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Longstanding Crystalline Retinopathy Secondary to Intravitreal Triamcinolone Injection

Abstract

Background: Crystalline retinopathy has many disparate etiologies with varying potentials in visual outcome. Due to the potential severity of these outcomes, differentiation of etiology is critical to guide both follow up and treatment regimen. Diagnosis can be facilitated with a thorough medical history, clinical presentation, and imaging such as optical coherence tomography (OCT).

Case Report: This case demonstrates a rare incidence of crystalline retinopathy in a 65-year-old male attributed to a single intravitreal triamcinolone acetonide (IVTA) injection with 8 year follow up data, followed by a review of other types of crystalline retinopathy secondary to pharmaceutical agents.

Conclusion: A complete case history, including medications, systemic disorders and surgical history are critical. Ancillary testing, such as OCT can be diagnostic. This patient's history of IVTA injection for diabetic macular edema and the OCT showing preretinal hyperreflective refractiles lead to the diagnosis of triamcinolone crystalline retinopathy.

Keywords

Crystalline retinopathy, intravitreal Kenalog/triamcinolone

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INTRODUCTION

The differentials for crystalline retinopathies secondary to pharmaceutical agents are diverse and range from oral supplements to cancer treatments.¹ In addition, crystalline retinopathies may occur due to genetic disorders, degenerative processes, or be iatrogenic.¹ Many of these cause a chronic yet benign presentation, while others lead to decreased vision secondary to retinal edema or atrophy. Visual outcome and possible treatment of crystalline retinopathy varies depending upon etiology. Thorough clinical case history including medication review, fundoscopic examination, and multimodal imaging can differentiate pathologies. One potential etiology of crystalline retinopathy is triamcinolone (Kenalog) which was first detailed in 2010 after intravitreal injections for macular edema and, to date, few studies have monitored for potential long term sequelae.² This paper will review a case of crystalline retinopathy secondary to one intravitreal injection of triamcinolone while also reviewing and highlighting contrasting features of differential medication related crystalline retinopathies.

CASE REPORT

A 65-year-old African American male presented for an annual diabetic eye exam. He reported that he had been diagnosed with type 2 diabetes in 1997 and is currently treated with insulin. His fasting glucose was unknown; however, his hemoglobin A1c had been measured earlier that week at 9.6%. The patient also had a positive history of hyperlipidemia, treated with atorvastatin, and hypertension, treated with carvedilol, hydrochlorothiazide, and losartan. His only known medical allergy was lisinopril. He reported a limited surgical history consisting of intravitreal injection procedures. Ocular history was remarkable for refractile retinal deposits and a misdiagnosis of asteroid hyalosis. This was first clinically noted in 2012 and photographed in 2014. During the 2011 exam, the patient's best corrected visual acuity had dropped from 20/20 right eye (OD) and left eye (OS) to 20/25 OD and OS with clinically significant macular edema, as well as exudates and microaneurysms within 500um of the fovea. Macular optical coherence tomography (OCT) confirmed swelling which was treated with a single dose of intravitreal triamcinolone OD. Further treatment was required with intravitreal ranibizumab OS between 2011 and 2014 for the development of diabetic macular edema. The crystals appeared no earlier than 2014, as evidenced by fundus photos in **Figure 1**.

At the present visit, visual acuities were 20/20-1 OD and OS. Entrance testing was unremarkable. Intraocular pressures were measured as 21/19 mm Hg OD/OS with applanation tonometry and slit lamp examination was within normal-limits.

Both optic nerves were pink and distinct with a cup to disc ratio of 0.30 in each eye. The macula of the right eye was remarkable for yellow crystalline deposits which were absent from the left eye, as shown in **Figures 1 and 2**. There were isolated scattered microaneurysms just beyond the arcades in both eyes. The peripheral retina was unremarkable in both eyes.



