CASE REPORT

Livedo reticularis heralding hypercalcaemia of malignancy

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Accepted 17 April 2014

SUMMARY

The term livedo reticularis is used to describe net-like purple rash usually on the lower limbs. It is an important clinical sign with diverse aetiologies. Hypercalcaemia is an uncommon but important clinical entity, sometimes associated with livedo reticularis. Generally, hypercalcaemia of renal failure and secondary hyperparathyroidism has been reported with this condition. We report a case of livedo reticularis heralding onset of hypercalcaemia of malignancy.

BACKGROUND

Livedo reticularis (LR) is the mottled, reticular lace-like reddish-purple discolouration of the skin mainly affecting the limbs. Pathologically, it is due to an interruption of blood flow in the dermal arteries due to spasm, inflammation or vascular obstruction. It is associated with diseases of varying aetiology and severity. We report a case of livedo reticularis heralding the onset of hypercalcaemia of malignancy (HCM).

CASE PRESENTATION

A 49-year-old man, a known case of squamous cell carcinoma (SCC) of oral cavity was admitted for re-evaluation in view of disease progression. For SCC he underwent surgery followed by post-operative radiochemotherapy. He was not diabetic or hypertensive. This time, he had symptoms of generalised body ache. General physical and systemic examination revealed local recurrence at retromolar trigone area.

INVESTIGATIONS

Complete blood counts, liver and kidney function tests, serum electrolytes including serum calcium were within normal limits. As oral intake was poor, supportive care in the form of intravenous fluid and parenteral analgesics were provided. Next day in the morning, he reported appearance of rash on his lower limbs (figure 1). Purple-reddish lacy reticular rash was observed on both lower extremities, that is, LR. His blood pressure was normal and he was afebrile. Routine investigations were sent which again turned out to be normal. Serum procalcitonin, D-dimer and fibrinogen degradation product assay were within normal limits. On day 4 of admission, he was found to be less responsive and confused. His Glasgow Coma Scale score was 12/15 (E4/V4/M4). Serum calcium was sent again, which was found to be elevated (15.6 mg/dL; normal 8.5–10 mg/dL). Serum parathyroid hormone (PTH) level (14.6 pg/mL; 10–55 pg/mL) was within normal

limits, but serum vitamin D₃ level (15.8 nmol/L; 75–250 nmol/L) was low. A diagnosis of HCM was made. Most probable pathogenesis was secondary to PTH-related protein (PTHrP) secretion, but could not be confirmed as its assay is not available in our hospital.

TREATMENT

Intravenous fluid therapy and loop diuretics were started. Zoledronic acid and calcitonin therapy was added.

OUTCOME AND FOLLOW-UP

Over the next 7 days his general condition improved, serum calcium normalised, kidney function improved and rash disappeared.

DISCUSSION

The term livedo reticularis is derived from the Latin words, 'livere' meaning bluish and 'reticular' which refers to the net-like appearance. Some authors distinguish reticular eruptions between LR (frequently benign, often reversible, symmetrically distributed, network pattern with complete, regular 'unbroken' rings) and livedo racemosa (permanent, pathological, asymmetrically distributed, network pattern with incomplete, irregular 'broken' rings).¹ The latter is always considered secondary to organic rather than functional disorders. Moreover, compared with LR, livedo racemosa is more generalised (can involve trunk, buttocks, hands, feet and face), often painful and associated with other cutaneous abnormalities (purpura, nodules and ulcerations). However, the term LR is more commonly used for all types of processes.¹

Gibbs *et al*² categorise LR into two groups based on the presence or absence of systemic associations. LR without systemic association is of three subtypes based on its duration and relationship with the ambient temperature: physiological, primary and idiopathic LR. LR with systemic association can be categorised on the basis of pathogenesis of interruption of blood flow, and is due to varied aetiologies (table 1).

Livedo arises from either deoxygenation or venodilation within the venous plexus. Deoxygenation can be due to decreased arteriolar perfusion (more common) or increased resistance to venous outflow (deep venous thrombosis). Physiological arteriolar vasospasm produces the reversible cutaneous discolouration of benign LR. Arteriolar thromboemboli, inflammation or hyperviscosity underlie the skin changes of pathological LR. While initial

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To cite: Sundriyal D, Kumar N, Kumar G, *et al*. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-201371

Figure 1 Lower limb having mottled, purple-reddish lacy reticular rash known as livedo reticularis.

reduction of blood flow causes LR, haemorrhagic infarcts follow complete interruption of blood flow. Infarcted areas initially present as reticular purpuric lesions (retiform purpura). In later stage, it becomes visibly ecchymotic and eventually forms extensive areas of necrosis, ulceration, gangrene or sepsis.^{2 3}

Disease associations of LR are many (table 1). In cases with systemic association, workup should be directed to clue from the associated clinical findings (autoimmune, vasculitic and haematological process; table 1). Skin biopsy is also required only in latter cases. Multiple biopsies particularly large punch biopsies and biopsies from satellite lesions (nodule and ulcers) are ideal. From a management angle, a patient with LR without systemic association should avoid cold, do episodic limb elevation and rarely may need vasodilator drugs. In cases with systemic association, treatment should be directed to the primary underlying process. Treatment options often considered are anticoagulation, antiplatelet agents, pentoxifylline, immunosuppressants, danazol, tissue plasminogen activator and hyperbaric oxygen therapy.

