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Case Report

POEMS syndrome with glomeruloid haemangioma: a case report

POEMS 綜合徵伴腎小球樣血管瘤案例一宗

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A 56-year-old Chinese male presented with a few months' history of multiple erythematous nodules over the trunk and proximal arms. His past medical history included right iliac plasmacytoma, chronic inflammatory demyelinating polyneuropathy and membranoproliferative glomerulonephritis. Skin biopsy showed cherry haemangioma with focal glomeruloid haemangioma pattern. These clinical features together supported the diagnosis of POEMS syndrome.

五十六歲男性患者數月來於其身驅及上臂出現多發性紅色結節。其既往病史包括有：右髂漿細胞瘤，慢性炎性脫髓鞘性多發性神經根神經病及膜增生性腎炎。皮膚活組織檢查顯示櫻桃色血管瘤及局灶性腎小球樣的血管瘤形態。以上各項臨床特徵均佐証 POEMS 綜合徵的診斷。

Keywords: Chinese, POEMS syndrome

關鍵詞：華人，POEMS 綜合徵

Introduction

POEMS syndrome is a rare plasma cell dyscrasia with multisystem involvement. It is characterised by polyneuropathy, organomegaly, endocrinopathy, monoclonal plasmaproliferative disorder/M protein, and skin changes. The condition is diagnosed according to a set of major and minor criteria. The skin changes are of particular interest to dermatologists, since they can be the presenting features or provide clues to the diagnosis. Of all the cutaneous features, glomeruloid haemangioma is a specific marker for POEMS syndrome.

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Case report

A 56-year-old Chinese male patient presented with a few months' history of multiple erythematous skin nodules, which were gradually increasing in

size and number. They were distributed over the trunk and proximal arms, and were asymptomatic. There was no systemic symptom associated with the onset of these nodules. The patient's past medical history included right iliac plasmacytoma diagnosed in 1995, which responded to radiotherapy. The last X-ray in August 2006 showed mixed lytic and sclerotic bone lesion in the right innominate bone. He was also diagnosed with chronic inflammatory demyelinating polyneuropathy in 1995 when he presented with numbness of the feet, which subsequently resolved. Membranoproliferative glomerulonephritis was diagnosed in 2003. Continuous ambulatory peritoneal dialysis for end-stage renal failure commenced in 2005. The patient also had congestive heart failure and hypertension. His medication included Frusemide, Prazocin, Caltrate, Pepcidine, Fortifer, Enervon C, Diltiazem, Epo injection and Slow K tablet. He was a non-smoker and a non-drinker.

Physical examination showed multiple erythematous nodules over the trunk and proximal arms (Figures 1 & 2). They range from 0.5 cm to 1.0 cm in diameter. There were also thickening and sclerodermatoid changes of the fingers. There was no clubbing, Raynaud's phenomenon, hyperpigmentation, lymphadenopathy or palpable organomegaly. Mild pitting oedema of ankles was noted. No papilloedema or neurological defect was detected. The clinical differential diagnoses for the erythematous nodules included cherry haemangioma, bacillary angiomatosis, pyogenic granuloma, angiokeratoma, amelanotic melanoma and Spitz naevus. An excisional biopsy was performed of a nodule from the upper arm. Histology showed an angioma with mainly cherry haemangioma pattern and focal glomeruloid pattern (Figures 3 & 4). The glomeruloid component was predominantly at the periphery and the deeper part of the lesion. Eosinophilic globules were readily seen and demonstrated polytypic light chain pattern (Figure 5).

