CASE REPORT

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Polyradiculoneuropathy, Organomegaly, Endocrinopathy, Monoclonal Plasma Cell Disorder, and Skin Changes (POEMS) Syndrome: A case report

Raneem Alraheili[1]✉, **Turki Alwasaidi**[2]

[1]College of Medicine, Taibah University, Al Madinah, Saudi Arabia

[2] Hematology Division, Medicine Department, Prince Mohammed Bin Abdulaziz Hospital, Ministry National Guard - Health Affairs, AL Madinah, Saudi Arabia - Medicine Department, College of Medicine, Taibah University, AL Madinah, Saudi Arabia.

✉**Corresponding author**

College of Medicine, Taibah University, Al Madinah, Saudi Arabia

Email: dr.raneemalraheili@gmail.com

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ABSTRACT

Polyneuropathy, Organomegaly, Endocrinopathy, M Proteins, and Skin changes (POEMS) syndrome is a rare type of plasma cell dyscrasia. It is a paraneoplastic syndrome with multiple systemic manifestations. Diagnosis of POEMS syndrome is commonly

challenging, due to its multisystemic involvement and its rarity. This case report described a 60 year old female patient who suffered from POEMS syndrome. The patient's symptoms were complicated. Initially, she was misdiagnosed as pulmonary tuberculosis. Subsequently, POEMS syndrome has been diagnosed based on clinical features and laboratory findings. After the diagnosis of POEMS syndrome, she treated with lenalidomide – dexamethasone regimen. The patient completed seven cycles with a significant response followed by a high dose of melphalan chemotherapy with autologous hematopoietic stem cell transplantation as consolidation therapy.

Keywords: Polyradiculoneuropathy; Organomegaly; Endocrinopathy; Monoclonal plasma cell disorder; Skin changes

1. INTRODUCTION

Polyradiculoneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder, and Skin changes (POEMS) syndrome is a rare multisystemic disease and paraneoplastic syndrome secondary to plasma cell dyscrasia (Dispenzieri, 2007). The acronym, which was coined in 1980 by Bardwick, refers to some, but not all of the features of this syndrome (Dispenzieri et al., 2003). Diagnosis of POEMS syndrome is commonly challenging and does not require the patient to present with all clinical manifestations in the above-mentioned acronym. There are several important clinical features and laboratory findings not included in the acronym, including sclerotic bone lesions, papilledema, thrombocytosis/erythrocytosis, extravascular volume overload, abnormal pulmonary function tests, and high Vascular Endothelial Growth Factor (VEGF) levels (Dispenzieri, 2017). Some cases of POEMS syndrome have been reported in the United States China, France, India, and Japan (Dispenzieri, 2007). Nevertheless, the prevalence and incidence of POEMS syndrome are still unknown due to the complexity of the clinical features (Dispenzieri, 2007). The peak incidence is in the fifth and sixth decades of life (Warsame et al., 2017). The prevalence is about 0.3 per 100000 which was calculated in 2003 by a nationwide Japanese survey (Dispenzieri, 2005).

Our knowledge about the pathophysiological mechanism by which plasma cells cause POEMS syndrome remains unclear and not fully understood until now. Neovascularization induced by up-regulation of growth factors and several pro-inflammatory cytokines is suggested to be important in the pathogenesis of this syndrome.These cytokines include Interleukin-6 (IL-6), VEGF, Tumor Necrosis Factor-a (TNF-a), and Interleukin-1b (IL-1b) among others (Dispenzieri, 2019). The treatment of POEMS syndrome includes two main parts: the first part is directing to the plasma cells, which includes chemotherapy, radiation, Autologous Stem Cell Transplantation (ASCT); the second part is directing to the rest of POEMS syndrome, for example, the high VEGF levels (Dispenzieri et al., 2003; Dispenzieri, 2019). POEMS syndrome is potentially fatal if it is not treated properly. Also, it is associated with a significant deterioration in the quality of life through anasarca, cachexia, neuropathy, and thromboembolic events. Early diagnosis and treatment with a multidisciplinary approach may reduce the long-term irreversible morbidity (Kumar & Sharma, 2015).

2. CASE PRESENTATION

A 60 years old female was admitted to Prince Mohammed Bin Abdulaziz Hospital (PMBAH) in Al-Madinah on 16-5-2018 due to intermittent dry cough and shortness of breath on execration for 6 months, associated with progressive course weakness in her legs with numbness in the feet and fatigue for a long duration. Before the presentation to our hospital, the patient had been diagnosed with Pulmonary Tuberculosis (TB) and started anti TB medications. The patient was taking TB medications for 4 months without any clinical improvement. As a result, the doctors in the local hospital had adjusted the TB medications regimen many times but the treatment had failed to adequately control her symptoms. One month before presentation to our hospital, she had developed abdominal distension gradually without any obvious causes. The patient complained of having weight loss approximately 17 kg during the past two years, but in the last 6 months, she only lost 4 kg.

