

# A case report of an atypical POEMS syndrome

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**POEMS syndrome is a rare paraneoplastic syndrome that is defined by the presence of peripheral neuropathy, a monoclonal plasma cell disorder, and other paraneoplastic features, of which the most common include organomegaly, endocrinopathy and skin changes.<sup>1</sup> We report a case of POEMS syndrome in a 62-year old female who presented with worsening general condition, weight loss, asthenia and diarrhoea. Clinical examination showed the presence of ascites, peripheral oedema and a thickened skin with the presence of glomeruloid hemangioma. Further investigations showed the presence of three isolated FDG-avid bone lesions on PET-CT, a plasmacytoma with lambda restriction on bone marrow biopsy and elevated VEGF serum levels. The patient was treated with local radiotherapy with a total dose of 39 gray. Two months after radiotherapy, the patient already has a good clinical response with a reduction of ascites, fluid retention and diarrhoea, associated with a significant decline in the VEGF level.**

**After the case description, a review of the literature is presented.**

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## Introduction

POEMS syndrome is a rare paraneoplastic syndrome secondary to a plasma cell disorder and was first described by Bardwick in 1980.<sup>1</sup> The syndrome has also been called Osteosclerotic Myeloma, Crow-Fukase syndrome, Plasma Cell Dyscrasia, Endocrinopathy Polyneuropathy syndrome (PEP), or Takatsuki syndrome. Due to the complexity and multisystemic appearance of the disease, its exact prevalence is not known. In a recent national survey in Japan the prevalence of POEMS syndrome was estimated to be 0.0003 %.<sup>2</sup> The disease has a higher prevalence in men than women with a ratio of 2:1. Patients typically present with the disease in their fifth to sixth decade of life.<sup>3</sup>

In 2003, Dispenzieri et al. first described the principal criteria for diagnosis of POEMS syndrome based on data from 99 cases, but after the discovery in 2007 that vascular endothelial growth factor (VEGF) correlates

best with disease activity, the criteria were revised. The new criteria consist of two major mandatory criteria, three major criteria and six minor criteria. The mandatory major criteria are the presence of polyneuropathy and a monoclonal plasma proliferative disorder. The three major criteria are the presences of Castleman disease (angiofollicular lymph node hyperplasia), sclerotic bone lesions and elevated VEGF level. The minor criteria consist of organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema and thrombocytosis/polycythaemia.

To establish the diagnosis of POEMS syndrome, both mandatory criteria are required with the presence of at least one major and one minor criterion.<sup>4,5</sup>

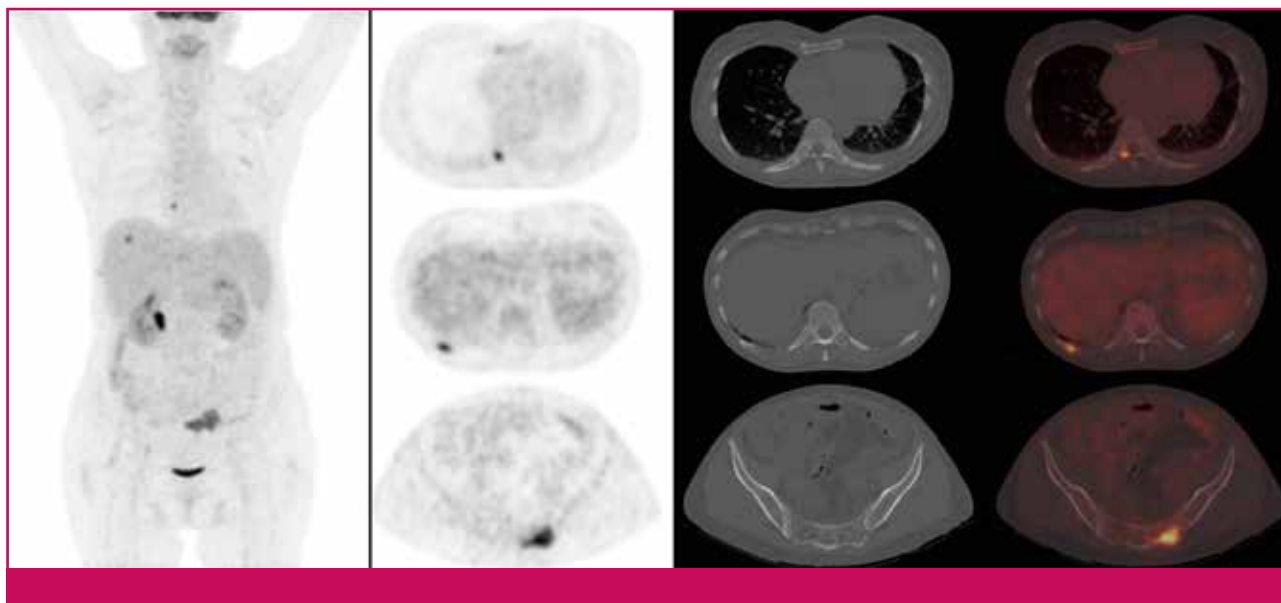
Other symptoms that are associated with POEMS syndrome are weight loss, diarrhoea, clubbing, hypertrichosis, pulmonary hypertension, restrictive lung disease and thrombotic events.<sup>6</sup>

