Systemic capillary leak syndrome as a prodrome of extranodal natural killer (NK)/T-cell lymphoma

B. Hodossy, MD[1], I. Vrelust, MD[1], S. Anguille, MD[1], V. Van Marck, MD, PhD[2], M. Maes, PharmD, PhD[3], K. Vermeulen, PhD[3], A. Van de Velde, MD[1], A. Gadisseur, MD, PhD[1], W. Schroyens, MD, PhD[1], Z. Berneman, MD, PhD, FRCP[1]

We present the case of a 58-year-old male patient with a long-standing, intermittent oedema of the lower extremities and significant spontaneous variations in haematocrit values. Repeated examinations failed to reveal a clear etiology until the patient suffered from a severely painful exacerbation of leg oedema and hypotension. Laboratory analysis showed hypoalbuminemia. The combination of oedema, hypotension, hypoalbuminemia and hemoconcentration was indicative of a systemic capillary leak syndrome. This condition is known to be associated with monoclonal gammopathy, as was the case in our patient. New investigations showed suspicious lesions in the nasopharynx, scrotum and breast. Biopsies of this breast mass as well as bone marrow biopsy showed the presence of an extranodal natural killer/T-cell lymphoma, nasal type. Polychemotherapy was administered according to the SMILE schedule leading to a remission after two cycles. The patient then underwent autologous hematopoietic stem cell transplantation. The patient is currently without signs of systemic capillary leak syndrome. This report illustrates that systemic capillary leak syndrome may occur as a prodrome of haematological malignancies, such as natural killer/T-cell lymphoma and documents that it is responsive to chemotherapy.
(Belg J Hematol 2014;5(4):148-53)

Introduction

Systemic capillary leak syndrome (SCLS), first described by Clarkson et al. in 1960, is a rare potentially life-threatening disorder characterised by episodic increases in capillary permeability causing fluid shifting from the intravascular to the extravascular compartments.[1,2] The classical clinical picture of SCLS consists of recurrent attacks of oedema and hypotension.[3] Attacks of SCLS vary in frequency, severity and duration. Because of non-specific presentation, SCLS may significantly be underdiagnosed. Hemoconcentration and hypoalbuminemia are the cardinal laboratory findings of this disorder.[3] Another laboratory abnormality commonly observed in patients with SCLS is monoclonal gammopathy.[4] Within this context, a growing body of evidence has pointed to an association between SCLS and plasma cell dyscrasias such as multiple myeloma.[5,6] We describe a patient in whom the diagnosis of SCLS was associated with and preceded the diagnosis of an extranodal natural killer (NK)/T-cell lymphoma, nasal type.

Case report

A 58-year-old man of Georgian origin was admitted with excruciatingly painful oedema in both legs and hypotension. This lower limb pain and oedema, already present since two years, had been gradually worsening in intensity. The recurrence of episodes led to regular large-scale radiological, endoscopic and laboratory investigations, without an underlying cause.

[1]Department of Haematology, [2]Department of Pathology, [3]Department of Clinical Biology, Antwerp University Hospital (UZA), Edegem, Belgium.
Please send all correspondence to: B. Hodossy, MD, Antwerp University Hospital (UZA), Department of Haematology, Wilrijkstraat 10, 2650 Edegem, Belgium, tel: +32 3 8213363, fax: +32 3 8214286, email: beata.hodossy@uza.be.

Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: extranodal natural killer (NK)/T-cell lymphoma, monoclonal gammopathy, prodrome of haematological malignancy, systemic capillary leak syndrome.

