A Remarkable Coexistence of Systemic Capillary Leak Syndrome and Diabetes in an 11-Year-Old Boy: A Case Report and Review of the Literature

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Systemic capillary leak syndrome (ISCLS) is a rare disease characterized by unexplained reversible capillary hyperpermeability followed by hypoperfusion, hemoconcentration, and either hypoalbuminemia or total hypoproteinemia [1]. Clarkson first described a case of ISCLS in 1960 [2]. To date, about 500 cases have been reported worldwide, of which most are white adults, and it is extremely rare in children [3, 4].

1. Introduction

Idiopathic systemic capillary leak syndrome (ISCLS) is a rare disease characterized by unexplained reversible capillary hyperpermeability followed by hypoperfusion, hemoconcentration, and either hypoalbuminemia or total hypoproteinemia [1]. Clarkson first described a case of ISCLS in 1960 [2]. To date, about 500 cases have been reported worldwide, of which most are white adults, and it is extremely rare in children [3, 4].

Attacks of ISCLS tend to demonstrate three phases: prodromal symptoms, capillary leak, and recovery [5]. The recorded cases show that in adult patients, monoclonal gammopathy was usually accompanied, while in pediatric cases, there was no reported gammopathy [6]. For proper diagnosis of ISCLS, sepsis, anaphylaxis, and certain drug
reactions need to be ruled out; there is no standard test for this diagnosis and the only way is through elimination. Here, we present a pediatric patient with the first attack of capillary leak with concordant diabetes mellitus (DM).

2. Case

An 11-year-old boy admitted with vomiting, generalized edema, and hyperglycemia, which was preceded by 5 days of coryzal symptoms, lethargy, and oral aft without fever. He was admitted to another hospital with hypotensive syncope and severe vomiting (20 times/day), and intravenous hydration was initiated. His blood glucose was 13.8 mmol/L, and urine glucose was +++ at admission. Initially, he was diagnosed with stress hyperglycemia and acute gastroenteritis. After one day, he was referred to our hospital because of his persisting symptoms and hyperglycemia. There was no specific indicative feature in his personal or family history. His weight was 30 kg (−1.02 SDS), height was 147 cm (+0.75 SDS), heart rate was 118/minute, and blood pressure was 90/40 mm/Hg, and generalized nonitching systemic edema was present on his physical examination.

The laboratory tests showed that severe hemoconcentration was present. His biochemical findings were as follows: white blood cell count: $1.8 \times 10^9$ L; hemoglobin: 184 g/L; hematocrit: 51.3%; sodium: 130 mmol/L; potassium: 4.8 mmol/L; chloride: 105 mmol/L; urea: 20 mmol/L; creatinine: 45 µmol/L; and blood glucose: 11.1 mmol/L. On arterial blood gas analysis, pH was 7.33 and HCO₃ was 13.6 mmol/L (Table 1). On sepsis work-up, CRP was 3 mg/L, and urine output was normal excluding renal diseases. To eliminate protein-losing enteropathies were excluded. Complete blood count was present. His biochemical findings were as follows: white blood cell count: $1.8 \times 10^9$ L; hemoglobin: 184 g/L; hematocrit: 51.3%; sodium: 130 mmol/L; potassium: 4.8 mmol/L; chloride: 105 mmol/L; urea: 20 mmol/L; creatinine: 45 µmol/L; and blood glucose: 11.1 mmol/L. On arterial blood gas analysis, pH was 7.33 and HCO₃ was 13.6 mmol/L (Table 1). On sepsis work-up, CRP was 3 mg/L, and urine, stool, and blood culture were negative. Respiratory virus panel PCR was positive for respiratory syncytial virus (RSV) and enterovirus.

