Added value of newer optical coherence tomography technologies in hyperphosphatemic familial tumoural calcinosis

In contrast to dystrophic calcification seen in several rare genetic disorders, such as pseudoxanthoma elasticum, generalized arterial calcification of infancy, and Keutel syndrome, hyperphosphatemic familial tumoural calcinosis (HFTC) is a rare disorder of phosphate metabolism characterized by hyperphosphatemia and primary ectopic or metastatic calcifications in various locations.[1]

A recently published review reported eye involvement in 16% of cases having this disorder.[2] Ocular involvement includes calcifications on the eyelids, conjunctiva, and peripheral cornea; optic nerve head drusen (ONHD); and angioid streaks (AS).[3–5]

The presence of ONHD and AS in HFTC was first described by Ghanchi et al. in 1996.[6] More recently, Pomerleau et al. reported a new case with these associated findings.[5]

We describe 2 cases of HFTC with AS and ONHD. Newer technologies such as EDI-OCT and SS-OCT provide further information regarding the extent and characteristics of both ONHD and AS.

Case Report

We present the cases of 2 siblings with HFTC and a mutation in the *GALNT3* gene. Their parents and 2 other siblings were phenotypically normal.

Case 1 (46-Year-Old Female)

This patient was diagnosed with HFTC in childhood due to calcified lesions in the para-articular regions. Laboratory evaluation revealed hyperphosphatemia (6.4 mg/dL). Serum calcium, parathyroid hormone (PTH) levels, 1,25-dihydroxyvitamin D levels, and renal tubular phosphate reabsorption were within normal limits.

Best-corrected visual acuity (BCVA) was 20/20 OU. Anterior segment examination revealed calcified deposits on conjunctiva and peripheral cornea.

Fundus examination showed prominent ONHD and discrete AS OU (Fig. 1A). Autofluorescence (AF) showed the typical hyperfluorescence pattern of ONHD more clearly than found on clinical examination (Fig. 1B). SwedIsh Interactive Thresholding Algorithms (SITA) fast

