# Case series on POEMS Syndrome- a rare paraneoplastic disorder

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POEMS syndrome, also known as Crow-Fukase syndrome or Takatsuki syndrome, is a rare paraneoplastic disorder linked to an underlying plasma cell neoplasm. The acronym POEMS stands for the key features of the syndrome: **Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Plasma Cell Disorder, and Skin changes** (1). In addition to these main features, patients may also experience **papilledema, fluid overload, sclerotic bone lesions, elevated blood cell counts (thrombocytosis/erythrocytosis), high levels of vascular endothelial growth factor (VEGF), a higher risk of thrombosis, and abnormal lung function tests** (2).

The condition was first described in an autopsy case by Scheinker in 1938 (3). It became recognized as distinct from multiple myeloma-associated neuropathy after Crow's 1956 report on osteosclerotic plasmacytomas (4). Initial case series from Japan in the early 1980s documented numerous cases of POEMS syndrome (5). A 2012 national survey in Japan estimated the prevalence at about 0.3 per 100,000 (6). Since then, case reports have emerged from France, the United States, India, and China (1, 7).
Here, we report two cases of middle-aged females presenting with **sensorimotor polyneuropathy and skin changes**, with lymph node biopsy findings suggestive of **Castleman disease**.

Case 1:
35 year old female, came to us with bilateral lower limb weakness of 1 year duration. It was associated with pins and needle sensation in both legs and feeling of walking on cotton wool. There was history of imbalance while walking which was more in the dark and used to increase on washing her face over the wash basin. She also had constitutional symptoms such as low grade fever, easy fatiguability and loss of appetite. She complained of diffuse darkening of her skin all over. She was diagnosed with Hypothyroidism and Primary adrenal insufficiency and was being treated for the same for the past 1 year at the endocrine department. She was also evaluated for celiac disease, with TTG-IGA elevated more than 10 times. She was being treated as Autoimmune Polyglandular syndrome. On examination she was conscious,

Oriented, with a Pulse rate of 80/min & BP was 200/120mmHg. B/L Cervical Lymphadenopathy was present. Grade 3 HTN Retinopathy was noted in Both eyes. Diffuse hyperpigmentation was present over face as well as limbs and trunk. She had hypotonia in both lower limbs with generalized areflexia. Power at B/L Hip & Knee was MMRC Grade 4, Ankle was Grade 2. Power in upper limbs was normal. Sensory examination – Exteroceptive sensations reduced by upto 25% till B/L knees, Vibration testing revealed early decay upto Anterior Superior Iliac Spine. Upper limb sensations were preserved. Patient also had B/L pitting oedema with distension of abdomen. On investigation, TSH was 26.44 (Ref 0.35-5.5) with Anti-TPO >1300 (Ref upto 60), Cortisol was normal. Nerve conduction revealed decreased conduction velocity, and increased Distal latency in B/L Ulnar, B/L Tibial And Peroneal nerve s/o sensorimotor demyelinating affection. Protein electrophoresis showed M-Band (0.34), with Beta-2 Microglobulin 4078ng/mL (ref range 670-2143) with Lambda free light chain.

