Retinitis Pigmentosa Sine Pigmento Masquerading as Normal-Tension Glaucoma. A Case Report

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SUMMARY

Aim: The aim of this publication is to highlight the diagnostic pitfalls in differentiating retinitis pigmentosa sine pigmento (RPSP) from normal-tension glaucoma (NTG).

Case Report: A 71-year-old patient was treated for 10 years with topical dual antiglaucoma therapy for NTG, which had been diagnosed based on optic disc pallor, a cup-to-disc ratio of 0.5, normal intraocular pressure, and visual field defects. During the course of subsequent monitoring, the patient developed progressive nyctalopia, concentric visual field constriction, and a marked decline in visual acuity from 1.0 to 0.1. Multimodal imaging, including fundus autofluorescence (FAF), optical coherence tomography (OCT), and perimetry, demonstrated photoreceptor degeneration that did not correlate with glaucomatous optic neuropathy. Genetic testing identified two heterozygous variants in the USH2A gene: one known pathogenic variant (c.11864G>A) and one novel variant (c.12544A>G). Based on these findings and the absence of typical bone spicule pigmentation on fundus examination, a diagnosis of RPSP was determined.

Conclusion: This case underscores the risk of misdiagnosing RPSP as NTG due to overlapping clinical features, and emphasizes the necessity of comprehensive multimodal evaluation, including FAF, OCT, electroretinography, perimetry, and genetic testing, in order to ensure accurate diagnosis and appropriate management.

Key words: retinitis pigmentosa sine pigmento, normal tension glaucoma, misdiagnosis

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INTRODUCTION

Retinitis pigmentosa (RP) covers a clinically and genetically heterogeneous group of hereditary retinal dystrophies caused by progressive dysfunction and depletion of photoreceptors, in which rod cells are primarily affected, followed by cone cells. The world-wide prevalence of RP is approximately 1 : 4 000 of the population [1]. The disorder is typically manifested in adolescents or in early adulthood in the form of nyctalopia, which is followed by progressive loss of the peripheral visual field and progressive deterioration of central visual acuity [1,2]. RP is associated with more than 80 genes and manifests various types of heredity, including autosomal dominant, autosomal recessive and X-linked forms. The fundoscopic finding in the classic form of RP incorporates degeneration of the type of bone cells, constricted blood vessels and waxy optic disc pallor. However, in atypical variants such as retinitis pigmentosa sine pigmento (RPSP) characteristic pigment changes are absent, which may lead to late diagnosis or its erroneous interpretation [1,2].

Normal-tension glaucoma (NTG) is a type of open-angle glaucoma, in which glaucomatous optic neuropathy occurs while normal intraocular pressure (IOP) is maintained. It is characterized by a progressive loss of ganglion cells, excavation of the optic nerve disc (OND) and corresponding blind spots in the visual field. Risk factors include vascular dysregulation, systemic hypotension, migraine and positive family medical history [3,4].

Due to overlapping clinical features between NTG and RPSP – in particular OND pallor and concentric visual field constriction – differential diagnosis of these two conditions may be difficult. Multimodal imaging such as optical coherence tomography (OCT), fundus autofluorescence (FAF), electroretinography (ERG) and targeted genetic testing play a key role in determining a precise diagnosis.

CASE REPORT

In 2022 a 71-year-old man was referred to the Department of Ophthalmology at the University Hospital in Trenčín due to progression of NTG in both eyes. The patient had been receiving treatment for approximately 10 years with local antiglaucoma agents (combination of dorzolamide + latanoprost) bilaterally. Until the age of 50 years the patient did not state any subjective ocular complaints, but from approximately the age of 60 he began to suffer from painless loss of peripheral vision, nyctalopia and disorder of color perception. The patient's family medical history was positive – the same visual complaints were present also in his 62-year-old brother. Significant factors in the patient's general medical history were a neuroendocrine tumor of the uncinate process of the pancreas, chronic pancreatitis, vascular nephrosclerosis and arterial hypertension.