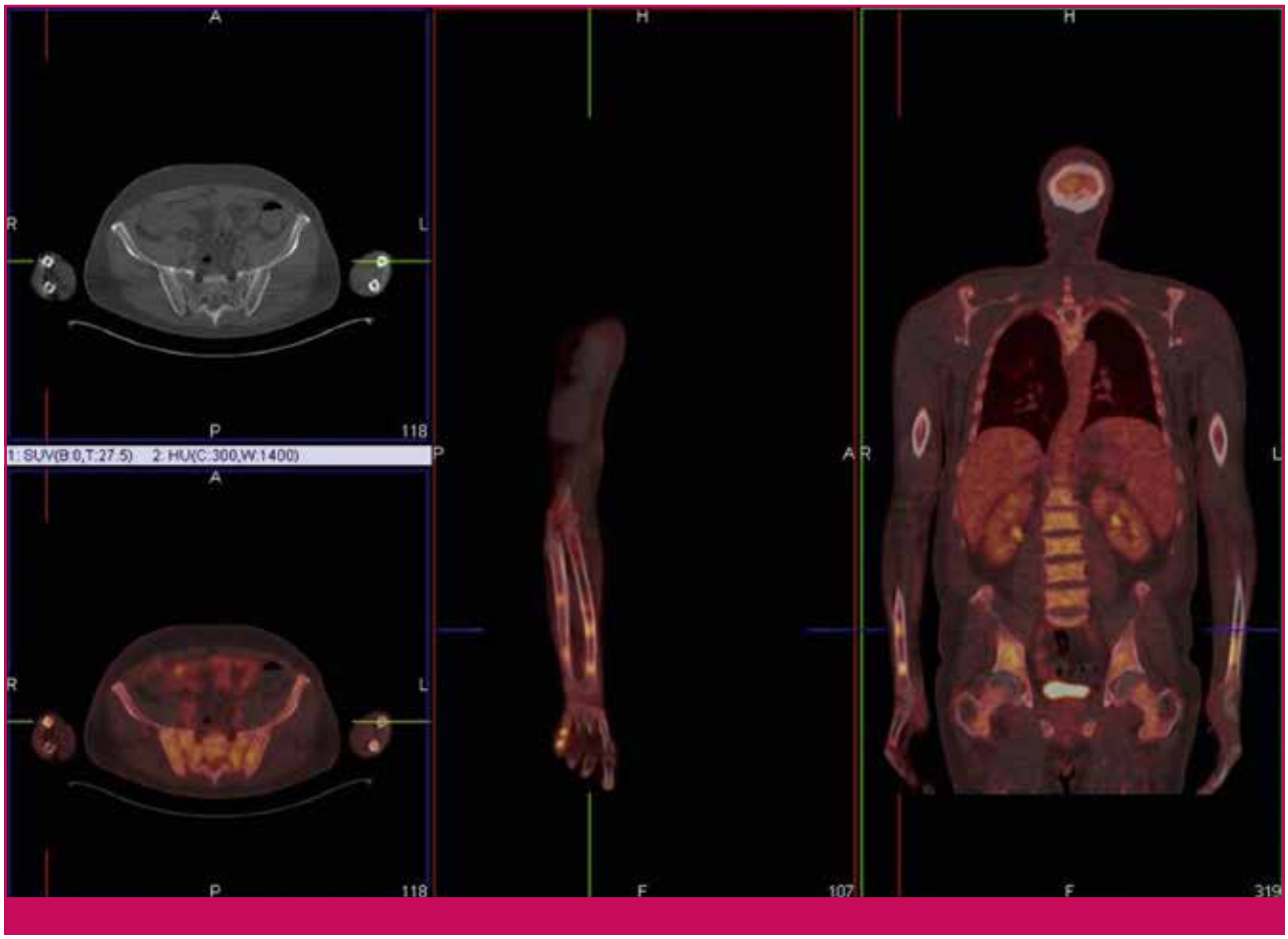

Figure 1A. Pierre-Marie-Bamberger-like picture with hypercaptation of the tubular bones on PET scan.

In past medical history there was only a single episode of seizures and arterial hypertension. In December 2011, the patient was noted to have a mass involving the right parotid gland with hypercaptation on positron emission tomography (PET) scan. Repeated examination of this lesion failed to disclose any malignancy and only yielded a positive culture for Candida glabrata. The right parotid gland lesion disappeared after two months of antifungal therapy and antibiotics. During the same period, the patient experienced an atypical thoracic pain accompanied by a mild hypotension. A percutaneous coronary catheterisation was normal. The haematocrit fluctuated within two days from 33.1 to 40.2 %, an increase of 21.5%.

