Overproduction of Proinflammatory Cytokines Imbalanced by Their Antagonists in POEMS Syndrome

By Romain K. Gherardi, Laurent Bèlec, Martin Soubrier, Denis Malaperf, Mathieu Zuber, Jean-Paul Viard, Liliane Intrator, Jean-Denis Degos, and François-Jérôme Authier

The polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes (POEMS) syndrome is a rare multisystem disorder of obscure pathogenesis associated with osteosclerotic myeloma. Circulating levels of proinflammatory cytokines (tumor necrosis factor-α [TNF-α], interleukin-1β [IL-1β], IL-2, IL-6, and interferon γ [IFNγ]), anti-inflammatory cytokines (transforming growth factor β [TGFβ], IL-4, IL-10, and IL-13), the cytokine carrier protein α2macroglobulin, IL-1 receptor antagonist (IL-1ra), soluble TNF receptors (sTNFr) p55 and p75, and soluble IL-6 receptor (sIL-6r) were determined in 15 patients with POEMS syndrome and 15 with multiple myeloma. Patients with POEMS syndrome had higher serum levels of IL-1β, TNF-α, and IL-6 and lower serum levels of TGFβ than did patients with multiple myeloma. Serum levels of IL-2, IL-4, IL-10, IL-13, IFNγ, α2macroglobulin, and sIL-6r were similar in both groups. IL-1ra and sTNFRs were increased in POEMS syndrome, but out of proportion to the increase of IL-1β and TNF-α. Serial evaluations in 1 patient showed that proinflammatory cytokine serum levels paralleled disease activity assessed by platelet count and neurologic involvement. Our results suggest that the manifestations of POEMS syndrome might be regarded as the result of a marked activation of the proinflammatory cytokine network (IL-1β, IL-6, and TNF-α) associated with a weak or even decreased (TGFβ1) antagonistic reaction insufficient to counteract the noxious effects of cytokines. © 1996 by The American Society of Hematology.

The POEMS syndrome is a rare multisystem disorder usually associated with osteosclerotic myeloma and characterized by the combination of polyneuropathy (chronic inflammatory demyelinating neuropathy), organomegaly, endocrinopathy, M protein (mainly IgG or IgA with a λ light chain), skin changes (hyperpigmentation, skin thickening, and hypertrichosis), and various other clinical and pathologic signs such as cachexia, fever, edema, finger clubbing, telangiectasias, thrombocytosis, and multicentric Castleman’s disease. Unlike polyneuropathies associated with IgM gammopathies, an autoimmune mechanism directed toward peripheral nerve components has not been shown in POEMS syndrome.

It has been suggested that pleiotropic proinflammatory cytokines, which act in synergy on the immune, nervous, and endocrine systems, could play a pathogenetic role in POEMS syndrome. Increased serum levels of interleukin-6 (IL-6) have been occasionally reported in patients with POEMS syndrome, but whether the finding was relevant to POEMS syndrome itself or to an associated Castleman’s disease was debated. In two preliminary reports from our group, other circulating cytokines were also found to be elevated: 3 patients had chronically elevated serum levels of tumor necrosis factor-α (TNF-α), a finding reminiscent of the increased TNF-α serum levels observed in patients with acute inflammatory demyelinating neuropathies, and 5 had elevated serum levels of IL-1β, likely related to a sustained activation of macrophages within tissues. IL-2 and interferon γ (IFNγ) that stimulate human monocytes/macrophages were not evaluated. The antagonistic mechanisms that modulate release and biologic activity of proinflammatory cytokines in vivo were also not evaluated. These mechanisms include (1) inhibition of human monocyte production of TNFα, IL-1β, and IL-6 by natural regulators such as IL-4, IL-10, and IL-13; (2) variation of serum levels of carrier proteins such as α2-macroglobulin; (3) binding of circulating cytokines by soluble forms of their cell surface receptors (eg, soluble TNF-α receptors [sTNFr] appear in serum in reaction to TNF-α release, block the molecule, and inhibit TNF-α activity by preventing its binding to cellular receptors); (4) competitive binding to cellular receptors of cytokine structural analogs devoid of biologic activity (this is the case of the IL-1 receptor antagonist [IL-1ra], a member of the IL-1 family that binds competitively to IL-1 receptors but does not induce signal transduction); and (5) release of functionally antagonistic cytokines such as transforming growth factor-β (TGF-β) that antagonizes the effects of TNFα, IL-1, IL-2, and IFNγ and behaves as a potent anti-inflammatory cytokine.

