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OPTIC DISK COLOBOMA AND CONTRALATERAL OPTIC DISK PIT MACULOPATHY TREATED BY VITRECTOMY IN A PATIENT WITH NOONAN SYNDROME WITH MULTIPLE LENTIGINES

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Purpose: To report a case of Noonan syndrome with multiple lentigines with unusual ocular features.

Methods: The authors describe a case of a 7-year-old girl with Noonan syndrome with multiple lentigines and anomalous optic disks.

Results: A 7-year-old girl with genetically proven Noonan syndrome with multiple lentigines (*PTPN11 gene* mutation) and anomalous optic disks was referred for treatment of persistent macular detachment after 1 year of conservative follow-up. The right eye demonstrated an optic disk coloboma with the best-corrected visual acuity of 20/32, the left eye demonstrated an optic disk pit with serous macular detachment (best-corrected visual acuity 20/50–20/80). Optical coherence tomography demonstrated a neurosensory detachment. Twenty-five gauge pars plana vitrectomy was performed with posterior hyaloid detachment, drainage over disk pit area, and SF6 20% gas tamponade. Surgery resulted in subretinal fluid reduction and improvement of the visual acuity to 20/32.

Conclusion: A case of Noonan syndrome with multiple lentigines with optic disk coloboma in the right eye and optic disk pit with related maculopathy in the left eye. To the best of the authors' knowledge, this is the first reported case describing the association of Noonan syndrome with multiple lentigines and congenital optic disk anomalies. Optic disk pit maculopathy was managed surgically because of its longstanding nature with the deteriorating visual acuity.

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Noonan syndrome with multiple lentigines (NSML), formerly known as LEOPARD syndrome, is a rare autosomal dominant RASopathy syndrome with multiple congenital anomalies depicted in the acronym LEOPARD: multiple lentigines, electrocardiographic conduction defects, ocular hypertelorism, pulmonary stenosis, abnormalities of the genitalia, retarded growth, and sensorineural deafness.

There are three main types of NSML: Type 1 is caused by mutations in the *PTPN11 gene*, Type 2 by mutations in the *RAF1 gene*, and Type 3 by mutations in the *BRAF gene*. Mutations in these 3 loci can be found in 95% of affected individuals.[1] Other cases are related to mutations in the *MAP2K1 gene*, and in some cases, the cause is unknown.

A missense mutation in the *PTPN11 gene* is found in approximately 85% of patients with a definite diagnosis of NSML. In 65% of these mutations, p.Tyr279Cys and p.Thr468Met are involved.[2]

Frequent ocular manifestations include ocular hypertelorism (100%), the occurrence of abnormal

