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Progressive Weakness as a presentation in Takatsuki (POEMS) Syndrome

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ABSTRACT :
POEMS (Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein elevation, and skin changes) Syndrome is a rare Paraneoplastic disorder. It is associated with increased Plasma Cell proliferation with a median survival rate of 8 - 14 years if left untreated.[2]
45 year old male patient known case of Diabetes Mellitus type 2, presented with complaints of progressive weakness in both upper and lower limbs since a month. There was a history of mild fever one month back. He also complained of swelling of both lower limbs with pigmentation of skin on the lower limbs.
Our patient met both the Mandatory Criteria, along with one major criteria (Raised VEGF) and multiple Minor Criteria (Organomegaly, Extravascular volume overload, Endocrinopathy, Skin Changes and Papilledema) and was thus diagnosed to be POEMS Syndrome.

I. INTRODUCTION :

POEMS (Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein elevation, and skin changes) Syndrome is a rare Paraneoplastic disorder. Other features associated with POEMS syndrome include Ascites, Pleural Effusion, Papilledema.[1]

It is associated with increased Plasma Cell proliferation with a median survival rate of 8 - 14 years if left untreated.[2]

Being a rare disorder and mimicking the symptoms of Multiple Myeloma, CIDP and other common ailments it is likely to be missed. Thus it is important to diagnose POEMS syndrome since successful treatment can increase the life expectancy of the patient.

POEMS Syndrome is not diagnosed on the basis of one or two symptoms but on a diagnostic criteria consisting of Mandatory, Major and Minor Criteria with diagnosis being made on following all Mandatory, one major and 2 minor criteria.[3]

The estimated prevalence of POEMS Syndrome in India is approximately 3 in 100000

We describe a rare case of a 48 year old male patient who presented classically with all the criteria necessary for the diagnosis of POEMS syndrome.

II. CASE SUMMARY

45 year old male patient known case of Diabetes Mellitus type 2, presented with complaints of progressive weakness in both upper and lower limbs since a month. There was a history of mild fever one month back. The patient was unable to get up from sitting position. The patient also complained of difficulty in breathing with decreased air entry on the left side. He also complained of swelling of both lower limbs with pigmentation of skin on the lower limbs.

General Physical Examination revealed non-pitting oedema of both lower limbs with dry and thickened skin. Neurologic examination showed areflexic quadriparesis with glove and stocking sensory loss, bilateral claw hand, and foot drop There was no cranial nerve involvement. Hepatomegaly was found. Ophthalmic examination showed papilledema. Higher mental functions were normal. Cardiovascular examination showed tachycardia. Respiratory system examination revealed tachypnea and decreased breath sounds in the bilateral lower zones. Gastrointestinal system examinations was mostly normal.

Investigations at the time of admission showed hemoglobin of 7.8 mg/dL (reference range {N}: 12-16 mg/dL), platelet count of 2.70x105/cu mm (N: 1.5-4 105/cu mm), with normal peripheral smear. Kidney Function Tests revealed Creatinine of 1.5, Total Sodium to be 138 mMol/L (136 - 146 mMol/L), total Potassium to be 5.31 mmol/L (3.5 - 5.1 mmol/L) serum Calcium : 8.7 mg/dl (8.8-10.6 mg / dl)

Nerve Conduction Studies were done which were suggestive of Demyelinating Polyneuropathy.

In view of Polyneuropathy, Endocrinopathy, Pedal Oedema and Skin Changes,

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patient was evaluated for monoclonal Gammopathy.

An ultrasound of the abdomen showed mild Hepatosplenomegaly along with mild diffuse gall bladder wall Oedema.

A Chest X-Ray revealed Left sided pleural effusion along with increase in Cardiac Size.

Echocardiography showed a small pericardial effusion. CSF analysis showed albuminocytological dissociation. Serum Protein Immunofixation was done which was suggestive of Peak of Lambda Chain in Gamma Globulin Chain. To rule out Multiple Myeloma, Haematology Consultation was taken and Bone Marrow Biopsy was done which ruled out Multiple Myeloma due to absence of Blast Cells.Bone marrow biopsy revealed Focal Megaloblastic Changes with normal Blast cells.

Pet-CT screening for sclerotic bone lesions showed no uptake.C ANCA and P ANCA were Negative and C4 Compliment was within normal limits. ANA by LIA was negative.

After aligning clinical features with investigations, the diagnosis of POEMS syndrome was made.

Patient was managed on IV Immunoglobulin. He was given 130 gm of IV Immunoglobulin over 5 days. (Normal Dose - 2gm/Kg of body weight over 4 - 5 days). And was referred for Stem Cell Transplant which is the definitive treatment in patients eligible for stem cell transplant.Patient is in outpatient follow-up without any new complaints with improving symptoms.

