

A case report of capillary leak syndrome with recurrent pericardial and pleural effusions

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Background

Capillary leak syndrome (CLS) is a rare connective tissue disease, triggered by the leak of serous fluid into the interstitial spaces, characterized by a hallmark of oedema and effusions in confined spaces. The limiting factor in CLS management appears to be its diagnosis rather than treatment, which is usually to contain the disease progression rather than a cure.

Case summary

We report a case of a 51-year-old woman with recurrent life-threatening presentations of pericardial effusions, pleural effusions, and generalized swelling of face and extremities. The only notable past medical history was of Type 1 diabetes. Numerous investigations did not lead to specific disease accounting for pericardial effusions and pleural effusions. Eventually, the diagnosis of CLS was made based on hypovolaemic shock, hypoalbuminaemia, and haemoconcentration without the presence of albuminuria. She was managed with steroids to reduce system inflammation and later with immunoglobulins and tumour necrosis factor to contain the disease process. Since her diagnosis and subsequent appropriate management, she has not had further admissions with cardiac tamponade 16 months of follow-up.

Discussion

The diagnosis of CLS is difficult to make unless there is a high degree of suspicion and until other causes have been ruled out. It remains a challenging condition to manage as the treatment options are limited and patients recurrently present with emergencies until the correct diagnosis is made and the optimal treatment is provided.

Keywords

Clarkson's disease • Systemic capillary leak syndrome • Pericardial effusion • Pleural effusion • Case report

Learning points

- Systemic capillary leak syndrome, a rare disease that occurs in those of middle age, is usually diagnosed after a considerable delay from onset of symptoms.
- Capillary leak syndrome should be suspected in patients with a triad of severe hypotension, hypoalbuminaemia without albuminuria, and haemoconcentration but might be absent in the setting of aggressive fluid resuscitation.
- Intravenous immunoglobulins have shown to reduce attacks and Etanercept has shown to prevent relapse in medium-term follow-up.

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Introduction

Recurrent acute pericardial and pleural effusions are rare and can signify inadequately treated underlying conditions. Capillary leak syndrome (CLS) is a rare connective tissue disease triggered by the leak of serous fluid into the interstitial spaces. Capillary leak syndrome is characterized by the hallmark of fluid collection in confined spaces such as the pericardial and pleural cavities. The main challenge in CLS management remains the diagnosis rather than its treatment. Management of CLS consists of steroids that reduce the generalized inflammation and, in some cases, pulsed monthly immunoglobulin infusions are required to contain the disease progression.^{1,2} We report a case of a 51-year-old woman with recurrent pericardial effusions resulting in tamponade requiring repeated pericardiocentesis until the diagnosis of CLS.

progressive facial swelling, leg swelling, dyspnoea, and orthopnoea. She had gained 5 kg of weight in 6 weeks. She gave a short, self-limiting history of having viral gastroenteritis 2 weeks before her onset of symptoms.

On examination, she appeared restless with blood pressure dropped from 99/63 mmHg to 93/54 mmHg, and heart rate was 90 b.p.m., respiratory rate of 20 per minute, and oxygen saturation of 96% on room air. There was generalized pitting oedema over her entire body, more pronounced over areas of dependency such as legs and lower abdomen. JVP was raised, and cardiac auscultation over the precordium revealed muffled heart sounds. Respiratory auscultation revealed air entry bilaterally, with scattered bilateral basal crackles over the lung fields. Intravenous (IV) fluid challenges were given every 15 min with no sustained improvement of the blood pressure. Urgent CXR was performed to assess lung fields, and surprisingly it showed pleural effusions and a globular heart (see [Figure 1](#)).