Figure 1: Multi-color photos obtained with Heidelberg OCT in October 2019 show crystalline deposits throughout the macula OD which are absent OS. The central white dots are artifacts OU



Figure 2: Baseline fundus photo with a Topcon retinal camera from 2014 showing peri-foveal refractile yellow deposits OD

The photos of the posterior pole were obtained (**Figure 1**) to compare to baseline photos from 12/30/14 (**Figure 2**) and showed grossly stable crystalline deposits OD with slight migration of crystals. Macular OCT (Heidelberg) showed small cystic pockets of edema near the fovea OS (not pictured) and was also remarkable for hyperreflective crystalline deposits on the posterior hyaloid face of the vitreous OD (**Figure 3**). Most of the crystals were still flush with the surface of the internal limiting membrane (ILM) but followed the vitreous in areas of early vitreous detachment (**Figure 4**). The crystals were also visible in black and white photos (**Figure 5**).

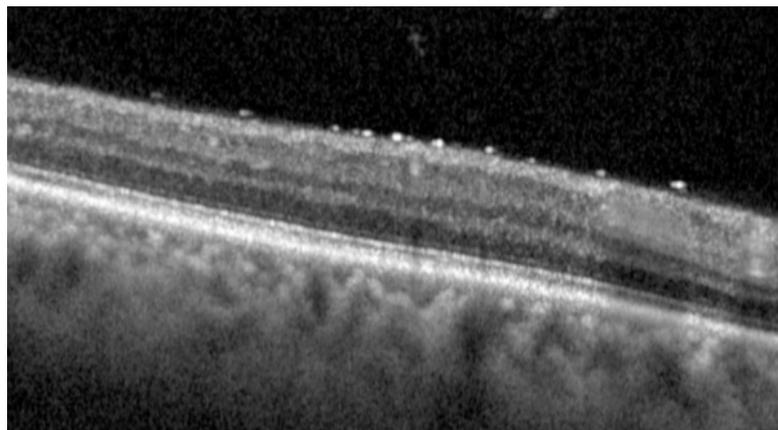


Figure 3: Heidelberg Spectralis SD-OCT raster scan showing hyperreflective crystalline deposits on the innermost surface of the retina

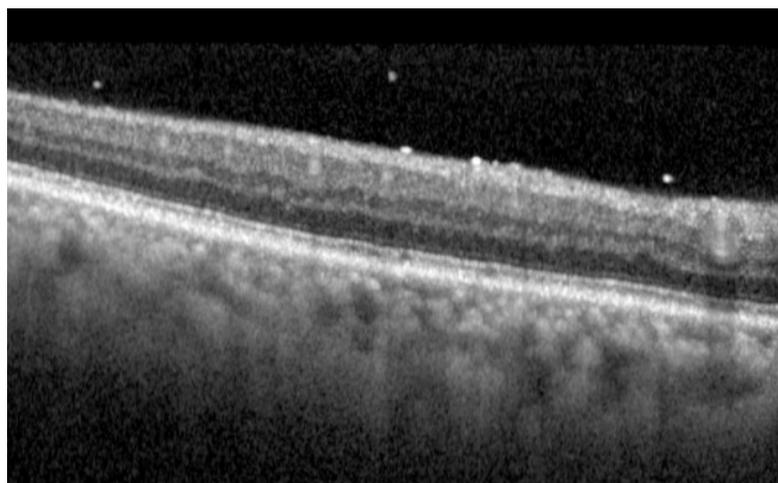


Figure 4: Heidelberg Spectralis SD-OCT raster scan showing hyperreflective crystalline deposits on the posterior hyaloid face

Due to poor control of his blood sugar and diabetic macular edema OS, the patient was referred to a retinal specialist for further intervention. While the crystals OD can be clearly observed in previous fundus photos, they had been mentioned only as a secondary clinical finding, without determination of etiology. The patient also had a history of being misdiagnosed with asteroid hyalosis. Diagnosis of crystalline retinopathy secondary to triamcinolone was made due to the unilaterality and location of the crystals on OCT combined with the patient's medical history of intravitreal injection OD. This was supported by the stability of findings and excellent visual acuity, and as such was monitored on an annual basis.