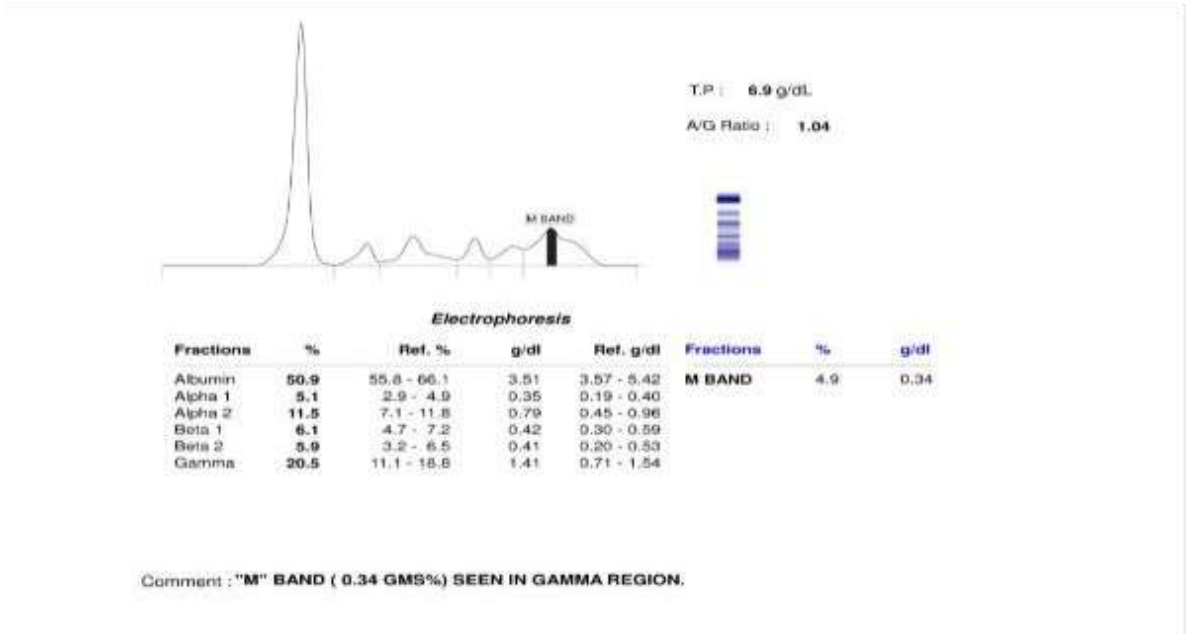
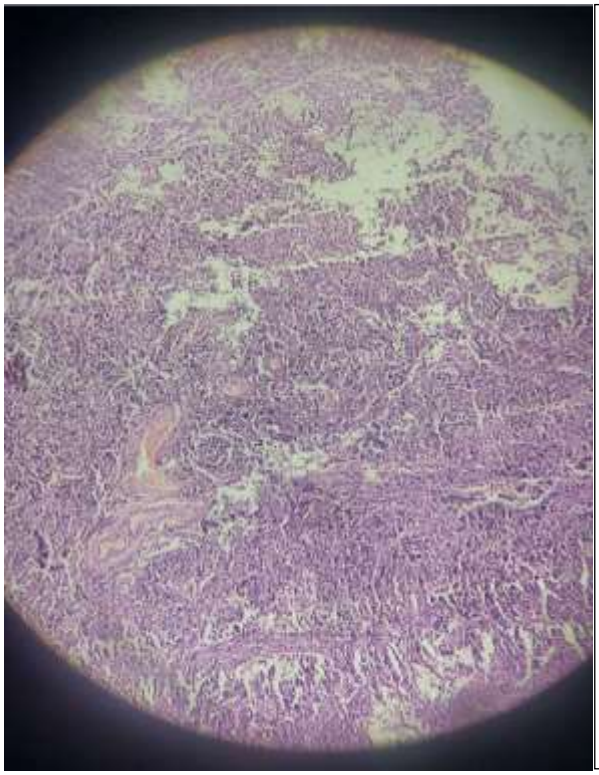



**Figure 1**

Contrast Enhanced CT Abdomen & Thorax to rule out malignancy was negative. Excision Biopsy from cervical lymph node with IHC revealed castlemann's disease (Hyaline variant). Thus, the diagnosis of POEMS syndrome was confirmed, with fulfilment of 2 mandatory major criteria: Demyelinating Polyneuropathy and Monoclonal Plasma cell Disorder with minor criteria: Lymphadenopathy (Organomegaly), ascited, pedal oedema (Volume overload) with Endocrinopathy (Hypothyroidisim, adrenal insufficiency), Hyperpigmentation (Skin changes) in addition to weight loss and constitutional symptoms.



Germinal Centres : Posi0ve for CD23.
Interfollicular areas : CD3 & CD5 positive T cells.

Plasma cells : Positive for CD138.
Overall study favouring castleman's disease.

**Figure 2**

Note the diffuse hyperpigmenta0on over the face, more in the perioral area and over the forehead.

