

Acquired C1 inhibitor deficiency with lymphoma causing recurrent angioedema

R. Mathur, P.J. Toghil and I.D.A. Johnston

University Hospital, Nottingham NG7 2UH, UK

Summary: A 52 year old man who developed recurrent, massive and generalized angioedema for the first time during adult life was found to have an acquired deficiency of C1q esterase inhibitor (C1 INH) in association with a B cell lymphoma producing a paraprotein. He had low levels of C4 and C1 INH during the attacks which returned to normal after the successful treatment of lymphoma. An underlying lymphoproliferative disease should always be considered in adult patients with this immunological profile, recurrent angioedema and a negative family history.

Introduction

Lymphoma causing an acquired deficiency of C1q esterase inhibitor (C1 INH) resulting in recurrent angioedema is a recognized but extremely rare association. The clinical features may be indistinguishable from hereditary angioedema but a useful parameter in the differential diagnosis is the finding of a normal C1 level in the hereditary type in contrast to low levels in the acquired disease. We describe a case of acquired angioedema due to C1 INH deficiency with an underlying lymphoma and identify some important clinical features and the immunological profile of this condition.

Case report

A 52 year old man was referred with a 3 month history of massive, non-pitting, non-pruritic, generalized oedema along with several episodes of colicky, central abdominal pains. He had no previous history suggestive of atopic illness and there were no identifiable precipitating factors for his oedema. There had been no improvement in his symptoms either with oral anti-histamine drugs or with corticosteroids both of which were administered to him on several occasions. There was no history of similar illness in the family.

On examination, he had extensive angioedema over the face, lips, scrotum and limbs. The liver was enlarged 10 cm below the right costal margin and

the spleen enlarged 15 cm below the left costal margin. He had no peripheral lymphadenopathy, urticarial lesions or vasculitic rashes.

Full blood count showed haemoglobin of 14 g/dl, total white cell count $7 \times 10^9/l$ and platelets $250 \times 10^9/l$ with an ESR of 8 mm at one hour. There was a modest elevation in alkaline phosphatase and gamma glutamyl transpeptidase at 326 IU (normal range 98–280 IU) and 59 IU (normal range 11–50 IU), respectively. Ultrasound, isotope and computed tomographic (CT) scans of the abdomen revealed a diffusely enlarged liver and spleen with no focal abnormalities. There were no enlarged abdominal lymph nodes. X-ray of the chest was normal. A percutaneous needle biopsy of the liver showed mild non-specific hepatic changes. Trephine bone biopsy was considered to be normal. Immunological investigations showed normal C3 levels at 1.53 g/l (normal range: 0.79–1.60) and a low C4 at 0.08 g/l (0.12–0.36). Serum immunoglobulin levels, including IgE, were normal. There was an IgM lambda paraprotein spike of 3 g/l C1 INH levels were markedly reduced to 8% of normal (ELISA). We do not have a precise value for C1q.

The patient was thought to have acquired angioedema due to C1q esterase inhibitor deficiency with a high suspicion of an underlying lymphoma though no definite evidence was present at this stage. He was initially treated with tranexamic acid 1 g orally twice a day for several weeks without significant improvement. Subsequently he was treated with danazol with considerable initial reduction in the severity and frequency of angioedema attacks. His hepatosplenomegaly per-

sisted and repeat abdominal CT scan showed no change. The monoclonal IgM paraprotein persisted in the serum (3.6 g/l). After 2 years of danazol therapy, his angioedema relapsed with frequent attacks of massive grotesque oedema accompanied by severe crampy abdominal pains. A trephine bone biopsy was repeated which this time showed definite infiltration of the marrow by small non-cleaved lymphocytes and immature lymphoid cells. An unequivocal diagnosis of low grade non-Hodgkin's lymphoma (B cell on phenotyping) was therefore established.

He was commenced on chlorambucil 10 mg/day. Within a few weeks his angioedema subsided dramatically and the abdominal pains disappeared. After 6 months of continuous chlorambucil treatment in a dosage of 5 mg/day his hepatosplenomegaly had regressed completely. He had no detectable circulating monoclonal paraprotein and the C1q esterase inhibitor levels rose to 88% of normal. C3 and C4 fractions of the complement became normal at 0.98 and 0.16 g/l, respectively. Chlorambucil was stopped after a total of 6 months treatment and 8 months later he remains well and asymptomatic with a normal immunological profile.

Discussion

A clear-cut remission of symptoms and signs, and improvement in the immunological profile with successful treatment of the low grade non-Hodgkin's lymphoma shows that our patient had angioedema due to an acquired deficiency of C1q esterase inhibitor protein.