At the baseline examination conducted at our center, best corrected visual acuity (BCVA) was 0.1 bilaterally and IOP was within the range of 13–15 mmHg in both eyes. Fundoscopy showed OND pallor with a cup-to-disc ratio of 0.5, peripapillary atrophy, constricted blood vessels, while the macular and remainder of the retina did not manifest deposit or pigment changes (Figure 1). A perimeter glaucoma test detected bilateral ring scotomas and pronounced concentric visual field constriction with preservation of narrow central vision, with mean deviations of –17.69 dB/–17.2 dB (Figure 2). FAF showed slightly increased perifoveal autofluorescence and pronounced hyopautofluorescence from the vascular arcades to the central periphery bilaterally and symmetrically (Figure 1).

OCT of the macula detected pronounced perifoveal reduction of the outer retinal layers, such as the outer nuclear layer, outer plexiform layer, ellipsoid zone and retinal pigment epithelium with central preservation of these layers (Figure 3). OCT of the OND showed only slight partial atrophy, with average retinal nerve fiber layer (RNFL) thickness of 81 µm in the right eye and 76 µm in the left eye (Figure 4). The results of the imaging examinations did not correlate with the previous diagnosis of NTG. Genetic testing identified two heterozygous variants in the USH2A gene. The first was the known pathogenic variant c.11864G>A, localized in exon 61. The second variant was c.12544A>G, which is new and had not been previously described in population databases. The patient did not state any disorder

