

Bilateral non-simultaneous optic neuropathy and unilateral macular edema in a patient with POEMS syndrome

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PURPOSE. *To report a case of bilateral non-simultaneous optic neuropathy and unilateral macular edema in a patient with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome.*

METHODS. *A 61-year-old man with POEMS syndrome had bilateral anterior optic neuropathy and unilateral macular edema.*

RESULTS. *Visual field testing showed bilateral superior altitudinal field defect. Fluorescein angiography revealed unilateral pooling of fluid consistent with cystoid macular edema. Optical coherence tomography (OCT) showed bilateral loss of retinal nerve fiber layer thickness. The erythrocyte sedimentation rate and C-reactive protein values were normal. The serum vascular growth factor measurement was elevated.*

CONCLUSIONS. *This is the first reported case of ophthalmoscopic, angiographic, and OCT evidence of non-simultaneous optic neuropathy and macular edema in this syndrome. The increased vascular permeability could explain all these factors. (Eur J Ophthalmol 2009; 19: 166-9)*

KEY WORDS. *Macular edema, Optic neuropathy, POEMS syndrome, VEGF*

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INTRODUCTION

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare paraneoplastic syndrome secondary to a plasma cell dyscrasia. A rise in the blood levels of vascular endothelial growth factor (VEGF) is a hallmark of the disease (1). VEGF increased the microvascular permeability and several manifestations of increased vascular permeability are been reported such as edema, ascites, pleural effusion, optic disc edema, and cystoid macular edema (CME) (1-3).

We present a patient with POEMS syndrome who had bilateral non-simultaneous optic neuropathy, unilateral CME, and increased levels of VEGF as evidence that increased vascular permeability could explain the ophthalmic disease in this case.

Case report

A 61-year-old man with POEMS syndrome was referred complaining of superior hemianopia in the right eye for 3 days. He related sudden painless onset of blurred superior visual field on awakening in the morning. Over a 5-year course, he had previously demonstrated all the findings on which the acronym is based. Evaluation was significant for sensorimotor peripheral neuropathy. Endocrinopathy signs were type 2 diabetes mellitus (DM), gynecomastia, hyperprolactinemia (650 mIU/L), and hypogonadism. Splenomegaly and lymphadenopathy were also present. He had a medical history of hypertension, peripheral edema, ascites, polycythemia, and renal dysfunction. Skin changes were hypertrichosis and hyperpigmentation. Serum protein electrophoresis revealed a monoclonal lambda gammopathy. He presented one scler-

Fig. 1 - Ophthalmoscopy shows right disk pallor and left inferior disk and macular edema.

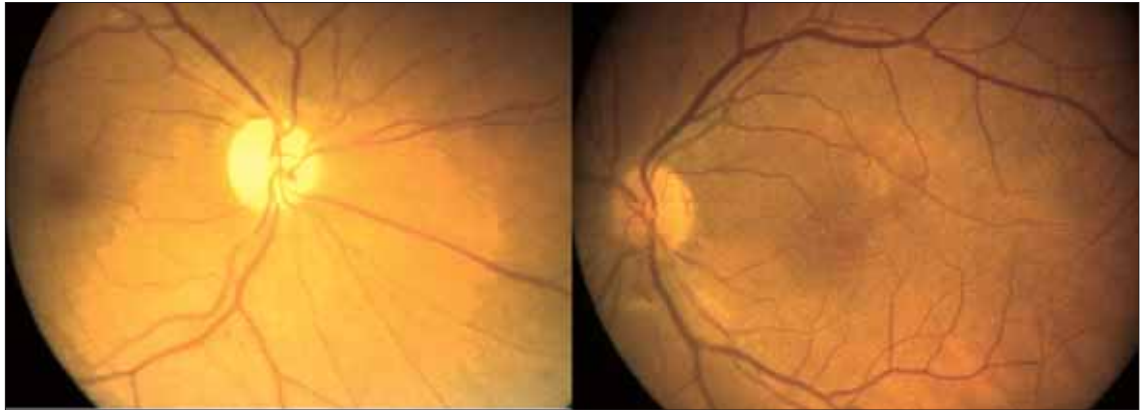
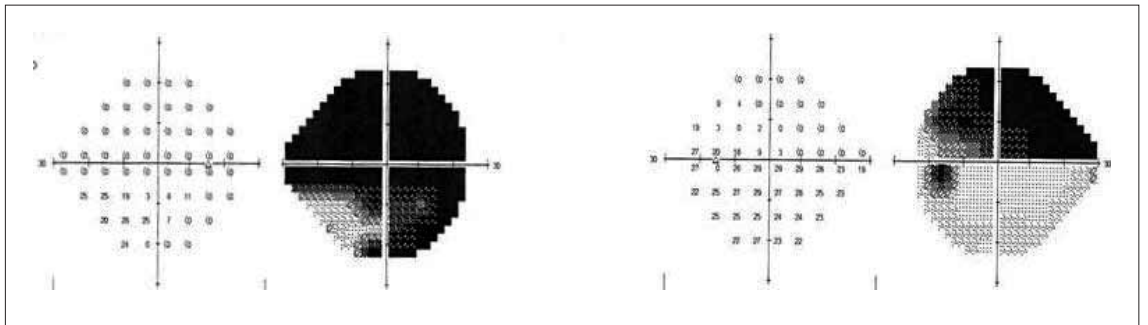