Physical examination revealed a cachectic female patient with acrocyanosis and flushing over the cheeks with stable vital signs. The examination of lymph nodes showed palpable, soft, rubbery not painful lymph nodes about 1.5 cm in the left inguinal lymph node and right axillary fossa with small palpable lymph nodes in the right inguinal. Regarding cardiorespiratory examination, there was dullness at the lung bases with bilateral decreased air entry and inspiratory crackles with normal heart sounds. The patient's abdomen was distended with massive hepatosplenomegaly. Neurological examination revealed 4 out of 5 muscle strength in the lower limbs, and normal tone and reflexes in the upper and lower limbs. However, funduscopic examination showed papilledema in both eyes that were confirmed by slit-lamp examination by an ophthalmologist.

Laboratory investigations demonstrated mild polycythemia (RBCs 5.54 $x10^{12}$ cells/L, Hb 162 g/L and HCT 55%) and high corrected reticulocytes (94.4 $x10^{9}$ cells/L). Low serum calcium level with the normal level of other electrolytes. Impaired kidney function tests are (eGFR[1] 46mL/min/L, creatinine 111 µmol/L, urea 18 mmol/L). Normal total protein level with decreased serum

albumin is (total protein 64 g/L and albumin 31 g/L). The results of endocrine hormones analysis showed decreased Free Tetraiodothyronine (Free T4) and increased Thyroid-Stimulating Hormone (TSH). Arterial blood gas showed a decreased level of bicarbonate (HCO_3^-) with a normal anion gap. However, the liver function test and coagulation profile were within normal limits. Serology, connective tissue diseases, and vasculitis workup were negative. Serum protein electrophoresis and immunofixation demonstrate trace monoclonal IgG kappa (region M – spike 0.60 g/L). Serum free light chain analysis showed high kappa (κ) light chain 72.13 mg/L (normal range: 3.3-19.4) and lambda (λ) light chain 32.28 (normal range: 5.7-26.3) with high kappa/lambda ration 2.23. However, Serum immunoglobulins, α, and β globulins were within the normal range (Table 1).

Table 1 Laboratory Tests Results of the Initial Assessment of the Patient

Test	Value	Change Relative to Normal Value	Normal Range
Complete Blood Count:			
Red blood cells, $x10^{12}$ cells/L	5.54	↑	4 – 5.4
Hemoglobin (Hb), gm/L	162	↑	120 – 160
Hematocrit (HCT), %	55	↑	36 – 54
White Blood Cells, $x10^9$ cells/L	11.0		4 – 11
Neutrophils, $x10^9$ cells/L	6.63		2 – 7.5
Lymphocytes, $x10^9$ cells/L	3.45		1 – 4.4
Monocytes, $x10^9$ cells/L	0.61		0.1 – 1.1
Eosinophils, $x10^9$ cells/L	0.11		0.1 – 0.7
Basophils, $x10^9$ cells/L	0.06		0.00 – 0.1
Reticulocytes $x10^9$ cells/L	94.4	↑	24 - 84
Platelet, $x10^9$ cells/L	323		150 – 400
ESR, mm/h	8		0 – 20
Electrolytes:			
Sodium, mmol/L	140		136 – 145
Potassium, mmol/L	4.4		3.5 – 5.1
Adjacent Calcium, mmol/L	2.25	↓	2.2 – 2.5
Phosphate, mmol/L	1.39		0.74 – 1.52
Magnesium, mmol/L	0.99		0.66 – 1.07
Arterial Blood Gas:			
CO_2	36		35 – 45
HCO_3	22	↓	24 – 33
Anion Gap	11		10 – 15
Kidney Function Tests:			
eGFR, mL/min/L	46	↓	=>60
Urea, mmol/L	18	↑	3.5 – 7.2
Creatinine, µmol/L	111	↑	50 – 98
Uric Acid, µmol/L	340		150 – 350
Coagulation Profile:			
Prothrombin time, seconds	14.1		11 – 14.5
aPTT, seconds	28.7		26.1 – 37.3
INR, %	1.19		0.8 – 1.2
Serology, Connective Tissue Diseases, and Vasculitis workup:			
C-ANCA	<2.3		
P-ANCA	<3.2		
Anti-nuclear antibody	Negative		Negative
CCP -IgG, U/Ml	1.0		<= 4.9
C-Reactive Protein, mg/L	7.8	↑	0 – 5
HIVAg/Ab	Negative		Negative

