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Refractory Treatment of Chronic Inflammatory Demyelinating Polyneuropathy Revealing POEMS Syndrome

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Abstract

Background: POEMS syndrome is a paraneoplastic syndrome resulting from abnormal plasma cell proliferation and associated polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal gammopathy (M), and skin changes (S). **Case report:** We report the case of a 43-year-old male patient who, since 2015, had presented with a motor deficit with paresthesia and intense pain in both lower limbs that had progressively set over a year. The electromyoneurography (EMNG) was consistent with demyelinating sensorimotor polyradiculoneuropathy predominating in the lower limbs, and a diagnosis of CIDP was made. The patient was administered Ig-IV for five days, followed by azathioprine and corticosteroids. Three years later, the evolution was marked by the appearance of abundant ascites and skin abnormalities such as hyperpigmentation. Abdominal and pelvic MRI revealed, in addition to the Budd Chiari, a sacral osteosclerotic lesion. Serum protein electrophoresis was in favor of monoclonal gammopathy with IGG Lambda light chain, the hormonal profile showed an elevated thyroid-stimulating hormone (TSH), and the vascular endothelial growth factor (VEGF) assay was elevated to 1740 pg/ml. The patient was scheduled for radiotherapy and stem cell transplantation; however, the clinical worsening and deterioration of the patient's general condition were rapid and fatal. **Conclusions**: The early diagnosis of POEMS syndrome presents a challenge for clinicians. It is important to conduct detailed interviews and meticulous physical examinations to examine systemic involvement.

Subject Areas

Neurology

Keywords

POEMS Syndrome, CIDP, Polyneuropathy, VEGF, Monoclonal Gammopathy

1. Introduction

POEMS syndrome is a paraneoplastic syndrome resulting from abnormal plasma cell proliferation and associated polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal gammopathy (M), and skin changes (S) [1]. It is a rare disease whose worldwide prevalence remains unknown and manifests itself towards the beginning of the 6th decade [2].

Its major criterion is rapidly progressive, disabling, and painful demyelinating polyneuropathy, which can sometimes be confused with chronic inflammatory demyelinating polyneuropathy (CIDP), especially in the absence of other systemic signs, causing a delay in diagnosis and a real therapeutic challenge [2]. Through this case report, we reviewed the clinical and electrophysiological features of polyneuropathy in POEMS syndrome.

2. Case Presentation

A 43-year-old patient was admitted to the neurological emergency department for motor deficits with paresthesia and intense pain in both lower limbs, which evolved progressively over a year. According to the patient's history, he had weaned himself off cigarettes three years earlier, smoked 20 packs a year, and occasionally consumed alcohol.

On admission, he was afebrile, and his vital signs were as follows: blood pressure, 138/85 mmHg; respiratory rate, 14 cycles/min; oxygen saturation, 99% on room air; and heart rate, 91 beats/min. Physical examination revealed a normal mental status and speech. Motor examination demonstrated muscular weakness with a Medical Research Council scale of 2/5 proximally and distally in the lower limbs and 4/5 proximally and distally to the upper extremities. Deep tendon reflexes were abolished in all four limbs. Sensory examination revealed tactile hypoesthesia in the lower limbs and plantar hyperesthesia in the feet. Plantar and abdominal skin reflexes were normal. cranial nerves were normal. The thyroid gland, lymph nodes, and overall examination results were all normal.

ENMG was consistent with demyelinating sensorimotor polyradiculoneuritis, which was predominant in the lower limbs (**Table 1**). Cerebrospinal fluid analysis revealed hyperproteinorachia, normoglycorachia, and normocytorachia. Therefore, the diagnosis of CIDP was confirmed. The patient was administered Ig-IV for five days, followed by azathioprine and corticosteroids. The patient's state remained unchanged for approximately three years.

Sudden, abundant ascites, melanoderma, and hypertrichosis appeared, with a weight loss of 10 kg over one year and deterioration of the general condition (**Figure 1**).

Abdominal ultrasound revealed a heterogeneous dysmorphic liver with Budd-Chiari syndrome involving hepatic occlusion of the medial and right hepatic veins and medium ascites (Figure 2). Abdominal and pelvic magnetic resonance imaging (MRI) revealed a sacral osteosclerotic lesion.

Table 1. ENMG results for the four limbs.

