CASE REPORT

Intravascular lymphoma presenting with postural hypotension

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SUMMARY

An 84-year-old woman presented with severe postural hypotension. Further assessment revealed weight loss, fatigue and fever at night. On examination, she had bilateral skin lesions on the inner thighs and skin biopsy revealed intravascular high grade B cell lymphoma. This was successfully treated with curative chemotherapy. The cause of the postural hypotension in this case was felt likely to be autonomic neuropathy caused by neurovascular infiltration by intravascular lymphoma. Treatment of the lymphoma has resolved the postural hypotension, although some symptoms of postural instability persist.

BACKGROUND

Elderly patients often present to hospital with 'dizziness', and postural hypotension is frequently detected, usually as a side effect of medication, cardiac reasons, severe anaemia or autonomic neuropathy associated with ageing or diabetes.¹ This case was important as it suggested an alternative, potentially treatable, cause for her rapidly progressive postural hypotension, and which we would have missed without a full clinical assessment.

CASE PRESENTATION

An 84-year-old Caucasian woman was referred by her general practitioner (GP) with a 3-month history of a progressively disabling feeling of 'dizziness' on standing. She had a medical history of angina, hypertension, hypothyroidism, osteoarthritis and gastric angiodysplasia. She had stopped taking isosorbide mononitrate because she found it made her postural symptoms worse. Further enquiry revealed a 3-month history of weight loss, fatigue and fevers at night. She had noticed lumps in the skin of her inner thighs and the GP had considered a diagnosis of thrombophlebitis.

Her medications on admission were clopidogrel 75 mg OM, atenolol 50 mg twice a day, telmisartan 80 mg nocte, levothyroxine 150 mcg OM, quinine sulfate 300 mg nocte, tramadol 100 mg pro re nata max four times a day. She had recently stopped ISMN XL 30 mg OM, furosemide 20 mg OM and calcichew D3 one tablet twice a day.

On examination, she was mildly cachectic. She had a feeling of presyncope on standing with a significant postural drop in blood pressure from 101/58 mm Hg when lying to 72/49 mm Hg on standing. The skin of both inner thighs had a brownish discolouration; the skin felt tethered and

woody, with several firm, tender nodules ranging in size from 10 to 40 mm. Additionally, there was an easily palpable firm, non-tender, right submandibular mass, 3.5 cm in length.

She lived with her son in an isolated rural location, reliant on a generator for electricity and had no bath or shower. She had been coping well until fairly recently, but described three falls in recent months, related to a feeling of dizziness.

INVESTIGATIONS

Blood results revealed a mild macrocytic anaemia (haemoglobin 103 g/dL (120–160), mean corpuscular volume 100.6 fL (82–98)), thrombocytopaenia (platelets $70 \times 10^9/L$ (150–400)) and a normal white cell count ($5.5 \times 10^9/L$ (3.6–11.0)). The lactate dehydrogenase (LDH) was markedly raised (LDH 986 IU/L (240–490)). Her thyroid stimulating hormone was 1.42 mU/L (0.27–4.2).

A skin biopsy from one of the thigh nodules revealed a very unusual appearance, with a purely intravascular infiltrate of high grade, large B cell lymphoma cells within both the dermis and subcutis of the specimen. The histological diagnosis was of intravascular large B cell lymphoma (IVLBCL). A biopsy of the right submandibular mass revealed salivary gland tissue infiltrated by solid diffuse large B cell lymphoma cells.

A staging CT scan of the neck, thorax, abdomen and pelvis showed the right submandibular nodule and a solitary 2.1 cm para-oesophageal nodule, but no other lymphadenopathy. There was bilateral adrenal enlargement.

Cortisol was measured because of severe postural hypotension and adrenal enlargement. A random cortisol level at 08:30 was 427 nmol/L (>320 nmol/L indicating that adrenal insufficiency is unlikely). Adrenocorticotrophic hormone (ACTH) was 46 ng/L (0–46 ng/L). A short Synacthen test was also done, with the predose cortisol being 460 nmol/L, rising to 560 nmol/L. This is an acceptable rise in cortisol from a normal baseline in an older person, suggesting maintained adrenal function. Our patient did not have hyponatraemia or hypoglycaemia, providing further support for maintained adrenal function.

The severe postural hypotension meant that we withheld medications which this patient had previously taken for ischaemic heart disease and hypertension, including beta blockers, nitrates and angiotensin II antagonists. However, despite this, the postural hypotension persisted, suggesting that these medications were not the cause. Unfortunately,

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on day 16 of her admission, she developed an episode of chest pain. An ECG showed new anterior T-wave inversion and she had a significant rise in serum troponin. She was diagnosed with a non-ST elevation myocardial infarction (NSTEMI). Our management of this acute coronary syndrome was complicated by her ongoing postural hypotension and thrombocytopaenia. She underwent emergency left heart catheterisation, which demonstrated triple vessel disease, and percutaneous coronary intervention (PCI) was successfully carried out at the site of a 95% stenosis in the proximal left anterior descending artery. An echocardiogram showed akinesia in the inferior basal segment of the left ventricle but only mild left ventricular dysfunction. The right heart was normal and there was no significant valve disease.

DIFFERENTIAL DIAGNOSIS

The primary diagnosis was of intravascular high grade B cell lymphoma.

The most likely cause for the postural hypotension is autonomic neuropathy caused by neurovascular infiltration by intravascular lymphoma. Differential diagnoses in this patient include paraneoplastic autonomic dysfunction, adrenal insufficiency secondary to adrenal gland infiltration by lymphoma, cardiovascular disease and side effects from medications or anaemia.

