New Perspectives in Acquired Angioedema

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First described by Caldwell et al. in 1972 [1], acquired angioedema is an extremely rare disease characterized by a complement C1-inhibitor deficiency, hyperactivation of the classical pathway of the complement, with potentially recurrent attacks of abdominal pain and life-threatening laryngeal involvement due to bradykinin-mediated angioedema. There are slightly fewer than 200 AAE patients reported in the literature. Clinically, the angioedema symptoms that characterize AAE cannot be differentiated from those present in patients with the hereditary type who have a deficiency of C1-INH due to mutations in one of the two alleles coding for this protein [2]. Angioedema recurs at unpredictable intervals that last from 2 to 5 days and presents with disfiguring, non-pitting, non-pruritic edema of the skin (face, limbs, genitals), and severe abdominal pain from edema of the gastrointestinal mucosa leading to temporary bowel occlusion.

AAE has traditionally been considered to consist of two types. Type I AAE is associated with lymphoproliferation and excessive C1-INH consumption. Type II EAA is secondary to anti-C1-INH autoantibody production and is usually associated with a monoclonal gammopathy of unknown significance or, occasionally, with a lymphoid hemopathy. It subsequently became clear, however, that this distinction is artificial, since many patients have lymphoproliferative diseases together with autoantibodies to C1-INH. Treatments for AAE are the same as those for HAE, with the exception of anti-CD20 monoclonal antibodies, such as rituximab, which was recently introduced and is aimed at depleting B lymphocytes.

A recent Danish article [3] summarized national data on nine patients with AAE, making it the largest group ever described in a single publication. All the patients were older than 40 years at the time of their first angioedema attack, in accordance with the reported age at onset being past the fourth decade of life in 94% of affected individuals. The Danish patients had low values of complement C1-INH antigen, C1-INH function, C4 and C1q at least once. Five patients had been tested for anti-C1-INH autoantibodies, and the results were positive in 2 of them, concurring with 71 positive patients among 136 patients. Six patients were diagnosed as having a hematologic condition during the follow-up period. None of the nine patients had a lymphoproliferative disorder when the angioedema first appeared. Two patients had abnormal blood counts and/or enlargement of lymph nodes at the initial hospital presentation for AAE, and further examinations led to their being diagnosed as having splenic marginal zone lymphoma and small lymphocytic lymphoma. Flow cytometric analyses of peripheral blood were performed in three patients, and the results led to a presumptive diagnosis of a hematological condition that was confirmed by bone marrow biopsy.

Branellec and his group [4] described seven patients with AAE (six with type II and 1 with type I) who were treated with rituximab. Clinical efficacy was complete for three and partial for two, while the remaining two were therapeutic failures (one failure was the patient with type I AAE). Only two patients had improved biological parameters, with normalization of their C1-INH levels and diminished anti-C1-INH autoantibodies, and those outcomes were observed 1–9 months after the last infusion of the second rituximab cycle. An associated lymphoproliferation did not affect the response to treatment.

In a study published in this month's issue of *IMAJ* [5], Dreyfus and colleagues present evidence that rituximab therapy results in reduced levels of immunoglobulin G autoantibodies binding C1-INH protein, suggesting that the reduction of autoantibody levels may be the mechanism of successful rituximab therapy. Their 41 year old female patient suffered from autoimmune disease and was diagnosed as having HAE based on low C1q, C2, C3 and C4, and the presence of anti-C1esterase inhibitor. She failed to respond to ecallantide, a novel kallikrein inhibitory peptide, as well as to methylprednisolone and androgens. She was then treated with four infusions of rituximab at a dose of 375 µg/m^2, after which her angioedema resolved completely, with normal C1-INH level and undetectable anti-C1-INH antibody. The authors proposed that the monitoring of both total serum IgG and autoreactive antibodies against C1-INH protein be standard treatment, both prior to and following rituximab treatment, in order to establish diagnosis and guide therapy.

The good news is that modern pharmacology can benefit patients with AAE. Rituximab can be offered if antibody to C1esterase inhibitor is detected in their blood. The level of autoreactive antibodies

AAE = acquired angioedema
C1-INH = complement C1-inhibitor
HAE = hereditary angioedema

should be periodically checked to assist in monitoring the therapeutic results and adjusting the treatment accordingly.

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