Bilateral Disc Edema Associated with POEMS Syndrome

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Abstract

POEMS syndrome is a rare paraneoplastic disorder that is named after its multi-systemic presentation of: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. Though the predominant feature is progressive polyneuropathy, bilateral optic disc edema is present in the majority of patients. Not only do eye care providers play a significant role in the treatment of the patient, but also measure treatmentresponse.

Given the high incidence of bilateral optic disc edema in POEMS syndrome, eye examinations are indicated at the timeofdiagnosis.Further,ocularmanifestationsofPOEMS syndrome are reflective of the disease severity and offer prognosticvalue.POEMSsyndromeaffectsmultiplaspects of a patient's functionality; therefore, a multidisciplinary holisticapproachtopatientcareprovidesthebestoutcome.

POEMS syndrome is known by several names: Crow- Fukase syndrome;[1,2]Takasuki disease;[2] plasma cell dyscrasia, endocrinopathy, and polyneuropathy (PEP) syndrome;[3]and osteoscleroticmyeloma,[4]butitismostcommonlyreferredtoas POEMSsyndrome.ScheinkerfirstreportedPOEMSsyndrome in an autopsy in 1938, but it was not until 1980 when Bardick et al.[5] coined the term POEMS syndrome as an acronym for the clinical presentation: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.[6]The disease was first reported in Japanese men and thought to be exclusively among the Japanese; however, it has since been reported in females and in differentcountries.[7,8]

Castleman Disease has a significant association with POEMS syndrome, as 11-30% of patients with POEMS syndrome have Castleman Disease. [3,9-11] The diagnosis of Castleman Disease is vital to the care of the patient because it can affect multiple organs, significantly decrease the quality of life, and have a poorer prognosis.[12-14]

Castleman Disease associated with POEMS syndrome is a rare entity. However, our patient presented with an even more rare combination of POEMS syndrome, multicentric Castleman Disease, and moyamoya disease. This is the first reported case ofallthreeconditions.POEMSsyndromeisnotcurrentlylisted as one of the typical causes of secondary moyamoya disease, but has been reported in one other case report as a possible cause.[15,16] Given that POEMS syndrome was diagnosed twoyears before the diagnosis of moyamoya disease in our patient, it is likely that moyamoya disease developed as a result of the vascularchangesthatoccurredinPOEMSsyndrome;therefore, moyamoya disease will be referred to as quasi-moyamoya disease (the term used to distinguish from through the rest of thepaper.

The diagnosis of POEMS syndrome is frequently delayed and initially misdiagnosed because of the diverse disease presentation, which causes improper treatment andprogression of debilitating syndromes. Therefore, it is vital for multi- discipline practitioners to include POEMS syndrome in their differentialdiagnosis.

Case Report

M.S., a 51-year-old white female presented with complaints of "splotches" in the vision of both eyes that had been ongoing over the last year but increasing in frequency over the last few months. The splotches occurred a few times per day with each episode lasting 15-30 minutes. In addition, she reported mild parietal headaches over the last 3 months, numbness in both legs as well as dizzy spells that were brought on by high sugar intake.

MedicalhistorywassignificantforPOEMSsyndromediagnosed 10 years previous, with polyneuropathy, hypersplenism, hypothyroidism, and low-level serum IgA-lambda monoclonal immunoglobulin. Her serum protein electrophoresis was initiallynegativeformonoclonalgammopathy,butshowedlow-levelIgAlambdaimmunoglobulininaconcentrationtoolowto

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Références : 1. Monographie de VYZULTA[MC]. Bausch & Lomb Inc. 27 décembre 2018. **2.** RAMQ*. Liste des médicaments. Consulté le 30 avril 2024 à l'adresse https://www.ramq.gouv.qc.ca/fr/a-propos/liste-medicaments.

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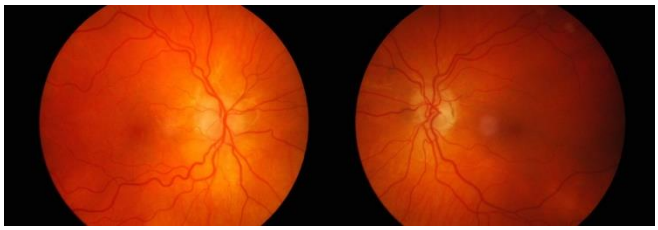

Figure1. Fundusphotographyofthebotheyesattheinitialvisit.Right eye:Clearmediawithopticnerveheadedema360degreeswithindistinct margins. Moderate vessel tortuosity and mild macular mottling. Left eye: Indistinct margins nasal and superior of the optic disc, indicatingdisc edema.Opticnervealsopresentswithmildpallorindicatingopticdisc atrophy.Retinalvasculatureisnormalcaliberandappearance.Maculais evenlypigmented.

quantitate only with immunofixation on repeat testing. She had also been diagnosed with HHV-8 negative,HIV-negative multicentricCastlemandisease,thrombocytopeniaandanemia due to hypersplenism, stage 4 kidney disease, aortic stenosis, mitral valve insufficiency, quasi-moyamoya syndrome, and Asperger syndrome. The patient reported undergoing a bilateral superficial temporal artery to middle cerebral artery bypass with encephaloduroarteriomyosynangiosis (EDAMS) on the left and right side for treatment of quasi-moyamoya syndrome, breast reduction, ankle surgery, aortic valve replacement, and mitral valve replacement.

Her medications included Amour Thyroid, Coumadin, metoprolol tartrate, alpha lipoic acid, vitamin B complex, vitaminC,vitaminD3,calcium,magnesium,coenzymeQ10, folic acid, conjugated linoleic acid, and safflower oil. The patient has a history of recreational drug use (she would not share the drugs she used), currently uses marijuana daily, is a former smoker, and does not currently consume alcohol. She reported no significant ocular or family medicalhistory.

Upon greeting M.S., she demonstrated poor hearing and a slow response time that continued throughout the course of the exam. She exhibited poor coordination and was slow moving. She had a distended abdomen and reddish skin lesions covering visible areas of her arms and legs.

