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Serum immunoglobulin free light chain measurements and heavy chain isotype usage provide insight into disease biology in patients with POEMS syndrome

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Abstract

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes) syndrome is a rare paraneoplastic syndrome in which nearly all patients have a monoclonal lambda restricted plasma cell disorder. We investigated whether patients with POEMS have abnormal serum immunoglobulin free light chain (FLC) ratios. Fifty patients with newly diagnosed POEMS syndrome were assessed. Cystatin C levels were measured to discern whether subclinical renal insufficiency could account for FLC elevations in the presence of a normal FLC ratio. Forty-five patients (90%) had elevated lambda FLC; however, only nine (18%) had abnormal FLC ratios. The rise in serum FLC of POEMS patients appeared to be multifactorial—both a function of sub-clinical renal insufficiency and polyclonal activation of medullary and extramedullary plasma cells. Those patients expressing a clonal IgA were more likely to have clonal plasmacytosis observed on iliac crest biopsy than those with IgG. In summary, serum immunoglobulin profiles are unique in POEMS syndrome as compared to other plasma cell disorders.

Keywords

monoclonal gammopathy; osteosclerotic myeloma

Introduction

POEMS syndrome, also referred to as Takatsuki syndrome, Crow-Fukase syndrome, or osteosclerotic myeloma, refers to a paraneoplastic syndrome that includes *poly*neuropathy, *organ*omegaly, *endo*crinopathy, *mono*clonal gammopathy, and skin changes. This unique syndrome was first described by Crow in 1956; in 1980, Bardwick *et. al.* coined the

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acronym POEMS to describe the key features of the disorder.(1) Other important manifestations of this disease not described by the acronym include sclerotic bone lesions, Castleman's disease, extravascular volume overload, thrombocytosis, weight loss, and elevated levels of vascular endothelial growth factor (VEGF). The vast majority of these patients also present with a monoclonal λ restricted plasma cell disorder. Monoclonal plasma cell disorders typically lead to abnormal concentrations of κ or λ free light chains (FLC) ultimately producing an abnormal serum immunoglobulin light chain ratio (FLC-R), which reflects clonal excess.(2,3) However, it is also recognized that elevations of the absolute values of both κ and λ FLC can occur with preservation of their ratio within the reference range can occur in patients with renal failure or with polyclonal B-cell activation. (4–6) Since all plasma cell disorders studied to date have been found to have a sub-group of patients with abnormal FLC-R, (7–12) we sought to determine whether this is true for POEMS syndrome patients.

Methods

Of the 68 patients with POEMS syndrome seen at Mayo Clinic Rochester between February 2002 and June 2007, 50 had been diagnosed within 4 months of presentation to our clinic and had serum immunoglobulin FLC assays run as part of their clinical workup. These were the patients included in this Institutional Review Board approved retrospective study. Clinical and laboratory data associated with POEMS syndrome were collected including beta-2 microglobulin, VEGF, bone marrow results, extravascular volume overload, peripheral neuropathy, organomegaly, endocrinopathy, skin changes, serum creatinine, serum and urine immunofixation (Hydragel 9IF kit, Sebia, Evry, France, Sebia Hydrasys LC) and serum immunoglobulin FLCs (Freelite™, The Binding Site Limited, Birmingham, U.K.). The FLC assay (Freelite™, The Binding Site Limited, Birmingham, U.K.) was performed on a Dade-Behring Nephelometer.(2,3) The Freelite™ assay consists of 2 separate measurements, one to detect free- κ (reference range, 3.3 to 19.4 mg/L) and the other to detect free- λ (reference range, 5.7 to 26.3 mg/L) light chains.(3) In addition to measuring the concentrations of FLCs, the test also allows an assessment of clonality based on the ratio of κ/λ FLC-R (normal reference range, 0.26 to 1.65). Patients with a κ/λ FLC ratio <0.26 are typically defined as having a monoclonal lambda FLC and those with ratios >1.65 are defined as having a monoclonal kappa FLC. Forty-three patients had serum samples collected and stored within 30 days of their presentation to our clinic, and Cystatin C levels were measured (Latex Cystatin C kit, Dade-Behring, Newark, DE on a Dade-Behring BNII nephelometry analyzer) to more accurately assess renal function. Reference range is 0.59–0.91 mg/L.

