Case Report

Poems Syndrome

Ravina N Rajdeo[1], Sanjay G Raut[2], Rakhee W Joshi[3]

ABSTRACT

POEMS Syndrome (Acronym for : polyneuropathy, organomegaly, endocrinopathy, M protein elevation and skin changes) is a rare multisystemic paraneoplastic disease characterized by a combination of polyneuropathy, variable endocrine features, organomegaly, monoclonal gammopathy, skin changes, sclerotic bone lesions, extravascular volume overload, castleman disease and papilledema. A 32-year-old male presented to us with weakness in both lower limbs since 5 years worsened since past 7 months and also swelling over both lower limbs, abdomen and breathlessness since 7 months. Physical examination revealed axillary and inguinal lymphadenopathy, pitting edema in both lower limbs and back, hyperpigmentation, clubbing, bilateral papilledema and paraparesis. Investigations revealed thrombocytosis, polycythemia, hypothyroidism, hepatomegaly, splenomegaly, ascites and bilateral mild pleural effusion on imaging, sensory motor neuropathy predominantly motor demyelinating with axonal damage on nerve conduction studies, faint M band in Lambda region on immunofixation and histopathology of axillary lymph node showed features of castleman disease of hyaline subtype. Subsequently patient was diagnosed as a case of POEMS Syndrome with castleman variant and is currently on chemotherapy.

The diagnosis of POEMS syndrome is often delayed because the syndrome is rare and can be mistaken for other neurological disorders as sometimes it is difficult to get any evidence of monoclonal gammopathy in the early stages. Also there is lack of awareness of castleman variant of this syndrome that occurs without evidence of a clonal plasma cell disorder. Delay in diagnosis increases morbidity and reduces survival in POEMS Syndrome.

Introduction :

Polyneuropathy, organomegaly, endocrinopathy, M proteins, and skin changes (POEMS) syndrome, also known as Crow Fukase syndrome, osteosclerotic myeloma, and Takatsuki syndrome[1-4], is the paraneoplastic clinical manifestation of monoclonal plasma cell dyscrasia. Other important clinical features include fever, papilledema, extravascular volume overload, sclerosis, bone lesions, thrombocytosis, erythrocytosis, elevated vascular endothelial growth factor (VEGF) levels, abnormal pulmonary function, predisposition toward thrombosis, etc.[2,3,6,7] Early diagnosis is a challenge because of the diverse clinical manifestations that are often accompanied with multiple organ injury. Here, we have reported a patient with the Castleman disease variant of POEMS syndrome, which hopefully will increase the index of suspicion among physicians in such scenario.

[1]Junior Resident, [2]Associate Professor, [3]Assistant Professor, Department of Medicine, Indira Gandhi Government Medical College, Nagpur

Address for Correspondence -
Dr. Ravina N. Rajdeo
E-mail : ravinarajdeo222@gmail.com
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Case Presentation :

A 32-year-old male presented with weakness in both lower limbs since 5 years when he was diagnosed to have AIDP. Patient gradually recovered to the extent that he could walk with support. However, 7 months back weakness in both lower limbs worsened and he could not even walk with support. Along with worsening paraparesis, this time patient noticed paresthesias. He also had swelling over both lower limbs, abdominal distension and breathlessness since past 7 months. He was diagnosed to have hypothyroidism and is on Tab. Thyroxine 75 mg OD. On examination, patient's vitals were stable. He had bilateral axillary & inguinal lymphadenopathy, pitting edema in both lower limbs and back, hyperpigmentation over both lower limbs and upper limbs ***(Fig. 1),*** clubbing and white nails ***(Fig. 2).*** Patient also had bilateral papilledema and areflexic paraparesis with grade 2 power.

