Calciphylaxis in POEMS Syndrome: A Case Treated with Etidronate

Mika Yoshikawa[1], Hisashi Uhara[1], Fuyuko Arakura[1], Hiroshi Murata[1], Hitomi Kubo[1], Minoru Takata[1], Kunihiro Yoshida[2] and Ryuhei Okuyama[1]

Departments of [1]Dermatology and [2]Neurology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan. E-mail: rokuyama@shinshu-u.ac.jp

Accepted June 17, 2010.

POEMS syndrome is a plasma cell lymphoproliferative disorder associated with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin abnormalities. We report here a case of calciphylaxis associated with POEMS syndrome. Calciphylaxis is a rare disease presenting as systemic deposition of calcium salts (1, 2). Cutaneous manifestations of calciphylaxis begin as painful, purple-coloured, mottled lesions, similar to livedo reticularis, which eventually progresses to ischaemic necrosis with grey-black eschars and gangrene of the surrounding tissues. As calciphylaxis occasionally leads to sepsis and death, patients with POEMS syndrome should be followed up carefully for the development of calciphylaxis and occurrence of livedo-like skin changes and ulcers.

CASE REPORT

A 57-year-old man had 10 years previously been diagnosed with POEMS syndrome based on lower-limb paraesthesia and hyposthenia, gynaecomastia, IgGκ monoclonal gammopathy, hypertrichosis and pigmentation on the bilateral upper extremities. He had been prescribed oral prednisolone and immunosuppressive agents at gradually decreasing dosages. Recently, his condition had been maintained by oral prednisolone and thalidomide at daily doses of 25 mg and 100 mg, respectively. Livedo-like reticular changes and ulcers appeared bilaterally on his thighs 4 month prior to presentation, and systemic oedema developed 3 months later. Bruising on his lower legs had triggered formation of the new ulcers, and he was referred to our hospital in June 2008. On physical examination, the patient had ulcers on his lower extremities in regions affected by reticular purple-coloured erythema, some of which were covered with necrotic tissue (Fig. 1). Laboratory examination revealed the following: white blood cell count 11,820/μl (normal value 2,970–9,130/μl); erythrocyte count 452×10^4/μl ($414–563 \times 10^4$/μl); haemoglobin 14.9 g/dl (12.9–17.4 g/dl); platelets 26.6×10^4/μl ($14.3–33.3 \times 10^4$/μl); protein C 82% (70–140%); protein S 78.8% (60–150%); creatinine 0.58 mg/dl (0.60–1.00 mg/dl); blood urea nitrogen 24 mg/dl (9–22 mg/dl); C-reactive protein 0.20 mg/dl (0.00–0.10 mg/dl); total protein 5.3 g/dl (6.8–8.3 g/dl); albumin 2.0 g/dl (4.2–5.1 g/dl); calcium 8.7 mg/dl (8.7–9.9 mg/dl); inorganic phosphate 3.6 mg/dl (2.2–4.1 mg/dl); parathyroid hormone (PTH) 31.8 pg/dl (10.0–65.0 pg/dl); vascular endothelial growth factor (VEGF) 4,240 pg/dl (0–38.3 pg/dl). A skin biopsy revealed calcification in the dermis and subcutis (Fig. 2a, b), while an X-ray of the thigh showed linear white-coloured changes, indicating widespread vessel calcification.

A diagnosis of calciphylaxis was made. The patient's ulcers expanded rapidly from the lower extremities to the trunk and upper extremities. Debridement was performed, together with local wound care using povidone-iodine sugar ointment. In addition, hyperbaric oxygen therapy was performed once a week, although the patient's cutaneous conditions showed no improvement. Next, we administered bisphosphonate etidronate disodium at a daily dose of 200 mg, even though serum levels of calcium, phosphate and PTH were within their respective normal ranges. While their levels were stable, the skin ulcers gradually decreased in size in parallel with an increase in granulation that followed administration of etidronate. After 1 month of this treatment, the skin ulcers had reduced to less than half their size. However, the patient died suddenly due to cardiorespiratory failure 3 months later. No post-mortem examination was performed.

