Original Article

DOI: 10.21276/APALM.1986

Spectrum of Clinico-Pathological Profile of Poems Syndrome: An Extensive Analysis on Laboratory Interpretations

Anandraj Vaithy K*, Shanmugasamy K, Bhavani and Koteeswaran G

Department of Pathology, Mahatma Gandhi Medical College & Research Institute, Pillaiyarkuppam, Puducherry Pondicherry-607402 India

ABSTRACT

Background: Plasma cell Dyscrasias being an unique hematological neoplasm characterized by monoclonal B cell proliferation of Plasma cell, it is usually associated with paraneoplastic syndromes having many differentials. Among the types, POEMS syndrome is an unusual condition characterized by spectrum of clinical manifestations involving hematopoietic and systemic manifestation with many co-morbidities. Laboratory diagnosis remains as the mainstay of diagnosis often making the clinician to examine retrospectively.Among various laboratory tests, Hematological parameters allied with biochemical values and radio-imaging are contributory. In the present study we analyzed the spectrum of Clinical manifestations of POEMS syndrome and emphasized the fact that clinico-pathological correlation helps in early diagnosis of POEMS syndrome, thereby prompt treatment can be initiated.

Methodology: Specific criteria was fixed to label POEMS syndrome based on the knowledge gained by previous Research works. A clear clinical details was collected from the patients in a prescribed proforma. Among the studied cases the criteria to label POEMS syndrome included the following clinical manifestations and its subsequent laboratory interpretations Polyneuropathy, M-protein, Organomegaly (hepatomegaly, splenomegaly or lymphadenopathy), Endocrinopathy (hypothyroidism, diabetes mellitus, hypoadrenocorticismorhypogonadism), skin changes (hyperpigmentation, hypertrichosis, or thickening), and Effusion or Peripheral edema.Three of these abovesix criteria were kept as minimal requirement for thediagnosis.While the first two were kept as major criteria, the rest are assumed to be minor criteria.

Results: The study period was for a period of seven years and included a series of 9cases.Male preponderance was noted with high incidence in middle age. At many instances it was evident that laboratory diagnosis especially hematological parameters reinforced retrospective evaluation by Clinician to clinch the diagnosis.WhileM- band electrophoresis and high ESR was uniformly seen in all cases, the associated co-morbidities are variable with skin lesions and bone marrow plasmacytosis. Biochemical & radiological reports were contributory in picking up the condition.

Conclusion: POEMS syndrome is a paraneoplastic condition affecting the middle age individuals with male preponderance unlike other classical myeloma. The present study showed that incidence of POEMS syndrome is fairly higher and judicious correlation of laboratory interpretations especially hematological parameters will definitely aid in better health care management of the patients.

Keywords: *POEMS Syndrome, Plasmacytosis, Laboratory Investigations, M-band Electrophoresis.*

Introduction

Plasma cell dyscrasias is a spectrum of cancer of immune system involving hematological and systemic neoplastic pathological disorder often manifesting in elderly males with various associated co-morbidities.[1] It is characterized by apparent increase in number of neoplastic of plasma cell which is derived from B-Lymphocytes lineage in the circulation with secreting of light chain immunoglobulins (paraprotein-M protein) in circulation.[2]The rare condition accounts for <10 % of hematological malignancies very often associated with paraneoplastic syndromes and POEMS syndrome is commoner among the occurrence.[1,2,3]

POEMS syndrome is an acronym representing a rare hemato-pathological paraneoplastic syndrome generated due to clonal proliferation of neoplastic plasma cells.[4]POEMS is an acronym for spectrum pathological conditions first coined by Schiekner in 1938 and it includes Polyneuropathy, Organomegaly, Endocrinopathy, Myeloma cells (M band- paraprotein), Skin lesions.[4,5] Osteosclerotic myeloma or Takatsuki disease or Crow Fukase syndrome are the other unusual terms of this condition.[3]The etiopathogenesis of this condition is elusive with many proposed theories.[6,7,8]

