• Letter to the Editor •

Vitreous amyloidosis caused by Lys55Asn mutation in TTR with peripheral neuropathy onset: a case report of FAP-related complications

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Received: 2024-03-27 Accepted: 2024-05-30

DOI:10.18240/ijo.2025.01.24

Citation: Xue YW, Xiao YQ. Vitreous amyloidosis caused by Lys55Asn mutation in TTR with peripheral neuropathy onset: a case report of FAP-related complications. *Int J Ophthalmol* 2025;18(1):184-186

Dear Editor,

We present a case of vitreous amyloidosis in a patient who was previously confirmed as familial amyloidosis polyneuropathy (FAP) because of peripheral neuropathy symptom onset. Even though the patient had already undergone liver transplantation 5y prior, the extracellular deposition of amyloid in vitreous body greatly infected the patient's visual function. FAP is a rare inherited disorder with variable expressivity characterized by the accumulation of amyloid in peripheral nerves and the involvement of several organs and tissues, including the eye[1]. In hereditary amyloidosis, the accumulation of transthyretin (TTR) variants is the most common cause of amyloidosis and can result in progressive polyneuropathy[2]. This is a rare case in which FAP patients with Lys55Asn mutations had obvious peripheral neuropathy, especially five years after liver-transplant treatment. Hence, examining ocular manifestations accompanied by rare neuropathies such as FAP may be valuable. This study was conducted in compliance with the tenets of the Declaration of Helsinki. Written informed consent to publish this case report has been obtained from the patient(s).

A 60-year-old woman came to our ophthalmology clinic complaining of gradual vision loss, especially in the left eye, during the past half-year. She presented with numbness and weakness in four limbs six years ago and was ultimately diagnosed with FAP. Electromyography showed motor and sensory polyneuropathy with axonal involvement. Echocardiography revealed nonobstructive hypertrophic cardiomyopathy. Considering multiple organ damage, she underwent liver transplantation in 2018 in hopes of controlling the progression of her illness.

At the time she came to our hospital, her visual acuity was 0.15 in her right eye, and counting fingers at one-foot in her left eye. Intraocular pressure was normal in both eyes. The light pupillary reflex was sensitive, and there was no sign of synechia. Slit-lamp examination after mydriasis revealed white spots similar to foot plates on the posterior surface of the lens in both eyes. The fundus examination was very blurred because of glass wool-like vitreous opacities. Eye ultrasonography revealed irregular, massive regiment opacities in the vitreous body, partly attached to the retina.

The patient first underwent 25-G pars plana vitrectomy in the left eye due to poor visual acuity. During surgery, we found severe vitreous amyloid deposition with vitreous-retinal adhesion, but no sigh of retinal detachment was found. After the vitreous was completely removed, spot-like hemorrhage could be observed in the nasal and superior retina (Figure 1).

The vitrectomy tissue samples showed positive Congo-red staining, and further exhibited apple green birefringence under polarized light (Figure 2). The patient's genetic test in 2018 revealed 2 nucleotide substitutions, c.165 G>C, and c.70-4C>G. According to past reports, the c.165 G>C is a virulence gene of FAP that replaces the protein Lys55Asn. Together with the postoperative pathological analysis, we came to a conclusion that this patient should be diagnosed with FAP complicated with vitreous amyloidosis.

FAP is a progressive autosomal dominant neurodegenerative disease. Past studies have reported more than 130 TTR mutation points, among which Val30Met comprised the largest proportion[3]. Among TTR-related FAP patients, approximately 10% have ocular complications, and the incidence of vitreous opacities in patients with different FAP genotypes varies from 5.4% to 35%. In China, TTR Gly83Arg was a mutation

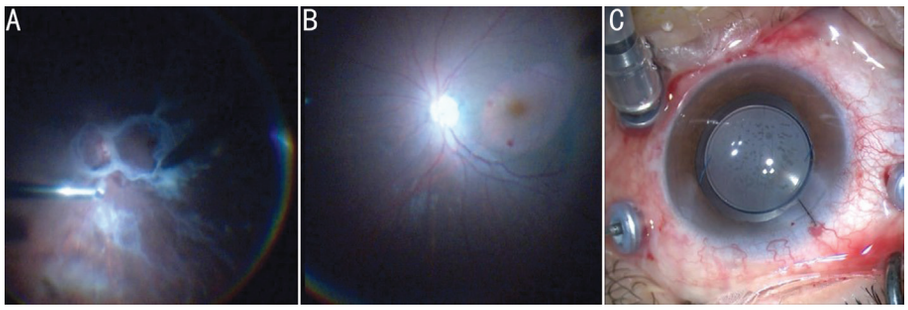

Figure 1 Images taken during the first operation A: Severe vitreous amyloid deposition with vitreous-retinal adhesion; B: Spot-like hemorrhage could be observed in the nasal and superior retina; C: White spots similar to foot plates on the posterior surface of the lens can be found in both eyes.

