



Scientific Letter

VEGF and IL-6 Correlation in POEMS: a Potential Upcoming Marker of Active Disease and Early Autologous BMT Response

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To the editor.

POEMS is a paraneoplastic syndrome due to an underlying plasma cell neoplasm¹ characterized by polyneuropathy, organomegaly, endocrinopathy, M-protein accumulation, and skin changes, even if not all necessarily present in the same patient at the same time.

VEGF function may be responsible for most of POEMS manifestations,² and it is considered a reliable marker of disease, used for both diagnosis and follow-up, as it correlates well with disease status. However, the shortage of centers performing ELISA testing for VEGF poses the need to look for more largely available markers for POEMS diagnosis and follow-up.

COVID-19 era arose increasing interest for inflammatory cytokines, with particular focus on Interleukin-6 (IL-6): therefore, many laboratories developed and strengthened the analysis of its level in the blood, which, at the same time, opened us a window of opportunity for further investigation in the field of POEMS physiopathology and surveillance.

Recently, inflammatory pathways have gained considerable interest as an important mediator of the molecular mechanisms leading to hematological malignancies. VEGF production is stimulated by the cytokines IL-6 and IL1 β , whose concentrations appear to be elevated in clonal plasma cell diseases.³ Previous studies have found chronically elevated serum IL-6 in patients (patients) diagnosed with POEMS syndrome, compared to patients diagnosed with other clonal disorders, which points out a possible role of IL-6 function in POEMS development.⁴ Case reports have also investigated the presence of IL-6 in some of the involved organs, finding even higher levels in pericardial effusion,⁵ ascites,⁶ and renal glomeruli⁷ compared to serum.

Even if the role of IL-6 as a marker of disease activity is largely recognized,⁸ so far, there is no proof of any correlation between serum levels of VEGF and IL-6. Nevertheless, their dosage at various stages of the

disease, particularly in the peri-transplant period, aims to understand if they have a comparable pattern, and therefore IL-6 could be used in clinical practice for disease monitoring.

Materials and Methods. In the present analysis, performed as a monocentric study at "Policlinico Gemelli" in Rome, we measured circulating levels of VEGF and IL-6 in 8 patients diagnosed with POEMS. Three of them have been studied before and after eradicating therapy with Melphalan 200mg/mq followed by autologous BMT, particularly the day after the infusion and after one month, so that data are available for both periods. Four of them have been periodically examined for a long period, only later after transplant, each at multiple time points over two to 17 years after BMT, so that late-stage data are available. Furthermore, we analyzed a newly diagnosed POEMS patient and detected his baseline assessment of serum VEGF and IL-6.

Cytokine profiles were determined on serum samples using Immunoassay panels (i.e., anti-IL-6 and anti-VEGF ELISA kit). Detection of cytokines and growth factors was performed per the manufacturer's instruction.

Results. The first three patients, observed before transplant, presented with elevated serum levels of both VEGF and IL-6 since they were on active disease. The measurement performed the day after the infusion of autologous stem cells, instead, showed a steep decrease of both serum markers, likely due to the pre-transplant conditioning regimen, followed by a modest increase in the late post-transplant phase (**Figure 1a**).

In the group of four patients tested only after the transplant, one patient was observed at three-time points every four months starting two years after transplantation and presented with steady normal IL-6

