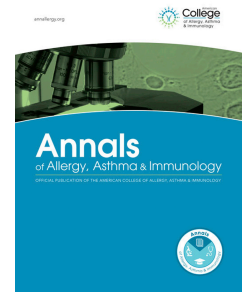


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Clinical Communication: Systemic Capillary Leak Syndrome Due to Mast Cell Activation?

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Clinical Communication: Idiopathic Anaphylaxis Masquerading as Systemic Capillary Leak Syndrome

Allergists and immunologists are consulted when a patient presents with sudden swelling and hypotension, and if there are repeated episodes and a cause is unapparent, idiopathic anaphylaxis (IA) with or without mast cell activation (MCA) may be suspected.¹ Systemic capillary leak syndrome (SCLS) is defined by episodic bouts of peripheral edema and the “3 Hs”: hypotension, hemoconcentration, and hypoalbuminemia.² The clinical findings overlap IA. We report a pediatric patient initially diagnosed with SCLS, but subsequently with IA, and consider whether the two are separate syndromes.

A previously healthy 9-year-old boy had sudden abdominal pain, facial flushing, and emesis in school. No exercise or medications were reported. A nurse administered epinephrine and he was transported to an emergency department (ED) where he was hypotensive (89/57), tachycardic (124 bpm), and had conspicuous swelling of the hands, feet, face, and lips. The ED found, hemoconcentration (hemoglobin 16.9 gm/dl, hematocrit 50%) and hypoproteinemia (total protein 5.5 gm/dl, nl = 5.8–7.9 gm/dl, albumen 3.2 gm/dl, nl = 3.8–4.8 gm/dl). The patient was fluid resuscitated and discharged after 8 hours of observation.

Four months later the patient returned to the ED with similar symptoms plus syncope. Again, he was hypotensive (99/82), tachycardic (140 bpm), and had facial and peripheral swelling, with hemoconcentration (hemoglobin 16.9 gm/dl) and hypoproteinemia (total protein 5.5gm/dl, albumen 3.2 gm/dl). The patient was hospitalized with a presumptive diagnosis of SCLS.

Anaphylaxis was thought unlikely due to the absence of urticaria and a causative allergen, as well as the presence of hemoconcentration and hypoproteinemia. While hospitalized, the swelling soon resolved, the hemoglobin decreased to 11.9 gm/dl, and serum proteins normalized. Total IgE, complement C4, and C1inh levels were normal; however a serum tryptase drawn 6 hours after symptom onset revealed a total tryptase of 20 ng/ml and mature tryptase of 12ng/ml (nl = 15 ng/ml total, 1ng/ml mature). There was no urticarial pigmentosa. Extensive skin testing for food and environmental allergens was negative and a serum total tryptase was 1 ng/ml, serum protein electrophoresis was normal. The diagnosis was revised to IA in view of the elevated tryptase. Two additional bouts of IA occurred over the next 2 years despite ongoing treatment with cetirizine, and responded to IM epinephrine. The patient has now been asymptomatic for 6 years off of all medications

IA and SCLC share overlapping clinical presentation of sudden episodes of swelling, hypotension, and tachycardia without any apparent provoking event. Both involve non-hemorrhagic vascular hyperpermeability, and while hemoconcentration and hypoproteinemia are central to the diagnosis of SCLS, most clinicians do not associate them with anaphylaxis; although, both have been described.^{3,4} Elevated tryptase is absent in SCLS and in some cases of anaphylaxis (e.g. food related). Possible explanations offered for normal tryptase in anaphylaxis include activation of mast cells remote from the systemic vasculature; activation of basophils or of tryptase poor mast cells; mast cell secretion of vasoactive mediators generated de novo such as prostaglandin D2, platelet activating factor, and leukotrienes^{5,6,7}; and activation of the contact system as heparin released from mast cell granules generates bradykinin, resulting in vascular hyper permeability.⁸ The definition of elevated tryptase has also recently been expanded to

include levels that are $2 \text{ ng/ml} + 1.2 \times$ a baseline tryptase level,¹ which might encompass some anaphylaxis originally thought to have normal tryptase. Nonetheless, anaphylaxis with normal tryptase occurs, and a recent review has suggested that cytokine storm represents a form of anaphylaxis, adding pro-inflammatory cytokines to the list of anaphylactogenic compounds.⁹

The shared clinical signs and laboratory findings, and the expanded definition of anaphylaxis have caused us to question whether SCLS and IA are actually distinct syndromes or rather parts of a spectrum. The finding of elevated tryptase proved diagnostic in the case described, but, as noted, it is not invariably present in anaphylaxis. Except for the tryptase elevation, this case having peripheral edema and the “3 Hs” would have been diagnosed as SCLS. Determination of whether these are separate syndromes is important because fatal outcomes may occur, while currently recommended treatment of acute episodes and prophylaxis against future episode is different for each. Treatment of acute SCLS includes volume replacement, inotropes, glucocorticoids, IVIG, methylxanthines, and beta-2 agonists.² Acute anaphylaxis therapy emphasizes prompt epinephrine administration with volume replacement and oxygen as needed.^{5,10} Recommended prophylaxis for SCLS attacks has been beta-2 agents taken orally (i.e. terbutaline), methylxanthines, and IVIG²; IA prophylaxis has been H-1 antihistamines and, if attacks are frequent, oral glucocorticoids.¹⁰ As Allergy/Immunology progresses toward an era of precision medicine, a central registry for reporting intermittent, unexplained episodes seeming to be due to non-physiologic release of potent vasoactive mediators, together with a recommended diagnostic protocol and participation of research laboratories, may help to determine whether these syndromes with overlapping clinical features have a single or distinct pathophysiologies. From this may emerge improved specific recommendations for acute and prophylactic therapy.

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