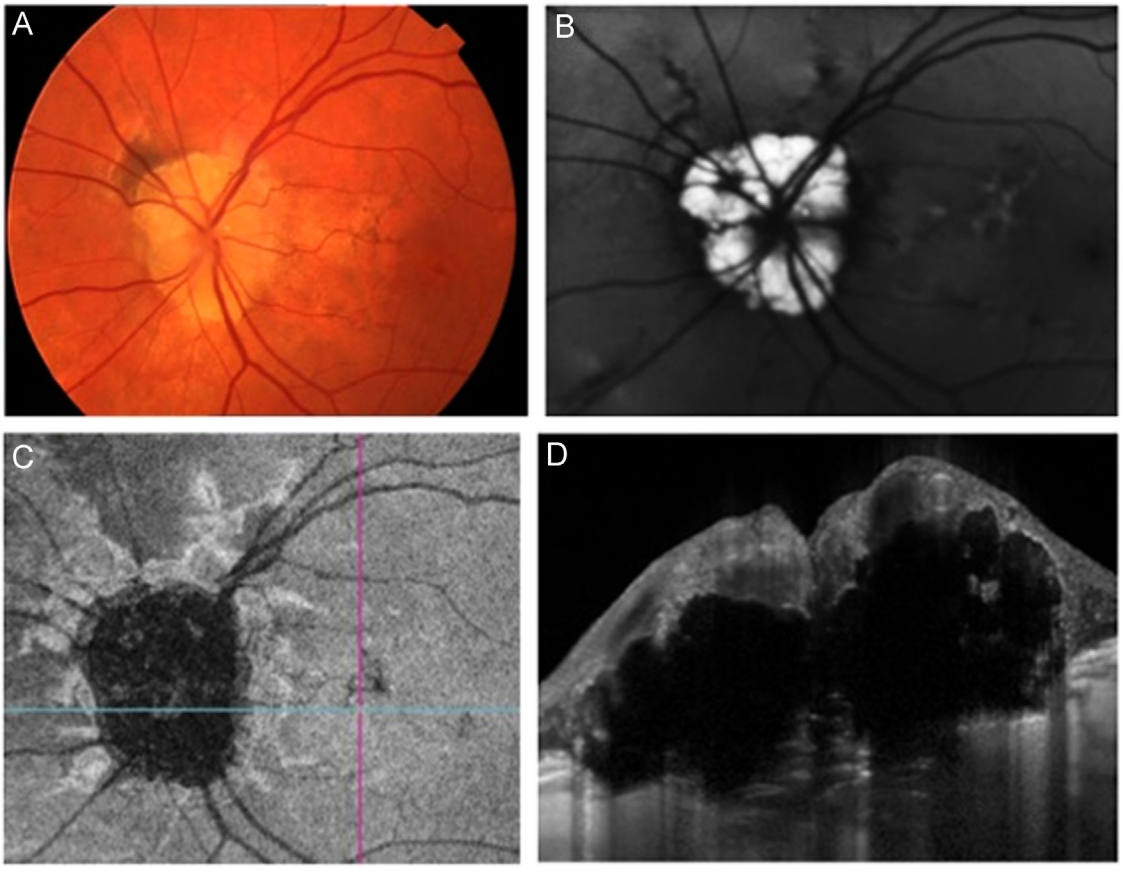

Fig. 1—Case 1. (A) Fundus photograph of the left eye showing optic nerve head drusen. (B) Autofluorescence of the left eye showing the typical hyperfluorescence pattern of optic nerve head drusen. (C) En face swept-source optical coherence tomography showing the hypoautoflorescence pattern of angioid streaks originating at the optic disc and radiating out toward the periphery. (D) Enhanced depth imaging optical coherence tomography showing optic disk drusen as ovoid regions of low reflectivity with hyper-reflective curvilinear borders.

24-2 Humphrey visual field (HVF) testing showed an enlarged blind spot OD and an inferior arcuate scotoma OS. En face imaging by SS-OCT more clearly delineated the AS, which originated at the optic disk borders as hyporeflective linear cracks (Fig. 1C). EDI-OCT revealed the substantial volume occupied by ONHD within the optic canal OU (Fig. 1D).

Case 2 (48-Year-Old Male)

The second patient was the oldest of 4 siblings and was diagnosed with HFCT due to intracraneal calcifications. He had an elevated serum phosphate level (6.4 mg/dL) and elevated RPTR levels (95.25%) with normal serum calcium, PTH, and 1,25-dihydroxyvitamin D levels.

BCVA was counting fingers OD and 20/20 OS. Slit-lamp examination revealed conjunctival and limbal calcified deposit (Fig. 2A). A macular fibrotic membrane secondary to a choroidal neovascular membrane (CNVM) was present OD. Prominent ONHD and AS were present OU. HVF testing showed a central scotoma OD and no visual fied defects OS. Central scotoma OD could be explained by macular CNVM. AF and EDI-OCT findings were remarkable and similar to the aforementioned for his sister (Fig. 2B–D).

Discussion

HFTC is associated with autosomal recessive mutations in 3 different gene regulators of phosphate metabolism (*FGF23, GALNT3,* and *KL*), leading to reduced levels of fibroblast growth factor 23 (FGF23) and soft tissue calcifications. Although hyperphosphatemic hyperostosis syndrome (HHS) was thought to be a separate disease, both HHS and HFTC share the same genetic defects and mutations, currently, these disorders are considered different manifestations of the same genetic defect, and in some families the same mutation can lead to either phenotype.[2] Our patients carried a mutation in the *GALNT3* gene, which was the first gene described as responsible for the familial form of HFTC,[7] although it is rarely associated with this disease in Caucasians.[8]

Eye abnormalities are relatively common and include calcifications in various locations, such as conjunctival calcific nodules, calcific band keratopathy, ONHD, and AS.[3–5] All of these were noted in our patients (Figs. 1 and 2).

Conjunctival and corneal calcification is often located in the perilimbal region, as in our cases, and does not affect visual acuity (Fig. 2A).

