CASE REPORT

Spontaneous regression of acquired C1 esterase inhibitor deficiency associated with splenic marginal zone lymphoma presenting with recurrent angio-oedema

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A 52 year old woman with marginal zone lymphoma developed recurrent episodes of angio-oedema and was found to have C1 esterase inhibitor deficiency. She declined chemotherapy for the lymphoma. Fourteen months after her initial presentation she was found to be in partial remission, and this was confirmed by peripheral blood film and bone marrow examinations. This was associated with normalisation of C1 esterase inhibitor, C1q, and C4 values. Regression of acquired C1 esterase inhibitor deficiency associated with spontaneous partial remission of lymphoma has not been reported previously.

Acquired deficiency of C1 esterase inhibitor causing angio-oedema has been reported as a rare phenomenon associated with non-Hodgkin's lymphoma.^{1–3} We report a case of acquired C1 esterase inhibitor deficiency in a patient with splenic marginal zone lymphoma who subsequently showed spontaneous regression.

CASE REPORT

A 52 year old woman was referred to the haematology department for the investigation of lymphocytosis, discovered on routine testing. She was asymptomatic and denied fever, night sweats, or weight loss. Physical examination revealed no abnormality and in particular no palpable lymphadenopathy or hepatosplenomegaly.

Subsequent investigations revealed: haemoglobin, 130 g/litre; white cell count, 27×10^9 /litre (differential: neutrophils, 5.6×10^9 /litre; lymphocytes, 15.4×10^9 /litre), and platelet count, 278×10^9 /litre. The peripheral blood film showed atypical lymphoid cells with irregular cytoplasmic outline, suggesting splenic marginal zone lymphoma. The serum urea, creatinine, electrolytes, and liver function tests were normal. The chest x ray was normal. A computed tomography scan of the chest, abdomen, and pelvis was normal, with no evidence of hepatosplenomegaly or lymphadenopathy. Serology for Epstein-Barr virus and cytomegalovirus was negative.

A bone marrow aspiration revealed 46% atypical lymphocytes, similar to those seen in the peripheral blood. Normal

haemopoiesis was well preserved. A trephine biopsy demonstrated a diffuse infiltration of small lymphocytes, which showed positive staining with anti-CD20. Immunophenotyping on the peripheral blood lymphocytes showed positive staining for CD19, CD20, CD79b, IgM, and λ light chains. The cells were negative for CD5, CD11c, CD23, and CD103. There was weak positive staining for CD25. These results were considered to be consistent with a diagnosis of splenic marginal zone lymphoma.⁴ No paraprotein was demonstrated in the serum or urine by immunofixation. Tests for antinuclear antibody, rheumatoid arthritis latex, and antineutrophil cytoplasmic antibody were negative, as were tests for IgG and IgM anticardiolipin antibodies.

It was decided to adopt a "wait and watch policy" and the patient attended the clinic for regular follow up. Eight months after her initial presentation she was admitted to the medical emergency unit with an episode of swelling of the lips and tongue associated with stridor and urticarial skin rash. She had a total of three such episodes of angio-oedema affecting the lips and the tongue over a period of two to three months. One mild attack resolved spontaneously at home. Two of these episodes needed hospital admission and were treated with intravenous hydrocortisone, chlorpheniramine (chlorpheniramine), and intramuscular epinephrine (adrenaline; 1/1000; 0.5 mg/dose). Each episode resolved completely within 24 hours. On no occasion did she need ventilatory support. There was no previous history of urticaria, angio-oedema, or allergy and she did not suffer from allergic rhinitis, hay fever, or bronchial asthma. There was no family history of urticaria or angio-oedema. She was discharged with a supply of Epipen (epinephrine) injections.

The possibility of an acquired deficiency of C1 esterase inhibitor was considered and further investigation revealed a low C4 (0.04 g/litre) and normal C3 values (table 1). The C1 esterase inhibitor concentration was low at 0.13 g/litre and the C1q value was reduced at 47% (table 1), consistent with acquired C1 esterase inhibitor deficiency. The complement assays were done using rate nephelometry on a Beckman array system. Repeat serum electrophoresis and an autoantibody screen were normal. A repeat computed tomography scan of the abdomen and thorax showed no evidence of lymphadenopathy but some increase in splenic size compared with the previous scan eight months before.