The present study was performed (1) to substantiate the finding of increased serum levels of proinflammatory cytokines in a series of 15 patients with POEMS syndrome; (2) to compare the balance between proinflammatory cytokines and their antagonists in POEMS syndrome and multiple myeloma (MM); and (3) to correlate disregulation of the cytokine network in POEMS syndrome with disease markers.

PATIENTS AND METHODS

Patients

Fifteen patients with POEMS syndrome were included. Clinical and pathologic findings in patients 1 through 5 and patient 9

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were previously published. When the multiple clinical manifestations of the syndrome were classified into the six categories shown in Table 1, 13 of the 15 patients were represented under all six categories and 2 under five. All patients had sensorimotor polyneuropathy and elevated cerebrospinal fluid (CSF) protein levels. Nerve conduction velocities were in the range of demyelinating disorders in 14 patients and normal in 1. Organomegalgy included hepatomegaly (13 patients), splenomegaly (10 patients), and lymphadenopathy (11 patients). All patients had at least one biological endocrine abnormality. Monoclonal protein consisted of IgGλ (10 patients), IgAκ (3 patients), and both IgGα and IgGε (1 patient). Serum levels of the α light chain-bearing monoclonal protein ranged from undetectable (patient 1, who only had free λ light chain in blood and urine) to 7 g/L (patient 15). Radiographic bone abnormalities were present in 14 patients and were multiple in 13. Myeloma was documented histologically in 8 patients. Fourteen patients had at least one typical skin change.

Weight loss was noted in 14 patients and was marked in 10. Other manifestations of the disease included peripheral edema, anasarca, hypoalbuminemia, chronic diarrhea, behavioral changes, depression and other psychiatric disturbances, glomerular nephropathy, severe diffuse noninflammatory arteriopathy, hypertriglyceridemia, and thrombocytosis. Causseman’s disease-like lesions were detected by lymph node biopsy in 6 patients. The follow-up of patients ranged from 1 to 15 years, and 8 patients died within 1 to 9 years after the first symptoms.

Serum measurements of patients with POEMS syndrome were compared with those obtained in 15 patients with MM without neuropathy in whom the serum monoclonal protein level ranged from 10 to 40 g/L.

In an attempt to correlate serum cytokine levels and disease markers at the individual level, serial evaluations were performed in patient 15. Subsequent to one cure of cytotoxic chemotherapy and pelvic bone tumor irradiation, circulating cytokine levels had returned to normal limits. No treatment was administered during the following 70 days while blood sampling was performed every 10 days to assess platelet count, monoclonal IgAA, and cytokine levels. The neurologic status was evaluated clinically, using the neuropathy disability score (NDS),29 and by the study of nerve conduction velocities.

**Serum Measurements**

*Serum sampling.* Determinations of serum cytokines levels were performed prospectively, except in patients 4 and 5. Peripheral blood was taken in dry tubes at 8 AM, the storage of the whole blood was performed at room temperature, the serum was separated within 1 hour, and the sera were kept frozen at −70°C until analyzed. Blood samples were obtained in the absence of fever, shock, and overt infection.

**Measurements of proinflammatory cytokines (TNF-α, IL-1β, IL-2, IL-6, and IFNy).** Commercially available kits for enzyme-linked immunosorbant assays (ELISA) were used to detect total TNF-α, ie, TNF-α bound and unbound to sTNFRs, IL-1β, IL-6 (Immunotech, Marseille, France), IL-2, and IFNy (Genzyme, Cambridge, MA). Using these tests, the TNF-α serum levels upper limit is 15 pg/mL in healthy subjects, for IL-1β is 5 pg/mL, for IL-2 is 100 pg/mL, for IL-6 is 10 pg/mL, and for IFNy is 100 pg/mL. Biologic activity of TNF-α was kindly assessed on D-actinomycin-treated L929 cells by S. Chouaib (Institut Gustave Roussy, Villejuif, France) in 5 patients with POEMS syndrome and 5 with MM.

**Measurements of suppressor cytokines (IL-4, IL-10, IL-13, and TGF-β1).** IL-4 and IL-10 were measured by commercial ELISA (Genzyme). The sensitivity of ELISA tests was 15 pg/mL for IL-4 and 5 pg/mL for IL-10. Healthy controls have IL-4 and IL-10 serum levels less than these threshold values. Domestic ELISA for IL-13 was kindly performed by A. Minić (Sanofi, Labège, France) in 3 patients with POEMS syndrome and 2 patients with MM. Threshold of detection with this test is 200 pg/mL. TGF-β1 was measured by the Predicta ELISA test (Genzyme). The normal range of TGF-β1 is 24 to 104 ng/mL (mean, 70 ng/mL).