Motor Conductions			
Nerve	Distal latency (ms)	Amplitude (mV)	Velocity (m/s)
	5.3	10.1	
Median (L)	12.4	8.0	33.8
	15.5	7.5	32.3
	4.5	12.8	
Ulnar (L)	11.5	9.9	38.6
	14.5	8.9	48.9
	4.3	9.6	
Median (R)	11.1	7.6	35.3
	15.4	8.4	30.2
	4.2	13.2	
Ulnar (R)	10.5	9.5	43
	13.5	9.1	40
Fibular (L)	NO	NO	NO
Tibial (L)	NO	NO	NO
Fibular (R)	NO	NO	NO
Tibial (R)	NO	NO	NO
Sensory conductions			
Median D	NO	NO	NO
Ulnar D	3.7	4.3	32.8
Radial D	3.0	14.5	39.5
Median G	NO	NO	NO
Ulnar G	3.2	4.5	30.2
Radial G	2.5	5.4	50.4
Sural D	NO	NO	NO
Sural G	NO	NO	NO

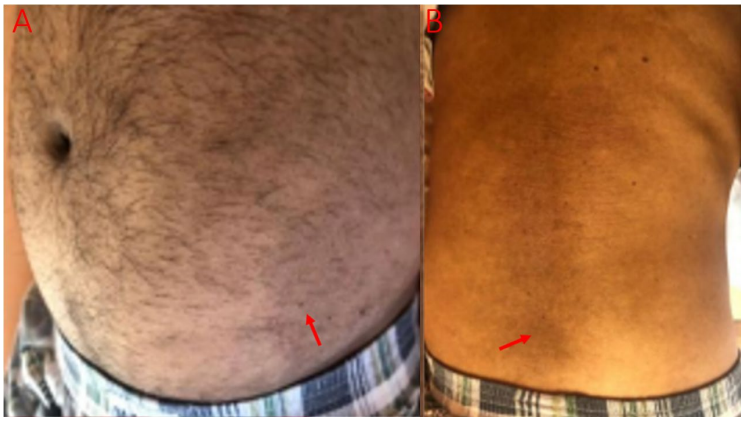

Figure 1. Images showing skin changes: (A) Abdominal hypertrichosis; (B) Areas of hyperpigmentation on the back.

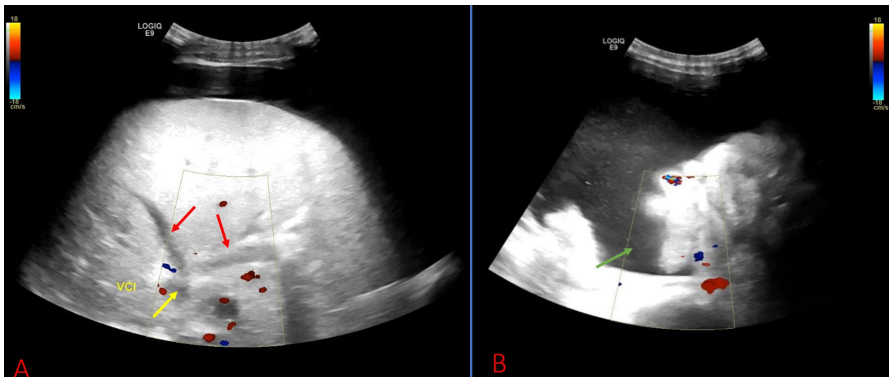

Figure 2. Abdominal ultrasound revealed (A) Thrombus of the inferior vena cava (yellow arrow), right and medial hepatic veins (red arrow), and (B) Medium ascites (green arrow).

The ascites fluid was punctured, showing a clear appearance with a high protein rate at 14.98 g/l, glucose at 1.16 g/L, LDH at 64.30 IU and white blood cells at 186 with 69% lymphocytes. Laboratory tests included normal complete blood cell counts, electrolytes, renal and hepatic function, hepatitis B and C, HIV serology, coagulation parameters, and immunological panels, namely, anti-DNA antibodies, anti-Sjögren's syndrome A (anti-SSA), anti-Sjögren's syndrome B (anti-SSB), and antineutrophil cytoplasmic antibodies (ANCA). Serum protein electrophoresis favored monoclonal gammopathy with an IGG Lambda light chain. The thyroid function test results revealed peripheral hypothyroidism (TSHus = 10.6 micro-IU/ml). The vascular endothelial growth factor VEGF assay was elevated to 1740 pg/ml, while the myelogram showed no malignancy.

Based on the clinical and laboratory data, we diagnosed POEMS syndrome based on the following major criteria: chronic demyelinating polyneuropathy, monoclonal gammopathy with IGG Lambda light chain, osteosclerotic lesion in the sacral region, and elevation of VEGF, and on the presence of minor criteria: skin changes, venous thrombosis, endocrinopathy, and ascites.

The ascites was evacuated along with intravenous perfusion of albumin,

methotrexate, and dexamethasone. The patient was scheduled for radiotherapy and stem cell transplantation; however, the clinical worsening and deterioration of the general condition were rapid and fatal.

