Acquired angioedema: a new target for rituximab?

Haematologica 2004; 89:(8)e104-e105

Acquired angioedema (AAE) is a rare disorder characterized by recurrent attacks, late onset of symptoms and a marked decrease of C1 levels. Pathogenetically it is caused by an accelerated consumption of C1-inhibitor (C1-INH), resulting in C1-INH deficiency and uncontrolled complement activation. We describe successful treatment of a patient with AEE due to C1-INH autoantibody, administering 4 weekly infusions of rituximab (anti-CD20), thereby suggesting a possible therapeutic role for this biologic agent.

A 67 year-old man presented with one day history of colick abdominal pain and vomiting. His medical history included hypertension, nephrolithiasis and chronic renal failure of unknown etiology. The patient only received treatment with amlodipine for hypertension. He also had an artificial pacemaker due to sinus node dysfunction.

On physical examination, the arterial pressure was 140/70 mmHg, heart rate was 70 bpm and temperature was 37°C. Auscultation revealed normal breath and heart sounds and a systolic murmur of 3/6 over the cardiac apex. The abdominal examination revealed a slight dilation and diminished bowel sounds. Stool examination was negative for blood. The ultrasonographic study of the abdomen excluded aortic dissection and ureteral obstruction. Hematologic and blood chemical tests revealed mild normochromic, normocytic anemia (hemoglobin value of 12.4 g/dL) and serum creatinine of 2.0 mg/dL. A serum and urine protein electrophoresis/immunofixation study revealed a monoclonal IgMκ component and free κ light chains respectively. Urinalysis gave a + positive test for protein. In a 24-hour urine specimen the protein was 400 mg. A CT scan of the abdomen only revealed dilatation of the duodenum, cecum and ileus with mucosal edema. A decision to avoid any major surgical intervention was made and the patient was admitted to our department for further evaluation and follow up. The following day the abdominal pain resolved itself, clinical evaluation was completely normal, and the patient looked well. When a detailed history was taken the patient disclosed that he had experienced intermittent episodes of non-pitting edema of the upper extremities lasting a few hours and spontaneously disappearing. Complement cascade assay showed a low C1 level and a very low C4. Plasma concentration and functional activity of C1-INH were measured by a nephelometric and a chromogenic assay (Baxter AG, Vienna, Austria) respectively and both yielded abnormal results (40% and 60% of the normal values respectively). Given the patients' age and his negative family history an AAE was suspected. C1-INH autoantibodies detected by enzyme-linked immunosorbent assay confirmed the diagnosis of AAE type II.[1] Bone marrow biopsy revealed 2% infiltration of a CD5+CD19+CD20+CD23+ B-cell clone. Further staging procedures did not reveal overt lymphoma. Renal biopsy was compatible with nephrosclerosis without evidence of immunoglobulin deposition disease. Despite prophylactic treatment with danazol and tranexamic acid the patient experienced recurrent bouts of abdominal pain. During these attacks, he was managed with a replacement therapy of C1-INH concentrate. Immunosuppressive therapy with monthly intravenous cyclophosphamide was started resulting in a remission of the episodes. After 4 cycles of cyclophosphamide, this treatment was withdrawn because the patient developed pneumocystis carinii pneumonia. A *wait and see* policy was adopted with regular monitoring for an underlying lymphoproliferation. A six-year follow up displayed no evidence of lymphoma. Attacks were infrequent, averaging 5-6 episodes per year, moderate in severity and self-limiting within 24hours.

Frequency and severity of attacks increased dramatically last year. Upon extensive reevaluation bone marrow biopsy remained unchanged, quantitive immunoglobulin assay revealed slightly elevated IgM, with a monoclonal IgM(κ) component in immunofixation and no further evidence of lymphoma. Plasmapheresis was considered as an alternative treatment but the first course was complicated by deep vein thrombosis of the right femoral vein and extensive bleeding followed anticoagulation treatment. Rituximab (anti-CD20) was started as a salvage therapy at a dose of 375 mg/m^2, weekly, for a month. Following treatment, the attacks became less severe with an attack-free interval lasting six months. Angioedema without urticaria occurs with C1-INH deficiency that may be hereditary as an autosomal dominant characteristic or may be acquired. Organs most commonly involved are the skin, upper respiratory tract and gastrointestinal tract. Gastrointestinal involvement is present with abdominal colic, with or without nausea and vomiting, occasionally managed with unnecessary surgical intervention. The acquired form of C1-INH deficiency has clinical manifestations that are indistinguishable from hereditary angioedema with the only difference being the lack of a familial element and the reduction of C1 protein. Type I of AAE coincides with lymphoproliferative disorders, in which C1-INH is consumed by various mechanisms. A second acquired form of C1-INH deficiency with angioedema, type II, is due to the appearance of a C1-INH blocking autoantibody that leads to a nonfunctional cleaved form of C1-INH.[2] It has recently been noted that some patients with acquired angioedema type II also have an underlying lymphoproliferative disorder.[3,4] Thus type I and II of acquired C1-INH deficiency should not be distinguished by the presence or absence of lymphoma but rather by the presence of autoantibodies to C1-INH.

Modern treatments of autoimmune diseases are based on immunological therapies. Rituximab induces a targeted B-cell depletion with the aim of eradicating autoreactive clones in various autoimmune disorders, with minor side effects. Encouraging results were reported in patients affected by idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia, as well as those with diseases such as lupus and acquired hemophilia. Although best results are described in autoimmune hemolytic anemia, there is also clear evidence for improvement in many other disorders of an autoimmune background. In all these cases the number of complete or partial remission, though temporary, is in excess of 50%.[5]

This is the first case suggesting a possible therapeutic role of anti-CD20 in acquired angioedema. Targeting B lymphocytes with the aim of interrupting antibody formation and the resulting phenomena of C1-INH antibody-mediated deficiency is an attractive hypothesis though its therapeutic or palliative effects are still unclear.

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