Acquired C1 Esterase Inhibitor Deficiency

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Acquired C1 esterase inhibitor deficiency is a rare condition associated with autoimmune or low-grade lymphoproliferative disorders. Adults or elderly patients are most commonly affected. The diagnosis is suspected when patients present with recurrent angioedema and low serum levels of C4 with normal levels of C3. Low levels of C1q and low C1 esterase inhibitor activity confirm the diagnosis.

In this paper, we summarize experience with 22 cases of acquired C1 esterase inhibitor deficiency in the context of a review of the published literature on diagnosis and treatment of this condition.


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The complement system was first described in the late 19th century as the property of fresh serum to cause in vitro cell death after agglutination. It represents the oldest identified component of the immune system. The complement system consists of a series of about 20 different serum proteins that are part of the body’s first-line, innate immune defenses (Figure 1). As such, the complement system is a triggered cascade of highly amplified proteolytic reactions ultimately leading to enhanced adherence of offending microorganisms, stimulation of more effective inflammation and phagocytosis, and direct lysis of the offending cells. The complement system is divided into two pathways on the basis of the trigger of the complement cascade. The classic pathway is activated when C1 binds to the Fc fragment of IgM or IgG in immune complexes. The inactive C1 molecule has three subunits—C1q, C1r, and C1s—that are held together by ionic calcium. The C1q component binds to immunoglobulin in the immune complex. With the binding of C1q, C1r undergoes enzymatic cleavage of its two subunits, exposing active proteolytic sites. The activated proteolytic site on C1r cleaves the C1s peptide, exposing its active enzymatic site. In turn, activated C1s acts as a protease for both C4 and C2. With the activation of C4 and C2 into C4b,2a complex, the C3 convertase enzyme is created (Figure 1). The activation of the alternate complement pathway is somewhat less clear. It involves the activation of C3 by a C3-convertase complex consisting of C3b,Bb. Under normal circumstances, low levels of turnover of C3 to C3b take place. During inflammation, low levels of C3b bind factor B, which then undergoes enzymatic cleavage by factor D to generate C3b, Bb. This in turn acts as a potent C3 convertase, amplifying the complement cascade. Therefore, successful generation of a C3-convertase enzyme complex is central to the process of complement activation by either pathway.

C1 esterase inhibitor is a serum α2-globulin molecule and a member of the serpin family of protease inhibitors. It is encoded on chromosome 11 as a 17,000-base pair gene interrupted by at least seven introns. It is translated as a single-chain glycoprotein (α2-globulin) containing 478 amino acid residues with a molecular weight of 105 kDa (1). The physiologic function of this hepatocyte-produced protein is inhibition of the catalytic subunits of the first component of the classic complement pathway (C1r and C1s), as well as inhibition of the function of kallikrein, plasmin, and coagulation factors XIa and XIIa. Because there are two esterase sites in C1r and C1s, each molecule of C1 binds four molecules of C1 esterase inhibitor. The binding of C1 esterase inhibitor to C1r results in loss of detectable C1r antigen activity with assay antisera. The measurement of C1r levels is therefore used to clinically follow C1 activation or inactivation. In the absence of C1 esterase inhibitor activity, activated C1 and plasmin generate activated C2 kinin (Figure 2). Activated C2 kinin is thought to be the mediator of the angioedema observed in patients with C1 esterase inhibitor deficiency.

