

Letter to the Editor

Idiopathic systemic capillary leak syndrome: Novel therapy for acute attacks

To the Editor:

Idiopathic systemic capillary leak syndrome (ISCLS) is a life-threatening disorder of unknown cause that should be included in the differential diagnosis of angioedema. Patients typically present in the fifth and sixth decades of life with intermittent acute attacks of peripheral edema, hypotension, hypoalbuminemia, hemoconcentration, weight gain, and a monoclonal gammopathy.^{1,2} Rhabdomyolysis, compartment syndrome, and acute renal failure are common clinical findings; however, pulmonary edema is rare.³ During an acute attack, there is an unexplained capillary hyperpermeability with a shift of plasma from the intravascular to the interstitial space.⁴ Acute attacks are followed by a resolution phase, with fluid shifts leading to intravascular volume overload and associated severe pulmonary edema. The mortality rate ranges from 30% to 76%.^{1,5} A prophylactic regimen of theophylline and terbutaline has been shown to decrease the frequency of attacks.⁵ However, there is no effective therapy for acute attacks. We report novel and effective treatments for acute attacks in 3 patients.

Patient A was a 48-year-old man presenting with recurrent episodes of peripheral edema, hypovolemia, hemoconcentration, profuse sweating, facial flushing, nausea, generalized weakness, and compartment syndromes necessitating 4 limb fasciotomies. He had a monoclonal gammopathy, and his serum TNF- α level was increased at 44.9 pg/mL (Table I). Eosinophil counts and tryptase, C-1 esterase inhibitor, and C4 levels were normal. The patient's acute attack was managed with supportive care, and he was discharged on a prophylactic regimen of terbutaline and theophylline. He continued to be symptom free for 13 months, after which he had an acute attack. At the time of this admission, his serum theophylline level was 2.9 mg/dL. His theophylline dose was adjusted, and dramatic clinical improvement was noted once serum theophylline levels were maintained between 20 and 25 mg/dL. Subsequently, it was observed that he would have an acute attack when his theophylline level decreased to less than 15 mg/dL, with prompt resolution once the theophylline level was increased. Approximately 2 years after his initial diagnosis, he experienced a severe acute attack with respiratory distress requiring intubation and compartment syndrome. Despite aggressive supportive care and increasing his theophylline dose to achieve a serum level of 25.9 mg/dL, his symptoms did not improve. Serum TNF- α levels were persistently increased (Table I), and treatment with TNF- α antagonists was recommended. The family declined treatment, and the patient died after withdrawal of supportive care.

Patient B was a 59-year-old woman with bilateral upper extremity swelling and orthostatic hypotension after a viral upper respiratory tract infection. Hemoconcentration and hypoalbuminemia were noted, and within 24 hours of admission, she experienced diffuse anasarca, worsening hypotension, hypoalbuminemia (1.2 g/dL), acute renal failure, and a weight increase of 9.3 kg. Eosinophil counts and tryptase, C-1 esterase inhibitor, and C4 levels were normal. Immunophenotyping demonstrated evidence of T-cell activation, with 31.5% of her T cells being CD25⁺. She had a monoclonal gammopathy. Serum TNF- α , IL-6,

TABLE I. Serum cytokine profiles: Patient A

	TNF- α (pg/mL)	IL-6 (pg/mL)	IL-1 β (pg/mL)
Mild episode, day 2	44.9		
Severe episode, day 1	55.1		
Severe episode, day 6	56.9		
Severe episode, day 13	66.0	0.0	4.5

Control TNF- α , IL-6, and IL-1 β levels were undetectable on all occasions. Levels were measured by means of ELISA.

TABLE II. Serum cytokine profiles: Patient B

	TNF- α (pg/mL)	IL-6 (pg/mL)	IFN- γ (pg/mL)	IL-10 (pg/mL)	IL-1 α (pg/mL)	IP-10 (pg/mL)
Hospital, day 5	17.4	39.27	0.0	64.39	22.46	608.8
Hospital, day 19	20.73	54.23	1.58	112.02	148.07	300.6

The following cytokines were also measured, and levels were not significantly different from control values: IL-1 β , IL-2, IL-4, IL-5, IL-7, IL-8, IL-12, IL-13, IL-15, IL-17, IFN- γ , granulocyte colony-stimulating factor, GM-CSF, eotaxin, monocyte chemoattractant protein 1, and macrophage inflammatory protein 1 α . Control values for TNF- α , IL-6, IL-10, IL-1 α , and IFN- γ -inducible protein 10 (IP-10) were all undetectable in control sera. Levels were measured with the LUMINEX BIOPLEX assay by using the Human Cytokine 21 Plex Kit (Linco Research, Inc, St Charles, Mo).

IL-10, IL-1, and IFN- γ -inducible protein 10 levels were increased on hospital days 5 and 19 (Table II). Despite supportive care, terbutaline, and intravenous theophylline to achieve a serum theophylline level of 15 to 20 μ g/mL, her symptoms did not improve. Increasing theophylline levels to 20 to 25 μ g/mL, however, resulted in marked improvement, and an inverse relationship was noted between body weight (an indicator of interstitial edema) and theophylline levels (Fig 1, A). She was discharged on terbutaline and theophylline dosed to achieve a level of 15 mg/dL. Over the ensuing 29 months, she did well, with the exception of one minor flare necessitating theophylline dosage adjustment.

