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REVIEW

Diagnosis and Management Strategies in Sclerochoroidal Calcification: A Systematic Review

Ahmet Kaan Gündüz[1,2,*], Diğdem Tetik[1,*]

[1]Department of Ophthalmology, Ankara University Faculty of Medicine, Ankara, Turkey; [2]Private Eye Clinic, Farilya Business Center 8/38, Ankara, 06510, Turkey

*These authors contributed equally to this work

Correspondence: Ahmet Kaan Gündüz, Farilya Business Center 8/38, Ufuk Universitesi Cad, Çukurambar, Ankara, 06510, Turkey, Email drkaangunduz@gmail.com

Abstract: Sclerochoroidal calcification (SCC) is a rare disease which is characterized by calcium deposition in the sclera. The choroid is secondarily involved. Typical localization is in the midperipheral region, outside the vascular arcades. SCC is mostly located in the superotemporal quadrant. Often times, the patients are referred with the diagnosis of an amelanotic tumor. SCC may be dystrophic or metastatic. Metastatic SCC lesions are associated with conditions altering calcium and phosphate metabolism including primary and secondary hyperparathyroidism, vitamin D intoxication, renal failure, hyperphosphatemia, and destructive bony lesions. SCC lesions have a characteristic appearance and appear as distinct, ill-defined, yellow-white, elevated scleral/choroidal masses funduscopically. The purpose of this literature review is to review the current knowledge on SCC, highlight the imaging features, and discuss the differential diagnosis as well as management options.

Keywords: sclerochoroidal calcification, hyperparathyroidism, renal failure, ultrasonography, fluorescein angiography, optical coherence tomography

Introduction

Sclerochoroidal calcification (SCC) is a rare degenerative disorder which is characterized by calcium deposition in the sclera. As it is an uncommon condition, it is often misdiagnosed. Over the last two to three decades, there has been a growing interest in this subject leading to the publication of several papers.

In 1979, Wong et al reported calcification of sclera and choroid for the first time in a patient with hyperparathyroidism. Their case had keratopathy, cataracts, and SCC confirmed by histopathological examination.[1] Until early 1980s, SCC was not a well-recognized clinical entity. In 1982, Goldstein et al published the first article on SCC in a patient with hyperparathyroidism with all its characteristic features on funduscopic examination, fluorescein angiography (FA), and ultrasonography (USG).[2] The term "idiopathic sclerochoroidal calcification" was first mentioned by Lim et al in 1989. They reported a case with bilateral multiple calcific choroidal foci with no hypercalcemia or any other ocular diseases.[3] In 1991, Sivalingam et al published the first case series comprising seven SCC patients, initially misdiagnosed with different ocular diseases.[4]

The exact pathogenesis of SCC is still not fully understood. Calcification in tissues occurs in two distinct mechanisms: dystrophic and metastatic.[5] In dystrophic calcification, local deposition of crystalline calcium occurs in the damaged or necrotic tissues. In this situation, serum calcium and phosphorus levels are normal. Examples of dystrophic calcification in the eye include band keratopathy in cornea, senile scleral plaques anterior to the insertions of horizontal rectus muscles, optic nerve head drusen, and calcification in necrotic areas within retinoblastoma.[6] In metastatic calcification, abnormal calcium and phosphorus metabolism leads to deposition of calcium in normal undamaged tissue. Common etiologies are primary and secondary hyperparathyroidism, vitamin D intoxication, renal failure, hyperphosphatemia, and neoplastic destructive bony lesions including multiple myeloma or metastases.[5,6] In metastatic calcification, the localization of calcification includes the uveal tract, sclera, Bowman's membrane, superficial stroma in the cornea, and subepithelium of the conjunctiva.[7]

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The aims of this systematic review were to analyze the demographics, associated systemic findings, ancillary testing methods used, results of treatment, and follow-up results in patients with SCC.