Timeline

04 December 2017 to 07 December 2017	A 51-year-old woman presented with dyspnoea, face, and limb swelling. Transthoracic echocardiography (TTE) showed moderate pericardial effusion. Blood test did not show specific disease pattern. Immunoglobulins, immunofixation—negative.
08 December 2017	Discharged home with out-patient follow-up in a week with repeat TTE.
13 December 2017 to 15 December 2017	Review in acute admission unit. Progressive symptoms, worsening of pleural effusions on chest x-ray. Admitted to hospital for further management. Viral serology and TB screen negative.
19 December 2017	Repeat TTE showed large pericardial effusion with haemodynamic compromise. Drained 800 mL of exudate. Computed tomography chest/abdomen/pelvis—no evidence of malignancy. Discharged home as she was haemodynamically stable.
29 December 2017 to 17 January 2018	Second admission with dyspnoea. Transthoracic echocardiography confirmed large pericardial effusion with 500 mL of exudate drained. Compliment level and carcinoembryonic antigen levels normal. Pleural tap also confirms exudate. Angiotensin-converting enzyme levels, amyloid screen negative. Bone marrow biopsy and tap normal. No infiltrative or infective diseases on cardiac magnetic resonance imaging. Discharged home on oral steroids.
18 June 2018	Cardiology follow-up with repeat TTE. Clinical improvement in symptoms and swelling.
15 August 2018	Review by immunologist in specialist centre, diagnosis of capillary leak syndrome. Advised pulsed immunoglobulins for relapse.
02 November 2018	Started on anti-tumour necrosis factor (TNF).
23 April 2019	Off steroids, on anti-TNF therapy Etanercept, TTE showed reduction in pericardial fluid (posterior wall 1 cm, right ventricular free wall 1.1 cm).
28 June 2019	On weekly Etanercept therapies, there is minimal pericardial effusion and no relapse of generalized oedema.

Case presentation

A 51-year-old woman, with a past medical history of Type 1 diabetes mellitus, presented to the hospital with a 2-week history of

Transthoracic echocardiography (TTE) showed global pericardial effusion with a maximum of 2.9 cm around the apex and anterior left ventricular (LV) wall ([Figure 2](#)). There was a collapse of the right

atrium and ventricle along with transvalvular Doppler velocities consistent with tamponade. Left ventricular ejection fraction was greater than 55%. An inotropic support for temporary improvement was considered but she appeared stable enough for urgent pericardiocentesis to be performed safely. Pericardiocentesis drained 500 mL of blood-stained exudative fluid (serum protein: fluid protein > 0.5) with numerous white blood cells. Blood pressure rebounded quickly to 143/76 mmHg and stabilized with range between 106/72 mmHg and 118/76 mmHg over the next 24 h. No organisms or malignant cells were identified in the fluid. Admission blood tests did not show a remarkable abnormality including haematocrit of 0.48 (0.36–0.47 L/L). These tests included complete blood count, urea and electrolytes, liver function tests, thyroid function tests, brain natriuretic peptide, cortisol, C-reactive protein (CRP), alpha-1 antitrypsin, and ESR. Viral serology including hepatitis and HIV screening was negative except

for Varicella zoster immunoglobulins (IgG antibodies) which were deemed positive.

Cardiac magnetic resonance imaging ruled out structural heart disease and myocardial infiltration with LV thickness less than 10 mm with no signs of inflammation. The computed tomography chest/abdomen/pelvis did not show any cause of presentation or evidence of malignancy. Ultrasound of the kidneys showed both kidneys to have a regular outline and consistency measuring 10 cm in bipolar length. Nephrotic syndrome was excluded with healthy protein–creatinine ratio. There was no evidence to suggest renal or intestinal losses of protein.

The patient was readmitted within 15 days with the same presentation. A pleural tap was negative for *Mycobacterium tuberculosis* bacteria and did not reveal any diagnosis during microbiology and cytology analysis. A TTE showed accumulation of pericardial effusion with features of cardiac tamponade. Urgent pericardiocentesis drained more than 500 mL of exudative fluid. An autoimmune panel was requested to assess for features to support the diagnosis of CLS. ANA was weakly positive in low titres of <400. Monoclonal antibodies, serum paraproteins, and protein electrophoresis excluded myeloma. Autoimmune and complement factors were in normal range. Amyloidosis was ruled out after a bone marrow biopsy was performed. Negative blood cultures, pericardial fluid cultures, urine cultures, and maximum CRP of 37 mg/L (<10 mg/L) excluded infectious source of her presentation.

