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## Asymmetric optic disc edema in a young patient with POEMS: A rare presentation of a rare disease

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## ABSTRACT

**Purpose:** To describe a case of asymmetric optic disc edema presenting as the initial ocular feature of POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin changes) syndrome.**Observations:** A 29-year-old female patient presented with 3 weeks history of blurred vision, proptosis, and peripheral neuropathy as well as hypothyroidism. Fundoscopy revealed optic disc edema associated with visual loss in the left eye. Following a computed tomography (CT) scan and a positron emission tomography/CT (PET/CT) scan which respectively revealed hepatomegaly and multiple osteosclerotic lesions, as well as laboratory findings of monoclonal gammopathy and elevated vascular endothelial growth factor (VEGF) levels, she was diagnosed with POEMS syndrome. After treatment with an autologous stem cell transplant, the optic disc edema and blurred vision resolved.**Conclusions and importance:** The most reported ocular manifestation of POEMS syndrome, a rare and complex multisystem disorder, is bilateral optic disc edema that typically occurs in older males. Therefore, this report presents an uncommon case of asymmetric optic disc edema in a younger, female patient.

## 1. Introduction

POEMS syndrome, also known as Crow-Fukase syndrome, osteosclerotic myeloma, or Takatsuki syndrome, is a rare, multisystem paraneoplastic disorder associated with peripheral neuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal gammopathy (M), and skin changes (S), although not all features must be present for diagnosis.<sup>1</sup> Other major criteria include osteosclerotic lesions and elevation of serum vascular endothelial growth factor (VEGF) levels.<sup>2</sup> Ocular manifestations are also important to consider, as papilledema is one of six minor criteria for POEMS diagnosis according to the most recent assessment by Dispenzieri.<sup>2</sup> Specifically, optic disc edema<sup>3–11</sup> is the most frequent ocular finding in POEMS patients, with recent reports citing an incidence of 52%,<sup>10</sup> 67.5%<sup>11</sup> and 79%,<sup>12</sup> and has presented bilaterally at the initial visit in all but one 13 individual case report. Furthermore, the syndrome is typically diagnosed in male patients ranging from 40 to 65 years of age. Therefore, we present a rather

unique POEMS case in a 29-year-old female patient with asymmetric optic disc edema.

## 2. Case report

A 29-year-old female patient was referred for a neuro-ophthalmological consultation prompted by symptoms of blurry vision and photopsias for 3 weeks. Her past medical history was notable for chronic migraines. Her recent medical history included menstrual dysfunction, hand and feet paresthesias, fatigue, bilateral arm rashes, joint pain and swelling, abdominal distention, and hair loss throughout the past six months. She had noted a 20-pound weight gain for the past three-to-four months despite a consistent workout regimen and was recently started on synthroid for newly diagnosed hypothyroidism.

Ophthalmologic examination showed an uncorrected visual acuity of 20/20 in both eyes and 1 mm of proptosis in the left eye with diffuse conjunctival injection. Intraocular pressures were 14 mmHg in both

