Senior-Loken syndrome secondary to *IQCB1* mutation in association with retinitis pigmentosa

Senior-Loken syndrome (SLS) is a rare autosomal recessive disease characterized by nephronophthisis and early-onset retinal degeneration.[1] Nephronophthisis leads to end-stage renal failure. Several genes can cause SLS, including NPHP1-6 and NPHP10.[2] We herein report a case of SLS type 5 caused by *IQCB1* mutation.

A 17-year-old boy came with progressive diminution of vision and photophobia in both eyes since childhood. The visual disability was the same in the daytime as it was at night. He was diagnosed with some nonspecific pigmentary retinal degeneration. Best corrected visual acuity was 6/60, N6 in right eye and 6/60, N8 in left eye. Anterior segment examination was unremarkable. Fundus examination of both eyes showed mid-peripheral retinal pigment epithelium (RPE) alterations and pigment clumps, relatively sparing maculae, and narrowing of retinal arterioles (Figs. 1A and 1B). Fundus autofluorescence (FAF) showed decreased autofluorescence in the mid-periphery and a perifoveal ring of increased autofluorescence, suggesting a bull's-eye maculopathy (Figs. 1C and 1D). Spectral domain optical coherence tomography (SDOCT) revealed a barely detectable inner–outer photoreceptor segment junction in the central macula corresponding to the area inside of the ring of increased autofluorescence (Figs. 2A and 2B). Humphrey visual field 30-2 of both eyes showed constricted fields (Fig. 2C). Electroretinogram was performed under The International Society for Clinical Electrophysiology of Vision (ISCEV) standards. It showed extinguished scotopic and photopic responses (Fig. 2D).

The boy had no family history of similar problems and was born out of a nonconsanguineous marriage (Fig. 3). When inquired about his systemic condition, he disclosed a history of chronic renal failure from childhood, leading to end-stage renal disease and renal transplantation performed 6 years ago. The renal problems started by the age of 2 years old. Parents were not able to comment on delayed milestones. The cause of renal failure was not known despite all laboratory investigations and despite being under the care of pediatric nephrologist from a young age. He received a kidney donation from his father. Both parents gave no history of visual complaints and, suspecting a syndromic association, we examined both the parents. The father had undergone a retinal detachment surgery and the mother had a normal fundus evaluation. There were no features of pigmentary retinal dystrophy in both the parents. The mother was earlier found unsuitable for kidney donation when she was evaluated 6 years back because she had practically one functional kidney and the other kidney was atrophic. The boy was short statured with good intelligence and hearing. He had no other musculoskeletal problems. The systemic features along with the retinal condition brought us to a differential diagnosis of SLS and patient underwent genetic testing. Targeted gene sequencing was done by MedGenome laboratories, Bangalore, India. A heterozygous nonsense variation was detected in exon 13 of the *IQCB1* gene (p.Arg461Ter; c.13181C>T) and heterozygous single base pair deletion in exon 4 of the *IQCB1* gene (p.Cys62AlafsTer26; c.184del). Heterozygous single base pair deletion in exon 4 of the *IQCB1* gene (chr3:g.121547397del; Depth:65x) that results in a frameshift and premature truncation of the protein 26 amino acids downstream to codon 62 (p.Cys62AlafsTer26; ENST00000310864.6) was detected. This mutation was found to be novel. No other variants were noted. This was suggestive of SLS type 5 with retinitis pigmentosa (RP) like picture. The parents refused to be tested to confirm whether each parent carried one mutant allele. The patient was referred back to the nephrologist and internist for complete evaluation for the ciliopathy and underwent low-vision assessment and was provided with a dome magnifier.