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**Figure 1.** FDG-PET/CT. On the left are the PET images with top down respectively the bone lesion at the 9<sup>th</sup> dorsal vertebra, the 10<sup>th</sup> right rib and the left hemisacrum. On the right, the corresponding CT images and PET-CT fusion images are displayed.

## Case report

A 62-year old woman was admitted to the hospital because of worsening general condition, weight loss, asthenia and diarrhoea.

Nine months before presentation, she had a dry cough, which started after a two-week business trip to China. Her general practitioner advised her to take antibiotics with improvement of symptoms after seven days of treatment. The next six months, she experienced progressive asthenia, loss of appetite and weight loss of four kilograms. Subsequently, she developed fever with a flu-like syndrome for a couple of days, followed by an episode of watery diarrhoea. The diarrhoea gradually worsened over the following months with a frequency of 3-4 bowel movements per day for which she did not seek medical advice. After a second business trip to China, two months before admission, she noticed intermittent ankle oedema, most profound in the evening. The month prior to admission she experienced progressive asthenia, weight loss and persisting diarrhoea. Also the oedema became more prominent. In the days before she was hospitalised, the patient developed a swollen abdomen, dry mouth and dry eyes.

The patients' medical history revealed a cholecystectomy, an appendectomy and malaria. She was childless, a non-smoker and denied any illicit drug abuse. No chronic medication was recorded. Clinical examination showed an alert, adequately oriented, and afebrile patient. Her weight was 59 kilograms for a height of 166 centimetres. Cardiorespiratory parameters were respectively: blood

pressure 173/85 mmHg, regular 96 beats per minute, respiratory rate of sixteen breaths per minute and pulse oxygen saturation of 93%. Breath sounds were diminished at the basal parts of both lungs. Bowel sounds were hypoactive and ascites was present. No enlarged lymph nodes were palpated, but the spleen was slightly enlarged. Heart sounds were normal. Small red papules were present on the right shoulder and abdomen. The skin of her hands was thickened and dry with white fingernails. During hospitalisation she also developed a sensory loss in the lower legs.

Biochemistry showed a haemoglobin level of 10.2 g/dL (normal 12.0-16.0 g/dL), a white blood cell count of  $7.00 \times 10^9/l$  (normal  $4.00-10.00 \times 10^9/L$ ) and  $262 \times 10^9/L$  (normal  $150-450 \times 10^9/L$ ) blood platelets. The CRP was elevated to 50 mg/L (normal  $<5.0$  mg/L). Renal function was reduced with a creatinine of 1.47 mg/dL (normal 0.51-0.95 mg/dl), an estimated clearance of 38 mL/min/1.73 m<sup>2</sup> and a normal ionogram. Viral screening for hepatitis B, C and human immune deficiency virus (HIV) was negative. Auto-immune screening (ANA and ANCA) was also negative. Carcinoembryonic antigen (CEA) titer was within normal range. Endocrine screening showed a subclinical hypothyroidism (TSH 9.27 mIU/L (normal 0.27-4.20 mIU/L) with normal T3 and T4 levels), a normal cortisol dosage and a normal glycaemic profile. Serum protein electrophoresis showed a monoclonal spike in the beta zone which was identified as an IgA paraprotein type lambda by immunofixation. There were bilateral pleural effusions on chest radio-