As a distinct entity, the clinical syndrome caused by C1 esterase inhibitor deficiency was described in 1881 (2); it was linked with C1 esterase inhibitor deficiency in 1963 (3), and an acquired form of the disease was described in 1972 (1, 4). There are two forms of C1 esterase inhibitor deficiency. The inherited form is usually detected in the first or second decade of life and has a typical autosomal dominant type of inheritance. The acquired form primarily affects adult or elderly patients with no family history for this disease. These two forms can be distinguished by measurement of serum C1q: Levels of C1q are normal in the inherited form of C1 esterase inhibitor deficiency and are decreased in the acquired form. This distinction between the two forms of C1 esterase inhibitor deficiency stems from the
observation that the rate of catabolism of C1 esterase inhibitor and C1q is markedly elevated in patients with the acquired form of the disease. In the acquired form, in the setting of lymphoproliferative disorders, the large numbers of idiotypic–anti-idiotypic immune complexes consume the available C1q molecules, which in turn consume large amounts of C1 esterase inhibitor, resulting in quantitative and functional deficiency of the C1 esterase inhibitor. A distinct subtype of acquired C1 esterase inhibitor deficiency related to autoantibodies directed specifically at the C1 esterase inhibitor molecule has been described (2). C1q is consumed and the inhibitor activity is decreased despite normal C1 esterase inhibitor antigen levels. In the inherited form of C1 esterase inhibitor deficiency, the defect is in synthesis of the C1 esterase inhibitor protein. It may be produced in very small quantities (subtype A or 1, which accounts for 85% of all cases), or it may be produced in normal quantities but with functional impairment of the protein (subtype B or 2, which accounts for 15% of cases). In either form, C1 activation proceeds unabated, resulting in normal levels of C1q. In both the acquired and inherited forms of C1 esterase inhibitor deficiency, levels of C2 and C4 are decreased because of the uncontrolled activity of C1s. On these basis of observations, in patients with the corresponding clinical syndrome, acquired C1 esterase inhibitor deficiency is diagnosed by laboratory evidence of decreased C1q, C2, and C4 levels. Normal levels of C1q along with decreased levels of C2 and C4 suggest the diagnosis of inherited C1 esterase inhibitor deficiency.

The major focus of this discussion is the acquired form of C1 esterase inhibitor deficiency. As mentioned above, this type manifests itself in two forms, one associated with lymphoproliferative disorders and the other with specific autoantibodies directed against the C1 esterase inhibitor molecule (6). Although it is a rare disorder, acquired C1 esterase inhibitor deficiency has been described in diverse clinical scenarios, including HIV (7), multiple myeloma (8), Waldenstrom macroglobulinemia (9, 10), gastric carcinoma (11), B-cell lymphoma (12, 13), rectal adenocarcinoma (14), breast carcinoma (15), chronic lymphocytic leukemia (16), systemic lupus (17), Churg–Strauss vasculitis (18), acute hepatitis B (19), plane xanthomatosis (20), and *Echinococcus granulosus* infection (21). In addition, acquired C1 esterase inhibitor deficiency has been reported in a patient with myelofibrosis (22) and a patient with *Helicobacter pylori* infection (23). Most reports represent small series or single case reports.

We present the largest case series of acquired C1 esterase inhibitor deficiency published to date. This discussion includes a description of two typical patients with acquired C1 esterase inhibitor deficiency, a summary of our experience, and a review of the available literature on this topic.

**Methods**

After obtaining approval by the institutional review board, we searched the Mayo Clinic medical record computerized diagnosis database for cases of angioedema and acquired C1 esterase inhibitor deficiency. A period of 28 years was reviewed. The search revealed 4439 cases of angioedema; only 28 cases were clinically suspected of being due to acquired C1 esterase inhibitor deficiency. After careful review, only 22 cases contained the appropriate supporting data for the diagnosis of acquired C1 esterase inhibitor deficiency.

To review the available published literature on acquired C1 esterase inhibitor deficiency, we searched the MEDLINE database. All available published articles were reviewed and included in the manuscript.
Clinical Cases

Case 1

Mr. O. is a 44-year-old man with no significant medical history who presented with acute-onset swelling in his right hand and foot. He had no associated pain or pruritus in these areas, nor could he recall any antecedent trauma. The swelling resolved over 24 to 36 hours. During that time, Mr. O. took some antihistamines, which may have contributed to the resolution. Ten months later, the patient awoke with scrotal and lower abdominal swelling. Again, he recalled no antecedent trauma and had no pain or pruritus associated with the edema. The patient applied cold packs to the affected areas, and the symptoms resolved over 3 to 4 days. The third episode occurred 4 months later. This time, facial swelling gradually increased over 2 to 3 days. The patient was seen by an allergist and received corticosteroids and antihistamines (fenofenadine), with rapid resolution of symptoms. A month later, Mr. O. had yet another episode of scrotal and lower abdominal swelling. This episode spontaneously resolved after 24 hours. Work-up during that time demonstrated an undetectable level of C4, a normal C3 level, and low C1 esterase inhibitor activity. C1q levels were also low, suggesting acquired C1 esterase inhibitor deficiency. Appropriate testing yielded evidence of a chronic B-cell lymphoproliferative disorder. Flow cytometry analysis identified a small population of monoclonal B cells in the peripheral blood. Bone marrow biopsy demonstrated about 10% involvement of the bone marrow by small lymphocytes (monoclonal B lymphocytes). The patient began therapy with danazol, 200 mg twice daily, for recurrent angioedema. No therapy was initiated for the B-cell lymphoproliferative disorder.