Many diseases can present with oculorenal symptoms (Table 1).[2] SLS is a rare disease included in ciliopathies with a combination of nephronophthisis and retinal degeneration, which was first described by Senior and Loken in 1961.[1,3] There are variable visual presentations ranging from RP to Leber congenital amaurosis.[4] SLS is caused mainly by mutation in the *IQCB1* gene (also known as NPHP5), located on chromosome 3q21.1. *IQCB1* encodes the protein nephrocystin-5, expressed in the connecting cilia of photoreceptors and in primary cilia of renal epithelial cells. In the retina, nephrocystin-5 co-localizes with retinitis pigmentosa GTPase regulator involved in X-linked

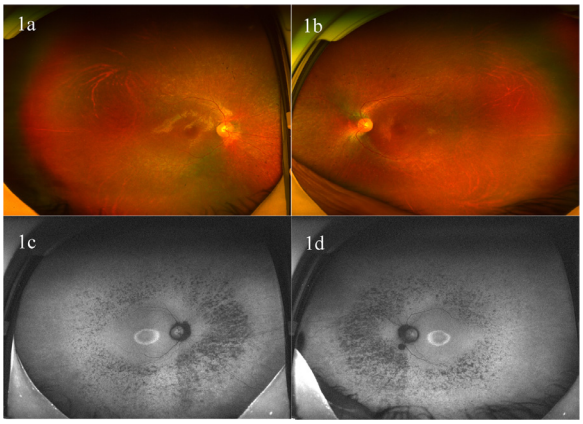

Fig. 1—Ultrawide color fundus photograph (OPTOS) of both eyes (A and B) showing mid-peripheral retinal pigment epithelium (RPE) alterations and pigment clumps, relatively sparing maculae, and narrowing of retinal arterioles. Ultrawide fundus autofluorescence (OPTOS) (C and D) showing decreased autofluorescence in the mid-periphery and a perifoveal ring of increased autofluorescence.