In October 2012, the patient was hospitalised with a severe exacerbation of oedema in both legs for several days. On admission, physical examination revealed a hemodynamically unstable patient with a blood pressure of 70/50 mmHg, a heart rate of 90 per minute, a body temperature of 36.5°C and markedly oedematous lower extremities. Laboratory analysis revealed a leucocyte count of $1.5x10^9$/L, a platelet count of $28x10^9$/L and a haemoglobin concentration of 7.9 g/dL. Liver and kidney function tests were normal. Serum protein electrophoresis showed hypoalbuminemia (2.0 g/L) and for the first time monoclonal gammopathy, with a main IgG lambda monoclonal band. The diagnosis of SLCS was considered on the basis of the characteristic clinical (oedema and hypotension) and laboratory findings (hemoconcentration on previous occasion, hypoalbuminemia and monoclonal gammopathy). Fluid administration was insufficient to reverse hypotension and the patient received vasopressors at the intensive care unit. Whole body PET/CT imaging showed a 'Pierre-Marie-Bamberger'-like pattern, which is characterised by a periosteal reaction of the tubular bones (*Figure 1A*). Although this condition can be associated with bronchial carcinoma, no evidence for it was found. PET/CT also demonstrated hypercaptation of the nasopharynx, ethmoid sinus, right scrotum and subcutaneous tissue of the left breast (*Figure 1B and 1C*). Biopsies from the latter site showed infiltration with atypical lymphoid cells exhibiting an immunophenotype compatible with the