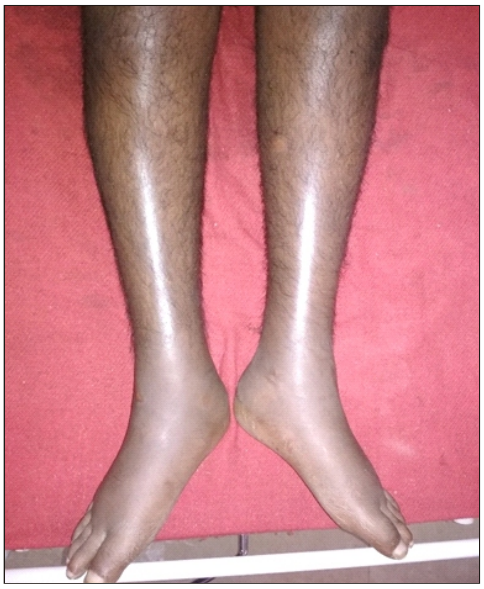

Fig. 1 : **showing swelling over both lower limbs, shiny skin, hyperpigmentation and hypertrichosis**

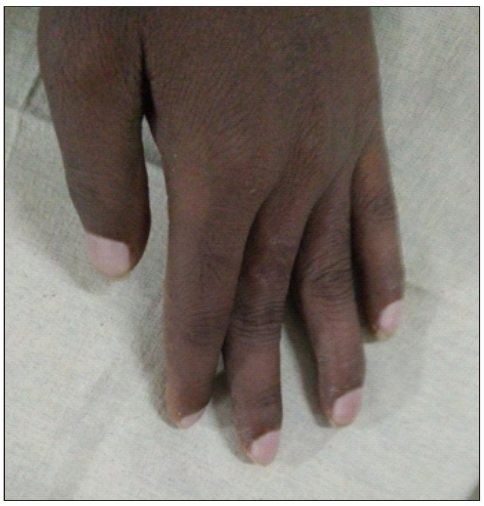

Fig. 2 : **showing grade 3 clubbing, white nails and hyperpigmentation**

Investigations revealed that he had thrombocytosis, polycythemia, hypothyroidism (serum TSH -18 uIU/ml), deranged creatinine (2.3 mg/dl), proteinuria (575 mg / 24 hour urine), low voltage complexes on ECG ***(Fig. 3).*** Chest X ray revealed cardiomegaly ***(Fig. 4).*** Ultrasonography gave evidence of hepatomegaly, splenomegaly, ascites and bilateral mild pleural effusion. Electromyography and nerve conduction study showed sensory motor neuropathy, predominantly