Overall, the findings of cherry haemangioma with focal glomeruloid haemangioma pattern,

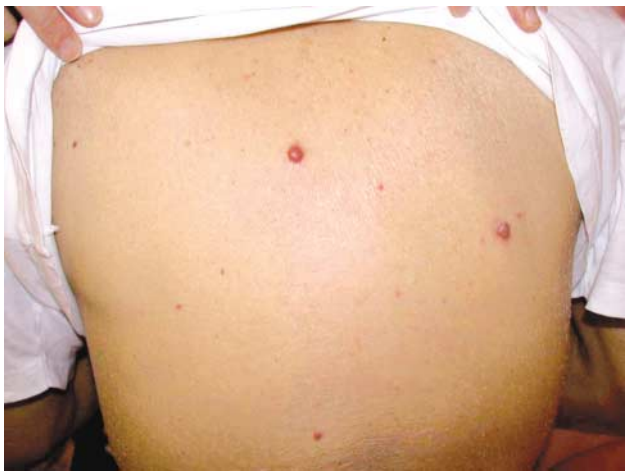

Figure 1. Multiple haemangiomas over back.

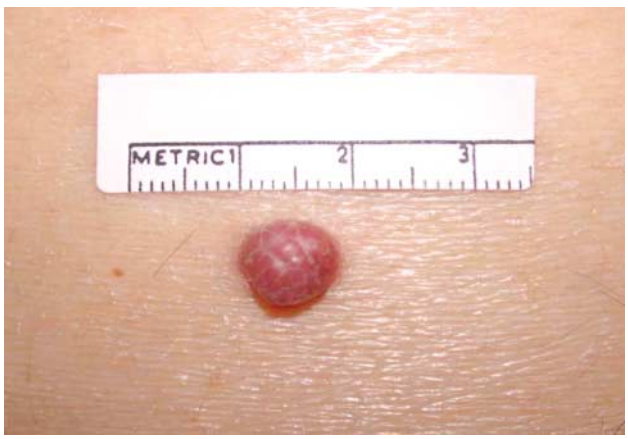

Figure 2. One of the larger haemangiomas measuring 1 cm in diameter.

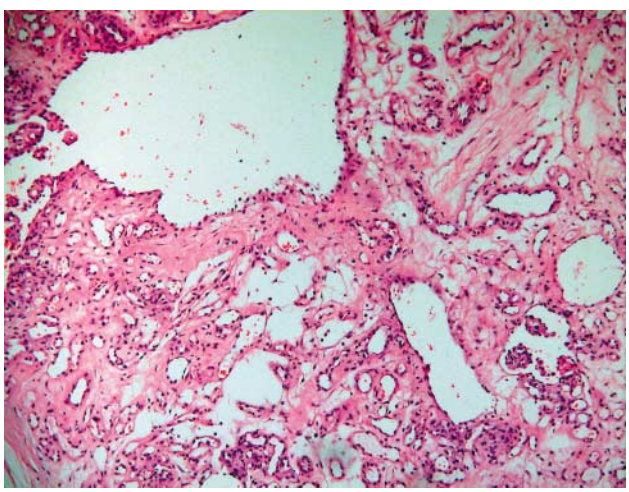

Figure 3. Low power of the vascular tumour shows cherry-type haemangioma with focal minute "glomeruloid" changes at the right lower zone (H&E stain, 40x).

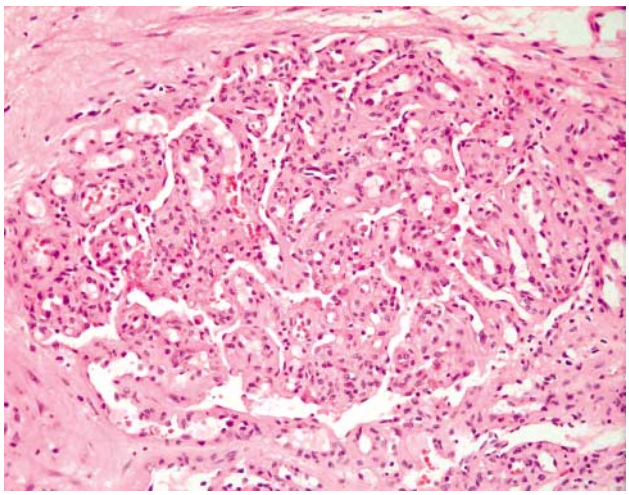

Figure 4. More careful search reveals more diagnostic glomeruloid pattern. A cluster of eosinophilic globules can be seen at the left (H&E stain, 200x).