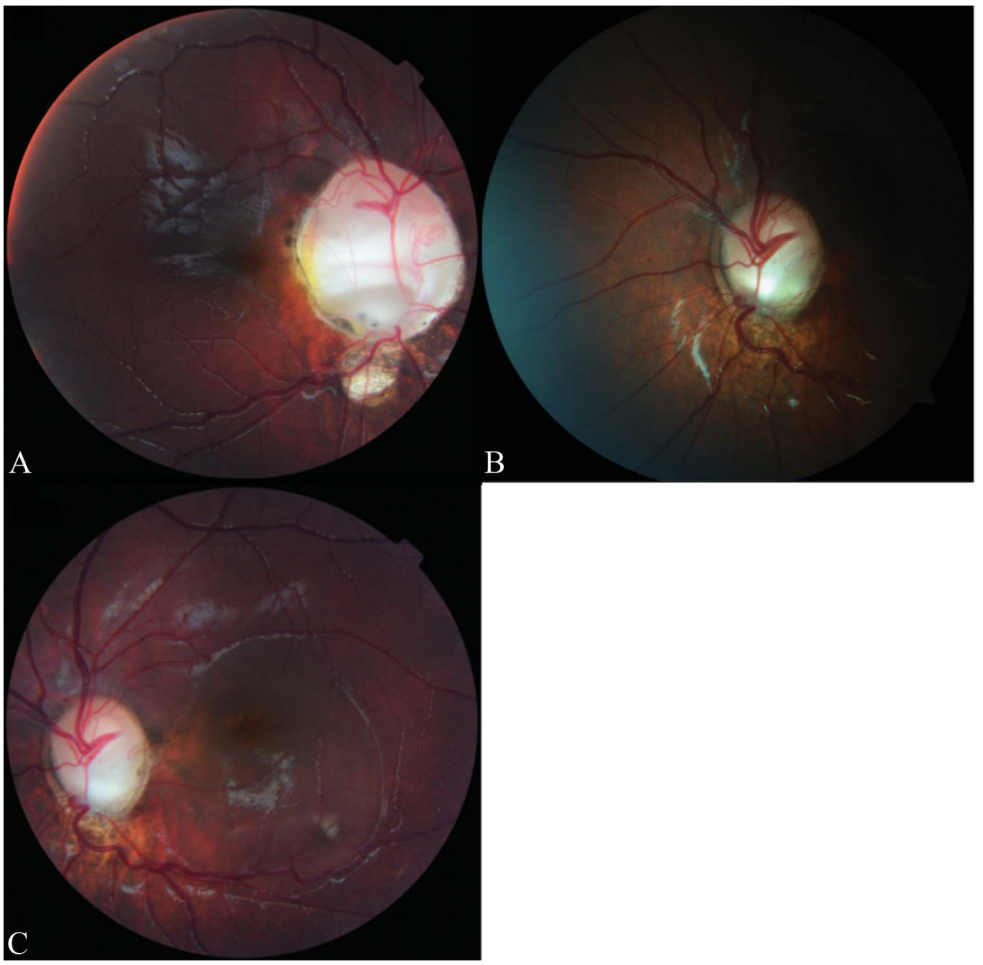

Fig. 1. A. Fundus photograph in the right eye (2020) showing optic disk coloboma. **B.** Fundus photograph in the left eye (2016) showing optic disk pit. **C.** Fundus photograph in the left eye (2020) showing optic disk pit and serous macular detachment. The serous macular detachment is contiguous with the optic disk through a visible isthmus of subretinal fluid.

ocular movements and stereopsis.[1] Other ocular features are uncommon and consist of palpebral ptosis and nystagmus. One case report describes a mother and her two identical monozygotic twins with NSML and colobomas of the iris, the retina, and the choroid.[3]

In 1882, Wiethe et al were the first to describe an optic disk pit (ODP), which is a rare congenital defect. It presents as an oval depression that usually occurs inferotemporally within the optic disk, is usually unilateral and has a grayish color. Normally, patients with an ODP are asymptomatic, but associated vision loss can occur because of secondary serous macular detachment. The intraretinal and subretinal fluid is believed to originate from the vitreous, the cerebrospinal fluid, or even leaking blood vessels at the ODP base or the choroid.[4,5]

Case Report

This 7-year-old girl, known with a proven NSML (heterozygous de novo c.836 G > A p.(Tyr279Cys) mutation in *PTPN11 gene*), has been followed by her pediatric ophthalmologist at the Antwerp University Hospital since age 1.

Her systemic evaluation was significant for small stature, valvular pulmonary stenosis and multiple small ventricular septal defects, unilateral deafness, lentigines since 2017, and bilateral hydroureteronephrosis. In 2013, a brain MRI was performed which