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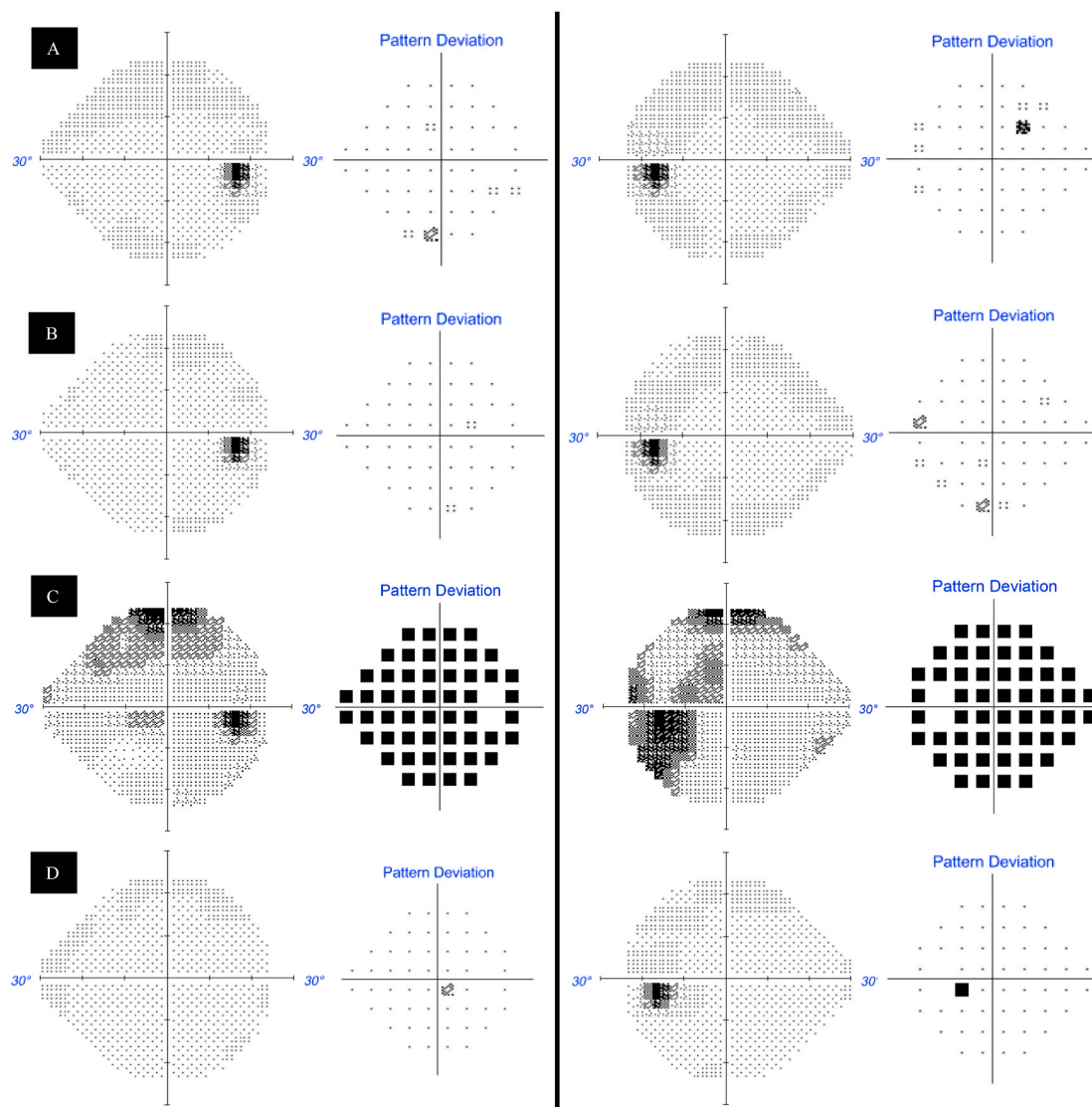
eyes. AOHRR color plates, sensorimotor testing and slit-lamp examination did not demonstrate any abnormalities. She was emmetropic in both eyes and upon testing, there was an afferent pupillary defect in the left eye. Visual field testing showed fluctuations nasally and in the blind spot of the left eye and was normal in the right eye (Fig. 1A). Dilated fundus examination showed normal right optic nerve and optic disc edema without vitritis in the left eye (Fig. 2A). Optical coherence tomography of the optic nerve corroborated the clinically-observed disc edema in the left eye and did not exhibit subclinical edema in the right eye (Fig. 3A).

Further work-up included a brain and orbit MRI showing bilateral prominence of the lacrimal gland and extra-ocular muscles without optic nerve enhancement (Fig. 4). Lumbar puncture showed an opening pressure of 20.5 mmHg and CSF protein of 70. She was discharged on Diamox, pending further workup.