A diagnosis of CLS was established based on hypoalbuminaemia without albuminuria, hypovolaemic shock without causal evidence. Her blood pressure readings at previous doctor office visits were in the normal or mild hypertensive range. The acute deterioration was due to cardiac tamponade and due to systemic state of hypovolaemia supported by higher haematocrit.

The patient showed improvement in blood pressure to 138/78 mmHg with resolution of her oedema on IV methylprednisolone 1 g for 2 days and switched to oral prednisolone 40 mg o.d. Any effort to wean the steroids down led to reaccumulating pericardial and pleural effusions. Monthly IV immunoglobulins at dose of 1 mg/kg

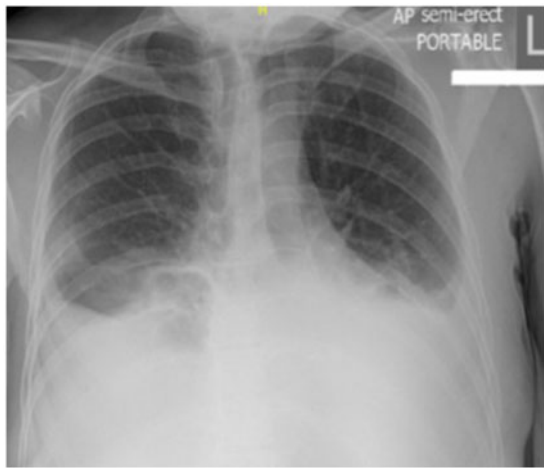


Figure 1 Chest X-ray in AP showing bilateral pleural effusions.

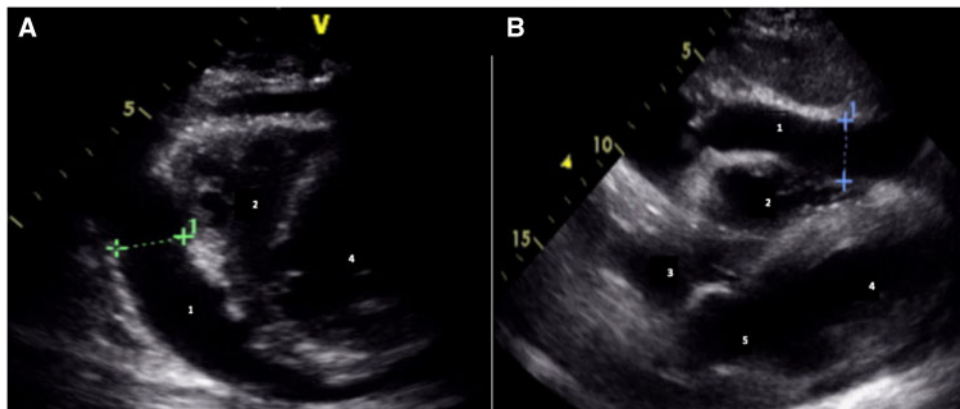


Figure 2 Parasternal short axis (A) and subcostal view (B) showing features of cardiac tamponade during early diastolic phase. Pericardial effusion measuring 2.9 cm (1), collapsed right ventricle (2), compressed right atrium (3), left ventricle (4), and left atrium (LA).

were arranged following her second admission to minimize reaccumulating fluid and albumin into interstitial spaces.

She was reviewed three monthly for the first year following her initial presentation and has remained haemodynamically stable with no further hospital admission. Her repeat TTE showed persistent global pericardial effusion with maximum accumulation around the right ventricle at 1 cm with no haemodynamic compromise. Since the IV immunoglobulins (IVIG) did not resolve the pericardial effusion, she was commenced on tumour necrosis factor (TNF) alpha inhibitor (Etanercept) to prevent disease recurrence at a dose of 50 mg subcutaneous injections once a week. On follow-up over 7 months, there has been no relapse of CLS or accumulation of pericardial effusion on echocardiograms.