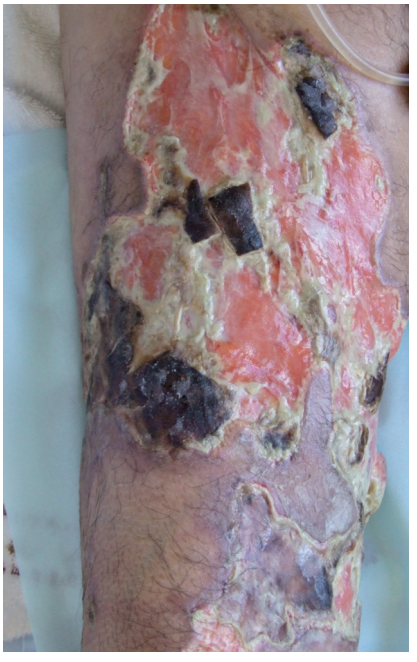

Fig. 1. Clinical features. Ulcers in regions of the lower extremities affected by reticular changes.

DISCUSSION

To our knowledge, this is the second case of POEMS syndrome with calciphylaxis reported to date. De Roma et al. (3) reported a previous case that did not involve renal failure or hyperparathyroidism. These cases indicate the need to include POEMS syndrome among the diseases associated with calciphylaxis. The pathogenesis of calciphylaxis remains obscure, but is considered to involve abnormal calcium metabolism and hyperparathyroidism. Most patients have end-stage renal disease, and some receive haemodialysis or peritoneal dialysis. Patients with calciphylaxis frequently have increased serum levels of calcium, phosphate and/or PTH which appear to promote calcium deposition within blood vessels. However, calciphylaxis is not always associated with metabolic abnormalities in

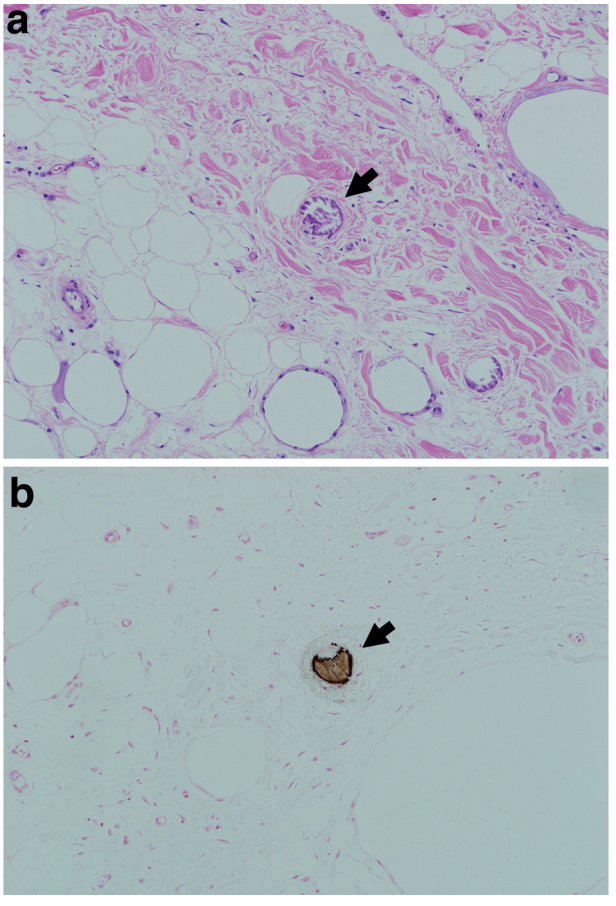

Fig. 2. (a, b) Histopathology of a biopsy specimen from an ulcer on the thigh. (a) Haematoxylin-eosin and (b) von Kossa's staining revealed dense calcium deposits (arrows) (original magnification ×100).

these patients. In the present case, it is not clear how POEMS syndrome was connected to the occurrence of calciphylaxis. However, vascular manifestations have previously been described as a systemic manifestation of POEMS syndrome (4). POEMS syndrome patients frequently have elevated VEGF levels (5), which may account for the vascular damage because VEGF increases vascular permeability (6). In addition, VEGF is an activator of the coagulation pathway (6, 7). Chronically elevated VEGF activity may be involved in the development of vessel calcification. Furthermore, interleukin (IL)-1β, IL-6 and tumour necrosis factor-α have also been implicated in POEMS syndrome (8–10), and these factors may also have roles in the pathogenesis of calciphylaxis.