III. DISCUSSION

POEMS Syndrome also known as Crow - Fukase Syndrome or Takatsuki Syndrome is a rare multi system disorder which consists of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes and is associated with Plasma Cell Dyscrasia.[4]

One of the Predominant feature of the syndrome is Progressive Peripheral Neuropathy. And the peak incidence occurs at the age of 50 - 60 years.[5] The overall 5 year survival rate of POEMS Syndrome is known to be around 60% [6]

The exact mechanism of POEMS syndrome is not clearly understood but it involves increase in serum Vascular Endothelial Growth Factor (VEGF), Interleukin 6 (IL6), Tumour Necrosis Factor-α and IL1β.[7] VEGF is the most commonly increased cytokine in case of POEMS and corresponds to disease progression or regression.[8, 9]

For Diagnosis of POEMS Syndrome, along with Mandatory criteria, one major and one minor criteria should be met.

Table	The table is adapted from Dispenzieri (2019) [10]
	DIAGNOSTIC CRITERIA FOR POEMS SYNDROME
Mandatory Criteria	Polyneuropathy and monoclonal plasma cell proliferative disorder
Other Major Criteria	Castleman disease or angiofollicular lymph node hyperplasia, osteosclerotic lesions, elevated serum or plasma VEGF levels.
Minor Criteria	Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy), extravascular volume overload (peripheral edema, ascites, or pleural effusion), endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, or pancreatic), skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails), papilledema, thrombocytosis or polycythemia.

Our patient met both the Mandatory Criteria, along with one major criteria (Raised VEGF) and multiple Minor Criteria (Organomegaly, Extravascular volume overload, Endocrinopathy, Skin Changes and Papilledema).

The differentials in case of POEMS Syndrome can be Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Multiple Myeloma, Monoclonal Gammopathy of Undetermined Significance (MGUS) [11]

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In our patient, since there were no oligoclonal bands on immune electrophoresis and Serum calcium was normal, Multiple Myeloma was ruled out which was confirmed on Bone Marrow biopsy.

End Organ damage like Anaemia and Organomegaly that are associated with POEMS Syndrome are not associated with other conditions with M protein on Electrophoresis like the MGUS.[12]

The symptoms of demyelinating polyneuropathy and the results of Clinical investigations like the CSF and Nerve Conduction Studies are similar in case of CIDP, but the presence of Skin Changes, Endocrinopathy and Pleural Effusion along with fulfilment of criteria of POEMS Syndrome led us to diagnose the patient as a case of POEMS Syndrome.

Treatment of POEMS syndrome depends on the extent of bone marrow involvement [13]. Radiotherapy as the first line treatment has shown a 10 year survival rate of 70% in cases with ≤3 isolated bone lesions with out clonal plasma cells. [14] Systemic therapy is recommended in cases of disseminated bone marrow involvement. [15]

The clinical studies on successful systemic therapies for POEMS Syndrome are limited. There are multiple regimens that are being followed but the most effective have been High-dose melphalan plus autologous stem cell transplant (ASCT), melphalan plus dexamethasone, and lenalidomide plus dexamethasone[13,16-18].

Since POEMS is a multi-system disorder, Supportive therapy like Physiotherapy, continuous positive airway pressure (CPAP), analgesics such as Tramadol and Gabapentin can play an important role in the recovery of the patient.[13]

Serum VEGF can be used to check the treatment response[10] and PET CT scans can detect relapses in the patient. Thus it is important to call the patient for follow up quarterly to check the treatment response and relapses. [13]

There have been some studies which support the use of IV Immunoglobulin in patients of POEMS Syndrome because of its similarity to Chronic Inflammatory Demyelinating Polyneuropathy in terms of inflammation and endoneurial deposits of immunoglobulins.[19,20]. On the other hand there is also a school of thought according to which the use of IV Immunoglobulin in case of POEMS Syndrome is debatable.[21] Our patient was started on IV Immunoglobulin and showed signs of improvement after the 1st dose and thus the IV Immunoglobulin course was completed along with Analgesics, Chest Physiotherapy and CPAP and was then discharged on Steroids and advised regular Chest Physiotherapy along with referral to the Oncology department for Radiotherapy and further evaluation.

IV. CONCLUSION

POEMS Syndrome is a unique multi system disorder, one that is likely to be missed on diagnosis owing to its rarity and similarity to other common conditions like the CIDP and Multiple Myeloma. Which if left untreated, can cause severe morbidity and mortality. Thus vast amounts of Clinical Trials need to be done to find out the accurate treatment modalities since early treatment can prevent the Morbidity / Mortality and prolong and improve the quality of life of the patient.

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