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POEMS Syndrome Presenting as Long-term Refractory Ascites

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POEMS syndrome is a rare multisystem disease with a wide spectrum of clinical features characterized by polyneuropathy, organomegaly, endocrinopathy, M protein production and skin changes. We present a patient who had suffered refractory ascites of unknown etiology for three years. She had sought medical attention at several hospitals because of skin hyperpigmentation, ascites and polyneuropathies. POEMS syndrome was finally diagnosed by bone marrow biopsy. The patient was commenced on thalidomide therapy and remains in a stable condition. This case report is to remind clinicians to consider this syndrome whenever confronting a patient with refractory ascites of unknown cause and with acquired peripheral neuropathy refractory to treatment.

Key words: POEMS syndrome, hyperpigmentation, ascites

INTRODUCTION

POEMS syndrome is an unusual atypical plasma cell disorder involving some organ systems with five dominant features characterized by polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes[1]. Most cases have been reported from Japan and it predominates in middle-aged men. It is strongly associated with plasma cell dyscrasia; many other abnormalities have been described including papilledema, pleural effusion, ascites, thrombocytosis, osteosclerotic bone lesions, renal dysfunction and pulmonary hypertension[2-4]. Herein we report a patient who presented with refractory ascites and neurological symptoms. We stress several learning points for the clinician.

CASE REPORT

A 51-year-old woman was admitted to our hospital because of progressive weakness and numbness in the distal upper and lower limbs that had lasted for one year. She had also been suffering from refractory ascites and pleural effusion without any identifiable cause for three years. She had sought help in many hospitals, but no apparent cause of the ascites was found. She received only abdominal tapping for symptom relief every one to two months. Based on the symptom of refractory massive ascites, ovarian cancer with peritoneal carcinomatosis had been suspected at another hospital two years previously. She had undergone bilateral adnexectomy, but the pathology report yielded no evidence of malignancy. She had lost more than 10 kilograms in body weight in the previous two years. Both the patient and her mother had thalassemia.

A clinical examination revealed a chronically ill appearance with sunken cheeks and hollow temples. The patient's vital signs were stable without fever, except for mild dyspnea caused by the massive ascites. A systemic review revealed tachycardia, abdominal distention and shifting dullness. Dermatology disclosed diffuse skin thickening with sclerodermoid changes and hyperpigmentation especially at the upper extremities (Fig. 1A), lower extremities and abdomen (Fig. 1B), with restricted function of both hands. Hypertrichosis (Fig. 1C) was seen in both upper and lower limbs, and white fingernails and toenails were noted. A neurological examination showed distal weakness and paresthesia in the upper and lower limbs with arreflexic tetraparesia. A cranial nerve examination was normal except for papilledema.

In the laboratory examinations, the erythrocyte sedimentation rate was 64 mm/h and the C-reactive protein level was 4.31 mg/dL. The white blood cell count was 11600/μL and the hemoglobin level was 7.3 g/dL. Endocrinology showed a free T4 level of 0.52 ng/dL (reference

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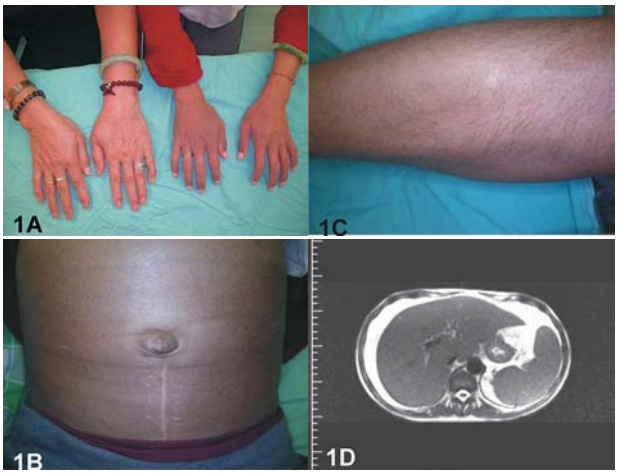

Fig 1: Diffuse hyperpigmentation and sclerodermoid changes of bilateral hands, white fingernails were noted compared with her mother (left side) (1A), the same skin changes were also noted at abdomen (1B). Hypertrichosis of right lower leg was found (1C). Coronal T2 weighted magnetic resonance images showed massive ascites and splenomegaly (1D).