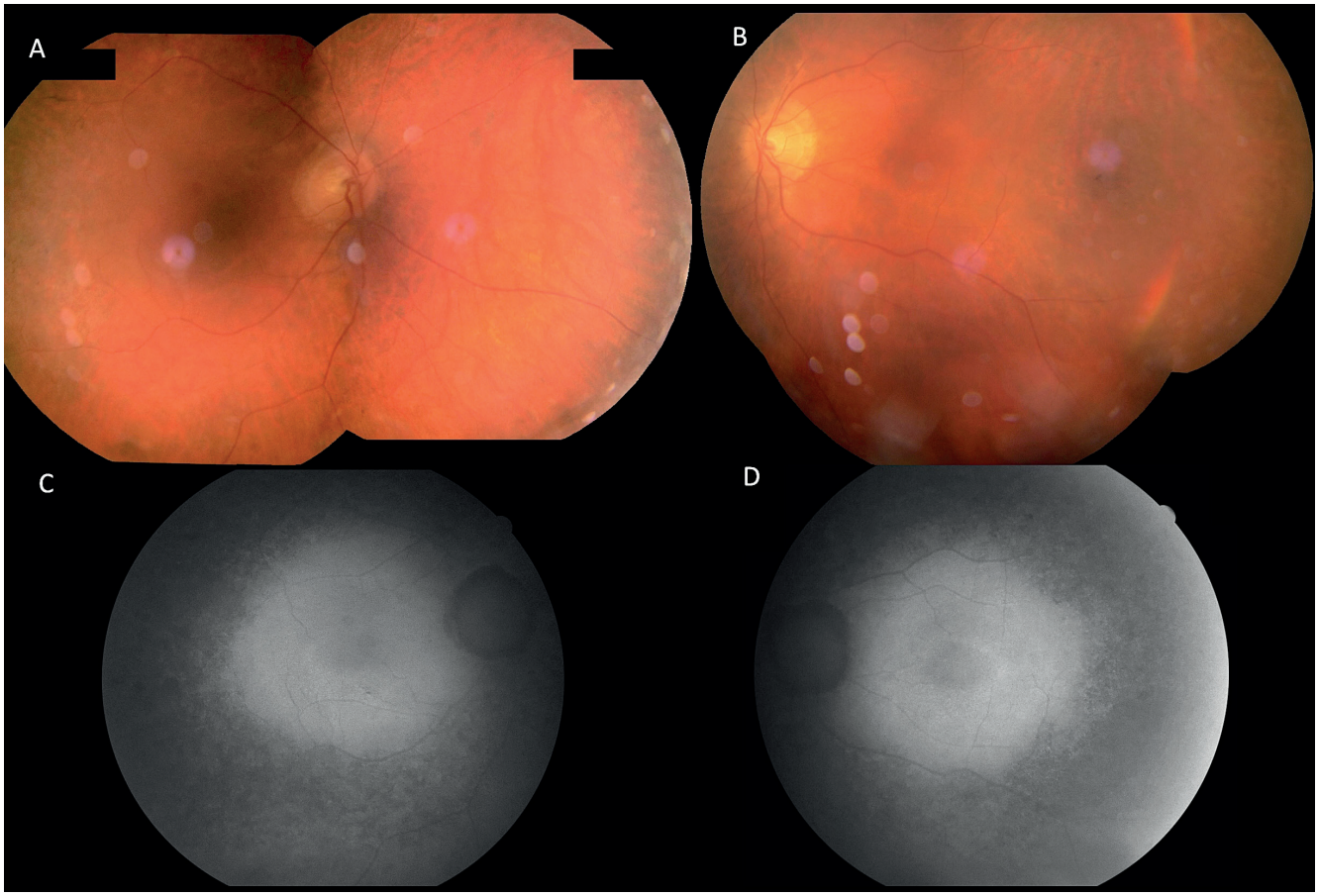

Figure 1. Fundus photographs (**A, B**) show pale optic nerve heads with a cup-to-disc ratio of 0.5, peripapillary atrophy, narrowed retinal vessels, and a retina without pigmentary changes. Fundus autofluorescence images (**C, D**) demonstrate a subtle perifoveal hyperautofluorescent ring and abnormal diffuse hypoautofluorescence extending from the vascular arcades to the mid-periphery in both eyes