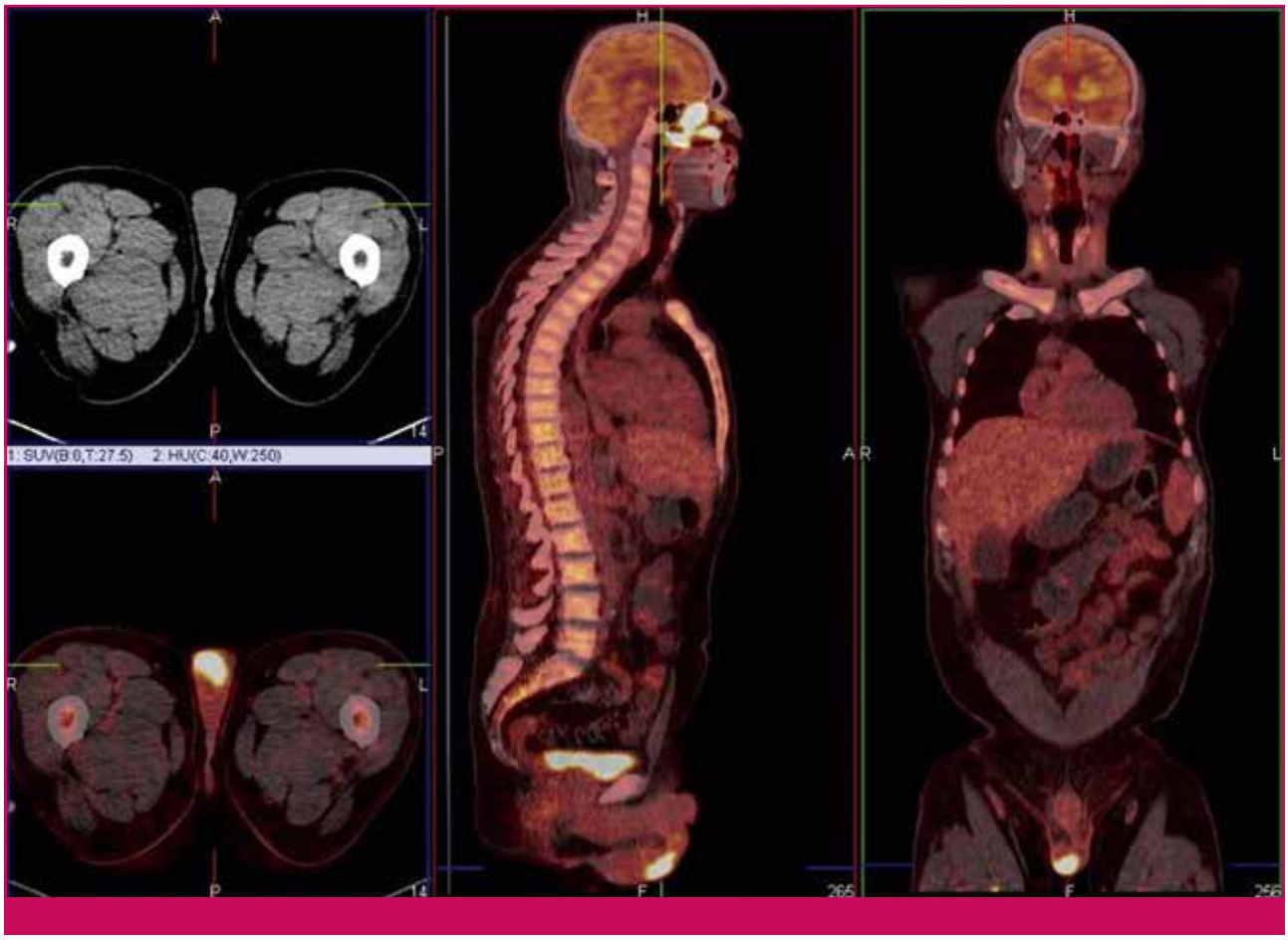

Figure 1B. Hypercaptating PET scan lesions at nasopharynx, ethmoid sinus and right scrotum.

diagnosis of an extranodal NK/T-cell lymphoma, nasal type (CD2+, (cytoplasmic) CD3+, CD56+, TIA-1+, CD30-) (*Figure 2*). Similar findings were made in the bone marrow biopsy, in particular with regard to CD2 and CD56 positivity (*Figure 3*); the aberrant lymphoid cells were negative for surface CD3. T-cell receptor gene rearrangement analysis on bone marrow revealed a monoclonal band in a polyclonal background. Serology showed IgG but not IgM antibodies to Epstein-Barr virus (EBV) with a high antigenemia of that virus (4.77 x 10^5 copies/mL), compatible with the strong association of EBV with extranodal NK/T-cell lymphoma, nasal type. Chemotherapy was started, according to the SMILE schedule (d1: methotrexate 2000 mg/m^2, d2-4: folinic acid rescue, dexamethasone 40 mg daily, ifosfamide 1500mg/m^2 daily (with Mesna protection), etoposide 100 mg/m^2, six injections of E. Coli L-asparaginase 6000 U/m^2 (1^{st} cycle) and nine injections of Erwinase 20000 U/m^2 (2^{nd} cycle)).[7] The PET scan lesions and SCLS symptoms disappeared, EBV antigenemia decreased to <500 copies/ml and blood cytology normalised. The patient then underwent autologous hematopoietic stem cell transplantation (HSCT) following a BCNU, etoposide, arabinoside-C and melphalan (BEAM) conditioning. The monoclonal gammopathy and EBV antigenemia disappeared following HSCT.

Discussion

Our patient was diagnosed with an extranodal NK/T-cell lymphoma, nasal type after a long-standing unexplained SCLS. Nasal type extranodal NK/T-cell lymphoma is a rare form of non-Hodgkin lymphoma most common among middle-aged Asian men.[8] The primary sites of involvement are the nasopharynx, sinuses and palate, although 'extranasal' sites may also be involved (e.g. skin, soft tissues, testis).[8] The pancytopenia was due to bone marrow involvement by the lymphoma, which is seen in approximately 10% of patients with nasal type extranodal NK/T-cell lymphoma.[8]

The classical clinical picture of SCLS is one of recurrent episodes of oedema and hypovolemic hypotension.[1] Our patient had a more chronic course with painful leg oedema being the most prominent feature. Such chronic forms of SCLS, which often lack the typical 'cyclic'