The clinical presentation is often vague except for constitutional symptoms often making the Clinician to make evasive diagnosis due to many differentials encountered, thus relying on Pathologist's opinion.[9,10] Laboratory investigations includes Complete Hematological profile

with Bone marrow aspirate analysis which directs the Pathologist to perform M –protein Electrophoresis. [11] It had been proposed that Laboratory interpretation of data by Pathologist often redirects the Physician to take retrospective examination of the patients to rule out POEMS syndrome.[12]Thus, combination of clinico-pathological profile with laboratory interpretation analysis remains as mainstay of diagnosis with contributions from biochemical parameters and immune electrophoresis.[13]

Research studies on laboratory diagnosis part of POEMS syndrome is sparse especially among Tropical countries like India.[14]Even the available studies pertains only to clinical modalities rather than diagnostic criteria and clinico-pathological profile.[14,15] A series of cases with diagnostic modalities on this condition is seldom available.[15]In the present research study we performed an extensive analysis on Clinico-hematopathological profile, biochemical and radiological parameters where the clinical and diagnostic results correlated emphazing the role of Pathologist in picking up POEMS syndrome thereby aiding the Physician in starting prompt diagnosis.

Methodology

Study Design: The present Cross sectional study Research analysis was conducted for a period of Ten years from 2007 to 2017. The study populations included cases from various socio-demographic domains from the Tropical Country**.** A well framed proforma was generated to enter the case details which included all the informations pertaining to the study cases. The criteria to define POEMS syndrome was based on postulates of Nankanishi etal,in the year 1984 and Dispenzieri et al. in 2003.[1]All the 10 patients studied in the analysis met the diagnosis criteria as postulated.

Diagnostic Criteria: Among the studied cases the criteria to label POEMS syndrome included the following clinical manifestations and its subsequent laboratory interpretations - **P**olyneuropathy, **M**-protein, (Monoclonal proliferative dirorder) **O**rganomegaly (hepatomegaly, splenomegaly or lymphadenopathy), **E**ndocrinopathy (hypothyroidism, diabetes mellitus, hypoadrenocortism), skin changes (hyperpigmentation, hypertrichosis, or thickening), and **E**ffusion or **P**eripheral edema. While the first two were kept as major criteria, the rest are assumed to be minor criteria. Three of these above six criteria (2major and one minor) were kept as minimal requirement for labelling the diagnosis in reference to standard Literatures. the present study an analysis on general features ,symptoms and signs, laboratory tests and other information are documented in proforma.

Laboratory interpretations: 1.Hematological parameters included Complete blood count including ESR levels Urine analysis(Bence Jones Protein) of the patients which were done routinely are entered in Tables including their subsequent Bone marrow aspirations for demonstrating Neoplastic Plasmacytosis. **Biochemical** tests were mostly done to rule out Endocrine disorder which included Blood sugar levels (for Diabetes Mellitus), Thyroid functions tests, Sex hormones levels estimations. Monoclonal protein demonstration was based on Immunofixation Gel Electrophoresis with cellulose acetate strip plate keeping Ladder pattern as standard control. M protein band was detected visually and the expression was compared and correlated with other hematological/clinical findings. All the staining procedures and Laboratory investigations and interpretations are done as per Standard Operating Procedures in reference to standard textbooks.

Statistical Tools: Being a cross sectional descriptive study, The total study population (10 cases) were taken as ‘n’ and all the observations are entered in percentage(%).

Results

The present study included cases from various geographical regions with a study population of 10 cases over a period of 10 years. POEMS syndrome is defined and criteria for labeling the disease was followed in concordance with prior Literatures.[1].The observations were segregated into various categories and spectrum of findings were analyzed.