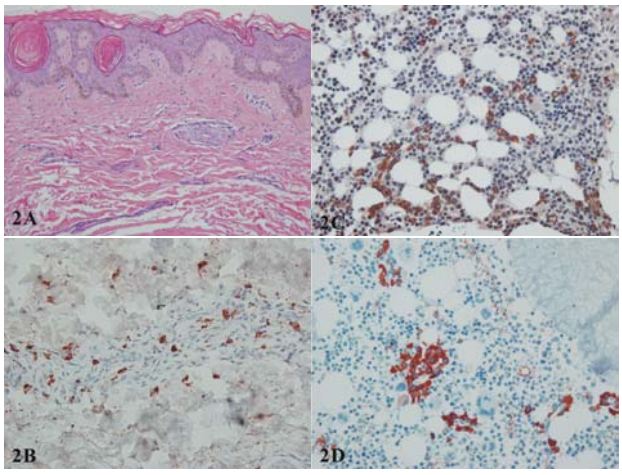

Fig 2: Histopathologic examination of the specimen taken from the sclerodermoid patch of abdomen revealed irregular acanthosis, sparse perivascular inflammatory cells infiltrate, and hyperpigmentation of basal layer. Besides, thickened collagen bundles with increased number of fibroblasts were also noted. (2A, H&E stain, 200X). Perivascular infiltrate of the same specimen were principally mast cells which were highlighted immuno-histochemically by tryptase (2B, tryptase, 400X). In addition, immuno-histochemical stain of the bone marrow with CD138 highlighted increased population of plasma cells (2C, CD138, 400X). Lambda monoclonality was also found in bone marrow biopsy (2D, lambda light chain, 400X).

range 0.8-2.0 ng/dL) and TSH was 11.30 UIU/mL (reference range 0.2-3.3 UIU/mL) suggesting primary hypothyroidism. Liver function tests were within normal limits. Renal function tests showed a BUN level of 57 mg/dL and a creatinine level of 3.2 mg/dL, indicative of renal dysfunction. Urinalysis showed traces of protein and red blood cells. The serum Beta-2 microglobulin level was elevated at 20.88 μg/L (reference range 1.0-2.4 μg/L). Chest X-rays revealed blunting of both costophrenic angles and elevation of the right hemidiaphragm. Whole body bone scan and other X-ray survey disclosed no significant findings. Magnetic resonance imaging of the abdomen showed pleural effusions of both costophrenic angles, massive ascites, para-aortic lymph node enlargement and splenomegaly (Fig. 1D).

A skin biopsy taken from a sclerodermoid patch of the abdomen revealed irregular acanthosis, basal layer hyperpigmentation, sparse perivascular inflammatory cells infiltration, and slightly increased fibroblast numbers and amount of collagen (Fig. 2A). The perivascular infiltrate of the sclerodermoid abdominal skin comprised mast cells principally (Fig. 2B). Histopathology and immunohistochemistry of a bone marrow biopsy showed atypical plasma cell proliferation (Fig. 2C) with lambda monoclonality (Fig. 2D). No evidence of amyloid deposition or malignancy was noted.