Angioedema, first described by Quincke in 1882,¹ is characterized by non-pitting, painless and non-pruritic lesions.^{2,3} Neurological and cardiac involvement have occasionally been described.⁴⁻⁶

Although angioedema is often multifactorial,⁷ the first description of the association between acquired deficiency of C1 IHN and lymphoma was in 1972 in two patients with lymphosarcoma and circulating 7S IgM who had low serum levels of C1q, C4, C2 and C1 INH with normal levels of C3.⁸ One of these patients had recurrent angioedema, indistinguishable clinically from the inherited form. Since 1972, approximately 50 additional cases with angioedema and lymphoproliferative disorders have been reported, mostly with a B cell disorder.⁹⁻¹¹ Radiotherapy and/or chemotherapy has been shown to result in remission of symptoms of angioedema and increase in C1 INH levels. The deficiency again becomes manifest with subsequent exacerbation of the B cell disease.¹¹

Both hereditary and acquired angioedema are complement mediated and are characterized by low levels of C4, C2 and C1 INH during and between the attacks. However, C1q levels are low only

in acquired angioedema.^{8,12,13} Circulating paraprotein, cryoglobulins and autoantibody can directly activate C1 via the classical pathway in the acquired angioedema due to C1 INH deficiency. This particular clinical syndrome is usually associated with B cell lymphoma.⁸ In cutaneous vasculitis and systemic lupus-like diseases, circulating immune complexes activate C1 with resultant angioedema. Low levels of C3 along with low C4, C2, C1 INH and C1q point towards this pathophysiological mechanism of C1q activation.¹⁴ Likewise, C1 INH deficiency may be due to IgG anti-C1 INH antibodies in the patient's serum. This is not associated with B cell lymphoproliferative disease.¹⁵⁻¹⁷

Complement consumption with acquired C1 INH deficiency may occur in various ways. In one case, cold reactive IgM anti-lymphocyte antibody in the serum was demonstrated.¹⁸ In another patient, tumour tissue was shown to directly interact with C1 and activate it with subsequent depletion of C1 INH.¹⁰ More recently, C1q fixation by an anti-idiotypic antibody bound to immunoglobulin on the surface of autologous B cells or plasma cells has been shown.¹⁹ C1 fixation by idiotypic-anti-idiotypic interaction may result in very rapid consumption of C1 INH protein.

Local trauma, dental extraction, emotional stress, menses³ and pregnancy²⁰ have all been implicated as precipitating factors of acquired angioedema. These triggering factors activate Hageman factor which leads to the generation of plasmin from plasminogen, thereby activating C1. Active C1 cleaves C2 and a C2 cleavage product is thought to result in angioedema by increasing capillary permeability.^{21,22} If C1 INH is deficient, this conversion can occur unopposed and with minimal stimulation.

The characteristic association of acquired C1 INH deficiency with monoclonal paraprotein as described initially by Caldwell and colleagues⁸ was observed in our patient. Apart from B cell lymphoma, conditions such as chronic lymphatic leukaemia, macroglobulinaemia, B cell lymphoma, multiple myeloma and essential macroglobulinaemia have all occasionally been described in association with angioedema and acquired C1 INH deficiency. No case, however, of T cell lymphoma with angioedema has ever been reported in association with C1 INH deficiency. This clearly illustrates that the malignant clone of B lymphocytes produces the monoclonal immunoglobulins which directly activate the first component of complement. Furthermore, successful treatment of lymphoma with chlorambucil in our patient resulted in disappearance of the circulating monoclonal immunoglobulin thereby terminating attacks of angioedema and normalizing the immunological profile.