Her best corrected visual acuities were $6/6^{-2}$ right eye and $6/9^{-1}$ left eye. Pupils were equal, round, and reactive to light without a relative afferent pupillary defect. Confrontation visual fields were full in each eye. Extraocular muscle motilities showed no restrictions. Intraocular pressures measured with Goldmann applanation tonometry was 19mm Hg OD and 16 mm Hg OS at 4:07pm.

Anterior segment examination was unremarkable in both eyes. A dilated fundus exam (Figure 1) of the right eye showed 0.2/0.2 cup to disc ratio with a swollen optic nerve

	OD	OS
Average RNFL Thickness	155 µm	61 µm
RNFL Symmetry	63%	
Rim Area	1.77 mm²	1.48 mm²
Disc Area	1.72 mm²	1.62 mm²
Average C/D Ratio	0.07	0.28
Vertical C/D Ratio	0.06	0.30
Cup Volume	0.000 mm³	0.027 mm³

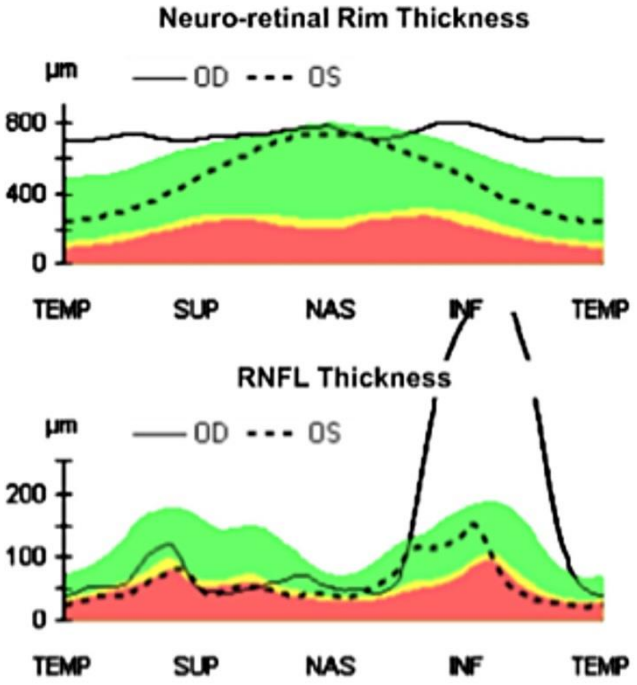

Figure2. RNFLOCTattheinitialvisit.RNFLOCTwithsignificantRNFL thickening inferiorly (393 um) and temporally but significant thinning superiorlyintherighteye.Thelefteyedemonstratedsuperiorandtemporal RNFLthinning.TheaverageretinalRNFLthicknesswas155umintheright eyeand61uminthelefteye.

head 360 degrees, disc pallor, and an oedematous retinal nerve fiber layer (RNFL) greatest inferiorly. Blood vessel tortuosity was present. The left eye demonstrated 0.3/0.3 cup to disc ratio, as well as optic nerve oedema superiorly and nasally with slight optic nerve pallor. Blood vessel tortuosity was present as well as mottling of the macula. The vitreous and peripheral retina were unremarkable in both eyes.

Ishihara colour testing and red cap testing were both unremarkable. An evaluation of cranial nerves V, VII, and VIII was performed with normal findings bilaterally. An