**Measurements of α2-macroglobulin.** Serum α2-macroglobulin (normal range, 1.2 to 3.2 mg/L) was determined by ELISA (Immunodiagnostik, Bensheim, Germany).

**Measurements of IL-1ra and soluble cytokine receptors (sTNFRs and sIL-6r).** Serum IL-1ra and sIL-6r were determined using the ELISAs Quantikine (R&D Systems, Minneapolis, MN). Using these assays, the upper limit of IL-1ra serum levels in healthy subjects is 250 pg/mL and that of sIL-6r is 46 ng/mL. Serum sTNFR (p55) and sTNFR (p75) levels were determined by the Cobas-Core enzyme-linked immunobiologic assay (Roche Diagnostic Systems, Basel, Switzerland). Using this assay, the upper limits of sTNFR (p55) and sTNFR (p75) serum levels in healthy donors never exceeded 1,700 pg/mL and 5,500 pg/mL, respectively. To estimate whether the elevations of cytokine antagonist levels were proportional to that of their relevant cytokine in POEMS syndrome and MM, we calculated the following ratio:

\[
R = \frac{[\text{Mean Antagonist Level in POEMS Syndrome}]}{[\text{Mean Cytokine Level in POEMS Syndrome}]} \times \frac{[\text{Mean Cytokine Level in MM}]}{[\text{Mean Antagonist Level in MM}]} 
\]

**Statistical Analysis**

Concentrations were expressed as the mean ± standard error (SE). Statistical analysis was performed using the Mann and Whiney U test for comparison of average serum concentrations of cytokine and cytokine antagonists, the Fisher’s exact test for comparison of prevalences of elevated values, and the Spearman’s test for correlation between cytokines and cytokine antagonist serum levels. A P value less than .05 was considered significant.

**RESULTS**

**Proinflammatory Cytokines (TNF-α, IL-1β, IL-2, IL-6, and IFNy; Fig 1)**

In the POEMS syndrome group, serum IL-1β was increased (>5 pg/mL) in 14 patients, TNF-α (>15 pg/mL) in 10, and IL-6 (>10 pg/mL) in 10. In the MM group, serum IL-1β was increased in 1 patient, TNF-α in 4, and IL-6 in 1.

The average serum concentrations of IL-1β, TNF-α, and IL-6 were greater in patients with POEMS syndrome than in control patients with multiple myeloma (Fig 1). The mean concentration of IL-1β was 161 ± 73 pg/mL in patients with POEMS syndrome and 3 ± 3 pg/mL in MM (P < .0001; 95% confidence interval [CI], 5 to 317 and 0 to 9, respectively). The mean TNF-α concentration was 102 ± 36 pg/mL in POEMS syndrome and 10 ± 5 pg/mL in MM (P < .005; 95% CI, 25 to 179 and 0 to 20, respectively). The mean IL-6 concentration was 40 ± 9 pg/mL in POEMS syndrome and 4 ± 3 pg/mL in MM (P < .0001; 95% CI, 20 to 60 and 0 to 11, respectively).

Serum concentrations of IL-2 and IFNy were similar in POEMS syndrome and MM. The mean IL-2 concentration...
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<td>8</td>
<td>&gt;7</td>
<td>&gt;3</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>&gt;15</td>
<td>&gt;1</td>
<td>12</td>
<td>&gt;4</td>
<td>&gt;1</td>
</tr>
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</table>

Abbreviations: MNVC, motor nerve conduction velocity; CSF, cerebrospinal fluid.

* In this patient, electrophysiologic tests were consistent with a distal axonal polyneuropathy.
The mean concentration of serum TGF-P1 was significantly higher in patients with POEMS syndrome (n = 15) and MM (n = 15). Serum levels of IL-2 are expressed as $10^{1} \times \text{pg/mL}$ (*).

Suppressor Cytokines (IL-4, IL-10, IL-13, and TGF-β1; Fig 2)

IL-4 and IL-10 were not detected in the serum of patients with POEMS syndrome and MM. In the 3 POEMS and 2 MM patients evaluated, IL-13 serum levels were greater than 200 pg/mL were not observed. Serum levels of TGF-β1 were within normal limits (24 to 104 ng/mL) in 9 of 14 patients with POEMS syndrome and 14 of 14 patients with MM. The mean concentration of serum TGF-β1 was significantly lower in POEMS syndrome than in MM (43 ± 9 pg/mL in POEMS syndrome and 79 ± 11 pg/mL in MM; P < .04).