General Conditions & Clinical Manifestations: The results showed male preponderance(90%) with male female ration of 7:1 and average age of incidence being 45-55years as described in Table1. Clinical manifestations among the cases were multifactorial which sensory disorders, organomegaly, endocrine disorder and Skin lesions as elaborated in Table-2. Accessory findings included vascular changes, increased basal temperatures altered hemodynamics, cardio-thoracic pathology and ocular complications(Papilledema)

A. Polyneuropathy:Majority of patients had peripheral neuropathy(90%) characterized by numbness, loss of sensation and 10% of cases showed sensory-motor deficits.

B. Oraganomegaly: This was the Universal sign which included Splenomegaly(50%), Hepatomegaly (30%), lymphadenopathy(20%). All the cases were proved clinically and radiological tools.

C. Endocrinopathy: Hormonal imbalance disorder included Diabetes mellitus (50%), Hypothyroidism(40%), Impotency(10%).

D. Skin Lesions: majority cases showed Hyperpigmented Macules in extremities (60%) followed by Hypertrichiosis and Scleroderma in 20% cases each.

Laboratory Diagnostic Data Interpretations:

1. The study analysed various hematological and biochemical test results and correlated with clinical presentation retrospectively as elaborated in Table-3.
2. M-protein: Monoclonal protein being secreted by neoplastic plasma cells of light chain series, IgG(lambda) was seen in 60% cases followed by IgA(lambda) in 40% cases
3. Hematological tests remained as mainstay for the diagnosis characterized by uniform elevation of high levels of ESR ranging from more than 100mm; anaemia ranging from 7 to 9 gm/dl and leucocytic disorders mainly leukocytosis ranging from 15-20 $x10^9$/L .Bone Marrow aspiration was done in all cases with fever of unknown origin and abnormal blood parameters as indications and all the aspirates showed bone marrow neoplastic plasmacytosis as tabulated in Table-3
4. Urine Analysis was done in all cases in which 7 cases (n=10) showed Light chain Bence Jones proteinuria and 3 cases (30%) showed albuminuria from Trace to Nephrotic range as shown I Table-3.
5. Biochemical tests showed elevated Blood sugar levels in in 50% cases; low thyroid levels in 40% cases and low serum cortisol levels in 10%. Renal Function test showed elevated Serum urea and creatinine levels in 7 cases (n=10) and 3 cases increased serum uric acid (30%).
6. Radiological investigations were contributory in picking up the bony lesions (osteolytic/sclerotic) and extent of sclerosis/lytic changes.

Table 1: Age and Gender Distribution of cases.

Age Distribution(in years)	Gender Distribution MALE FEMALE
30-40	- 1
41-50	4 1
>50	3 1

Table 2: Clinico-Pathological spectrum of cases:

Clinical spectrum of POEMS	General clinical features	Total number of cases; n=10
Polyneuropathy	Peripheral Neuropathy Papilledema	9/10 (90%) 1/10 (10%)
Organomegaly	Splenomegaly Hepatomegaly Lymphadenopathy	5/10 (50%) 3/10(30%) 2/10(20%)
Endocrine disorders	Diabetes mellitus Hypothyroidism Ammenorrhea	5/10(50%) 4/10(40%) 1/10(10%)
M protein band (Light chain Paraprotein)	IgG (Lambda) IgA (Lambda)	6/10 (60%) 4/10(40%)
Skin Lesions	Hyperpigmented Macules Scleroderma Hypertrichiosis	6/10(60%) 2/10(20%) 2/10(20%)
Edema & Effusions	Peripheral edema Ascitis Pleural effusion	5/10 (50%) 2/10(20%) 2/10(20%)

Table 3: Analysis on Laboratory interpretations and hemato-biochemical profile.

