Acquired C1-inhibitor deficiency presenting with nephrotic syndrome

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We present a case report of a 73 year old man who presented to nephrology clinic with nephrotic syndrome.

He had been diagnosed with acquired angioedema due to C1-inhibitor deficiency (AAE-C1INH) 4 years previously, having presented with acute laryngeal swelling requiring intubation. At that time serum IgM levels were raised at 13.78g/L, C4 levels were undetectably low, and low levels of functional C1-inhibitor were present.

At the time of presenting to nephrology clinic he was requiring prophylactic twice weekly C1-inhibitor concentrate infusions to prevent recurrent attacks of angioedema, and was unable to work as a musician due to persistent tongue swelling. The triad of nephrotic syndrome was present, with nephrotic range proteinuria of 477umol/L, serum albumin of 30g/L and peripheral oedema. He was hypertensive, and renal excretory function was preserved. Serum cryoglobulins were negative on three occasions. He was treated with diuretics and an angiotensin II receptor blocker. He underwent a renal biopsy which on immunofluorescence showed strong glomerular staining for IgM and kappa light chains, and on electron microscopy showed large subendothelial electron dense deposits consistent with IgM deposition associated glomerulonephritis. Bone marrow biopsy showed a marginal zone lymphoma. He was treated with rituximab and bendamustine chemotherapy, and both the nephrotic syndrome and the AAE-C1INH resolved as his serum IgM levels decreased. He was able to discontinue diuretics and prophylactic C1-inhibitor concentrate infusions, and return to work as a music teacher.

AAE-C1INH is a rare and life-threatening disorder, and is often associated with underlying lymphoproliferative B-cell disorders. It often presents with non-pitting, asymmetrical oedema of the face, upper airway, gastrointestinal tract or extremities. The three key features seen are angioedema, low serum C1-inhibitor levels and evidence of hyperactivation of the classical complement system. The angioedema is driven by increased vascular permeability mediated by increased bradykinin levels, which occur when low levels of C1-inhibitor are present, often due to neutralising antibodies associated with a paraproteinaemia.

Difficulties in managing patients with AAE-C1INH due to a lymphoproliferative disorders include deciding when to treat with chemotherapy, as it may be beneficial to treat associated lymphomas that otherwise would only warrant surveillance. However given that other case series describe treating with rituximab in preference to proceeding with C1-inhibitor concentrate prophylaxis, in our patient treatment was clearly warranted given the additional indication of nephrotic syndrome. A specific challenge in this case was considering the use of ACE-inhibitors or angiotensin II receptor blockers to manage the nephrotic syndrome and hypertension, due to concern that the recognised side-effect of increased bradykinin levels could trigger an angioedema attack. Therefore close communication with immunology colleagues was required to facilitate giving C1-inhibitor concentrate immediately prior to introduction of candesartan. Given that
trauma can also trigger angioedema attacks, C1-inhibitor concentrate cover was also required prior to renal and bone marrow biopsies.