POEMS syndrome was eventually diagnosed according to the presence of polyneuropathy, splenomegaly, primary hypothyroidism, atypical monoclonal plasma cell proliferation in the bone marrow and skin lesions. In addition, the patient showed other associated abnormalities such as pleural effusion, ascites, papilledema, hematologic disorders and renal dysfunction. The patient was treated with oral thalidomide (100 mg every 12 h daily), abdominal tapping and supplementation with thyroid hormone during hospitalization. She was discharged in a stable condition. During a four-month follow-up after commencing the thalidomide therapy the patient developed side effects such as constipation, drowsiness and skin itching, starting at two weeks. However, she gradually came to tolerate the drug and these side effects had disappeared by four weeks. Serial laboratory follow-ups at the outpatient department showed no obvious improvement. Hemoglobin levels were 6.6 g/dL and 6.7 g/dL at two and four months, respectively, after starting therapy. The creatinine level, indicating renal function, was 3.3 mg/dL at two months and 3.2 mg/dL at four months. However, there was a substantial clinical

Table 1 Criteria for the diagnosis of poems syndrome [a].

Major criteria	1. Polyneuropathy
	2. Monoclonal plasma cell-proliferative disorder (almost always λ)
	3. Sclerotic bone lesions
	4. Castleman disease
	5. Vascular endothelial growth factor elevation
Minor criteria	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
	7. Extravascular volume overload (edema, pleural effusion, or ascites)
	8. Endocrinopathy (adrenal, thyroid, [c] pituitary, gonadal, parathyroid, pancreatic [c])
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata,plethora, acrocyanosis, flushing, white nails)
	10. Papilledema
	11. Thrombocytosis/polycythemia [b]
Other symptoms and signs	Other symptoms and signs
	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B12 values
	Possible associations
Possible associations	Arthralgias, cardiomyopathy (systolic dysfunction), and fever

POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes.
[a] Polyneuropathy and monoclonal plasma cell disorder present in all patients; to make diagnosis at least one other major criterion and 1 minor criterion is required.
[b] Anemia and/or thrombocytopenia are distinctively unusual in this syndrome unless Castleman disease is present.
[c] Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.

improvement. The patient required less frequent abdominal tapping and the intermittent dyspnea caused by massive ascites and pleural effusion gradually subsided. In addition, the numbness of the distal upper and lower limbs declined gradually after the treatment. The blurred vision caused by papilledema also improved. The patient currently continues to be followed up at our outpatient department.

DISCUSSION

POEMS syndrome was first reported by Scheinker in 1938[5] and the acronym POEMS was coined by Bardwick et al. in 1980 to refer to several dominant features of the syndrome including polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes[1]. However, the first cases with clinical features similar to the syndrome were observed by Crow in 1956[6], who described two patients with neuritis, osteosclerotic plasmacytomas and other associated features, and later by the Japanese investigator Fukase in 1968[7]. It was therefore also known as Crow—Fukase syndrome. Case reports around the world showed a high prevalence of this syndrome in Asia, especially in Japan, with a male predominance in most series[4,5,8,9]. Moreover, there are several associated features found in patients with POEMS syndrome, including fever, anasarca, pleural effusion, ascites, papilledema, hematologic disorders, osteosclerotic myeloma, renal dysfunction, finger clubbing and Castleman disease. In 2007, Dispenzieri et al. proposed revised criteria for the diagnosis of POEMS syndrome (Table 1)[5]. Our patient had two major criteria: polyneuropathy and a monoclonal plasmaproliferative disorder. She had five minor criteria with organomegaly (splenomegaly), extravascular volume overload (pleural effusion and ascites), endocrinopathy (primary hypothyroidism), skin changes (hyperpigmentation, hypertrichosis, white nails) and papilledema. These dominant clinical features were consistent with the POEMS diagnosis. Clinicians should be aware that some patients who present with POEMS syndrome-like features do not fulfill the complete set of diagnostic criteria. Those patients should be evaluated carefully to prevent the misdiagnosis of an atypical presentation of POEMS syndrome. Once there is a high suspicion, efforts should be made to treat the patients as having this disorder[10].