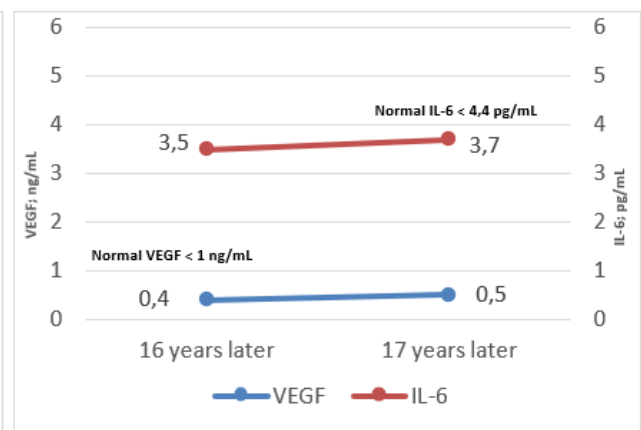
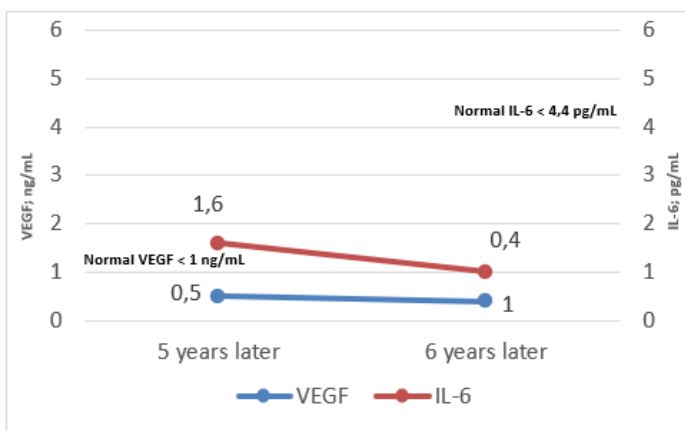
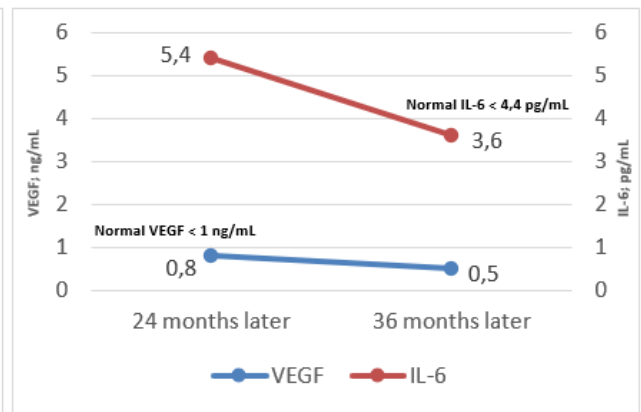
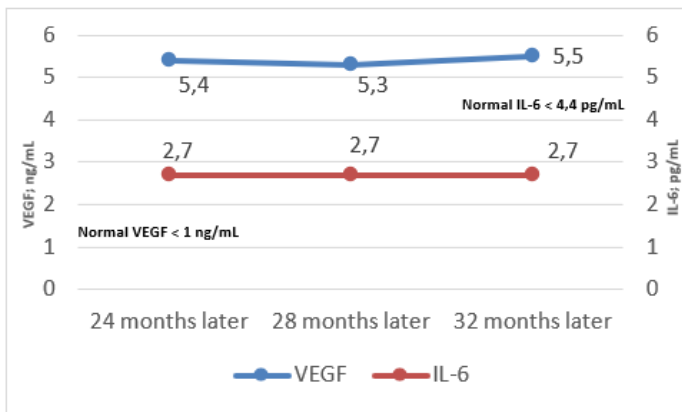
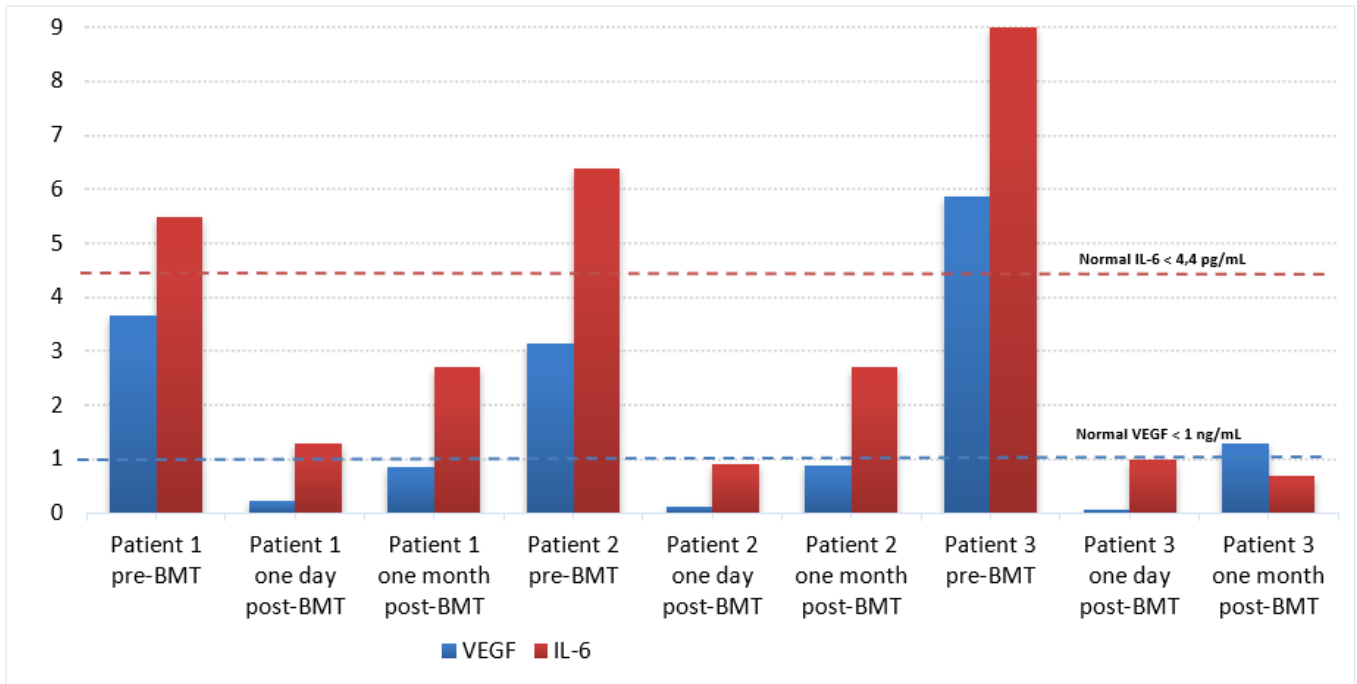