Relationships among nominal and continuous variables were detected using Fisher's exact test and Spearman's rho, respectively. Differences between nominal and continuous variables were assessed using Kruskal-Wallis tests. Survival was estimated using the method of Kaplan and Meier. All analyses were performed using JMP 7.0.1 software (SAS, Cary, North Carolina).

Results

Patient characteristics at presentation are shown in Table 1. Of the 50 patients, 62% were male. The median age was 49.5 (range 29–69). The majority had peripheral neuropathy, organomegaly, endocrinopathy, extravascular volume overload, classic skin findings, high plasma vascular endothelial growth factor levels, and thrombocytosis. Thirty-four percent had papilledema, and 17% had coexistent Castleman Disease. Only two patients did not have a monoclonal protein detected in their serum by immunofixation, but both had biopsy proven monoclonal λ plasmacytomas. Within the serum, twenty-six patients (52%) had a

detectable monoclonal IgA λ (one of whom was a bi-clonal patient who also had an IgG κ), 21 patients (42%) a monoclonal IgG λ , and one patient (2%) a monoclonal IgM λ .

The median number of plasma cells seen in the iliac crest biopsies was 4%, range 1–20%. Twenty-six patients had bone marrow plasma cells κ : λ ratios less than 1:1, sufficient to be designated as containing monoclonal λ . One patient had 20% κ restricted plasma cells in his iliac crest biopsy, but monoclonal λ plasma cells in his large pelvic plasmacytoma. The remaining 23 patients had a normal κ : λ ratio of bone marrow plasma cells and were designated as having polyclonal iliac crest biopsies.

Forty-five patients (90%) had increased λ FLC levels with an overall median of 63.8 mg/L (range 18.4–253), but only 9 of these patients had an abnormal FLC-R (median FLC-R was 0.44; range 0.05–1.74). The uninvolved FLC (uFLC), which in all cases was κ FLC, was elevated in 68% of patients with a median of 27.2 mg/L (range 5.78–275). The correlation coefficients between bone marrow plasmacytosis and any of the FLC measurements (κ FLC, λ FLC or FLC-R) were poor (data not shown). Overall, 82% of patients had normal FLC-R despite having a documented λ clonal plasma cell disorder.

To dissect this unexpected finding of high λ FLC but normal FLC-R, the FLC data were analyzed in the context of renal function. Only 15% of patients had a serum creatinine level above 1.5 mg/dL. Because serum creatinine is less reliable for renal function in patients with significant muscle wasting (13), cystatin C levels were measured in the 43 patients who had stored serum available from the time of presentation. The characteristics of these 43 patients were no different from the entire 50 patient cohort (data not shown). Thirty-one patients (72%) were found to have elevated cystatin C levels. As shown in Figure 1A, the correlation coefficient between cystatin C and creatinine in this population was only fair (ρ 0.50, p <0.001). Figure 1A also illustrates the relationships between FLC measurements, markers of renal function, and beta-2 microglobulin, the last of which is a composite variable of renal function and plasma cell burden. There was a good correlation between serum beta-2 microglobulin and κ FLC (ρ 0.79, p <0.0001).

To further examine the relationship between FLC, clonality, and renal function, a subset analysis was performed using the 43 patients with cystatin C measurements, plus one patient without cystatin C but with clonal free λ excess in the blood as determined by FLC-R, for a total of 44 patients (Figure 2). Of this cohort, 18% had an abnormal FLC-R, consistent with clonal λ excess in the serum. However, based on the FLC definition of clonality, 31 patients had a high λ FLC, but normal FLC-R, i.e. a non-clonal FLC-R. Of these 31, 24 had elevated cystatin C, consistent with some element of renal insufficiency. Not surprisingly, 21 of these also had increased κ serum FLC levels. There were, however, 5 patients with normal cystatin C, but elevated serum κ and λ FLC levels. To better explain this last finding, we investigated the percent of patients with reported polyclonal increase of bone marrow plasma cells (BMPC) and found that only 1 had increased polyclonal BMPC, whereas 3 had clonal λ BMPC and 1 normal polyclonal BMPC.