Patient C was a 6-year-old boy presenting with fever, nausea, vomiting, periorbital edema, hypotension, hemoconcentration, and hypoalbuminemia. He had no response to methylprednisolone, antibiotics, and intravenous immunoglobulin (for possible Kawasaki disease). He had compartment syndrome requiring 4 limb fasciotomies. Although ISCLS is unusual in children, it has been reported in children as young as 3 years of age.⁵ He was started on terbutaline and aminophylline to achieve a serum theophylline level of 20 mg/dL. Despite these treatments, he experienced worsening hypoalbuminemia (1.5 g/dL), renal failure, rhabdomyolysis, and disseminated intravascular coagulation. Serum TNF- α levels were increased (Table III), and treatment with the TNF- α antagonist infliximab (10 mg/kg) was initiated. Prompt and dramatic clinical improvement was seen (Fig 1, B), and the patient was discharged on prophylactic theophylline and terbutaline. His serum cytokine profile is shown in Table III.

Although our patients differed in age, sex, and presenting symptoms, all had hypotension, hemoconcentration, hypoalbuminemia, renal failure, increased weight, and edema. Two patients demonstrated monoclonal gammopathies, a finding reported in 50% to 86% of patients.^{1,5,6} Although pathogenesis is unknown, the findings in our patients suggest this is in part an immune-mediated disorder. Patient B demonstrated an increased percentage of CD25⁺ T cells, indicating activation of

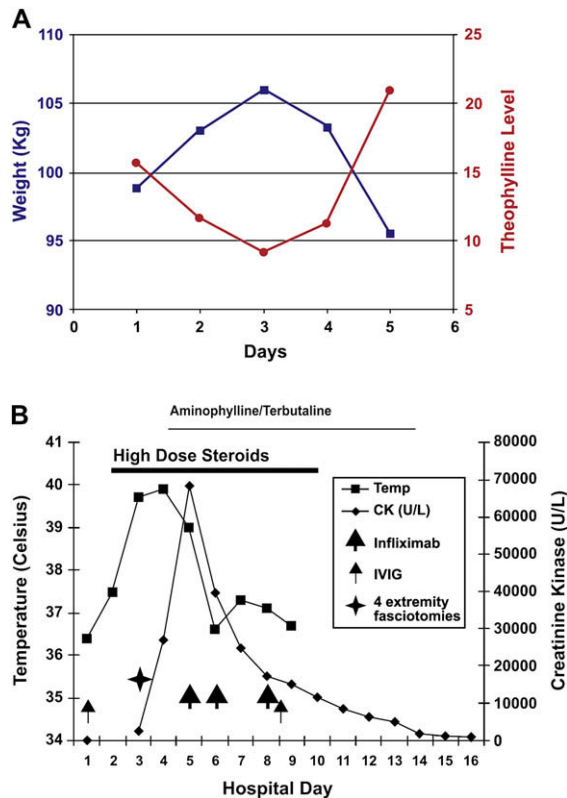


FIG 1. A, An inverse relationship between body weight and serum theophylline level demonstrated in patient B. **B,** Time sequence and treatment of patient C. Treatment with infliximab led to rapid temperature defervescence and a decrease in creatinine kinase (CK) levels. IVIG, Intravenous immunoglobulin.

T cells during an acute episode. Cytokine profiling in this patient revealed increases in IL-10 and IFN- γ -inducible protein 10 levels, also suggesting activation of the immune system. All patients demonstrated increases in TNF- α levels, although to differing degrees, and patients B and C demonstrated increased levels of several other serum cytokines (Tables II and III), lending further support to an immune-mediated mechanism for this syndrome.

The causes of increased capillary permeability in this syndrome are unknown. However, TNF- α is known to stimulate the release of endothelial cytokines and increase vascular permeability.^{7,8} Increases in TNF- α levels were observed in all 3 of our patients during acute attacks. Patient C, who was treated with anti-TNF mAb, demonstrated a dramatic clinical response. On a molecular level, increased cyclic adenosine monophosphate (cAMP) levels are known to decrease endothelial cell permeability.⁹ Terbutaline (by inducing adenylyl cyclase) and theophylline (by inhibiting phosphodiesterase) should increase the cAMP level.¹⁰ It is possible that higher theophylline levels (as required in our 3 patients) are needed to achieve effective pharmacologic inhibition of phosphodiesterase and result in clinical improvement.¹⁰

In summary, although the underlying pathogenesis is unknown, our findings strongly support an immunologic basis for this syndrome. The ability of TNF- α to increase vascular permeability and increases in levels of this cytokine during acute attacks in our 3 patients lend credence to the use of TNF antagonists. The usefulness of theophylline and terbutaline in this syndrome, both acutely and for prophylaxis, likely relates to their ability to

TABLE III. Serum cytokine profiles: Patient C

	TNF- α (pg/mL)	IL-6 (pg/mL)	IFN- γ (U/L)	IL-1ra (pg/mL)	sIL-6R (ng/mL)
Hospital, day 5 AM	76.3	41.29	6747		13.2
Hospital, day 5 PM	104.68	37.8	6286	27401	18.1
Hospital, day 6	110.01	9.21	6520	6083	26.7
Hospital, day 8	137.49	22.54	1195	1484	30.4

Soluble tumor necrosis factor-receptor II (sTNF-RII) levels were normal. IL-6 was measured by using the Quantikine high-sensitivity ELISA kit (normal range, 0.38–6.11 pg/mL). Soluble IL-6 receptor (sIL-6R) and IL-1ra levels were measured by using the Quantikine ELISA kit (R&D Systems, Minneapolis, Minn; no normal range for IL-6R and IL-1ra). TNF- α levels were measured by using the TNF- α EASAI kit (Biosource International, Camarillo, Calif; normal range, 4.8–20.5 pg/mL), and IFN- γ levels were measured by using the Immunotech EIA (Beckman Coulter, Fullerton, Calif; normal range, <50 U/L).

increase cAMP and thus decrease endothelial cell permeability. Thus we propose a 2-step approach for treatment of acute attacks of ISCLS. Theophylline and terbutaline would be the first approach, followed, if necessary, by TNF antagonists.

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