Brief report
The utility of plasma vascular endothelial growth factor levels in the diagnosis and follow-up of patients with POEMS syndrome

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The POEMS syndrome is associated with elevated vascular endothelial growth factor (VEGF) levels. Several studies have compared serum VEGF levels between POEMS patients and other disease entities showing higher serum VEGF in POEMS syndrome; however, it is unknown whether serum levels are reliable and reproducible given variable platelet release of VEGF. We therefore compared plasma levels of VEGF in 29 patients with POEMS syndrome with those of other disorders (n = 76). We demonstrated that plasma VEGF levels are useful in differentiating POEMS from other plasma cell dyscrasias, neuropathic processes, and multisystem illnesses. Plasma VEGF is also useful in monitoring disease activity after treatment and correlates with clinical improvements better than hematologic response. (Blood. 2011;118(17):4663-4665)

Methods
This study was approved by the Mayo Clinic Institutional Review Board. We undertook a retrospective search of our patient database for plasma VEGF levels done as part of routine clinical care at the Mayo Clinic, Rochester, MN between December 5, 2005 and July 31, 2010. Plasma VEGF levels were performed using plasma samples collected in an EDTA tube by the ELISA method. Testing was performed at the Quest Diagnostics Nichols Institute, San Juan Capistrano, CA. Normal values ranged between 31 and 86 pg/mL. Clinical data of these patients were abstracted and analyzed using JMP software (SAS). The Fisher exact test and the Kruskal-Wallis method were used to ascertain differences between nominal and continuous variables, respectively.

Results and discussion
Plasma VEGF levels were performed in 105 patients with POEMS syndrome (N = 29), Castleman disease (N = 9), multiple myeloma (N = 9), monoclonal gammopathy of undetermined significance (MGUS; N = 2), amyloidosis (N = 4), peripheral neuropathy (N = 29), capillary leak syndrome (N = 2), connective tissue disease and/or vasculitis (N = 9), and miscellaneous other diseases, (“other”; N = 12) at the time of diagnosis (Figure 1). Patients with Castleman disease were those patients who had a clonal plasma cell disorder and lymph node biopsy-proven histology (ie, POEMS with Castleman disease). The group with peripheral neuropathy included 20 patients who also had a monoclonal protein (5 with an IgM monoclonal protein), and the remainders were patients with chronic idiopathic demyelinating polyradiculoneuropathy, inflammatory, hereditary, and idiopathic peripheral neuropathy. The group with connective tissue diseases and/or vasculitis included patients with lupus, scleroderma, polymyalgia rheumatica, Moyamoya disease, necrotizing vasculitis, Churg-Strauss syndrome, microscopic polyangiitis, and cerebral vasocnstriction syndrome. The “other” disease group included a patient each with Hodgkin lymphoma, amyotrophic lateral sclerosis,
chronic pain syndrome, and neuromuscular hyperexcitability, and all of the other cases were patients who were not diagnosed with a disease entity. Plasma VEGF levels in patients with POEMS syndrome and Castleman disease were markedly elevated compared with patients with other plasma cell dyscrasias (P < .001), peripheral neuropathy (P < .001), and connective tissue disease/vasculitis (P < .009). Twenty patients with peripheral neuropathy, 5 patients with connective tissue disease/vasculitis, and 7 of the others group also had a monoclonal gammopathy. Median plasma VEGF levels for these patients were separately assessed and found to be 53 pg/mL (peripheral neuropathy with MMUS), 58 pg/mL (connective tissue disease/vasculitis with MMUS), and 48 pg/mL (“other” with MGUS). Four patients with POEMS had normal baseline VEGF; 3 of them were either receiving or had received high-dose steroids within 2 weeks for a presumptive diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy. Eighteen patients with neither POEMS nor Castleman disease had a high VEGF. These included both patients with capillary leak syndrome, 5 patients with connective tissue disease/vasculitis, and 2 patients with myeloma who had coexisting connective tissue disease and vasculitis. A patient with multiple myeloma and peripheral neuropathy each had plasma VEGF levels done during hospitalization for acute illness and had levels of 271 ng/mL and 180 ng/mL, respectively. The remaining patients (1 myeloma, 1 MGUS, 2 peripheral neuropathy, and 3 other disease group) had mildly elevated plasma VEGF levels between 88 and 134 pg/mL. Using receiver operating characteristic analysis, the best VEGF cut-off for POEMS diagnosis was 146 pg/mL; however, a cut-off of 200 pg/mL had a specificity of 95% with a sensitivity of 68% in support of a POEMS diagnosis. We conclude that, like serum VEGF, plasma VEGF levels are useful in diagnosing POEMS syndrome and Castleman disease and can help differentiate from other plasma cell dyscrasias as well as diseases presenting with similar features (ie, peripheral neuropathy, connective tissue disease, and vasculitis). Elevated plasma VEGF levels have been described in several types of cancer,11 rheumatologic illnesses,12,13 renal diseases,14 and in sepsis.14 The sensitivity of plasma VEGF increases further when used in the appropriate clinical setting, and after accounting for acute illnesses, and medications (corticosteroid use).