α2-Macroglobulin (Fig 2)

Mean serum α2-macroglobulin levels were in the normal range (1.2 to 3.2 mg/L) in both groups (1.20 ± 0.07 mg/L in POEMS syndrome and 1.37 ± 0.11 mg/L in MM; NS).

IL-1ra and Soluble Cytokine Receptors (sTNFRs and sIL-6r; Fig 3)

In the POEMS syndrome group, serum IL-1ra was increased in 3 patients, sTNFR(p55) in 13, sTNFR(p75) in 10, and sIL-6r in 7. In the MM group, IL-1ra was increased in 1 patient, sTNFR(p55) in 13, sTNFR(p75) in 4, and sIL-6r in 7.

The average serum concentrations of IL-1ra, sTNFR(p55), and sTNFR(p75), but not of sIL-6r, were greater in POEMS syndrome than in MM (Fig 2). The mean concentration of IL-1ra was 193 ± 58 pg/mL in patients with POEMS syndrome and 119 ± 69.2 pg/mL in MM (P < .03; 95% CI, 67 to 320 and 0 to 267, respectively). The mean sTNFR(p55) concentration was 6,900 ± 1,100 pg/mL in POEMS syndrome and 3,300 ± 500 pg/mL in MM (P < .01; 95% CI, 4,100 to 8,700 and 1,900 to 4,100, respectively). The mean sTNFR(p75) concentration was 8,300 ± 1,100 pg/mL in POEMS syndrome and 4,600 ± 700 pg/mL in MM (P < .01; 95% CI, 5,500 to 10,500 and 2,800 to 5,800, respectively). The mean sIL-6r concentration was 51 ± 4 ng/mL in POEMS syndrome and 48 ± 4 ng/mL in MM (NS).

Balance Between Proinflammatory Cytokines and Their Antagonists

Increase of IL-1ra levels was less frequent than increase of IL-1β levels in POEMS syndrome (P < .005). This was not the case in MM, in which a single patient had elevation of both IL-1ra and IL-1β serum levels (NS). Mean levels of IL-1ra were not proportional to mean IL-1β levels in POEMS syndrome and MM (R = 1.3). Serum IL-1ra concentrations correlated positively with those of IL-1β in POEMS syndrome (r = .74; P < .005).

Increase of sTNFR(p55) levels was more frequent than increase of TNF-α levels in both POEMS syndrome (P < .05) and MM (P < .001). No difference was found for sTNFR(p75) (NS). Mean levels of sTNFRs were not proportional to
mean TNF-α levels in POEMS syndrome and MM \( R = 4.9 \) for sTNFr (p55); \( R = 15.6 \) for sTNFr (p75). Consistently, the detected TNF-α was biologically active in patients with POEMS syndrome, as shown by the killing of L929 cells, whereas no biologic activity of TNF-α was detected in patients with MM. In POEMS syndrome, no significant correlations could be established between sTNFr (p55) or sTNFr (p75) levels and TNF-α levels. In MM, sTNFr (p75) levels correlated positively with TNF-α levels \( (r = .75; P < .002) \), whereas sTNFr (p55) levels did not.

Increase of sIL-6r levels was more frequent than increase of IL-6 levels in MM \( (7/14 v 1/15, P < .02) \), but not in POEMS syndrome \( (7/14 v 10/15, \text{NS}) \).

**Clinical Correlations**

Cross-sectional correlations between point evaluations of serum cytokines levels and clinical or biologic manifestations of the disease collected over a long period of time could not be established.

At the individual level (patient 15), increase of proinflammatory cytokines and decrease of TGF-β1 detected in blood from day 1 to day 70 were observed at the time of worsening of the neuropathy (assessed by the neuropathy disability score and nerve conduction velocities) and increase of the platelet count above normal values (Fig 4). Serial evaluations \( (n = 7) \) showed positive correlation between serum IL-6 levels and platelet count \( (r = .9; P < .003) \).

Patient 11 had no detectable circulating IL-1β, TNF-α, IL-6, IL-1ra, and sTNFr (p75) levels, but he did have markedly elevated levels of sTNFr (p55) \( (10,200 \text{ pg/mL}) \). He had been treated using long-term cytotoxic and steroid therapy and was considered to be in complete remission. This patient had the longest survival time of the series \( (> 15 \text{ years}) \).