Laboratory division	Parameter	Observations	No. of cases in %n=10
Hematology	RBC	Anaemia	60%
		Erythrocytosis	40%
		Rouleaux Formation	60%
	WBC	Leucocytosis	80%
		Leucopenia	20%
	Platelets	Thrombocytosis	70%
		Thrombocytopenia	30%
	Bone marrow aspiration	Neoplastic Plasmacytosis	100%
Urine analysis	Urine proteinuria	Bence Jones Protein	60%
		Albuminuria	40%
Biochemical tests	Hormonal profile imbalance	Elevated Blood glucose	70%
		Hypothyroidism	30%

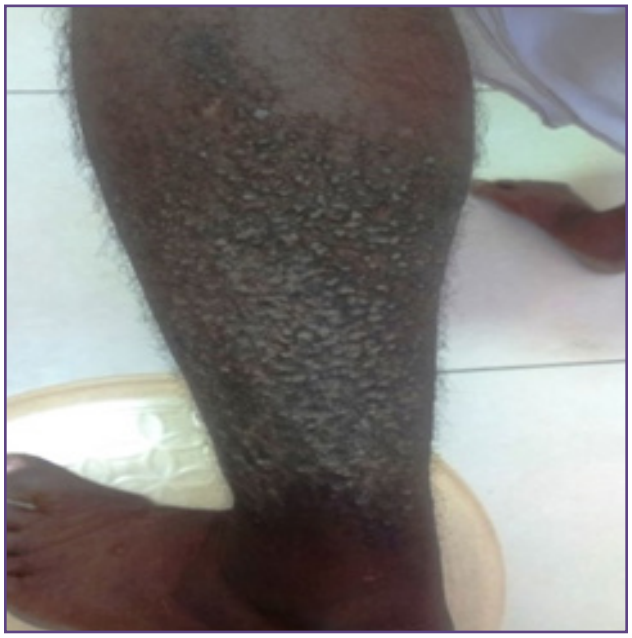

Fig. 1: Skin lesions showing Hyperpigmentation associated with hypertrichiosis in lower extremeties.

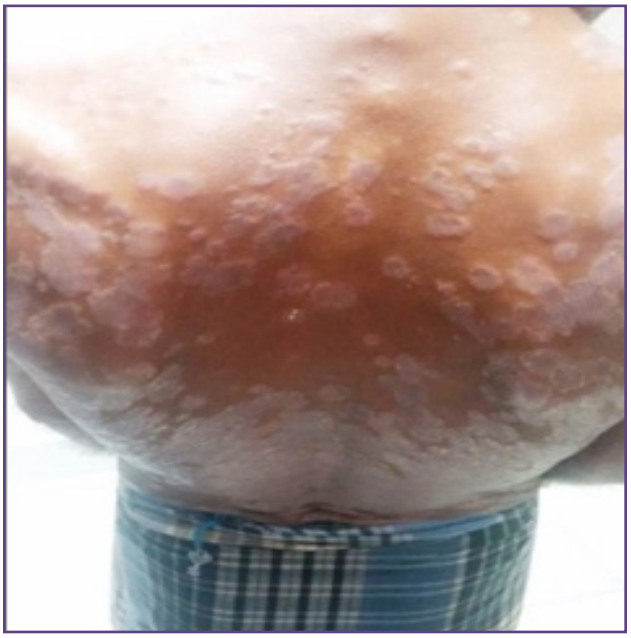

Fig. 2: Skin lesion showing maculopapular rashes in truncal regions with few pustules.

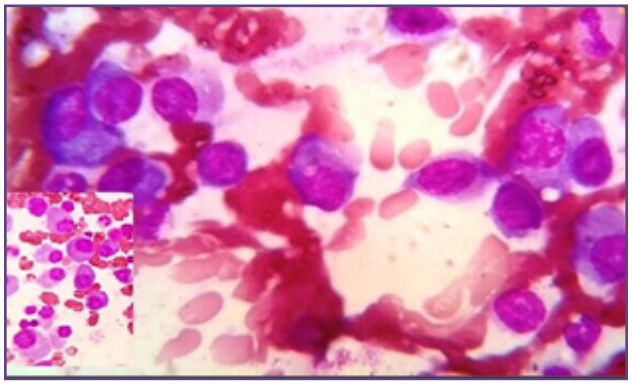

Fig. 2: Skin lesion showing maculopapular rashes in truncal regions with few pustules.