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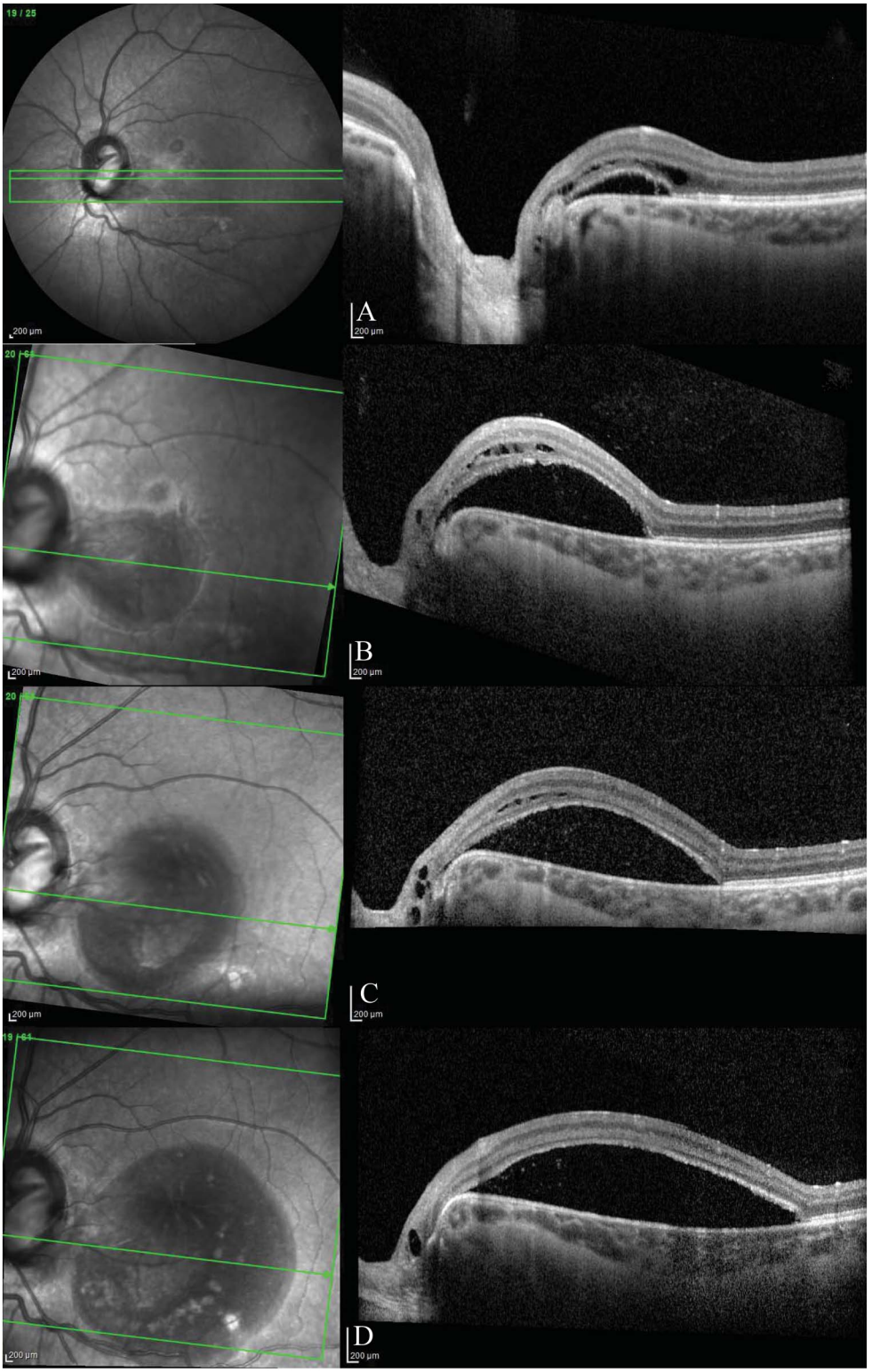

Fig. 2. Serial OCT images of the left eye showing progressively increasing amount of intraretinal and subretinal fluid over time. **A.** March 2019. **B.** April 2019. **C.** June 2019. **D.** October 2019.