ONHD are deposits of calcium buried or at the surface of the optic disc. Methods for detecting and imaging disc

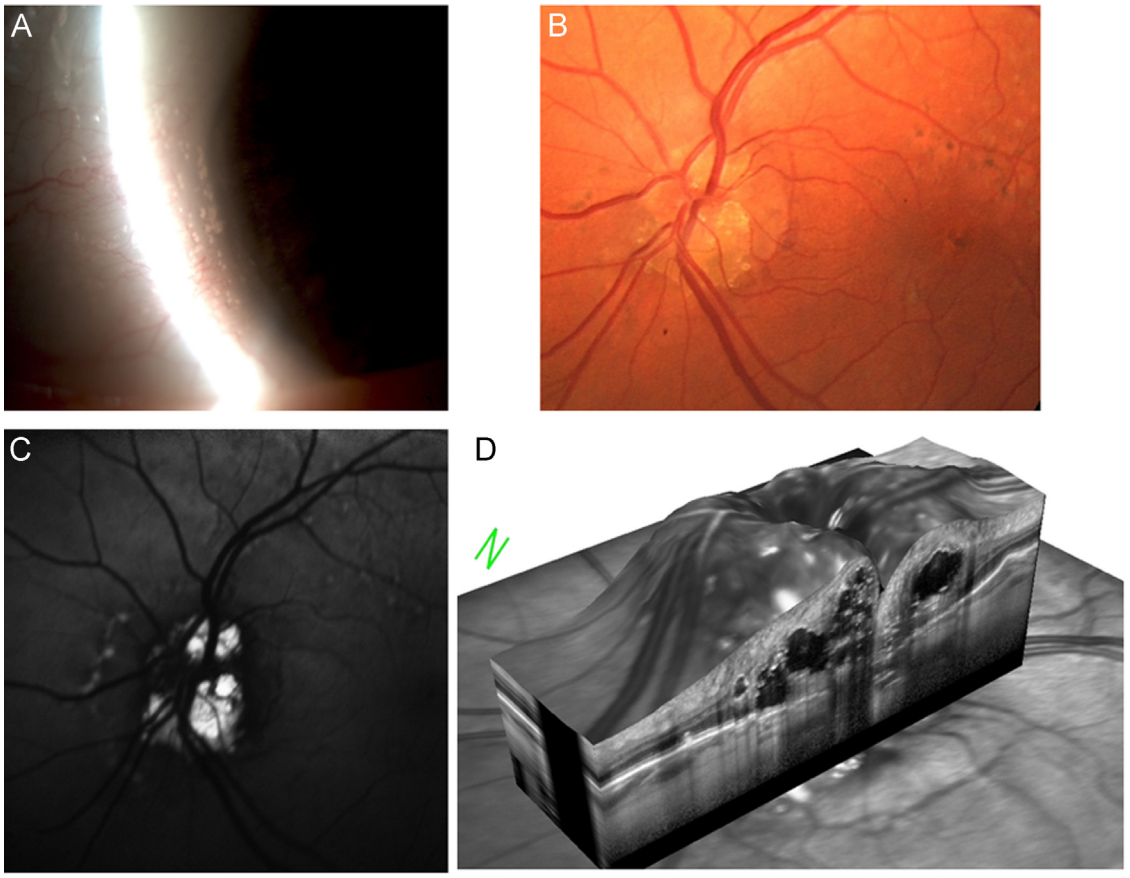

Fig. 2—Case 2. (A) Slit-lamp examination showing conjunctival and corneal calcification located in the perilimbal region. (B) Optic nerve head drusen in a colour fundus photograph of the left eye. (C) Hyperfluorescence pattern in the left eye corresponding to optic nerve head drusen seen in autofluorescence. (D) 3D view of optic nerve head drusen using enhanced depth imaging optical coherence tomography.

drusen include B-scan ultrasonography, fundus AF, and OCT. These modalities are limited by low resolution or poor penetration of deep structures. Sato et al.[9] demonstrated that EDI-OCT had a high ability to detect ONHD, obtaining images of the posterior limits of disc drusen and measuring drusen area. Undoubtedly EDI-OCT provides more information regarding the shape, structure, and extent of disc drusen than AF, which may have implications for visual function. Larger ONHD and those described as confluent hyporeflective structures are more commonly found in patients with visual field defects.