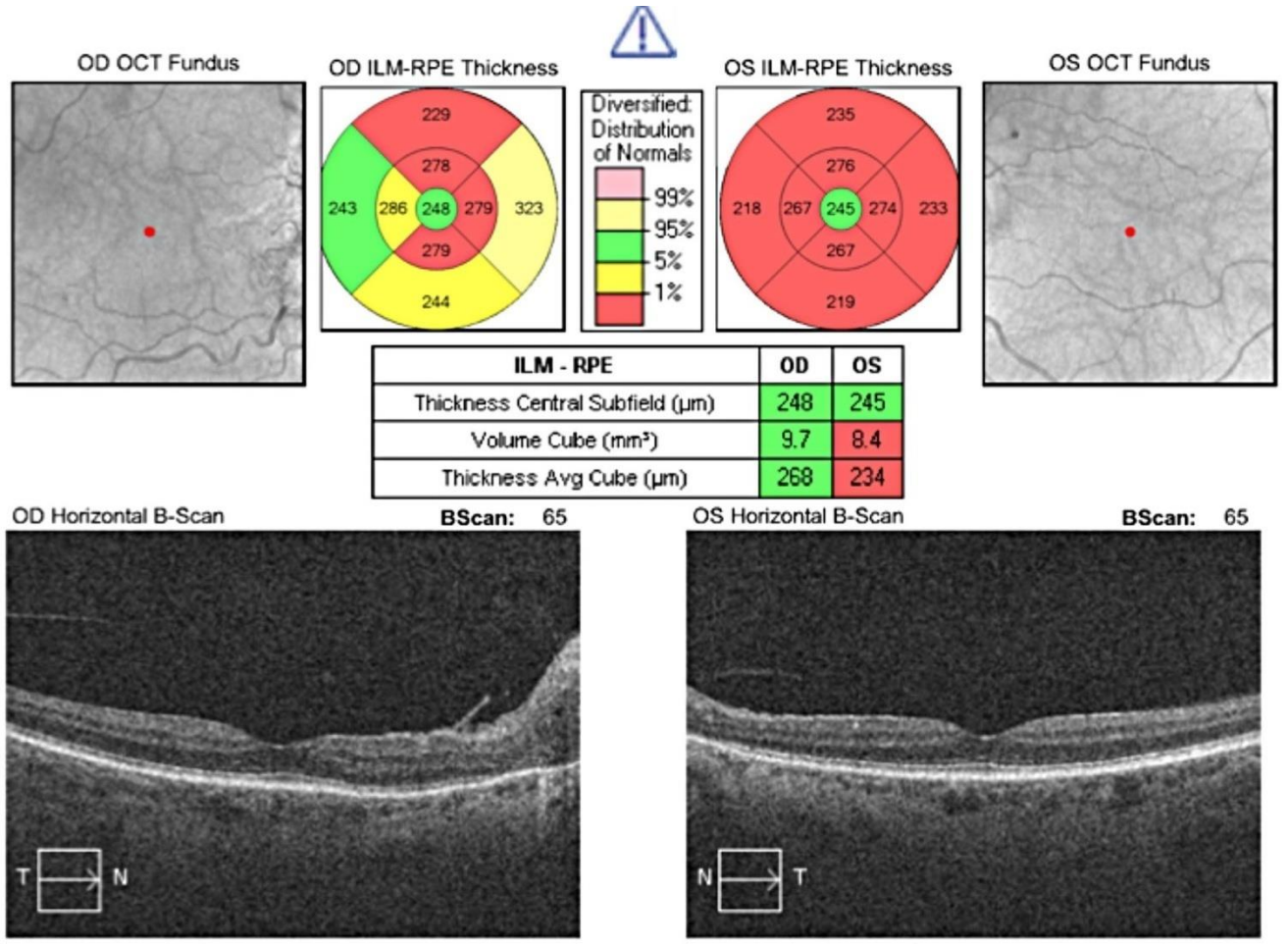

Figure3. MacularthicknessOCTattheinitialvisit.MacularOCTwithsuperiorthinningreflectingareasofRNFLatrophyaroundtheopticnerve.Thenasal regionisthickenedwhichcorrelateswiththetemporal RNFLthickening.Thelefteyehasmacularthinningcorrelatingwith ONHatrophyreflectedinthe reduced RNFLthickness.

optic nerve optical coherence tomography (OCT, Figure 2) showed significant RNFL thickening inferiorly (393 um)and temporally but significant thinning superiorly in the right eye. The left eye demonstrated superior and temporal RNFL thinning. The average retinal RNFL thickness was: 155 um right eye and 61 um left eye. A macular OCT (Figure 3) showed significant perimacular thinning, greater in the left eye compared to the right. A Humphrey SITA standard 30-2 visualfield(Figure4)showedinferonasaldefectsinbotheyes with an enlarged blind spot in the righteye.

She was felt to have chronic papilloedema with atrophic changes secondary to POEMS disease. The patient reported having a lumbar puncture previously and refused to have another. We were unable to find the results of this procedure. She stated that an MRI was also performed previously, and signed a release so we could obtain these scans. A CTwithoutcontrastwasorderedtoruleoutcausesof papilloedema. After phone consultation with the oncologist, she was prescribed methylprednisolone 4 mg, 6 tablets the first day, decreasing one tablet per day. She was hesitant to take methylprednisolone since she had significant weight gain the last time she took prednisone. When told that due to the short-term use, this was unlikely this time, she agreed to take the methylprednisolone.

Follow up #1

M.S.returnedtotheneuro-ophthalmicdiseasespecialtyclinic three weeks later. She had not taken the methylprednisolone andreportedhervisualsymptomshadworsenedsincethelast visit. She had seen her oncologist since the last visit where laboratory testing showed normal complete blood cell count and white blood cell differential, and high BUN (58 mg/dL) and creatinine (3.2 mg/dL). Additional studies measuring IL-6 and VEGF levels wereordered.

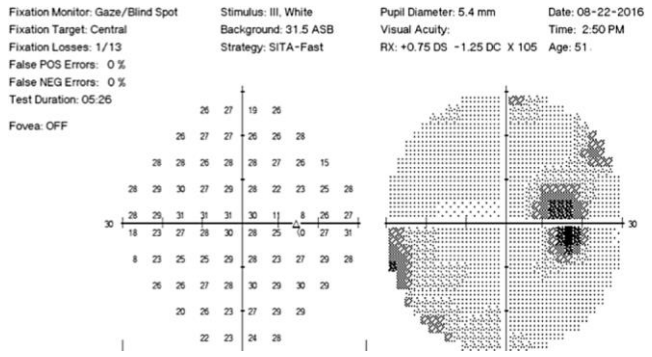

Figure4. HumphreySITAstandard30-2visualfieldattheinitialvisit.

Righteye:Goodreliabilitywithanenlargedblindspotandinferonasal defectrespectingthehorizontalmidline.

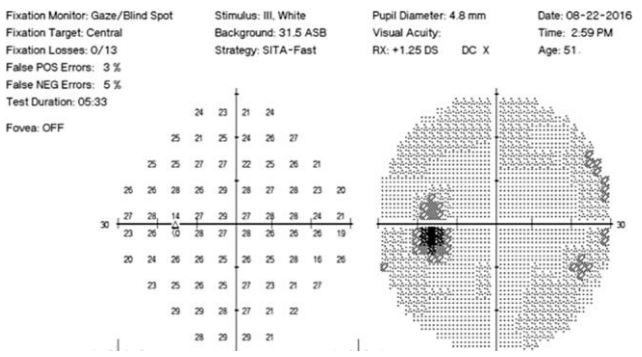

Figure4. HumphreySITAstandard30-2visualfieldattheinitialvisit.

Lefteye:Goodreliabilitywithslightlyenlargedblindspotandnasal defects,mostlyconcentratedintheinferonasalregion.

Distance visual acuities were $6/7.5^{-1}$ right eye and $6/12^{-2}$ left eye. Extraocular muscle movements, pupils, colour vision, confrontation visual fields, cover test, anterior segment, and fundus examination were unchanged from previous exams. An optic nerve OCT indicated that inferior swelling was stable from prior exam.

ImagesfromapreviousMRIofthebrainwithoutcontrastand MRA were obtained. This showed an empty sella (Figure 5), no flattening of the globe, questionable nerve sheathdilation, and encephalomalacia and bone defects from a previous craniotomy.MRAdemonstratedminimalflowintheinternal, middle cerebral, and anterior cerebral arteries (Figure6). The current head CT showed no reason forpapilledema.

Shewasonceagainencouragedtotakethemethylprednisolone andwasaskedtoreturntoclinicin3-4weeksforreevaluation of the disc oedema following steroidtherapy.

Follow up#2

Four weeks later M.S. returned to the neuro-ophthalmic diseaseclinic.Afteradditionaldiscussionwithheroncologist she initiated the steroid regimen. The patient reported that visual disturbances had resolved while on the prednisone, but symptoms had since recurred. The oncologist planned to initiatetreatmentwithsiltuximab,targetingIL-6andreducing VEGFlevels.