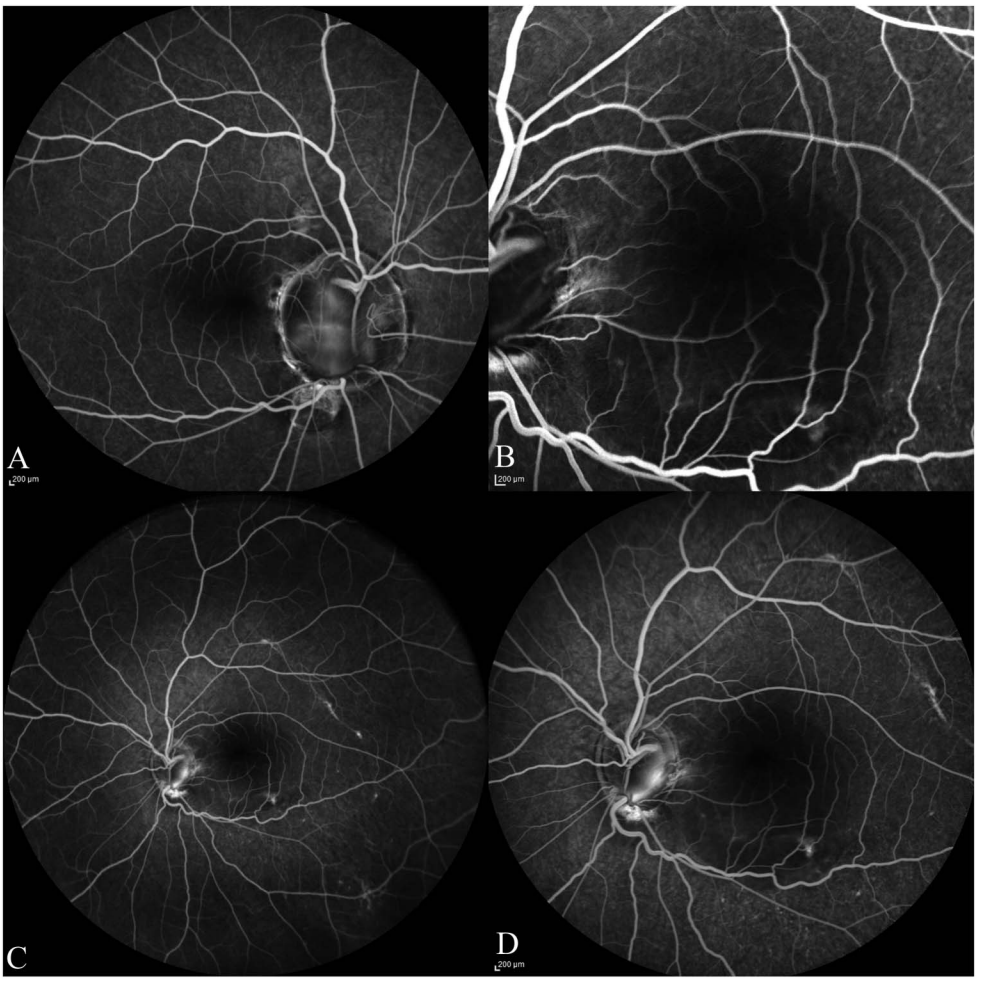

Fig. 3. Fluorescein angiography images of the (**A**) right eye with optic disk coloboma and (**B**) optic disk pit. Images (**C** and **D**) demonstrate late phase hyperfluorescence and fluorescein migration from the base of the ODP area into the serous detachment.

did not show any midline or retrobulbar abnormalities and a normal corpus callosum.

Up to 2 years of age, the grating acuity using the Teller acuity cards was equal in both eyes. Fundoscopy revealed anomalous optic disk (right eye more than the left).

In 2015, when the patient was 3 year old, the best-corrected visual acuity (BCVA) was 20/50 in the right eye and 20/125 in the left eye. The patient was given refractive correction, and occlusion therapy was started (0.00 D in the right eye; $+1.00 -2.00 \times 160^{\circ}$ in the left eye). Despite these treatment measures, the BCVA in the left eye did not improve significantly. Optical coherence tomography (OCT) macula could not be procured at this time because the patient was uncooperative.

In June 2018, OCT imaging showed intraretinal and subretinal fluid. Since these changes were minimal and the cause was unknown, the patient was followed conservatively. After 1 year of OCT observation, macular detachment was persistent and progressive (Figure 2). Because of decreasing BCVA, progressive macular detachment on OCT and because of the onset of left esotropia, empirical treatment with oral acetazolamide syrup (20 mg/kg/day) was started. In December 2019, this treatment was stopped after 2 months, given its side effects and lack of visual improvement.

In February 2020, after one-and-a-half year of conservative follow-up and 2 months of oral acetazolamide syrup, the patient was referred to our vitreoretinal department. Fundoscopy demonstrated an optic disk coloboma (ODC) with visual acuity of 20/32 BCVA in the right eye, whereas the left eye demonstrated an ODP with serous macular detachment and BCVA fluctuating between 20/50-20/80 (Figures 1 and 2). In the left eye, a diagnosis of ODP with ODP maculopathy (ODP-M) was made.