Fig. 2 - Visual fields (24-2 Humphrey test) show superior altitudinal defects in both eyes.



rotic rib lesion, whose biopsy showed a monoclonal lambda sclerotic plasmocytoma. He was under treatment with oral prednisone (40 mg/d).

The ophthalmic history was unremarkable. On examination, the distance best-corrected visual acuity (BCVA) was 2/20 right eye (RE) and 10/20 left eye (LE). Near visual acuity was 20/80 RE and 20/30 LE. He correctly identified 1 of 10 Ishihara pseudochromatic color plates RE and 10 of 10 LE. Right relative afferent pupillary defect was observed. Intraocular pressures were 18 mmHg in both eyes. Ophthalmoscopy revealed inferior right disk edema and a left disk at risk. A 24-2 (III stimulus) Humphrey visual field (VF) (Carl Zeiss, Inc., San Leandro, CA) demonstrated right superior altitudinal visual field defect; left VF was normal. Erythrocyte sedimentation rate (ESR) and C-reactive protein were normal. One month later, his distant BCVA was count fingers at 1 meter RE and 10/20 LE. Near visual acuity was 20/400 RE and 20/30 LE. Right disk temporal pallor was observed. Six months later, the patient complained of decreasing vision LE. Distant BCVA was count finger at 1 meter RE and 2/20 LE. Near visual acuity was 20/400 RE and 20/80 LE. He could identify 1 of 10 Ishihara pseudochromatic color plates in both eyes. Ophthalmoscopy showed right disk pallor and inferior left

disk edema. In addition, we found left macular edema (Fig. 1). Fluorescein angiography revealed late leakage of dye from the left optic disk and left pooling consistent with CME. Nonperfused areas, intraretinal microvascular abnormalities, or retinal neovascularizations were not observed. Examination and ancillary tests ruled out causes of vasculitis such as giant cell arteritis, Wegener granulomatosis, rheumatoid arthritis, systemic lupus erythematosus, or sarcoidosis. Serum levels of angiotensin-converting enzyme (ACE), rheumatoid factor (RF), complement, antinuclear antibodies (ANA), and antineutrophil cytoplasmic antibodies (ANCA) were normal. Serum ESR and C-reactive protein were also normal.

The patient was treated with left grid macular photocoagulation. One month after treatment, his left BCVA improved to 10/20 and the macular edema had disappeared. One month later, left disk pallor appeared. VF showed superior altitudinal defect in both eyes (Fig. 2). Brain and orbit MRI demonstrated symmetric normal-diameter optic nerves of normal signal intensity without pathologic contrast enhancement. There was no pathologic contrast enhancement, mass, or mass effect within the orbits or the brain. Visual evoked potentials were extinguished in the RE and there was a decrease in ampli-

tude with normal latency in LE. Optical coherence tomography (OCT) revealed bilateral loss of retinal nerve fiber layer thickness in both eyes. Serum vascular endothelial growth factor (VEGF) was 450 pg/mL (normal 31–86 pg/mL). At the moment, ophthalmologic examination is unchanged.

DISCUSSION

To our knowledge, this is the first reported example of ophthalmoscopic, angiographic, and OCT evidence of the combination of bilateral non-simultaneous optic neuropathy, CME, and elevated VEGF in this syndrome.

POEMS syndrome is an unusual paraneoplastic syndrome secondary to a plasma cell dyscrasia. A high blood level of VEGF is usually confirmatory and more than 95% of patients have monoclonal lambda sclerotic plasmocytoma (1). The pathogenesis is complex; the coagulation pathway and its relationship to VEGF has also been proposed. VEGF normally targets endothelial cells and induces a rapid and reversible increase in vascular permeability and plasma and serum levels of VEGF are markedly elevated in patients with POEMS and correlated with the activity of the disease. Increased VEGF may account for the organomegaly, edema, skin changes (1), and ophthalmology disorders. Increased VEGF has been found in ascitic fluid and the cerebrospinal fluid (1). It could be an important regulator of osteoblastic differentiation (1). There are therapies that benefit patients with POEMS syndrome, including radiation therapy, alkylator based therapies, and corticosteroids (1). Osteosclerotic lesions could be treated with radiation. High dose chemotherapy with peripheral blood transplant is yielding promising results (1).