Distance visual acuities were $6/6^{-1}$ right eye and $6/12^{-2}$left eye. Extraocular muscle movements, pupils, colour vision, confrontationvisualfields,covertest,andtheanteriorsegment and fundus examination was unchanged from previous exams. An optic nerve OCT showed slightly reduced RNFL thicknesscomparedtothelastvisit(Figure7).TheRNFL thinning was consistent with the previous visit.

The oncologist of the patient was contacted to discuss possible treatment options. The patient was scheduled to return to the clinic in 6 weeks to monitor the condition while onsiltuximab.

Follow up#3

At the 6-week follow-up, the "splotchy" vision remained stable from the previous exam. The oncologist had initiated treatment with siltuximab.

Distance visual acuities were 6/6 right eye and 6/9 left eye. Extraocular muscle movements, pupils, colour vision, confrontation visual fields, cover test, anterior segment and fundus examination appeared unchanged from previous exams. An optic nerve OCT showed a significant decrease RNFL thickness inferiorly (326 um) in the right eye (Figure 8). The remainder of the RNFL remained stable. Average RNFL thickness was: 131 um right eye and 62 um lefteye. A Humphry SITA standard 30-2 visual field continued to show defects with improvement from the initialvisit.

The chronic papilledema secondary to POEMS disease had improvedfrompreviousexams.Thepatientwasscheduledto returntoclinicin6weekstomonitorforfurtherimprovement.

Follow up #4

The patient did not show for further follow-up, but records from the oncologist indicate that shortly after the last follow-up visit the patient developed ischemia of the lower extremities. She was evaluated by a vascular surgeon who recommended against revascularization. Over the next few

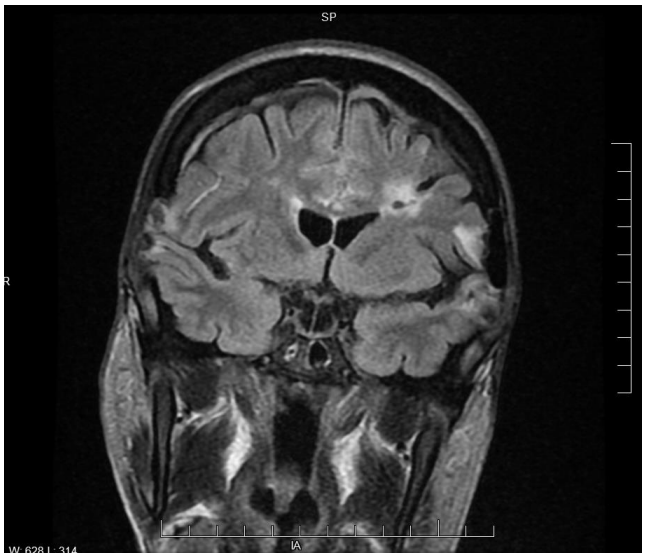

Figure5.MRIT2-FLAIRshowsemptysellawithencephalomalaciaalong themarginoftheinferiorlateralleftfrontalandtemporallobe

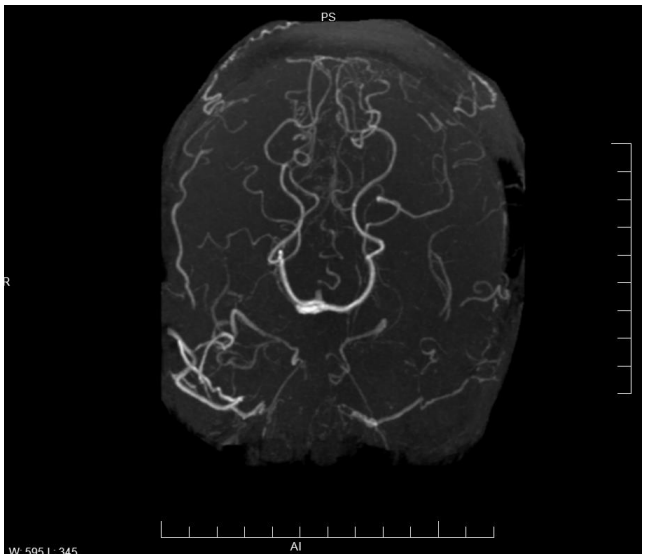

Figure6.MRAimageobtainedfrompatient'soncologistatapriorexam. MRAwithnarrowedbilateralICAandminimalsignalinthedistalbranches

	OD	OS
Average RNFL Thickness	143 µm	60 µm
RNFL Symmetry	78%	
Rim Area	1.61 mm²	1.56 mm²
Disc Area	1.58 mm²	1.64 mm²
Average C/D Ratio	0.07	0.23
Vertical C/D Ratio	0.06	0.19
Cup Volume	0.000 mm³	0.020 mm³

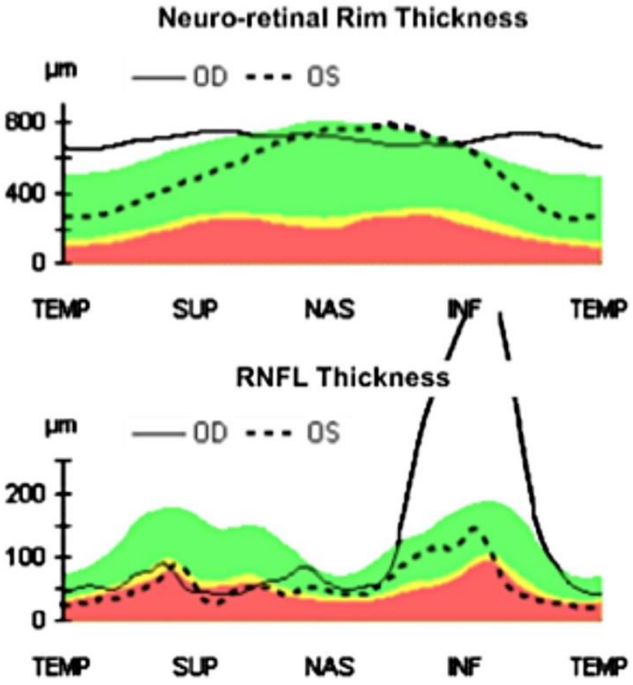

Figure 7. RNFL OCT following prednisone therapy. Decrease in RNFL edemaoftherighteye.TheRNFLofthelefteyeisunchangedduetothe stable nature of opticatrophy.

weeks she developed gangrene of the tissue of both lower extremities and had both legs amputated below the knee. During hospitalization, her renal function worsened and she developed hypercalcemia. The patient refused to be treated with corticosteroids and siltuximab.

