J R Coll Physicians Edinb 2007; **37**:18–20
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Acquired angioedema in a case of chronic lymphocytic leukaemia

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ABSTRACT Acquired angioedema is a rare condition, which occurs usually in association with lymphoproliferative disorders. It is due to the presence of C1 inhibitor antibodies. We report here a case of chronic lymphocytic leukaemia which presented with abdominal pain and angioedema. The patient was treated with rituximab, a monoclonal antibody directed against B lymphocytes, in combination with cytotoxic chemotherapy. The C1 inhibitor levels increased and the patient's clinical condition improved.

KEYWORDS Acquired angioedema, chronic lymphocytic leukaemia, rituximab

LIST OF ABBREVIATIONS Computerised tomographic (CT)

DECLARATION OF INTERESTS No conflict of interests declared.

Published online ***March 2007***

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CASE REPORT

An 80-year-old male presented with an episode of abdominal pain, distension and vomitings. He had no significant past medical history. On examination, he had no evidence of intestinal obstruction or pancreatitis. Initial investigations revealed Hb 12·7 g/l, white cell count 20·8 x 10^6/mm^3, lymphocyte count 15·6 x 10^9/ mm^3, platelet count 210 x 10^9/mm^3, with serum biochemistry including amylase, calcium and liver enzymes within the normal limits.

Flow cytometry performed on the peripheral blood confirmed the presence of a B-cell lymphoproliferative disorder. A diagnosis of chronic lymphocytic leukaemia was made. and the patient evaluated by the haematologists. As he had no B symptoms and no palpable lymphnodes, liver or spleen on examination, he was not advised chemotherapy at the time, but kept under surveillance.

He continued to have three further episodes of abdominal pain over the following year. He was then noted to have splenomegaly, measuring 7cm below the left costal margin. The history of the pain did not conform to that due to a splenic infarct or haemorrhage. A CT scan of his abdomen was performed and this showed a 16 cm long spleen with no intestinal lesion (see Figure 1).

During a subsequent clinic visit he mentioned that he had also noted swelling of his lips during these attacks. He said that this had been relieved by chlorpheniramine injections which he received at his local surgery. He had received no other medications. His lymphocyte count had increased to 21·1 x 10^9/mm^3.

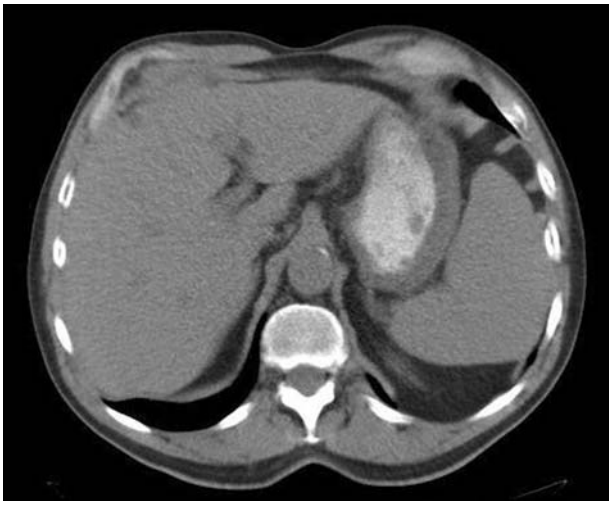

FIGURE 1 CT abdomen of the patient revealing splenomegaly.

Further investigations for angiodema showed C3 level to be 65 mg/dl with a normal range of 75 to 165 mg/dl, C4 level to be less than 2 mg/dl with a normal range of 20 to 65 mg/dl, C1 inhibitor to be less than 0·06g/l with a normal range of 0·15 to 0·35 g/l, and C1 inhibitor functional activity was 1% with a normal range of 40 to 50%.

We planned to treat him with three-weekly infusions of rituximab with cyclophosphamide, vincristine and prednisolone (R-CVP regimen). At the time of writing he remains asymptomatic after completing six cycles of chemotherapy. The episodes of abdominal pain did not recur following the initial infusion of rituximab. The C1 inhibitor level increased to 0·18g/l and C1 inhibitor functional activity to 84% after two cycles of chemotherapy.

DISCUSSION

Angioedema, which is caused by C1 esterase inhibitor deficiency is a potentially life threatening condition and may be either inherited or acquired. The latter is rare.[1] It presents as subcutaneous and submucosal swellings in any part of the skin, respiratory tract, or gastrointestinal tract, and often abdominal pain.[2]

Genetically determined defects in C1 esterase inhibitor cause hereditary angioedema.[3] It is a rare autosomal dominant condition, characterized by low serum C4 and absent or greatly reduced C1 inhibitor level or function.

Acquired angioedema occurs in older patients with no family history and is associated with lymphoproliferative disease or less commonly auto-immunity.[2] The acquired form is usually due to the presence of circulating antibodies which cause an accelerated consumption of C1-inhibitor, and this occurs usually in association with lymphoproliferative diseases,[5] but can be seen in association with other malignancies, immune disorders, and infections.[6] Of the lymphoproliferative disorders, chronic lymphocytic leukaemia has been reported to be one of the causes of acquired angioedema.[7]

Recurrent abdominal attacks are the most distressing symptom of angioedema due to C1 esterase inhibitor deficiency. They are characterised by crampy pain, but may include vomiting, diarrhoea, and other features.[8]

The diagnosis of acquired angioedema is suspected when patients present with recurrent angioedema and are found to have low serum levels of C4 with normal levels of C3. Low levels of C1q and C1 esterase inhibitor activity confirm the diagnosis.[9] Distinguishing hereditary from acquired angioedema facilitates therapeutic interventions and family planning or testing. Analysis of C1q can help differentiate between these two types of angioedema. Measuring autoantibodies against C1-INH would be helpful, but the test is only available in research laboratories.[10] The presence of autoantibodies to C1-inhibitor (C1-INH-Abs) is a hallmark of acquired C1-inhibitor deficiency.[11]

Management of patients with acquired angioedema should cover their acute and longer term needs. Initially, consideration should be given to a course of tranexamic acid. Antifibrinolytic agents inhibit plasminogen activation with consequent sparing of C1 inhibitor usage. If tranexamic acid is ineffective, attenuated androgens increase the hepatic production of C1 inhibitor protein.[12] Danazol is known to increase C1 esterase inhibitor activity.[13] Steroids, antihistaminics and epinephrine have limited effect in these conditions.[14] In an acute emergency C1 inhibitor concentrate may be used but patients may be resistant to this form of replacement therapy.[16] Self-administration of C1-inhibitor concentrate could be a valuable and convenient treatment modality to prevent or treat angioedema attacks in patients with C1-inhibitor deficiency.[15]

Rituximab is a monoclonal antibody against CD20 transmembrane protein on the surface of mature and malignant B cells which has been used for the treatment of acquired angioedema in association with systemic lupus erythematosus.[17] It is also an active agent in the treatment of chronic lymphocytic leukaemia.[18] Four weekly infusions of rituximab are used to treat acquired angioedema due to the presence of C1-inhibitor autoantibody.[19] Hence, we used rituximab to target the chronic lymphocytic leukaemia and the acquired angioedema.

In the future newer products should be considered including genetically engineered C1 esterase inhibitors, kallikrein inhibitors and bradykinin B2 receptor antagonists.[20]

CONCLUSION

Acquired angioedema can be a presentation of lymphoproliferative disorders such as chronic lymphocytic leukaemia. There are a number of treatment modalities available. In our case treatment consisted of rituximab based combination chemotherapy. The clinicians knowledge and familiarity with innovative regimes is important.[21]

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