https://doi.org/10.1016/j.jcjo.2021.01.010
ISSN 0008-4182

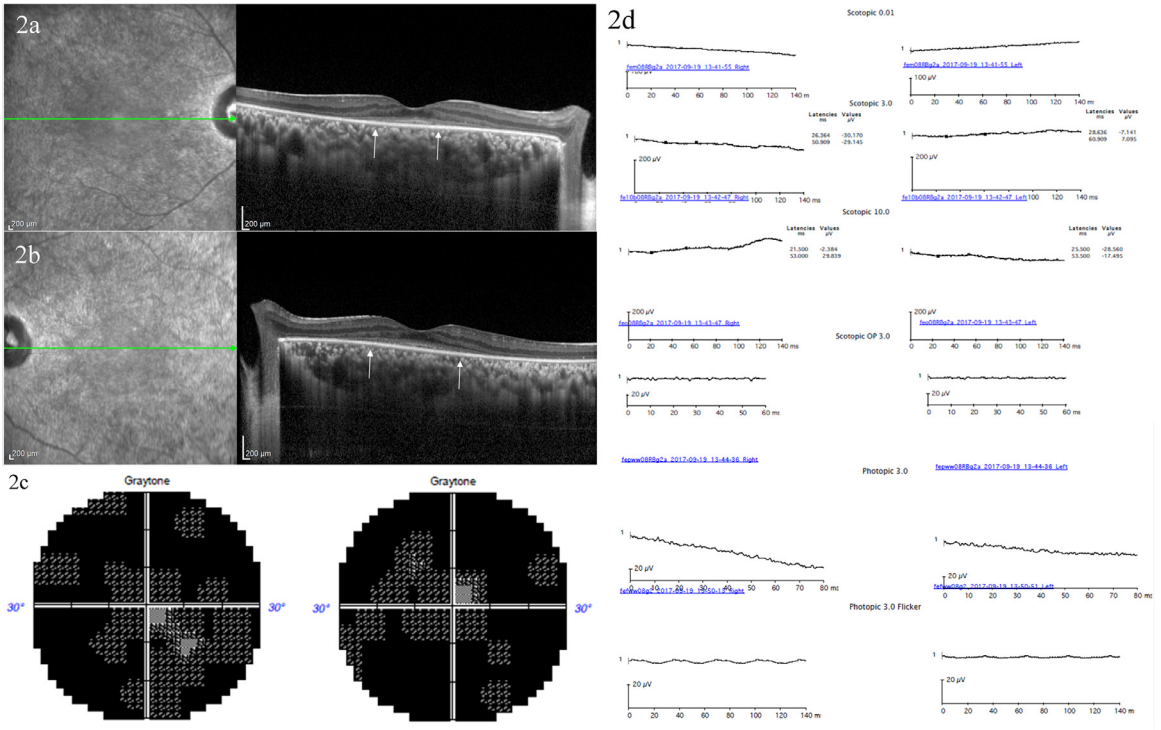

Fig. 2—Spectral domain optical coherence tomography (A and B) showing a barely detectable inner–outer photoreceptor segment junction in the central macula (arrows) corresponding to the area inside of the ring of increased autofluorescence. Humphrey visual field 30-2 of both eyes (C) showing constricted fields. Electroretinogram of both eyes (D) showing extinguished scotopic and photopic responses.

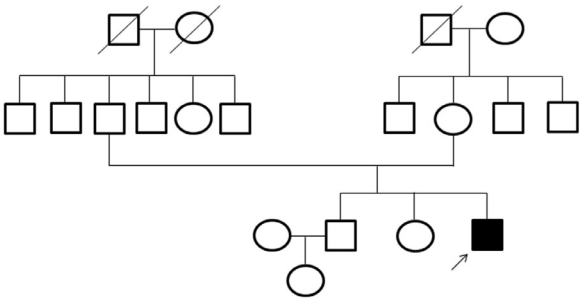

Fig. 3—The pedigree with Senior-Loken syndrome (SLS) is shown. Circles represent females, whereas squares represent males. The index case is arrowed. Filled symbol denotes presence of SLS.

Table 1—Syndromes with oculorenal symptoms

Bardet-Biedl syndrome	Truncal obesity, polydactyly, cognitive impairment, hypogonadotropic hypogonadism, renal abnormalities, retinitis pigmentosa
COACH syndrome	**C**erebellar vermis hypoplasia/aplasia, **O**ligophrenia, **A**taxia, **C**oloboma, and **H**epatic fibrosis
Alström disease	Nephronophthisis, severe deafness, cardiomyopathy, retinal dystrophy
Jeune dystrophy	Skeletal deformity, respiratory insufficiency with retinal dystrophy and nephronophthisis
Joubert syndrome	Hyperpnea, hypotonia, oculomotor apraxia, mental retardation, ataxia, retinal degeneration
Meckel syndrome	Encephalocele, hepatic ductal dysplasia and cysts, and polydactyly, cystic kidneys
Senior-Boichis syndrome	Liver fibrosis, nephronophthisis, tapetoretinal degeneration
Usher syndrome	Hearing loss, retinitis pigmentosa, and balance problems
Senior-Loken syndrome	Nephronophthisis and retinal degeneration
RHYNS syndrome	**R**etinitis pigmentosa, **H**ypopituitarism, **N**ephronophthisis, and **S**keletal dysplasia
Arima syndrome	Cerebellar anomalies, retinopathy, and polycystic kidneys

RP, and it is responsible for epithelial cell integrity, resulting in renal cyst formation in cases of protein dysfunction in the kidneys.[5] Patients with nephronophthisis usually have polyuria, polydipsia, and nocturia owing to loss of urinary concentration ability. Progressive failure of kidney function occurs because of degeneration or loss of function of the small collecting tubes (tubules) in the kidney. In the present case, the boy had typical ophthalmic and renal presentation of SLS type 5. Patients may present with severe vision loss from infancy with nystagmus and hyperopia Leber congenital amaurosis or may present with progressive vision loss presenting later with RP-like presentation.