Discussion

The Dispenzieri criterion for the diagnosis of POEMS syndromeisbasedonlaboratoryfindingsandclinicalfeatures (Table 1).[8,17] The patient presented in our case report is not a classicPOEMSpatient,sinceshedoesnotfulfillthemandatory criteria of quantifiable monoclonal plasma cell-proliferative disorder. Instead, this case is more correctly classified as the Castleman Disease variant of POEM syndrome.[17]The difference in clinical presentation is that the neuropathy in patients with Castleman Disease is predominantly sensory without a motor component, which is proven in the ability of the patient to ambulate despite being diagnosed 10 years ago.[17]

Furthermore, the patient has a unique combination of quasi-moyamoya disease, Castleman Disease and POEMS syndrome,allofwhichcontributetohervasculardeficiencies. Moyamoyadiseasetranslatesfrom"puffofsmoke"in

	OD	OS
Average RNFL Thickness	131 µm	62 µm
RNFL Symmetry	79%	
Rim Area	1.57 mm²	1.46 mm²
Disc Area	1.54 mm²	1.60 mm²
Average C/D Ratio	0.07	0.29
Vertical C/D Ratio	0.06	0.32
Cup Volume	0.000 mm³	0.027 mm³

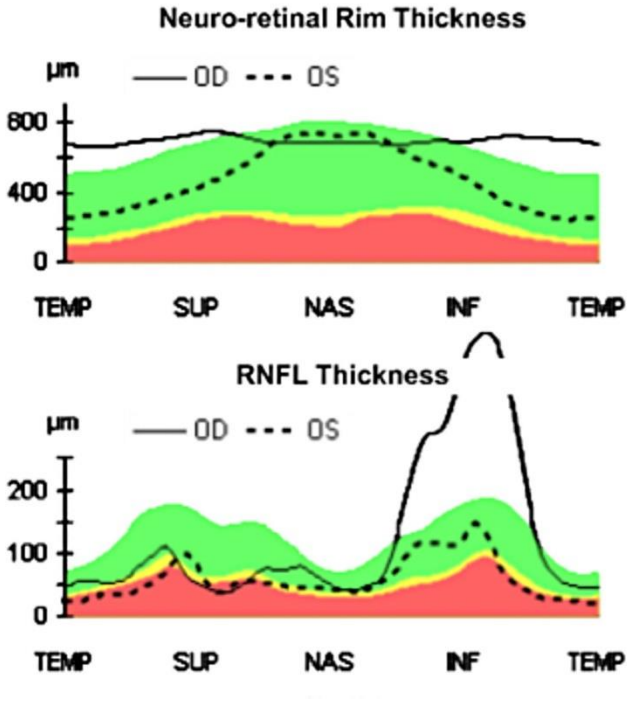

Figure8.RNFLOCTfindingsatthe3rdvisit.Therightopticnervehasa significantdecreaseinRNFLedemafromtheinitialvisit.Theleftoptic nerve isstable.

Japanese, which refers to the appearance of collateral vessels formedatthebaseofthebrainasaresultofstenosisorocclusion of the internal carotid arteries and their proximalbranches.[18,19]Moyamoya disease and POEMS syndrome share similarities in their pathological stenosis of vessels where narrowing of the internal carotid artery and the proximal branches is a suggestedmechanismforcerebralvascularaccidentinpatients with POEMS syndrome.[19,20] Moyamoya disease presents with isolated moyamoya vasculopathy, whereas quasi-moyamoya disease is moyamoya vasculopathy associated with various diseases.[16,21] Though POEMS syndrome is not yet recognized as a typical cause of quasi-moyamoya disease, the suggested pathogenesis of secondary vasculopathy is elevated VEGF levels found in POEMSsyndrome.[15,16,21]

Epidemiology

A national survey conducted in Japan in 2003 reported a prevalence of POEMS syndrome of 0.3 per 100,000.[22]The average age of onset is 46 to 53 years old, but it has been reported in patients as early as 26 years.[7,23,24]POEMSsyndrome is more common among males, with a gender predilection of2:1.[7,23,24]

Clinical Manifestations

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy,monoclonalgammopathy,andskinchanges) is a paraneoplastic syndrome caused by an underlying plasma cell neoplasm that triggers a multi-systemic presentation.[8,25] The signs and symptoms associated with POEMS syndrome are not all present at initial diagnosis but accumulate as the disease progresses. Because of the varied presentation of POEMS syndrome, the median time between onset of symptoms and diagnosis is 15 months.[3]

Changes Polyneuropathy

Peripheral neuropathy is the predominant feature in POEMS syndrome.[26] About 50% of patients show polyneuropathy asthe initial symptom, which later presents in all patients.[3,7,24]Symptoms consist of numbness, coldness, and paresthesia followed by muscle weakness and muscle atrophy that begin in the lower extremities in a relatively symmetric and homogenous pattern.[1,3,9,24] As POEMS syndrome progresses, muscleweaknessismoreseverethansensoryloss.[9]Overhalf ofpatientsdevelopsevereweakness,resultingintheinability to climb stairs, grip objects firmly, and arise from achair.[9]

The pathogenesis of polyneuropathy is a mix of destruction and demyelination of axons.[1,3,27,28] Sural nerve biopsy shows axon degeneration and segment demyelination.[1,3,27]Polyneuropathy from POEMS syndrome is associated with narrowing of the vasa nervorum, antithrombin III deposition, andpolymorphonuclearandmononuclearcellinfiltration.[2,25,27]

Changes Organomegaly

Enlargement of the organs, particularly the liver, spleen, and lymph nodes are present in 50-82% of patients with POEMS syndrome.[3,28] The liver is palpable in nearly 50% of patients, where splenomegaly and lymphadenopathy are less common.[12]Thepathogenesisoforganomegalyisexplainedby elevatedlevelsofvascularendothelialgrowthfactor(VEGF), causing neovascularization andvasopermeability.[29,30]

