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Commentary

From observation to diagnosis: Implications of calcified sclero-choroidal choristomas in mosaic RASopathies

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Commentary

The identification of calcified sclero-choroidal choristomas (CaSCCs) in patients with mosaic RASopathies introduces a new dimension to understanding ocular manifestations in these genetic disorders. These findings highlight distinct clinical features that differentiate CaSCCs from traditional choroidal osteomas, as well as their shared characteristics. Based on the localization, pattern of calcification, systemic manifestations, and specific imaging characteristics, CaSCCs can be distinguished from other hypothetical diagnoses, including amelanotic choroidal melanoma, metastatic tumors, and diffuse sclerochoroidal calcifications.

Traditional choroidal osteomas, as described by Gass et al. and Shields et al., typically present as benign ossifying tumors within the choroid, with marrow spaces filled with loose connective tissue and dilated, thin-walled blood vessels [1,2]. CaSCCs are characterized by their ability to impact both the sclera and the choroid, a feature that distinguishes them from traditional choroidal choristomas, which are confined to the choroid. The pattern of choroidal vessel involvement may help to distinguish these lesions. In CaSCCs, if the choroidal vessels stop at the border of the lesion and are not visible within it, this suggests that the lesion involves both the sclera and the choroid, leading to a disruption of the normal choroidal vascular architecture. If the choroidal vessels are visible within the lesion, then the CaSCC must be intrascleral or episcleral, sparing the choroidal vasculature.

Both CaSCCs and choroidal osteomas present as well-defined lesions on fundus examination. Choroidal osteomas are typically yellow-white or yellow-orange in color due to the underlying changes in the retinal pigment epithelium and choroid. The pigmentation may vary, with some lesions showing clumping of brown or gray pigment [3]. In our cases, on Retcam and Optos imaging, CaSCCs appear as slightly elevated, creamy-yellow projections (with or without pigmentation) extending supero-nasally from the optic nerve and partially surrounding it. These modalities provide visual cues for diagnosis, but primarily capture surface details and may not adequately assess calcification extent.

B-scan ultrasound of both choroidal osteomas and CaSCCs typically reveals hyperechogenic areas with posterior acoustic shadowing, indicative of significant calcification. These choristomas persist at reduced gain after other soft tissue echoes have disappeared. While effective at identifying calcification, B-scan ultrasound provides limited detail about the lesion's structure. Both types of lesions appear as areas of low signal intensity on T1 and T2 weighted MRI images due to the dense calcification. Each patient in the case series with an MRI available had a posteromedial focal defect representing the CaSCC. MRI aids in assessment of the extent of the lesion and involvement of surrounding structures, but may not visualize calcification as clearly as CT.

In traditional choroidal choristomas, CT scans reveal well-demarcated calcified lesions that are confined to the choroid [4]. CT scan is highly sensitive to calcification and helps to delineate involvement of adjacent structures. Unlike traditional choroidal choristomas, CaSCCs demonstrate scleral and sometimes choroidal calcification, and may involve the medial rectus muscle. Two of the four patients with sclero-muscular calcification on CT scan exhibited abnormal extraocular movements, while the other two had preserved ocular motility, raising questions about the specific conditions under which calcification affects extraocular movements. This discrepancy may be due to differential calcification of the global and orbital components of the eye in these patients.

The global component of the extraocular muscles is primarily responsible for moving the eye within the orbit, while the orbital component supports the global component and helps maintain eye position. We speculate that ocular motility deficits may only arise with calcification of both of these components. One patient had contiguous calcification of his vestigial fibrous right medial rectus muscle and right globe, likely implicated in his right eye being fixed in adduction. Another patient had a right gaze deficit involving both eyes, with focally contiguous calcification of the left medial rectus muscle and left globe - as this patient is developmentally delayed, it cannot be determined if this deficit is primarily ocular or neurological. In the two cases with intact extraocular movement, we speculate that the sclero-muscular calcification was focal, only impacting the orbital component without interfering with the contraction of the global component.

The demographic differences between choroidal choristomas and CaSCCs present an area for speculation on their underlying pathophysiologic differences. Typical choroidal osteomas have predominantly been described in young adult females [2]. In our case series, 5 out of the 7 patients were male. Furthermore, the age at presentation of the patients in this case series ranged from 4 days old to 15 years old, suggesting that it is possible that CaSCCs affect a distinct population from traditional choroidal osteomas.

