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Management of Acute Episodes of Clarkson Disease (Monoclonal Gammopathy-Associated Systemic Capillary Leak Syndrome) With Intravenous Immunoglobulins

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Abstract

Monoclonal gammopathy-associated idiopathic systemic capillary leak syndrome (ISCLS, Clarkson disease) is a rare disorder defined by transient but recurrent bouts of hypotensive shock and anasarca resulting from plasma extravasation. Although prophylactic treatment with high-dose intravenous immunoglobulins (IVIG, 1–2 g/kg/mo) prevents most disease flares, its utility for acute episodes of ISCLS is unclear. Here, we report the results of a retrospective study of subjects with acute ISCLS treated at or near the onset of symptoms with IVIG. We found that administration of IVIG with minimal additional intravenous fluids was safe and associated with rapid clinical improvement. IVIG given close to the onset of ISCLS-related symptoms is associated with a favorable outcome.

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Disclosures

Disclosure forms are available with the article online.

Keywords

Intravenous immunoglobulin; Systemic diseases; Shock; Retrospective studies; Edema; Capillaries; Blood plasma

Introduction

Clarkson disease is characterized by acute episodes of hypotension, hemoconcentration (elevated hemoglobin/hematocrit), and hypoalbuminemia (1). This “leak” phase is associated with multiorgan dysfunction syndrome, anasarca, and thrombosis but is usually self-limited. This is followed by a “recruitment” phase during which edema is resorbed, which may result in intravascular volume overload and pulmonary edema. Although most patients are treated with large amounts of intravenous (IV) fluids (2), cumulative fluid therapy (≳10 L) is significantly associated with mortality because of compartment syndromes and rhabdomyolysis (1).

IV immunoglobulin (IVIG) has typically been given during the later stages of the episode as a “rescue” therapy, if at all (3). Although Lambert et al. reported in 2008 that IVIG administered at or near the onset of flares resulted in rapid symptom resolution in 3 patients (4), this approach has not been widely embraced (1, 2). In a recent cohort study (1), acute IVIG therapy was not linked to increased survival and was suggested to be contraindicated during acute flares because of potential nephrotoxicity (1). Here, we report the utility of IVIG as initial therapy for ISCLS episodes in lieu of IV fluid resuscitation.

Methods

Patients were enrolled in a National Institutes of Health protocol (09-I-0184) approved by the National Institutes of Health institutional review board. The patients provided informed consent before enrollment and consented to publication of this article.

Case Series

The clinical course and laboratory abnormalities in 6 patients treated with IVIG at or near the onset of idiopathic systemic capillary leak syndrome (ISCLS) episodes are summarized in Tables 1 and 2.

Case 1

Patient 1 is a 72-year-old man diagnosed with ISCLS in 2005; complications of his initial flares included deep vein thromboses, acute renal failure, and compartment syndromes of both lower legs and forearms that required fasciotomies and led to neuropathies and motor weakness. He was initially treated with theophylline and terbutaline but experienced 9 additional exacerbations over the next 4 years. In 2009, IVIG prophylaxis (2 g/kg/mo) was initiated, and he had no further disease flares until January 2020, when he presented with symptoms of upper respiratory infection (URI), diaphoresis, and syncope 4 days before his next scheduled dose of IVIG. He took 100 mg prednisone and was brought to the emergency

department (ED). His blood pressure (BP) was 104/65 mm Hg. A nasal swab was positive for influenza A; oseltamivir and an additional dose of 100 mg prednisone were given. IVIG (1 g/kg) and albumin (25 g) were administered urgently; additional isotonic crystalloid fluids totaled <500 mL. The next day, his BP stabilized (118–124/91–94 mm Hg); he developed minimal swelling in the right forearm but no compartment syndrome. A second dose of IVIG (1 g/kg) was administered on the second day. Symptoms resolved on day 3, and he was discharged.