Materials and Methods

We conducted a systematic literature review in PubMed, Web of Science and Scopus databases as of March 2023 using the keywords "sclerochoroidal calcification", "sclerochoroidal calcification and related systemic diseases", "idiopathic sclerochoroidal calcification", "sclerochoroidal calcification and imaging modalities", "sclerochoroidal calcification and treatment modalities", "ocular calcification", "calcium metabolism and eye", "retinal pseudotumor", "differential diagnosis of retinal tumors". Also, reference lists of identified literatures were also screened for further information. Unpublished articles, photo essays, letters to journal, articles with insufficient data, and papers not published in English were excluded. This systematic review was registered with PROSPERO (International Prospective Register of Systematic Reviews) to validate its methodology (ID: CRD42023437352).

Statistical analysis of idiopathic SCC and SCC associated with systemic disease was made with respect to certain variables for which enough data was available in the literature search. The normality test and Pearson's correlation test were used to reveal statistical differences.

Results

We retrieved 88 manuscripts upon our initial review process. Six manuscripts were excluded because they were review articles (n=3) or were irrelevant (n=3). Eighty-two manuscripts were further evaluated for screening. Twenty-one of them were excluded because they were not in English literature (n=13), had insufficient data (n=4), or were in incomplete case presentation formats including photo essays (n=2), letter to journal (n=1), and ahead of print (n=1). The flowchart for study design and manuscript selection is given in Figure 1.

Sixty-one manuscripts were found to be suitable for inclusion in this review article. Of 61 articles, 50 were single-case reports and 11 were case series. The demographics, clinical features, and diagnostic methods used are summarized in Table 1.[1–4,8–64]

In this literature review, 477 eyes of 300 patients were found to have SCC. Among these, 169 (56.3%) patients were female, 125 (41.7%) patients were male, and information regarding 6 (2.0%) patients were not available. The mean patient age was 68.4 (26–88) years. One hundred and seventy-seven (59.0%) patients showed bilateral presentation while 113 (37.7%) had unilateral involvement. Laterality of 7 (2.3%) patients was not specified. Among 477 eyes, 147 eyes (30.8%) had multifocal lesions, 104 (21.8%) had unifocal lesions, and in the other 226 eyes (47.4%) multifocal vs unifocal involvement was not specified.

The Shields group had multiple papers on SCC, and there is a possibility that succeeding papers may have included the cases presented in the previous papers. Notwithstanding, all SCC cases reported by this group were included in the analysis. Therefore, the total number of patients included in our review may be more than the real sum total.

The reported imaging modalities used in the diagnosis of SCC were evaluated. Among 300 patients, data in 176 patients were available. In the remaining 124 patients, the number of patients and imaging modalities used were not specifically stated. The most common diagnostic method used in the evaluation of SCC was USG (66.0%) followed by optical coherence tomography (OCT) (47.7%), FA (20.5%), computed tomography (CT) (19.3%), fundus autofluorescence (FAF) (13.1%), indocyanine green angiography (ICGA) (6.3%), optical coherence tomography angiography (OCTA) (2.3%), visual field analysis (VF) (0.6%), and magnetic resonance imaging (MRI) (0.6%).

Systemic work-up was performed in 96 of 300 patients. Among these, 32 patients had no associated systemic disease and therefore classified as idiopathic SCC. In this group of 32 patients, the mean age was 69.6 (41–88) years. Bilateral presentation was seen in 26 patients (81.3%) and multifocal involvement in 19 (59.4%). Of the remaining 64 patients, primary hyperparathyroidism was found in 14 patients, Gitelman syndrome in 14, parathyroid adenoma in 9 patients, hypomagnesemia in 6, Bartter syndrome in 4, pseudogout in 3, hypercalcemia in 3, kidney failure in 3, familial chondrocalcinosis in 3, hypervitaminosis D in 1, hypovitaminosis D in 1, glomerulonephritis in 1, Albright's hereditary osteodystrophy in 1, and calcium intoxication in 1. In 64 patients with systemic disease, precise information regarding demographic and ophthalmological findings could be found in 28. The mean age of patients with systemic associations was 58.4 (26–85) years. Of these patients, bilateral presentation was seen in 26 (92.9%) and multifocal involvement in 23 (82.1%).