Table 1 Concentrations of complement components and C1 esterase inhibitor

Date	C3 (g/l)	C4 (g/l)	C1 esterase inhibitor (g/l)	C1q
May 2000	1.12	0.04	0.13	47%
November 2000	1.06	0.04	0.13	
August 2001	1.25	0.15	0.16	95%

Normal ranges: C3, 0.75–1.65 g/l; C4, 0.14–0.54 g/l; C1 esterase inhibitor, 0.15–0.35 g/l; C1q, 75–125%.

Based on these results, a diagnosis of acquired C1 esterase inhibitor deficiency secondary to marginal zone lymphoma was made. Chemotherapy for the lymphoma was considered but the patient declined treatment and she was followed up regularly. During the follow up period of 14 months she had no recurrence of angio-oedema and remained asymptomatic. Over the same period, the full blood count showed a gradual reduction in the white cell count to $6.5 \times 10^9/\text{litre}$, consistent with spontaneous regression, and a bone marrow aspirate and trephine biopsy 14 months after presentation showed a $> 50\%$ reduction in atypical lymphocytes (21%), consistent with partial remission of the lymphoma. Repeat assays of C1q, C4, and C1 esterase inhibitor were initially low, but subsequently returned to normal, consistent with regression of the acquired deficiency of C1 esterase inhibitor (table 1).

DISCUSSION

Acquired C1 esterase inhibitor deficiency is a rare complication of lymphoproliferative disorders.^{1 2 5 6} The association between acquired deficiency of C1 esterase inhibitor and lymphoma was first described in 1972 in two patients with lymphosarcoma.⁵ The pathogenesis of angio-oedema in association with lymphoma probably involves consumption of C1 esterase inhibitor following complement activation via the classical pathway by the tumour tissue.³ In addition, a circulating paraprotein can directly activate C1 via the classical pathway, causing C1 esterase inhibitor deficiency and angio-oedema, which is usually the mechanism in B cell lymphoproliferative disorders.⁵ This is supported by the demonstration of a low C1q concentration (C1q is the primary recognition unit of the classical complement activation pathway). Low C1q values are a feature of acquired angio-oedema, and are not seen in hereditary angio-oedema. Our patient was found to have low concentrations of C4, C1 esterase inhibitor, and C1q, consistent with a diagnosis of acquired C1 esterase inhibitor deficiency associated with splenic marginal zone lymphoma. This is an indolent lymphoproliferative disorder with a median survival of more than 12 years.⁴ Spontaneous regression, either partial or complete, is well described in patients with indolent non-Hodgkin's lymphoma,^{7 8} and in our patient spontaneous partial remission of the lymphoma was also accompanied by regression of the angio-oedema. This clinical remission was accompanied by normalisation of C1q, C4, and C1 esterase inhibitor values.

"Our patient was found to have low concentrations of C4, C1 esterase inhibitor, and C1q, consistent with a diagnosis of acquired C1 esterase inhibitor deficiency associated with splenic marginal zone lymphoma"

Several groups have reported cases of angio-oedema and acquired C1 esterase inhibitor deficiency in association with B cell lymphoproliferative disorders.^{1 2 6} Usually, as in our case, angio-oedema develops after the diagnosis of lymphoma has been made, but can predate the diagnosis of lymphoma.⁹ Bain *et al* reported two patients with angio-oedema associated with splenic marginal zone lymphoma.² In one of these patients,

Take home messages

- Acquired C1 esterase inhibitor deficiency with resultant angio-oedema is a rare complication of lymphoproliferative disorders, which usually resolves after treatment
- However, this is the first reported case of spontaneous regression of the lymphoma accompanied by spontaneous remission of the C1 esterase inhibitor deficiency and angio-oedema

angio-oedema preceded the diagnosis of lymphoma by eight years and a monoclonal IgM paraprotein was present in the serum. The angio-oedema resolved after treatment with danazol and no treatment for the lymphoma was needed. The second patient required splenectomy and treatment with chlorambucil, following which no further episodes of angio-oedema were noted. There are similar case reports describing regression of angio-oedema after treatment of the lymphoma,^{1 10} but spontaneous regression of lymphoma accompanied by spontaneous remission of the C1 esterase inhibitor deficiency and angio-oedema, as in our case, has not been reported previously.

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