We next assessed whether there was a relationship between organomegaly and a seemingly non-specific (i.e. proportional) elevation in serum FLCs. Both κ FLC (30.8 versus 13.0 mg/L, p =0.002) and λ FLC (75.1 versus 34.8 mg/L, p =0.001), but not FLC-R (0.43 versus 0.45, p =0.9) were higher in patients with organomegaly. There was a trend toward higher cystatin C levels in patients with organomegaly (1.2 versus 1.1, p =0.08), but it did not reach significance.

This observation led us to explore whether there was differential immunoglobulin heavy chain usage, postulating that IgA secreting plasma cells are more likely to be extramedullary. The findings were mixed (Table 2). IgA secreting cases were more likely to

have high κ FLC (85% versus 43% of patients, $p=0.009$), but those monoclonal IgA λ cases were more likely to have clonal λ plasma cells detected in their iliac crest biopsy (74% of IgA λ versus 26% of IgG λ patients, $p=0.009$). The IgA λ patients also had higher serum beta-2 microglobulin levels (4.89 versus 2.95, $p=0.001$). The elevations in the beta-2 microglobulin levels and the serum κ FLC could not be explained purely on the basis of abnormal renal function since there was no difference between the IgA and non-IgA patients with regards to serum creatinine or cystatin C levels.

With a median follow-up of 32 months, only 6 patients have died. To date overall survival was not affected by λ FLC, κ FLC, FLC-R, heavy chain usage or cystatin C.

Discussion

POEMS syndrome is a poorly understood paraneoplastic syndrome driven by a small plasma cell clone. Since serum FLC levels have been shown to be valuable both for prognostication and serial measurements in diseases like immunoglobulin light chain amyloidosis and multiple myeloma, (7–12) we evaluated if the assay was of value in patients with POEMS syndrome.

Despite the fact that serum λ FLC are elevated in 90% of cases of POEMS syndrome, only 20% of these patients (or 18% of the total) have an abnormal FLC-R. We first looked to impaired renal function as a cause for increased levels of both κ and λ FLC due to impaired light chain catabolism (3,5). Since cystatin C measurement is a better marker for renal insufficiency in patients with muscle atrophy, we measured cystatin C levels and found that the elevation of λ FLC in the absence of an abnormal ratio was due to subclinical renal insufficiency for the majority (77%) of patients. We also postulated that the discordance between serum λ FLC and the FLC-R might be explained by a polyclonal increase in bone marrow plasma cells, but this proved to be the case for only 1 patient incrementally over renal insufficiency. The last hypothesis for proportionately elevated κ and λ FLC levels was that patients might have polyclonal plasma cells in other tissues that harbor B-cells, i.e. lymph nodes, spleen, and liver. Indeed, this appeared to be the case. Seventy-nine percent of patients with serum κ levels above the reference range had organomegaly in comparison to 21% with normal κ levels. This held true for patients with and without renal insufficiency. The other association made between an apparent polyclonal activation of light chains (and organomegaly) was IgA heavy chain usage. Patients with IgA restricted heavy chains were more likely to have a diffuse clone detected in their bone marrow than their IgG counterparts. These findings lead one to speculate that patients who have IgA lambda secreting clones may have more disseminated and/or active disease than those patients with IgG lambda secreting clones. The notion that IgA POEMS syndrome may somehow be more advanced than IgG POEMS syndrome is not inconsistent with what we know about IgA myeloma patients, who have a worse prognosis than IgG myeloma patients. With a median follow-up of 32 months and only 6 patients dead, overall survival does not appear to be influenced by λ FLC, κ FLC, FLC-R, immunoglobulin heavy chain usage or cystatin C.