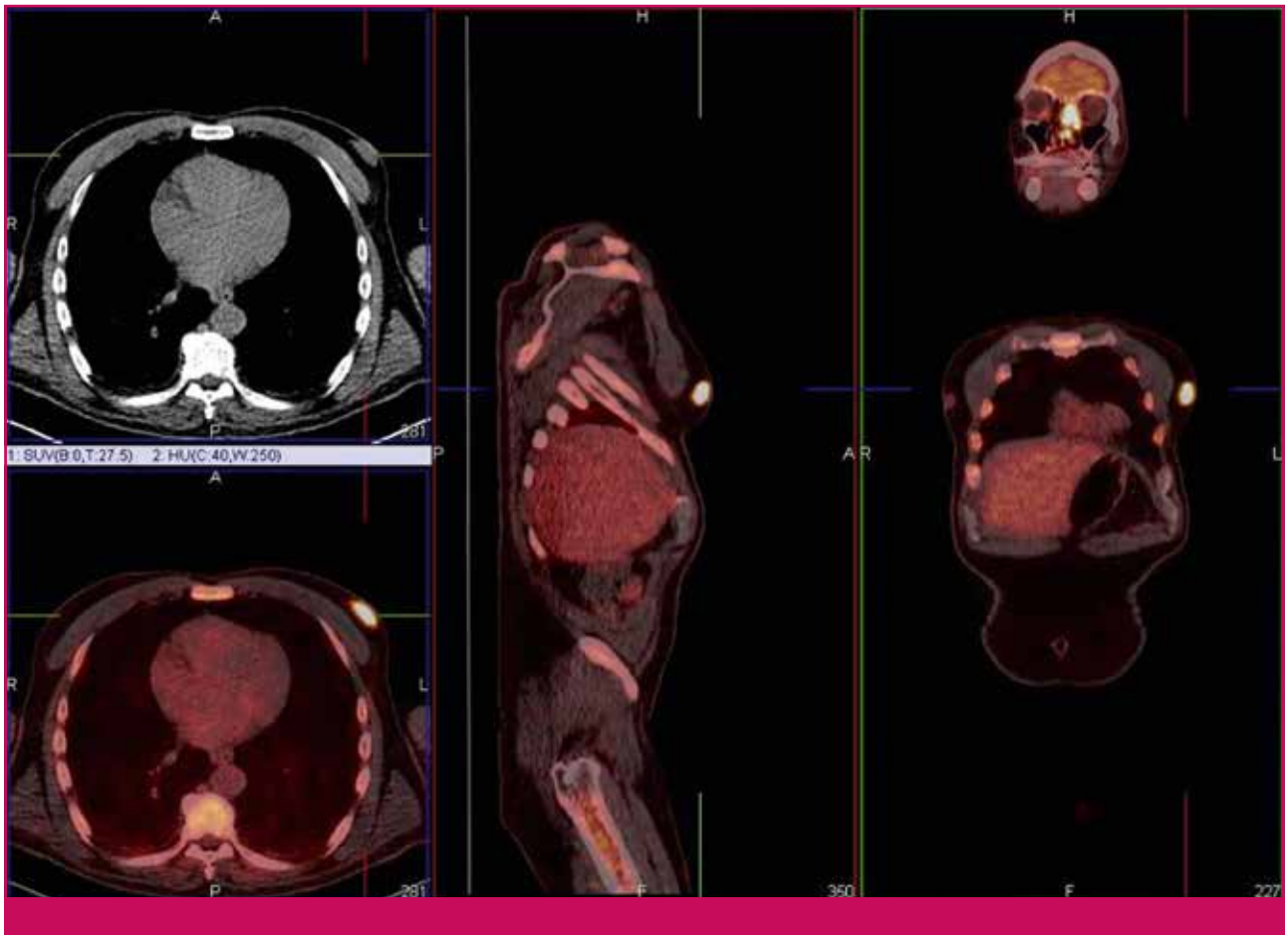

Figure 1C. Hypercaptating PET-scan lesion at left breast with histological presence of a NK/T-cell lymphoma.

occurrence of oedema and overt hypotension, have been described in the literature.[2] We first suspected the diagnosis of SCLS in our patient when he presented with marked oedema of the legs and hypotension. This suspicion was further raised after exclusion of other, more common, causes of anasarca and hypotension, such as congestive heart failure, chronic liver disease, nephrotic syndrome and enteropathy.[3] Four diagnostic criteria have been established to consider a diagnosis of SCLS: oedema, hypovolemic hypotension in the absence of an alternative diagnosis, hemoconcentration and hypoalbuminemia without albuminuria.[3] Our patient fulfilled all diagnostic criteria. The presence of monoclonal gammopathy is not considered a mandatory diagnostic criterion, but further strengthens the diagnosis of SCLS.[3]

