

The challenge of detecting monoclonal protein in POEMS syndrome: two case reports

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Case presentations

Case 1

A 60-year-old woman presented to United Christian Hospital in 2019 with a 2-month history of progressive generalised ascending weakness and numbness affecting all four limbs. On clinical examination, she had significant oedema involving her hands and feet. Proximal limb power was full while distal limb power was rated grade 3 on the Medical Research Council scale. Sensory modalities involving pinprick, light touch and proprioception were all diminished distally. She had generalised areflexia. Nerve conduction study revealed markedly reduced motor conduction velocity at 18 to 28 m/s (normal range, >50) in the upper limbs, consistent with demyelination. There was evidence of secondary axonal injury. Limited by significant oedema, lower limb nerve compound muscle action potential and sensory nerve action potential were unrecordable. Cerebrospinal fluid study showed elevated protein level at 899 mg/L with normal white blood cell count. The patient was managed as presumed chronic inflammatory demyelinating polyneuropathy (CIDP). Evaluation of monoclonal gammopathy with serum protein electrophoresis (SPE), urine Bence Jones protein and serum immunoglobulin pattern was unrevealing. Systemic steroid was commenced followed by intravenous immunoglobulin due to disease progression but the patient deteriorated further with distal power grade 0 and became wheelchair bound.

Repeated SPE and urine Bence Jones protein test failed to detect any monoclonal gammopathy. Serum free light chain assay of the patient showed persistently raised lambda light chain but normal kappa/lambda ratio. Serum immunofixation was negative. Six months after her initial presentation, positron emission tomography-computed tomography (PET-CT) scan revealed multiple hypermetabolic bony lesions in the skeleton. The dominant lesions were mixed lytic-sclerotic lesions at the left sacrum (maximum standardised uptake value=22.4) and left L5 vertebra (maximum standardised uptake value=16.3). Mild inactive

bilateral pleural effusion, pericardial effusion as well as diffuse subcutaneous oedema were also noted. Random trephine bone marrow examination performed at the right iliac crest was unremarkable.

At this juncture, the patient developed skin changes with plethora, white nails, flushing, and hypertrichosis of the trunk and limbs (Fig). She was oedematous with orthopnoea and paroxysmal nocturnal dyspnoea. A diagnosis of POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) was strongly suspected in view of her polyneuropathy, skin changes, lytic-sclerotic bone lesion, and extracellular volume overload. Plasma vascular endothelial growth factor was checked and was markedly elevated at 370 pg/mL (reference range, <96.2).

The patient's fluid overload symptoms deteriorated with respiratory distress. She was oxygen dependent and diuretic therapy was only partially helpful. Therapeutic thoracentesis of the left chest drained 700 mL of transudative fluid. She subsequently underwent CT-guided bone biopsy (Fig). Her sacrum bone biopsy revealed plasmacytoma with lambda light chain restriction. A diagnosis of POEMS was confirmed.

Around the same time, DNA from the previous random bone marrow blood was extracted from the patient for immunoglobulin heavy chain and kappa light chain B-cell clonality assay (BIOMED-2 polymerase chain reaction assay). Results revealed clonal gene rearrangement (targeting V_k-J_k segments of immunoglobulin kappa gene) consistent with the presence of a clonal B-cell population.

The patient was prescribed a combination of bortezomib, cyclophosphamide and corticosteroid. Oedema resolved first with subsequent improved limb power and dexterity. Her follow-up PET-CT scan after 10 months showed similar bony lesions with reduced metabolic activity.

Case 2

A 40-year-old man presented to Queen Elizabeth Hospital in 2013 with progressive generalised