**DISCUSSION**

In the present study, 14 of 15 patients with POEMS syndrome had increased IL-1β, 10 had increased TNF-α, and 10 had increased IL-6 serum levels. Serum concentrations of IL-1β, TNF-α, and IL-6, but not IL-2 and IFNγ, were higher in POEMS syndrome than in MM without neuropathy. These results substantiate our previous findings31 and confirm that an increased release of proinflammatory cytokines occurs in patients with POEMS syndrome. These cytokines are functionally related as IL-1 and TNF-α stimulate one another, and both IL-1 and TNF-α stimulate IL-6.31 Our findings, therefore, strongly suggest an activation of the proinflammatory cytokine network. The primary site and the cause of activation of cytokine production are undetermined. Production of IL-1β in POEMS syndrome has been evidenced in lymph node interfollicular areas in 2 patients. The lymph nodes were devoid of monotypic B-cell infiltration, and it was likely that nodal production of IL-1 reflected a systemic activation of the monocyte/macrophage system. In the same way, the finding of normal levels of IFNγ and IL-2 levels similar to controls in the present study suggests that activation of macrophages rather than T cells is the primary process in POEMS syndrome. However, activation of cytokine production appears to be linked in some fashion to a unique property of the plasma cell clone, or its secretory products, because complete recovery of POEMS syndrome occurs in patients with a solitary plasmocytoma after surgery and local irradiation.29 One can speculate that the monoclonal gammopathy or its λ light chain triggers the monocyte/macrophage system to produce proinflammatory cytokines. Alternatively, the tumor itself may produce cytokines, as increased production of IL-6, IL-1, and TNF-α by bone marrow cells from patients with myeloma has been occasionally shown in vitro.29

A balance between production of cytokines and their antagonists, ie, either functionally antagonistic cytokines or specific cytokine antagonists, is important in determining host responses. Among suppressor cytokines, TGF-β1 was significantly lower in serum of patients with POEMS syndrome than in patients with MM. Knockout mice experiments have shown that suppressed TGF-β production is as
associated with severe systemic inflammation. It is established that TGF-β1 antagonizes the effects of proinflammatory cytokines and acts as a macrophage deactivating factor by decreasing hydrogen peroxide and nitrous oxide production as well as IL-6 and TNFα production. It is currently believed that the biologic effects induced by a given concentration of IL-1 are inhibited by 10 to 100 times more IL-1ra. In our series, only 3 patients with POEMS syndrome had increased IL-1ra levels, which contrasted with the almost constant increase of circulating IL-1β in this group. The mean concentration of IL-1ra was of the same order as the mean concentration of IL-1β. Thus, it is likely that IL-1ra production in POEMS syndrome was insufficient to buffer the effects of increased IL-1β production. Increased sTNFs levels suggest that of the TNF-α system were observed in both POEMS syndrome and MM. However, concentrations of sTNFr (p25) and (p75) relative to the homologous concentrations of TNF-α were about fivefold less important in POEMS syndrome than in MM, suggesting that increase of sTNF receptors was weak with regard to that of TNF-α. Biologic activity of TNF-α was consistently shown in vitro with sera of patients with POEMS syndrome but not with MM. The sIL-6r increase was similar in POEMS syndrome and MM (7/14 patients in each group). The feature was associated with a frequent increase of IL-6 in POEMS syndrome (10 patients) but not in MM (1 patient).

The strong activation of the proinflammatory cytokine network in POEMS syndrome and the imbalance between productions of cytokines and their antagonists support the view that cytokines may be implicated in the expression of the disease. A correlation was found at the individual level between proinflammatory cytokine serum levels and disease activity assessed by platelet count and both clinical and electrophysiologic severity of the neuropathy. In fact, it is not possible to ascribe one symptom to a single cytokine because TNF-α, IL-1β, and, to a lesser extent, IL-6 have widely overlapping biologic activities and act synergistically. However, in light of human and experimental studies, chronically elevated TNF-α levels correlate well with inflammatory demyelinating neuropathy, organoangelysis affecting liver and spleen, endocrine dysfunctions of the POEMS syndrome, including hypopitosternomegaly and basal hypothymic reaction. Their Role in Disease and Therapy. Cambridge, MA, Blackwell Science, 1995, p 55

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REFERENCES

14. de Malefyt RW, Abrams J, Bennett B, Figdor CG, de Vries


23. Roberts AB, Sporn MB: Physiological actions and clinical applications of transforming growth factor-β (TGF-β). Growth Factors 8:1, 1993


Overproduction of proinflammatory cytokines imbalanced by their antagonists in POEMS syndrome

RK Gherardi, L Belec, M Soubrier, D Malapert, M Zuber, JP Viard, L Intrator, JD Degos and FJ Authier