In December 2021, the patient, who had received 3 doses of COVID-19 vaccine (mRNA-127, Moderna), with the most recent dose 4 months before the episode, developed URI symptoms. Two days later (9 days before his scheduled IVIG infusion), he presented to the ED with lightheadedness; his systolic BP was 100 mm Hg. A nasal swab polymerase chain reaction (PCR) was positive for SARS-CoV-2. IVIG (1 g/kg) was administered promptly, without additional IV fluids. His BP normalized rapidly, and 18 hours later, he received a second dose of IVIG (1 g/kg) together with Ringer's lactate (1 L). Two days after admission, he developed edema of the thighs bilaterally, and hemoglobin level remained high (10.55 mmol/L); prednisone (60 mg) was given. On hospital day 3, the patient felt well; his urine output increased, his peripheral edema decreased, and he was discharged.

Case 2

Patient 2 is a 55-year-old man diagnosed with ISCLS 10 years before his most recent flare. Large amounts of crystalloid fluid were given during his initial crisis, which was complicated by acute renal failure and a compartment syndrome in the right lower extremity that required fasciotomy. Several months later, in 2011, treatment with IVIG (2 g/kg every 4 weeks) was initiated. Because of fatigue and myalgias following the infusions, he was subsequently given IVIG in split doses (1 g/kg every 2 weeks).

The patient had no further disease exacerbations until January 2019 when he noted myalgias, fatigue, lightheadedness, and palpitations on the day of a scheduled outpatient IVIG administration. IVIG was administered, and his symptoms resolved. Two weeks later, on the evening before his next scheduled IVIG dose, he developed myalgias, lightheadedness, decreased urine output, and peripheral edema. He presented to the ED, where his BP and heart rate (HR) were 108/72 mm Hg (baseline ~130/90 mm Hg) and 82 beats/min, respectively, and lower extremity edema was present. A nasal swab for respiratory pathogens was negative. IVIG (1 g/kg) was given, but he received no additional IV fluids. On hospital day 2, his BP had returned to baseline, with spontaneous diuresis and resolution of edema, and he was discharged the next day.

Two weeks later, the day before his next scheduled IVIG infusion, he awoke feeling weak, diaphoretic, and fatigued. He had no urine output, and his hemoglobin level, checked at home (by HemoCue), was 11.36 mmol/L. In the ED, his BP and HR were 140/80 mm Hg and 92 beats/min, respectively, with orthostasis (standing BP 94/66 mm Hg, HR 116 beats/min). Extremities were without edema. A respiratory pathogen panel was negative. He was treated with IVIG (1 g/kg), but no additional IV fluids. The next day, orthostasis had resolved with spontaneous diuresis (urine output >50 mL/h). On hospital day 3, the patient

felt well and was discharged. His prophylactic IVIG dosage was increased to 1.25 g/kg every 2 weeks, and he has not experienced any further exacerbations.

Case 3

Patient 3 is a 68-year-old man who experienced 6 acute ISCLS flares from 2003 to 2005, which were managed with IV fluid resuscitation (~20–30 L crystalloid). Sequelae included angina, cardiac tamponade, and deep venous thrombosis. He started treatment with IVIG (2 g/kg/mo) in 2005 and had no further episodes. He received 3 doses of COVID-19 vaccine (BNT162b2, Pfizer BioNTech), including a booster dose in December 2021. In February 2022, 2 days before the next scheduled IVIG infusion, he experienced fatigue, URI symptoms, oliguria, and exertional dyspnea. The next day, he presented to the ED with abdominal discomfort and presyncope. His BP was 120/80 and HR was 60–80 beats/min; bilateral lower extremity edema was evident. A nasal swab PCR for SARS-CoV-2 was positive. IVIG (2 g/kg) was infused over the next 4 hours. He received a single dose of prednisone (20 mg) before the infusion to prevent headache but minimal additional IV fluids. Dyspnea resolved, and oxygen saturation was 100% on room air. By the next day, his leg edema had resolved and spontaneous diuresis occurred (~50 mL urine/h). The patient was discharged 12 hours after admission.

Case 4

Patient 4 is a 44-year-old man diagnosed in 2015 following 4 prototypical episodes in the preceding 7 years, the first in 2008 at the age of 30 years. The most severe episode occurred in 2015, during which transient cardiogenic shock (left ventricular ejection fraction ~10%–15%), acute kidney injury, and compartment syndromes in the lower extremities developed. He began treatment with IVIG (2 g/kg/mo), which was subsequently lowered to 0.65 g/kg/mo because of intolerable side effects, and he did not experience further exacerbations.

