

CASE REPORT

Acquired C1 esterase inhibitor deficiency or serendipity? The chance finding of a paraprotein after an apparently low C1 esterase inhibitor concentration

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Acquired C1 esterase inhibitor deficiency is a rare condition, usually presenting after the 2nd decade of life, and is often related to underlying conditions such as autoimmune and lymphoproliferative disorders. This case report describes a man whose initial clinical presentation with acute angioedema and whose initial estimation of a low C1 esterase inhibitor concentration indicated that he had an acquired angioedema, possibly secondary to a B cell neoplasm. A paraprotein was detected, and although its detection was serendipitous because it hinged on a spurious C1 esterase inhibitor result, this case confirms the role of C4 concentrations in the investigation of C1 esterase inhibitor deficiency. It also confirms the need to obtain repeat confirmatory samples before arriving at a diagnosis, however convincing the clinical signs may be.

Acquired C1 esterase inhibitor deficiency is a rare condition, usually presenting after the 2nd decade of life, and is often related to underlying conditions such as autoimmune and lymphoproliferative disorders, whereas the hereditary form of the condition is inherited via an autosomal dominant trait and usually presents earlier in life.¹ Both the acquired and hereditary forms present in a similar clinical manner, usually as painless swellings that subside over 24–48 hours, but if these occur in an older patient, the possibility exists of a low C1 esterase inhibitor concentration being secondary to a B cell neoplasm. Multiple myeloma can sometimes present in this manner.²

Here, we present a patient whose paraprotein was discovered following a spurious low C1 esterase inhibitor concentration.

CASE REPORT

SR is a 74 year old man who presented to the accident and emergency (A/E) department with an acutely swollen tongue, palate, and submandibular region, one to two hours after waking. On examination, he was alert and he could breathe and swallow but was unable to talk. There was no previous personal or family history of angioedema noted. Previous medical history included a right leg below knee amputation as a result of trauma, benign prostatic hypertrophy, peripheral vascular disease, and non-insulin dependant diabetes. He was not taking an angiotensin converting enzyme (ACE) inhibitor at the time. On admission, his initial treatment consisted of 100 mg hydrocortisone and 4 mg Piriton. He recovered well, and by the next morning he could talk, the swelling had subsided, and he was discharged from hospital.

Routine blood samples taken on admission showed slight increases in urea and creatinine at 8.8 mmol/litre (reference

range, 3.3–6.7) and 130 μ mol/litre (reference range, 60–120), respectively. C reactive protein was increased at 74 mg/litre (reference range, < 5). All other routine biochemistry was normal and he was normocalcaemic. A full blood count showed mild anaemia (haemoglobin, 119 g/litre; reference range, 130–180). After admission to A/E beds, complement and IgE studies were requested as part of a standard protocol to investigate angioedema. The C4 concentration was towards the bottom end of the reference range at 0.17 g/litre (reference range, 0.14–0.54), C3 was slightly high at 1.85 g/litre (reference range, 0.7–1.60), and C1 esterase inhibitor was low at 0.09 g/litre (reference range, 0.15–0.35). These assays were performed on a Behring BNII nephelometer (Dade Behring GmbH, Marburg, Germany) (external and internal quality control performance was acceptable). A functional C1 esterase inhibitor assay was not offered locally and was not included in the initial investigative protocol; if the C4 is low and C1 esterase inhibitor is normal, such samples would be referred elsewhere for a functional assay. Total IgE was 16 kU/litre (reference range, < 81). No allergen specific IgE studies were requested by the A/E department and none was suggested by us in view of the IgE concentration and complement results.

With the clinical presentation of acute angioedema and the low C1 esterase inhibitor concentration, immunoglobulin studies were instigated by us to investigate the possibility of an acquired angioedema secondary to a B cell neoplasm. These showed slightly suppressed IgA (0.77 g/litre; reference range, 0.8–4.0) and IgM (0.31 g/litre; reference range, 0.5–2.0) and a monoclonal IgG κ paraprotein band of 9.8 g/litre. The electrophoresis strip showed a slightly low polyclonal γ region, indicating a low polyclonal IgG concentration. The serum B₂ microglobulin concentration was estimated at 3.5 g/litre (reference range, < 2.4), but this may reflect his slightly impaired renal function. Total urine protein was 0.41 g/litre but there was no Bence Jones proteinuria present. The erythrocyte sedimentation rate was raised at 97 mm/hour (reference range, < 10). He was referred to the haematologists for investigation of a possible B cell malignancy, but failed to attend his first appointment. Eventually, repeat blood samples were received from his general practitioner to confirm these results. These showed a complete recovery of the complement profile (C3, 1.34 g/litre; C4, 0.17 g/litre; and C1 esterase inhibitor, 0.44 g/litre). However, the IgG paraprotein was still present at 10.0 g/litre.

During his clinical examination by the haematologists, neither splenomegaly nor lymphadenopathy were noted. There was insufficient evidence at presentation to warrant

Abbreviations: ACE, an angiotensin converting enzyme; A/E, accident and emergency

computerised tomography studies. Bone marrow aspirate and trephine samples were taken, but these showed no evidence of increased plasma cell numbers, no collections of lymphocytes, and the Congo Red stain was normal—there was no evidence of myeloma, lymphoma, or amyloid present.