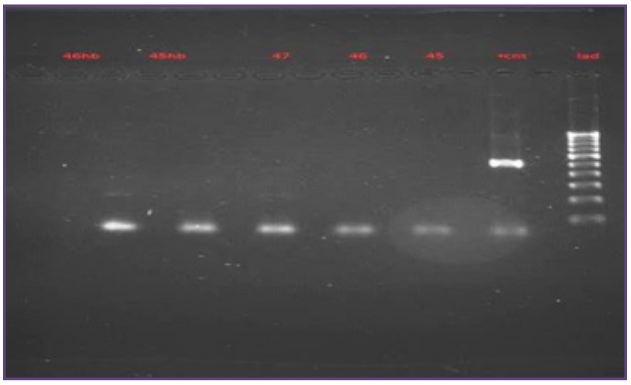

Fig. 3: Bone marrow aspirates showing neoplastic plasmacytosis ,Leishman stain-40x. Inset: Oil Immersion,100x

Discussions

POEMS syndrome being an unusual paraneoplastic syndrome, is well known to present with varied clinical manifestation which is an unique feature of its kind.[1,2] The term POEM syndrome was first described by Scheinker and his workers. Later the term was coined and established by Bardwick in 1980 as incidental entity on autopsy.[3,6] Increased production and circulation of inflammatory mediatory (cytokines) and factors promoting angiogenesis are the hallmark agents in contributing to the pathogenesis of this disorder[4,6] Increased release of interleukins, Growth factors (mainly Vascular endothelial Growth factors& Tumour Necrotic factors) are the additional key players.[5,7]

Being a multi-system disorder it is often warrants laboratory interpretation for definite opinion and subsequent treatment.[8] Laboratory work-up warrants a programmed panel of investigations and it includes predominantly Hemato-pathology, Biochemical tests and Radiological films where the former test plays a crucial role as reflected in the present study and prior studies as well.[9]

Dispenzieri et al. had performed extensive analysis on POEMS syndrome investigating around 100 patients in 2003 and proposed observations on the median age being 45 years with male preponderance which is similar to that of our present results in the study.[1,11]The major clinical feature which was uniformly present was of this syndrome is a chronic progressive polyneuropathy with sensory and motor difficulties[9]. In our study, the initial symptoms of most patients are loss of sensation followed and also motorial disabilities.

The next common symptom observed in the present is skin lesions with varying distribution and sites. The commonly presented lesions are tabulated where hyperpigmentation is the top manifestation followed by pustular lesions especially in extremeties and truncal regions [Fig-1&2]. Similar findings are also observed by other workers concording with our observations. The reason attributed for exorbent skin lesions is the immune response of the surface immune complex and central antigenic property of the cells.[10,11]

Organomegaly is an usual component of this condition with varying proportions of hepatosplenomegaly & lymphadenopathy[12]While splenomegaly is the commonest manifestation, the extramedullary hematopoietic immunological behaviour is the postulated underlying reason for the etiopathogenesis as observed by Watanbe etal mirroring with our analysis as well[12].

Monoclonal –M Protein was detectable in variable quantification by Electrophoresis method showing M-Band. Mostly the test had been done retrospectively based on clinical signs and results from other laboratory investigations especially elevated ESR and proteinuria. As per the observations of Dispenzieri M protein can be demonstrated only if bone marrow plasmacytosis is established which in turn secretes more monoclonal Growth factors in serum which was reflected in the present scenario as well.[12,13][Fig3&4]

Endocrinopathy was manifested as hypothyroid and elevated blood Glucose levels. Invariably all cases with endocrine manifestation showed bone lytic lesions. The reason attributed in increased levels of Interleukins and S. Creatinine which in turn promotes proliferation of osteoclastic cells activity. Also the mass clonal effects impacted by the destructive activity of the mutated myeloma cells often associated with release of inflammatory mediators, cytokines, hormones (endocrine) and immunoglobulins (myeloma proteins) contribute to endocrinopathy. [14]