The patient received 3 doses of COVID-19 vaccine (BNT162b2, Pfizer BioNTech), including a booster in November 2021. In January 2022, family members tested positive for SARS-CoV-2. One day later, the day after his maintenance IVIG infusion, he developed headache, nausea, fatigue, polydipsia, and myalgias but no respiratory symptoms. These worsened, and he was hospitalized. Physical examination results included hypotension (BP 97/71 mm Hg, baseline 140/60 mm Hg) and clear lungs to auscultation. A nasal swab PCR was positive for SARS-CoV-2. IVIG (2 g/kg) was administered over the next approximate 18 hours together with remdesivir (100 mg IV/day × 3 days), but no additional fluids. The following morning, the patient felt subjectively improved, and BP normalized (100–121/84 mm Hg). The patient continued to feel well and was discharged on hospital day 3.

Case 5

Patient 5 is a 55-year-old man who had his first episode at age 48 years. He was initially treated with theophylline prophylaxis (200 mg 3 times daily). Six months later (January 2015), he presented to the ED within 2 hours of the onset of flulike symptoms, fatigue, and

bilateral upper extremity edema. During triage evaluation, he collapsed; his BP was 80/40 mm Hg and his HR was 130 beats/min. Despite fluid resuscitation with Hemaccel (2 L) and saline (1.5 L) solutions, hypotension persisted. The next morning, IVIG (1 g/kg) was then administered (~18 hours after symptom onset). His condition improved over the next 24 hours, with normalization of BP, and he was discharged from the hospital on day 11. He started receiving regular IVIG prophylaxis (1 g/kg/mo) and has not experienced any further exacerbations.

Case 6

Patient 6 is a 61-year-old man who experienced his first ISCLS episode in 2015. He decided to forego IVIG prophylaxis but had no further attacks until March 2022, when he presented with weakness, myalgias, and diffuse peripheral edema. His BP was 130/90 mm Hg, and HR was 90 beats/min. Ten hours after admission to the hospital, IVIG (0.5 g/kg/d for 4 days) was prescribed with minimal additional IV fluids (1 L saline/d for 4 days). His symptoms and peripheral edema resolved approximately 15 hours after the first dose of IVIG, and he was discharged on hospital day 4.

Discussion

In this retrospective case series, ISCLS flares were preceded by a URI prodrome suggestive of a viral trigger (5/9 episodes), including documented influenza (1 case) and COVID-19 (3 cases). Two patients had not been receiving preventive IVIG therapy; 6 episodes occurred just before the scheduled administration of monthly prophylaxis, and 1 flare occurred in a patient receiving low prophylactic doses.

Efficacy of acute therapies for ISCLS is difficult to evaluate. Controlled trials are impractical because of disease rarity and delayed or incorrect diagnosis. Various interventions including methylene blue (5) and bevacizumab (6) have shown promise in case reports, but none has been validated in larger scale studies. The beneficial effects of IVIG may depend on the timing of administration; the benefits are maximal within the first 24 hours of the flare onset rather than days later when used as rescue therapy. We did not observe any change in renal function associated with IVIG. The mechanism by which IVIG rapidly reverses acute ISCLS episodes is unclear. Several patients had rapid diuresis and stable creatinine levels, suggesting that it leads to improved clinical outcomes through mechanisms other than simple restoration of plasma volume. These mechanisms could include neutralization of proinflammatory cytokines or M-proteins.

Although all of the patients had immunoglobulin G monoclonal gammopathy, its contribution(s) to disease diagnosis and pathogenesis remain unclear. Because acute ISCLS episodes and responses to IVIG prophylaxis are similar in patients with and without monoclonal gammopathy of undetermined significance (7), early administration of IVIG for acute ISCLS episodes in patients lacking monoclonal gammopathy of undetermined significance should be strongly considered.