References

1. Quincke, H. On acute localised oedema of the skin. *Monatshfte Prakt Dermatol* 1882, **1**: 129.
2. Osler, W. Hereditary angioneurotic oedema. *Am J Med Sci* 1888, **95**: 362–367.
3. Donaldson, V.H. & Roesn, F.S. Hereditary angioneurotic oedema: a clinical survey. *Pediatrics* 1966, **37**: 1017–1027.
4. Fowler, P.B.S. Epilepsy due to angioneurotic oedema. *Proc R Soc Med* 1962, **55**: 601.
5. Shaw, A.B. & Finnegan, T.R.I. Epilepsy and Quincke's disease. *Guys Hosp Rep* 1952, **101**: 126.
6. Siegel, S.C. & Bergeron, J.C. Urticaria and angioedema in children and young adults. *Ann Allergy* 1954, **12**: 241.
7. Champion, R.H., Roberts, S.O.B., Carpenter, R.G. & Roger, J.H. Urticaria and angioedema: a review of 554 cases. *Br J Dermatol* 1969, **81**: 588.
8. Caldwell, J.R., Ruddy, S., Schur, P.H. & Austen, K.F. Acquired C1 inhibitor deficiency in lymphosarcoma. *Clin Immunol Immunopathol* 1972, **1**: 39–52.
9. Rosenfeld, S.I., Staples, P. & Leddy, J. Angioedema and hypocomplementemia: unusual feature of lymphoma. *J Allergy Clin Immunol* 1975, **55**: 104.
10. Schreiber, A.D., Zweiman, B., Atkins, P., Goldwein, F., Pietra, G., Atkinson, B. & Abdun, N.I. Acquired angioedema with lymphoproliferative disorder: association of C1 inhibitor deficiency with cellular abnormality. *Blood* 1976, **48**: 567.
11. Shefer, A.L., Austen, K.F., Rosen, F.S. & Fearon, D.T. Acquired deficiency of the inhibitor of the first component of complement: report of five additional cases with commentary on the syndrome. *J Allergy Clin Immunol* 1985, **75**: 640.
12. Donaldson, V.H. & Evans, R.R. A biochemical abnormality in hereditary angioneurotic oedema: absence of serum inhibitor of C1 esterase. *Am J Med* 1963, **35**: 37–44.
13. Rosen, F.S., Charache, P. & Donaldson, V. Hereditary angioneurotic oedema: two genetic variants. *Science* 1965, **148**: 957–958.
14. Provost, T.T., Zone, J.J., Synkowski, D., Maddison, P.J. & Reichlin, M. Unusual cutaneous manifestations of systemic lupus erythematosus. 1. Urticaria like lesions: correlation with clinical and serological abnormalities. *J Invest Dermatol* 1980, **75**: 495–499.
15. Jackson, J., Sim, R.B., Whelan, A. & Feifery, C. An IgG antibody which inactivates C1 inhibitor. *Nature* 1986, **323**: 722–724.
16. Alsenz, J., Bork, K. & Loos, M. Autoantibody mediated acquired deficiency of C1 inhibitor. *N Engl J Med* 1987, **316**: 1360–1366.
17. Malbran, A., Hammar, C.H., Frank, M.M. & Fries, L.F. Acquired angioedema: observations on the mechanism of autoantibodies directed against C1 esterase inhibitor. *J Allergy Clin Immunol* 1988, **81**: 1199–1204.
18. Day, N.K., Winfield, J.B., Winchester, R.J., Gee, T.S. & Kunkel, H.G. Evidence of immune complexes involving anti-lymphocyte antibodies associated with hypocomplementemia in chronic lymphocytic leukemia (CLL). *Clin Res* 1975, **23**: 410a.
19. Geha, R.S., Quinti, I., Austen, K.F., Cicaroli, M., Sheffer, A. & Rosen, F.S. Acquired C1 inhibitor deficiency associated with antiidiotypic antibody to monoclonal immunoglobulin. *N Engl J Med* 1985, **312**: 534.
20. Stillier, R.J., Kaplan, B.M. & Andreoli, J.S., Jr. Hereditary angioedema and pregnancy. *Obstet Gynecol* 1984, **64**: 133.
21. Ghebrehwet, B., Randazzo, B.P., Joseph, T.D., Silverberg, M. & Kaplan, A.P. Mechanism of activation of the classical pathway of complement by Hageman factor fragment. *J Clin Invest* 1983, **71**: 1450.
22. Donaldson, V.H., Rosen, F.S. & Bing, D.H. Role of second component of complement (C2) and plasmin in kinin release in hereditary angioneurotic plasma. *Trans Assoc Am Phys* 1977, **40**: 174.

Postgrad Med J (1993) **69**, 648–650

© The Fellowship of Postgraduate Medicine, 1993

Malignant change in dermatitis artefacta

J.C. Alcolado, K. Ray, M. Baxter, C.W. Edwards and P.M. Dodson

Department of Medicine, Undergraduate Centre, East Birmingham Hospital, Bordesley Green East, Birmingham, B9 5ST, UK

Summary: Dermatitis artefacta is a chronic skin lesion produced by self-trauma. Avoidance of further trauma, topical steroids and psychological therapy all play a part in the treatment of such lesions. Unresolved lesions may become large and disfiguring and subject to infection. We report a case of one such lesion in an elderly woman who persistently excoriated a cholecystectomy scar over 40 years. Malignant transformation occurred in a manner analogous to the neoplastic change observed in other types of chronic ulcer (Marjolin's ulcer). The squamous cell carcinoma presented with widespread metastases from which the patient eventually died. Recent literature concerning Marjolin's ulcers is reviewed and it is noted that this is the first reported case of death caused by malignant change in dermatitis artefacta.

Introduction

Dermatitis artefacta is the term applied to a skin lesion produced, or significantly exacerbated by, self-inflicted trauma.¹ Recurrent excoriation causes

Correspondence: J.C. Alcolado, D.M., B.M., (Hons.), M.R.C.P., Prince Charles Hospital, Gurnos Road, Merthyr Tydfil, UK.

Accepted: 14 December 1992