graphy, no arguments for venous thrombosis on venous duplex of the lower limbs, and ascites and a discrete elevated volume of the spleen on echography of the abdomen. On echography of the kidneys there were no arguments for a post renal factor as cause of the diminished renal function. There was a normal systolic function (ejection fraction 65%) on transthoracic echocardiography without signs of pulmonary hypertension. On colonoscopy and gastroscopy there were no arguments for a malignancy of the gastrointestinal tract. Gynaecological examination and mammography to exclude a tumour of gynaecological origin was also normal. A glandular biopsy of the salivary gland was performed with a histological image suggestive of lymphocytic infiltration. Lumbar puncture displayed the presence of a high protein level without the presence of malignant cells. FDG-PET/CT-scan revealed three hypermetabolic bone lesions respectively in the 10<sup>th</sup> right rib, in the left hemisacrum and in the 9<sup>th</sup> dorsal vertebra.

On electromyography (EMG) there were characteristics of neuropathy without arguments for demyelination. Papilledema was ruled out with ophthalmoscopy. Bone marrow aspiration was within normal range, but on bone marrow biopsy the presence of a plasmacytoma with lambda restriction was shown. We did not interpret this as bone marrow involvement because of the negative bone marrow aspiration and because one third of patients with POEMS have localised bone marrow plasmacytoma without widespread bone marrow involvement.<sup>29</sup>

A skin biopsy of the red papule was suggestive for a glomeruloid hemangioma. A plasma VEGF dosage was performed and was elevated with a value of 492 pg/mL (reference value < 80 pg/mL). Based on the above findings, the diagnosis of POEMS syndrome was made (mandatory criteria: plasma cell disorders, peripheral neuropathy; major criteria: osteosclerotic lesions, elevated VEGF levels; minor criteria: splenomegaly, skin changes (angiomas), endocrine dysfunction (thyroid), ascites, with additional anorexia, weight loss and chronic diarrhoea).

Because of the presence of three isolated bone lesions, we preferred to treat the patient with local radiotherapy above systemic therapy. A total dose of 39 Gy was given in thirteen fractions at the sacrum, the rib cage and the 9<sup>th</sup> dorsal vertebra. Two months after radiotherapy, the patients had already significantly improved. The ascites, fluid retention and diarrhoea disappeared. Plasma VEGF levels were reduced to 131 pg/mL. On FDG-PET/CT, performed two months after termina-

tion of radiotherapy, the hypermetabolic bone lesions were still present. However, this could be explained by the delayed response of sclerosation after radiotherapy, which had not taken place yet.

## Discussion

This case report is a rather atypical presentation of a POEMS syndrome. In classical POEMS syndrome the dominating clinical symptom is peripheral neuropathy that is typically ascending, symmetrical and affecting both sensory and motor nerves. In this patient, polyneuropathy was not present when she showed initial symptoms. She only developed sensory loss in the lower legs twelve months after initial symptoms started. Her EMG also showed no demyelination, which is typical for POEMS syndrome.<sup>7</sup> Because the presence of polyneuropathy presented gradually over time, it took nine months to make the final diagnosis in this case.