**Figure 3**

Note the abdominal distension due to ascites

**Figure 4**

**Case 2:**

A 36-year-old female presented with progressive bilateral lower limb weakness over the past 8 months, which extended to bilateral upper limb weakness over the subsequent 4 months. Initially, she had difficulty climbing stairs and experienced slippage of footwear and foot dragging. Within a month, she required significant

assistance for mobility. The weakness progressed to involve her upper limbs, affecting grip strength and the ability to perform daily activities such as dressing. Eventually, she became bedridden with complete quadriplegia in the last 2 months.

Associated symptoms included significant weight loss of 15 kg and diffuse skin hyperpigmentation over the past 2 years. Neurological examination revealed complete quadriplegia (power 0/5) and absent deep tendon reflexes, with pansensory loss in both lower limbs up to the thighs and in both upper limbs up to the mid-forearms.

Laboratory investigations showed polycythemia (Hb: 16.6 g/dL) and thrombocytosis (606,000/µL), along with elevated TSH (10.81) and a positive ANA (titre: 1:160). Nerve conduction studies indicated severe sensorimotor axonal neuropathy with unrecordable potentials across all modalities. Cerebrospinal fluid analysis revealed lymphocytic pleocytosis (100% lymphocytes) with elevated protein (180 mg/dL) and normal glucose (72 mg/dL).

Diagnostic imaging including CECT thorax, abdomen, and pelvis was unremarkable for occult malignancy. X-ray for osteosclerotic lesions was negative. Serum protein electrophoresis and immunofixation assay showed elevated kappa and lambda light chains, but no monoclonal band was identified. Lymph node biopsy from the right inguinal region demonstrated atrophic follicles with hyalinized germinal centers, onion-skin appearance of lymphoid follicles, numerous plasma cells, and prominent vascular proliferation, consistent with Castleman's disease (hyaline variant).

These findings supported the diagnosis of POEMS syndrome, considering the combination of polyneuropathy, monoclonal plasma cell disorder, lymphadenopathy, endocrinopathy, and skin changes. Further investigation into potential vasculitis or paraneoplastic etiology was deemed unnecessary based on the clinical and histopathological evidence.

Injection IvIg ( 2g/kg) , a total dose of 100 g was given over 5 days with mild improvement in sensory symptoms. Patient was then planned for chemotherapy and referred to hematologist for chemotherapy treatment and continues to be in followup.

Note the diffuse skin hyperpigmentation and shiny skin.

**DISCUSSION** –

**POEMS Syndrome: A Complex and Rare Neurological Challenge**

POEMS syndrome is a rare, multisystem paraneoplastic disorder associated with plasma cell neoplasms. The syndrome is named for its cardinal features: **Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy (M-protein)**, and **Skin changes**. Despite its well-defined criteria, the clinical presentation can vary widely, often mimicking other conditions such as multiple myeloma, amyloidosis, and other plasma cell dyscrasias, making diagnosis a significant challenge. Neurologically, the polyneuropathy in POEMS syndrome is one of its most debilitating features and often serves as a cornerstone for diagnosis.

**Neurological Manifestations**

Polyneuropathy in POEMS syndrome is predominantly demyelinating with secondary axonal degeneration, leading to progressive motor and sensory impairment. Patients often present with distal weakness, paresthesia, and imbalance. Nerve conduction studies typically reveal reduced conduction velocities, prolonged distal latencies, and conduction block, suggesting a demyelinating process with variable axonal involvement (8). This neuropathy can progress to severe disability if untreated, as illustrated in our second case of quadriplegia. The extent of neurological involvement and its refractory nature to conventional therapies underscore the neurologically challenging nature of the syndrome.

**Systemic Features**

Organomegaly is another hallmark of POEMS syndrome and can include hepatomegaly, splenomegaly, and lymphadenopathy, often detected through imaging techniques such as ultrasound or CT scans (9). Endocrinopathy is almost universally present, manifesting as hypothyroidism, adrenal insufficiency, diabetes mellitus, or other glandular dysfunctions. Skin changes, such as hyperpigmentation, thickened skin, and papules, are notable findings, with skin biopsies sometimes revealing amyloid deposits (10).

Additionally, volume overload symptoms, including edema, ascites, and pleural effusions, are frequently observed. These features complicate the diagnostic picture and often necessitate a multidisciplinary approach. Constitutional symptoms such as weight loss, fatigue, and low-grade fever are also common, further adding to the complexity of diagnosis.