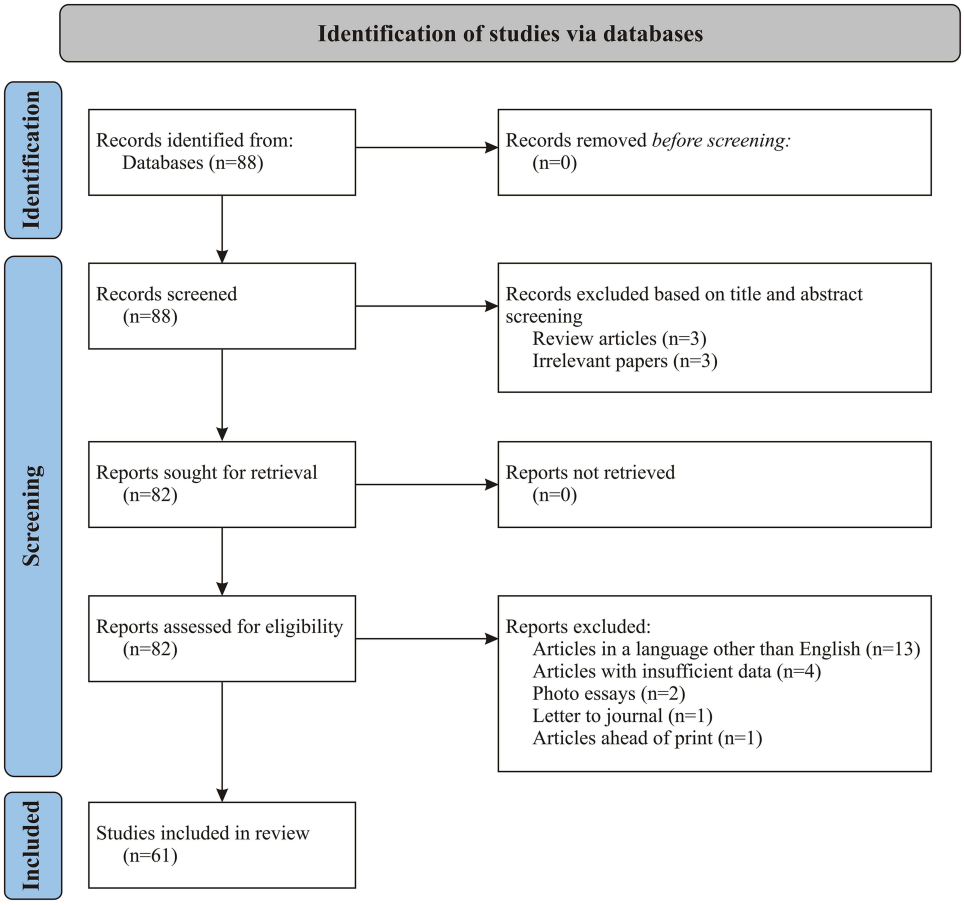

Figure 1 Flowchart for study design and manuscript selection.

There was not enough data to perform statistical correlation in many of the aspects the review addressed. We could only evaluate the differences between idiopathic SCC and those associated with systemic diseases with respect to age, laterality, and unifocal vs multifocal involvement in a limited number of patients. The normality test significance values were p=0.925 for the idiopathic group and p=0.594 for the systemic disease group with respect to age, laterality, and unifocal vs multifocal involvement. Subsequently, Pearson's correlation test revealed no differences between the idiopathic and systemic disease groups with respect to these parameters (p=0.777). However, the correlation coefficient was r=0.343 indicating that there was a positive relationship between systemic involvement and parameters including younger patient age, bilaterality, and multifocality.