Optical coherence tomography imaging and fluorescein angiography were performed to confirm the clinical diagnosis of ODP and to exclude other causes, particularly central serous chorioretinopathy, trauma, and neoplastic or inflammatory conditions. Optical coherence tomography depicts the neurosensory detachment communicating with the temporally located ODP. In some sections, limited intraretinal fluid cavities can be seen in the papillomacular area. No pachychoroid or other anomalies were seen. Fluorescein angiography demonstrates late phase hyperfluorescence and fluorescein migration from the base of the ODP area into the serous detachment (Figure 3). No other leakage points or abnormalities were seen. An insignificant area of late staining was seen in the inferotemporal macula. This confirms our diagnosis of ODP-M and excludes central serous chorioretinopathy in this NSML case.

Because of lack of patient cooperation, OCT imaging was not possible until June 2018, when intraretinal and subretinal fluid was seen. We therefore believe limited ODP-M may have been left undiagnosed for quite some time in this case.

Serial OCT images revealed progressive increase in the amount of subretinal fluid with variably deteriorating visual

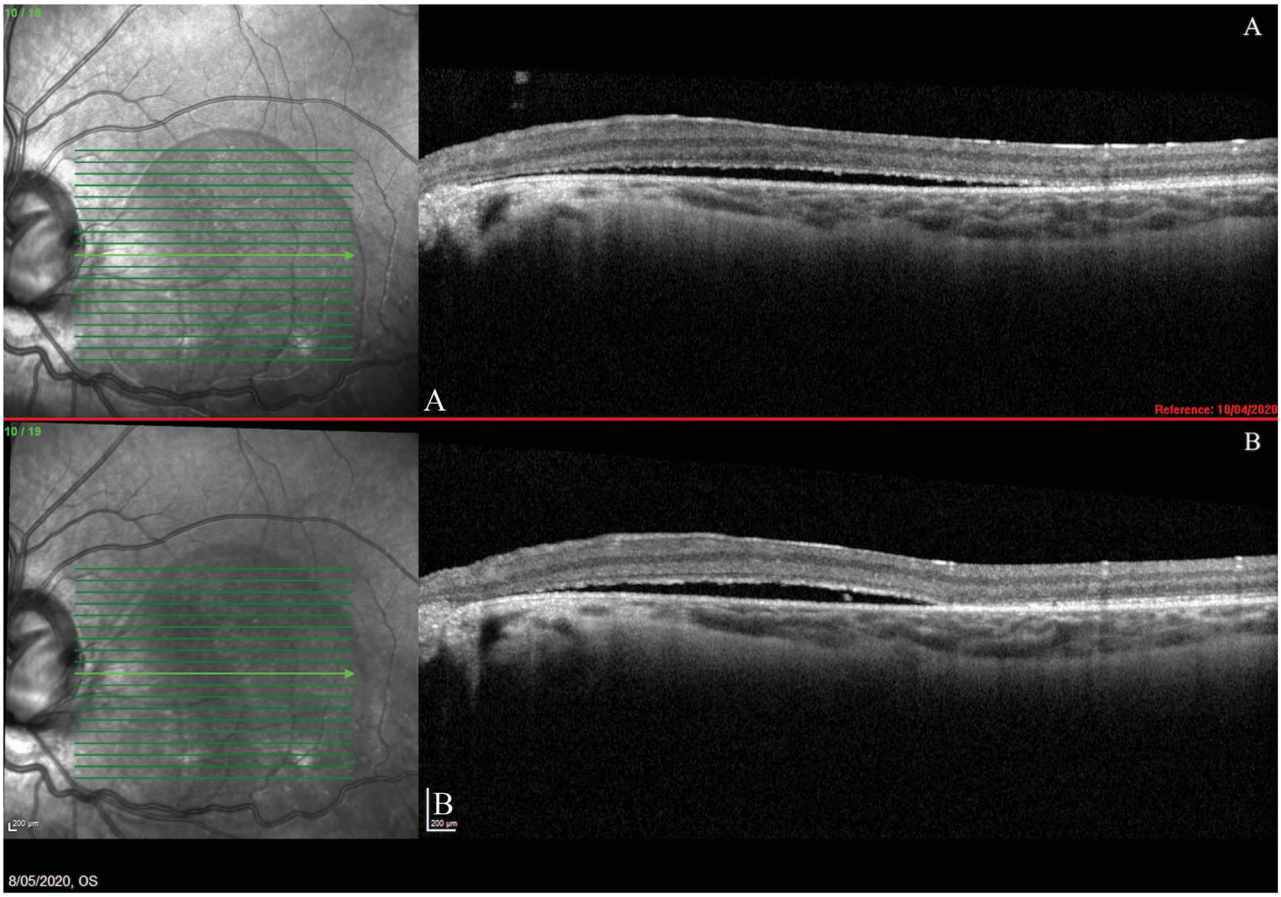

Fig. 4. Postoperative OCT images at (**A**) 1 week after surgery and (B) 1 month after surgery showing progressive decline in subretinal fluid.

acuity. Therefore, after one year of conservative treatment and 2 months of oral treatment with acetazolamide, surgery was planned.

On 2 April 2020, 25 gauge pars plana vitrectomy (PPV) was performed to induce detachment of the posterior hyaloid to remove vitreous traction from the macula and the optic disk. 3D visualization and intraoperative OCT clearly demonstrated the connection between the macular detachment and the temporally located ODP. During fluid air exchange, aspiration over the ODP induced a decrease of the submacular fluid. Also, without further