Changes Endocrinopathy

Endocrinopathy is present in 60-84% of POEMS patients with hypothyroidism and hypogonadism as the most common clinical presentations followed by glucose metabolism abnormalities and adrenal insufficiency.[1,3,23,26,30]Endocrinopathy presents early in the course of the disease.[3] Hypogonadism manifests as

testicularatrophy

Table 1: Dispenzieri Criteria for the Diagnosis of POEMS Syndrome[8]

Mandatory major criteria‡ (both required)	1. Polyneuropathy
	2. Monoclonalplasmacell-proliferativedisorder†
Other major criteria‡ (one required)	3. Castlemandisease
	4. Sclerotic bonelesions
	5. Vascularendothelialgrowth factorelevation
Minor criteria‡ (one required)	6. Organomegaly
	7. Extravascular volume overload
	8. Endocrinopathy
	9. Skinchanges
	10. Papilledema (requires lumbarpuncturefordiagnosis)
	11. Thrombocytosis/polycythemia
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B_{12} values

†The CD variant of POEMS syndrome occurs without evidence of a clonal plasma cell disorder.
‡The diagnosis of POEMS syndrome requires both mandatory major criteria,oneoftheothermajorcriteria,andoneoftheminorcriteria

and gynecomastia with lowered testosterone levels in males.[3,9] Females can develop irregular menses and, rarely, galactorrhea.[3] The pathogenesis of endocrinopathy is unknown.[26]

Monoclonal Gammopathy

POEMSsyndromeisclassifiedasasubtypeofmonoclonal gammopathywherethereisaproliferationofasingleplasma cellclonethatproducesmonoclonalprotein(Mprotein).[1,3,4,31] Each M protein has two heavy chains which define the type of immunoglobulin (IgG, IgD, IgA, IgM, IgE) and two associated light chains (kappa or lambda).[4] M protein is detected as a narrow peak or spike on high-resolution agarose gel electrophoresis and can be confirmed with immunofixation.[4,7,31] Lambdalightchainfragmentsareseen in95%ofpatientswithPOEMSsyndrome,andmonoclonal protein spikes of IgG and IgA are also present in some patients.[4,7] Because POEMS syndrome has a widespread systemicpresentation,identificationoftheMproteincanbea helpful first clue todiagnosis.[31]

Skin Changes

Another prominent sign of POEMS is skin changes, which occurs in 58-98% of patients.[1,3,8,11,23] The most common clinicalpresentationsarehyperpigmentation,skinthickening, and hypertrichosis especially on the extremities.[1,3,9] Elevated levels of VEGF causing neovascularization and increased vascular permeability are responsible for these skin changes.[9,17,29] Biopsy of the skin reveals small clusters of vessels surrounded by plasma cells and lymphocytes.[30] However, biopsy of normal appearing skin alsodemonstrates abnormalities in vasculature with frequent anastomoses and capillary loops that normalize withtreatment.[32]

Additional Features

Although the acronym POEMS attempts to encompass the major signs of POEMS syndrome, there are other important features. Extravascular volume overload, papilledema, sclerotic bone lesions, thrombocytosis, Castleman's disease, and elevated VEGF levels are additional key features of POEMS syndrome that are included in the revised diagnostic criteria for POEMS syndrome.[3,8,9] In addition to the POEMS acronym, the acronym PEST throws a wider net on the presenting signs of this syndrome: papilledema, extravascular volume overload, sclerotic bone lesions, and thrombocytosis.[17]

OpticdiscoedemamaybeanearlysignofPOEMSsyndrome and usually presents bilaterally in 29-73% of patients.[1,7,33-35] In a review of 33 patients, 52% had bilateral optic disc oedema, and 29% of those with optic nerve head oedema were asymptomatic.[34] When optic nerve oedema is chronic, atrophy and thinning of the RNFL occurs, as in this case. Additional ocular signs and symptoms that may present in patients include ocular pain, blurred vision, diplopia, and macular edema secondary to optic disc oedema.[33,34] Unless theopticdiscoedemaispersistentandsevere,visualchanges are mild, with enlarged blind spots as the most common visual field defect, accompanied by non-specific visual field defects.[1,34,36] Bilateral optic disc oedema fluctuates with the disease activity and usually does not completelyresolve.[34,37,38]

The cause of optic disc oedema is suggested to be both elevated VEGF and elevated intracranial pressure.[34,39,40] A 10-year retrospective chart review showed that there was no statistical difference between the lumbar puncture opening pressure in POEMS patients with and without optic disc oedema.[34] Several studies suggest VEGF as a causative factor for optic disc oedema.[39,41,42] In patients with opticdisc oedema, there is a correlation between VEGF levels at the time of diagnosis and VEGF levels when the optic disc oedema resolves.[34] The proposed mechanism is that elevated VEGF levels allow plasma to leak into the fenestrated choriocapillaris, which allows the VEGF to diffuse into theopticnerveheadthroughthebordertissueofElschnig,

causing leakage.[42] This is evidenced by a correlation between subfoveal choroidal thickness and VEGF levels.[40] Also, choroidal thickness mirrors the decrease in VEGF levels in response to treatment.[37] However, a study by Yokouchi et. al[34] demonstrated no correlation between serum VEGF levels and optic disc oedema although the authors suggest elevated intracranial pressure may have been a tertiary factor in their analysis.

