Acquired Angioedema Responding to Rituximab

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Angioedema (AE) due to C1 inhibitor (C1 INH) deficiency is frequently refractory to treatment and even life-threatening. It is classified into hereditary (HAE) and acquired (AAE) forms. HAE is an autosomal dominant disease resulting from mutations in the C1 INH gene (1). It affects 1:50,000 subjects in the general population and is classified into three types (2). AAE, as in the case of our patient, commonly starts in middle age and is usually associated with lymphoproliferative disorders (1, 3), solid neoplasia, autoimmune or infectious diseases. AAE type 1 is due to increased consumption of C1 INH by paraproteins or immune complexes (4), whereas type 2 results from direct cleavage of C1 INH by auto-antibodies. As we have pointed out elsewhere (5), and as shown in our present case, this classification of AAE is of a limited value, as some patients cannot be clearly classified because they have both paraprotein and anti-C1 INH auto-antibodies. Whether the paraprotein may act as antibody is not known.

An efficient prophylactic therapy is mandatory. As illustrated by this case report, rituximab may be a promising therapy. It is a monoclonal antibody against lymphocytes B-CD20 that blocks the production of antibodies.

CASE REPORT

An 84-year-old woman had recurrent attacks of oedema affecting her face and limbs. Diagnosis of AAE type 2 was confirmed by biological findings showing decreased plasma levels of C4 (0.06 g/l, normal: 0.10–0.40 g/l) and C1 INH (antigenic levels: 0.08 g/l, normal: 0.21–0.34 g/l and functional levels: 2.0 U/ml, normal: 17.2–27.4 U/ml) with IgM auto-antibodies against C1 INH (620 arbitrary unit (AU), ELISA, normal: 2–100). A 20-month treatment with attenuated androgens and tranexamic acid was not successful in preventing 6–8 severe monthly attacks. The patient received infusions of C1 INH concentrate upon 6 life-threatening attacks over a period of 18 months. Aetiological investigation revealed a monoclonal gammopathy of undetermined significance of IgM kappa type with no evolution towards multiple myeloma.

Four weekly infusions of 375 mg/m^2 of rituximab (MabThera®, Roche, Basel, Switzerland), followed one year later by a maintenance dose of 1,000 mg, were performed. Since the first rituximab infusion, a significant clinical improvement appeared with only 2–3 mild monthly attacks that did not require treatment with C1 INH concentrate or bradykinin B2 receptor inhibitor. The patient was followed for more than two years. Clinical improvement was maintained and C1 INH functional levels were improved to 3.1 U/ml while the auto-antibodies rate remained stable (614 AU) one year after the 4 initial infusions then declined to 269 AU 12 months after the 1,000 mg maintenance dose.

DISCUSSION

AE due to C1 INH deficiency is a local, episodic, self-limited, often recurrent oedema of the subcutaneous or the submucosal tissues. Severe complications and life-threatening conditions may occur when it involves the airways or the intestinal mucosa. The disease is due to reduced plasma levels or altered function of C1 INH. This deficiency will amplify key steps in the complement pathway and in the contact system of coagulation, leading to increased production of bradykinin and subsequent release of substance P from endothelial nerve fibres, promoting increased vascular permeability and oedema (6, 7).

The therapy of AE is complex. Simultaneously with the treatment of the crisis and of any underlying condition, prophylactic therapy is mandatory. C1 INH concentrate and icatibant, which are efficient treatments for the attacks, are also used in short-term prophylaxis prior to high-risk conditions, such as surgery (8). For long-term prophylaxis, attenuated androgens are commonly used, which increase C1 INH production, as are fibrinolysis inhibitors, which reduce peripheral consumption of C1 INH. In the case of AAE with auto-antibodies, as in the case described here, when this prophylactic treatment is not sufficient to prevent crisis, rituximab may be, from a theoretical point of view, a good alternative. Rituximab led to a significant clinical improvement in abdominal crisis due to AAE (9). Three other patients were treated successfully with rituximab with clinical remission and biological improvement 10 months later. Interestingly, only one of these patients had antibodies against C1 INH (10). In our patient, who was refractory to other therapies, rituximab allowed a dramatic attenuation and spacing of the crisis. However, its mechanism of action has to be more clarified as it has shown efficacy even in some cases without antibodies.

The authors declare no conflicts of interest.

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