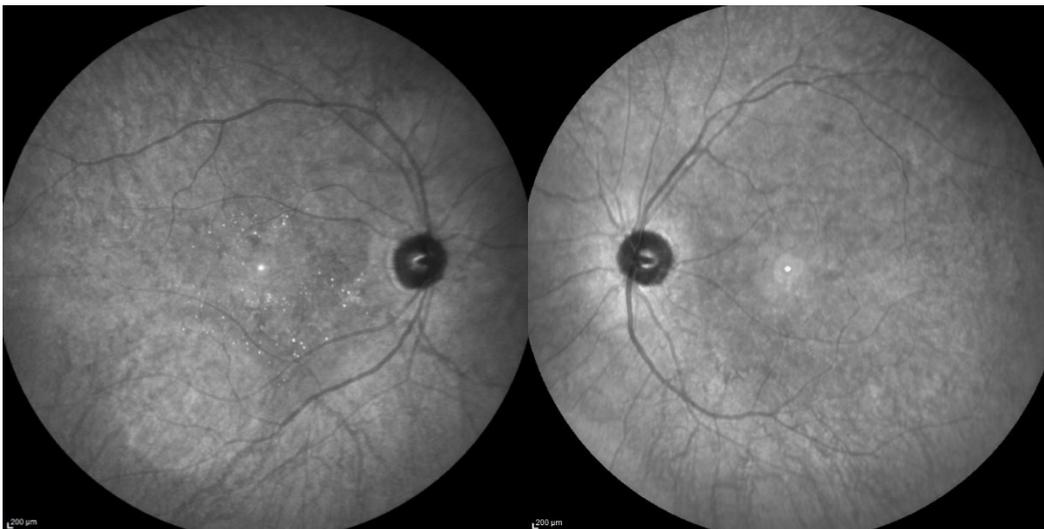


Figure 5: Photos showing crystals OD; the white central dot OU and inferior temporal circular hypopigmentation OD are artifacts

DISCUSSION

Many forms of crystalline retinopathy have a similar fundoscopic appearance, making them difficult to distinguish without ancillary testing (**Table 1**). Case history is critical, particularly regarding past and present medications and systemic disorders. Imaging techniques are important as well to determine etiology. In fact, OCT pinpoints the precise location of the crystals, which can vary depending on the underlying cause.¹ However, some disorders are associated with vascular disturbances, and are best appreciated with forms of angiography such as fluorescein angiography.¹

Triamcinolone (Kenalog) is a steroid indicated to treat chronic cystoid macular edema (CME) as seen in diabetic patients or after cataract extraction.³⁻⁵ Triamcinolone maculopathy is one form of medication induced crystalline

retinopathy. While supported in clinical literature, there is only a small body of research concerning the long-term effects of this retinopathy. Two reports detail six or greater years of follow up data and stability.^{6,7} This case provides further documentation and confirms the limited body of longitudinal case reports of crystals lingering for at least eight years after a single intravitreal triamcinolone acetonide (IVTA) injection. These findings were first documented in 2010 to be superficial and refractile in nature, distributed asymmetrically and clustered around the macula, often with foveal sparing.² The annular distribution likely follows the anatomy of the bursa premacularis, a fluid channel in the vitreous anterior to the macula, which sequesters the crystals centrally.^{7,8} Multiple sources agree that crystals can present after both preserved and non-preserved formulations.^{1,2,6} Crystals can appear anywhere between 7-48 months after injection, and have been previously documented to remain for at least six to nine years.^{6,7} The long term presence of crystals is surprising, as the half-life of triamcinolone is only 3-18 days and the drug should be entirely eliminated by 3 months. Fine et al hypothesized that these preretinal crystals unexpectedly persist due to being sequestered within the bursa macularis. This positioning would also explain crystal migration due to changes in the posterior hyaloid over time.⁷

Ancillary testing reveals crystals to be isofluorescent upon both auto-fluorescence and fluorescein angiography; no vascular defect is characteristic with this maculopathy.^{2,7} Macular OCT shows preretinal refractiles on the posterior hyaloid face following posterior vitreous detachment or on the retinal surface, as above, unlike most other forms of this retinopathy.^{1,2} Crystals may slowly migrate over time and remain attached to the vitreous when it detaches from the retina. In eyes that have had pars-plana vitrectomy and subsequent IVTA, crystals have been documented to coalesce along the retinal vasculature, simulating frosted branch retinal angiitis.⁹ Given the consistent lack of adverse effects that define retinopathy, it has been recommended by some that this condition be known as “drug-induced benign crystalline hyaloidopathy”.⁶