While receiving danazol, the patient was free of recurrent angioedema but developed a skin rash. The rash was thought to be related to danazol therapy, and the regimen was changed to stanozolol, 2 mg three times daily. At 1 month of follow-up, the patient had not had any more episodes of rash or angioedema.

Mr. O. remained symptom-free for the next 11 months, at which time he noted mildly enlarged cervical lymph nodes. Evaluation at that time demonstrated persistently low C4 levels with normal C1 esterase inhibitor activity. He was also noted to have developed mild splenomegaly. At this point, a working diagnosis of stage IV low-grade non-Hodgkin lymphoma was made. Because of the patient's relatively small tumor burden and asymptomatic status, Mr. O. and his physicians decided on observation rather than initiating chemotherapy.

One year later, Mr. O. continues to take stanozolol. He has had no recurrence of angioedema, and his low-grade lymphoma remains under observation.

Case 2

Mrs. V. is a 74-year-old woman with no significant medical history. She suddenly awoke one night with swelling on the left side of her mouth. The swelling worsened progressively over the ensuing hours, prompting Mrs. V. to visit the emergency department. There she was given a dose of epinephrine and began therapy with diphenhydramine. The symptoms subsided over the following day. The patient stopped taking diphenhydramine 1 day after her symptoms subsided. Over the next month, Mrs. V. had recurrent episodes of swelling of the left side of her face, which lasted for about 20 hours and responded to oral diphenhydramine therapy. The episodes occurred every 3 to 4 days. In an attempt to control her symptoms, Mrs. V. was given fenofenadine, followed by loratadine and astemizole. These agents had no prophylactic effect on the recurrent angioedema; daily cetirizine therapy was finally effective. Two months later, the patient remained asymptomatic. Work-up at that time demonstrated a low C4 level, a normal C3 level, and undetectable functional C1 esterase activity with a normal quantitative level of C1 esterase inhibitor, despite the lack of symptoms. Flow cytometry analysis of the peripheral blood demonstrated a small population of monoclonal circulating B cells. The phenotypic characteristics of the monoclonal B cells were those of a mantle-cell lymphoma. Bone marrow biopsy was negative for lymphoma.

Five months later, the patient remains symptom-free while receiving cetirizine therapy and observation continues for early mantle-cell lymphoma.

Cumulative Experience with 22 Cases of Acquired C1 Esterase Inhibitor Deficiency

Diagnosis

To diagnose acquired C1 esterase inhibitor deficiency, one has to combine clinical clues with laboratory data. A clinical history of recurrent angioedema in middle-aged or elderly patients should raise suspicion for acquired C1 esterase inhibitor deficiency. Low levels of C4 and normal levels of C3 support the diagnosis. Quantitative and functional measurements of C1 esterase inhibitor activity confirm the diagnosis. Low levels of C1q suggest the diagnosis of acquired C1 esterase inhibitor deficiency, whereas normal levels of C1q suggest the diagnosis of the inherited form. Except for age at
onset and positive family history in the inherited variety, the two syndromes are clinically indistinguishable.