Aggressive fluid replacement was initiated at admission due to hypotension. Although urine output was normal during the first two days of hospitalization, his diuresis was inadequate on the third day (0.3 cc/kg/hr), and so 3000 cc/m² 5% dextrose and 0.45% NaCl were administered as maintenance fluid therapy. The patient’s serum albumin levels, as well as his globulin levels, were highly reduced as maintenance fluid therapy. -´_he patient’s serum albumin

| Test                          | Result | Reference values |
|-------------------------------|--------|-----------------|
| White blood cell count (10⁹ L) | 1.8 (N) | (4.5–13)        |
| Neutrophil (10⁹ L)            | 1.4 (L) | (1.8–8)         |
| Red blood cell count (10⁹ L)  | 6.4 (N) | (3.9–5.1)       |
| Hemoglobin (g/L)              | 184 (H) | (120–150)       |
| Hematocrit (fraction of RBC) | 0.51 (H) | (0.34–0.43)     |
| MCV (L)                       | 79 (N)  | (76–90)         |
| Platelet (10⁹ L)              | 476 (H) | (150–450)       |
| Glucose (mmol/L)              | 13.6 (H) | (3.3–5.5)       |
| Aspartate aminotransferase (µkat/L) | 0.35 (N) | (<0.58) |
| Alanine aminotransferase (µkat/L) | 0.15 (N) | (<0.58) |
| GGT (µkat/L)                  | 0.10 (N) | (<0.92) |
| Alkaline phosphatase (µkat/L) | 0.78 (L) | (2.15–6.96) |
| Cholesterol (mmol/L)          | 1.63 (N) | (<5.18) |
| Triglyceride (mmol/L)         | 2.01 (H) | (<1.69) |
| Sodium (mmol/L)               | 130.3 (L) | (136–145) |
| Potassium (mmol/L)            | 4.8 (N)  | (3.5–5)         |
| Cholesterol (mmol/L)          | 105 (N)  | (96–110)        |
| Calcium (mmol/L)              | 1.90 (L) | (2.15–2.50)     |
| Phosphorus (mmol/L)           | 1.20 (N) | (1–1.94)       |
| Anti-idiotype IgA              | Negative |
| Anti-endomysium IgA           | Negative |
| Troponin T (µg/L)             | <13 (N) | (<14)          |
| Creatine phosphokinase (µkat/L) | 0.52 (L) | (0.55–3.11) |
| Lactate dehydrogenase (µkat/L) | 2.82 (N) | (2–5)         |
| Immunoglobulin G (g/L)        | 1.87 (L) | (8.22–12.8)    |
| Immunoglobulin A (g/L)        | 0.43 (N) | (0.72–1.58)    |
| Immunoglobulin M (g/L)        | 0.4 (L)  | (0.63–1.41)    |
| Immunoglobulin E (µU/L)       | 6.43 (N) |                |
| Thyroid-stimulating hormone (mU/L) | 2.5 (N) | (0.37–4.2) |
| Thyroxine free (pmol/L)       | 19.05 (N) | (11.97–21.88) |
| Stool alpha-1 antitrypsin (µg/g) | 130 (N) |
| Total protein (g/L)           | 46 (L)  | (64–83)         |
| Albumin (µg/L)                | 22 (L)  | (35–52)         |
| Urea (mmol/L)                 | 20 (H)  | (3.57–17.85)    |
| Creatinine (µmol/L)           | 45.75 (N) | (22.88–76.25) |
| Uric acid (µmol/L)            | 0.35 (H) | (0.12–0.33)    |
| C-reactive protein (mg/L)     | 3 (N)   | (0–5)           |
| Urine density                 | 1033 (N) |                |
| Urine ketone (mmol/L)         | 14.6 (+) |                |
| Arterial pH                   | 7.33 (N) |                |
| Arterial pCO₂ (mmHg)          | 25.9 (N) |                |
| Arterial lactate (mmol/L)     | 1.9 (N)  |                |
| Arterial HCO₃ (mmol/L)         | 13.9    |                |
| Arterial base excess (mmol/L) | −11.7   |                |
| C3 complement (µg/L)          | 1.17 (N) | (0.9–1.8)      |
| C4 complement (µg/L)          | 0.15 (N) | (0.1–0.4)      |
| Serum amyloid A (mg/L)        | <3.3 (N) |                |
| Antinuclear antibody, ANCA    | Negative |
| D.Coombs                      | +2      |                |
| C 1 esterase inhibitor (mg/L) | 366 (N) | (210–390)      |
| Antiglutamic acid decarboxylase (nmol/L) | 0.01 (N) | (<0.02) |
| Anti-insulin antibody (nmol/L) | Negative |
| Islet cell antibody           | Negative |
| Parvovirus B19 IgM            | Negative |
| Rubeola IgM                   | Negative |
| (Varicella zoster) antibody IgM | Negative |
| Antirubella IgM               | Negative |
| HBsAg                         | Negative |
generalized edema increased, albumin values dropped to 1.9g/dL, he had diarrhea, and he gained 3 kg of weight. Subcutaneous insulin treatment started with a dose of 0.3IU/kg/day at the end of the second day. Intravenous human albumin treatment was given on the 2nd, 4th, and 7th day of admission. On the fourth day, the patient was given the ISCLS diagnosis by ruling out other causes. Following the diagnosis, intravenous immunoglobulin (IVIG) treatment was given on two consecutive days (Figure 1). His edema decreased on the fifth day, and he was deemed clinically well on the 7th day, weighing 29 kg. As for the systemic effects of ISCLS, there was seldom amount of free fluid in the abdomen, the diameter of the appendix was increased, and minimal pleural effusion was found bilaterally. There was no compartment syndrome, rhabdomyolysis, or pulmonary edema during the recovery period.