We also evaluated the use of plasma VEGF in the follow-up of patients with POEMS. Again, all published experience with serial VEGF levels among patients with POEMS syndrome is with serum levels.15-18 Twenty-five patients with POEMS syndrome and/or Castleman disease had plasma VEGF levels done at baseline and on at least 2 separate occasions. Hematologic response to treatment was defined according to the International Myeloma Working Group criteria.19 Based on these criteria, a complete response (CR) was defined as negative immunofixation in serum and urine with disappearance of any plasmacytomas and > 5% plasma cells in the bone marrow. Therapies included autologous stem cell transplantation in 18 patients (with a CR in 9), radiation therapy in 5 (with a CR in 1), and 2 patients treated with combination chemotherapy (one patient received rituximab, cyclophosphamide, and prednisolone, and the other patient received 3 different chemotherapy regimens with lenalidomide/dexamethasone, bortezomib, and cyclophosphamide) with no CRs. All patients who had treatment showed clinical improvement and a reduction in plasma VEGF, but only 10 (40%) achieved a CR. The respective median baseline, day 180, and last follow-up plasma VEGF measurements for the 10 CR and 15 non-CR patients were: 378 and 349 pg/mL, 131 and 75 pg/mL, and 60 and 65 pg/mL. There was no significant difference in plasma VEGF levels on day 180 or at last follow-up between patients who had achieved a CR or not. Plasma VEGF levels correlated with the clinical outcome but not with the depth of hematologic response (Figure 2). It is noteworthy that the one patient who was treated with bevacizumab at relapse (Figure 2B green cross) had normalization of his VEGF, as would be expected with an anti-VEGF antibody but had clinical worsening and eventual death.

We have demonstrated that plasma VEGF levels are useful both for diagnosing and monitoring patients with POEMS syndrome. As in the case of the utility of serum VEGF,2,6,7,20 plasma VEGF is neither 100% sensitive nor specific for the syndrome but can play an important role in making the diagnosis. Moreover, we have shown that plasma VEGF levels correlate better with clinical response than with CR. Although we have not directly compared serum VEGF with plasma VEGF in this study, and knowing that platelets are a major source of VEGF in serum samples in POEMS,21 we contend that plasma VEGF is at least as good, if not better, test. We therefore conclude that plasma VEGF may be used as an option to serum VEGF to aid in the diagnosis of POEMS and Castleman disease.

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Authorship
Contribution: A. D’Souza abstracted the data, performed statistical analysis, and wrote the manuscript; S.R.H., F.B., M.M., M.Q.L.,
A. Dispenzieri designed the concept, analyzed and interpreted the data, and wrote the manuscript; and all authors reviewed the final draft of the manuscript.

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References

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