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Low C1q alone should not be taken as diagnostic of acquired angioedema in a kindred with familial type 1 C1-inhibitor deficiency and overlapping systemic lupus erythematosus

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acquired angioedema, C1-inhibitor deficiency, C1q, hereditary angioedema, systemic lupus erythematosus

Dear Editors,

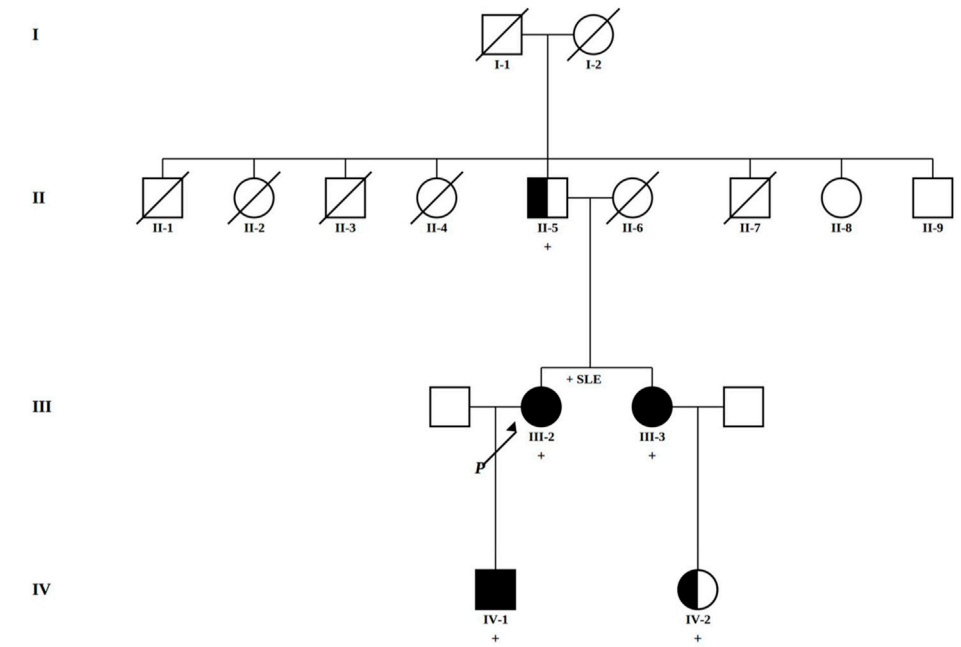
Low C1q alone should not be taken as diagnostic of acquired angioedema due to C1-inhibitor (C1-INH) deficiency (AAE-C1-INH). Although low C1q is common in AAE-C1-INH and usually normal in hereditary angioedema due to C1-INH deficiency (HAE-C1-INH), current diagnostic evaluation still requires interpretation with age at onset, family history, and confirmatory testing [1, 2]. We report a Japanese kindred with biochemical type 1 C1-INH deficiency in which the proband had overlapping systemic lupus erythematosus (SLE) and profoundly suppressed C1q, thereby closely mimicking AAE-C1-INH.

The proband, a woman in her late 40s, had recurrent non-pitting edema of the face, extremities, and abdomen from her mid-teens, with an estimated 15–20 attacks annually. Attacks lasted 2–4 days, occurred without urticaria, and were unresponsive to antihistamines, glucocorticoids, or epinephrine. She had no exposure to angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, dipeptidyl peptidase-4 inhibitors, or exogenous estrogens. Her SLE had been diagnosed in adolescence but was clinically quiescent at re-evaluation, with stable low-dose prednisolone and no recent flare, clinically significant proteinuria, serositis, or active mucocutaneous disease.

Repeated testing in 2020 and 2022 showed persistently low C4 (3.0/3.0 mg/dL), low C1-INH antigen (7/5 mg/dL), and low C1-INH function (31%/<25%), consistent with type 1 C1-INH deficiency. However, C1q was below the assay detection limit at both time points (<1.5/<1.5 mg/dL). Because profoundly low C1q is classically associated with AAE-C1-INH, this result initially raised concern for an acquired process [1, 2]. Serum protein electrophoresis with immunofixation showed no monoclonal protein, and computed tomography showed no lymphadenopathy. Anti-C1q antibodies, anti-C1-INH antibodies, and *SERPING1* sequencing had not been performed at the time of writing and are planned; therefore, we do not claim definitive exclusion of AAE-C1-INH.