For the differential diagnosis of DM, his fasting serum glucose was 13.8 mmol/L, simultaneous C-peptide was 0.44 nmol/L, HbA1c was 64 mmol/mol, and urine ketone was positive. Antigliutamic acid decarboxylase, anti-insulin antibody, and islet cell antibody were negative. The patient harbors type 1 DM predisposing HLA II haplotypes as follows: DRB1*0301, DRB1*0302, and DRB1*0201. Although there was no family history for DM, since his autoantibodies were negative, next-generation gene sequencing for 14 MODY genes including GCK, HNF1A, HNF4A, HNF1B, PDX1, CEL, KLF11, NEUROD1, PAX4, INS, and BLK was analyzed, and they were all negative. Whole exome sequencing of the patient for candidate genes is ongoing. At the 6th and 12th month marks, as well as at the last outpatient visit, his insulin dose was still 0.4 IU/kg/day and HbA1c was 40 mmol/mol.

3. Discussion

ISCLS is seen primarily in middle-aged adults and is rare in children, with only cases or case series being reported in children [3, 7–10]. While the general clinical features of this syndrome in children are similar to those of adults, there is no monoclonal gammapathy, and the pathogenesis and pathophysiology of ISCLS are relatively unknown due to its rarity [11]. Reports usually describe a viral prodrome and proven viral infections such as influenza virus, parainfluenza virus, enteroviruses, RSV, and rotavirus in children [7, 8, 12]. In our case, the existing prodromal symptoms and PCR results which were positive for both RSV and enterovirus suggested these viral infections had triggered the clinical findings of this case.

In its first phase, ISCLS is indistinguishable from viral infections with the symptoms of coryza, diarrhea, fatigue, and vomiting. It is this phase where patients are usually referred to a hospital, where in the second phase, the patient can be observed experiencing extravasation characterized by edema, syncope, hypotension, shock, and organ failures. This is also the critical period to diagnose and treat this disease, since if the diagnosis is given later than this stage, the mortality rate can be high as 19% due to risk of pulmonary edema, renal failure, brain edema, or shock [5].

