



Letter

Mimicker of hereditary angioedema: Idiopathic systemic capillary leak syndrome successfully treated with intravenous immunoglobulin

Idiopathic systemic capillary leak syndrome (ISCLS) is a rare, potentially life-threatening disease characterized by episodic attacks of systemic capillary hyperpermeability and vascular collapse accompanied by hypoalbuminemia, hemoconcentration, and edema.^{1–3} We describe the case of a 46-year-old man with recurrent abdominal pain and facial edema, long believed to have recurrent angioedema, who was ultimately diagnosed with ISCLS.

He presented to our allergy-immunology clinic in 2015 with a 2-year diagnosis of recurrent angioedema starting at 43 years of age, with monthly episodes of abdominal pain, facial swelling, shortness of breath, and back and leg tightness. He reported generalized facial swelling during these attacks without associated urticaria. Some of these episodes required hospitalization for concurrent hypotension, and each was treated as sepsis and ultimately without an identified source of infection. Computed tomography of the abdomen and pelvis during an acute attack in 2013 showed an edematous pancreas without bowel edema, with normal lipase and amylase levels. C1 esterase inhibitor level checked during 1 acute attack in 2014 was low at 19 mg/dL (reference laboratory value [ref] 21–39 mg/dL) with normal function at 81% (ref $\geq 40\%$); C3 and C4 levels were low (Table 1). Multiple baseline and event tryptase levels were normal. An extensive rheumatologic workup was unremarkable. Because of an abnormal serum protein electrophoresis result, he underwent a bone marrow biopsy that showed monoclonal gammopathy of undetermined significance. He was treated with prednisone, montelukast, scheduled high-dose H₁ and H₂ antihistamines, and a proton pump inhibitor for 1 year, but he had continued breakthrough episodes. His family history was notable for his father who also had recurrent angioedema and died at 66 years of age of a myocardial infarction.

We repeated his C1 esterase inhibitor laboratory tests in March 2015, and the results were normal (Table 1). Given his family history, we considered whether the patient had type III hereditary angioedema (HAE) and attempted to trial the patient on icatibant for on-demand therapy during acute attacks, but this was not started because of copayment difficulties. In the meantime, the patient presented to an outside hospital in 2016 with 3 weeks of abdominal pain and facial edema and was found to have significant leukocytosis and polycythemia (white blood cell count $29.8 \times 10^9/L$, ref $3.4\text{--}10.0 \times 10^9/L$; hematocrit 61.8 g/dL, ref 41–53 g/dL; platelet count $146 \times 10^9/L$, ref $140\text{--}450 \times 10^9/L$) and hypoalbuminemia (3.1 g/dL, ref 3.5–4.8 g/dL). Computed tomography of the chest and abdomen depicted a new 12-mm pericardial effusion. He became increasingly hypotensive with systolic blood pressure in the 50s, requiring fluid resuscitation and vasopressor support. He had

anasarca, including generalized facial swelling without isolated swelling elsewhere. He was intubated for respiratory distress. Transthoracic echocardiography displayed pericardial effusion with cardiac tamponade, requiring emergency pericardiocentesis that removed 200 mL of straw-colored fluid. Pericardial fluid cell count, gram stain, culture, and cytology were unremarkable. He also developed shock-associated liver dysfunction and acute kidney injury and was transferred to our hospital for further management.

Our allergy-immunology service was consulted, and we believed that although type III HAE was still a possibility given his family history and normal C1 esterase inhibitor results, his concomitant hypotension, pericardial effusion, and polycythemia argued against this diagnosis. His clinical presentation and prior diagnosis of monoclonal gammopathy of undetermined significance, a frequently coexisting condition,³ were more consistent with ISCLS. Thus, he was given high-dose intravenous immunoglobulin (IVIG; 2 g/kg) in addition to ongoing supportive care. The patient's hypotension eventually resolved, and he came off of ventilatory and vasopressor support. After a 2-week hospitalization notable for delirium, he regained his normal mental status with resolution of his kidney and liver dysfunction and was discharged home. He has since been on prophylactic monthly high-dose IVIG (2 g/kg) and has not had recurrence of any further episodes from his ISCLS for the past 10 months at the time of writing this report.

The etiology of ISCLS is unknown, and it remains a diagnosis of exclusion. Proposed hypotheses to explain ISCLS include abnormally high levels of vascular endothelial growth factor and angiopoietin-2 during attacks, endothelial cell apoptosis leading to leakage, and potential involvement of interleukin-2, interleukin-17, and paraproteins in its pathophysiology.^{3–6} The attacks often present in 3 stages: (1) a prodromal phase with generalized symptoms of fatigue, abdominal pain, and myalgia; (2) a fluid extravasation phase with hypovolemic hypotension, hemoconcentration, and hypoalbuminemia; and (3) a recovery phase with extravasated fluids returning back to the intravascular space.^{2,3} This patient's most recent attack followed this 3-phase clinical trajectory. Pericardial effusion also can be a clinical presentation of this disease,² as was seen in this case. There is a high incidence of monoclonal gammopathy in 68% to 85% of patients with ISCLS,^{3,5} which was a clue that led to his underlying diagnosis. His low C4 level, initially low C1 esterase inhibitor level, and family history positive for angioedema were red herrings in this case, misleading the initial clinicians to the early presumptive diagnosis of HAE. His C1 esterase inhibitor function level was normal, which would have been inconsistent with type I and II HAE, and his low C4 would have been inconsistent with type III HAE. Although patients with ISCLS should

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Table 1
Trend of Patient's Complement Levels

	Complement levels				
	April 2014 (during attack)	May 2014 (during attack)	June 2014	July 2014	March 2015
C1 esterase inhibitor (ref 21–39 mg/dL)	19	25	29	31	35
C1 esterase inhibitor function (ref $\geq 40\%$)	81%	88%	111%	107%	>100% ^a (ref >67%)
C1q antigen (ref 5.0–8.6 mg/dL)	N/A	N/A	N/A	N/A	5.6
C3 (ref 90–180 mg/dL)	40	55	N/A	99 ^a (ref 91–210 mg/dL)	90 ^a (ref 71–159 mg/dL)
C4 (ref 16–47 mg/dL)	6	8	N/A	15 ^a (ref 18–56)	N/A
CH50 (ref 31–60 mg/dL)	21	N/A	N/A	128 ^a (ref 60–144 mg/dL)	N/A

Abbreviations: N/A, not available; ref, reference laboratory value.

^aThe reference laboratory value changed and the appropriate value is reflected accordingly.

have normal C4 levels, this patient's low C4 and C1 esterase inhibitor levels might have been due to protein loss as evidenced from his hypoalbuminemia or to a consumptive process related to his acute illness.

Treatment for ISCLS during acute episodes includes supportive care to maintain adequate end-organ perfusion and treatment of complications such as pulmonary edema and compartment syndrome. High-dose IVIG during an acute episode has been supported in case reports, as have anti-vascular endothelial growth factor antibody and combination terbutaline and aminophylline.^{7–9} Although more robust data are needed, 2 of the more frequently reported prophylactic therapies include IVIG and terbutaline plus theophylline.^{7,10} ISCLS is a diagnostically challenging disease that can mimic angioedema and anaphylaxis. It requires a high index of suspicion in patients presenting with recurrent angioedema with atypical features.

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