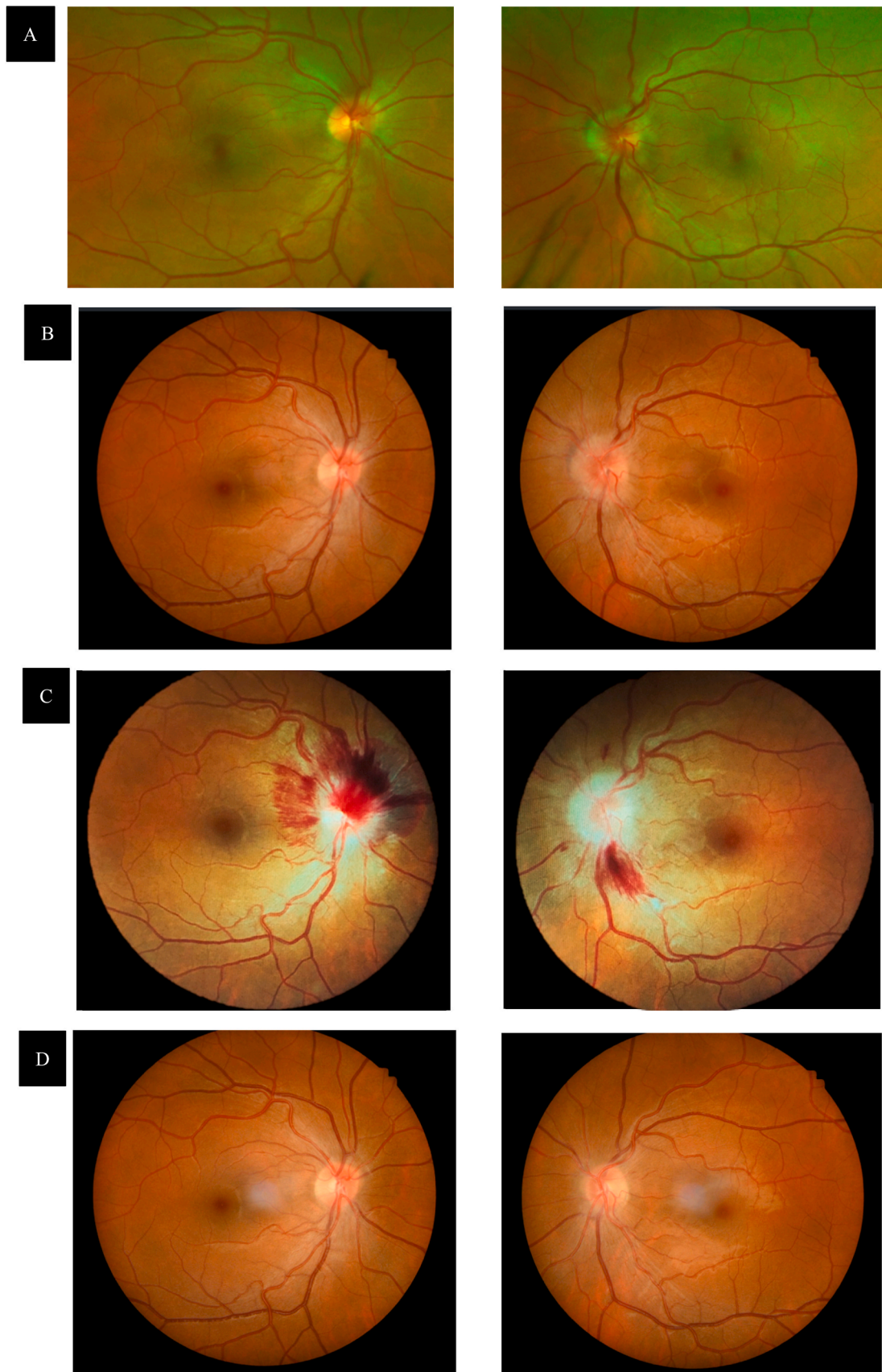
Follow-up visits after discharge showed increasing disc edema (Figs. 1B, 2B and 3B), hand and feet paresthesias, and monoclonal gammopathy with IgG lambda levels of 900 mg/dL. Consultation with neurology corroborated a suspected diagnosis of POEMS. Subsequent work-up indicated VEGF levels of 409 (normal: 9-86), mild

erythrocytosis and thrombocytosis (platelet count of  $407 \times 10(3)/\mu\text{L}$ ), presence of monoclonal IgG gammopathy (1494 mg/dL) and a kappa light chain level of 1.96 mg/dL (range: 0.33–1.94 mg/dL) with a kappa to lambda ratio of 0.32 (range: 0.26–1.65). An electromyogram also demonstrated chronic multifocal demyelinating sensorimotor polyneuropathy. CT imaging of chest, abdomen and pelvis revealed hepatomegaly (18.1 cm) as well as multiple spine and pelvic osteolytic lesions with central sclerosis. A bone marrow biopsy failed to show a clonal plasma cell population, therefore a sacral lesion biopsy was performed and revealed sheets of lambda-restricted plasma cell neoplasm (Fig. 5). Finally, a PET/CT scan evidenced multiple osteosclerotic lesions along the spine and pelvic bone, demonstrating multifocal hypermetabolic bone involvement (Fig. 6).