OUTCOME AND FOLLOW-UP

Our patient completed six cycles of curative chemotherapy treatment using rituximab, gemcitabine, cyclophosphamide, vincristine and prednisolone. She is now in remission with resolution of the skin thickening and no clinical signs of lymphadenopathy, including resolution of the submandibular mass. A repeat CT scan has shown disappearance of the previously demonstrated para-oesophageal mass, and no mediastinal, hilar or axillary lymphadenopathy. No change was seen in the appearance of her adrenal glands. A year after the initial presentation, our patient still has a feeling of postural instability on standing, but her blood pressure is stable and she is no longer suffering with disabling postural hypotension.

DISCUSSION

IVLBCL is a rare type of non-Hodgkin's lymphoma in which neoplastic cells grow primarily in the lumina of small to medium blood vessels.² The disease can present with a very wide array of symptoms, many of which are related to occlusion of small blood vessels in different body systems. IVLBCL has been described as 'medicine's greatest imitator'³ and should be considered as a differential diagnosis in complex patients presenting with multisystem symptoms where a unifying diagnosis is elusive. Lymphadenopathy is less common than with other forms of non-Hodgkin's lymphoma, making diagnosis more challenging. However, cutaneous features are seen in 25%–30%.^{2,4} In Western countries, skin lesions are more common in the legs than elsewhere, with a variety of red to greyish-blue nodules, plaques and macules described.⁴ Intravascular lymphoma can be very difficult to diagnose when skin lesions are lacking. Our patient had abnormal skin lesions and the diagnosis was made relatively quickly after biopsy of one of these lesions. However, in cases where intravascular lymphoma is thought to be a possible diagnosis, but where abnormal skin lesions are not seen, random skin biopsy of apparently normal looking skin can reveal pathological changes and confirm the diagnosis.³

Neurological features are common in intravascular lymphoma, and pathological examination of the nervous system was

informative in early characterisation of the disease in the 1980s.⁵ In a large series of 654 cases of intravascular lymphoma, 52% of patients had neurological involvement.⁶ Of those with neurological involvement, 82% had central nervous system disease and 19% had peripheral and autonomic nervous system disease.⁶ The cause of the neuropathy in these cases is direct vascular damage to neurons.⁶ Thus, we propose that our patient's severe postural hypotension was due to autonomic neuropathy caused by neurovascular infiltration by intravascular lymphoma. An alternative cause for the autonomic neuropathy in this case could have been an autoimmune paraneoplastic syndrome. However, paraneoplastic syndromes, other than limbic encephalitis and polymyositis, are rare in lymphoma and tend to occur late in the disease or after chemotherapy.⁷ Of these rare lymphoma-related paraneoplastic syndromes, paraneoplastic autonomic ganglionopathy is rarer still.⁷ It therefore seemed more likely that our patient's postural hypotension, which was a presenting feature of the disease, may have been related to direct infiltration of the autonomic nervous system by intravascular lymphoma rather than an autoimmune paraneoplastic syndrome. Unfortunately, however, we did not have confirmatory muscle or central nervous tissue biopsy proof of infiltration to confirm this conclusion.

Adrenal insufficiency is unlikely to have caused the postural hypotension in this case. Intravascular lymphoma can present with severe adrenal insufficiency, and adrenal involvement is not uncommon in the disease.^{4,8,9} However, in our patient, the cortisol, ACTH and Synacthen tests demonstrated maintained adrenal function. The staging CT of the abdomen showed enlarged adrenal glands suggesting the possibility of adrenal infiltration by lymphoma. Adrenal enlargement with preserved function has been observed in intravascular lymphoma.¹⁰ However, in our patient, the adrenal enlargement remained unchanged after successful curative treatment of the lymphoma with chemotherapy. Benign adrenal enlargement is very common with age, particularly in people with hypertension,¹¹ and is a possible alternative explanation for the adrenal enlargement we observed.

The triple vessel coronary disease resulting in a NSTEMI during her investigations may also have contributed to—or explained—her postural hypotension, with her coronary stent treatment to her left anterior descending coronary artery subsequently aiding her recovery from this debilitating symptom. Exercise-induced hypotension has been associated with severe stenosis of the left anterior descending artery.¹² Our patient had severe postural hypotension simply on standing. Without tissue biopsies confirming IVLBCL infiltration of the muscle or central nervous tissue biopsy, we cannot discount the possibility of a cardiac cause, but on balance we feel autonomic neuropathy due to neurovascular infiltration by intravascular lymphoma is more likely in this case.

Finally, postural hypotension is a common symptom in many older people presenting to hospital and is often related to dehydration, drugs and diabetes. Despite our familiarity with these common causes, this case highlights the importance of making a full assessment and keeping an open mind, as this may reveal symptoms and signs that point to less common, but potentially treatable pathology. In our patient, postural hypotension occurred in the context of unusual symptoms (night sweats, fatigue, weight loss) and signs (odd skin lesions), and this led to the diagnosis and successful treatment of a rare form of lymphoma. Although hearing hoof beats does not always mean zebras, sometimes, when you look about and find yourself on the African plain, hearing hoof beats really *does* mean zebras.¹³

Learning points

- Postural hypotension may have more unusual causes, especially in the context of other unusual features—make a full assessment and keep an open mind.
- Thorough examination, including a complete dermatological exam, can occasionally yield vital findings.
- Older patients with lymphoma can do very well with curative chemotherapy treatment.

Contributors All authors were involved in the conception and design of the article after caring for this patient on admission to hospital as detailed in the report. CP subsequently acquired the initial patient information and wrote the first draft of the clinical aspects of the case; this was revised by SVH who also wrote the first draft of the literature review. CP and JB obtained follow-up information regarding the patient and JB critically reviewed and revised the manuscript. SVH finalised the manuscript. All authors approved the final submitted version and also agreed to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved.

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