Increased vascular permeability and neovascularization from elevated VEGF levels lead to capillary leak syndrome, which is present in 29-91% of patients.[3,9,11,33,34] Pitting oedema of the lower extremities is present in most patients, and ascites and pleural effusion occur in a third.[7,9]

Sclerotic bone lesions occur in 50-96% of patients and are included in the major diagnostic criteria for POEMS syndrome.[3,7,9] Most patients have a solitary lesion though multiple lesions can occur.[3] The bone lesions tend to occur in the spine, pelvis, and ribs with a sclerotic rim or a mix of sclerotic and lytic components[3,7,30] Bone lesions are detected through X-ray or CT scans and biopsy of sclerotic bone lesions reveals dense neoplastic plasma cells that are usually <5% of the bone marrow.[9,43] In contrast to conventional myeloma and sclerotic myeloma, bone pain does not typically occur in patients with POEMS syndrome.[43]

Thrombocytosis is the most prominent haematological abnormality in patients.[23,27] 54-76% of patients have thrombocytosis.[3,23,44,45] Platelet levels assess the risk of thrombotic events such as cerebrovascular accidents, which occurs in about 10% in patients with POEMS.[44,46] Thrombocytosis combined with elevated VEGF levels cause chronic and accelerated intravascular coagulation around endothelial cells.[46-48]

Although the connection between Castleman disease and POEMS syndrome is unclear, 11-30% of patients with POEMS syndrome have Castleman Disease.[3,9-11] Castleman Disease presents as either unicentric, with one site of lymphadenopathy, or multicentric, with multiple sites of lymphadenopathy.[49] Unicentric Castleman Disease occurs in younger individuals with fewer symptoms, as opposed to multicentric Castleman Disease, which occurs in older individuals with more systemic manifestations and is associated with POEMS syndrome.[49,50] In fact, 32% of patients with multicentric Castleman Disease develop POEMS syndrome.[49] Localized Castleman Disease usually presents with no systemic involvement, whereas multicentric Castleman Disease presents with multiorgan involvement, such as weight loss, fever, night sweats, dyspnoea, and organomegaly.[12,14,49,51] Biopsy of enlarged lymph nodes confirms the type of Castleman Disease: the plasma cell type with plasma cell proliferation and capillary proliferation, or the hyaline vascular type with lymphoid follicles and concentric layers of lymphocytes surrounded by blood vessels.[7,9,50,51] Most cases of multicentric Castleman Disease display the plasmacell type.[52] The aetiology and pathogenesis of multicentric Castleman Disease is unique in that when it is associated with HIV, the patient is almost always HHV-8 positive.[12,13] In this case, the patient tested negative for both HIV and HHV-8. These enlarged lymph nodes may secrete VEGF.[52] However, the predominant and overly expressed cytokine in Castleman Disease is IL-6.[12,13,17,49]

Though there are several cytokines that are elevated in POEMS syndrome, VEGF levels reflect the disease severity and is used as a diagnostic marker.[22,39,53] Therefore, it suggests that VEGF is involved in the pathogenesis and symptom presentation of POEMS syndrome.[25,34,53,54] Plasma cells, platelets, and lymph nodes are proposed as the culprits for the overproduction of VEGF, but the main contributor for VEGF remains unclear.[9,34,47,52-55] Solitary sclerotic bone lesions tend to be plasmacytomas and resection of the lesions or radiation therapy reduces VEGF levels, suggesting that monoclonal plasma cells are responsible for VEGF section.[2,8,53] Another source is platelet aggregation on the endothelial wall releasing excessive amounts of VEGF.[47,48,56] VEGF levels differ significantly between serum and plasma measurements. VEGF levels are high in both serum and plasma; however, the serum levels are 10 to 50 times higher because of the release of VEGF from platelets during processing.[47,48] Lymph nodes in Castleman Disease have also been reported to overproduce VEGF.[2,52] Regardless of the source, much of the pathological findings are explained by VEGF, which promotes neovascularization and vascular permeability.[2,40,54] VEGF is so integral to the clinical presentation of POEMS syndrome that Dispenzieri revised the major diagnostic criteria to include VEGF levels in 2015.[8]

Pathogenesis

The pathogenesis of POEMS syndrome is poorly understood with multiple systemic contributing factors, but plasma cell dyscrasia producing excess VEGF is the suggested main contributor.[2,34,39,53] The plasma cells are lambda light chain restricted over 95% of the time.[3,7-10] One theory is that the restricted lambda light chains interact with a VEGF protein that causes excessive VEGF secretion.[55] Though VEGF plays a major role in the clinical presentation of POEMS, treatment with anti-VEGF therapy gives variable results, suggesting that VEGF is not the only factor in the pathogenesis.[8,57-59]

Treatment

In the 1980s, patients were primarily treated with corticosteroids, which resulted in a poor prognosis and a mean survival time of 33 months after the onset of symptoms.[10]

Treatment options for POEMS syndrome have changed significantly since then, but the treatment for POEMS syndrome is still not standardized because the pathogenesis is not clear.[3,37] Furthermore, there were no randomized controlled trials of POEMS syndrome treatment optionsuntil recently.[9,28,60,61] The first and only randomized control trial for POEMS treatment is the J-POST Trial, which examined the efficacy and safety of thalidomidetherapy.[60,61]

Treatment of POEMS syndrome depends on the extent of plasmacellinvolvement,whichcanbeassessedbyiliaccrest biopsyandX-rayorCTscanoftheskeletalsystem.[8,17,45]Ifthe iliaccrestbiopsyispositiveforclonalplasmacells,orifthere arethreeormoreskeletallesions,systemicchemotherapywith peripheral blood stem cell transplantation for a disseminated disease presentation is more effective than radiation alone.[9,45,53,54] Peripheral blood stem cell transplantation hasshowntobeeffectiveinimprovingperipheralneuropathyand other symptoms of POEMS syndrome.[53,62-64]Chemotherapy treatment plans, including melphalan, thalidomide, cyclophosphamide, and lenalidomide, are borrowed from other plasma cell disorders.[63] After chemotherapy combined with peripheral blood stem cell transplantation, neutrophil and platelet levels normalize 15 days after treatment.[63,65]Within6monthsthereisasignificantneurologicrec overyand improvement in VEGF levels.[54,63,65] The proposed mechanism is that the high dose chemotherapy with peripheral blood stem cell transplantation decreases the number of dyscrasic plasma cells.[63]

However, chemotherapy combined with peripheral blood stem cell transplantation is not a viable option forindividuals overtheageof65yearsorthosewithpoorpulmonaryreserve, active infection, or serious organ involvement.[63-66]Adverse effects from treatment include myelodysplastic syndrome and acute leukemia from melphalan use, transplant-related death, and respiratory complications.[3,63,64] However, because of better supportive care, transplant related death has been reduced to 3.3%.[67] The risk of complications is significantly reduced with appropriate patient selection.[65]