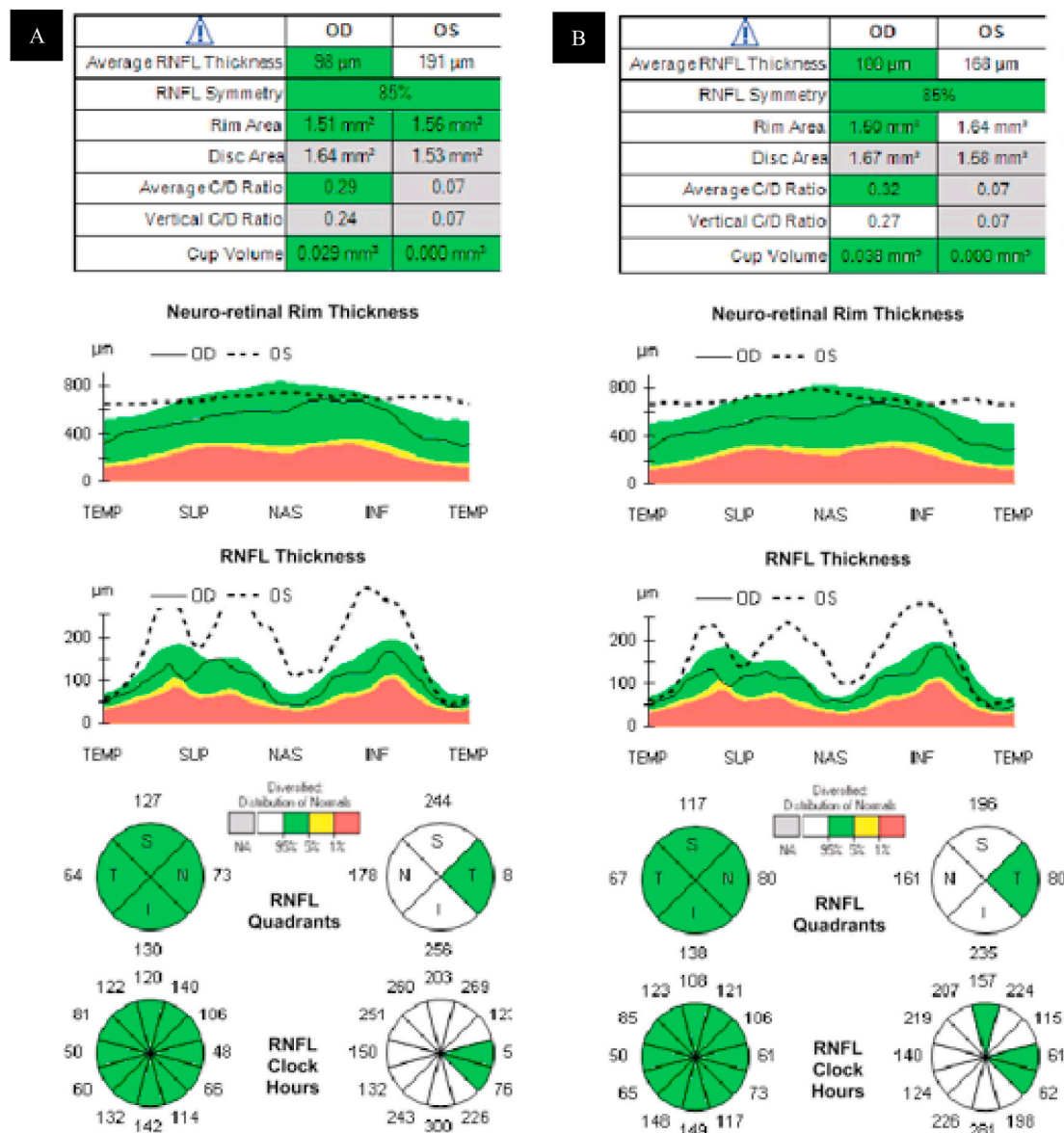
After a series of hematology and oncology consultations, a treatment course of Melphalan200 ( $200 \text{ mg}/\text{m}^2$ ) conditioning and autologous stem cell transplantation (ASCT) was selected. Prior to initiating treatment, the patient chose to cryopreserve her eggs. Stem cell steady state mobilization was induced with 10 mg/kg GCSF divided twice a day for four days, with stem cells collected by apheresis on the fifth day. The patient exhibited typical post-transplant complications such as



**Fig. 1.** Visual fields of right and left eyes before and after treatment with autologous stem cell transplant. (A) At initial visit, visual field of right eye is normal and the left eye shows fluctuations nasally and in the blind spot. (B) One week after baseline assessment, visual field of right eye is normal and the left eye shows fluctuations in the blind spot. (C) 12 days post-treatment, visual field of right eye shows superior and central defects and the left eye shows an enlarged blind spot with extension into the superior field. (D) Seven months post-treatment, visual field of right eye is normal and the left eye shows a minimally enlarged blind spot.