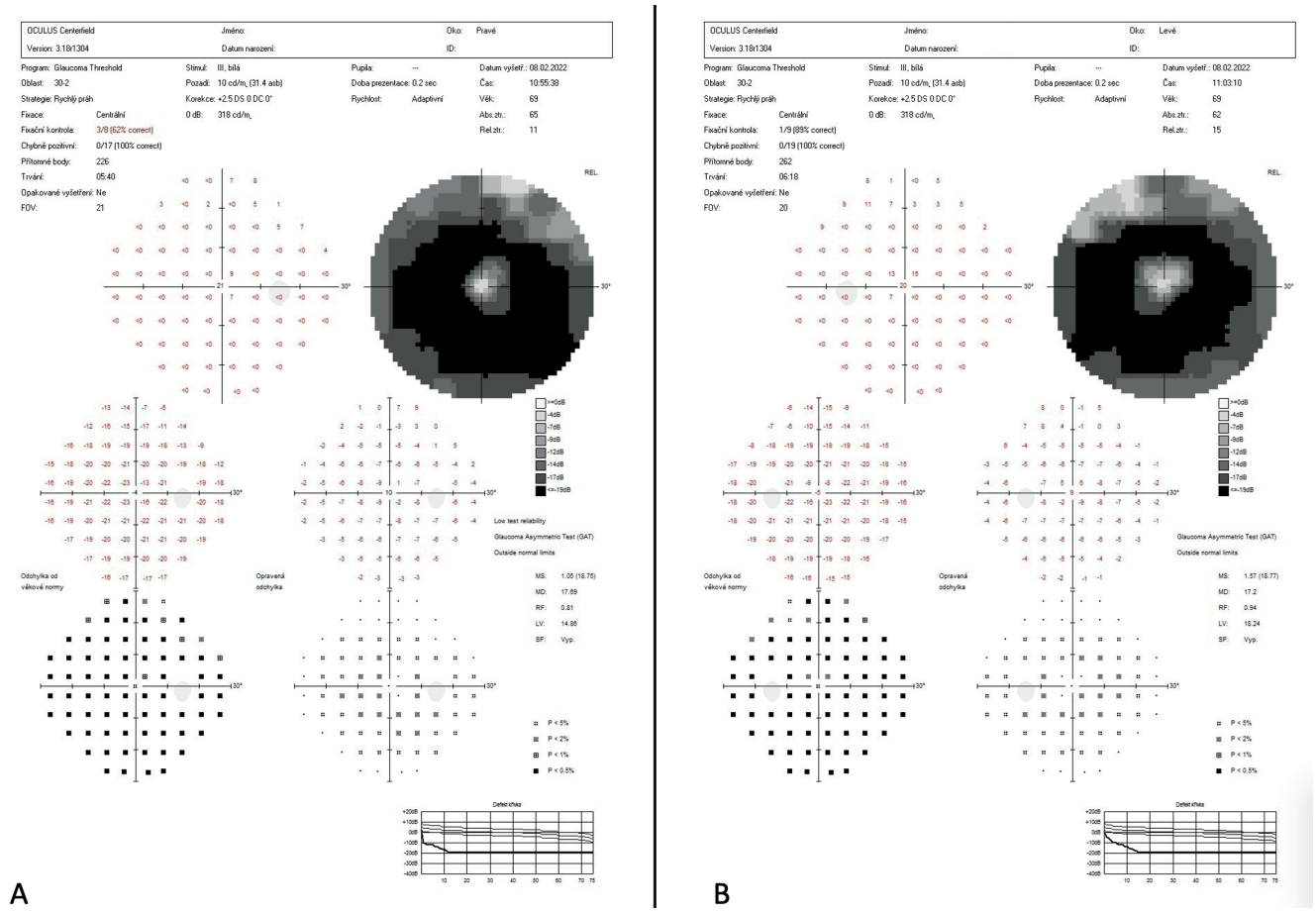

Figure 2. Glaucoma threshold perimetry demonstrates bilateral ring scotomas and concentric narrowing of the visual fields with foveal sparing and mean deviations of –17.69 dB/–17.2 dB

of hearing, and an audiometric examination also did not confirm any pathology. Based on these findings a diagnosis of autosomal retinitis pigmentosa was determined, specifically RPSP. ERG was not performed due to the unavailability of an ERG instrument at our center, and the patient refused to travel further afield for an examination. At present the pathology is progressing and BCVA has deteriorated to the value of 0.01.

DISCUSSION

This case illustrates the importance of multimodal imaging methods in differentiating NTG from RPSP. Although OND pallor and visual field constriction are common to both disorders, their fundamental pathophysiology, course and management differ considerably. In NTG visual field defects are typically arcuate or paracentral, and correlate with structural changes of the OND, such as RNFL depletion and excavation of the OND [3,4]. By contrast, RPSP occurs as a consequence of progressive degeneration of the photoreceptors, leading to nyctalopia and concentric visual field constriction [1,2].

OCT in RPSP detects perifoveal atrophy of the outer retinal layers and an almost preserved RNFL, whereas NTG affects only the RNFL [2,3]. Even when classic pigment deposits are absent on the ocular fundus, RPSP has a very characteristic image on FAF. A typical FAF finding in RPSP is the presence of a hyperautofluorescent ring (Robson–Holderov ring) surrounding the fovea, which represents a transitional zone between the preserved and dystrophic photoreceptors, while the central periphery manifests diffuse or mottled hyperfluorescence as a consequence of RPE atrophy and loss of lipofuscin. FAF is normal as a rule in the case of NTG, because this primarily concerns a disorder of the ganglion cells and nerve fibers and not a disease of the RPE and photoreceptors. In addition, electrophysiological examinations such as full-field ERG are pronouncedly pathological in the case of RP, with reduced or absent responses of rod and cone cells, whereas in the case of NTG they are usually within the norm [1–4].

A genetic analysis is essential in order to confirm a diagnosis of RP, especially in the case of atypical clinical manifestations. In this case, the identification of two heterozygous variants in gene USH2A supported the diagnosis of autosomal recessive RP. The USH2A gene is most commonly associated with Usher syndrome type 2, characterized by sensorineural hearing disorder and RP, or with isolated RP without hearing disorder. The USH2A gene encodes the usherin pro-