To the best of the authors' knowledge, this is the first report of the association between extranodal NK/T-cell lymphoma, nasal type and SCLS. Despite being an extremely rare condition, SCLS has been previously reported in relation with other types of non-Hodgkin lymphomas, plasma cell disorders and solid malignancies (e.g. breast carcinoma).[6,9-14] In some of these cases and similar to what is described here, SCLS preceded the diagnosis of the malignancy.[5,10-13] SCLS can also occur following anti-neoplastic treatment (e.g. interleukin-2, bortezomib, gemcitabine) or G-CSF administration.[12,15-17] It is important to mention that most patients with SCLS were found to have a monoclonal gammopathy, which has been suggested to play a pathogenic role in this syndrome.[2,4,18] Support for this hypothesis comes from the observation that a reduction of paraprotein levels in myeloma patients with SCLS is associated with remission of SCLS.[5,19] Furthermore, cytotoxic lymphocytes are thought to play a pivotal role in the etiopathogenesis of SCLS by causing direct endothelial injury, further strengthening the link between SCLS and lymphoid malignancies.[12] The role of different inflammatory cytokines, including tumour necrosis factor (TNF)-α, as mediators of SCLS has been examined but remains unclear at present.[2] A diagram for the clinical physiopathology of SCLS has been published elsewhere.[2] Symptomatic treatment of SCLS, especially with ami-

