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Paraneoplastic Progressive Vasculopathy as the Presenting Manifestation of POEMS: A Case Report

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Abstract

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy or Edema, M-spike, and Skin Manifestations) is a rare multisystem disease. There are very few reports of stroke as the presenting manifestation of POEMS. We report a patient with ischemic stroke due to an underlying vasculopathy as the initial presentation of POEMS. This case highlights the importance of recognizing ischemic stroke as a presenting sign for POEMS as early diagnosis and treatment in patients with POEMS may prevent progression of multisystem involvement and potentially stabilize the vasculopathy associated with it.

Keywords

POEMS; Vasculopathy; Ischemic Stroke

Background

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy or Edema, M-spike, and Skin Manifestations) is a rare multisystem disease.^{1, 2} While ischemic stroke has been reported in patients with POEMS³, the cause of stroke in these patients is unclear, and there are very few reports of stroke as the presenting manifestation of POEMS.⁴ It is important to recognize ischemic stroke as a presenting manifestation of POEMS since it could help physicians diagnose and treat POEMS early to prevent progression.

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Case

The patient was a 32 year-old right-handed man with no known prior medical history who was in his usual state of health until 2 months prior to presentation, when he started having right retro-orbital headaches and nasal congestion. He was diagnosed with sinusitis and treated with antibiotics and over the counter medications including pseudoephedrine and sympathomimetic nasal sprays. A few weeks later, he presented to the emergency room after developing several episodes of transient right monocular blindness without any other associated symptoms. He had a 10-pack year smoking history but no alcohol or illicit drug use. His medications included the pseudoephedrine and other sympathomimetic nasal sprays. General examination was unremarkable and his blood pressure was 120/70 mm Hg. Neurological examination, including full fundoscopic exam and visual acuity, was normal.

His diagnostic evaluation included brain magnetic resonance imaging (MRI) that showed multiple small infarcts in the right corona radiata in the internal borderzone territory (Figure 1) and magnetic resonance angiography (MRA) of the head and neck that showed reduced flow in the right supraclinoid internal carotid artery that was confirmed by conventional angiography (Figure 1). Due to the headaches and history of sympathomimetic use, he was diagnosed with reversible cerebral vasoconstriction syndrome and discharged home on aspirin and verapamil.

Three months later, he presented with right hand numbness, right facial paresis, and dysarthria. Brain MRI showed multiple small infarcts in the left corona radiata and MRA showed reduced flow in the left middle cerebral artery (Figure 1). A vasculitic process of the central nervous system was suspected. His diagnostic evaluation included an extensive panel of inflammatory, rheumatological, and autoimmune laboratory tests which were all non-revealing (Table 1). Cerebrospinal fluid (CSF) analysis showed normal cell count and glucose, and a mildly elevated protein at 74 mg/dL. A viral panel including CSF Varicella Zoster Virus (VZV) IgG, IgM, and PCR was negative. Due to concern for CNS vasculitis, the patient underwent brain, leptomeningeal, and temporal artery biopsies that were negative for any inflammatory process but showed thickening of blood vessels. He was diagnosed with biopsy-negative CNS vasculitis and treated with intravenous methylprednisolone 1 gram per day for 5 days followed by a slow taper of oral prednisone over 6 months.

At the end of the prednisone taper, he developed burning pain and bluish discoloration and clubbing of hands and feet, as well as painless violaceous macules on arms, trunk and back (Figure 2). He further endorsed intermittent low-grade fevers, weight loss, and fatigue. Laboratory tests were notable for progressive thrombocytosis (platelets 700–900K), climbing erythrocyte sedimentation rate (from 5 mm/hr to 64 mm/hr), C-reactive protein 114 mg/L, and positive rheumatoid factor (Table 1). Serum protein electrophoresis demonstrated a low concentration of immunoglobulin A lambda with preservation of polyclonal immunoglobulins. A computerized tomography (CT) scan of the chest, abdomen, and pelvis showed mild hepatosplenomegaly, splenic infarcts, and subcentimeter nodes in the mediastinum and axilla and a 1.4 cm subcarinal lymph node. Neck lymph node fine needle aspiration showed a polymorphous population of mostly small lymphocytes. Bone marrow biopsy revealed a very small population (< 1% of total cells) of lambda-restricted

(monoclonal) plasma cells (CD138+ and lambda+, and CD45-) suspicious for plasma cell dyscrasia. Biopsy of the skin lesions showed angiomas, clear cell acanthomas, and pyogenic granulomas.

He was restarted on prednisone, and cyclophosphamide was added due to concern for systemic vasculitis. He was treated for 2 years and his symptoms improved. He was maintained on prednisone 10 mg daily and cyclophosphamide was stopped. Six months later, he abruptly discontinued prednisone on the advice of a relative and soon after, he was admitted with pleuritic chest pain. Laboratory studies were significant for proteinuria, free T4 0.9 pg/ml (normal 2.4 pg/ml-4.2 pg/ml), and hypogonadism (Luteinizing Hormone 7.6 mIU/ml (normal post-puberty values < 10 mIU/ml), testosterone <2 ng/dL, Follicle Stimulating Hormone 5.4 mIU/ml (normal post-puberty <10 mIU/ml; Table 1)). Nerve conduction studies performed for upper and lower extremity paresthesias showed electrophysiological evidence of a demyelinating greater than axonal sensorimotor polyneuropathy. Vascular endothelial growth factor (VEGF) levels were markedly elevated (plasma VEGF level=648 pg/ml (ref 0 pg/ml-115 pg/ml), serum VEGF level=11,668 pg/ml (ref 62 pg/ml-707 pg/ml)). Repeat CT of the chest, abdomen, and pelvis showed splenomegaly, mild ascites, and bilateral pleural effusions.

