

## Acquired angioedema associated with chronic hepatitis C

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C1-esterase inhibitor (C1-INH) deficiency is known to result in generalized angioedema.<sup>1</sup> In addition to its hereditary form, an increasing number of diseases, including tumors and autoimmune disorders, were described in association with C1-INH deficiency (acquired angioedema [AAE]).<sup>1</sup> Hepatitis C virus (HCV) has been considered among the most important causes of chronic liver disease, as well as an inducer of autoimmunity.<sup>2</sup>

### Abbreviations used

|          |                            |
|----------|----------------------------|
| AAE:     | Acquired angioedema        |
| C1-INH:  | C1-esterase inhibitor      |
| HCV:     | Hepatitis C virus          |
| HCV-RNA: | Genom of hepatitis C virus |

The cases of 2 women with chronic hepatitis C are reported herein; both had frequent, severe attacks of angioedema caused by deficiency of C1-INH.

### CASE REPORTS Patient 1

A 58-year-old woman was admitted for evaluation of recurrent, nonpruritic, nonpitting edematous attacks occurring on the face and upper limbs, which did not affect the airways. These symptoms had been recurring almost monthly and lasted for 3 to 4 days. Her medical history was remarkable for salpingo-oophorectomy, cholecystectomy, and multiple blood transfusions. Because her liver function test results were found to be

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**TABLE I.** Complement parameters of patients

|           | <b>C3</b><br>(0.7-1.8 g/L)* | <b>C4</b><br>(36%-144%)* | <b>C1-INH</b><br>concentration (65%-166%)* | <b>C1-INH activity</b><br>(85%-125%)* | <b>C1</b><br>(4000-33,000 CH63/mL)* |
|-----------|-----------------------------|--------------------------|--------------------------------------------|---------------------------------------|-------------------------------------|
| Patient 1 | 1.2 g/L                     | 19.4%                    | 62%                                        | 29.8%                                 | 1999 CH63/mL                        |
| Patient 2 | 0.65 g/L                    | 12.4%                    | 58%                                        | 46.4%                                 | 2072 CH63/mL                        |

\*Values in parentheses are normal ranges.

repeatedly abnormal for years, a detailed analysis was performed to reveal chronic liver disease. The presence of serum anti-HCV antibodies and HCV-RNA, as well as liver histology (Knodel score: 8),<sup>3</sup> confirmed the diagnosis of chronic HCV. Furthermore, the patient had AAE established by markedly decreased levels of classical complement components, as well as low C1-INH serum concentration and activity (Table I). Cryoproteins were not present in her serum, and other known causes of AAE were also excluded.

## Patient 2

A 32-year-old woman was first seen with severe edematous episodes affecting the face and limbs, as well as weekly bouts of colicky abdominal pain. Laryngeal edema was also noted a year earlier. The symptoms usually lasted for 3 days. Her medical history was otherwise uneventful. Complement studies (Table I) confirmed our tentative diagnosis of AAE. At her first presentation, abnormal liver function test results (alanine aminotransferase: 228 U/L [normal range <37 U/L],  $\gamma$ -glutamyl transferase: 240 U/L [normal range <50 U/L]) and hepatomegaly were found. Chronic hepatitis C with mild histologic activity (Knodel score: 4)<sup>3</sup> was diagnosed. Cryoproteins could not be detected. Because of the history of severe edematous attacks, she was started on danazol therapy (Danova, KRKA), 400 mg per day. Edematous attacks did not recur during the subsequent 6 months.

## METHODS

Hepatitis B surface and e antigens, antibodies to e and core antigens, and antibodies to hepatitis A and C viruses were also tested with immunoassays (Abbott Laboratories). The presence of anti-HCV antibodies was confirmed by a second-generation recombinant immunoblot assay (Chiron RIBA II, Ortho Diagnostic System). A branched-chain DNA assay was used (Quantiplex, Chiron Corporation) to detect HCV-RNA in serum.

C1 hemolytic activity was measured according to the method of Nelson et al.<sup>4</sup> To quantify C4-, C3-, and C1-INH protein levels, radial immunodiffusion was applied by using antibodies from ATAB and an in-house calibrator serum. C1-INH activity was measured by kinetic assay with a commercially available C1-INH kit (Behringwerke AG). Autoantibodies to C1-INH were tested by the method of Cicardi et al.<sup>5</sup>

## RESULTS

Markedly decreased C1 hemolytic activity and C4 serum level, low C1-INH serum concentration, and activity accompanied by normal or slightly diminished C3

level confirmed the diagnosis of AAE in both patients (Table I). Autoantibodies to C1-INH could not be detected in either patient. Remarkably, a close correlation between increases of ALT activity and the occurrence of angioedema attacks was observed in patient 2.

## DISCUSSION

AAE is an uncommon disorder that produces symptoms of hereditary angioedema.<sup>1</sup> Its characteristic serologic features include low serum levels of early complement factors (C2, C4, and C1), as well as diminished serum level and/or activity of C1-INH. The role of the complement system in the pathogenesis of hepatic and extrahepatic diseases is largely unknown in patients with chronic HCV infection. HCV can elicit an immune response manifested by the production of autoantibodies against different target antigens. Furthermore, patients with chronic HCV infection frequently have mixed cryoglobulinemia accompanied by hypocomplementemia. Both autoantibodies and cryoproteins may be responsible for the decreased complement level.

This demonstration of 2 cases is the first report on the coexistence of chronic HCV and AAE. Complement values were characteristic for AAE, although their changes were not so dramatic as those reported by Agostoni and Cicardi.<sup>1</sup> Autoantibodies to C1-INH and cryoproteins were absent. Therefore hypocomplementemia and C1-INH deficiency appear to be induced by HCV or HCV-containing immune complexes. Nevertheless, the essential factors of the pathomechanism remain to be elucidated by further studies.

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