**Fig. 2.** Fundus images of right and left eyes before and after treatment with autologous stem cell transplant. (A) Posterior poles of wide-field fundus photos at initial visit show a normal optic disc in the right eye and mild optic disc edema in the left eye. (B) Fundus photos one week after baseline assessment show no frank optic disc edema in the right eye and worsening optic disc edema in the left eye. (C) Fundus photos 12 days post-treatment show optic disc hemorrhage and worsening edema in both eyes. (D) Fundus photos seven months post-treatment show resolution of the optic disc edema in both eyes.



**Fig. 3.** Optical coherence tomography (OCT) findings before and after treatment with autologous stem cell transplant. (A) OCT at initial visit shows a normal retinal nerve fiber layer in the right eye and elevation in the left eye. (B) OCT one week after baseline assessment continues to show a normal retinal nerve fiber layer in the right eye and disc edema in the left eye. (C) OCT 12 days post-treatment shows elevation of the retinal nerve fiber layer in both eyes. (D) OCT seven months post-treatment shows a normal retinal nerve fiber layer in the right eye and possible retinal nerve fiber layer thinning in the left eye.

mucositis, as well as engraftment syndrome which was treated with a prolonged steroid taper. Ophthalmologic examination 12 days after the transplant also showed optic disc hemorrhage and worsening edema (Figs. 1C, 2C and 3C). The patient was discharged after 68 days once all complications had resolved. Follow-up visit seven months post-transplant showed improvement in rashes, blurred vision and the optic disc edema (Figs. 1D, 2D and 3D), in addition to significant improvement in the serum M protein level. VEGF levels normalized approximately eleven weeks following the transplant.

**3. Discussion**

Due to its variety of clinical features, POEMS syndrome is not thoroughly understood and can be quite challenging to diagnose. While our patient was a 29-year-old female, a Mayo Clinic study involving 291 POEMS patients, two-thirds of which were male, cited a median age of 52 years at baseline<sup>14</sup> and a recent nationwide survey of Japanese

POEMS patients noted a 1.5 ratio of diagnosed men to women and a median age of 54 years at onset.<sup>15</sup> Few case reports involving younger women have been published.<sup>16-18</sup> Current theories link the manifestation of POEMS to elevated cytokine levels, primarily vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), and interleukin-12 (IL-12).<sup>1,2</sup> In particular, elevated serum and plasma VEGF levels have become an important element in distinguishing POEMS from similar disorders such as other plasma cell dyscrasias, monoclonal gammopathy of undetermined significance (MGUS), and/or peripheral neuropathy.<sup>2,19,20</sup>

Optic disc edema (ODE) is considered the most common ocular manifestation in POEMS patients. In addition, findings of macular edema, retinal hemorrhages, retinal serous detachments, and increased choroidal thickness have also been reported so far.<sup>6,8,10,11,21</sup> Most cases of ODE in POEMS tend to be either asymptomatic or present with blurred vision.<sup>10,11</sup> The term papilledema has been preferentially used in studies that describe the diagnostic features of POEMS,<sup>2,9</sup> however, whether or