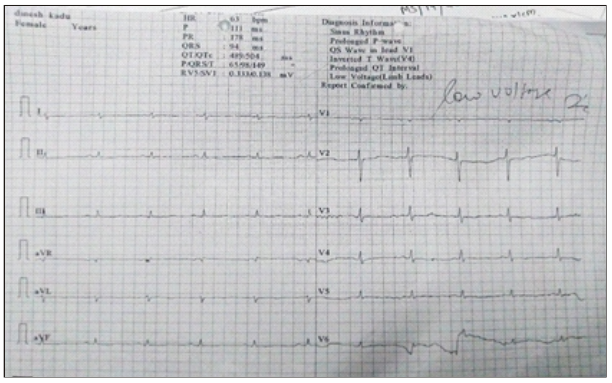

Fig. 3 : **12 lead ECG showing low voltage complexes**

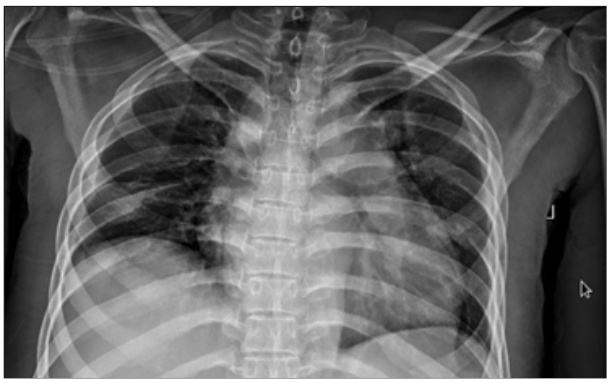

Fig. 4 : **X-ray chest (PA view) showing gross cardiomegaly**

motor demyelinating with axonal damage. Sural nerve biopsy showed chronic axonal and demyelinating neuropathy. 2D Echo was suggestive of severe pulmonary hypertension with RV systolic dysfunction. Bone marrow aspiration showed trilineage hyperplasia with negative JAK 2 mutation analysis. Auto antibody panel-negative, anti TTG negative and duodenal biopsy showed mild duodenitis. His serum and urine electrophoresis negative, urine immuno fixation - negative, serum immuno fixation showed faint M band in Lambda region with elevated free kappa / lambda light chain ratio and also elevated beta 2 microglobulin. Histopathology of axillary lymph node showed features of castleman disease of hyaline subtype ***(Fig. 5,6).*** Subsequently patient was diagnosed as a case of POEMS Syndrome meeting both the mandatory major, one of the other major and all minor criteria.

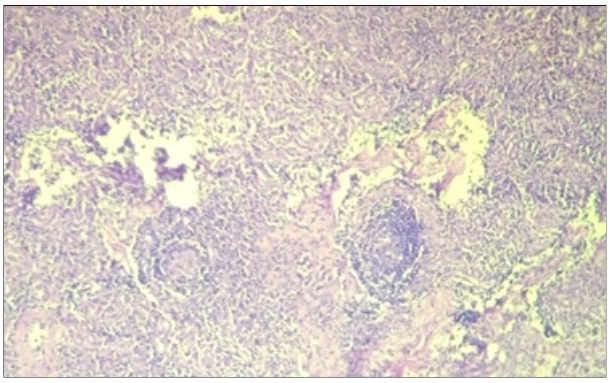

Fig. 5 (H&E 10X) : **follicular aggregates of mature lymphocytes & increased number of vessels surrounded by fibrohyaline eosinophilic material giving 'onion skin appearance'**

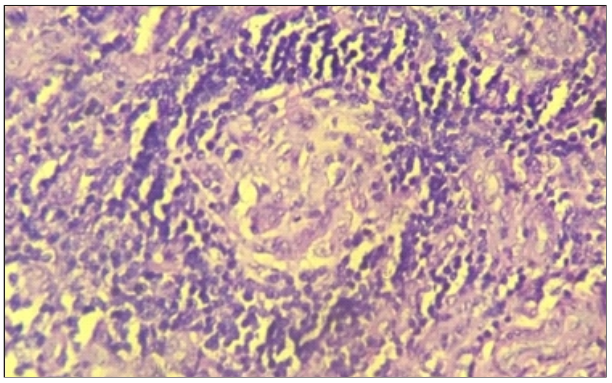

Fig. 6 (H&E 40X) : **small calibre blood vessel surrounded by mature lymphocytes & eosinophilic hyaline material**

Discussion :

POEMS syndrome was first reported by Scheinker in 1938. The acronym, which was coined by Bardwick in 1980, refers to several, but not all, of the features of the syndrome: polyradiculo neuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes. Not all of the features within the acronym are required to make the diagnosis. There are other important features not included in the POEMS acronym, including papilledema, extravascular volume overload, sclerotic bone lesions, thrombocytosis / erythrocytosis (P.E.S.T.), elevated vascular endothelial growth factor (VEGF) levels, a predisposition toward thrombosis, and abnormal pulmonary function tests which are also presenting and diagnostic features of this rare syndrome. There is also a Castleman variant of POEMS syndrome that may or may not be associated with aclonal plasma cell disorder. Our patient had almost all the features of POEMS syndrome which were polyneuropathy, hepatomegaly, splenomegaly, and multiple enlarged peripheral lymph nodes (Histopathology showed castleman disease with hyaline subtype), hypothyroidism, extravascular volume overload, monoclonal gammopathy (faint M band on immunofixation), pulmonary hypertension, papilledema, skin hyperpigmentation, clubbing and hypertrichosis.