As a result of asking a simple question about whether serum FLC or FLC-R is relevant in patients with POEMS syndrome, we have made a number of novel related observations. First, serum λ FLC are elevated in 90% of patients with POEMS syndrome, but only 18% have an abnormal FLC-R. This rate of abnormal FLC concentration and FLC-R is markedly different from that seen in other plasma cell disorders (7–12). Second, mild renal impairment is more prevalent in patients with POEMS than previously realized (1). Third, the cause for normal FLC-R in patients with elevated λ FLC is multifactorial, i.e. related to both subclinical renal impairment and a background of potentially extramedullary polyclonal plasma cell activation. Fourth, it appears that those patients with POEMS

syndrome who produce the IgA heavy chain isotype are more likely to have diffuse—albeit mild—bone marrow involvement by their clone than their IgG producing counterparts. Finally, there is no clear role for FLC measurement in these patients. Our findings raise as many questions as answers, but provide novel information about immunoglobulins and renal function in patients with POEMS syndrome.

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Figure 1. Relationships between serum immunoglobulin free light chain (FLC) measurements, markers of renal function, and bone marrow plasmacytosis 1. FLC measurements, markers of renal function, and beta-2 microglobulin. The numbers in each of the boxes are the Spearman rho correlation coefficients. * $p < 0.001$

Legend / Characteristic	n	n	n
Both normal renal & κ FLC	3*	2	3
Both abnormal renal & incr. κ FLC	3	21	0
Increased κ FLC but normal renal	0	5	0
Abnormal renal only	2	3	2
Total, n	8	31	5
	%	%	%
Both normal renal & κ FLC	6.8	4.5	6.8
Both abnormal renal & incr κ FLC	6.8	47.7	0
Increased κ FLC but normal renal	0	11.4	0
Abnormal renal only	4.5	6.8	4.5
Total, %	18	70.5	11.4

Figure 2.

The interactions between renal function and serum immunoglobulin free light chains (FLC). Forty-four patients included (43 with Cystatin C measurement and 1 (*) without measurement but elevated λ FLC). All patients with abnormal FLC-R had elevated λ FLC. Abnormal renal function was defined as elevated cystatin C.

Table 1

Patient characteristics (n=50)

	N*	Median	Range	%
Age		49.5	29–69	
Gender, M				62
Race, Caucasian/African-American/Hispanic				76/10/10
Polyneuropathy				100
Organomegaly				76
Hepatomegaly				39
Splenomegaly				68
Lymphadenopathy				61
Endocrinopathy				84
Monoclonal protein				98
Skin disorders				82
Extravascular volume overload				96
Edema				90
Pleural effusions				35
Ascites				33
Pericardial effusions				29
Weight loss				66
Papilledema				34
VEGF elevated [†]	32			90
Castleman's disease				17
Sclerotic bone lesions				80
Ig heavy chain isotype, IgA/IgG/IgM/none				53/43/2/2
Bone marrow PC percentage	4		1–20	
Bone marrow PC clonality, κ/λ/polyclonal				2/52/46
Platelet count, X10(9)/L		415	123–1066	
Serum creatinine, mg/dL [‡]	48	1.1	0.5–3.6	
Serum cystatin C, mg/L [§]	43	1.12	0.26–3.63	
Serum λ FLC, mg/L		64	18.4–253	
Serum κ FLC, mg/L		27	5.8–275	
Serum FLC-R		0.44	0.05–1.74	
Beta-2 microglobulin, mcg/mL*	42	3.91	1.45–12.4	

* N=50 for all measurements, except were noted otherwise

Table 2

Impact of IgA Isotype on Patient Characteristics

	Criteria	IgA (n=26) %	Not IgA (n=24) %	p-value
Organomegaly	<i>Present</i>	96	57	0.002
Iliac crest biopsy λ vs poly	<i>Clonal λ</i>	74.1	26.1	0.001
Beta-2 microglobulin, mcg/mL	<i>Median</i>	7.7	2.9	0.009
Serum κ FLC, mg/dL	<i>>1.94</i>	85.2	43.5	0.007
Serum λ FLC, mg/dL	<i>>2.63</i>	96.3	78.3	0.1
FLC-R	<i><0.26</i>	81.5	78.3	0.6
Creatinine, mg/dL	<i>≥ 1.5</i>	25.9	8.7	0.1
Cystatin C, mg/L	<i>≥ 0.91</i>	70.4	52.2	0.3
BMPC, %	<i>≥ 2</i>	85.2	73.9	0.4
	<i>≥ 5</i>	55.6	30.4	0.08