Tamoxifen is a nonsteroidal estrogen receptor antagonist used to treat breast cancer that can cause crystalline retinopathy. However, complications are more common with higher doses, which can occur in patients being treated for brain cancer, or with long-term use to prevent relapse. This is most commonly seen when the cumulative dose reaches 100g.¹⁰⁻¹² Higher doses are more likely to cause crystalline retinopathy and CME, which is associated with decreased visual acuity.^{11,13,14} Retinopathy is less common now that the standard dosage has been lowered to <20mg/day; however, lower doses may still lead to pseudocystic cavitation within the central macula, which can progress to form a macular

hole.^{10,13,15} Other less common complications include keratopathy, cataract, and optic neuritis.¹⁵⁻¹⁹

Medication	Appearance	OCT location	Outcome
Triamcinolone	iridescent crystals with perifoveal distribution	posterior hyaloid face	benign
Tamoxifen	fine crystals in dense peri-foveal ring	NFL, IPL, CME common	Fair after CME resolves
Anastrozole	Gold parafoveal crystals	OPL, INL	mild VA decrease
Methoxyflurane	crystals following arteries throughout retina	RPE	irreversible
Allopurinol*	likely benign yellow dot retinopathy	isofluorescent	temporary
Flupentixol [^]	crystals throughout posterior pole	IPL	mild VA decrease
Nitrofurantoin [^]	circinate crystals throughout posterior pole	superficial and deep intraretinal layers	mild VA decrease
Ganciclovir [^]	Yellow perifoveal crystals	no data	poor due to intravitreal overdose
Canthaxanthin*	annular, perifoveal distribution of yellow crystals	IPL, NFL	benign, temporary
Lutein [^]	yellow foveal crystals	inner retinal layers	benign
Talc	intra-arterial crystals in posterior pole	inner retinal layers	typically benign; can cause atrophy

Table 1: summary of fundus appearance, OCT findings, and outcome; * Disputed, [^]Atypical

Tamoxifen is also likely to worsen type 2 macular telangiectasia as discussed by Behrens et al, who recommend not treating these patients with tamoxifen. Behrens et al theorized that this effect could be due to multiple factors that result in destruction of Müller cells, which have a significant role in retinal structure and function.^{18,19} Patients being treated with tamoxifen should have a baseline eye exam and be followed at least every two years.¹⁷ If retinal changes are observed,

discontinuation of tamoxifen should be discussed with the prescribing provider. After discontinuation, both keratopathy and CME have been shown to resolve, though crystals remain. However, some reports indicate that the crystals may decrease in density with time.^{12,14} OCT testing is beneficial, showing hyper-reflective refractiles in both the nerve fiber layer (NFL) and inner plexiform layer (IPL).¹⁶ FA will show hyperfluorescence of pseudocystic cavitation or CME. FA damage has been attributed to retinal pigmented endothelial loss as well as Müller cell loss.¹

Anastrozole is an oral nonsteroidal aromatase inhibitor used in the treatment of breast cancer with documented ocular side effects including retinal hemorrhages, bilateral optic disc swelling, vitreo-retinal traction, dry eyes and possibly uveitis and macular edema.²⁰ There is a case report by Weider et al of a patient reporting blurry vision after treatment with 1 mg/day of anastrozole. The patient was found to have isofluorescent crystalline deposits at the outer plexiform layer (OPL) and inner nuclear layer (INL). These crystals presented earlier than those observed from tamoxifen, at six months rather than twelve months.²⁰ Vision and macular appearance were unchanged at the six month follow up.