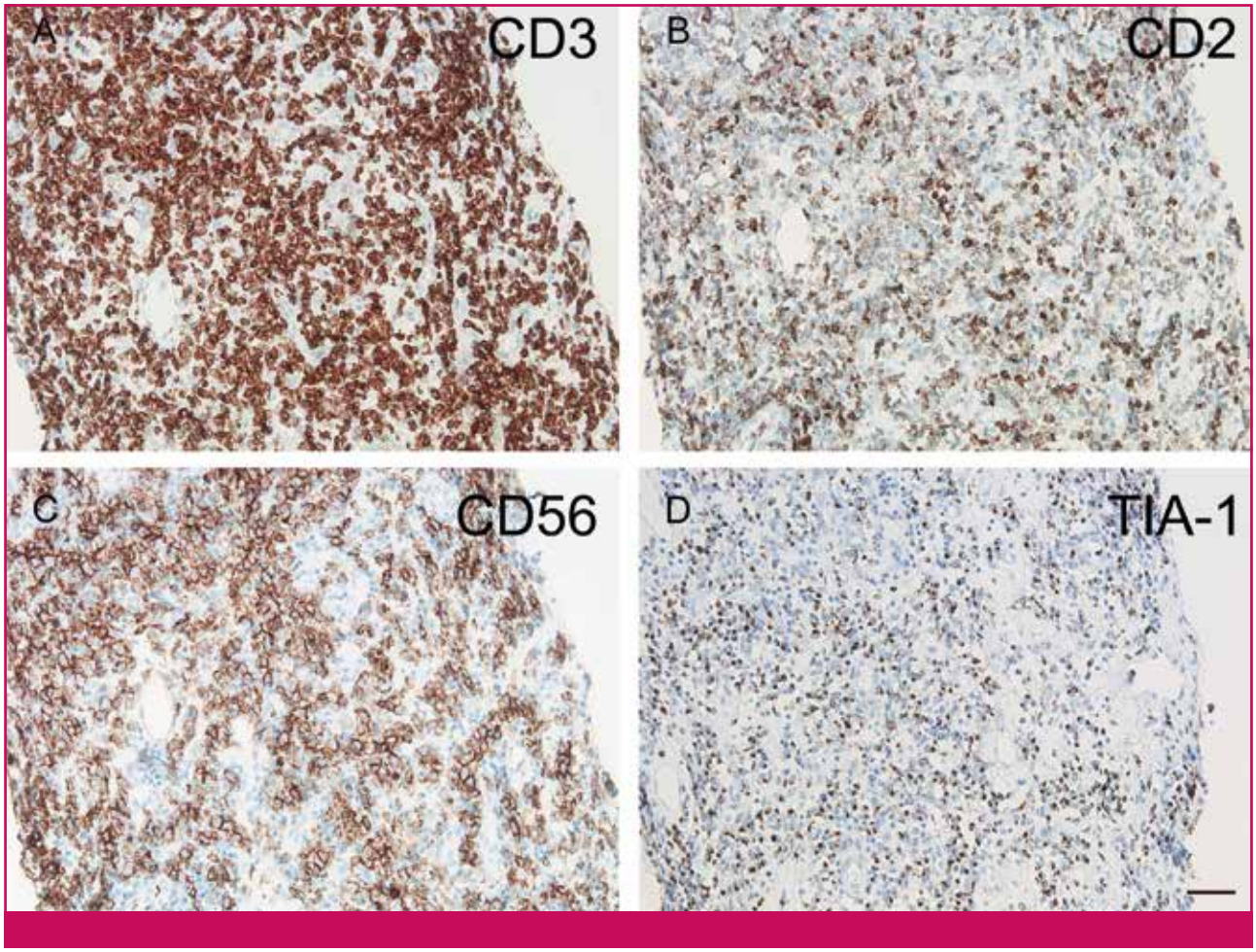

Figure 2. Needle biopsy from subcutaneous mass in the left breast, histologically processed. Photomicrographs of representative immunohistochemically stained sections, showing a diffusely infiltrating population of (cytoplasmic) CD3 positive lymphoid cells (A), of which large proportions show co-expression of CD2 (B), CD56 (C) and TIA-1 (D). *Bar*: 50 µm.

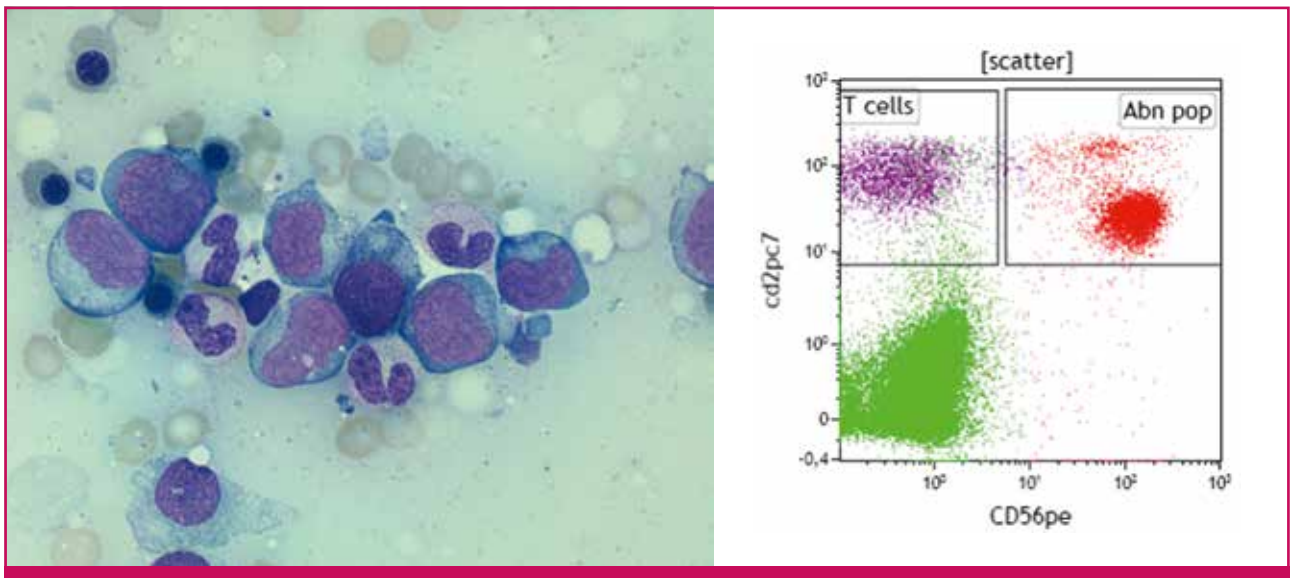

Figure 3. Bone marrow aspirate. Left: A population of abnormal lymphoid cells with irregularly folded nuclei with multiple clear nucleoli and basophilic cytoplasm with a perinuclear halo. Right: Flow cytometry revealed a CD2+CD7-CD25+ CD56+ phenotype, fitting the diagnosis of NK/T-cell lymphoma.

Key messages for clinical practice

1. The hallmark laboratory features of systemic capillary leak syndrome are hemoconcentration, hypoalbuminemia and monoclonal gammopathy.
2. Oedema and hypotension due to systemic capillary leak syndrome can be the presenting symptom of non-Hodgkin lymphoma or other haematological malignancies.
3. Although rare, the possibility of systemic capillary leak syndrome should be considered in a patient with oedema in whom more common causes are excluded.

nophylline and terbutaline, has been reported.[5] In our case, hydration only had limited success. The SCLS symptoms only resolved following SMILE chemotherapy, which has an appreciable success rate for extranodal NK/T-cell lymphoma, nasal type.[7] This scheme includes L-asparaginase, but it is impossible to distinguish the effect of that compound from other chemotherapeutic agents in controlling the SCLS. The autologous HSCT was performed as a consolidation treatment for the high-risk NK/T-cell lymphoma, with the purpose of avoiding or delaying relapse of the lymphoma and SCLS. In conclusion, this case report illustrates that SCLS can be associated, and in some cases even heralds, an underlying haematological malignancy such as an extranodal NK/T-cell lymphoma and that it can be brought under control by treating the tumour.