This disease was initially thought to be more common in patients of Japanese descent, given the most numerous initial reports from Japan[3,8]. However, over the years, large series have also been reported from France, the United States, China, and India[9-13]. A national survey conducted in Japan in . A national survey conducted in Japan in 2003 showed a prevalence of approximately 0.3 per 100,000[14]. The pathogenesis of the syndrome is not understood. To date, VEGF is the cytokine that correlates best with disease activity.[15,16,17] Although it is likely not the driving force of the disease VEGF is known to target endothelial cells, induce a rapid and reversible increase in vascular permeability, and be important in angiogenesis.

Castleman disease (CD, or angio follicular lymph node hyperplasia) is a rare lymphoproliferative disorder[18], first described by Castleman et al.[19] in 1956. The clinical features of Castleman disease are classified into two categories : localized and multicentric[20]. There are also three histological forms of CD : (1) Hyaline vascular form, (2) Plasma cell form, (3) Mixed. Multicentric Castleman disease (MCD) is generally the plasma cell type, but the histological findings in our case are highly suggestive of hyaline vascular form of Castleman disease. Castleman variant of POEMS Syndrome can occur without any evidence of monoclonal Gammopathy[21].

Mandatory Major Criteria (Both required)	1. Polyneuropathy 2. Monoclonal plasma cell proliferative disorder
Other Major Criteria (One of three required)	1. Sclerotic bone lesions 2. Castleman's disease 3. Elevated levels of vascular endothelial growth factor (VEGF)
Minor Criteria	1. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) 2. Extravascular volume overload (edema, pleural effusion, or ascites) 3. Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, and pancreatic) 4. Skin changes (hyperpigmentation, hypertrichosis, glomeruloidhemangiomata, plethora, acrocyanosis, flushing, and white nails) 5. Papilledema 6. Thrombocytosis / Polycythemia

The diagnosis of POEMS syndrome is confirmed when both of the mandatory major criteria, 1 of the 3 other major criteria and 1 of the 6 minor criteria are present

Our patient presented first with features of polyradiculopathy 5 years back when he was thought of having AIDP (Acute Inflammatory Demyelinating Polyneuropathy) and then over a period of time developed other features of extra vascular volume overload, skin changes, hypothyroidism, hepatomegaly, splenomegaly, lymphadenopathy, lately monoclonal gammopathy and so the diagnosis of this rare syndrome was entertained. The diagnosis of POEMS syndrome is often delayed because the syndrome is rare and like in our case, is often mistaken for other neurological disorders[22]. This is because patients with polyneuropathy might not have any evidence of monoclonal gammopathy until very late or not at all. Also monoclonal gammopathy not being common in castleman variant of this syndrome can delay the diagnosis. Such cases not fulfilling the diagnostic criteria in early stages are therefore not benefitted from the timely management of the disease which worsens survival.

Therapy for POEMS syndrome includes radiation, chemotherapy, peripheral blood stem cell transplant, targeting therapy, intravenous gammaglobulin therapy, plasmapheresis, corticosteroids, etc chosen on the basis of extent of the plasma cell infiltration of bone marrow[23]. Our patient is currently receiving chemotherapy consisting of cyclophosphamide, bortezomib and dexamethasone. The course of POEMS syndrome is chronic; patients survive three times longer compared with multiple myeloma. Death usually occurs from inanition or aterminal bronchopneumonia. Overall median survival was 13.7 years in the Mayo Clinic series[6], while those with clubbing or extravascular volume overload had median survivals of 2.6 and 6.6 years respectively.

Conclusion :

Early diagnosis and timely management of POEMS syndrome is known to improve survival and morbidity. This syndrome being rare, having a multisystemic and varied presentation makes it difficult to diagnose in early stages. We hope our patient with castleman variant of POEMS Syndrome will increase index of suspicion for early diagnosis and thus avoid crucial delay in management.

