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CORRESPONDENCE

Intravitreal aflibercept confounds interpretation of plasma VEGF (vascular endothelial growth factor) levels in POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome

To the Editors,

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome is a rare plasma cell disorder where the diagnostic criteria include the presence of monoclonal plasma cells and polyneuropathy and at least one major (sclerotic bone lesions, elevated vascular endothelial growth factor [VEGF], or Castleman disease), and one minor (volume overload, organomegaly, endocrinopathy, skin changes, polycythemia, or thrombocytosis) criteria [1]. Due to the heterogeneity of manifestations, POEMS syndrome is a challenging diagnosis for clinicians to make with a median delay to diagnosis of 12 months [2]. Here we report a patient with a classic presentation for POEMS syndrome but unexpectedly normal plasma VEGF level due to intravitreal aflibercept which later markedly increased with clearance of aflibercept, in order to raise awareness of this previously unknown phenomenon for clinicians who see patients with suspected POEMS syndrome.

A 65-year-old male was found to have new left optic disc edema during surveillance of macular edema following retinal vein occlusion (MEfRVO) that was previously managed with intravitreal aflibercept in the right eye. On further questioning, he reported several months of unexplained fatigue, weight loss, leg weakness and paresthesias, lower extremity edema, along with recent diagnoses of hypothyroidism and hypogonadism. Further evaluation of the new optic disc edema led to brain magnetic resonance imaging demonstrating pachymeningeal enhancement. Chest, abdomen, and pelvic computed tomography (CT) imaging revealed diffuse lymphadenopathy, splenomegaly, and innumerable sclerotic bone lesions, some of which were intensely fludeoxyglucose-18 avid on positron emission tomography CT. Serum immunofixation showed 0.09 g/dL immunoglobulin A lambda monoclonal protein. Supraclavicular lymph node biopsy showed a plasma cell variant of Castleman disease, and bone marrow biopsy showed multiple lymphoplasmacytic aggregates. These findings clinically established POEMS syndrome as the diagnosis. However, plasma VEGF was unexpectedly normal at 8.7 pg/mL (normal, ≤96.2 pg/mL).

VEGF measurement is an important test for POEMS syndrome as a sensitive and specific marker, and VEGF levels correlate with disease activity [1, 3]. It is striking that this patient's VEGF level was normal despite fulfilling the criteria for POEMS syndrome. The recent treatment with intravitreal aflibercept proved noteworthy (Figure 1). Aflibercept is a decoy receptor that binds VEGF-A, VEGF-B, and placental growth factor and is approved for treating colorectal cancer (given intravenously) and exudative macular degeneration, diabetic macular edema, and MEfRVO (given intravitreally) [4]. Intravitreal aflibercept is known to markedly decrease systemic levels of VEGF [5]. In this patient, five weeks after injection and with clearance of aflibercept, the plasma VEGF dramatically increased from 8.7 to

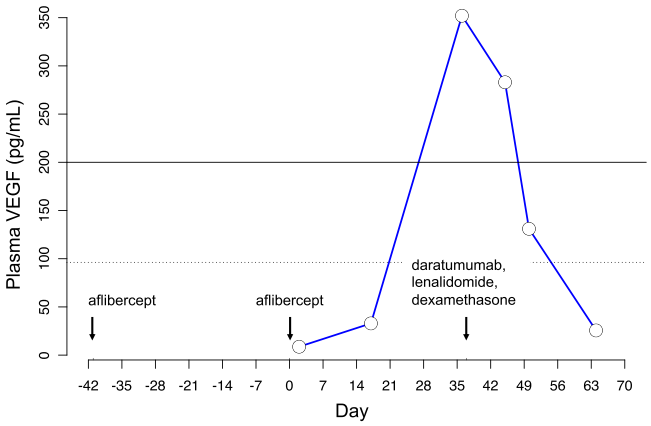

FIGURE 1 Plasma vascular endothelial growth factor (VEGF) levels and relationship to intravitreal aflibercept with respect to the day of presentation with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome. Arrows indicate days that the patient received intravitreal aflibercept 2 mg. After the last aflibercept treatment, plasma VEGF level rose from 8.7 to 352 pg/mL and then decreased after treatment with daratumumab, lenalidomide, and dexamethasone. The upper limit of normal VEGF is 96.2 pg/mL (dotted line). In POEMS syndrome, plasma VEGF levels typically exceed 200 pg/mL (solid line) [1, 3].

352 pg/mL, an elevated level that is characteristic of POEMS syndrome. He started treatment with daratumumab, lenalidomide, and dexamethasone [6]. Within weeks of starting treatment, he improved with gains in strength in his lower extremities and a reduction in lower extremity edema, which correlated with a decrease in VEGF (Figure 1).

Given the diagnostic challenges with POEMS syndrome and the increasing reliance on VEGF level for diagnosis, we highlight how intravitreal aflibercept confounds the interpretation of VEGF level. Clinicians may not be aware that local administration of this drug in the eye can have such significant effects on systemic levels of VEGF. To our knowledge, this is the first time the clinical relevance of this effect has been reported, which is notable as aflibercept and similar anti-VEGF medications are increasingly used by retina specialists for treating a variety of conditions. We caution clinicians evaluating patients with suspected POEMS syndrome on the interpretation of VEGF level when the patient's medication history includes intravitreal aflibercept.

AUTHOR CONTRIBUTIONS

Mary C. Boulanger, Marisa G. Tieger, Dean Eliott, and Andrew J. Yee wrote and revised this Correspondence.

CONFLICT OF INTEREST STATEMENT

Mary C. Boulanger and Marisa G. Tieger declare no conflict of interest. Dean Eliott reports consulting for Alcon, Allergan, Dutch Ophthalmic, and Genentech, research funding from Neurotech and Unity Biotechnology, and stock and royalties from Aldeyra Therapeutics. Andrew J. Yee reports consulting for AbbVie, Adaptive Biotechnologies, Amgen, BMS, Celgene, GSK, Janssen, Karyopharm, Oncopeptides, Pfizer, Prothena, Regeneron, Sanofi, Sebia, and Takeda.

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DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

PATIENT CONSENT STATEMENT

The patient provided consent for his case to be reported.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

Mary C. Boulanger[1,2]
Marisa G. Tieger[3]
Dean Eliott[2,3]
Andrew J. Yee[1,2]

[1]*Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA*
[2]*Harvard Medical School, Boston, Massachusetts, USA*
[3]*Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA*

Correspondence
Andrew J. Yee, Center for Multiple Myeloma, Massachusetts General Cancer Center, 55 Fruit Street, Boston MA, 02114, USA.
Email: ayee1@mgh.harvard.edu

Present address
Marisa G. Tieger, New England Eye Center, Tufts Medical Center

ORCID

Mary C. Boulanger https://orcid.org/0000-0002-1368-6350
Marisa G. Tieger https://orcid.org/0000-0003-2346-1814
Andrew J. Yee https://orcid.org/0000-0003-3623-7491

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