References

1. Clarkson B, Thompson D, Horwith M, et al. Cyclical oedema and shock due to increased capillary permeability. Am J Med. 1960;29:193-216.
2. Druey KM, Greipp PR. Narrative review: the systemic capillary leak syndrome. Ann Intern Med. 2010;153:90-8.
3. Kapoor P, Greipp PT, Schaefer EW, et al. Idiopathic systemic capillary leak syndrome (Clarkson's disease): the Mayo Clinic experience. Mayo Clin Proc. 2010;85:905-12.
4. Gousseff M, Arnaud L, Lambert M, et al. The systemic capillary leak syndrome: a case series of 28 patients from a European registry. Ann Intern Med. 2011;154:464-71.
5. Amoura Z, Papo T, Ninet J, et al. Systemic capillary leak syndrome: report on 13 patients with special focus on course and treatment. Am J Med. 1997;103:514-9.
6. Hiraoka E, Matsushima Y, Inomoto-Naribayashi Y, et al. Systemic capillary leak syndrome associated with multiple myeloma of IgG kappa type. Intern Med. 1995;34:1220-4.
7. Yamaguchi M, Kwong YL, Kim WS, at al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-Cell Tumor Study Group study. J Clin Oncol. 2011;29:4410-6
8. Au WY, Weisenburger DD, Intragumtornchai T, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. Blood. 2009;113:3931-7.
9. Takimoto Y, Imanaka F, Sasaki N, et al. Gamma/delta T cell lymphoma presenting in the subcutaneous tissue and small intestine in a patient with capillary leak syndrome. Int J Hematol. 1998;68:183-91.
10. Jillella AP, Day DS, Severson K, et al. Non-Hodgkin's lymphoma presenting as anasarca: probably mediated by tumour necrosis factor alpha (TNF-alpha). Leuk Lymphoma. 2000;38:419-22.
11. Umemoto T, Watanabe T, Ogose T, et al. Capillary leak syndrome: initial presentation in a patient with ALK+ anaplastic large cell lymphoma associated with increased levels of serum cytokines. Leuk Lymphoma. 2011;52:1139-42.
12. Lourdes LS, Al-Quran SZ, Dang NH, et al. Systemic capillary leak syndrome as an initial presentation of ALK-negative anaplastic large cell lymphoma. Case Rep Hematol. 2012;2012:954201.
13. Ghosh K, Madkaikar M, Iyer Y, et al. Systemic capillary leak syndrome preceding plasma cell leukaemia. Acta Haematol. 2001;106:118-21.
14. Bencsath KP, Reu F, Dietz J, et al. Idiopathic systemic capillary leak syndrome preceding diagnosis of infiltrating lobular carcinoma of the breast with quiescence during neoadjuvant chemotherapy. Mayo Clin Proc. 2011;86:260-1.
15. Hsiao SC, Wang MC, Chang H, et al. Recurrent capillary leak syndrome following bortezomib therapy in a patient with relapsed myeloma. Ann Pharmacother. 2010;44:587-9.
16. De Pas T, Curigliano G, Franceschelli L, et al. Gemcitabine-induced systemic capillary leak syndrome. Ann Oncol. 2001;12:1651-2.
17. Deeren DH, Zachee P, Malbrain ML. Granulocyte colony-stimulating factor-induced capillary leak syndrome confirmed by extravascular lung water measurements. Ann Hematol. 2005;84:89-94.
18. Xie Z, Ghosh CC, Patel R, et al. Vascular endothelial hyperpermeability induces the clinical symptoms of Clarkson disease (the systemic capillary leak syndrome). Blood. 2012;119:4321-32.
19. Zhang W, Ewan PW, Lachmann PJ. The paraproteins in systemic capillary leak syndrome. Clin Exp Immunol. 1993;93:424-9.