References :

1. Crow RS. Peripheral neuritis in myelomatosis. Br Med J 1956; 2:802-4.
2. Nakanishi T, Sobue I, Toyokura Y, Nishitani H, Kuroiwa Y, Satoyoshi E, Tsubaki T, Igata A, Ozaki Y. The Crow-Fukase syndrome:a study of 102 cases in Japan. Neurology 1984;34:712-20.
3. Takatsuki K, Sanada I. Plasma cell dyscrasia with polyneuropathy and endocrine disorder: clinical and laboratory features of 109 reported cases. Jpn J ClinOncol 1983;13:543-55.
4. Fukase M, Kakimatsu T, Nishitani H. Report of a case of solitary plasmacytoma in the abdomen presenting with polyneuropathy and endocrinological disorders. ClinNeurol 1969;9:657.
5. Bardwick PA, Zvaifler NJ, Gill GN, Newman D, Greenway GD, Resnick DL. Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes: the POEMS syndrome. Report on two cases and a review of the literature. Medicine (Baltimore) 1980;59:311-22.
6. Dispenzieri A, Kyle RA, Lacy MQ, Rajkumar SV, Therneau TM, Larson DR, Greipp PR, Witzig TE, Basu R, Suarez GA, Fonseca R, Lust JA, Gertz MA. POEMS syndrome: definitions and long-term outcome. Blood 2003;101:2496-506.
7. Dispenzieri A. POEMS syndrome: 2011 update on diagnosis, risk-stratification, and management. Am J Hematol 2011;86:591-601.
8. Dispenzieri A. POEMS Syndrome. Hematology Am SocHematol Educ Program 2005:360-7.
9. Singh D, Wadhwa J, Kumar L, Raina V, Agarwal A, Kochupillai V. POEMS syndrome : experience with fourteen cases. Leuk Lymphoma 2003;44(10): 1749-1752.
10. Soubrier MJ, Dubost JJ, Sauvezie BJ. POEMS syndrome: a study of 25 cases and a review of the literature. French study group on POEMS Syndrome. Am J Med 1994;97(6):543-553.
11. Zhang B, Song X, Liang B, et al. The clinical study of POEMS syndrome in China. Neuro EndocrinolLett 2010;31(2):229-237.
12. Li J, Zhou DB, Huang Z, et al. Clinical characteristics and long-term outcome of patients with POEMS syndrome in China.Ann Hematol 2011;90(7): 819-826.
13. Kulkarni GB, Mahadevan A, Taly AB, et al. Clinicopathological profile of polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes (POEMS) syndrome. J ClinNeurosci 2011;18(3):356-360.
14. Nasu S, Misawa S, Sekiguchi Y, et al. Different neurological and physiological profiles in POEMS syndrome and chronic inflammatory demyelinating polyneuropathy. J NeurolNeurosurg Psychiatry 2012;83(5):476-479.
15. Watanabe O, Arimura K, Kitajima I, Osame M, Maruyama I. Greatly raised vascular endothelial growth factor (VEGF) in POEMS syndrome [letter]. Lancet 1996;347(9002):702.
16. Soubrier M, Guillon R, Dubost JJ, et al. Arterial obliteration in POEMS syndrome: possible role of vascular endothelial growth factor. J Rheumatol 1998;25(4):813-815.
17. Nishi J, Arimura K, Utsunomiya A, et al. Expression of vascular endothelial growth factor in sera and lymph nodes of the plasma cell type of Castleman's disease. Br J Haematol 1999;104(3):482-485.
18. Dispenzieri A. POEMS syndrome: 2014 update on diagnosis, risk-stratification, and management. Am J Hematol 2014;89:214-23.
19. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. Cancer 1956;9:822-30.
20. Aguilar-Rodriguez R, Milea SL, Demirci I, Herold S, Flasshove M, Klosterhalfen B, Kinkel H, Janßen H. Localized retroperitoneal Castleman's disease: a case report and review of the literature. J Med Case Rep 2014;8:93.
21. Dispenzieri A. Castleman disease. Cancer Treat Res2008;142:293-330.
22. Paulo Eduardo MestrinelliCarrilho, et al.Poems syndrome without "M"-Could it be possible?.Neurology 2017;88(16):6.119
23. Dispenzieri A. How I treat POEMS syndrome. Blood 2012;119:5650-8.