Demographic Characteristics of Patients

Review of our experience uncovered 22 cases of acquired C1 esterase inhibitor deficiency (5 men and 17 women; mean age, 50 years). The most common associated diagnoses (14 of 22 patients) were low-grade lymphoproliferative disorders (low-grade lymphoma, chronic lymphocytic leukemia, or monoclonal gammopathy of undetermined significance). Of note, 1 case of Hodgkin disease and 1 case of primary systemic amyloidosis were also associated with acquired C1 esterase inhibitor deficiency. Of the 22 cases of acquired C1 esterase inhibitor deficiency, 2 were not associated with any identifiable underlying disease and 4 were associated with autoimmune disorders.

Clinical Presentation

Most patients with acquired C1 esterase inhibitor deficiency in our sample presented with swelling or angioedema of the head, neck, or extremities. Patients noted recurrent sensations of tongue, cheek, and upper-airway swelling that was sometimes associated with sensations of breathlessness. Others mentioned recurrent swelling of the hand, forearm, thigh, or calf. Seven patients had abdominal symptoms as the major manifestations of the disease (recurrent episodes of abdominal cramping, nausea, vomiting, and loose stools). In most of these patients, the irritable bowel syndrome was thought to be the diagnosis at some point in the work-up. Upper-airway angioedema with predominantly respiratory symptoms was noted in three patients. Swelling of the uvula and tongue was noted in 3 patients each. In all patients, symptoms were mild to moderate and did not require emergency medical interventions. Of note, the average time to diagnosis of acquired C1 esterase inhibitor deficiency from onset of symptoms was 2.3 years (range, 0 to 8 years). With regard to neoplastic disorders associated with acquired C1 esterase inhibitor deficiency, only in systemic amyloidosis did the signs and symptoms of acquired C1 esterase inhibitor deficiency develop after amyloidosis was diagnosed. In all other patients with neoplasms associated with acquired C1 esterase inhibitor deficiency (16 of 22), the symptoms occurred 0 to 7 years before the diagnosis of the malignant condition. Three of the four patients in whom acquired C1 esterase inhibitor deficiency was not associated with neoplasm already had a rheumatologic diagnosis when angioedema developed.

Clinical Course

Because of the delay in diagnosis of acquired C1 esterase inhibitor deficiency, most untreated patients reported recurrent episodes of symptoms. The episodes occurred at intervals ranging from 1 to 9 months; symptoms were similar each time. Patients who had uvular swelling had recurrence of that symptom only and no new symptoms of angioedema. The time between symptom episodes varied greatly for each patient, from weeks to months. Most episodes lasted 1 to 2 days; some lasted up to 1 week. The duration, severity, and anatomic distribution of symptoms were largely uniform for a given patient. Follow-up time varied depending on the frequency of symptoms. In our series, most patients were seen at 2- to 6-month intervals. Clinical and laboratory monitoring (measurement of complement levels) was performed at each visit.

Treatment

In accordance with standard recommendations, most (12 of 22) patients received androgen therapy. One patient received high-dose corticosteroids, one received epinephrine injections on an as-needed basis, one received loratadine plus nizatidine, and one received cetirizine. Twelve of the 22 patients received systemic therapy for their neoplastic or autoimmune disorder. Response to treatment varied. Glucocorticosteroid and androgen (danazol or stanozolol) therapies were both effective, symptoms resolved after therapy was begun. In the absence of androgen therapy, tapered doses of corticosteroids resulted in relapse of symptoms. In the setting of acute symptoms, corticosteroids alone or in combination with epinephrine (for severe throat swelling) were effective in aborting the paroxysm. Long-term androgen therapy along with therapy for underlying diseases seemed to be the most effective strategy in preventing symptom recurrence (11 of 22 patients). In isolated cases, very-low-dose androgens (danazol, 100 mg/d) were effective in preventing symptom recurrences. Of note, resolution of symptoms did not always correlate with laboratory evidence of increased C4 complement levels. One patient with splenomegaly and a low-grade lymphoproliferative disorder responded to splenectomy alone.