During ISCLS flares, transient spikes in circulating angiogenic proteins, known to trigger vascular hyperpermeability (e.g., angiopeptin 2 and vascular endothelial growth factor (VEGF)), have been detected [13]. Elevated levels of cytokines and chemical mediators (granulocyte colony-stimulating factor (G-CSF), interleukin-6 (IL-6), interleukin-8 (IL-8), and monocyte chemotactic protein-1 (MCF-1)) were reported in some cases. Some authors also found elevated levels of interleukin-1β (IL-1β), C-Motif chemokine ligand-2 (CCL2), and C-X-C motif chemokine 10 (CXCL10) during the acute phase, suggesting that ISCLS may have clinically varying forms of presentation. This leads to the assumption that within the group of patients with ISCLS, different cytokines may mediate capillary leak. In an Italian girl, serum eosinophilic cationic protein was found to be elevated during acute attacks [14]. These findings demonstrate that patients with ISCLS have different cytokine profiles, which further suggests that ISCLS may consist of a heterogeneous group of disorders with the common endpoint of capillary leak [15].

The frequency and severity of episodes differ from one patient to another. Acute treatment depends on aggressive fluid replacement and crystalloid solutions [16, 17]. Corticosteroid therapy against cytokine-mediated endothelial damage along with plasmapheresis and intravenous immunoglobulin has proved to be successful in the acute phase.
ongoing. Whole exome sequencing of patient for candidate genes is susceptible to ISCLS or whether the two happened to be genes were negative. Whether his DM made him more mutations for mostly known MODY.

ConflictsofInterest
The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

References
[1] J. Kerketta, M. Lodh, and K. Mandal, “Clarkson disease—systemic capillary leak syndrome in a 6-year-old girl: case report,” Paediatrics and International Child Health, vol. 35, no. 2, pp. 160–163, 2015.
[2] B. Clarkson, D. Thompson, M. Horwith, and E. H. Luckey, “Cyclical edema and shock due to increased capillary permeability,” The American Journal of Medicine, vol. 29, no. 2, pp. 193–216, 1960.
[3] R. Sion-Sarid, T. Lerman-Sagie, L. Blumkin, D. Ben-Ami, I. Cohen, and S. Houri, “Neurologic involvement in a child with systemic capillary leak syndrome,” Pediatrics, vol. 125, no. 3, pp. e687–e692, 2010.
[4] N. U.-A. Baloch, M. Bikak, A. Rehman, and O. Rahman, “Recognition and management of idiopathic systemic capillary leak syndrome: an evidence-based review,” Expert Review of Cardiovascular Therapy, vol. 16, no. 5, pp. 331–340, 2018.
[5] P. Kapoor, P. T. Greipp, E. W. Schaefer et al., “Idiopathic systemic capillary leak syndrome (Clarkson’s disease): the Mayo clinic experience,” Mayo Clinic Proceedings, vol. 85, no. 10, pp. 905–912, 2010.
[6] M. Gousseff and Z. Amoura, “Syndrome de fuite capillaire idiopathique,” La Revue de Médecine Interne, vol. 30, no. 9, pp. 754–768, 2009.
[7] M.-A. Bozzini, G. P. Milani, M. G. Bianchetti, E. F. Fossali, and S. A. G. Lava, ”Idiopathic systemic capillary leak syndrome (Clarkson syndrome) in childhood: systematic literature review,” European Journal of Pediatrics, vol. 177, no. 8, pp. 1149–1154, 2018.
[8] T. Perme, M. Pokorn, G. Markelj et al., “Two episodes of systemic capillary leak syndrome in an 8-year-old boy, following influenza a virus infection,” The Pediatric Infectious Disease Journal, vol. 33, no. 2, pp. 222–224, 2014.
[9] K. Kulihova, M. Prochazkova, J. Semberova, and J. Janota, “Fatal primary capillary leak syndrome in a late preterm newborn,” The Indian Journal of Pediatrics, vol. 83, no. 10, pp. 1197–1199, 2016.
[10] S. Kawabe, T. Saeki, H. Yamazaki, M. Nagai, R. Aoyagi, and S. Miyamura, “Systemic capillary leak syndrome,” Internal Medicine, vol. 41, no. 3, p. 211, 2002.
[11] P. Hsu, Z. Xie, K. Frith et al., ”Idiopathic systemic capillary leak syndrome in children,” Pediatrics, vol. 135, no. 3, pp. e730–e735, 2015.
[12] M. Gousseff, “The systemic capillary leak syndrome: A case series of 28 patients from a European registry,” Annals of Internal Medicine, vol. 154, no. 7, p. 464, 2011.
[13] L. Mo, G. Xu, C. Wu et al., “Key regulatory effect of activated HIF-1α/VEGFA signaling pathway in systemic capillary leak syndrome confirmed by bioinformatics analysis,” Journal of Computational Biology, vol. 27, no. 6, pp. 914–922, 2020.
[14] G. P. Milani, R. M. Dellepiane, M. L. Castellazzi, M. B. M. Mazzoni, M. G. Bianchetti, and E. F. Fossali, “Episodic idiopathic systemic capillary leak syndrome in a girl,” Pediatrics International, vol. 55, no. 4, pp. e81–e82, 2013.
[15] Z. Xie, C. C. Ghosh, S. M. Parikh, and K. M. Druy, “Mechanistic classification of the systemic capillary leak syndrome: Clarkson disease,” American Journal of Respiratory and Critical Care Medicine, vol. 189, no. 9, pp. 1145–1147, 2014.
[16] P. Almagro, J. M. Martí, L. García Pascual, and M. Rodríguez- Carballeira, ”Successful treatment of systemic capillary leak syndrome with intravenous immunoglobulins,” Revista Clínica Española, vol. 212, no. 4, pp. 218-219, 2012.

