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Localized Bilateral Juxtafoveal Photoreceptor Loss in POEMS, a New Association

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A 48-year-old man with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes) syndrome presented with ~3 years of bilateral blurred vision. He did not report photopsias, floaters, or diplopia. He did not use any retinotoxic medications; there was no suspicion of infectious retinopathies. Visual acuity was 20/25 (right eye) and 20/20 (left eye). There were Paton's lines in peripapillary retina and an elevated optic nerve contour without intraretinal/subretinal hyporeflectivities (Fig. 1A,C). Near infrared reflectance (NIR-REF) showed a dark juxtafoveal region (Fig.1A) with mild short-wavelength (SW) hypoautofluorescence, focal photoreceptor outer segment (POS) signal attenuation and normal NIR fundus autofluorescence (FAF) (Fig.1B,C). Outer nuclear layer thickness (ONL=97 μ m) and the distance between photoreceptor ellipsoid zone (EZ) and the POS interdigitation zone (EZ-IZ=23 μ m) in this region were normal (normal mean $\pm$ SD:ONL=97 $\pm$ 11 μ m;EZ-IZ=25 $\pm$ 6 μ m)(Fig.1D). Foveal ONL thickness was normal (N) (108 μ m; N=111 $\pm$ 11 μ m). There was parafoveal (1.3 mm nasal) ganglion cell layer loss (GCL)(21 μ m; N=59 $\pm$ 7 μ m); this location receives input from nasal juxtafovea. The pericentral retina (between the peripapillary and juxtafoveal abnormalities) was normal (Fig. 1C,D). Longitudinal reflectivity profiles (LRPs) confirmed EZ band attenuation and IZ loss without gross EZ-RPE distance shortening (Fig.1D). OCT-angiography was normal. There was a diffuse central sensitivity loss by microperimetry with deeper defects in nasal and inferior retina (Fig.1E). Adaptive optics (AO) showed loss of cone outer (COS) and inner segments (CIS) in this region, interspaced with normal POS, associated with locally low (72% of normal) cone photoreceptor density (Fig.1F). Serum was positive for a 23-kDa (Rab6A) protein by Western Blot with moderate immunostaining in human retina exposed to the patient's serum.

Ocular findings in POEMS syndrome include papilledema, retinal hemorrhages, subretinal fluid, macular edema, and choroidal neovascularization, and are attributed to vascular endothelial growth factor elevation (patient's=38 pg/mL, N=9–86 pg/mL), and cytokine dysregulation.^{1–4} Localized photoreceptor loss has not been reported. Possible mechanisms for this association include retrograde degeneration from GCL/axonal damage and/or local

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autoimmune/inflammatory effects.⁵ Normality of the pericentral nasal retina makes intermittent extension of optic nerve edema with damage to RPE/juxtafoveal photoreceptors less likely a mechanism, unless foveal/juxtafoveal photoreceptors are locally more susceptible.

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Figure 1.

A,B. *En-face* color and NIR-REF (**A**) and FAF (SW and NIR) imaging (**B**) (Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany). Black stars marks location of foveal center on NIR-REF; arrows point to darker juxtafoveal region. **C.** 7.2 mm-long horizontal SD-OCT sections through the fovea demonstrate IZ signal attenuation and loss of the IZ signal in juxtafoveal retina co-localizing with the NIR-REF and SW-FAF abnormalities. White stars mark peripapillary orderly transition of loss of the IZ, the EZ and ONL thinning with increasing proximity to the nerve's edge. Right eye horizontally flipped for comparison with the left eye. Retinal layers are labeled. N: Nasal; T: Temporal. **D.** Magnified region framed on SD-OCT image in (**C**) of the patient's (**P**) right eye compared with same region in normal (**N**) subject. Arrow points to foveal flattening caused by GCL loss. Outer retinal bands numbered (1, external limiting membrane; 2, EZ; 3, IZ; 4, RPE) correspond to outer retinal signal peaks on overlaid colored LRPs. There is EZ signal peak attenuation and loss of the IZ and GCL signals. **E.** Visual sensitivity by microperimetry (MAIA, CenterVue Inc., Fremont, CA, USA) show a shift of the distribution toward lower values. **F.** AO images in the patient (**P**) compared to normal (**N**) subject; mildly reduced cone photoreceptor densities but locally severe COS loss correspond to EZ signal loss on SD-OCT.