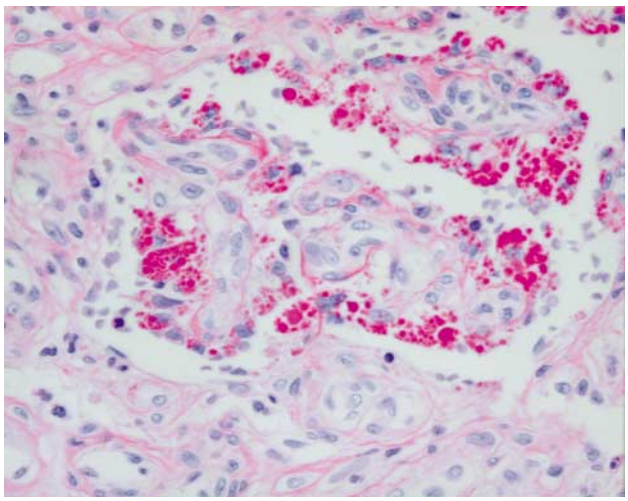

Figure 5. Eosinophilic globules can be highlighted by periodic acid-schiff with diastase (PASD) stain (400x). These globules are positive for both kappa and lambda light chain by immunohistochemical stains (not shown).

plasmacytoma, mixed sclerotic and lytic bone lesions, and chronic inflammatory demyelinating polyneuropathy supported the diagnosis of POEMS syndrome.

Discussion

POEMS syndrome is a rare, plasma cell disorder with multisystem involvement. The acronym 'POEMS' stands for *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonoplasmaproliferative disorder/*M* protein, and *s*kin changes.[1] The diagnosis depends on a combination of symptoms and signs. Some of these features are often detected at a sub-clinical level, therefore a high level of suspicion is required for diagnosis. POEMS syndrome also shows other important clinical features which are well-recognised but not included within the acronym. This syndrome is of interest to dermatologists because the various skin manifestations seen in POEMS syndrome can be the presenting feature or a clue to the diagnosis.[2]

The incidence of POEMS syndrome is unknown. It may be under-diagnosed and therefore under-reported. There is no specific racial association, but a preponderance of cases are reported in the Japanese literature. The male to female ratio is approximately 2.5:1. The age of onset is between the fifth and the sixth decade.[3]

The pathogenesis of POEMS syndrome is not well understood. It is known that the syndrome represents a plasma cell dyscrasia, but the mechanism by which this leads to the development of clinical features of the syndrome is unclear. Lambda light chains are present in more than 95% of cases. However, histological review of affected organs does not support the syndrome as a form of deposition disorder. Antibodies to Human Herpesvirus (HHV)-8 are seen in 78% of cases of POEMS syndrome with Castleman's disease. However, the role of HHV-8 is unclear. Other observations included increased levels of various cytokines (IL-1β, TNF-α and IL-6),[4] vascular endothelial growth factor (VEGF) and tissue inhibitor of metalloproteinases (TIMP). Recently, VEGF has particularly received more attention regarding its possible role in the pathogenesis of POEMS syndrome.[5] The serum level of VEGF seems to correlate with the clinical outcome and response to therapy in POEMS syndrome. VEGF is known to be important in angiogenesis by increasing vascular permeability. It is hypothesised that VEGF secreted from plasma cells and platelets

promote vascular permeability, angiogenesis, and monocyte and macrophage migration, which then leads to arterial obliteration. Hashiguchi demonstrated VEGF release from aggregated platelets in POEMS syndrome.[6]

The diagnosis of POEMS syndrome has been proposed to base on a list of major and minor criteria (Table 1).[7] Two major and at least one minor criteria are required for diagnosis. It should be noted that the clinical features that have been reported to be associated with POEMS syndrome are more extensive than those included in the diagnostic criteria.