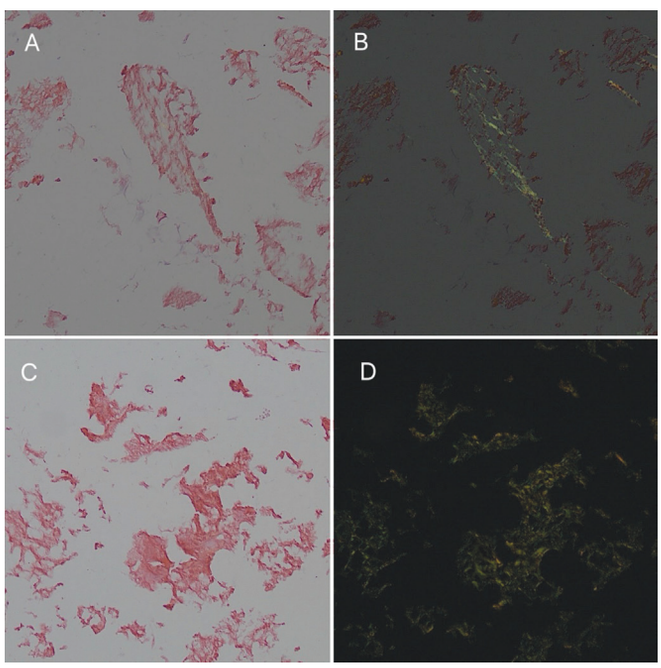

Figure 2 Histopathological examination of vitrectomy tissue samples The specimens exhibited positive Congo-red staining (A, C) and further exhibited apple green birefringence under polarized light (B, D).

specific to the Han population[4] and was mainly reported by ophthalmologists, revealing its potential connection with ocular involvement. Several cases of amyloidosis were reported, but most patients showed no sign of FAP related systemic disorders. To the best of our knowledge, our case was the first reported case of vitreous amyloidosis caused by the Lys55Asn mutation in TTR with peripheral neuropathy onset. Along with the trend toward longevity in FAP patients, complications such as vitreous amyloidosis greatly influence quality of life and need additional attention.

Since nearly 90% of TTR is synthesized in the liver, to decrease the synthesis of abnormal proteins, liver transplantation has been performed to prevent the progression of organ disturbances. However, TTR is also composed of other parts of the body, such as retinal pigment epithelium (RPE) cells and choroid plexuses. With the application of liver transplantation and emerging drugs or even gene editing therapy, the life span and pursuit of quality of life are increasing for FAP patients. Therefore, ocular manifestations have received increasing attention. Previous research initiated by Beirão *et al*[5] showed that the average duration at which FAP patients were diagnosed with vitreous opacities after liver transplantation was 7.2±3.8y. Our patient was regularly followed up for 5y after transplantation, during which time vision decreased.

Severe vitreous capacity and posterior capsule opacification greatly reduce visual acuity. Even though she has received liver transportation, the misfolded protein was still being synthesized in her eyes. During the yearly follow-up after surgery, the patient had a stable nervous and cardiac system despite her half-year history of worsening vision. The current standard treatment is surgery involving 25-gauge pars plana vitrectomy[6]. Strong attachment to retinal vessels and the posterior lens capsule increase the difficulty of performing posterior vitreous detachment during surgery, which requires meticulous surgical skills. Fortunately, the patient's visual acuity recovered to 0.4 in both eyes on postoperative day 1 and remained stable during the 5-month clinical follow-up.

Moreover, glaucoma is another common complication in FAP patients and has become increasingly prevalent, as liver transplantation allows FAP patients to survive longer[7]. Several researchers have noted that vitrectomy might increase the risk of chronic open angle glaucoma[8]. It was hypothesized that surgery may cause oxidative stress injury to the function of the trabecular mesh[9]. In particular, vitrectomy allows free circulation of mutated TTR and amyloid protofilaments in FAP patients[10], which might block the circulation of aqueous humor. Beirão *et al*[5] also noted that the number of patients who underwent complete vitrectomy and developed glaucoma was greater (58.6% *vs* 10.5%) and that the duration of complete vitrectomy was greater (8.0±3.6 *vs* 39.5±6.6mo) than that of incomplete vitrectomy. In our case, the intraocular pressure in both eyes was under control before and after surgery. Five months after her first surgery, her intraocular pressure in her left eye was 16 mm Hg. According to previous

research, long-term follow-up should be performed to achieve early detection and early treatment.

Here we report a patient with bilateral vitreous opacities secondary to FAP with nervous and cardiac system symptoms 5y after liver transplantation. According to the patient's genetic analysis, we speculated that Lys55Asn in the TTR variant is the key mutation and has rarely been reported. Together with the Congo-red stain, we diagnosed the patient with vitreous amyloidosis. Complete 25-G vitrectomy was given to the patient in both eyes, and her visual acuity recovered to 0.4 ocular uterque (OU) soon after surgery. During the postoperative follow-up, the intraocular pressure of both eyes has been stable, indicating no signs of secondary glaucoma. This is a rare case of a FAP patient with a Lys55Asn mutation who had obvious peripheral neuropathy, especially 5y after liver-transplant treatment. Hence, examining ocular manifestations accompanied by rare neuropathies such as FAP may be valuable.

ACKNOWLEDGEMENTS

Conflicts of Interest: Xue YW, None; **Xiao YQ,** None.

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