Among 300 patients, 161 patients had variable follow-ups ranging from 2 months to 20 years. A total of 150 patients (93.1%) remained stable during follow-up. Of the remaining 11 patients (6.8%), 9 developed choroidal neovascularization (CNV), 2 demonstrated lesion enlargement, and 1 showed increase in the surrounding atrophy area. Some patients had more than one mode of progression. Among eyes with CNV, 2 were treated with argon laser photocoagulation, 5 with intravitreal anti-VEGF (vascular endothelial growth factor) injections, and one with photodynamic therapy (PDT). Some eyes received more than one mode of treatment. Three eyes with CNV were observed without any intervention and remained stable thereafter. Bessette et al reported that CNV did not regress after 3 bevacizumab injections and PDT was administered as an adjunct.[43] In the study by Goerlitz-Jessen, intravitreal anti-VEGF medications were injected with subtenon triamcinolone, but the number of anti-VEGF injections was not specified.[47] In the case series of Battaglia Parodi, two patients complicated with CNV had intravitreal injections for several times.[55] The last case reported by Sulavikova et al received intravitreal ranibizumab injections for 7 times together with laser photocoagulation.[59]

Table 1 Demographics, Clinical Features, Treatment, and Follow-Up of Patients with Sclerochoroidal Calcification Included in This Review

Authors & Year of Publication	Sex	Age	Laterality	Unifocal/ Multifocal	Lesion Localization	Associated Findings	Ancillary Testing	CNV	Ocular Treatments	Follow-Up
Wong S et al, 1979[1]	Female	29	Bilateral	Unifocal	N/A	Pseudohypopara-thyroidism, consequent D vitamin intoxication	–	No	None	N/A
Goldstein BG et al, 1982[2]	Female	79	Bilateral	N/A	Superior to superotemporal arcades	Parathyroid adenoma	USG, FA	No	None	N/A
Lim JI et al, 1989[3]	Male	70	Bilateral	Multifocal	Superior quadrants	None	USG, CT	No	None	2 years, no progression
Sivalingam A et al, 1991[4]	Female (2/7) Male (5/7)	69 (mean)	Bilateral (7/7)	N/A	Above superotemporal quadrant	None	USG (7/7 patients), FA (N/A), CT (2/7 patients)	No	None (7/7)	6 months – 7 years no progression (7/7)
Munier F et al, 1991[8]	Female Male	71 63	Left Bilateral	Unifocal Right unifocal Left multifocal	ST R: ST L: ST and SN	None None	USG (2/2 patients), FA (2/2 patients), CT (2/2 patients)	No No	None None	N/A 2 years, no progression
Kobune M et al, 1992[9]	Male	39	Bilateral	Multifocal	ST and SN	Parathyroid adenoma	USG, FA, CT	No	None	2 months, no progression
Suzuki J et al, 1992[10]	Male	39	Bilateral	Multifocal	ST and SN	Primary hyperparathyroidism	USG, FA, ICGA, CT	No	None	N/A
Schachat AP et al, 1992[11]	Female (11/19) Male (8/19)	79 (mean)	Bilateral (16/19) Unilateral (3/19) (1 R, 2 L)	Multifocal (18/35) Unifocal (17/35)	Midperiphery, often ST	Hypercalcemia (2/9)	USG (35/35 eyes), FA (2/19 patients)	No	None (10/19)	1–120 months of follow up, no change (10/19)
Saatci AO et. al., 1996[12]	Female	35	Left	Unifocal	Posterior pole, temporal to the optic disc	Episodes of anterior scleritis	USG, FA, CT	No	No	1 year, no progression