In the current cases, ONHD were visible as ovoid regions of low reflectivity with hyper-reflective curvilinear borders and as clustered hyper-reflective bands (Fig. 1D). Apart from these poor signal regions, the shape and structure of associated deeper drusen were also detected by OCT, as well as isolated and/or clustered hyper-reflective bands without a poor signal core.

AS are bilateral, usually asymmetric, linear breaks in the areas of calcification of the Bruch's membrane originating at the optic disk and radiating out toward the periphery. Most are idiopathic, with 50% of cases associated with a specific systemic disease such as pseudoxanthoma elasticum, Paget's disease, Ehlers-Danlos syndrome, and HFTC.[5] They show a typical hypoautofluorescence pattern in autofluorescence imaging (Figs. 1B and 2C).

The AS pattern yielded by en face SS-OCT correlated with the hypoautoflorescence pattern (Fig. 1C). The visualization of AS originating at the optic disk is clearly improved with this technology. Both location and size of ONHD within the optic disc may change over time and affect the risk of visual field defect.

In conclusion, new imaging technologies, such as EDI-OCT, provide a means to quantify ONHD dimensions and examine the integrity of neighbouring structures in the retina and optic disc. These devices therefore provide the potential to better understand the relationships between disc drusen, RNFL loss, and visual field defects. They also provide a means to allow longitudinal assessment of drusen and may help to identify risk factors associated with drusen-related visual field loss, providing prognostic information.

En face SS-OCT provides better definition and more detailed information on AS than noninvasive AF or clinical examination; therefore, these image modalities can be helpful in expanding our knowledge on ONHD and AS. Although there is no treatment for drusen-related visual field loss, improved understanding of the mechanism of neuronal damage through enhanced imaging may lead to developments in this area.

Although rare, HFTC should be considered in the differential diagnosis of ONHD, especially when associated with AS.

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References

1. De Vilder EY, Vanakker OM. From variome to phenome: pathogenesis, diagnosis and management of ectopic mineralization disorders. *World J Clin Cases*. 2015;3:556-74.
2. Rafaelsen S, Johansson S, Ræder H, Bjerknes R. Long-term clinical outcome and phenotypic variability in hyperphosphatemic familial tumoral calcinosis and hyperphosphatemic hyperostosis syndrome caused by a novel GALNT3 mutation; case report and review of the literature. *BMC Genet*. 2014;15:98.
3. Li Voon Chong SW, Ah Kion S, Cullen MJ. A report of familial hyperphosphataemia in an Irish family. *Ir J Med Sci*. 1999;168:262-4.
4. McPhaul JJ Jr, Engel FL. Heterotopic calcification, hyperphosphatemia and angioid streaks of the retina. *Am J Med*. 1961;31:488-92.
5. Pomerleau D, Roe RH, McDonald HR, et al. Angioid streaks and optic nerve head drusen in hyperphosphatemic familial tumoral calcinosis. *Retin Cases Brief Rep*. 2009;3:54-6.
6. Ghanchi F, Ramsay A, Coupland S, Barr D, Lee WR. Ocular tumoral calcinosis. A clinicopathologic study. *Arch Ophthalmol*. 1996;114:341-5.
7. Topaz O, Shurman DL, Bergman R, et al. Mutations in GALNT3, encoding a protein involved in O-linked glycosylation, cause familial tumoral calcinosis. *Nat Genet*. 2004;36:579-81.
8. Specktor P, Cooper JG, Indelman M, Sprecher E. Hyperphosphatemic familial tumoral calcinosis caused by a mutation in GALNT3 in a European kindred. *J Hum Genet*. 2006;51:487-90.
9. Sato T, Mrejen S, Spaide RF. Multimodal imaging of optic disc drusen. *Am J Ophthalmol*. 2013;156:275-82. e1.

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Implantation pearl cyst after uncomplicated clear cornea phacoemulsification mimicking an iris tumour

Epithelial downgrowth (ED) is a serious, although rare, complication of ocular surgery and trauma that can result in irreversible vision loss.[1–6] In the ocular surgery group, cataract surgery, especially in the extracapsular era, accounted for 86% of cases[1] related to vitreous loss, persistent hypotony, capsule rupture, multiple surgeries, delayed wound healing, wound fistulas, and iris incarceration. According to the literature, 82% of cases presented