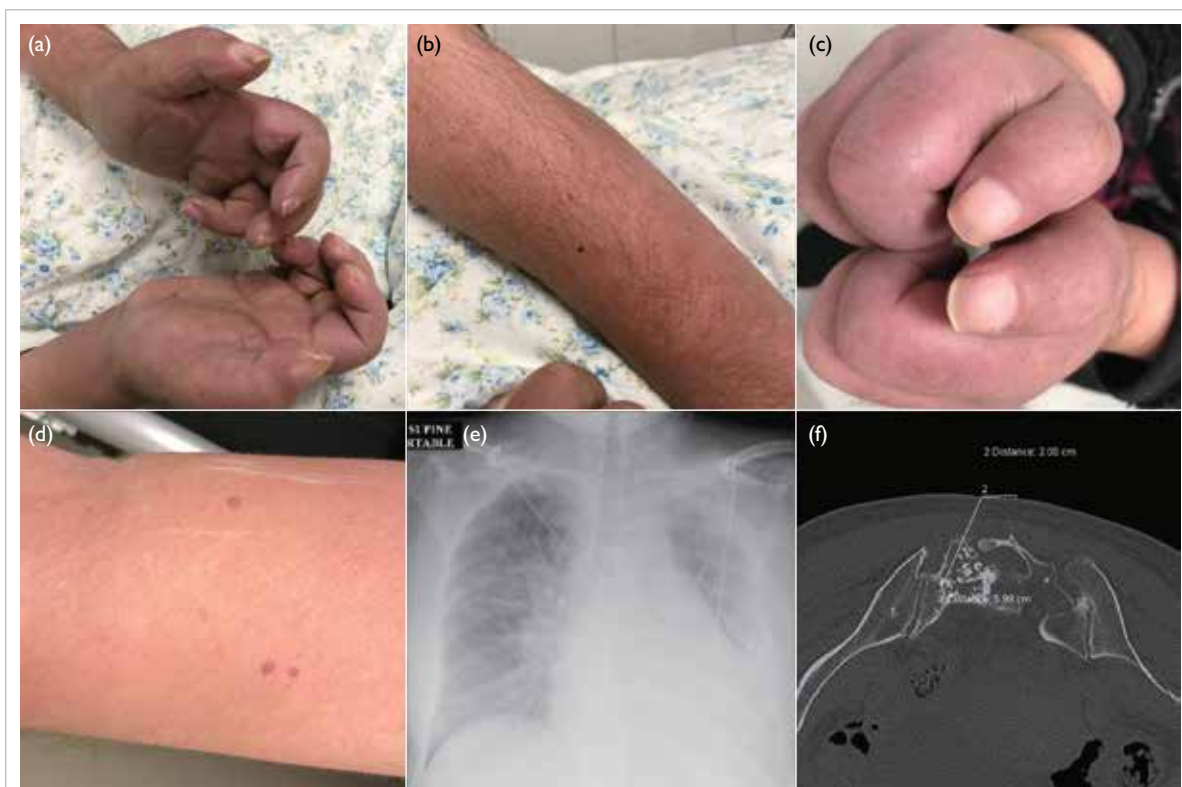


FIG. Case 1. Skin changes with (a) hyperpigmentation, (b) hypertrichosis, (c) flushing of skin and whitening of nail, and (d) haemangiomas. The patient's hands and fingers were oedematous as well. (e) Congested chest X-ray with left pleural effusion. (f) Mixed lytic-sclerotic bony lesion at sacrum. The markings were used to aid computed tomography-guided bone biopsy

oedema. He had had repeated admissions for bilateral lower limb oedema, dyspnoea and orthopnoea. Diuretics were partially helpful. Echocardiogram showed normal left ventricular ejection fraction but evidence of pulmonary hypertension. Serum and urine albumin level was normal. Computed tomography of the thorax and abdomen revealed bilateral pleural effusion, pericardial effusion and ascites. He subsequently developed severe distal limb weakness and became wheelchair bound. Nerve conduction study showed demyelinating sensorimotor polyneuropathy in his upper limbs. Lower limb nerves were unable to be assessed due to severe oedema. The patient developed other features of POEMS with hepatosplenomegaly, papilledema, skin changes with hypertrichosis and acrocyanosis. A PET-CT scan revealed sclerotic bony lesions over the left ilium and multiple thoracic and lumbar vertebral bodies.

Similar to Case 1, the patient's serum and urine were negative for paraprotein. Serum free light chain assay revealed an unremarkable kappa/lambda ratio. Random bone marrow aspiration and trephine biopsy revealed active marrow with mild plasmacytosis. Targeted left iliac bone biopsy showed plasmacytic

infiltrates with reversed kappa/lambda ratio. Although plasmacytoma was a concern, there were no definitive histological criteria. Nonetheless based on the highly compatible clinical features of POEMS, he was managed accordingly with cyclophosphamide and corticosteroid. His oedema resolved and he was subsequently able to mobilise with a stick.