Dermatologically, this patient presented with typical cutaneous findings of POEMS syndrome including hyperpigmentation, skin thickening with sclerodermoid change, hypertrichosis and white finger and toenails. However, several other skin features have been described in the literature and patients may show a variety of lesions. Dispenzieri et al.[5] compared three large series and found that cutaneous changes were present in 50%-90% of patients. The most common skin change was hyperpigmentation. As with our patient, most patients with POEMS syndrome have black, coarse and longer than normal hairs on the extremities. In addition, there are other skin changes including acrocyanosis, plethora, rapid accumulation of hemangiomata, telangiectasia, sclerodactylia and clubbing of the fingers[3,5]. Histopathology findings of the sclerodermoid lesions are usually nonspecific, showing hyperpigmentation of the basal layer with either an inflammatory infiltrate or a dermal fibrosis. Most hemangiomata seen in patients with POEMS syndrome show the features of a cherry angioma, but some patients may have the appearance of a glomeruloid hemangioma.The term ‘glomeruloid hemangioma’ was derived from a striking resemblance to renal glomeruli histologically. There are many extravascular spaces throughout the dermis, with luminal clusters of small congested capillaries surrounded by pericytes[11]. Dermatologists should be familiar with these skin changes and consider the possibility of POEMS

syndrome when a patient has these presentations.

The pathophysiology of this syndrome is not fully understood. Several pro-inflammatory cytokines have been implicated in the pathogenesis of the disorder, such as interleukin (IL)-1β, IL-6 and tumor necrosis factor-α[12-14]. Vascular endothelial growth factor (VEGF) appears to be the dominant driving cytokine in this complex syndrome[5,15]. Plasma and serum levels of VEGF are markedly elevated in patients with POEMS syndrome. Increased VEGF has also been found in the ascitic and cerebrospinal fluids. VEGF increases vascular permeability reversibly. Thus, Arimura et al. studied the direct effects of VEGF on blood ― nerve barrier function and found that it increased microvascular permeability inducing endoneurial edema[16]. They postulated that this factor could account for the nerve damage in patients with POEMS syndrome and suggested including elevated levels of VEGF as one of the diagnostic criteria. This was accepted by Dispenzieri et al. for inclusion in the updated criteria for the diagnosis of POEMS syndrome[5].

There is no standard treatment of this multisystem disorder and several treatment strategies have been suggested. Patients with isolated bone lesions can be treated successfully with radiation or surgical resection[8,17]. Systemic treatment with corticosteroids, alkylators, interferon alpha, azathioprine, intravenous immunoglobulin and plasmapheresis or combination with radiotherapy can be considered in patients with widespread lesions[9,18]. High-dose chemotherapy with peripheral blood stem cell transplantation has also shown effectiveness and could be an alternative therapy[19]. Thalidomide, a drug with known anti-angiogenetic, antiproliferative and anticytokine properties, has been used successfully to treat some immunologic disorders and has been applied to the treatment of patients with POEMS syndrome with promising results[20,21]. In our case, the patient was commenced on therapy with thalidomide after definite diagnosis. Side effects such as constipation, drowsiness and skin itching appeared in the early course of treatment, but the patient gradually became tolerant after one month of therapy. Substantial clinical improvement was observed in the four-month follow-up.

The prognosis for patients with POEMS syndrome has been poor in some reports, with median survival times ranging from 12 to 33 months[4,22,23]. However, the series reported by Dispenzieri et al.[5] revealed a longer median survival of 165 months. They also found that fingernail clubbing and extravascular volume overload (edema, effusion or ascites) carried a poor prognosis for survival. In addition, patients who underwent radiotherapy and had a good response also had superior survival[9].

In conclusion, POEMS syndrome is a very rare multisystem disorder with diverse clinical presentations. Patients may visit a variety of specialists because of a wide range of clinical manifestations. This case is a reminder to clinicians of different specializations, including dermatologists, to suspect this syndrome whenever encountering a patient with refractory ascites of unknown origin, diffuse skin thickening, or acquired peripheral neuropathy refractory to the standard treatment, especially those patients with other systemic symptoms simultaneously. Early diagnosis and treatment can halt the progression of POEMS syndrome and increase the survival rate. Clinicians should become familiar with these treatment strategies and make individually tailored treatment plans according to the various systemic manifestations to achieve a better clinical outcome.

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