McCabe CM et al, 1997[13]	Female	41	Bilateral	Multifocal	R: All four quadrants L: ST	None	USG, CT	No	None	N/A
Shields JA et al, 1997[14]	Female	49	Bilateral	Multifocal	R: ST L: IN	Pseudogout	USG, FA, CT	No	None	N/A
Cohen SY et al, 1998[15]	Female	74	Bilateral	Multifocal	R: superior to optic disc L: ST and N	Parathyroid adenoma	USG, FA	Left eye	ALPC for CNV	None
Bourcier T et al, 1999[16]	Female	58	Bilateral	Multifocal	Midperiphery, ST	Gitelman syndrome	USG, FAF, FA, CT	No	None	N/A
Leys A et al, 2000[17]	Female	80	Bilateral	Multifocal	Anterior to superior vascular arcades	Secondary hyperparathyroidism	USG, FA, CT	Left eye	ALPC for CNV	7 years, slight increase in atrophy
Zaheen M et al, 2000[18]	Male	54	Bilateral	Multifocal	Midperiphery, anterior to vascular arcades	None	USG, CT	No	None	N/A
Vezzoli G et al, 2000[19]	Female Female	50 26	Bilateral Bilateral	Multifocal Multifocal	ST IT	Gitelman syndrome Gitelman syndrome	USG,FA,ICGA USG,FA,ICGA	No No	No No	N/A N/A
Honavar SG et al, 2001[20]	Female (15/27) Male (12/27)	70 (mean)	Bilateral (11/27) Unilateral (16/27)	Multifocal (20/38) Unifocal (18/38)	Along or anterior to vascular arcades, macular	Hyperparathyroidism (1/19) Hypomagnesemia (6/13) Gitelman syndrome (4/19)	USG (38/38 eyes), FA (27/38 eyes), ICGA (2/38 eyes), CT (5/38 eyes)	1/38 eyes	None	N/A
Floegel I et al, 2002[21]	Male	65	Bilateral	Unifocal	ST, towards macula	Hyperparathyroidism	USG, FA, CT	No	No	1 year, no progression
Cooke CA et al, 2003[22]	Female (2/3) Male (1/3)	Mean 74.7	Bilateral (3/3)	Multifocal (3/3)	Along vascular arcades, ST (3/3), IT (1/3), N (1/3)	None	USG, FAF	No	None	N/A

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Table 1 (Continued).

Authors & Year of Publication	Sex	Age	Laterality	Unifocal/ Multifocal	Lesion Localization	Associated Findings	Ancillary Testing	CNV	Ocular Treatments	Follow-Up
Boutboul S et al, 2004[23]	Male	69	Bilateral	Multifocal	R: ST L: macular	Familial chondrocalcinosis	USG	No	None	24 years, tumor growth towards macula
Kim M et al, 2004[24]	Male	85	Bilateral	Multifocal	Midperiphery	None	USG, FA	No	None	N/A
Shields JA et al, 2004[25]	Male	55	Left	Unifocal	Along vascular arcade, ST	Membranoproliferative glomerulonephritis	USG, FA	No	None	N/A
Garuti S et al, 2005[26]	Female	66	Bilateral	Multifocal	Midperiphery	None	USG, CT	No	None	N/A
Gupta R et al, 2005[27]	Female	49	Bilateral	Multifocal	Along superior vascular arcade	Pseudogout and Gitelman syndrome	USG, FA	No	None	N/A
Sun H et al, 2005[28]	Female	42	Bilateral	Multifocal	R: ST L: ST and IT	Bartter syndrome	USG, OCT	No	None	6 months, no progression
Pakrou N et al, 2006[29]	Female	79	Bilateral	Multifocal	Along superior vascular arcade and above	None	USG, FA, CT	No	None	N/A
Lindstedt EW et al, 2007[30]	Female (6/8) Male (2/8)	79.3 (mean)	Bilateral (6/8) Unilateral (2/8)	Multifocal (1/8) N/A (7/8)	Along superior vascular arcade	Calcium intoxication (1/8) None (7/8)	USG (1/8 patients), FA (1/8 patients)	No	None	N/A
Choi JY et al, 2009[31]	Female	66	Bilateral	Multifocal	Post-equatorial, mostly superior quadrants	Parathyroid adenoma	USG	No	None	N/A
Miller KV et al, 2009[32]	Female	80	Bilateral	Multifocal	Along superior vascular arcade	None	USG, FA, OCT	No	None	N/A
Lee H et al, 2012[33]	Female	47	Bilateral	Unifocal	Superior quadrants	Albright's hereditary osteodystrophy	USG, CT, ERG	No	None	N/A