Hepatitis C	Negative		Negative
HBsAg	Negative		Negative
Liver Function Tests:			
Aspartate Aminotransferase, U/L	12		5 – 34
Alanine Aminotransferase, U/L	12		5 – 55
Albumin, g/L	32	↓	34 – 48
Total Protein, g/L	56	↓	60 – 83
Alkaline Phosphatase, U/L	45		40 – 150
Total Bilirubin, µmol/L	7.5		3.4 – 20.5
Thyroid Function Test:			
TSH, µIU/mL	7.92	↑	0.35 – 4.94
Free T4, pmol/L	8.9	↓	9 – 19
Serum Protein Electrophoresis:			
Serum Albumin, g/L	33.1	↓	40.2 – 47. 6
κ Light chain	72.13	↑	3.30 – 19.4
λ light chain	32.28	↑	5.71 – 26.3
κ/λ	2.23	↑	0.26 – 1.65
α1- globulins, g/L	2.4		2.1 – 3.5
α2- globulins, g/L	6.1		5.1 – 8.5
β- globulins, g/L	5.2		3.4 – 5.2
Imunoglobulin, g/L	6.2	↓	8 – 13.5
ESR, Erythrocyte sedimentation rate; eGFR, estimate glomerular filtration rate; aPTT, activated partial thromboplastin time; INR, international normalized ratio; C-ANCA, Central Antineutrophil cytoplasmic antibodies; P-ANCA, perinuclear cytoplasmic antineutrophil cytoplasmic antibodies; CCP, cyclic citrullinated peptide; HIV, human immunodeficiency virus; HBsAg, hepatitis b virus surface antigen.			

Chest radiograph demonstrated collapsed consolidation at left lung base and lingual with right paracardiac infiltrate with vascular congestion in both lung fields with bilateral pleural effusion and heart shadow within normal limits (Figure 1). Skeletal Survey showed multiple cervical lymphadenopathies on both sides in different triangles and bilateral axillary lymphadenopathy along with multiple prominent mediastinal lymph nodes, minimal pericardial effusion, and moderate bilateral pleural effusion. In addition to hepatosplenomegaly with heterogeneous enhancement is compatible with hepatic and splenic infiltrations with a moderate amount of ascites. Multiple lymphadenopathies are at splenic hilar and prominent inguinal lymph nodes. Also, it showed osteosclerotic bone lesions scattered in the ribs, body of the sternum, pelvis, and spine with mild diffuse osteopenia (Figure 2).

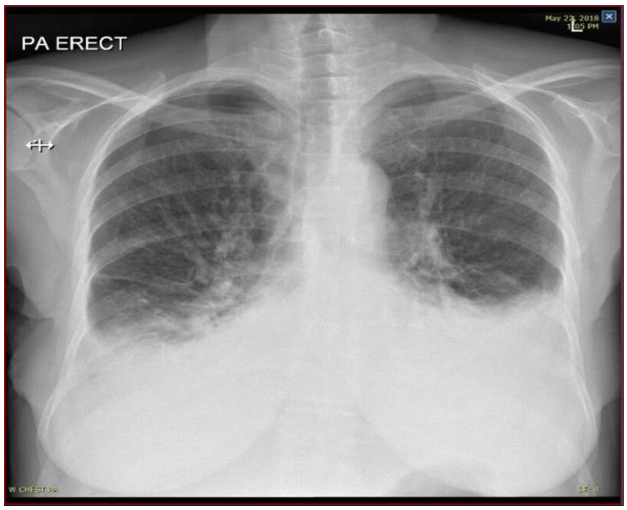

Figure 1 Chest X-ray showing collapsed consolidation at left lung base with bilateral pleural effusion.

