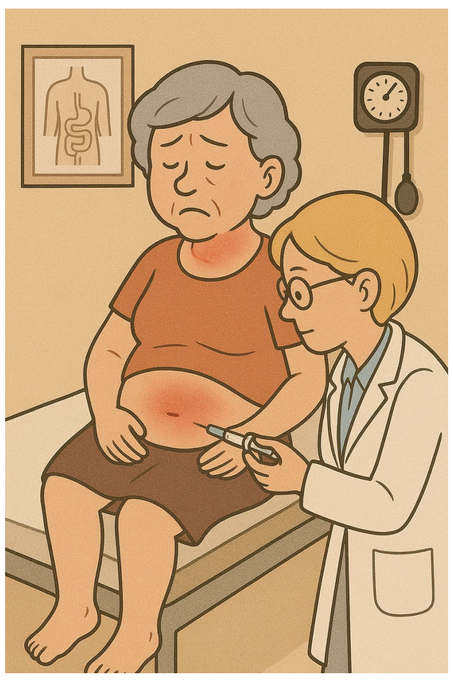
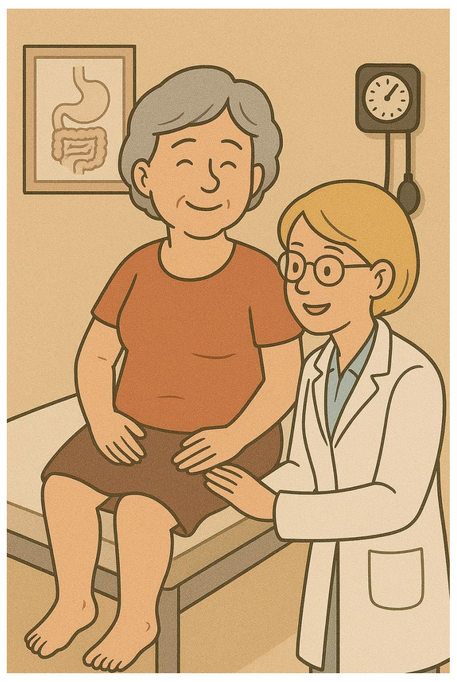
MAY 2023 – A 63-years-old woman with previously good clinical health presented to the emergency department with abdominal distension, swelling, and erythema of the left foot and upper limb, which were unresponsive to steroids and antihistamines.

↓C1INH + ↓C4 + ↓C1q + PET-positive pulmonary lesion

JANUARY 2024 – she was admitted to the Clinical Immunology Unit at AOU Federico II, where reduced antigenic C1INH, C4, and C1q levels, along with a PET-positive pulmonary lesion, led to the diagnosis of **"AAE-C1INH in a patient with pulmonary consolidation of the middle lobe".**
Icatibant and plasma derived C1INH were prescribed as on-demand treatment.



MARCH 2025 – she presented to our clinic with marginal erythema associated with an abdominal angioedema attack. **Icatibant** (B2 receptor antagonist) was administered, resulting in rapid resolution of abdominal and cutaneous symptoms. Due to the high frequency of attacks, long-term prophylaxis (LTP) with **Lanadelumab** (an anti-plasma kallikrein monoclonal antibody) was initiated 300 mg/14 days.



MAY 2024 – she underwent atypical pulmonary resection of the middle lobe, with histology confirming an **extranodal marginal zone B-cell lymphoma** (BALT).
NOVEMBER 2024 – she began treatment with **Rituximab** at a dose of 375 mg/m² IV once a week for 4 weeks, followed by administration every 2 months.
FEBRUARY 2025 – C4 and antigenic C1INH levels were rechecked and found to be within normal range

Angioedema	C1 INH antigenic	C1 INH functional	C4	C1q	Anti-C1 INH antibodies
HAE type I	<50%	<50%	reduced	normal	negative
HAE type II	>50%	<50%	reduced	normal	negative
AAE	**>50%/<50%**	**<50%**	**reduced**	**reduced in 70%**	**increased in 70%**

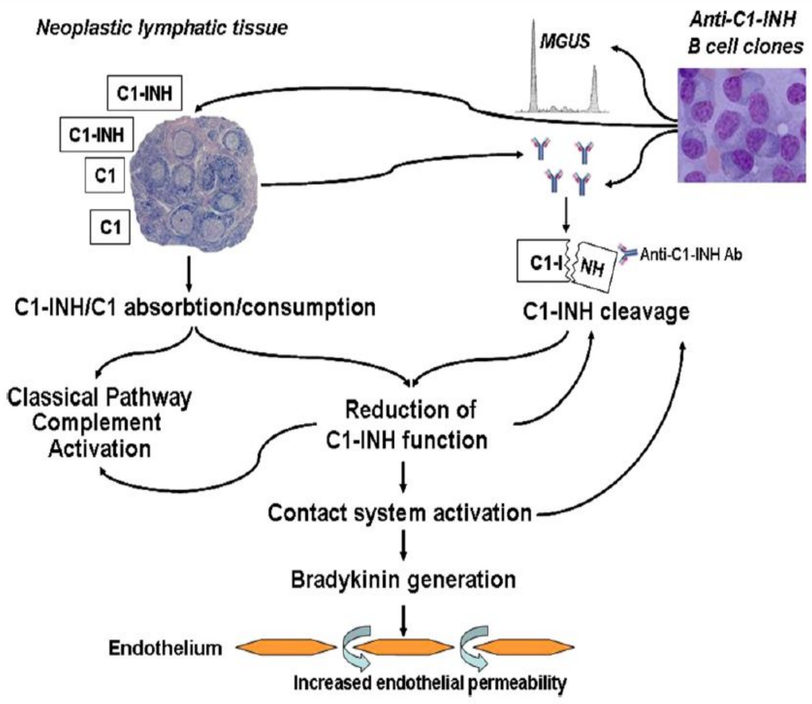


FIGURA 1. Ref. ***Cugno et al. Autoimmunity Reviews 2008; 8: 156***

Acquired bradykinin-mediated angioedema (AAE-C1INH) is a very rare condition, often associated with monoclonal gammopathy of undetermined significance (MGUS) or with lymphoproliferative disorders, autoimmune diseases, or solid tumors. It is caused by the **consumption of C1 inhibitor** (C1-INH) by neoplastic tissue and/or neutralizing anti-C1INH autoantibodies. It differs from HAE by the absence of a family history, later onset (>40 years), reduced C1q levels, and the presence of anti-C1INH antibodies. There are no approved treatment for AAE-C1INH "on demand" and on long-term prophylaxis (LTP). In some case the therapies approved for HAE are often employed off-label.

This case highlights the importance of **oncological and hematological screening** in patients with AAE not only at the time of diagnosis but also during follow-up, including targeted imaging studies in the presence of suspected associated disease. Furthermore, it confirms the effectiveness of HAE-approved therapies in patients with AAE and underscores the need for **shared decision-making** with other specialists to ensure early diagnosis and appropriate and effective treatment.