Comment on “An Unusual Case of Acquired Angioedema and Monoclonal Gammopathy of Renal Significance in a Middle-Aged Caucasian Female”

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To the Editor:

I read with interest the case report by Roy et al., but from the details provided the diagnosis of acquired angioedema (C1INH-AAE) is far from certain, and in fact some features almost rule it out as a diagnosis. My concerns relate to 3 aspects of the case.

First, the clinical presentation. The authors describe rash as a prominent manifestation of the patient’s presentation. They describe “waxing and waning maculopapular rashes,” “bilateral nonblanching papular rashes in both lower extremities,” with “on and off urticaria.” C1-esterase inhibitor deficiency (either acquired or hereditary) causes bradykinin-mediated swelling and is not associated with urticaria. Erythema marginatum may occur in patients with hereditary angioedema (C1INH-HAE) and can precede the onset of swelling, but it is bilateral pedal swelling is usually multifactorial and almost never angioedema.

Second, the response to treatment. Bradykinin-mediated angioedema does not typically respond to corticosteroids. Roy et al. describe the patient’s clinical features including rash subsiding after pulse methylprednisolone and oral prednisone. This would be very unusual, and provides circumstantial evidence that C1INH-AAE does not fully describe the clinical presentation. It is also notable that the allergy clinic prescribed an epinephrine pen, as bradykinin-mediated angioedema only responds minimally and transiently to epinephrine administration, possibly suggesting that the allergy clinic did not think a diagnosis of C1INH-AAE likely. I also expect that the device was provided for acute treatment, and not prophylaxis as the authors state.

Third, the investigations listed by the authors are incompletely described. They describe the capillary zone electrophoresis with no M spike (paraprotein), and that serum and urine electrophoresis showed no bands. It is important to clarify whether the samples underwent immunofixation or not, as that is a more sensitive assay to detect monoclonal bands. In Figure 5 and the caption of Figure 6 the authors state that the biopsy showed monoclonal immunoglobulin (Ig) G1 lambda immune deposits, although I cannot see how the IgG isotype can be drawn from the electron microscopy image in Figure 5, and the direct immunofluorescence photographs in Figure 6 show kappa excess (not lambda) and only stain for IgG (not the IgG1 isotype). What did C3, C1q, and other immunostains show? The authors also do not present the result of C1-inhibitor function, which despite the normal quantitative C1-inhibitor level should be low if the diagnosis of C1INH-AAE is correct, and they do not report anti-C1q antibody levels. Finally, the authors describe the complement testing results as “spurious,” implying that they were not in fact invalid, but they do not give an explanation regarding this.

My impression on reading the case report is that a diagnosis of hypocomplementemetic urticarial vasculitis needs to be strongly considered, certainly as being more likely than C1INH-AAE. This condition (also called anti-C1q vasculitis) can be associated with a variety of systemic diseases including systemic lupus erythematosus, Sjögren’s syndrome, and monoclonal gammopathy of uncertain significance. All cases have urticaria, which lasts longer than typical histamine-mediated urticaria and resolves with either atraumatic bruising or residual pigmentation. The nonblanching nature of this patient’s lower limb rash would support vasculitis as a cause, and biopsy of these lesions may be helpful. Renal disease is present in a significant proportion of cases, is variable in its histological features, and is associated with a poorer prognosis. The most common laboratory abnormalities are raised inflammatory markers and low complement levels as described in this patient, and anti-C1q antibodies, occasionally with other serological findings such as positive ANA or dsDNA.

Diagnosis requires the presence of 2 major criteria (recurrent urticaria for >6 months and hypocomplementemia) and at least 2 minor criteria (which include leukocytoclastic vasculitis on biopsy, arthralgia and arthritis, ocular inflammation,
abdominal pain, glomerulonephritis, and positive anti-C1q autoantibodies). The duration of urticaria in this patient is not mentioned, and there is insufficient description and workup in this case report to evaluate most of the minor criteria.

In summary, I do not believe this patient had C1INH-AAE, as the clinical features and response to treatment are out of keeping with this diagnosis. A far more likely possibility is hypocomplementemic urticarial vasculitis, which would account for the cutaneous, renal, and serological abnormalities described.

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