Transthoracic echocardiogram showed a dilated right ventricle with normal function and a small circumferential pericardial effusion with thickened pericardium. He met the criteria for POEMS. Bone marrow transplantation was planned, but he became too ill to tolerate it due to renal failure, and expired. Figure 3 shows a timeline of events of the patient.

Discussion

Our patient presented with an uncommon presentation of an uncommon disease. He had a progressive paraneoplastic cerebral vasculopathy, an extremely rare initial presentation of POEMS, leading to a prolonged time to diagnosis.⁴ He was initially diagnosed with other still rare but more common causes of stroke and vasculopathy such as RCVS and vasculitis.⁵ His diagnosis was also delayed because the immunosuppressive treatments used to treat those conditions may have prevented the development of other manifestations of POEMS until several years into his course, until abrupt cessation of his medications provoked a full relapse and the full spectrum of his POEMS became apparent.

POEMS is a very rare multisystem disease; its exact incidence is unknown given its complex multisystem clinical manifestations that may be indolent and easily missed.^{1, 2} It is thought to be due to a plasma cell dyscrasia. Clinical features include polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. Other important associated findings include elevated levels of vascular endothelial growth factor (VEGF), Castleman disease, sclerotic bone lesions, papilledema, and thrombocytosis.^{1, 2} The average age of onset is 50 years and the male to female ratio is 2:1. Optimal treatment is bone marrow transplantation. If untreated, it is progressive with 60% mortality at 5 years.^{1, 2}

Structural derangements of blood vessels, thought to be due to pro-angiogenic factors (including VEGF, as in our patient), may occur with POEMS.³ Ischemic stroke occurs in up

to 13% of patients diagnosed with POEMS followed for 5 years.⁶ A non-inflammatory large vessel vasculopathy is thought to be the cause of stroke. Thrombocytosis and bone marrow plasma cell proliferation increase risk of stroke⁶, although these features were absent or very mild in our patient at the time he presented with vasculopathy.

To our knowledge, our case is among the very few reported patients with POEMS to present with ischemic strokes, and he appears unique in the course of his progressive intracranial large vessel vasculopathy. Intracranial vasculopathy is not an uncommon presentation in young people with stroke, and the differential diagnosis is broad and includes many rare entities, including RCVS, primary CNS vasculitis, varicella zoster virus-associated vasculopathy, antiphospholipid antibody syndrome, and other entities. Our patient illustrates the importance of both considering paraneoplastic causes of vasculopathy and aggressively pursuing abnormal hematological abnormalities in such patients. Tests to consider in the diagnostic evaluation of such patients should include serum and urine protein electrophoresis, VEGF levels, and bone marrow biopsy, even for subtle abnormalities. An early diagnosis and treatment in patients with POEMS may prevent progression of multisystem involvement and potentially stabilize the vasculopathy associated with it.

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Figure 1.

Upper row: Diffusion weighted imaging MRI sequence (left) showing acute infarcts (arrow) in the right corona radiata and cerebral angiogram (right) showing narrowing of the right supraclinoid internal carotid artery and a pseudoaneurysm of the right middle cerebral artery (arrow). Lower row: Diffusion weighted imaging MRI sequence showing an acute infarct in the left corona radiata (arrow) and magnetic resonance angiography (right) showing reduced flow in the left middle cerebral artery (arrow).

Figure 2.
Skin manifestations including clubbing (left) and a macular rash on the back (right).

Figure 3.
Timeline of major events, symptoms and diagnoses (upper part) and treatments (lower part).

Table 1

Laboratory, radiological, and pathological findings in our patient over the course of his illness

Months from presentation	5 months	11 months	42 months
Hemoglobin	14 mg/dL	12 mg/dL	11 mg/dL
Platelets	550,000/ μ L	700,000/ μ L	900,000/ μ L
Urinalysis	normal	normal	proteinuria
ESR	6 mm/hr	64 mm/hr	88 mm/hr
Rheumatoid Factor	11.1 IU/mL	42.3 IU/mL	
Anti-nuclear antibody	negative	negative	
CSF WBC	1 per mm ³		
CSF Protein	74 mg/dL		
CSF VZV IgG and PCR	negative		
CSF VDRL	negative		
Brain Biopsy	Thickening of blood vessels, negative for inflammation		
SPEP		Low IgA lambda	
CT Chest/Abdomen/Pelvis		Mild hepato-splenomegaly Splenic infarcts Mediastinal and carinal lymph nodes	Hepatoplenomegaly and mild ascites and bilateral pleural effusions.
Transthoracic echocardiogram		normal	dilated right ventricle with normal function and a small circumferential pericardial effusion with thickened pericardium
Fine needle aspiration Lymph node		Polymorphous population of small lymphocytes	
Bone Marrow Biopsy		Suspicious for plasma cell dyscrasia	Suspicious for plasma cell dyscrasia
FSH			5.4 mIU/ml
LH			7.6 mIU/ml
Serum VEGF			11,688 pg/ml
Plasma VEGF			648 pg/ml
Free T4			0.9 pg/mL
Testosterone			<2 ng/dL
Nerve Conduction study			Electrophysiological evidence of a demyelinating greater than axonal sensorimotor polyneuropathy