Yohannan J et al, 2012[34]	Female	85	Bilateral	Multifocal	Along superior vascular arcade and above	Hyperparathyroidism	USG, FA, OCT	No	None	N/A
Rao RC et al, 2012[35]	Female Male	54 88	N/A N/A	Unifocal Multifocal	ST ST	None None	USG (2/2 patients), OCT (2/2 patients)	No	None None	N/A N/A
Hara K et al, 2013[36]	Female	57	Bilateral	Multifocal	Chorioretinal atrophy in all four quadrants	Renal failure, secondary hyperparathyroidism	USG, CT, VF	No	None	N/A
Wong CM et al, 2013[37]	Male	72	Bilateral	Multifocal	ST	None	USG, FA, OCT	No	None	3 months, no progression
Caminal-Mitjana JM et al, 2013[38]	Female (2/3) Male (1/3)	57.7 (mean)	Bilateral (3/3)	Multifocal (3/3)	ST	None (2/3) Bartter syndrome (1/3)	USG (3/3 patients), FAF (3/3 patients), OCT (3/3 patients)	No	None	N/A
Fung AT et al, 2013[39]	Female (4/9) Male (5/9)	Mean 74.0	Bilateral (4/9) Unilateral (5/9)	N/A	ST (12/17 lesions)	N/A	USG (17/17 lesions), FAF (16/17 lesions), OCT (17/17 lesions), CT (1/9 patients)	No	None	N/A
Zhang J et al, 2015[40]	Female	64	Bilateral	R: Multifocal L: Unifocal	Along the arcades	Adie's pupil, hyperopic shift	USG, FA, CT, MRI	No	None	14 months, no progression
Hasanreisoglu M et al, 2015[41]	Female (26/46) Male (20/46)	Mean 68.0	Bilateral (21/46) Unilateral (25/46)	Multifocal (14/67) Unifocal (53/67)	Midperiphery, ST	N/A	OCT	No	None	N/A

(*Continued*)

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Table 1 (Continued).

Authors & Year of Publication	Sex	Age	Laterality	Unifocal/ Multifocal	Lesion Localization	Associated Findings	Ancillary Testing	CNV	Ocular Treatments	Follow-Up
Shields CL et al, 2015[42]	Female (71/118) Male (47/118)	Mean 69	Bilateral (61/118) Unilateral (57/118)	Multifocal (52/179 eyes) Unifocal (127/179 eyes)	Between the arcades and equator, along the arcades, between the arcades	Hyperparathyroidism (9/33) Parathyroid adenoma (5/33) Bartter syndrome (1/53) Gitelman syndrome (6/53)	USG, OCT (numbers N/A)	No	None	48 months, no progression (118/118)
Bessette AP et al, 2016[43]	Male	72	Bilateral	Multifocal	ST and IT	None	USG, FA, ICGA, OCT	Right eye	Bevacizumab injections x 3, PDT, ALPC	17 months
Ali ZC et al, 2017[44]	Male	67	Bilateral	Multifocal	ST	Hypovitaminosis D	USG, FA, OCT, CT	No	None	N/A
Brahma VL et al, 2017[45]	Male	71	Bilateral	Multifocal	ST	None	USG, FA, ICGA, CT	No	None	N/A
Sugarman JA et al, 2017[46]	Male	67	Bilateral	Multifocal	ST	N/A (possibly calcium metabolism abnormality)	USG, OCT	No	None	N/A
Goerlitz-Jessen M et al, 2018[47]	Female	75	Bilateral	N/A	Extramacular	None	USG, FA, ICGA, OCT	Left eye	Intravitreal anti-VEGF, subtenon triamcinolone	N/A
Slean GR et al, 2018[48]	Male	74	Right	Multifocal	ST	None	USG, FAF, OCT	No	None	Subtle changes over 1 year follow up, growth of preexisting lesions and development of new lesions over 10 years
Abouzaid M et al, 2019[49]	Male	82	Bilateral	Multifocal	ST and SN	Primary hyperparathyroidism	USG, FAF, OCT, CT	No	None	N/A