3. Discussion

The diagnosis of POEMS syndrome is based on the Dispenzieri diagnostic criteria, which require the presence of two mandatory major criteria, one of three major criteria, and one of six minor criteria (**Table 2**) [3]. Although the median survival is estimated to be 14 years, severe respiratory and neurological complications are rapidly becoming fatal [2]. The clinical and electrophysiological overlap of polyneuropathy in POMES with CIDP and other neuropathies associated with monoclonal gammopathies, particularly monoclonal gammopathy of undetermined significance (MGUS), leads to a delay in diagnosis, with an average delay of 13 months [4].

Table 2. Diagnostic criteria for POEMS syndrome [3].

Major mandatory criteria	1) Polyneuropathy (typically demyelinating) 2) Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria (one required)	3) Castleman disease 4) Sclerotic bone lesions 5) Elevation of vascular endothelial growth factor
Minor criteria	6) Organomegaly (splenomegaly, hepatomegaly or lymphadenopathy) 7) Extravascular volume overload (oedema, pleural effusion or ascites) 8) Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) 9) Skin alterations (hyperpigmentation, hypertrichosis, glomeruloid haemangiomas, plethora, acrocyanosis, flushing, white nails) 10) Papilloedema 11) Thrombocytosis/polycythaemia

Increased serum VGEF levels have been observed in all patients with POEMS syndrome and are, therefore, considered a major diagnostic criterion [5]. VEGF levels could be useful not only for diagnosis but also for monitoring therapeutic response [5]. Current research attributes peripheral neuropathy to increased levels of inflammatory cytokines rather than to the invasion of clonal plasma cells [6]. The proposed mechanism of polyneuropathy is endothelial damage caused by the abnormal activation of endothelial cells by VEGF, which is overexpressed in the nerves of patients with POEMS, inducing microvascular changes, and leading to ischemic microangiopathy responsible for chronic axonal damage [7].

Peripheral neuropathy is an obligatory criterion for the syndrome and may be the only clinical manifestation at the time of first presentation, which poses a diagnostic problem with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) [3]. It is typically a subacute or rapidly progressive sensitivomotor polyneuropathy, symmetrical, ascending, distal, painful, and allodynia evolving towards polyradiculoneuritis [5]. Clinical examination reveals distal atrophy, motor weakness predominantly in the lower limbs, and hypo-or anesthesia affecting both large- and small-fiber sensory modalities [3].

Studies of nerve conduction have shown a greater slowing of conduction velocities in intermediate nerve segments, reflecting the demyelinating nature of the disease [8]. Although the mechanism of polyneuropathy in POEMS syndrome is essentially demyelination, a high degree of length-dependent axonal loss is observed, with a reduction in the amplitudes of action potentials, particularly in the lower limbs [8].

It is essential to diagnose POEMS syndrome early, as the results of treatment at an advanced stage are disappointing despite well-adapted treatment. As already mentioned, the delay in diagnosis is due to clinical and electrophysiological overlap with other acquired demyelinating polyneuropathies, particularly CIDP; however, a number of clinical and neurophysiological features should be systematically investigated (**Table 3**) [2].

Table 3. Clinical and paraclinical characteristics of the POEMS syndrome and CIDP.

	POEMS	CIDP
Subacute onset	+++	+
Muscular atrophy of the lower limbs	+++	+
Pain	+++	+
Conduction block	+	+++
Monoclonal gammopathy	+++	–
VGEF	+++	–

+++: common; +: uncommon; –: absent.

Treatments commonly used for acquired inflammatory polyneuropathy, such as intravenous immunoglobulin (IV IG) alone or in combination with steroids, are not beneficial. Current recommendations propose a therapeutic algorithm for each stage of disease. In localized POEMS syndrome, defined by the presence of a maximum of 3 lesions with no sign of clonal plasma cells, the proposed treatment is radiotherapy [9].

Systemic chemotherapy is strongly recommended for the disseminated forms with bone marrow involvement. A combination of high-dose chemotherapy and hematopoietic stem cell transplantation can be fairly effective, with neurological improvement in up to 100% of patients [10].

4. Conclusion

The early diagnosis of POEMS syndrome presents a challenge for clinicians. It is important to conduct detailed interviews and meticulous physical examinations to examine systemic involvement. Appropriate tests, such as protein electrophoresis to look for monoclonal lambda light chain gammopathy, VEGF assay, and bone X-ray, help to guide the diagnosis and rule out other etiologies that may mimic POEMS polyneuropathy, such as CIDP, amyloidosis, and MGUS neuropathy.

Conflicts of Interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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