Discussion

The POEMS is a rare paraneoplastic syndrome caused by plasma cell disorder. Presentation may mimic that of demyelinating polyneuropathy. The diagnostic criteria of POEMS include two mandatory criteria, namely, presence of monoclonal plasma cell disorder of lambda origin and demyelinating polyneuropathy. Major criteria include sclerotic bone lesions, elevated vascular endothelial growth factor, and Castleman disease; minor criteria include skin changes, organomegaly, endocrinopathy, extravascular volume overload, papilledema, thrombocytosis, and polycythemia.¹ The diagnosis of POEMS is often delayed. The median time for diagnosis has been reported to be 15 months in a longitudinal cohort of 100 patients, by which time

35% patients had become bed or wheelchair bound.²

The above two cases illustrate the difficulty in establishing monoclonal gammopathy even though neurologists and haematologists were alert to the possibility of POEMS. Repeated SPE test, Bence Jones protein test and random bone biopsy were all negative. Plasmacytoma can be demonstrated only on targeted bone biopsy. As a mandatory diagnostic criterion, failure to detect monoclonal gammopathy delays the subsequent management of POEMS. In a large retrospective series, positive monoclonal protein detection on SPE was only 24% to 54%.¹

Thorough investigations with serum, urine and histological samples are essential. These consist of performing serum protein electrophoresis, immunofixation, serum free light chain assay as well as urine equivalents. Failure to perform immunofixation and serum free light chain analysis may result in missing 30% of POEMS cases.³ Haematological advice and laboratory communication is of utmost importance to exhaust diagnostic means. For Case 1, immunofixation was performed after liaison with the laboratory. A similar situation arises in the United Kingdom where it is a common practice for laboratories to perform immunofixation only if a paraprotein is present in SPE, despite having superior sensitivity.⁴

Non-targeted bone marrow examination carries a high chance of missing the pathology, reflected by a prior case series of six patients in whom three had their pathology missed.⁵ Image guidance, eg, PET-CT, should be considered in the diagnostic workflow of POEMS. It plays a significant role not only in detecting abnormal bone lesions, but also in increasing diagnostic yield for plasmacytoma in biopsy.

Case 1 also illustrates the diagnostic delay of POEMS syndrome partly due to a trial of CIDP treatment, a not uncommon phenomenon. This issue was addressed in a cost-effective analysis of POEMS patients in the United Kingdom.⁴ The study introduced a diagnostic algorithm incorporating early mandatory vascular endothelial growth factor testing in acquired demyelinating neuropathy patients and helped avoid misdiagnosis and associated healthcare costs.⁴

The two cases are also similar in terms of the debilitation from significant oedema. One should be alert of POEMS when a CIDP patient presents with unexplained oedema. Extravascular volume overload is a common feature of POEMS and can occur in 90% patients, presumably due to a capillary leak phenomenon.¹ This includes leg oedema, pleural effusion, pericardial effusion, ascites, papilledema, and asymptomatic pachymeningeal thickening from fluid collection. Presence of oedema in POEMS should not be overlooked as it is a helpful diagnostic clue to differentiate POEMS from CIDP. It also

causes significant patient morbidity. Patients may require repeated paracentesis if the oedema remains refractory to diuretics.

These two cases illustrate the challenge of establishing monoclonal gammopathy in POEMS. Negative serum and urine paraprotein, immunofixation, serum free light chain assay, or a normal random bone marrow examination do not exclude POEMS and warrant further investigations. We should be aware of the limitation of test methods. Comprehensive clinical assessment, thorough investigations and multidisciplinary communication are essential for early diagnosis and management.

Author contributions

Concept or design: YN Mew, WC Fong.

Acquisition of data: All authors.

Analysis or interpretation of data: All authors.

Drafting of the manuscript: YN Mew.

Critical revision of the manuscript for important intellectual content: WC Fong, KF Hui.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

The patients were managed in accordance with the Declaration of Helsinki and provided informed consent for publication.

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