Discussion

Capillary leak syndrome or Clarkson's disease is a rare connective tissue disorder with approximately 300 reported cases worldwide. Dr Clarkson reported the first case in 1960 with loss of plasma from vascular bed resulting in cyclical oedema and shock.² It is potentially a fatal condition with attacks of varying intensity of hypovolaemic shock with raised haematocrit, generalized oedema with no albuminuria.¹ The exact mechanism of permeability in CLS remains unclear with several proposed hypotheses but lacking substantial evidence.^{3,4} Endothelial apoptosis, a possible mechanism during an acute attack, is supported by histological evidence of micro-vesicular body and bleb formation.⁵ Inflammatory mediators such as TNF-alpha, interleukin IL-2, and VEGFs (vascular endothelial growth factors) are thought to cause endothelial cell disruption and cell retraction altering cells permeability.⁶⁻⁸ The role of paraproteins, including monoclonal antibodies remains controversial in diagnosis although their levels rise in the acute phase with levels plummeting during remission.⁹

There are three phases described in the clinical spectrum of CLS; prodromal phase, leak phase, and post-leak phase.² Our patient reported all three phases. The prodromal phase consists of complaints varying in frequency and severity of fatigue, abdominal pain, nausea, myalgia, and weight gain. Thirty percent of the patients report viral or upper respiratory tract infection.¹⁰ Leak phase is characterized by leaking of capillary network with resultant intravascular hypovolaemia, and post-leak phase is characterized by reabsorption of the fluid back to the intravascular compartment resulting in pulmonary oedema. The response to the treatments shown to be variable and usually depends on how early the diagnosis is suspected. Patients with delay in diagnosis or those who have advanced complications from CLS have a poor prognosis. Serious complications include renal failure, rhabdomyolysis, compartment syndrome, neuropathy, pulmonary oedema, pleural effusions, pericardial effusion, cardiac tamponade, stroke, and multiorgan failure.³

The mainstay of treatment involves acute treatment to reduce systemic hypotension, reduce the inflammatory response, and support vital organ perfusion. This acute treatment includes oxygen replacement monitoring intravascular volume and perfusion of vital organs (urine output, neurology, liver function, and cardiac ischemia) using IV crystalloids fluid, steroids, IVIG, and early intervention of inotropic support.^{3,11} The aggressive fluid resuscitation can lead to relative haemodilution and normalization of haematocrit that can mislead the

diagnosis. The transition from the leak to post-leak phase needs early recognition to prevent intravascular overload and may require diuretics.

Prevention of relapses is by maintaining a stabilized immunomodulatory response by using immunoglobulins, oral steroids, and methylxanthines individually or in combination.¹¹ Terbutaline and theophylline prophylaxis increase the c-AMP, and inhibits rho-kinase pathways have been most effective in keeping remission.^{12,13} These drugs were excluded from the treatment due to local policies in availability. Leukotrienes inhibitors, immunomodulation, anti-VEGF, and TNF-alpha inhibitors have varying success.^{6,14,15}

Conclusion

In summary, we report a case of CLS presenting with recurrent cardiac tamponade, requiring drainage on two occasions. The diagnosis was based on sign and symptoms with no apparent cause identified, and a favourable initial response to steroids was observed. A trial of immunosuppression with anti-TNF Etanercept was provided while reducing steroids and although a small pericardial effusion remains, no further drainage of the pericardium has been necessary. On follow-up of 8 months after starting Etanercept, there was no relapse of CLS.

Lead author biography



Dr Habib R. Khan graduated from University of Peshawar, Pakistan in 2002. After completing resident training, he trained in medicine in Ireland and obtained MRCP Ireland and UK. He trained in Cardiology from 2008 till 2018 in East Midlands deanery. He is certified by European Examination in General Cardiology and Cardiac Rhythm Management certification in Devices by British Heart Rhythm Society. He is currently a PhD student (2015 to present) at the prestigious National Heart and Lung Institute—Imperial College London and at the writing thesis stage. In 2019, he started further training in Cardiac Rhythm Management at London Health Sciences Centre, Canada. Dr Khan regularly publishes in field of cardiovascular medicine.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: H.R.K. is an associate editor for EHJ-CR. All other authors have declared no conflict of interest.

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