decrease of macular elevation, viscous fluid could be seen emerging from the base of the ODP during aspiration. Therefore, the origin of the subretinal fluid in this case could possibly originate, at least partly, from the subarachnoid space. Sulfur hexafluoride (SF6) 20% gas tamponade was injected at the end of surgery.

One week after surgery, a remarkable decrease of subretinal fluid was observed on OCT (Figure 4A) with the BCVA being 20/40. One month later, serous detachment decreased further, and BCVA was stable (Figure 4B). The ODP area and the remaining serous detachment are no longer connected by an isthmus of subretinal fluid. Intraretinal fluid is no longer present. Five months after surgery, the BCVA improved to 20/32, and only a limited amount of subretinal fluid was present (Figure 5).

A video of this case is provided (see Video, Supplemental Digital Content 1, http://links.lww.com/ICB/A132).

Discussion

We present the case of a 7-year-old girl with ODC in the right eye and ODP with ODP-M in the left eye. To the best of our knowledge, this is the first case describing the association between NSML and congenital optic disk anomalies. The right optic disk demonstrates a typical coloboma of the optic nerve in conjunction with a contiguous coloboma of the choroid. A fistulous tract is present extending posteriorly, simulating a second optic nerve in appearance (Figure 1A). The left optic disk demonstrates a tilted optic disk with situs inversus of the retinal vessels and an optic nerve head pit with associated serous macular detachment (Figure 1C).

Optic disk coloboma and ODP probably represent manifestations along a spectrum of cavitary optic disk anomalies, each with its own morphological definition. Both are related to imperfect closure of the embryonic fissure. Slusher et al[6] described a myriad of morphologic optic disk variations in a family of 35 members spanning five generations with an autosomal dominant inheritance pattern: ODC, ODP, and morning glory