Choroidal neovascularization (CNV) is a common complication of choroidal osteomas, occurring in 31-47% of patients at 10 years, and more likely in cases where the lesion has an irregular surface or there is subretinal hemorrhage [4,5]. One patient in this case series had CNV with RPE reactive hyperplasia and was treated with multiple intravitreal bevacizumab injections, the standard therapy for this complication. While choroidal osteomas may show growth in up to half of cases at 10 years, they do not exhibit progressive involvement of adjacent issues like the sclera or extraocular muscles [2,5]. In our series, 8 of the lesions had sclero-choroidal involvement, while 2 had only scleral involvement. We speculate that over time the lesions with only scleral involvement may ultimately progress to involve the choroid as well. This theory will be monitored as we continue to follow up with these patients.

The potential for CaSCCs to progress to include scleral, choroidal, and muscular involvement raises important questions about the natural history of these lesions and how they are affected by pathological signaling or mechanical stress. As the pathogenesis of choroidal osteomas has yet to be fully elucidated, we can only speculate on the underlying pathways that lead to these distinct sclero-choroidal lesions. Mosaic RASopathies, characterized by mutations in genes involved in the Ras/MAPK signaling pathway, likely play a crucial role in the pathogenesis of CaSCCs. These mutations can lead to dysregulation of cell growth, differentiation, and survival, creating an environment that allows for the development of these lesions [6]. We hypothesize that these mutations may drive aberrant cellular signaling pathways, leading to abnormal tissue differentiation and calcification across multiple tissues. We suggest that this could also explain the variable presentations observed among patients, with some lesions affecting the sclera, choroid, and medial rectus muscle, some affecting the sclera and choroid, and some confined to the sclera only.

The variable presentation of CaSCCs among patients—including differences in extraocular movements to unilateral versus bilateral involvement—suggests that individual genetic and environmental factors may significantly influence disease expression. For instance, the extent and pattern of somatic mutations in ocular tissue could dictate the lesion's severity and distribution. The consistent supero-nasal localization of CaSCCs and their association with medial rectus muscle calcification may imply a localized pathological process possibly influenced by anatomical or vascular factors specific to this region. As most of the patients in our case series were males, hormonal influences that differentially affect ocular tissues could be implicated or there could be gender-specific genetic factors that predispose males with mosaic RASopathies to develop CaSCCs more frequently.

The molecular characteristics underlying these cases are of particular interest. Of the 25 cases of choroidal choristomas in mosaic RASopathy patients that were evaluated on literature review, only one patient had a molecular diagnosis provided - a *KRAS* (p.G12D) in an infant with LSNS. In our case series, 5 of the 7 patients had molecular diagnoses (**see Table 1**), all of which were identified as *KRAS* mutations. Allelic frequencies were calculated in 4 patients (ranging from 4.8% - 18.9% pathogenic variation) from cutaneous biopsies and do not appear to correspond with the degree of CaSCC involvement in these cases. The presence of a pathogenic KRAS variant was detected in DNA isolated from biopsied, affected skin tissue, but not in DNA isolated from a corresponding blood sample. These results are consistent with the diagnosis of a somatic etiology resulting in mosaic RASopathy. Molecular analysis was not pursued in ocular tissue.

This study's primary limitation was the small cohort of patients that presented with these lesions, but mosaic RASopathies in themselves are rare. Furthermore, an MRI was only available in five cases and a CT scan was only available in four cases. Due to its retrospective nature, this study is unable to determine any temporal relationship between medial rectus calcification and extraocular movement deficits. This study also lacks control groups. While some of these patients have been followed since 2014, there are other patients who have only been seen briefly or have been lost to follow-up. Future priorities include following up with the progression of these lesions in this cohort of patients and continuing to isolate patients that present with CaSCCs to provide a more robust overview of characteristic features. To identify these individuals, if a hypopigmented, creamy-colored lesion around the optic nerve is observed on fundus examination, we suggest evaluation with B-scan

Table 1. Demographics and Ocular Features.

Brief Description: Description of the relevant characteristics of each patient in our case series, including diagnosis and ocular features.