4. Conclusion
Early recognition of ISCLS is important for therapeutic awareness, since it is very rare in childhood and occurs usually without any precipitating factors in healthy children. Although there are not enough studies about acute treatment and prophylaxis, there are promising recommendations on a case basis. With the increase in awareness of the disease, knowledge and experiences about pediatric patients will also increase. We think that our case will contribute to the literature since there have been no pediatric diabetic patients with ISCLS reported.

Conflicts of Interest
The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.
[17] A. M. Marra, A. Gigante, and E. Rosato, "Intravenous immunoglobulin in systemic capillary leak syndrome: a case report and review of literature," *Expert Review of Clinical Immunology*, vol. 10, no. 3, pp. 349–352, 2014.

[18] T. Iwasa, H. Ohashi, K. Kihira et al., "10-year-old girl with life-threatening idiopathic systemic capillary leak syndrome: a case report," *BMC Pediatrics*, vol. 14, no. 1, p. 137, 2014.

[19] H. Yabe, M. Yabe, T. Koike, T. Shimizu, T. Morimoto, and S. Kato, "Rapid improvement of life-threatening capillary leak syndrome after stem cell transplantation by bevacizumab," *Blood*, vol. 115, no. 13, pp. 2723-2724, 2010.

[20] M. Lambert, D. Launay, E. Hachulla et al., "High-dose intravenous immunoglobulins dramatically reverse systemic capillary leak syndrome," *Critical Care Medicine*, vol. 36, no. 7, pp. 2184–2187, 2008.

[21] R. Mullane, E. Langewisch, M. Florescu, and T. Plumb, "Chronic systemic capillary leak syndrome treatment with intravenous immune globulin: Case report and review of the literature," *Clinical Nephrology*, vol. 91, no. 1, pp. 59–63, 2019.

[22] Y.-M. Li, J. Ran, H. Li, and C.-Y. Yan, "Risk factors for capillary leak syndrome in neonates," *Zhongguo Dang Dai Er Ke Za Zhi Chinese Journal of Contemporary Pediatrics*, vol. 13, no. 9, pp. 708–710, 2011.

[23] S. Lawson, D. T. Ward, C. Conner, C. Gallagher, G. Tsokos, and T. Shea-Donohue, "Diabetic hyperglycemia: A facilitating factor in systemic capillary leak," *Journal of Surgical Research*, vol. 105, no. 2, pp. 95–101, 2002.