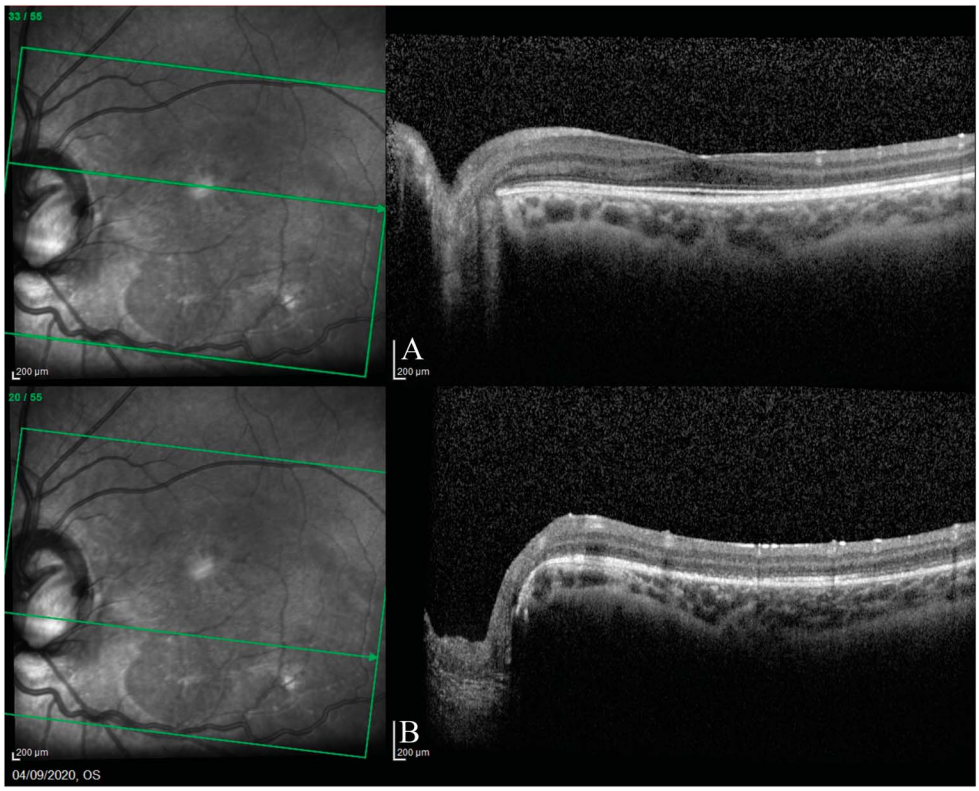

Fig. 5. OCT image 5 months after surgery. **A.** Foveal anatomy is restored, and (B) subretinal fluid has resolved.

syndrome. The rare coexistence of ODP in one eye and ODC in the other eye has been described by Abe et al.[7] In their report, ODC was associated with macular retinoschisis without serous detachment and did not require treatment.

The *PTPN11 gene* involved in this case encodes tyrosine-protein phosphatase nonreceptor type 11 (Src homology 2-containing protein tyrosine phosphatase 2, SHP2), which is required during development and regulates cell migration, proliferation, survival, and differentiation.

It would be interesting to investigate whether *PTPN11 gene* mutations could be involved in the occurrence of cavitary optic disk anomalies. Although many cases of optic disk coloboma with Noonan syndrome have been described, Vujanovic et al[8] were the first to describe the association between Noonan syndrome (which is closely related to NSML) and bilateral ODPs. Their case of Noonan syndrome also demonstrated a mutation in the *PTPN11 gene*, which is involved in 50% of Noonan syndrome cases.

The optimal treatment of ODP-M is controversial and can consist of laser photocoagulation at the temporal margin of the optic disk, intravitreal gas injection with or without laser photocoagulation (resolution of fluid in 50 - 75%), macular buckling (reported success rates up to 85% but complicated technique), and PPV (resolution of fluid in 50-95% of cases). It has been suggested that the clinical course of ODP-M is different and associated with better visual acuity in children because of spontaneous resolution.[9] Pars plana vitrectomy is currently the predominant treatment approach. Apart from posterior vitreous detachment induction, which is considered essential for relief of vitreous traction, many surgical strategies are available during PPV. These strategies include internal limiting membrane peeling, gas tamponade, sealing of ODP, laser photocoagulation, and the creation of inner retinal fenestrations.[10]

In our case, we decided to perform PPV with posterior vitreous detachment induction and SF6 gas tamponade. We did not perform laser at the temporal edge because there was still some subretinal fluid remaining at the end of the case. Moreover, laser treatment can be associated with visual field defects, and reported results are good in a high percentage of cases even without the use of laser. We did not perform internal limiting membrane peeling at this time for similar reasons.

Conclusion

To the best of our knowledge, this is the first case describing the occurrence of two unique congenital

optic disk anomalies in a patient with NSML type 1 (*PTPN11 gene* mutation): optic disk coloboma is seen in the right eye, ODP with optic disk pit-related maculopathy in the left eye. After 12 months of progressive subretinal fluid accumulation, vitrectomy with posterior vitreous detachment induction was performed in the left eye. We suggest that ophthalmic evaluation should be performed in NSML, as it is performed for the genetically closely related Noonan syndrome.

Key words: Noonan syndrome with multiple lentigines, LEOPARD syndrome, optic disk coloboma, optic disk pit, optic disk pit maculopathy, optic disk anomaly, vitrectomy.

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