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POEMS Syndrome: Failure of Newly Suggested Diagnostic Criteria to Anticipate the Development of the Syndrome

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POEMS syndrome is a unique clinical entity. Although it's a diagnosis of exclusion, it was previously described by the presence of several typical characteristics as paraproteinemia, polyneuropathy, organomegaly, endocrinopathy, and skin changes. Recently, new criteria were proposed, and the presence of two major and one minor criterion was claimed to suffice for a diagnosis. Both methods considered other important characteristics germane to the syndrome unessential for diagnosis. Retrospective evaluation of patients with lymphoproliferative disease was carried out to reveal the presence of the syndrome according to these different methods. Patients' clinical progression during follow-up will be used to validate the criteria's sensitivity and specificity. Six hundred twenty-nine consecutive files of patients with paraproteinemia who were followed-up at a tertiary medical center were reviewed. Of 12 patients who fulfilled the new criteria for diagnosis of POEMS, 3 remain stable during long-term follow-up and only 5 finally developed the full-blown syndrome. Four patients developed other diseases that accounted for their clinical findings. Patients presenting with neuronal vasculitic changes on biopsy, κ light-chain monoclonal gammopathy, and cryoglobulinemia were unlikely to develop POEMS syndrome, even though they fulfilled the newly suggested criteria. Although they are not in the criteria, sclerotic bone lesions were found only in patients who eventually developed the full syndrome. The diagnosis of POEMS syndrome according to the newly suggested criteria should not be definitive in the presence of atypical clinical features of the syndrome. Am. J. Hematol. 79:316–318, 2005. © 2005 Wiley-Liss, Inc.

INTRODUCTION

The first two patients with POEMS syndrome, described by Crow, suffered from a plasmocytoma and neuritis in association with other "striking features" [1], namely, organomegaly, endocrinopathy, M protein, and skin changes [2]. This rare syndrome, considered to be a variant of multiple myeloma, is characterized by unique clinical features including osteoblastic rather than osteolytic bone lesions, λ light-chain monoclonal gammopathy, and extramedullary plasmocytoma [3–5].

According to the new criteria, the existence of one of the "minor criteria" with these features—endocrinopathy, organomegaly, and skin changes in addition to lymphoproliferative disease and polyneuropathy—was proposed to suffice as valid definition of POEMS syndrome [6]. Persons with an M-protein spike without proven lymphoproliferative disease (mainly people with monoclonal gammopathy of unknown significance, MGUS) are not diagnosed with POEMS syndrome unless more clinical features emerge.

In this study, 629 consecutive files of patients with paraproteinemia and plasma-cell dyscrasias were reviewed. Twelve patients fulfilled the newly suggested criteria. Only five of them eventually fulfilled the classic diagnostic criteria for POEMS syndrome.

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We reviewed clinical characteristics of these patients at the time they presented and later during follow-up.

PATIENTS AND METHODS

Patients

We retrospectively reviewed 629 consecutive files of patients suffering from plasma-cell dyscrasias, including MGUS. All patients were followed up for at least 4 years at a single center in Hadassah University Hospital, Jerusalem, Israel, between the years 1988 and 2002.

Clinical Information

Data recorded included age, sex, underlying diseases, and concurrent illnesses. Clinical features included the presence of neuropathy, organomegaly, endocrinopathy, and skin disorders. Patients with polyneuropathy that could be clearly attributed to other causes, such as diabetes mellitus, amyloidosis, or medications, were excluded.

RESULTS

Patient Characteristics

Out of the 629 patients with plasma-cell dyscrasias and MGUS, 12 patients were identified with unexplained polyneuropathy. All 12 patients presented with monoclonal plasma cells in the bone marrow. Files of these patients were further explored for the presence of minor criteria in addition with both major criteria. During long-term follow-up, all 12 patients had at least one of the minor criteria, namely, impotence and hepatosplenomegaly. Five of these patients eventually developed the full-blown syndrome while the remaining 7 patients failed to develop other features of the syndrome. Of those 7 patients, 3 remain in stable clinical condition. MGUS is the hematological diagnosis in these 3 patients, and at the time of data collection, no other features were added. Although the other 4 patients, according to the newly suggested criteria, were eligible for diagnosis with POEMS syndrome, they eventually developed other diseases that accounted for their clinical findings. One patient's polyneuropathy was eventually recognized as being caused by essential mixed cryoglobulinemia. One patient developed acute inflammatory demyelinating polyneuropathy, which progressed to paraplegia and respiratory failure but eventually improved. Two patients were later diagnosed with polyarthritis nodosa, accounting for their neuropathy.