Several ophthalmic disorders have been described, such as optic disk swelling, bilateral papilledema, infiltrative orbitopathy, neovascularization of the disk, and CME (1-4). Previous published cases of optic neuropathy were about disk edema. Nevertheless, to our knowledge, the occurrence of bilateral permanent non-simultaneous optic neuropathy with sudden painless onset of blurred vision on awakening in the morning, decrease of color vision, altitudinal field loss, swelling disks that evolve to optic atrophy, and the association with CME in this disease has not been reported.

Optic neuropathy can be secondary to several causes such as vasculitis, demyelination, infiltrative diseases, compressive or infiltrative tumors, or ischemia.

With the information provided by examination, ancillary test, and history, we could rule out vasculitis in our patient. Serum levels of ACE, RF, complement, ANA, and ANCA were normal. Serum ESR and C-reactive protein were also normal. In addition, there was absence of vasculitis-related symptoms.

We dismissed demyelination because the brain and orbit MRI were normal and VEP showed an important decrease of amplitude but no latency. The polyneuropathy was symmetric, distal, and sensorimotor. Otherwise, the neurologic examination did not show any other signs of demyelination. Since demyelination was ruled out a lumbar puncture was not done.

Infiltrative or compressive tumors were also rejected because MRI was normal. Therefore, ischemic optic neuropathy is the most plausible explanation in our patient.

On the other hand, non-arteritis ischemic optic neuropathy (NAION) is the most common optic nerve disorder of individuals between 55 and 70 years. The conditions associated with NAION are systemic hypertension, DM, cerebrovascular disease, cardiac disease, hyperlipidemia, coagulopathies, acute blood loss, nocturnal hypotension, and cataract surgery (5). Sudden, painless onset of blurred central vision, altitudinal visual field, or loss of all vision can occur, usually on awakening. Usually, altitudinal field loss, mostly in the inferonasal quadrant, occurs. NAION shows a swollen disc either diffuse or focal and hyperemic in acute phase or pale after a few weeks. The usual structure of the optic disk is small and crowded (5, 6). The appearance of this type of disk is called "disk at risk." Several authors have postulated that when the axons are crowded there is a subclinical ischemia and swelling, and these disks are more prone to infarction (6). NAION is presumed to result from circulatory insufficiency with the optic nerve head due to dysregulation, but the specific location of the vasculopathy and its pathogenic mechanism remain unproven. The available evidence does, however, highlight one important fact: the infarctions were predominantly located in the retrolaminar region of the optic nerve head, with extension to the lamina and prelaminar layer in some. This pattern suggests that the vasculopathy responsible for NAION does not lie within the choroidal circulation, since the contribution of the choroid to the optic nerve head vascular supply is to the more anterior laminar and prelaminar layers (7).

Approximately one-third of the patients go on to develop NAION in the fellow eye, and although bilateral NAION is not common, it is seen more in diabetic patients.

Based on the above facts, we postulate that our patient may have bilateral non-simultaneous NAION.

Bilateral NAION and CME could have appeared in our patient due to several reasons. First, relative ischemia caused by systemic hypertension and DM in disks at risk could have caused the infarct in the nerve and DM could have caused the CME. However, bilateral NAION is unusual and we did not find other diabetic retinopathy signs in fluorescein angiography in his left eye. On the other hand, the presence of CME in POEMS syndrome has been well documented because VEGF induces an increase in vascular permeability and several articles have attributed to the elevated serum VEGF the appearance of leakage in the macular area. VEGF also has been related to acute arterial obliteration and in addition, plays a role in the increased permeability of small vessels, which may result in subperineural edema and lead to injury of the nerve axon (1, 8). This feature in disks with a small physiologic cup with crowding axons could have caused vascular dysregulation, stasis of axoplasmic flow, and disk swelling in our patient. Arimura (8) studied the direct effects of VEGF on blood-nerve barrier function using an animal model and found that VEGF increased the microvascular permeability inducing endoneurial edema. The authors postulate that this increased permeability

could allow serum components toxic to nerves to induce further damage.

We propose a cause-effect relation between increased vascular permeability secondary to high levels of VEGF and NAION in our patient. The increased levels of VEGF would have created a higher permeability state. This would have produced subperineural edema in a disk more prone to ischemia because it already had crowded axons. All these features would have created a higher level of optic disk ischemia which would have added to a possible microangiopathy caused by DM and hypertension. Finally, the accumulation of these would have led to vascular dysregulation and optic disk infarct.

In conclusion, the changes in microvascular permeability that occur in POEMS may explain the bilateral non-simultaneous neuropathy and unilateral macular edema in this patient.

The authors have no proprietary interest in any aspect of this report.

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