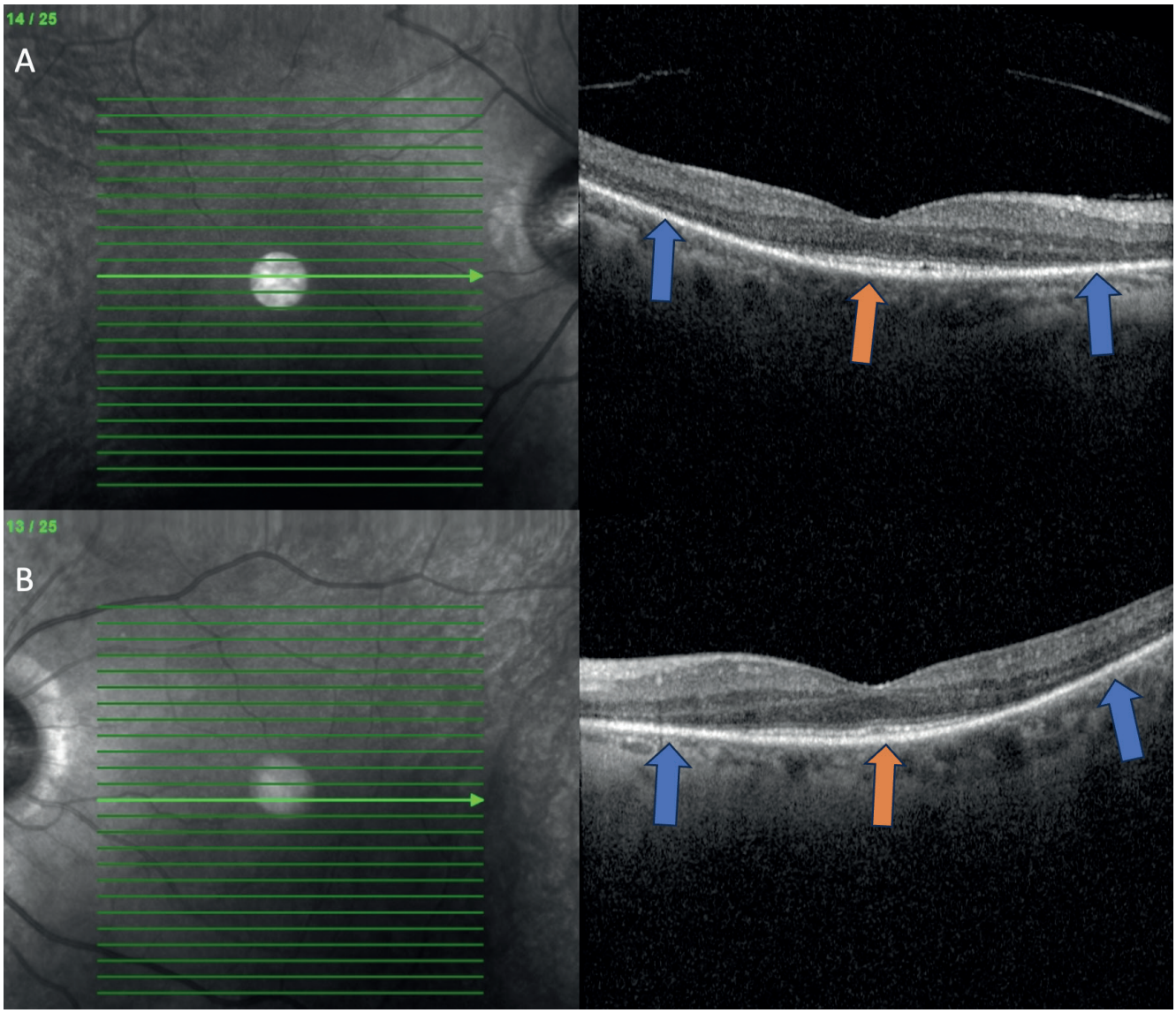

Figure 3. Macular optical coherence tomography (OCT) reveals perifoveal loss of the outer retinal layers, ellipsoid zone and retinal pigment epithelium (blue arrow), with central foveal sparing (orange arrow)

tein, which is essential for the function of the photoreceptors and inner ear cells [5]. RPSP has also been confirmed in connection with other genetic mutations such as KIF7 and USH1C [6,7].

A defining feature of RP is degenerations of the type of bone cells, though the clinical picture may be markedly variable. Lee analyzed 774 patients with RP, of whom 88 (11.4%) had RPSP. In 14 (22.6%) of the patients with RPSP, pigment degenerations of the type of bone cells appeared during the follow-up monitoring with an average time of almost 4 years, which indicates that pigment changes can occur during the course of the disease [8].

Similar publications exist in which RPSP has been misdiagnosed as myopia, glaucoma or chiasmal syndrome [9–11]. Differentiating between NTG and RP has profound therapeutic consequences. Treatment of glaucoma is targeted at reducing intraocular pressure, which is ineffective in the case of RP. By contrast, correct diagnosis of RP enables adequate patient consultancy, genetic examination of family members and the consideration of new genetic or neuroprotective therapeutic strategies.

CONCLUSION

This case underscores the risk of misdiagnosing RPSP as NTG. Overlapping features such as ODN pallor, concentric visual field defects and painless progressive deterioration of BCVA may lead to an erroneous classification of glaucomatous optic neuropathy. A comprehensive examination incorporating FAF, OCT, ERG, perimetry and genetic testing is essential in order to ensure the differentiation of these conditions and to ensure accurate diagnosis and appropriate management.