Characteristics of Patients Who Eventually Developed Full-Blown POEMS Syndrome

We retrospectively divided patients into those who finally developed classical POEMS syndrome and those who did not. We compared their clinical characteristics on presentation, as shown in Table I. The average age of patients with classical POEMS was lower (49 vs. 59 years, respectively); 71% of them were female compared to 60% in the other group.

Six patients were diagnosed to have MGUS based on M-protein and had 5–10% of monoclonal plasma cells in bone marrow as the only sign of plasma-cell dyscrasia. Only one of these patients eventually developed the features of the classical criteria for POEMS syndrome. Sclerotic bone lesions were identified in 80% and λ light-chain monoclonal gammopathy was identified in all patients with classical POEMS. All the patients who eventually did not develop POEMS syndrome had κ light-chain gammopathy. Three of these patients had vasculitis on nerve biopsy, while this was not found in any of the patients with classic POEMS syndrome. Elevated cerebrospinal fluid protein levels, leukocytosis, thrombocytosis, and extravascular volume overload were similarly present in patients from both groups.

DISCUSSION

The classical definition of POEMS syndrome includes five characteristic clinical features, namely paraproteinemia, polyneuropathy, endocrinopathy, organomegaly, and skin changes. The etiology for this syndrome is obscure, and thus the necessity of all features for diagnosis.

Our study suggests that diagnostic criteria for POEMS syndrome need to be modified. Four of the 12 patients who fulfilled the necessary criteria for diagnosis were eventually diagnosed with other diseases accounting for their symptoms. These patients were found at presentation to have features that were distinct from those required for the classic definition. Sclerotic bone lesions and λ light-chain monoclonal gammopathy are known to be typical features of POEMS syndrome and were exclusively found in POEMS patients on presentation. Presence of vasculitic neuronal changes, κ light-chain monoclonal gammopathy, and cryoglobulinemia should exclude patients from being this diagnosis. Establishment of diagnosis based on minimal criteria with respect to the presence of a typical feature may be misleading.

Substitution of the classic M protein with the requirement of lymphoproliferative disease is matched with our report. Only one of 4 patients

TABLE I. Clinical and Laboratory Features of Patients With and Without POEMS

Characteristics	Classical POEMS ($n = 5$)	POEMS did not develop ($n = 7$)
Median age (years)	49	59
Male sex	3/5	5/7
Type of light chain		
λ	5/5	0/7
κ	0/5	7/7
Marrow plasma cell more then 10%	1/5	1/7
Sclerotic bone lesions	4/5	0/7
Pathology of nerve-biopsy[a]		
Vasculitis	0/5	3/7
Demyelination	4/5	4/7
Organomegaly[b]		
Splenomegaly	3/5	2/7
Hepatomegaly	3/5	2/7
Lymphadenopathy	2/5	0/7
Endocrinopathy[b]		
Thyroid	2/5	1/7
Impotence	3/5	3/7
Other	Cushing, 1/5	0/7
Skin changes[b]		
Hyperpigmentation	4/5	0/7
Raynaud	2/5	1/7
Thickening	3/5	1/7
Cerebrospinal fluid protein > 50 mg/dl[a]	2	0
Detection of cryoglobulin	0/5	4/7
Extravascular volume overload	1/5	1/7
Thrombocytosis: PLT > 450,000/μL	2/5	0/7
Polycythemia, HGB: Women > 15 g/dL Men >17 g/dL	0/5	0/7

[a]Not all patients were tested.
[b]Symptoms and signs overlap in some patients.

with MGUS and neuropathy eventually fulfilled all the criteria of the syndrome.

Case studies, even of large series of patients, can reveal some features of a syndrome but cannot estimate these features' prevalence in clinically similar cases. Our findings suggest that the newly suggested diagnostic criteria are insufficient. Commonly occurring features should not be used alone for the establishment of a diagnosis. For this reason, in their article, Dispenzieri et al. excluded diabetes mellitus and hypothyroidism as minor endocrinological criteria if it stands alone [6]. Our data suggest that the same should be done with impotence and hepatomegaly. Presence of features not regularly associated with POEMS, such as vasculitis or κ light chain, should exclude patients from early diagnosis prior to development of all features.

Our study has several limitations. It is retrospective and as such subjected to bias. The small sample size of patients allows for descriptive analysis but is too small for statistical analysis. However, the relative high number of potential misdiagnoses as a result of the newly suggested criteria is alarming. We suggest that criteria should exclude patients with features which are unlikely to develop into the full syndrome.

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