Corticosteroids are effective as a short-term therapy or in combination with other treatments.[8,22] In a nationwide survey of practitioners in Japan, most used IV or oral steroids as a first line therapy, and then melphalan and oral prednisolone later in the disease course.[22] Though combination peripheral blood stem cell transplantation and chemotherapy treatment are currently replacing corticosteroid therapy alone, corticosteroids are used therapeutically in patients undergoing peripheral blood stem cell transplantation to reduce complications.[22,67]

The management of patients with localized involvement is more straightforward. These patients have only a solitary skeletal lesion and no plasma cells found during iliaccrest biopsy.[17,45]Resectionoftheskeletallesionorradiationover thelesionarefirstlinetherapyoptions.[2,22,27,29,53]Theresponse toradiationtherapyisnotapparentuntil3to6monthsafter treatmentandisoftencurativeinlocalizedinvolvement.[3,53,68]Ov er50%ofpatientshavesignificantclinicalimprovement fromradiation.[9,45]Ifthepatientcontinuestohaveprogression after3to6months,systemictherapyshouldbeconsidered.[8]

Anti-VEGF therapy has been investigated because of the likelycausativeroleofVEGFinthepathogenesisofPOEMS syndrome; however, the results are inconsistent.[8,9,29,45,58,59,69]VEGFlevelscorrespondtoclinicalimprov ementsinPOEMS syndrome, which indicates that the reduction of VEGF levels may be a useful therapy.[2] Bevacizumab is beneficial in some cases and has been the key for improvement in neurological symptoms.[70,71] However, the same therapy has made no improvement in other patients and has been associated with multiorgan failure and death.[58,72-74] The theory behind bevacizumab failure is that the sudden reduction of chronically elevated VEGF levels may lead to the collapse of newly formed blood vessels causing increased capillary leakage and multiorgan failure.[58,72-74] Therefore, bevacizumab therapy within 2 years of diagnosis increases the likelihood of success.[58,70,72] In contrast, bevacizumab therapy should beavoided as a therapy for patients with longstanding POEMS disease.[58,66] Though the results of bevacizumab therapy arecontroversial, it can be an alternative for individuals who are not candidates for high dosechemotherapy.[57,71]

Siltuximab therapy was offered, but was unfortunately refused by the patient. Siltuximab is an anti-IL-6 chimeric monoclonal antibody that is FDA approved for treatment of HIV negative, HHV-8 negative multicentric Castleman Disease.[75]Siltuximab has an effect of not only lowering the IL-6levels,butalsotheVEGFlevelsduetotheroleofIL-6in propagating the release of VEGF.[76]Given that our patient has multicentric Castleman Disease and POEMS syndrome, this would have been a promising therapy for ourpatient.

Ocular Management

Giventhatbilateralopticnerveheadoedemaispresentin29- 73% of cases, comprehensive ocular exams are indicated at the time of diagnosis.[7,33-35,37] There is currently no standard for treating bilateral optic nerve head oedema from POEMS syndrome; however, the management is based on the aetiology.[35]To differentiate bilateral optic nerve head oedema from an infiltrative process and an elevated intracranial pressure, lumbar puncture needs to be performed.[3,35] If the opening pressure is more than 25 cmH_2O, it is suggested that elevated intracranial pressure is the cause of the bilateral optic nerve head oedema and the patient can be treated with oral acetazolamide.[37] However, if the opening pressure isnormal,thecauseoftheoedemaissuggestedtobean

infiltrative process, which can be treated with anti-VEGF, or corticosteroids.[3,35,77] Unfortunately, this patient refused to do a lumbar puncture, but the optic nerve oedema was responsive to corticosteroids.

Furthermore, ocular examinations facilitate tracking disease progression and response to therapies.[37,40] Because optic nerve head oedema and choroidal thickness fluctuate with VEGF levels, the use of OCT is a noninvasive technique that provides supplemental data by measuring the RNFL thickness and choroidal thickness with enhanced depth imaging (EDI).[37,78] In patients with progressive disease, choroidal thickness correlates with VEGF levels, increasing thickness with elevated VEGF levels but returning to normal thickness following treatment.[37,40] Similarly, response to treatment is also seen in the resolution of RNFL swelling.[34,37] Systemic VEGF is suggested in the pathogenesis of choroidal thickening and RNFL thickening by increasing the optic nerve head vascular permeability through the choroidal blood flow.[41,42,77] Systemic VEGF levels are upwards of 30 times the normal value in those with RNFL or choroidal involvement; whereas vitreal VEGF levels are normal.[40,41,79] Therefore, OCT measurements of the RNFL and choroidal thickness offer important supplemental data as they are reflective of VEGF fluctuations.

Prognosis

POEMS syndrome usually follows a chronic course with an average survival period of 14 years.[3,7] A number of retrospective studies have found a correlation between specific clinical features and an increased risk of POEMS syndrome related mortality.[3,11,25,49,80] The number of clinical features is not prognostic for survival; however, extravascular volume overload and finger clubbing are correlated with an increased risk of mortality.[3] Also, single sclerotic bone lesions have better outcomes compared to those without bone lesions and those with multiple bone lesions.[11,49] Diagnosis of papilledema from eye care professionals also provides independent prognostic value.[80]

The most common causes of POEMS syndrome related deaths are cardiorespiratory failure and infection.[3,9] Patients with VEGF serum levels <1500 pg/mL have been observed to have more favorable responses to therapy.[25] In addition, those with favorable responses to radiation therapy have a longer period of survival.[3] Therefore, early diagnosis and therapy are important to reduce POEMS syndrome related complications and improve the quality of life.

Conclusion

Given the symptomatic diversity of POEMS syndrome, a holistic approach with multidiscipline providers allows the best results.[9] Monitoring choroidal and RNFL thickness helps establish baseline data for the severity of the disease and provides feedback for response to therapies.[34,37,78] Additionally, physical therapy and occupational therapy are vital for managing progressive polyneuropathy.[9] Respiratory assistance with overnight oxygen or continuous positive airway pressure may be necessary for patients with respiratory complications.[9] Given the diverse presentation of POEMS syndrome, it is possible that the condition is initially misdiagnosed or even undiagnosed.[24] Therefore, increased awareness of POEMS syndrome among multiple disciplines can expedite the diagnosis.

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