

Systemic capillary leak syndrome after granulocyte colony-stimulating factor (G-CSF)

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Capillary leak syndrome (CLS) commonly occurs in the intensive care setting. CLS is seen in conditions such as septic shock or may result from conditions such as multitrauma and pancreatitis, which result in the systemic inflammatory response syndrome (SIRS). We present two cases in which both patients suffered with CLS, which we believe was caused following administration of granulocyte colony-stimulating factor, to our knowledge not described in the intensive care patient previously. We discuss how these patients management differs from other intensive care unit patients with CLS and how it is important to diagnose this condition early in haematological oncology cases.

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Introduction

With capillary leak syndrome (CLS) the clinical findings of weight gain, generalized oedema, hypotension, prerenal failure, ascites and pericardial/pleural effusions are caused by loss of intravascular fluid into the interstitial space.¹ Oedema formation is a result of a high hydrostatic gradient, a low colloid osmotic gradient or a low reflection coefficient.² CLS has been reported after infusions of interleukin-2,³ tumour necrosis factor⁴ and granulocyte-stimulating factor.⁵ In the intensive care setting, CLS is a frequent complication in septic shock.⁶ We present two cases, where both received high-dose chemotherapy followed by rescue therapy with (G-CSF), which is routinely used to shorten the period of myelosuppression following intensive chemotherapy.⁷

Case reports

Case 1

A previously well 57-year-old male was diagnosed with IgG κ myeloma in December 2000. He initially underwent six courses of VAD, and in March 2001 was admitted to the intensive care unit (ICU) with pneumonia, which was successfully treated with continuous positive pressure airway pressure (CPAP) and anti-

biotics, although all microbiological cultures taken were negative. In April 2001, a bone marrow biopsy showed less than 50% plasma cell infiltrates with decreased paraproteins. In June 2001, he received two more chemotherapy courses, the second being cyclophosphamide 2 gm/m² for stem cell collection and G-CSF 300 mcg/m², which we refer to as day 1. On day 6, the dose of G-CSF was doubled for treatment of neutropenic sepsis and to facilitate adequate CD34 numbers. On day 8, a vasculitic rash developed and a G-CSF-induced leucocytoclastic vasculitis was diagnosed following skin biopsy. In addition, he developed respiratory distress, hypotension and oliguria, was very oedematous with pyrexia greater than 39°C and had a leucocytosis of 56 × 10⁹/l with warm dilated peripheries. This deterioration in his condition led to his admission to ICU on day 9. Despite aggressive vascular expansion with crystalloid, he required a noradrenaline infusion to maintain a mean arterial pressure (MAP) of >70 mmHg. CPAP treated his hypoxia and multiple cultures were taken in ICU and his antimicrobial and antifungal cover (ambisome, ceftazidime and vancomycin) was discontinued, as previous cultures were negative. He commenced enteral nutrition to assist improvement in his hypoalbuminaemia. He was successfully treated with intravenous methyl prednisolone 500 mg twice daily (reduced over a 2 week period) and organ support in ICU, including full ventilation, tracheostomy and inotropic support. He was discharged from ICU on day 22. He is alive and well and on maintenance thalidomide treatment 12 months later.

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Case 2

A previously well 37-year-old male was diagnosed with chronic myeloid leukaemia (CML) in January 1998. He was initially managed with leucopheresis and hydroxyurea. After 3 months this was changed to interferon, which achieved a normal blood profile for the subsequent year. Cytosine arabinoside (ARA-C), then had to be added. At 2 years after initial diagnosis, he entered the accelerated phase of CML, which was treated with STI 571. At 8 months later (3 years postoriginal diagnosis) he relapsed into blastic transformation. A planned matched unrelated donor transplant with cyclophosphamide and total body irradiation with possible additional radioisotope-conjugated antibody was then considered. He started fludarabine, cytosine, arabinoside, idarubicin (FLAG-Ida) and G-CSF (dose 300 mcg/m²) from day 1. On Day 3 his WCC increased to $72 \times 10^9/l$ and hydroxyurea was restarted. On day 4 he was noted to be anuric, oedematous, hypotensive and had features of sepsis. Acute renal failure developed and bullous skin lesions appeared on the left shoulder. There was marked oedema so he was venesected and transfused with 20% albumin. Methyl prednisolone was started on day 5 for presumed pyoderma gangrenosum and the G-CSF stopped as per protocol. All cultures were negative apart from an ear swab, which grew pseudomonas. He was treated empirically with vancomycin, erythromycin and ceftazidime, and in addition had been receiving ambisome three times a week as he had had problems with fungal infections in the past. Review by the intensive care physician revealed acute renal failure with gross peripheral oedema. Oxygen saturation was 92% on air, BP 100/68 and HR 110. He received aggressive fluid resuscitation for his renal failure, which had no effect. He was admitted to ICU with a presumed diagnosis of necrotising fasciitis, but death supervened on day 13 despite haemodialysis and invasive respiratory support.