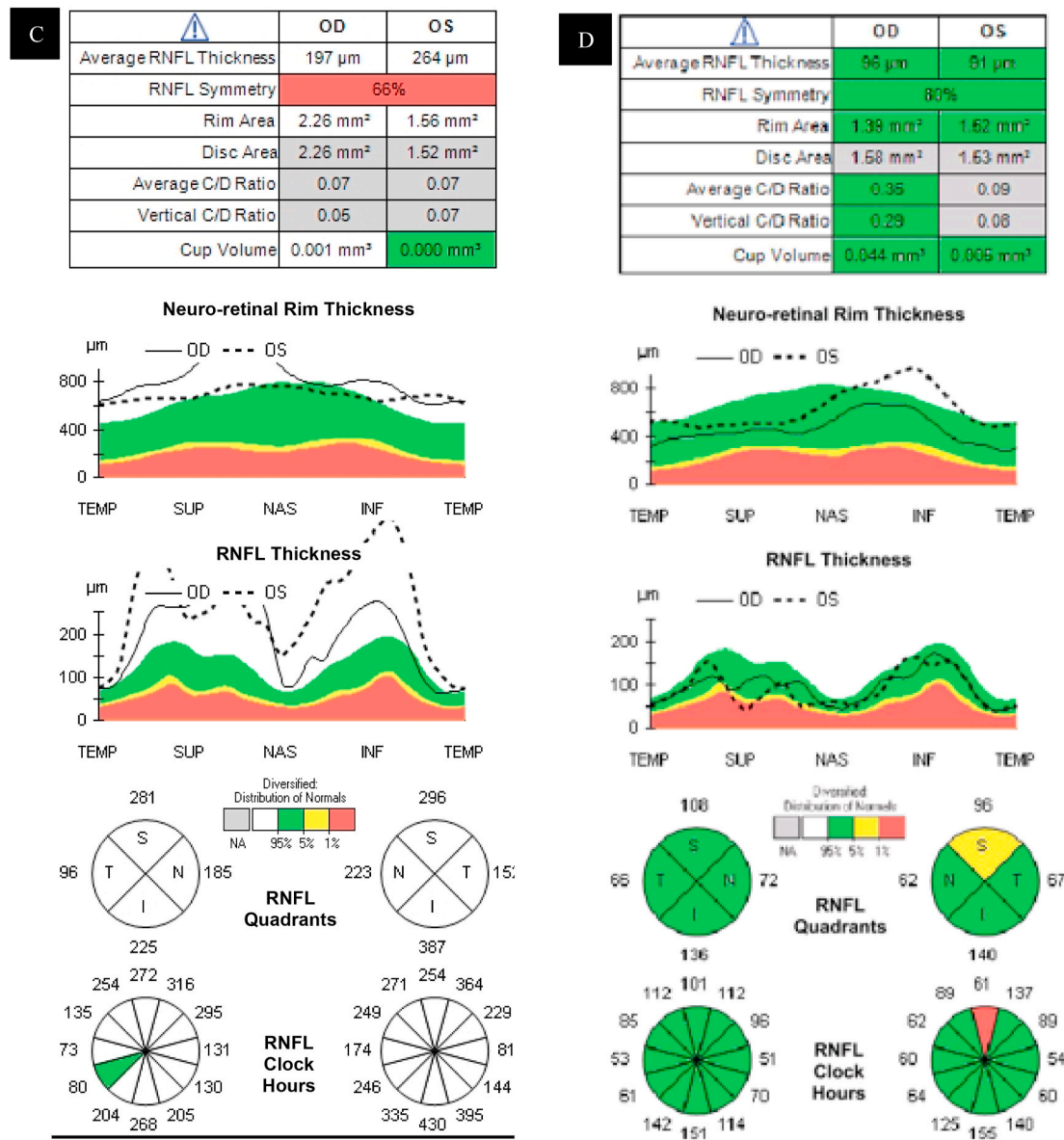


Fig. 3. (continued).

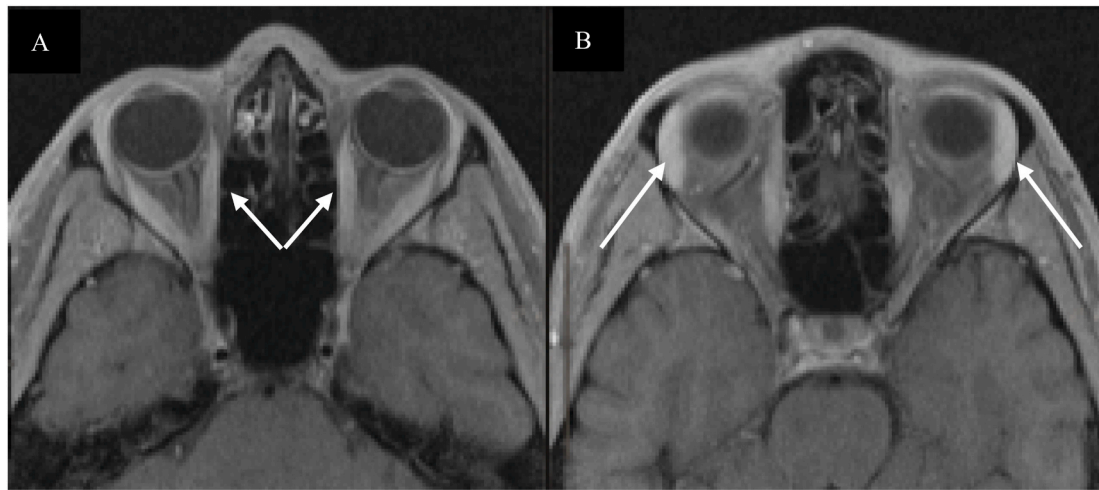
not intracranial hypertension (IH) is related to the presence of ODE in POEMS has yet to be confirmed, especially since a co-morbidity of IH and ODE has not been consistently reported in POEMS patients.<sup>5,8</sup> Literature exploring the relationship between ODE and increased serum VEGF levels have alternatively proposed vascular hyperpermeability due to angiogenesis as the mechanism behind ODE in POEMS,<sup>8,10,11</sup> especially as edema and ascites often present in other parts of the body.<sup>2</sup> While the majority of existing POEMS case studies have corroborated this particular theory, other proposed possibilities include infiltrative orbitopathy<sup>3</sup> and ischemia.<sup>1,22</sup>