Finally, although both COVID-19 and COVID-19 vaccine-induced exacerbations (many fatal) are now well documented (8–13), we report that COVID-19-associated ISCLS flares

can occur in vaccinated and boosted patients on IVIG prophylaxis. We suggest that IVIG should be given SARS-CoV-2$^+$ patients with a history of ISCLS, especially near the end of their IVIG infusion cycles.

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Table 1.

Patient Demographics and Hospital Course

Parameter	Patient 1 Episode 1	Patient 1 Episode 2	Patient 2 Episode 1	Patient 2 Episode 2	Patient 2 Episode 3	Patient 3	Patient 4	Patient 5	Patient 6
Age, y [*]	70	72	55	55	55	68	44	49	61
Sex	Male		Male			Male	Male	Male	Male
Race	White		White			White	African American	White	White
MGUS	IgG κ			IgG κ		IgG κ	IgG κ	IgG κ	IgG λ
Trigger	Influenza A	COVID-19	Unknown	Unknown	Unknown	COVID-19	COVID-19	Unknown	Unknown
Presenting signs and symptoms	Influenza-like symptoms, diaphoresis, near-syncope	URI symptoms, hypotension, and tachycardia	Myalgias, fatigue, lightheadedness, and palpitations	Fatigue, myalgias, lower extremity edema, oliguria, hypotension	Weakness, fatigue, diaphoresis	Fatigue, URI symptoms, oliguria, exertional dyspnea	Fatigue, myalgias, abdominal distention, near-syncope	Influenza-like symptoms, upper extremity edema, hypotension, and tachycardia	Weakness, myalgias, peripheral edema
Complications	Right forearm edema without compartment syndrome	Bilateral thigh edema without compartment syndrome	None	None	None	None	None	None	None
Treatments	IVIG (2 g/kg of body weight), IV fluids (<500 mL crystalloid)[¶], oseltamivir, prednisone[§]	IVIG (2 g/kg of body weight), prednisone[§]	IVIG 1 g/kg/body weight	IVIG (1 g/kg of body weight)	IVIG (1 g/kg of body weight)	IVIG (1 g/kg of body weight), prednisone	IVIG (2 g/kg of body weight), remdesivir	IV fluids [†], IVIG (1 g/kg of body weight)	IVIG (0.5 g/kg/day for 4 days)
Outcome	Discharged on hospital day 3	Discharged on hospital day 3	Outpatient, discharged home	Discharged on hospital day 3	Discharged on hospital day 3	Discharged on hospital day 2	Discharged on hospital day 3	Discharged on hospital day 11	Discharged on hospital day 4

Ig = immunoglobulin; IV = intravenous; IVIG = intravenous immunoglobulin; MGUS = monoclonal gammopathy of undetermined significance; URI = upper respiratory infection.

[*] At time of acute episode.

[¶] Isotonic saline.

[§] 100 mg orally, 1-time dose.

[†] Isotonic saline, albumin.

Table 2.

Laboratory Abnormalities During Hospitalization

Variable	Normal range*	Patient 1		Patient 2			Patient 3	Patient 4	Patient 5	Patient 6
		Episode 1	Episode 2	Episode 1	Episode 2	Episode 3				
Peak hemoglobin level, *mmol/L*	6.95–9.74	12.1	10.92	12.29	11.05	11.98	11.67	11.23	11.05	15.14
Post-IVIG hemoglobin level, *mmom/L*†	6.95–9.74	9.62	8.81	ND	7.45	7.51	9.37	8.69	8.32	8.07
Nadir albumin level, *g/L*	35–52	22	29	ND	26	26	33	26	16	25
Post-IVIG albumin level, *g/L*†	35–52	26	ND	ND	ND	ND	28.6	30	32.8	29
Peak creatinine level, *μmol/L*	48.63–106.1	151.2	122.9	ND	87.54	114.95	92.84	119.37	141.47	193.64
Post-IVIG creatinine level, *μmol/L*†	48.63–106.1	135.28	111.41	ND	84.88	83.11	61.89	114.06	79.58	85.77

IVIG = intravenous immunoglobulin; ND = not done.

*Based on National Institutes of Health Clinical Center guidelines.

†At or near the time of discharge from hospital.