An aliquot of the original sample taken on his admission to A/E, which had been stored at -20°C , was analysed for C1 esterase inhibitor by one of us (R.J.L.) in a different centre using a different instrument (Behring Prospec). The result was 0.49 g/litre, which is higher than normal and in keeping with an acute phase response. This original sample was returned and reanalysed on our Behring BNII nephelometer and the following results were obtained (C3, 1.85 g/litre; C4, 0.17 g/litre; and C1 esterase inhibitor, 0.42 g/litre). Similar profiles have been obtained on numerous occasions since then; his paraprotein concentration remains stable below 10 g/litre and he has not suffered a recurrence of these symptoms since his original acute attack.

The current diagnosis is idiopathic angioedema with a monoclonal gammopathy of undetermined importance; the monoclonal gammopathy will be followed up on a regular basis.

DISCUSSION

We describe a man whose initial clinical presentation with acute angioedema and whose initial estimation of a low C1 esterase inhibitor concentration led us to believe that he had an acquired angioedema, possibly secondary to a B cell neoplasm. In a patient of this age, and in the absence of a family history, we discounted the possibility of hereditary angioedema as a cause of his swollen tongue; hence, C1q, which would have been low in acquired angioedema and normal in the hereditary form, was not measured. Most patients with acquired angioedema present with head and neck symptoms, often with swollen tongue, cheeks, and upper airways.¹ Localised, non-demarcated, non-pruritic, subcutaneous, usually recurrent swellings that appear rapidly and resolve within 24–48 hours are the hallmarks of presentation of this condition. Therefore, a clinical history of angioedema in a middle aged or elderly patient should raise suspicions about a possible underlying lymphoproliferative disorder. One series noted that there was often a considerable delay in diagnosis (average time, 2.3 years)¹ for a diagnosis that has implications for the head and neck surgeon, the dermatologist, the haematologist (because of the possibility of a B cell malignancy), the anaesthetist (because of the possibility of upper airway obstruction caused by laryngeal angioedema³), the physician, and the general practitioner (because ACE inhibitors are contraindicated for patients with this condition). It is therefore worthy of concern.

“We can offer no explanation for our original low estimation of C1 esterase inhibitor concentration on the Behring BNII instrument, but a sampling problem would seem most likely”

The diagnosis is confirmed by low C4 and C1 esterase inhibitor concentrations. Previous work has emphasised the role of C4 in the diagnosis of this condition. Gompels *et al* showed that a combination of low C4 and C1 esterase inhibitor concentrations had 98% sensitivity and 96% specificity for C1 esterase inhibitor deficiency.^{4,5} They noted that all of the confirmed cases had a low C4 concentration, showing that if C4 is normal there is no need to proceed to C1 esterase inhibitor testing. However, on this occasion, we analysed both C4 and C1 esterase inhibitor and found an ostensibly low/normal C4 and a frankly low C1 esterase

Take home messages

- We report a man who presented with acute angioedema and a low C1 esterase inhibitor concentration, indicative of an acquired angioedema, possibly secondary to a B cell neoplasm
- After further investigations, the low C1 esterase inhibitor result was found to be spurious, although a paraprotein of undetermined importance was detected
- This case confirms the role of C4 concentrations in the investigation of C1 esterase inhibitor deficiency and the need to obtain repeat confirmatory samples before arriving at a diagnosis, however convincing the clinical signs may be

inhibitor concentration. In view of the raised C3 (and other acute phase changes), the low/normal C4 was interpreted as consumptive of the early classical pathway components. The clinical presentation combined with these results and the fact that our patient also had an IgG κ paraprotein was persuasive evidence of a link between the clinical picture and the laboratory findings.

C1 esterase inhibitor concentrations can return to normal after treatment with anabolic steroids. However, there are only rare cases of spontaneous recovery of C1 esterase inhibitor concentrations with no treatment,⁶ and we thought it possible that our patient was such an example until the C1 esterase inhibitor concentration in the original sample was retested in another centre. We can offer no explanation for our original low estimation of C1 esterase inhibitor concentration on the Behring BNII instrument, but a sampling problem would seem most likely (for example, an air bubble or clot). Study of the internal quality control showed no problems with the assay batch and the external quality control performance was acceptable for this analyte. The sample was lipaemic but neither of the instruments used flagged this as a problem for the estimation. Gompels *et al* described two patients who appeared to have undetectable concentrations of C1 esterase inhibitor on one system, but which could be measured on theirs, and who also had normal C4 concentrations.⁵ We still do not know what caused our patient's original angioedema: C1 esterase inhibitor deficiency has been excluded and allergy, although not excluded, looks unlikely; in addition, because the swelling subsided, amyloid is an unlikely explanation. Infection is possible because of his raised C reactive protein concentration, but he reported no changes in the drugs that he was taking, so that an adverse drug reaction seems unlikely, and no physical trauma was reported. ACE inhibitors have been implicated in cases of angioedema,^{7,8} but our patient was not prescribed these drugs.

Although the detection of this patient's paraprotein was serendipitous, in that it hinged on a spurious C1 esterase inhibitor result, this case confirms the role of C4 concentrations in the investigation of C1 esterase inhibitor deficiency. It also confirms the need to obtain repeat confirmatory samples before arriving at a diagnosis, however convincing the clinical signs may be.

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