Case	Age at Presentation	Sex	Clinical Diagnosis	Molecular Diagnosis	Ocular Choristomas	CaSCC	Optic Nerve Features	Vision at First Visit	Vision at Last Visit	Other Ocular Features	Systemic Features	Complications/ Interventions
Patient 1	4 days old	M	LSNS	KRAS mutation c.35G>A, p.G12D (allelic frequency of 18.9%)	Superotemporal CECC OD with temporal corneal neovascularization	CaSCC OD	Morning glory disc anomaly OD; C/D ratio 0.5 OD	Unable to perform	20/200 OD, 20/40 OS	RUL coloboma nasally; ptosis OD	Waxy alopecia on left scalp; sebaceous nevi on left side of face; temporal arachnoid cyst; hemi-megalencephaly; dilated kidney; vesicouteral reflux; coarctation of the aorta	CNV
Patient 2	4 days old	M	OES	KRAS mutation c.436G>A, p.A146T (allelic frequency of 16.3%)	Extensive CECC OD extending to 2/3 of the cornea with a CECC extension temporally and a CECC nasally; small CECC OS with inferior vessels	CaSCC OD	C/D ratio 0.4-0.5 OD, 0.1-0.2 OS	Unable to perform	20/70 OD, 20/25 OS	Lid notch OD; superficial superior corneal fibrovascular tissue OS	Nevus psiloliparus	N/A
Patient 3	2 month old	M	LSNS	KRAS mutation c.38G>A, p.G13D (allelic frequency of 7.2%)	Flat superior and inferior CECCs OD with a fibrovascular pannus; flat, superficial inferotemporal CECCs OS surrounded by fibrotic scar	CaSCCs OU	C/D ratio 0.4 OD, 0.6 OS	Blink to light	20/30 OD, 20/25 OS	Left inferior oblique overaction; skin lesions on both upper and lower lids OU	Waxy alopecia; nevus psiloliparus; plagiocephaly; muscle hemihypertrophy; torticollis	Scalp nevus excision
Patient 4	4 month old	M	LSNS	KRAS mutation c.436G>A, p.A146T (allelic frequency of 4.8%)	Supero- and inferonasal CECCs on an irregular cornea OD; superotemporal CECC on cornea and flat, reticular CECC with encroaching blood vessels OS	CaSCCs OU (OS >OD)	Slightly small OS with peripapillary pigmentation; no view OD	Blink to light	Cardiff acuity at 20/200 OU	Bilateral lid colobomas (despite repair); mild exposure keratopathy OS; corneal scarring OD	Abnormal skin lesions with waxy alopecia; plagiocephaly; prominent asymmetric extra-axial fluid spaces supratentorially	Optical iridectomy OS; insertion of conformer OD; ptosis repair RUL

Patient 5	3 year old	M	OES	KRAS mutation c.437C>T, p.A146V	Flat CECC extending into visual axis OD; extensive CECC affecting the cornea and conjunctiva OS	CaSCC OS	Healthy OD; C/D ratio 0.1 OD, no view OS	Unable to perform	Unable to perform	Coloboma of LUL; 360 degree peripheral vascularization OS; latent nystagmus	Large area of waxy alopecia on left scalp; cleft lip and palate	Excision of CECC OU; superficial lamellar transplant OD; excision of conjunctival cyst OD; lamellar graft had failed OS despite attempted limbal stem cell allograft; correction of LUL coloboma OS; cleft lip and palate repair
Patient 6	8 week old	F	OES	N/A - denied by insurance	Three CECCs OD extending towards visual axis with corneal neovascularization	CaSCC OD (two spots)	C/D ratio of 0.3-0.4 OD, 0.1 OS	Fix and follow binocularly	20/63 binocularly (logMAR 0.5)	N/A	Small spot of waxy alopecia on left scalp; hypo- and hyperpigmented lesions on right leg	Corneal transplant OD; subconjunctival injection of dexamethasone OD at two points of neovascularization on corneal graft
Patient 7	15 year old	F	ECCL	N/A	CECCs OU - nasal and superior epibulbar masses; encroaching onto superior cornea OS	CaSCCs OU (two spots OS)	Tilted OU with peripapillary atrophy OD; C/D ratio 0.5-.6 OD, 0.7 OS	20/60 OD and 20/80 OS	20/100 OD and 20/200 OS	Lid colobomas OU; sebaceous nevi on upper lids OU; horizontal jerk nystagmus OS; papillomatous changes at medial canthus	Intractable focal seizures; left hemisphere pachygyria; polymicrogyria	Corpus callosotomy; developmental delay

CaSCC: Calcified Sclero-Choroidal Choristoma; CECC: Complex Epibulbar and Corneal Choristoma; C/D: Cup-to-disc; CNV: Choroidal Neovascularization; ECCL: Encephalocraniocutaneous Lipomatosis; LSNS: Linear Sebaceous Nevus Syndrome; LUL: Left Upper Lid; OD: Right OS Eye; OES: Oculoectodermal Syndrome; OS: Left Eye; OU: Both Eyes; RUL: Right Upper Lid ultrasound to look for signs of a CaSCC. Molecular confirmation should be pursued in the presence of any dermatological and/or ocular surface features characteristic of mosaic RASopathies.

CaSCCs are distinct from traditional choroidal osteomas in several critical ways, including their propensity for sclero-choroidal and sclero-muscular involvement, consistent posteromedial localization, male predominance, and association with mosaic RASopathies. The variability in their presentation highlights the need for comprehensive approaches to diagnosis and management. Mosaic RASopathy patients with CT scans of the head available should have their imaging evaluated for CaSCCs, specifically for medial rectus involvement. Understanding the underlying genetic and molecular mechanisms driving these differences is essential for understanding the natural history of these lesions. To this end, further research is required.

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Conflict of Interest

None exists for any author.

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