Disorders of calcium and phosphorus metabolism in patients with advanced renal failure and hyperparathyroidism can cause metastatic calcifications in the small arteries, capillaries and other organs. It is known as calciphylaxis, which initially results in venular congestion, leading to net-like rash formation (ie, LR), and hence an early sign of calciphylaxis. Later on, complete obstruction of vessels leads to haemorrhagic infarcts, necrosis, ulcers and violaceous plaques on the limbs. Vessel wall disorders secondary to renal failure and malignancy contributes to this process. There is a high risk of calciphylaxis when the calcium-phosphorus product is greater than 65 mg/mL. Diagnosis can be made by identification of calcium in the walls of the superficial and deep dermal vessels in biopsy.

Neoplasias are uncommon causes of LR, and have been reported with multiple myeloma, lymphoma, leukaemia, renal cell carcinoma and metastatic breast carcinoma.^{4 5} The pathogenesis is not clear but could be due to obstruction in the venous plexus by the neoplastic process.

As discussed, though hypercalcaemia of renal failure and secondary hyperparathyroid is known to be associated with LR, we could not find in the literature HCM as a cause of LR. Hypercalcaemia is seen in 20–30% of patients with cancer and

Table 1 Classification of livedo reticularis with systemic association on the basis of pathogenesis of interruption of blood flow

Mechanism	Causes
A. Vessel spasm	Cold Drugs (ergotamine, cocaine and ephedrine amphetamines)
B. Vessel inflammation	
Non-infectious (vasculitis)	1. Polyarteritis nodosa 2. Wegener granulomatosis 3. Churg-Strauss syndrome 4. Microscopic polyangiitis 5. Drug-induced vasculitis 6. SLE or RA associated vasculitis
Infectious	1. Bacteria (pneumococcaemia, meningococcaemia, tuberculosis, <i>Mycoplasma pneumonia</i> and <i>Coxiella burnetii</i>) 2. <i>Spirochetes</i> (syphilis) 3. <i>Rickettsiae</i> (typhus fever) 4. Virus (hepatitis C) 5. Lucio's phenomenon
C. Vessel obstruction	
Thrombosis	1. Antiphospholipid syndrome 2. Sneddon syndrome 3. Livedoid vasculopathy 4. SLE, RA, Sjögren's syndrome and scleroderma 5. DIC 6. Cryopathies (cryoglobulinaemia, cryofibrinogenaemia and cold agglutinins) 7. Myeloproliferative syndromes 8. Procoagulant genetic factors (factor V) 9. Sickle cell anaemia 10. Drugs (coumarin, amantadine and gemcitabine) 11. Neurological (dysautonomias, paraplegia, stroke, multiple sclerosis, migraine, Divry-Van Bogaert syndrome) 12. Neoplasia (multiple myeloma, lymphoma, leukaemia, RCC and metastatic breast carcinoma)
Embolisation	Atrial myxoma Cholesterol
Wall disorder	Calciphylaxis Hyperoxaluria

DIC, disseminated intravascular coagulation; RA, rheumatoid arthritis; RCC, renal cell carcinoma; SLE, systemic lupus erythematosus.

is usually associated with breast cancer, lung cancer and multiple myeloma.⁶ However, it can also occur in any other malignancy. HCM is often considered a sign of advance cancer. Hypercalcaemia is defined as serum calcium concentration ≥ 10.5 mg/dL. It has three grades of severity: mild, moderate and severe with serum calcium concentrations of 10.5–11.9, 12–13.4, and ≥ 13.5 mg/dL, respectively. Based on the pathogenesis, HCM is of four types. First is humoral HCM secondary to secretion of PTHrP by tumour; it accounts for 80% of cases of HCM (eg, SCC and renal cell carcinoma). Second type is HCM due to metastasis or direct involvement of bone (20% of cases; eg, metastatic breast carcinoma, multiple myeloma and leukaemia). The other two causes are ectopic production of calcitriol and PTH by malignancy (eg, lymphomas and ovarian tumours). HCM should always be suspected in old age groups and rapidly developing symptomatic hypercalcaemia of short duration.

Immunoreactive PTH level is typically low-to-normal. Treatment of HCM is directed to primary cause.

In various studies, incidence of SCC of head and neck region associated hypercalcaemia ranges from nearly 3% to 25%.^{7–9} Although hypercalcaemia is considered as a terminal phenomenon, timely recognition of this clinical sign is important to reduce morbidity and prolong survival in patients with cancer.¹⁰ We conclude that in patients with a history of malignancy, rapidly developing LR can be a harbinger of hypercalcaemia of malignancy.

Contributors DS and NK contributed to the concept of paper, acquiring data, drafting and revising the manuscript. GK contributed to the concept of paper and acquiring data. MW participated in revising the manuscript. All the authors were involved in the patient management and gave final approval of the version to be published.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Learning points

- ▶ Livedo reticularis (LR) is a sign of systemic disease of varied aetiologies.
- ▶ As is the hypercalcaemia of renal failure and secondary hyperparathyroidism, hypercalcaemia of malignancy can present with LR.
- ▶ Although the exact pathogenesis of LR in patients with cancer is not known, this report suggests hypercalcaemia of malignancy as one important association between two conditions.
- ▶ Although hypercalcaemia is considered as a terminal phenomenon in a patient with malignancy, its timely recognition is important to prevent morbidity and prolongation of survival.

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