When the predominant symptom is neuropathy, differential diagnosis consists of chronic inflammatory polyradiculoneuropathy (CIDP), monoclonal gammopathy of undetermined significance (MGUS) and immunoglobulin light chain amyloid neuropathy. POEMS syndrome is differentiated from CIDP by the presence of bone lesions and the presence of monoclonal plasma cells.<sup>8</sup> Vascular endothelial growth factor (VEGF) allows the differentiation from MGUS and amyloid neuropathy. Due to VEGF there is capillary leak that is responsible for extra-vascular volume overload resulting in ascites, peripheral oedema and pleural effusions. VEGF also plays a role in the formation of haemangiomas and contributes to the presence of papilledema seen in patients with POEMS.<sup>9</sup> Dispenzieri et al. have reported that a plasma VEGF level of 200 pg/ml has a specificity of 95% with a sensitivity of 68% in support of diagnosis of POEMS syndrome.<sup>10</sup>

Organomegaly is seen in 50% of patients. Most frequently enlarged organs are the liver and spleen. Lymphadenopathy is also associated with POEMS.<sup>11</sup>

The typical endocrinological symptoms are present in the four major endocrine axes (gonadal, thyroid, glucose and adrenal). The exact mechanism causing these symptoms is not known. Our patient developed subclinical hypothyroidism and L-thyroxine was prescribed.<sup>12</sup>

The M-protein most frequently seen in POEMS is immunoglobulin A and G. Typically these plasmacytomas have a lambda restriction. According to Dispenzieri et al. 87% of patients with POEMS have a detectable M-protein in their serum or urine by immunofixation.<sup>5-13</sup>

The typical skin changes seen in POEMS syndrome are hyperpigmentation, hypertrichosis, sclerodermatous thickening, hyperhidrosis, digital clubbing, plethora, leukonychia ('white nails') and cutaneous haemangiomas. There are three types of haemangiomas: the cherry, lobular and glomeruloid type. The glomeruloid type is the most specific for POEMS syndrome. The most reported skin symptom in POEMS is diffuse hyperpigmentation, seen in more than 90% of patients.<sup>14,15</sup>

Another important criterion of the disease is the presence of osteosclerotic bone lesions. They are apparent in 95% of patients with POEMS syndrome and are characterised by diffuse infiltration of plasma cells. In contrast with multiple myeloma, bone lesions in POEMS are generally not associated with bone pain or an increased risk of fractures. The recommended standard investigations for identifying these bone lesions are a CT-scan or bone scintigraphy. CT is superior to X-ray in detecting bone lesions. However, CT is unable to differentiate active from non-active lesions. Whole body FDG-PET/CT is useful to detect hypermetabolic bone lesions and monitor treatment response for patients with FDG avid bone lesions.<sup>5-16,17</sup>

The main treatment target in POEMS is the underlying plasma cell clone. Because of the rarity of the disease, there are no randomised controlled trials available to guide treatment. It is important to underline that there is a time lag between completion of therapy and clinical response. Neurological improvement is typically seen six months after completion of therapy. Responses seen on FDG-PET/CT also have a time lag of six to twelve months. Other features like skin changes, oedema and papilledema may improve sooner. Therefore persistent symptoms should not lead to early discontinuation of therapy.<sup>4-17,18</sup>

In practice, treatment choices are made based on the extensiveness of the disease and the patients' characteristics. Radiotherapy is the treatment of choice for patients with localised sclerotic bone lesions. Dispenzieri proposed to reserve radiotherapy for patients with one to three bone lesions and no bone marrow involvement.<sup>19,20</sup> The administered median dose of radiation is 40 Gy. In a study of Humeniuk et al., 38 patients with limited bone lesions were treated with radiation therapy. The partial haematological response rate was 31%, the 4-year overall survival was 97% and the event-free survival was 52% after a median follow-up of 43 months.<sup>21</sup> High-dose melphalan (140 mg/m<sup>2</sup> - 200mg/m<sup>2</sup>) and autologous stem cell transplantation (ASCT) is an effective treatment in patients with disseminated disease