Methoxyflurane is an anesthetic that can cause crystalline retinopathy, however it is rarely used due to a high risk of kidney damage.¹ Crystals typically follow along the arterial or periarterial vasculature throughout the posterior pole at the layer of the retinal pigmented epithelium (RPE) rather than concentrating at the fovea.¹ This maculopathy is not reversible and vision changes are permanent.¹

Other medications have limited case reports of crystalline retinopathy due to atypical use. Allopurinol is used to reduce uric acid levels in chemotherapy patients, as well as the treatment of gout and kidney stones.^{21,22} A single case report from Cheah et al. detailed a patient with crystalline retinopathy secondary to allopurinol. However, there are no other reported cases and the medication is commonly prescribed.²¹ Dohaney et al. have suggested that this was actually “benign yellow dot maculopathy” as there are no corresponding changes on the OCT.²² There are limited reports of crystalline retinopathy secondary to flupentixol, nitrofurantoin, and ganciclovir. These are rare cases due to unusually high doses of the medication and have not been documented with standard use. Flupentixol, an antipsychotic, caused crystalline deposits throughout the posterior pole, when a patient consumed more than double the maximum recommended dose for two full years. These crystals were localized on OCT at the IPL.^{23,24} Nitrofurantoin is used to treat and prevent urinary tract infections.^{16,25} It more commonly causes extra-ocular motility imbalance, retinal hemorrhaging, and papilledema. It has also been documented to cause intraretinal crystals in a

circinate pattern about the macula, associated with decreased visual acuity.^{1,25} This occurred after using 100mg of nitrofurantoin for at least 19 years.²⁵ Overdose of intravitreal ganciclovir has also been documented to cause toxic crystalline retinopathy. A patient erroneously received 15mg/0.3mL instead of 2mg/0.04mL, a dose 8x larger than intended.²⁶ The patient experienced acute and permanent vision loss with no light perception. Immediate fundus examination revealed crystalline retinopathy.²⁶

Oral supplements have been reported to cause crystalline retinopathy. Canthaxanthin or β -carotene is a naturally occurring carotenoid used as a red dye. Pharmacologically, it has also been used to treat photosensitivity or as a supplement to increase sun-tanning.¹⁶ The Food and Drug Administration (FDA) does not approve any oral supplements for sun tanning, including the supplementation of canthaxanthin; it is only approved in small doses as a color additive in food.²⁷ It has been documented to cause yellow perifoveal crystals at the level of the IPL/NFL,^{16,17,28,29} with conflicting reports as to whether crystals diminish after cessation.^{16,28} Patients are asymptomatic and there is no associated decrease in visual acuity. There is a positive correlation between cumulative dose and retinopathy at a dose of >3mg.¹⁶ However, others refute the claim that canthaxanthin is the cause of this retinopathy and were unable to replicate the findings in subsequent case studies.³⁰ There is also a case report of crystalline retinopathy occurring after high doses of lutein supplementation. Choi et al reported a patient intaking at least three times the normal dosage of lutein secondary to 20-mg lutein supplement and a diet with an unusually high percentage of lutein rich foods. Over an eight-year time period the patient developed yellow macular crystals.³¹ Lutein is used in the AREDS 2 formulation, a supplement commonly prescribed by eye care providers for patients with macular degeneration, which includes 10mg lutein. Crystalline retinopathy has not been reported as a side effect of AREDS 2 when used at recommended doses but may be considered a differential when taken in association with extreme diets.

Talc retinopathy is characterized by small, irregular yellow refractile bodies contained predominantly in small retinal arterioles of the posterior pole.^{1,32} These particles are introduced from snorted or intravenous drug use of crushed oral medications used to make methamphetamine.^{1,33} Patients are typically asymptomatic. Talc rarely causes non-proliferative vascular changes and even more rarely causes proliferative changes that would require treatment. OCT reveals that refractiles lie within the inner retina. FA is remarkable only if there is ischemia. Chronic areas of ischemia can develop into atrophy. Particles are stationary and have not been documented to change with time.³⁴

CONCLUSION

A wide range of pharmaceuticals can cause crystalline retinopathy, with varying visual outcomes. Given this, correct differentiation is critical to determining appropriate treatment. A complete case history, including past and present medications, systemic disorders and surgical history are critical. Ancillary testing, such as OCT can be diagnostic depending on the condition. In this case, the patient's history of IVTA for diabetic macular edema and the OCT showing preretinal hyperreflective refractiles were diagnostic for triamcinolone crystalline retinopathy. This case adds to the body of literature and confirms the lone pre-existing report documenting stability of triamcinolone crystalline retinopathy over an eight-year time period. During this time period, the patient has demonstrated stable 20/20 vision OD/OS without changes to fundus appearance.

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