Discussion

Episodic angioedema associated with deficiency of C1 esterase inhibitor (acquired or inherited) is a rare clinical condition in which recurrent, localized, nondepressed, nonpruritic subcutaneous swellings appear rapidly and spontaneously and resolve within hours to days (5). Our case series of patients with
acquired C1 esterase inhibitor deficiency corroborates the existing literature and demonstrates that the areas most commonly affected by angioedema are the extremities and the head and neck. Most patients also had an associated low-grade lymphoproliferative disorder that was preceded by recurrent angioedema. In our case series, we identified acquired C1 esterase inhibitor deficiency in a patient with systemic amyloidosis and a patient with Hodgkin disease, neither of which have previously been reported. In addition, one patient had a complex syndrome of multiple environmental allergies in association with recurrent angioedema due to acquired C1 esterase inhibitor deficiency. Histamine blockade led to symptom resolution in that patient.

With regard to therapy, in the acute setting, high-dose corticosteroids with or without subcutaneous epinephrine seem to be effective, depending on the severity of symptoms. Treatment of the primary disease process (if identifiable) or long-term androgen therapy seems to be effective in preventing recurrence of angioedema.

Our experience with acquired C1 esterase inhibitor deficiency is largely in agreement with the published literature. Our series is the largest single collection of cases of this disorder, which allowed us a broader exposure to diverse patients and enabled us to develop an algorithm for the diagnosis, treatment, and follow-up of this unusual condition. Most other published reports are case reports or small case series that deal with the specific problems of particular patients.

**Diagnosis**

On the basis of our experience and data from published reports, we propose the following algorithm for the work-up of a patient with recurrent angioedema or otherwise unexplained abdominal symptoms (Figure 3). The key to diagnosis of acquired C1 esterase inhibitor deficiency is to be aware of the multiple clinical presentations of this condition and to confirm or disprove clinical suspicion by using laboratory analysis. Screening measurements of serum levels of C3 and C4 will support a diagnosis of C1 esterase inhibitor deficiency as the cause of angioedema. To distinguish between acquired and inherited C1 esterase inhibitor deficiency, the C1q level should be measured (Figure 3). Confirmatory laboratory testing should include measurements of levels and specific activity of C1 esterase inhibitor. In view of the likelihood that a patient with acquired C1 esterase inhibitor deficiency will have an underlying malignant condition, confirmation of the diagnosis in the suggestive clinical scenario will substantially affect further work-up and overall prognosis.

**Figure 3.** Proposed work-up flow sheet for patients with a clinical history of angioedema.
Table. Less Commonly Used Treatments of Acquired C1 Esterase Inhibitor Deficiency

<table>
<thead>
<tr>
<th>Treatment</th>
<th>As Emergency Therapy</th>
<th>As Long-Term Therapy</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>e-Aminocaproic acid</td>
<td>Not effective</td>
<td>Effective</td>
<td>Mostly used in hereditary C1 esterase inhibitor deficiency</td>
<td>25</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>Unknown</td>
<td>Effective</td>
<td>Reported use only in hereditary angioedema</td>
<td>26</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>Effective</td>
<td>Not effective</td>
<td>Provides C1 esterase inhibitor as well as C2 and C4, which may worsen symptoms</td>
<td>24</td>
</tr>
<tr>
<td>Plasmapheresis plus cyclophosphamide</td>
<td>Effective</td>
<td>Effective</td>
<td>Single report of plasmapheresis with 5% albumin</td>
<td>27</td>
</tr>
<tr>
<td>C1 esterase inhibitor concentrate</td>
<td>Effective</td>
<td>Not used</td>
<td>Used preoperatively when androgens do not elevate C1 esterase inhibitor levels; patients may require very high doses of the concentrate</td>
<td>28</td>
</tr>
<tr>
<td>Heparin</td>
<td>Effective</td>
<td>Not used</td>
<td>Inhibits activated C1 function in vitro; reported uses in hereditary angioedema</td>
<td>29</td>
</tr>
<tr>
<td>Interferon-γ</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Increases C1 esterase inhibitor synthesis in endothelial cells, monocytes, and synovial cells; used in normal volunteers</td>
<td>30</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Effective</td>
<td>Unknown</td>
<td>Mayo Clinic experience</td>
<td>–</td>
</tr>
</tbody>
</table>