Dispenzieri and his co-workers revised the diagnostic criteria of POEMS syndrome in late 1990's and proposed that to make diagnosis of POEMS at least one major criterion & 1 minor criteria is well enough.[11, 14]

Hemodynamic disorders and ocular complications are well known to coexist with POEMS syndrome as observed by previous studies.[14]In the present study, all the cases exhibited cardiothoracic manifestation with altered hemodynamics and ocular pathology. The main reason attributed is hyper viscosity of the blood altering the flow path associated with increased concentration of immunoglobulins[15]. Researchers postulated the same reason as the underlying cause for skin lesions as well with super addition of altered immunological response.[15]

Conclusion

POEMS syndrome is a paraneoplastic condition affecting the middle age individuals with male preponderance. From the present study it is evident that incidence of POEMS syndrome is fairly higher than assumed. Pathologist play a crucial role in diagnosing the condition often guiding the Clinician to make retrospective clinical examination in arriving at the diagnosis. Judicious application of clinico-pathological, biochemical and radiological correlation aids in early prompt diagnosis of the condition. Being associated with many co-morbidities, even the presence of associated complications, laboratory interpretations holds good to diagnose POEMS syndrome.

References

1. Dispenzieri A. POEMS Syndrome. Hematology Am SocHematolEduc Program 2005:359-65

2. Dispenzieri A, Kyle RA, Lacy MQ, et al. POEMS syndrome: definitions and long-term outcome. Blood 2003;101:2496–506.
3. Dispenzieri A, Gertz MA. Treatment of POEMS syndrome. Curr Treat Options Oncol2004;5:249– 55
4. Gandhi GY, Basu R, Dispenzieri A, et al. Endocrinopathy in POEMS syndrome: the Mayo Clinic experience. Mayo ClinProc2007;82:836–42.
5. Rajkumar SV, Dispenzieri A, Kyle RA. Monoclonal gammopathy of undetermined significance, Waldenstr m macroglobulinemia, AL amyloidosis, and related plasma cell disorders: diagnosis and treatment. Mayo ClinProc2006;81:693–703.
6. Bardwick PA, Zvaifler NJ, Gill GN, et al. 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. Journal of Hematology, 2012; 2: 34-39
7. Rathakrishnan R, Liu TC, Chan YC, B. K. C. Ong, POEMS syndrome—a case for more aggressive treatment," Annals of the Academy of Medicine Singapore, 2007; vol 2: 435–37.
8. Cui RT, Huang X, Pu CQ, "POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome in China," Internal Medicine Journal, 2011; 41: 481–85.
9. Miralles GD, O'Fallon JR, Talley NJ. Plasma-cell dyscrasiawithpolyneuropathy.The spectrum of POEMS syndrome.N Engl J Med 1992;327:1919–23
11. Dispenzieri A, Lacy MQ, Hayman SR, et al. Peripheral blood stem cell transplant for POEMS syndrome is associated with high rates of engraftment syndrome. European J Haematol2008;80:397–406.
12. Watanabe O, Arimura K, Kitajima I, et al. Greatly raised vascular endothelial growth factor (VEGF) in POEMS syndrome. Lancet 1996;347:702.
13. Vavricka SR, Burri E, Beglinger C, Degen L. Serum protein electrophoresis: An underused but very useful test. Digestion 2009;79: 203-10
14. Vijayashree N .The serum protein electrophoresis pattern in the chronically ill patients in a tertiary care hospital. Ind J Clin Biochem. 2009; 24: 204-07
15. Nayak BS, Mungrue K, Gopee D, Friday M, Garcia S, Hirschfeld E. The epidemiology of multiple myeloma and the role of the M band detection on the serum electrophoresis in a small developing country. A retrospective study. Arch Physiol Biochem.2011 Oct; 117(4): 236-40.