(bone marrow involvement or diffuse plasma cell infiltrates), a good performance status and no important comorbidities.<sup>23</sup> In a study of Nakaseko et al. 23 patients were treated with ASCT. A complete haematological response, defined by negative M-protein using immunofixation was achieved in 65% of patients. An improvement in clinical symptoms and a reduction in VEGF were observed in 22 patients (96.6%). At a median observational period of 51 months, the 3- and 5-year overall survival and progression-free survival (PFS) was 96% and 81% and 64.6% and 59.8%, respectively. Although there is a good overall response to this treatment, ASCT is associated with a high risk of transplant-related toxicities.<sup>22</sup> In a study of the Mayo clinic with sixteen patients transplanted, six patients (37.5%) were admitted to the intensive care unit, five patients (31%) required intubation and mechanical ventilation, and one patient (6.2%) died.<sup>24</sup>

There is no consensus therapy for patients who are not good candidates for high-dose melphalan (>65 or abnormal organ function) or who subsequently relapse.<sup>18</sup> In these patients, treatment with lenalidomide/dexamethasone or melphalan/dexamethasone can be considered. Lenalidomide is administered at a dose of 25 mg for 21 days in combination with dexamethasone 40 mg weekly in cycles of 28 days until disease progression. In a study of Zagouri et al., the PFS at twelve months was 93.9% after a median number of nine administered cycles. 95.3% achieved haematological response including 18.6% complete response, 39.5% partial response and 18.6% very good partial response. Unfortunately there are no data on long-term outcome.<sup>25</sup> Oral melphalan is administered at a dose of 10mg/m<sup>2</sup> in combination with oral dexamethasone 40mg on day 1 to 4 every 28 days. In a prospective study of Li et al., 31 patients received twelve cycles of melphalan/dexamethasone. 80.6% of patients achieved haematological response with 38.7% complete remission and 41.9% partial remission. All patients were alive, free of neurological relapse and had a VEGF reduction after a median follow-up of 21 months.<sup>26</sup>

In conclusion we can state that melphalan has a better haematological and PFS than lenalidomide. Lenalidomide is also not registered or reimbursed in Belgium for the treatment of POEMS syndrome. Prolonged use of melphalan can occasionally be associated with myelodysplasia or acute leukaemia.

If appropriately treated, the prognosis of POEMS is good, independent of the number of disease symptoms and ranges between eight to thirteen years. Although

## Key messages for clinical practice

1. POEMS syndrome is a rare plasma cell paraneoplastic phenomenon consisting of polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes.
2. Polyneuropathy and a monoclonal plasma cell disorder are the key symptoms in diagnosis.
3. Osteosclerotic bone lesions are present in almost all patients.
4. An elevated plasma VEGF supports the diagnosis and plasma VEGF levels are used as markers for disease activity.
5. The main target of therapy is the underlying plasma cell disorder.
6. Treatment options are radiotherapy for localised disease, high dose melphalan with autologous stem cell transplantation for disseminated disease and melphalan/dexamethasone for disseminated disease in fragile patients.

polyneuropathy, the dominant symptom that will develop eventually in every POEMS syndrome patient, is invalidating, it is not life threatening. The main causes of death are cardiorespiratory failure, renal failure, infection, stroke and complications associated with the treatment of the disease.<sup>4-27,28</sup>

### Conclusion

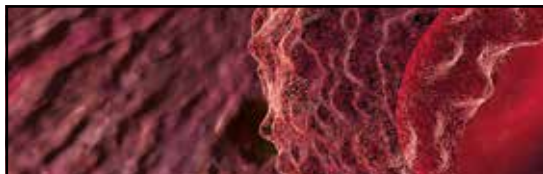
POEMS syndrome is a paraneoplastic syndrome associated with a clonal plasma cell neoplasm. Misdiagnosis of the disease is common due to its rarity and complexity. Patients present with multisystemic disease manifestations. Early diagnosis is vital to reduce the morbidity rate and increase survival rate. The best choice of therapy for younger patients with diffuse plasma cell infiltration and good organ function is an autologous stem cell transplantation. Melphalan/dexamethasone is a suitable alternative for patients with contraindications for autologous stem cell transplantation, whereas radiotherapy is preferred for patients with no more than three different osteosclerotic bone lesions. Novel agents such as lenalidomide have shown promising results, but additional clinical data are needed.

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