It is important to consider, however, that nearly all previous studies exploring the mechanism behind ODE in POEMS have specifically investigated ODE that presented bilaterally in the initial assessment. In two case series reports exploring this relationship,<sup>10,11</sup> the symmetry of the ODE at the time of the initial visit was not explicitly stated, and most of the ODE cases were generally described as bilateral. Only one individual case report thoroughly examines unilateral ODE.<sup>13</sup> Given that our patient exhibited bilateral ODE five weeks after the first visit (Fig. 3C), we believe this is the first clearly documented case of asymmetric ODE in POEMS, notably in a young woman additionally presenting with

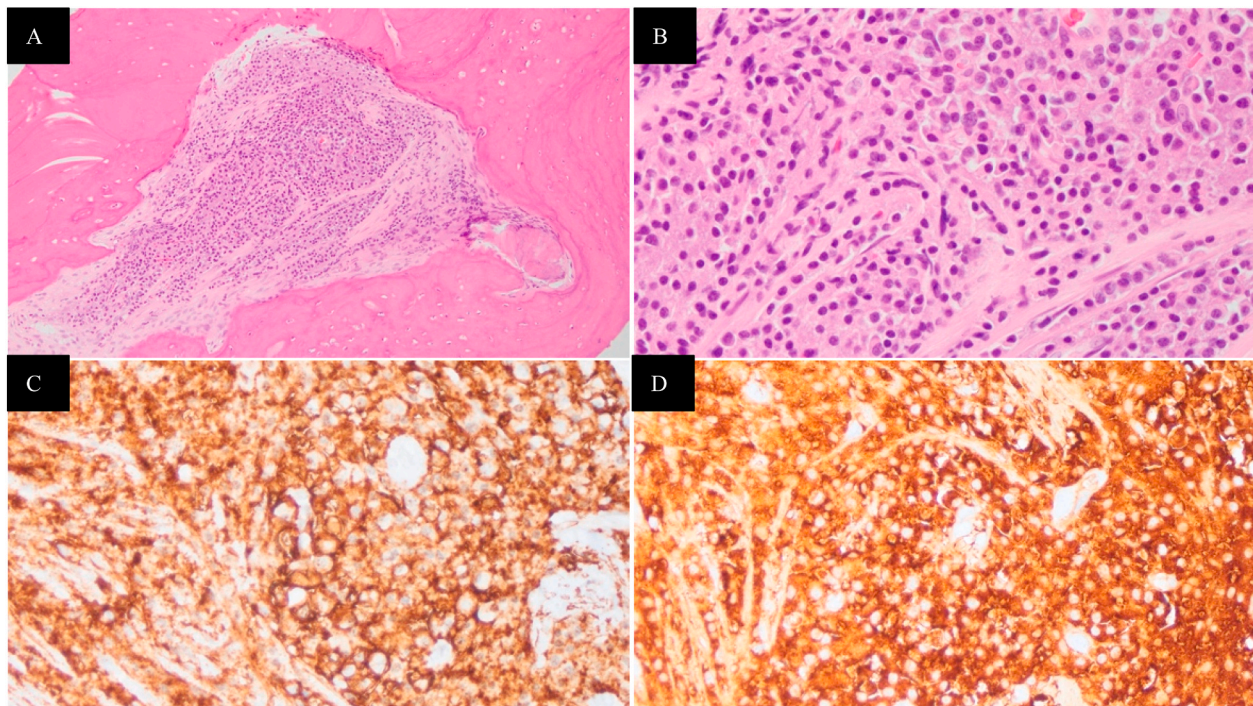
lacrimal gland and extra-ocular muscle enlargement. This is especially important as ODE can be an early sign of POEMS<sup>4,13</sup> and thus ophthalmologists should be aware that it can manifest asymmetrically.