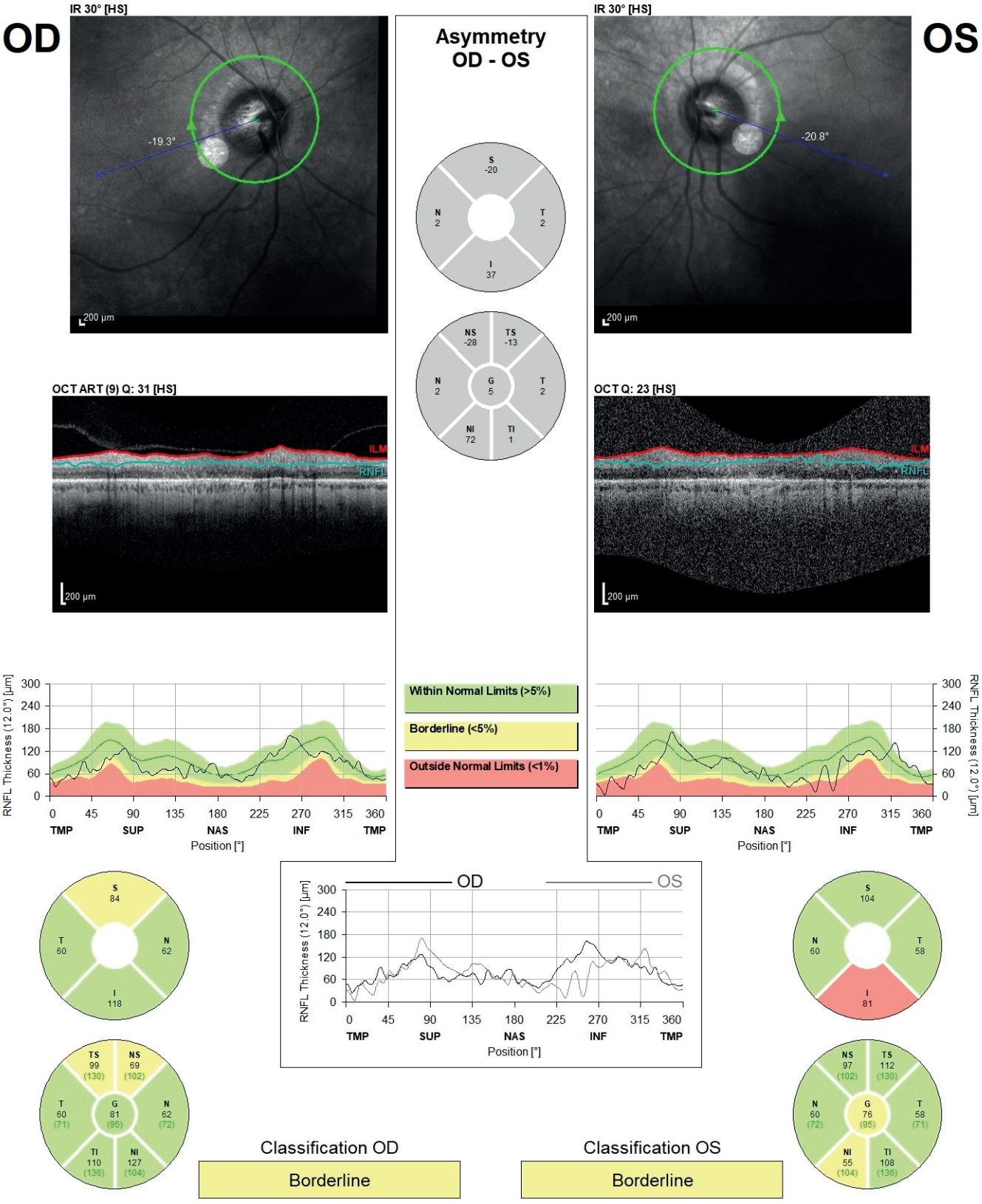

Figure 4. Optic nerve head OCT shows mild partial atrophy, with average retinal nerve fiber layer thicknesses of 81 µm in the right eye and 76 µm in the left eye

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