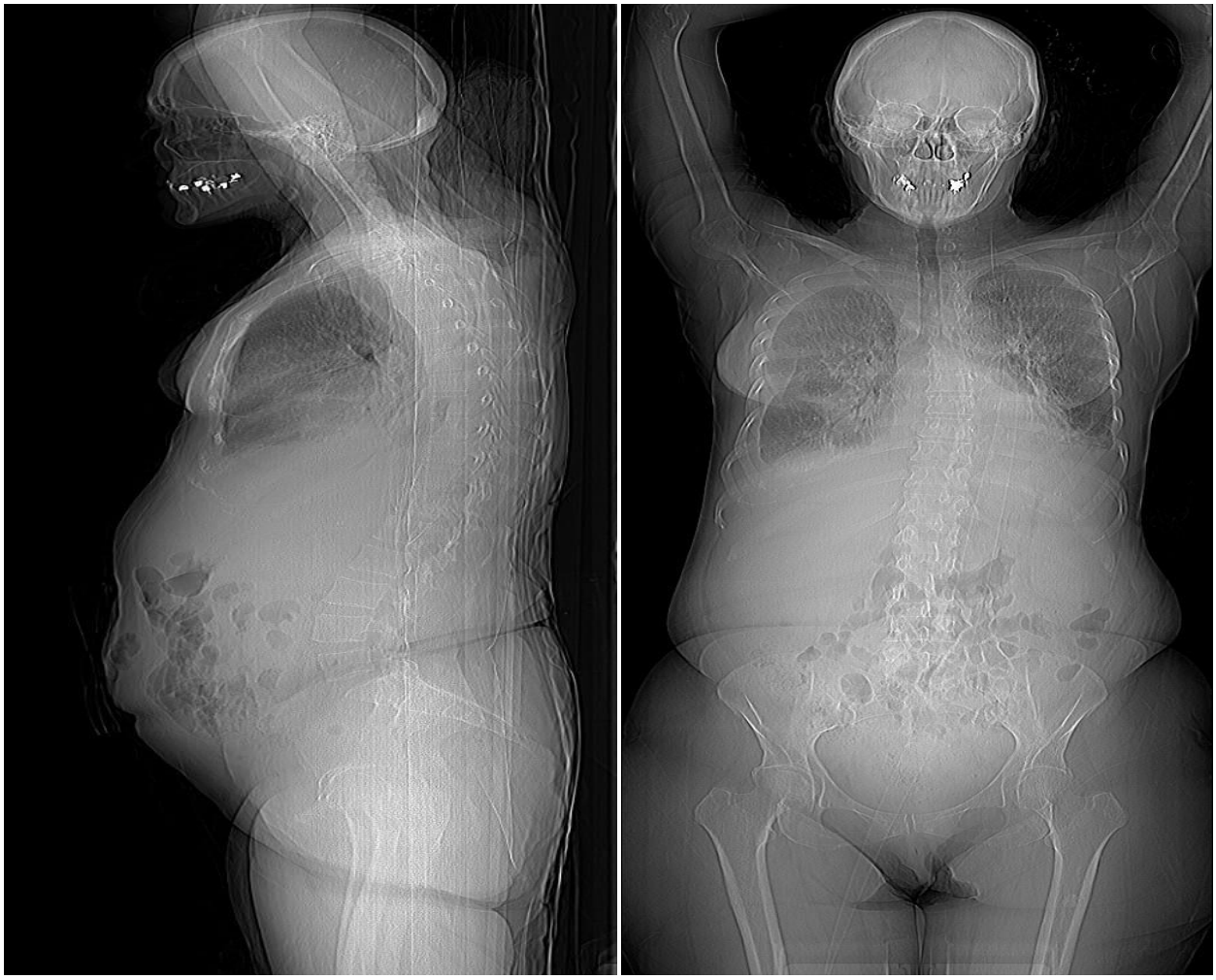

Figure 2 Anterior and lateral views of skeletal survey

A purified protein derivative skin test, TB Quantiferon, acid fast bacilli smear and sputum culturewere negatives. Pleural fluid examination showed exudate pleural effusion with typical lymphocytes. Analysis of pleural fluid using flow cytometry didn't detect any abnormal lymphoid population. The test showed around 83% mature T-cell with no aberrant loss or aberrant expression of T-cell marker with a CD4/CD8 ratio of 0.23, around 14% NK-cells, and around 0.6% polyclonal B-cells. Nerve Conduction Study (NCS) revealed mild motor and sensory polyneuropathy in lower limbs. The genetic study of Janus Kinase 2 (JAK2) mutation was negative. Left supraclavicular lymph node core biopsy showed mild chronic lymphadenitis without atypical lymphocytic changes. Immunohistochemistry confirmed the diagnosis of reactive follicular lymphoid hyperplasia. Histopathological examination of liver biopsy revealed lymphocytes infiltration with no evidence of malignancy. Bone marrow aspiration revealed the active proliferation of bone marrow cells without a significant increase in the plasma cells. Plasma cells have been reported polyclonal on kappa and lambda immunostaining.