The initially-unilateral presentation of ocular manifestations in this particular case may be due to multiple factors. However, the rare occurrence of asymmetric papilledema—especially in POEMS—, the systemic spread of vascular hyperpermeability, and the lack of evidence for local venous or arterial thromboses point to infiltrative orbitopathy as a potential driving force of ODE in our patient, which reflects the findings of the individual unilateral ODE case report.<sup>13</sup> This is further corroborated by the concurrent presence of extra-ocular muscle and lacrimal gland prominence and proptosis, which have been strongly linked to plasma cell infiltration in the context of multiple myeloma.<sup>23,24</sup> Further studies should confirm if cellular infiltration could indeed relate to the development of asymmetric ODE in POEMS.

Regarding POEMS treatment, Melphalan200 conditioning and ASCT was deemed the appropriate treatment for this case. An alternative such as radiation is considered more suitable for patients with limited or more localized lesions,<sup>25</sup> and recent literature has demonstrated more reliable outcomes with ASCT relative to other systemic treatments such as



**Fig. 4.** Axial section of orbital-cerebral magnetic resonance imaging (MRI) at initial visit. Images show bilateral prominence of the (A; arrows) extra-ocular muscles and (B; arrows) lacrimal gland without optic nerve enhancement.



**Fig. 5.** Sacral lesion biopsy at one month after initial visit. (A; 10x) showing osteosclerotic bone and (B; 40x) sheets of mature-appearing plasma cells that are (C; 40x) positive for CD138 and (D; 40x) cytoplasmic lambda light chain restricted.

proteasome inhibitor-based therapy or immunomodulatory imide drugs.<sup>2,14,26</sup>

#### 4. Conclusions

In summary, this case illustrates the rare, multisystem disease of POEMS syndrome as an uncommon cause of asymmetric optic disc edema. While it is often diagnosed in older males, ophthalmologists should consider POEMS in any patient initially presenting with bilateral or unilateral optic disc edema in conjunction with multiple systemic symptoms.

#### Patient consent

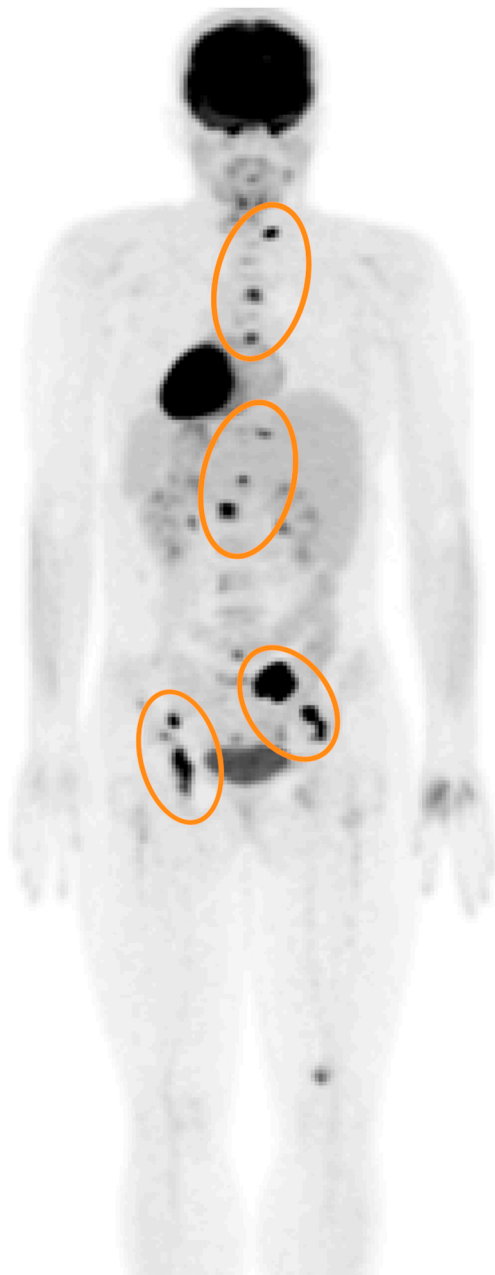
This report does not contain any personal identifying information. Patient consent is available.

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#### Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.



**Fig. 6.** Positron emission tomography (PET)/computed tomography (CT) scan at one month after initial visit featuring multiple spine and pelvic bone lytic lesions (orange circles).

#### Declaration of competing interest

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