The key discriminator was the family pattern (Figure 1). Five biologically related individuals across three generations, including a collateral line, underwent repeat testing. The proband's son, sister, niece, and father all showed reproducibly low C4 and low C1-INH antigen/function, whereas none had SLE. C1q remained within the reference range in the son (14.7/13.8 mg/dL), sister (10.1/11.0 mg/dL), and niece (12.4/10.7 mg/dL). Only the father showed subnormal C1q (6.9/6.1 mg/dL), but his position in the multigenerational pedigree still favored hereditary transmission over independent AAE-C1-INH. Thus, the

(A)



(B)

Person	Phenotype	Repeated C4/C1-INH pattern	C1q serial (mg/dL)
Proband	Symptomatic, mid-teens; +SLE	Low C4 + low antigen/function	**<1.5 / <1.5**
Father	Asymptomatic carrier	Low C4 + low antigen/function	**6.9 / 6.1**
Sister	Symptomatic, 20s	Low C4 + low antigen/function	10.1 / 11.0
Son	Symptomatic, childhood	Low C4 + low antigen/function	14.7 / 13.8
Niece	Asymptomatic carrier	Low C4 + low antigen/function	12.4 / 10.7

FIGURE 1
Simplified pedigree and compact laboratory summary of the kindred. **(A)** Simplified pedigree of the kindred, with tested individuals marked by plus signs. Filled symbols indicate symptomatic individuals; half-filled symbols indicate asymptomatic biochemical carriers. The arrow marks the proband. "+SLE" denotes overlapping systemic lupus erythematosus. **(B)** Compact serial laboratory summary. All five tested individuals showed repeated low C4 and low C1-inhibitor antigen/function consistent with type 1 C1-inhibitor deficiency, whereas C1q was profoundly low only in the proband and mildly subnormal in the father. The C1q reference range was 8.8–15.3 mg/dL. This discordance shows that low C1q alone should not be taken as diagnostic of acquired angioedema. C1-INH, C1 inhibitor; SLE, systemic lupus erythematosus.

overall pattern was not "AAE-C1-INH with low C1q," but familial C1-INH deficiency with discordant C1q values, with the most extreme reduction confined to the proband with overlapping SLE.

This distinction matters clinically. Hereditary angioedema and lupus have been reported together, and overlap can complicate complement interpretation [3]. Other causes of low serum C1q include inherited C1q deficiency, immune-complex-mediated classical-pathway consumption (for example, active SLE, hypocomplementemic urticarial vasculitis, or cryoglobulinemic vasculitis), and AAE-C1-INH associated with monoclonal gammopathy, lymphoproliferative disease, or autoimmunity. In this patient, the absence of childhood severe infections, urticarial vasculitis-like lesions, cryoglobulinemic features, monoclonal protein, or lymphadenopathy made these alternatives less likely; overlapping SLE remained the most plausible contributor to the extreme C1q reduction. In our case, labeling the proband as having

AAE-C1-INH on the basis of C1q alone would have been discordant with adolescent onset, a clear three-generation familial pattern, and repeated concordant deficiency of C1-INH antigen and function in relatives. Conversely, the low C1q result should not be ignored; it justifies structured surveillance and confirmatory testing, especially because acquired C1-INH deficiency can be associated with monoclonal gammopathy and hematologic disease [4].

Our report adds two points to the previous family description [5]: serial C1q measurements in all tested relatives, and demonstration that profound C1q reduction can coexist with hereditary C1-INH deficiency in a patient with overlapping SLE. The limitation is the absence of molecular and autoantibody confirmation. Even so, the most parsimonious interpretation is hereditary type 1 C1-INH deficiency with SLE-associated or immune-mediated C1q reduction in the proband, rather than AAE-C1-INH diagnosed by C1q alone.

In summary, low C1q alone should not be taken as diagnostic of AAE-C1-INH. In patients with recurrent angioedema, especially when onset is early and family clustering is evident, very low C1q should trigger confirmatory evaluation for acquired disease, but should not override a hereditary pattern.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request, subject to institutional ethics constraints relating to a rare disease pedigree.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki. Formal institutional review board approval was not required for this single-family case report under our institution's 130 policy. Written informed consent for publication, including for the pedigree and clinical and laboratory details, was obtained from the proband and from all family members shown in the pedigree.

Author contributions

AT and ST contributed equally to clinical care, data acquisition, and manuscript drafting. TF provided supervision and critical revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

ST has received lecture fees from Torii Pharmaceutical, Takeda Pharmaceutical, CSL Behring, AbbVie, UCB Japan, Janssen Pharmaceutical, Taiho Pharmaceutical, Maruho, Novartis Pharma, Kyowa Hakko Kirin, Eli Lilly, LEO Pharma, and Sanofi. TF has received lecture fees from Sato Pharmaceutical, Eli Lilly, AbbVie, and CSL Behring.

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. Generative artificial intelligence (AI) tools were used solely to assist with English-language editing, manuscript proofreading, and refinement of wording and formatting. The tools used were OpenAI ChatGPT (GPT-5; OpenAI, San Francisco, CA, USA) and Anthropic Claude (Claude Opus 4.7; Anthropic PBC, San Francisco, CA, USA). These tools were not used for clinical decision-making, data collection, laboratory analysis, interpretation of clinical or laboratory findings, literature selection, or generation of scientific conclusions. All AI-assisted edits were reviewed and approved by the authors, who take full responsibility for the accuracy, integrity, and final content of the manuscript.

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