Subsequently, POEMS syndrome has been diagnosed based on clinical manifestation and laboratory findings. As multiple features of this syndrome accumulated, the diagnosis of POEMS syndrome was made based on demyelinating polyneuropathy, hepatomegaly, splenomegaly, lymphadenopathy, hypothyroidism, IgG kappa monoclonal paraproteinemia, acrocyanosis associated with flushing over the cheeks, sclerotic bone lesions, pleural effusion, ascites, papilledema, and polycythemia. The patient started on the lenalidomide – dexamethasone regimen. The patient completed seven cycles followed by high-dose melphalan with autologous hematopoietic stem cell transplantation as a consolidation therapy that showed significate response. Paraproteinemia, peripheral neuropathy hepatosplenomegaly, lymphadenopathy, ascites, and effusions were resolved. Eastern Cooperative Oncology Group (ECOG) performance status changed from 3 to 0.

4. DISCUSSION

POEMS syndrome is a paraneoplastic syndrome with multiple systemic manifestations due to plasma cell dyscrasia (Dispenzieri et al., 2004). It is also known as Crow-Fukase syndrome, osteosclerotic myeloma, and Takatsuki syndrome (Jindahra et al., 2018). The

acronym represents some of the defining features of this syndrome, including polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (Dispenzieri, 2007). Regarding the International Myeloma Working Group (IMWG) criteria, POEMS syndrome is diagnosed when both of the mandatory major criteria, one of the three other major criteria, and one of the six minor criteria are present (Dispenzieri, 2019; Kuwabara et al., 2012) (Table 2). In this patient, POEMS syndrome was diagnosed based on the presence of two mandatory major criteria, one of the three other major criteria, and all six minor criteria, that shown in (Table 3).

Table 2 Criteria for the Diagnosis of POEMS Syndrome

Mandatory major criteria	Polyneuropathy (typically demyelinating) Monoclonal plasma cell-proliferative disorder (almost always k)
Other major criteria (one required)	Castleman disease[1] Sclerotic bone lesions Vascular endothelial growth factor elevation
Minor criteria	Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) Extravascular volume overload (edema, pleural effusion, or ascites) Endocrinopathy (adrenal, thyroid [2], pituitary, gonadal, parathyroid, pancreatic [2]) Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails) Papilledema Thrombocytosis/polycythemia
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B12 values

Table 3 Clinical Manifestations in our Patient

Criteria	Evidence
Polyneuropathy	Progressive weakness in the lower limbs and numbness. NCS revealed mild polyneu-ropathy in lower limbs.
Monoclonal plasmacell-proliferative disorder	IgG κ type of M protein (+)
Osteosclerotic bone lesions	Bone imaging showed multiple osteosclerotic bone lesions in pelvis, ribs, spine and body of the sternum.
Organomegaly	Hepatosplenomegaly and diffuse prominent lymphadenopathy
Extravascular volumeOverload	Pleural effusion, pericardial effusion, edema and ascites
Endocrinopathy	Hypothyroidism
Skin changes	Acrocyanosis and flushing
Papilledema	Confirmed by ophthalmology examination
Polycythemia	Complete blood count demonstrated mild polycythemia.

Nevertheless, the diagnosis of POEMS syndrome in this patient was very difficult. She was misdiagnosed as pulmonary TB with inappropriate anti TB medications. POEMS syndrome was diagnosed in this patient according to the 2019 update on diagnosis,

risk-stratification and management of POEMS Syndrome (Dispenzieri et al., 2004). Given the rarity of POEMS syndrome and its diverse symptoms, it is extremely difficult to make the accurate diagnosis from the first time particularly when the patient complained from numbness and weakness in the lower limbs while taking anti TB medications. It is the first case report about POEMS syndrome in Saudi Arabia. This case report may remind some doctors of this rare disease when they are facing an intractable case with some of the specific manifestations of POEMS syndrome. We recommend that more case reports concerning specific features of POEMS syndrome should be considered to improve the future diagnosis and treatment.

5. CONCLUSION

We described a 60 year old female patient diagnosed with POEMS syndrome. Making the diagnosed with this syndrome is challenging due to its rarity and complexity. Early diagnosis may reduce the mortality rate and long-term irreversible morbidity.

Author's contributions

Raneem Alraheili conducted the research, designed and conceived the study, designed figures, designed tables, wrote initial and final draft of article. Turki Alwasaidi conceived and designed the study, took an informed consent from the patient, provided supervision and logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Conflict of interest

The authors have no conflict of interest to declare.

Informed consent

Informed consent was obtained from the patient for publication of this case report. No patient's name, initials, hospital or ID numbers, dates of birth, other personal or identifying information were used.

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Data and materials availability

All data associated with this study are present in the paper.

Peer-review

External peer-review was done through double-blind method.

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