Successful Rituximab B Lymphocyte Depletion Therapy for Angioedema due to Acquired C1 Inhibitor Protein Deficiency: Association with Reduced C1 Inhibitor Protein Autoantibody Titers

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Numerous therapies for treating hereditary and acquired angioedema have become available in the past decade [1,2]. In the acquired form of angioedema, there is normal to increased synthesis of normal C1 inhibitor protein and either an excessive consumption of C1-INH or a formation of circulating anti-C1-INH antibodies that cleaves, blocks, or otherwise transforms C1-INH into a non-functional form. The acquired form of C1-INH has been divided into type I and type II, a distinction that may influence treatment. Type I acquired angioedema is associated with lymphoproliferative disorders and production of a clonal autoreactive C1-INH protein antibody. Chemotherapy of the underlying malignant or premalignant condition is the treatment for type I acquired angioedema.

Type II angioedema has been associated with autoimmune syndromes and may involve either production of a C1-INH protein-specific autoantibody or autoantibodies, or other mechanisms of inflammation, although it is possible that the two types of acquired angioedema overlap [3]. In patients with type II acquired angioedema related to autoimmune disease, a wide variety of therapies have been attempted including therapy with androgens which are also useful in hereditary angioedema; unsuccessful depletion of autoreactive antibodies through plasmapheresis; replacement of C1-INH protein; eternacept-blocking inflammatory tumor necrosis factor; as well as agents that interfere with generation of bradykinin by kallekrein or blockade of the bradykinin receptor. Remarkably, patients with type II angioedema also seem to respond to depletion of B lymphocytes with chimeric antibodies such as rituximab, a medication that might be expected to be effective only in type I angioedema due to lymphoproliferative disorders [4].

We report a case of acquired angioedema type II associated with autoimmune disease that responded to rituximab B lymphocyte depletion with sustained remission of angioedema. Furthermore, our report shows that a high affinity immunoglobulin G antibody or antibodies were present prior to therapy, and response to treatment occurred in association with reduced titers of bound and free C1-INH protein autoreactive immunoglobulin. Our results support the hypothesis that type II acquired angioedema results from a specific C1-INH protein autoreactive antibody or antibodies produced by B lymphocytes consistent with an autoimmune syndrome.

C1-INH = normal C1 inhibitor protein

PATIENT DESCRIPTION

A 41 year old woman with a past medical history of myasthenia gravis and antiphospholipid syndrome presented with severe diffuse abdominal pain. Antinuclear antibody was negative. She was diagnosed with acquired angioedema based on low C1q, C2, C3, C4 and the presence of anti-C1-INH protein autoantibody (immunoglobulin G binding C1-INH protein was determined at National Jewish Medical Center, Denver, CO, USA). She continued to have recurrent episodes of angioedema involving the colon and the larynx, necessitating intubations. She was treated with medications including loratidine, cetirizine and ranitidine for prevention, and methylprednisilone and androgens without improvement. She also did not appear to benefit from ecallantide, a novel kallekrein inhibitory peptide that is effective in hereditary or acquired angioedema in acute settings.

After reviewing the risks and benefits and signing consent for "off label use," she was treated with four standard infusions of rituximab at a dose of 375 mg/m^2 in the spring of 2011. Following rituximab she experienced complete resolution of angioedema episodes for more than 2 years. Remarkably, after the rituximab therapy,

C1-INH protein-specific autoantibody was no longer detected at elevated levels. On 18 February 2011, prior to rituximab therapy, free C1-INH protein antibody binding level was 59.2% STD (normal 0.89–36.1) and C1-INH bound autoantibody was 28.3% STD (normal 0.3–46.3), while on 3 April 2012, approximately one year after rituximab therapy, free C1-INH protein antibody binding level was within normal limits at 12.2% STD and bound antibody was not detected.

In conclusion, there are increasing reports of the successful use of B lymphocyte depletion in acquired C1-inhibitor deficiency [4]. Rituximab has been used successfully in autoimmune diseases such as rheumatoid arthritis, idiopathic thrombocytopenic purpura, idiopathic urticaria, autoimmune hemolytic anemia, systemic lupus erythematosus, multiple sclerosis, and acquired hemophilia. In all these disorders the mechanism of successful rituximab therapy could be through elimination of a clonal autoreactive antibody producing B lymphocyte. However, a pathogenic role of a specific autoantibody or autoantibodies has not been established in many autoimmune conditions, including acquired angioedema associated with autoimmune disease (type II acquired angioedema).

Our case clearly shows that B lymphocyte depletion by rituximab is an effective and possibly curative treatment for type II acquired C1-inhibitor deficiency occurring in the presence of autoimmune disease and also demonstrate, for the first time to our knowledge, that clinical remission of symptoms in type II acquired angioedema occurs simultaneously with reduction of a C1-INH protein-specific autoantibody. While this observation does not prove a causal role for anti-C1-INH protein autoantibody in type II acquired angioedema, based on related observations from type I acquired angioedema it seems likely that a high affinity or monoclonal antibody could play a significant role in both forms of the disorder. Rituximab therapy seems to be long-lasting and effective in patients resistant to multiple other therapies. Thus, we suggest that B lymphocyte depletion is the preferred and definitive treatment for this condition until a more specific therapy for elimination of autoantibodies against C1-INH protein is available.

Rituximab therapy also does not preclude the use of other therapies for angioedema, such as replacement of C1-INH protein and blockage of kallekrein synthesis of bradykinin or bradykinin receptors which may help to stabilize patients prior to rituximab. However, these therapies were not effective in our patient, presumably because of the high level of activity of her disease and autoreactive antibody or antibodies. Additional concerns regarding treatment of acquired angioedema with rituximab include possible relapse of the disease due to recovery of the autoreactive lymphocyte clone and secondary immunodeficiency due to non-specific effects of the rituximab on memory B lymphocytes. Therefore, we propose that monitoring the levels of autoreactive antibodies against C1-INH protein as well as total serum IgG should be standard both prior to and after rituximab therapy of acquired angioedema in order to establish the diagnosis conclusively and to guide subsequent dosing intervals while limiting non-specific toxic effects of the therapy.

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