Discussion

The postulated adverse consequences of oedema are gas exchange across the alveolar capillary membranes of the lungs and the potential for reduced diffusion of micronutrients to metabolizing tissue. The differential diagnosis for the causes of the clinical features of weight gain, generalized oedema, hypotension, prerenal failure, ascites and pericardial/pleural effusions are numerous. Septicaemia is highly likely in both these cases described above, although we failed to culture any organisms in case 1, while in ICU. Systemic inflammatory response syndrome (SIRS)⁸ is a response to a variety of clinical insults. These include vasculitis as with case 1. CLS has been previously reported in association with multiple myeloma⁹ and following G-CSF mobilization and collection of peripheral blood progenitor cells for allogeneic transplantation.¹⁰ To our knowledge, this has not been described following G-

CSF used in these circumstances in patients admitted to intensive care.

Large volumes of crystalloid will expand the interstitial space, although these need to be given to maintain the intravascular volume. Both the cases received large volumes of crystalloid. A poor nutritional state with reduced albumin would ensure a low colloid osmotic pressure (COP) and subsequent oedema, as explained below.

The avoidance of tissue oedema formation can be predicted by the Starling equation:¹¹

$$J_v = K_f[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

where J_v is the fluid flow across the capillary wall, K_f - the capillary filtration coefficient, a constant determined by the properties and surface area of the capillary, $(P_c - P_i)$ the hydrostatic pressure gradient across the capillary wall, $\sigma(\pi_c - \pi_i)$ the colloid osmotic gradient across the capillary wall and σ the reflection coefficient, a factor between 0 and 1, representing the proportion of colloid particles reflected back from the capillary wall on presentation (0 is no molecules reflected and 1 is when all molecules are reflected).

The mechanism for capillary leak is because of a low reflection coefficient, which most usually relates to an increased size of the transcapillary transport passages by endothelial cell contraction. These can either be from ischaemic-reperfusion or endotoxin-induced capillary leak, or from intracellular mechanisms of endothelial damage.² Figure 1 demonstrates the processes described by Starling. Figure 2 shows the mechanism of CLS.

Evaluation of noninvasive determinates for capillary leakage syndrome in septic patients was carried out by Marx.⁶ The results suggest that measurements of increased extracellular water using bioelectrical impedance analysis combined with a different response of colloid osmotic pressure to administration of albumin can discriminate noninvasively between patients with and those without CLS. However, this is not utilized in routine intensive care practice.

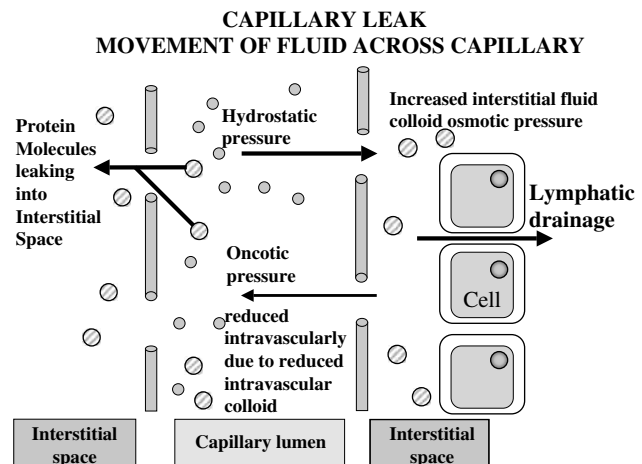


Figure 1 Movement of molecules and fluid in normal tissue.