**Diagnostic Approach**

The diagnosis of POEMS syndrome requires a comprehensive evaluation. The **mandatory diagnostic criteria** include:

1. **Peripheral neuropathy**, confirmed via nerve conduction studies, typically showing demyelination.
2. **Monoclonal plasma cell disorder**, identified through serum protein electrophoresis or immunofixation electrophoresis.

Additional major criteria include **sclerotic bone lesions**, **Castleman disease**, and elevated levels of vascular endothelial growth factor (VEGF), which contributes to the syndrome's vascular symptoms (11). Minor criteria include organomegaly, endocrinopathy, volume overload, skin changes, papilledema, thrombocytosis or polycythemia, and elevated VEGF levels. Advanced diagnostic tools, including bone marrow biopsy, high-resolution imaging, and genetic testing, are instrumental in confirming the diagnosis and differentiating POEMS syndrome from other plasma cell dyscrasias (12).

**Neurological Differential Diagnosis**

The neurological features of POEMS syndrome overlap significantly with other demyelinating neuropathies, such as chronic inflammatory demyelinating polyneuropathy (CIDP). However, POEMS syndrome neuropathy typically demonstrates greater axonal loss, is more painful, and is less responsive to standard CIDP treatments, such as corticosteroids or IVIg. The association with systemic features and the presence of monoclonal gammopathy are critical for differentiation (13).

**Management Strategies**

Treatment for POEMS syndrome is individualized, targeting the underlying plasma cell dyscrasia and associated manifestations. **Immunomodulatory agents**, such as thalidomide, lenalidomide, and pomalidomide, are commonly used and have shown efficacy in reducing neuropathic symptoms and controlling the disease (14). For systemic organ involvement, **bortezomib-based chemotherapy** is often employed, targeting the clonal plasma cell population (15).

Endocrinopathy management involves addressing specific glandular dysfunctions, such as thyroid hormone replacement in hypothyroidism or hydrocortisone in adrenal insufficiency. Volume overload is managed through diuretics and supportive care. Skin changes may require local or systemic treatments, depending on their severity. Neuropathy treatment remains challenging, with symptomatic relief often achieved through immunomodulatory therapy, though full neurological recovery is uncommon.

In the first case presented in this article, the patient had been managed for Addison’s disease for nearly a year, with her progressive lower limb weakness being erroneously attributed to generalized malaise and fatigue secondary to adrenal insufficiency. This misattribution delayed the recognition of the broader clinical picture and underscores the complexity of diagnosing POEMS syndrome when overlapping conditions are present.
The second case is particularly intriguing, as the initial presentation was limited to diffuse skin hyperpigmentation persisting for nearly two years before the emergence of more definitive systemic features. Consequently, the clinical evaluation was predominantly dermatologic in focus, with delayed consideration of systemic pathology.

These cases serve to highlight the paramount importance of meticulous clinical history-taking and thorough physical examination in identifying atypical presentations of rare syndromes. A holistic, multidisciplinary diagnostic approach is essential to avoid anchoring biases and ensure that subtle yet critical systemic manifestations are not overlooked. This report aims to emphasize the necessity of integrating clinical acumen with a comprehensive investigative strategy to achieve timely and accurate diagnoses in complex multisystem disorders such as POEMS syndrome.

**Prognosis and Future Directions**

The prognosis for POEMS syndrome varies depending on the timing of diagnosis and the initiation of treatment. Early recognition and intervention are associated with better outcomes, particularly in preventing irreversible neurological damage. However, the rarity of the syndrome and its clinical overlap with other conditions frequently result in delayed diagnosis.

Ongoing research is focused on understanding the pathophysiology of POEMS syndrome, particularly the role of VEGF and other cytokines in disease progression. The development of targeted therapies aimed at modulating these pathways offers promise for improving outcomes and quality of life for patients with this challenging disorder (16).

## CONCLUSION

POEMS syndrome remains a diagnostically and therapeutically challenging condition, particularly from a neurological perspective. Its multifaceted presentation necessitates a high index of suspicion and a multidisciplinary approach. Advances in diagnostic tools and therapeutic modalities have improved outcomes, but continued research and clinical awareness are essential for early diagnosis and effective management.

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