Corkscrew retinal vessels and retinal arterial macroaneurysm in a patient with neurofibromatosis type 1
A case report
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Abstract
Rationale: Neurofibromatosis type I (NF-1) is a multisystem autosomal dominant disease characterized by pigmentation and the growth of tumors along nerves in the skin, brain, and other organs of the body. It is caused by a mutation in the NF-1 tumor suppressor gene. NF-1 vascular disease is an important complication of the disease.

Patient concerns: The study reports a unique case of a patient with NF-1 with 2 simultaneous vascular abnormalities, involving tiny spiral venous changes (corkscrew retinal vessels) and retinal arterial macroaneurysms. Our patient was diagnosed with NF-1 as she met the following National Institutes of Health consensus criteria for the diagnosis of NF-1: more than 6 cafe au lait macules, of a maximum diameter ≥15mm, 2 neurofibromas within the dermis, and Lisch nodules on the iris.

Diagnoses: Retinal arterial macroaneurysm in the left eye, corkscrew retinal vessels related to NF-1 and Neurofibromatosis type I.

Interventions: Due to the possibility of automatic involution of macroaneurysms, recovery may not affect vision (4). A cardiologist advised the patient to take nifedipine tablets (30mg/d) to treat her high blood pressure while continuing observation of the macroaneurysms.

Outcomes: Preretinal, intraretinal, and subretinal hemorrhage near the retinal artery aneurysm in the patient showed partial absorption at 3 months of follow-up.

Lessons: Our analysis suggests that retinal macroaneurysm formed in the patient’s body are due to neurofibroma type I secondary hypertension. The case study also indicated the symptoms of newly discovered neurofibroma type I which led to retinal microvascular abnormalities. We believe that such changes in eye blood vessels are rare and this case provides an insight to the field of neurology and ophthalmology.

Abbreviations: FFA = fundus fluorescein angiography, ICGA = indocyanine green angiography, NF-1 = neurofibromatosis type I.

Keywords: corkscrew retinal vessels, neurofibromatosis type I, retinal arterial macroaneurysm

1. Introduction
Neurofibromatosis type I (NF-1) is an autosomal dominant disease caused by a mutation in the NF-1 tumor suppressor gene.[1] It involves the nervous system, bones, skin, and other organs, and is the most common neurocutaneous syndrome.[2] NF-1 vascular disease is an important complication of the disease, although its cause remains unclear. Neurovascular abnormalities in patients with NF-1 may vary from the commonly reported involvement of large artery stenosis and aneurysms to the less commonly reported vascular abnormalities of the eye. Recent reports have described microvascular retinal abnormalities present in a helical configuration in patients with NF-1.[3]

Here, we report the unique case of a patient with NF-1 with 2 simultaneous vascular abnormalities: tiny spiral venous changes (corkscrew retinal vessels) and retinal arterial macroaneurysms. To the best of our knowledge, such fundus lesions have not been published previously.

The study was approved by the Ethics Committee of China-Japan Union Hospital of Jilin University, and written informed consent was obtained from the patient.

2. Case report
A 66-year-old woman experienced sudden reduction of visual acuity in her left eye (OS), and presented to our institution with a 3-day history of continuous loss of vision. She had cafe au lait spots on her face and body since the age of 20 years. Her cafe au lait spots were considered to be age spots and were never treated. Her son and her granddaughter also had cafe au lait spots. Her medical history included a 30-year history of hypertension and an 8-year history of hypertensive coronary heart disease, which was not formally treated.
Her corrected visual acuity was 0.8 OD and 0.04 OS. Two Lisch nodules could be seen on the iris surface, with a diameter of 0.2 and 1.0 mm. The pupils were equal in size, round, and reactive to light, without an afferent pupillary defect. Goldmann applanation tonometry readings were 14 mm Hg OD and 16 mm Hg OS. A dilated fundus examination of the right eye revealed a healthy optic nerve and clear vitreous. Vasculature showed generalized attenuation of the arteries and mild tortuosity. The macular area was flat and clear. Dilated fundus examination of the left eye revealed a healthy optic nerve and clear vitreous. The vasculature showed slight twists and turns, and extensive arterial decay. The superior temporal retinal artery could be seen to have a balloon-like dilatation, and tiny spiral venous changes (Fig. 1A, B) and preretinal, intraretinal, and subretinal hemorrhage could be seen.

Figure 1. Fundus photographs of the left eye. (A) Fundus photograph of the left eye showing preretinal retinal hemorrhage at the bottom of the optic disc 2 PD (black arrow). (B) Fundus photograph of the left eye showing a large abnormal sac expansion of the arterial vessel wall with the first branch of the superior temporal retinal artery, as well as intravascular coagulation. Around the saccular expansion of the arterial vessel wall, deep bleeding can be seen in the retina, which also extends to the macular area (white arrow).

Fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) showed tiny veins twisted into a spiral shape (corkscrew retinal vessels), and a clear circular artery fluorescence accumulation area with subretinal hemorrhage, which was thought to be consistent with a retinal artery aneurysm (Fig. 2A–C). Optical coherence tomography revealed disappearance of the macular fovea of the left eye, macular edema, and mild detachment of the neurosensory retina. Eye-color-Doppler ultrasound revealed that the papillary temporal wall of the left eye was visible, 0.48 ± 0.25 × 0.26 cm. Uplift and slightly echogenic, with a clear boundary, and a visible blood-flow signal at the base. A systemic examination of the patients showed multiple cafe au lait spots, some spots with a diameter >1.5 mm, on the face and back. Two nodular, subcutaneous, and palpable masses were seen on her neck. The nodular masses were of different sizes, were longitudinally connected, and had a tough texture, smooth surface, and no tenderness. Her laboratory test data were as follows: triglycerides 2.54 mmol/L, fasting blood glucose 5.77 mmol/L, and blood pressure 178/93 mm Hg. She reported that she did not regularly use medication for high blood pressure. She refused to undergo renal artery ultrasonography and head magnetic resonance imaging for economic reasons.

Based on the above-mentioned findings and observations, we diagnosed retinal arterial macroaneurysm in the left eye, and corkscrew retinal vessels related to NF-1. Due to the possibility of automatic involution of macroaneurysms, recovery may not affect vision (4). A cardiologist advised the patient to take nifedipine tablets (30 mg/d) to treat her high blood pressure while continuing observation of the macroaneurysms. Peraretinal, intraretinal, and subretinal hemorrhage near the retinal artery aneurysm in the patient showed partial absorption at 3 months of follow-up.

3. Discussion

Cafe au lait macules, intertriginous freckling, Lisch nodules, and neurofibromas are often seen in patients with NF-1.[4] Our patient was diagnosed with NF-1 as she met the following National Institutes of Health consensus criteria for the diagnosis of NF-1: more than 6 cafe au lait macules, of a maximum diameter ≥15 mm, 2 neurofibromas within the dermis, and Lisch nodules on the iris.

The NF-1 is an autosomal dominant disorder caused by a mutation of NF-1 located on the long arm of chromosome 17 (17q11.2). [5] NF-1 encodes neurofibromin, a tumor suppressor protein that is widely expressed throughout human blood vessels. [6] Loss of function of neurofibromin is associated with endothelial proliferation, degeneration, healing, smooth muscle loss, and fibrosis leading to arterial stenosis or aneurysm in patients with NF-1. [7] Aneurysms found in NF-1 are mainly cystic aneurysms, similar to the distribution seen in the general population. [8] One of the more common vascular conditions in NF-1 is hypertension. [9] Hypertension is a major risk factor associated with retinal arterial macroaneurysms. [10] About 75% of hypertensive patients may develop macroaneurysms. [11]

Tiny venous helical changes are also known to be NF-1-associated retinal vascular abnormalities. Muci-Mendoza et al. [3] reported new retinal findings in NF-1: unique microvascular abnormalities, which have a spiral appearance in the retina. Most of the abnormalities are limited to small veins that are easily overlooked. Fluorescein angiography enhances this abnormality, but does not show leakage of the stain.

It is rare to find 2 types of ocular vascular abnormalities in patients with NF-1, such as those we describe here. In our patient, we observed hypertension, macroaneurysms, and small retinal venous changes. These changes are associated with NF-1. FFA and ICGA revealed that contrast agent entered the tumor via the superior temporal artery of the retina. Initially, the contrast agent was masked by intravascular coagulation, but subsequently, the contrast agent accumulated into an oval-shaped fluorescent region, which is consistent with the angiographic features of macroaneurysms. We also observed the unique spiral-shaped tiny retinal blood vessels described by Muci-Mendoza et al. [5] Our experience with FFA was the same as that reported earlier, in that it enhanced the abnormality, but did not show stain leakage.
Figure 2. Fundus fluorescein angiography and indocyanine green angiography. (A) In the early phase, the fluorescein angiogram shows a saccular macroaneurysm at the bifurcation of a first-order artery of the superior temporal retinal artery; the lesion irregularly fills with dye immediately after filling the retinal artery. (B) Tiny spiral venous changes in the first branch of the superior temporal retinal venous, and macular microvascular bending can be seen. (C) Macroaneurysm showing hemorrhage at the subretinal and prehyaloid levels. In the late phase, the mass lesion shows intense hyperfluorescence due to leakage and pooling of the dye.
We believe that formation of the retinal macroaneurysm was mainly due to the patient’s high blood pressure, which is a complication of NF-1. The retinal microspiral venous changes and retinal arterial macroaneurysms occurred in the same quadrant of the vascular cross-site, and thus whether these 2 vascular changes are independent or are related to each other requires further study. The coexistence of these different types of vascular lesions associated with NF-1 further supported the association between retinal vascular abnormalities and NF-1. The primary goal of treatment is to prevent aneurysm rupture and avoid secondary vitreous hemorrhage. Laser photocoagulation of the retina can help in accelerating the absorption of retinal hemorrhage.

Author contributions
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