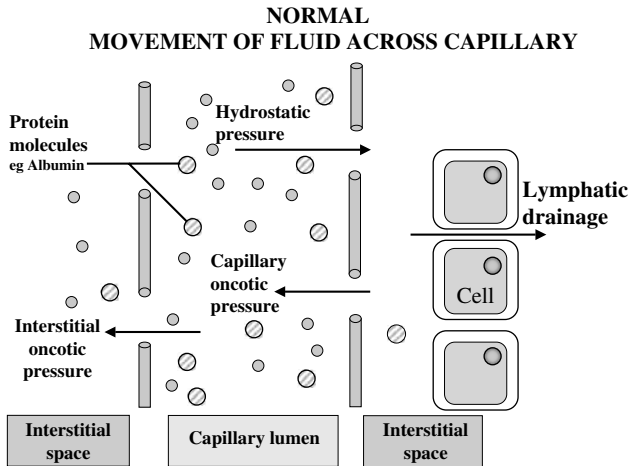


Figure 2 Movement of molecules and fluid in CLS.

The mainstay of the management of CLS is supportive with an emphasis on trying to stop the process stimulating the capillary leak. We believe that both the

cases described had CLS from the rare, but previously reported administration of G-CSF in nonintensive care patients. The successful outcome of case 1 may have been because of the fact that the process driving the CLS, namely the leucocytosis from the G-CSF, was arrested by the use of high-dose methyl prednisolone. Although our cases did not get as far as becoming recipients of bone marrow transplants (BMT), it must be remembered that BMT recipients who require mechanical ventilation have an appalling outcome when admitted to intensive care.¹²

In conclusion, if capillary leak syndrome is diagnosed during G-CSF treatment intensive supportive measures should be instituted, the leucocytosis treated aggressively and any infection present identified and eliminated effectively to maximize chances of survival.

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References

- 1 Teelucksingh S, Padfield PL, Edwards CR. Systemic capillary leak syndrome. *Q J Med* 1990; **75**: 515–524.
- 2 Webb AR. Capillary leak pathogenesis and treatment. In: Braschi A, Gattinoni L, Pesenti A, Raimondi F (eds). *Simposio mostra anestesia rianimazione e terapia intensiva*. Milan: Minerva Anestesiologica, 24–26 March 2000.
- 3 Rosenstein M, Ettinghausen SE, Rosenberg SA. Extravasation of intravascular fluid mediated by the systemic administration of recombinant interleukin 2. *J Immunol* 1986; **137**: 1735–1742.
- 4 Remick D, Kunkel R, Larrick J, Kunkel S. Acute *in vivo* effects of human recombinant tumour necrosis factor. *Lab Invest* 1987; **56**: 583–590.
- 5 Oeda E, Shinohara K, Kamei S, Nomiya J, Inoue H. Capillary leak syndrome likely the result of granulocyte colony-stimulating factor after high-dose chemotherapy. *Intern Med* 1994; **33**: 115–119.
- 6 Marx G, Vangerow B, Burczyk C, Gratz K, Maassen N, Cobas Meyer M *et al*. Evaluation of noninvasive determi-
- nants for capillary leak syndrome in septic shock patients. *Inten Care Med* 2000; **26**: 1252–1258.
- 7 Metcalf D. The granulocyte-macrophage colony-stimulating factors. *Science* 1985; **229**: 16–22.
- 8 Bone RC, Sprung CL, Sibbald WJ. Definitions for sepsis and organ failure. *Crit Care Med* 1992; **20**: 724–726.
- 9 Hiraoka E, Matsushima Y, Inomoto-Naribayashi Y, Nakata H, Nakamura A, Kawanami C *et al*. Systemic capillary leak syndrome associated with multiple myeloma of IgG kappa type. *Intern Med* 1995; **34**: 1220–1224.
- 10 de Azevedo A, Goldbery Tabak D. Life-threatening capillary leak syndrome after G-CSF mobilization and collection of peripheral blood progenitor cells for allogeneic transplantation. *Bone Marrow Transplant* 2001; **28**: 311–312.
- 11 Hinds C, Watson D. *Intensive Care. A Concise Textbook*, 2nd ed. London, Philadelphia, Toronto, Sydney, Tokyo: Saunders, 1996.
- 12 Denardo SJ, Oye RK, Bellamy PE. Efficacy of intensive care for bone marrow transplant patients with respiratory failure. *Crit Care Med* 1989; **17**: 4–6.