Progressive photoreceptor death in RP ultimately causes RPE atrophy at the macula, which can be assessed by FAF and SDOCT. FAF detects abnormal distribution of lipofuscin in RPE derived from photoreceptor's outer segment phagocytosis. SDOCT delineates the junction between the inner and outer segments of the photoreceptors. In our case, inner—outer photoreceptor segment junction was barely

detectable in the central macula suggesting initial ciliary junction disorganization before photoreceptor death. These noninvasive investigations can help in monitoring the patients. They may benefit from various visual aids such as a 4X dome magnifier, which was recommended for our patient. Genetic counselling should be done for patients and their families. These patients might require regular follow up with the internist for systemic associations.

The case presents an interesting diagnosis by an ophthalmologist for a multisystem disease, and it stresses the importance of good systemic evaluation along with eye examination.

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Originally received Oct. 14, 2020. Final revision Jan. 1, 2021. Accepted Jan. 11, 2021.

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Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.

Optical coherence tomography angiography in choroidal metastasis before and after treatment

Choroidal metastases represent the most common intraocular malignant tumor in adults.[1] With the advent of optical coherence tomography angiography (OCTA), there is a unique opportunity to visualize choroidal vascular pathologies in more detail using a noninvasive technique concurrent with anatomical evaluation of the retina, retinal pigment epithelium (RPE), and choroid. Depth-selective characterization is one of the most significant advantages of OCTA, allowing better visualization of choroid circulation and, particularly, the choriocapillaris layer, which is the main source of perfusion to the RPE and photoreceptors. Previous investigators have shown the role of optical coherence tomography (OCT) in assessment of choroidal metastasis.[2–4] In addition, there are reports of its dramatic response to epidermal growth factor receptor (EGFR) inhibitors,[5] but OCTA findings in choroidal metastasis has not been described.

Here, we present a case of asymptomatic choroidal metastasis, leading to the primary diagnosis of stage IV EGFR-positive lung adenocarcinoma, with OCTA findings in the choriocapillaris at presentation. Choroidal changes in OCTA almost completely resolved with near normal restoration of choriocapillaris vascular perfusion signal, even in areas without visible choroidal lesions, only 3 weeks after systemic treatment with EGFR inhibitor.

Case Report

A 50-year-old Hispanic woman presented for annual examination with no specific complains. She had a past medical history of migraines and was taking oral multivitamin supplements. She had no history of smoking. On examination, visual acuities were 20/30 in each eye. Intraocular pressures and pupillary exam were within normal limits, and anterior segments were unremarkable. Dilated fundus examination was notable for a hypopigmented lesion in the inferior macula of the right eye (Fig. 1A) and multiple yellowish deep lesions with overlying hyperpigmented brown stippling in the central and inferior macula of the left eye (Fig. 1B). Fluorescein angiogram (FA) indicated early hypofluorescence with increasing multifocal hyperfluorescence corresponding to choroidal lesions (Fig. 1 C, D). Enhanced depth spectral domain (EDI-SD) OCT (Spectralis, Heidelberg, Germany) showed multiple discrete hyper-reflective nodules in choroid highly suggestive of choroidal infiltrative process (Fig. 1 E, F).

OCTA (RTVue-XR Avanti, Optovue, Fremont, Calif) in the right eye showed multiple scattered areas of dark, hypointense flow voids surrounded by a more uniform flow pattern of choriocapillaris structure (Fig. 2A1, A2); in the left eye, there were more distinct and larger areas of dark, hypointense flow voids in variable sizes and shapes, causing a general reduction in signal density in favor of choroidal infiltration (Fig. 2 C1, C2). The patient was urgently referred for systemic work-up of metastasis. Whole-body positron emission tomography revealed multiple lung and bone lesions; subsequent lung biopsy was compatible with asymptomatic stage IV adenocarcinoma of the lung with positive EGFR mutation. Systemic therapy with erlotinib, an EGFR-inhibitor, was initiated. Three weeks after treatment, visual acuity remained stable in both eyes, and OCTA showed resolution of flow voids throughout the macula in both eyes. In the right eye, the scattered areas of flow void noted at presentation were largely replaced by