'P' in POEMS syndrome represents polyneuropathy, which usually manifests as tingling and paraesthesia over distal regions with symmetrical, progressive and proximal spread. Sensory symptoms are later followed by motor symptoms. Respiratory compromise is possible. Needle electromyography and nerve biopsy may be required to differentiate POEMS-associated polyneuropathy from other causes. 'O' in POEMS syndrome represents organomegaly. Hepatomegaly is seen in 50% of patients. Splenomegaly and lymphadenopathy are present in almost the same frequency. 'E' represents endocrinopathy. Diabetes mellitus and gonadal dysfunction are the most common endocrinopathies. Adrenocortical insufficiency and parathyroid abnormalities have also been reported. 'M' represents monoclonal plasmaproliferative disorder, which is a major diagnostic criteria. Various plasma cell disorders have been reported in POEMS, but the more common types include osteosclerotic myeloma and Monoclonal gammopathy of undetermined significance. 'S' represents skin changes, which are seen in 50-90% of patients.[8] Hyperpigmentation, hypertrichosis and skin thickening are the most common cutaneous features. Others include acrocyanosis, clubbing, hyperhidrosis, alopecia, flushing, acquired ichthyosis, vasculitis, livedo reticularis, Sweet's syndrome-like lesions and multiple seborrhoeic keratosis. Furthermore, angiomas are seen in 24-44% of Japanese patients. They are usually multiple, dome-shaped, purple-red, firm, papulnodular lesions distributed over trunk, proximal limbs and face. Various histological subtypes of angiomas are seen in POEMS syndrome, which include cherry-type capillary haemangioma, glomeruloid haemangioma, tufted angioma, immature vascular tumour, microvenular haemangiomas and multinucleated cell angiohistocytomas. Glomeruloid haemangioma is a specific cutaneous marker of POEMS syndrome.[9-11] It is a benign vascular proliferation that occurs inside ectatic blood vessels, producing a pattern resembling a renal glomeruli. This histologically distinct type of angioma was first described in 1990.[12] It is thought to represent a reactive endothelial proliferation in response to angiogenic stimuli, rather than a true neoplasm.

Table 1. Proposed criteria for diagnosis of POEMS syndrome.[7]

Major criteria (must have both)
- Polyneuropathy
- Monoclonal plasma cell-proliferative disorder

Minor criteria (must have at least one)
- Sclerotic bone lesions
- Castleman disease
- Organomegaly (splenomegaly, hepatomegaly, lymphadenopathy)
- Oedema (oedema, pleural effusion, ascities)
- Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)
- Skin changes (hyperpigmentation, hypertrichosis, pleothora, haemangiomata, white nails)
- Papilloedema

Other clinical features have also been associated with POEMS syndrome. They include weight loss, thrombocytosis, polycythaemia, papilloedema, ascities and pleural effusion. Renal dysfunction, as in our patient, is uncommon. The histological features that have been described include membranoproliferative glomerulonephritis-like lesions, microangiopathic glomerulopathy and mesangiolytic lesion.[13]

As POEMS syndrome is a rare entity, its treatment is based mainly on case reports and case series. The choice of treatment depends on the extent of disease. Isolated plasmacytoma can be treated with local radiation or surgical excision. For diffuse disease, systemic therapy is required.[14] Corticosteroids, alkylating agents like cyclophosphomide and melphalan, thalidomide, all-*trans*-retinoic, and Bevacizumab,[15] which is a recombinant, humanised, monoclonal antibody that inhibits VEGF, have been used. For severe or rapidly progressive disease, peripheral blood stem cell transplantation can be considered.[16] The treatment options for angiomas include intralesional steroid injection, sclerotherapy, surgical excision, laser therapy and systemic corticosteroid. POEMS syndrome often runs a chronic course. Relapse and additional new features may arise over time. The number of 'POEMS' features does not seem to affect survival.

In summary, POEMS syndrome is a rare plasma cell disorder with multisystem involvement. Its diagnosis requires a high index of suspicion, and the cutaneous features should not be overlooked.

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