Figure 1. IL-6 and VEGF values correlation in POEMS. **a)** Patients before, soon after (day +1) and long after transplant (day +30), obtained by serial serum measurement. **b), c), d), e)** Patients in later phases after transplant, obtained at long-term follow-up.

values over the time despite a significantly elevated VEGF (**Figure 1b**); another patient was observed twice with a one-year time span starting two years after transplantation and presented with elevated IL-6, but decreasing until it became normal, despite a stable normal value of VEGF (**Figure 1c**); the last two patients

were observed annually twice, in the late post-BMT phase (i.e., starting 5 and 16 years after BMT, respectively) and a correlation between the two values was detected, being both within the normal range (**Figure 1d and 1e**).

Regarding the patient who was observed just at diagnosis, thus on active disease, his baseline assessment showed strikingly high levels of both serum VEGF (5,6 ng/mL, with normal values < 1 ng/mL) and IL-6 (21,6 pg/mL, with normal values < 4,4 pg/mL).

Discussion. The patients studied before and after transplant showed concordance in the values of VEGF and IL-6 at the three different time points; the decrease immediately after the stem cells infusion is probably explained by the sharp therapeutic effect of eradicating regimen, which constitutes the only curative treatment for POEMS nowadays and is therefore used as frontline therapy.⁹ Furthermore, the pattern of the two markers displayed some similarities; thus, it could eventually be asserted that the two values correlate in the peri-transplant phase of the disease.

Alternatively, the other four patients showed variable VEGF and IL-6 serum levels, which only correlate in two patients in complete remission after the autologous BMT transplantation and who had no comorbidities. Normal IL-6 but elevated VEGF detected in the fourth patient could be justified by a relapsed active disease after many lines of treatment, including autologous BMT, even if the mechanism underlying this lack of concordance remains unclear. The swinging values of IL-6 compared to normal values of VEGF of the other patient in this group could be due to the secondary

development of multicentric Castleman disease (MCD),¹⁰ whose pathogenesis is known to be driven by IL-6 in some patients and to increase the overall cytokine levels by itself, regardless of the concomitant presence of POEMS. However, how the cellular and cytokine profiles between POEMS-MCD and classic POEMS syndrome differ is unknown.¹¹ Thus, the two markers should be considered separately as markers of two distinct diseases in this patient.

Furthermore, the concordance between the baseline values of serum VEGF and IL-6 at a stage of severe and active disease detected in the last patient could suggest that IL-6 may be a reliable marker of disease burden.

In conclusion, further patients' analysis should be prompted to confirm an existing relation between VEGF and IL-6: the use of IL-6 as a marker of disease would allow easier monitoring of the disease status, particularly regarding the active phase of the disease and the peri-transplant period. However, there is no sufficient evidence about IL-6 behavior at later stages or long follow-up in post-transplant patients. Moreover, several confounding factors, such as the occurrence of comorbidities or Castleman disease, could alter the IL-6 values, independently of POEMS status.

So far, to the best of our knowledge, IL-6 could be considered reliable up to the very first months after BMT, after which its accuracy appears to be lost due to unknown factors, still to be investigated.

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Competing interests: The authors declare no conflict of Interest.

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