Further Evaluation and Follow-up

Considering the high concordance of acquired C1 esterase inhibitor deficiency and malignant disease, once the syndrome is diagnosed, work-up for an underlying malignant condition should follow. We recommend an evaluation that includes immunophenotyping of peripheral blood lymphocytes for circulating malignant B cells; serum protein electrophoresis and immuno-electrophoresis for underlying dysproteinemia; and computed tomography of the chest, abdomen, and pelvis to identify evidence of lymphoproliferative or other solid tumors. Bone marrow biopsy may also be helpful. In view of the prolonged lag time between the occurrence of the syndrome and diagnosis of underlying malignant disease (up to 7 years), a negative initial work-up should not dismiss the possibility of an underlying disorder. Follow-up visits every 3 to 6 months should be geared toward early diagnosis of an underlying malignant condition. In the presence of recurrent symptoms, complement testing should be repeated.

Therapy

The most effective therapy for acquired C1 esterase inhibitor deficiency is treatment of the underlying disease process. However, if no such process is discovered, the most common treatment is androgenic steroids, alone or in combination with glucocorticosteroids. First described by Spaulding in 1960, androgens are the most commonly used therapy for acquired C1 esterase inhibitor deficiency; they bring about dramatic decreases in both the frequency and severity of attacks. The mechanism of action seems to be related to an increase in the production of C1 esterase inhibitor by the liver. In the acute setting, androgens may not be sufficient to control symptoms and have usually been combined with glucocorticosteroids. Androgens are used mostly for long-term control of symptoms. The exact dosing of androgens may vary among individual patients and should be adjusted to control symptoms.

Glucocorticosteroids have also been used to treat acquired C1 esterase inhibitor deficiency. These agents have been used primarily in the emergency setting; the dose is tapered once patients have begun taking an androgen. In patients in whom glucocorticosteroids were used initially to control symptoms and in whom doses were subsequently tapered without the concurrent use of androgens, symptoms have uniformly recurred. Much like the androgens, glucocorticosteroids induced increased synthesis of C1 esterase inhibitor in the liver as part of the acute phase reaction.

Published reports also describe the utility of other pharmaceutical agents in the effective treatment of the symptoms of acquired C1 esterase inhibitor deficiency (Table). Although use of fresh frozen plasma and C1 esterase inhibitor concentrate have been reported, they have been used only in patients with the inherited form of the disease and only in a limited number of patients (24, 31). Use of e-aminocaproic acid for prophylaxis of angioedema has also been reported (32). None of our patients underwent any such therapy.

Not all patients with documented acquired C1 esterase inhibitor deficiency require long-term therapy. In some patients in whom attacks are mild and rare, it is feasible to just treat the acute episodes. Patients with known C1 esterase inhibitor deficiency who are undergoing surgery may be at risk for an acute attack of edema, especially laryngeal edema, during surgery. This is mostly a feature of hereditary angioedema, and no good evidence indicates that this occurs in patients with acquired C1 esterase inhibitor deficiency. However, in our experience, patients who underwent surgical procedures were pretreated with androgens or the androgen dose was increased. The goal of therapy was normalization of C1 esterase inhibitor function.

A frequently noted concern in patients with ac-
quired or inherited C1 esterase inhibitor deficiency is the use of angiotensin-converting enzyme inhibitors. Indeed, more frequent and more severe episodes of angioedema have been reported in patients with C1 esterase inhibitor deficiency who are receiving angiotensin-converting enzyme inhibitors. However, a direct association between the two has never been documented. Nonetheless, this clinical observation has created a general acceptance that use of angiotensin-converting enzyme inhibitors should be avoided in patients with a history of inherited or acquired C1 esterase inhibitor deficiency.

Although acquired C1 esterase inhibitor deficiency is in general a nonfatal condition, it may be fatal if acute attacks of edema go untreated and can produce dramatic symptoms. Most patients undergo extensive work-up before the final diagnosis is made, particularly patients with primarily abdominal symptoms. Once the diagnosis is made, therapeutic options are relatively simple. Androgens play a major role in symptom control, although corticosteroids and epinephrine are also commonly used in the acute setting. However, identification and treatment of the underlying cause of angioedema make up the most appropriate mode of therapy.

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Grant Support: From the Mayo Foundation.

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