Bisphosphonates have been reported to be effective in treating calciphylaxis with renal failure by lowering calcium levels (11). Analogues of inorganic pyrophosphate, an endogenous regulator of calcium metabolism that prevents ectopic calcification, their administration is a first-line therapy for treating osteoporosis, in which they suppress bone resorption by inactivating osteoclasts, cells of monocyte-macrophage origin that regulate bone resorption. Furthermore, they suppress the development of atherosclerosis by inactivating macrophages, which play a key role in atherogenesis (12). In atherosclerosis, inactivation of macrophages not only reduces lipid accumulation in vessel walls, but also alleviates arterial calcification. Therefore, bisphosphonates appear to be an effective treatment for calciphylaxis, as they control macrophages without affecting serum calcium levels. Calciphylaxis occasionally leads to sepsis due to the presence of infectious foci within skin ulcers, and death occurs in more than half of such cases (1, 2). The present case suggests that bisphosphonates are effective in treating calciphylaxis, even in patients with normal serum calcium levels. Early administration of bisphosphonates may be useful in the treatment of calciphylaxis.

The authors declare no conflicts of interest.

REFERENCES

1. Guldbakke KK, Khachemoune A. Calciphylaxis. Int J Dermatol 2007; 46: 231–238.
2. Arseculeratne G, Evans AT, Morley SM. Calciphylaxis – a topical overview. J Eur Acad Dermatol Venereol 2006; 20: 493–502.
3. De Roma I, Filotico R, Cea M, Procaccio P, Perosa F. Calciphylaxis in a patient with POEMS syndrome without renal failure and/or hyperparathyroidism. A case report. Ann Ital Med Int 2004; 19: 283–287.
4. Lesprit P, Authier FJ, Gherardi R, Belec L, Paris D, Melliere D, et al. Acute arterial obliteration: a new feature of the POEMS syndrome? Medicine (Baltimore) 1996; 75: 226–232.
5. Watanabe O, Maruyama I, Arimura K, Kitajima I, Arimura H, Hanatani M, et al. Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Crow-Fukase (POEMS) syndrome. Muscle Nerve 1998; 21: 1390–1397.
6. Dvorak HF. Angiogenesis: update 2005. J Thromb Haemost 2005; 3: 1835–1842.
7. Senger DR, Ledbetter SR, Claffey KP, Papadopoulos-Sergiou A, Peruzzi CA, Detmar M. Stimulation of endothelial cell migration by vascular permeability factor/vascular endothelial growth factor through cooperative mechanisms involving the alphavbeta3 integrin, osteopontin, and thrombin. Am J Pathol 1996; 149: 293–305.
8. Mandler RN, Kerrigan DP, Smart J, Kuis W, Villiger P, Lotz M. Castleman's disease in POEMS syndrome with elevated interleukin-6. Cancer 1992; 69: 2697–2703.
9. Gherardi RK, Belec L, Fromont G, Divine M, Malapert D, Gaulard P, et al. Elevated levels of interleukin-1 beta (IL-1 beta) and IL-6 in serum and increased production of IL-1 beta mRNA in lymph nodes of patients with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome. Blood 1994; 83: 2587–2593.
10. Gherardi RK, Chouaib S, Malapert D, Belec L, Intrator L, Degos JD. Early weight loss and high serum tumor necrosis factor-alpha levels in polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes syndrome. Ann Neurol 1994; 35: 501–505.
11. Hanafusa T, Yamaguchi Y, Tani M, Umegaki N, Nishimura Y, Katayama I. Intractable wounds caused by calcific uremic arteriolopathy treated with bisphosphonates. J Am Acad Dermatol 2007; 57: 1021–1025.
12. Bevilacqua M, Dominguez LJ, Rosini S, Barbagallo M. Bisphosphonates and atherosclerosis: why? Lupus 2005; 14: 773–779.