Ciaffi J et al, 2020[50]	Female	40	Bilateral	Multifocal	N/A	Pseudogout	OCT, CT	No	None	N/A
Fortes BH et al, 2020[51]	Male	87	Bilateral	Multifocal	ST	Subretinal fluid	FAF, FA, OCT, OCTA	Right eye	None	3 months, no progression
Mitamura M et al, 2020[52]	Male	70	Bilateral	Multifocal	Inferior midperiphery, SN and IN	Renal dysfunction, secondary hyperparathyroidism	USG, FAF, FA, ICGA, OCT, CT	No	None	7 months, no progression
Sharifi M et al, 2021[53]	Female	70	Bilateral	N/A	Beneath superotemporal arcade, macular region	Dural optic nerve sheath calcification	USG, OCT, CT	No	None	N/A
Thomson AC, et al, 2021[54]	Male	62	Bilateral	Multifocal	ST, midperipheral	None	USG, FAF, FA, ICGA, OCT	No	None	6 months of follow up, no progression
Parodi MB et al, 2021[55]	N/A	N/A	N/A	N/A	ST	N/A	FAF, FA, OCT, OCTA (Numbers N/A)	2/5 eyes	Several anti-VEGF injections (2/5 eyes)	6 years (2/5 patients)
Lassandro NV et al, 2022[56]	Male	63	Right	Multifocal	ST	Chronic renal failure	USG, ICGA, OCT, CT	No	None	N/A
Dedina L et al, 2022[57]	Female	78	Left	Unifocal	ST	N/A	USG, FA, OCT	Left eye	None	N/A
Nabih O et al, 2022[58]	N/A	65	Bilateral	Multifocal	Supramacular area	Chondrocalcinosis	USG, FA, ICGA, OCT	No	None	12 months, no progression
Sulavikova Z et al, 2022[59]	Male #1 Female #2	63 68	Bilateral Bilateral	Multifocal Multifocal	#1 R,L:ST and nasal #2 R: ST and IT L: ST	#1 Right BRVO #2 Left macular hole	#1 USG, FAF, FA, OCT #2 USG, FA, OCT	No No	#1 R: Intravitreal Ranibizumab x 7 and laser photocoagulation #2 None	#1 2 years, no progression #2 N/A
Tetik D et al, 2022[60]	Male	52	Left	Unifocal	ST	Retinochoroidal shunt vessel	USG, FAF, FA, OCT, OCTA	No	None	1 year, no progression

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Table 1 (Continued).

Authors & Year of Publication	Sex	Age	Laterality	Unifocal/ Multifocal	Lesion Localization	Associated Findings	Ancillary Testing	CNV	Ocular Treatments	Follow-Up
Nieves-Martines IM et al, 2022[61]	Female	57	Right	Unifocal	Juxtapapillary	No	USG, OCT, OCTA	No	No	3 years, no progression
Stevenson M et al, 2022[62]	Female	66	Bilateral	Multifocal	Superior to superior vascular arcades	Bartter Syndrome	USG, OCT, CT	No	No	N/A
Yildirim TD et al, 2022[63]	Female	60	Bilateral	Multifocal	ST	Calcium pyrophosphate deposition disease	CT	No	No	N/A
Mani X et al, 2023[64]	Male	41	Right	Unifocal	ST	Incidental discovery upon examination for orbital fracture to rule out intraocular foreign body	OCT, CT	No	No	N/A

Abbreviations: ALPC, argon laser photocoagulation; BRVO, branch retinal vein occlusion; CNV, choroidal neovascularization; CT, computed tomography; ERG, electroretinogram; FAF, fundus autofluorescence; FA, fundus fluorescein angiography; ICGA, indocyanine green angiography; IN, inferonasal; INL, inner nuclear layer; IT, inferotemporal; L, left; MRI, magnetic resonance imaging; N/A, not available; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; PDT, photodynamic therapy; R, right; SN, superonasal; ST, superotemporal; USG, ultrasonography; VEGF, vascular endothelial growth factor; VF, visual field.

Discussion

Clinical Features of SCC

SCC is usually seen in elderly patients. There seems to be no gender predilection; however, a slight female predominance was noted in some series. Almost all the reported patients are whites.[4] SCC is usually found as an incidental finding during routine eye examination and patients mostly tend to be asymptomatic. SCC has a characteristic appearance ophthalmoscopically. It manifests as a flat or minimally elevated yellow calcified mass (Figure 2A). It may be unilateral

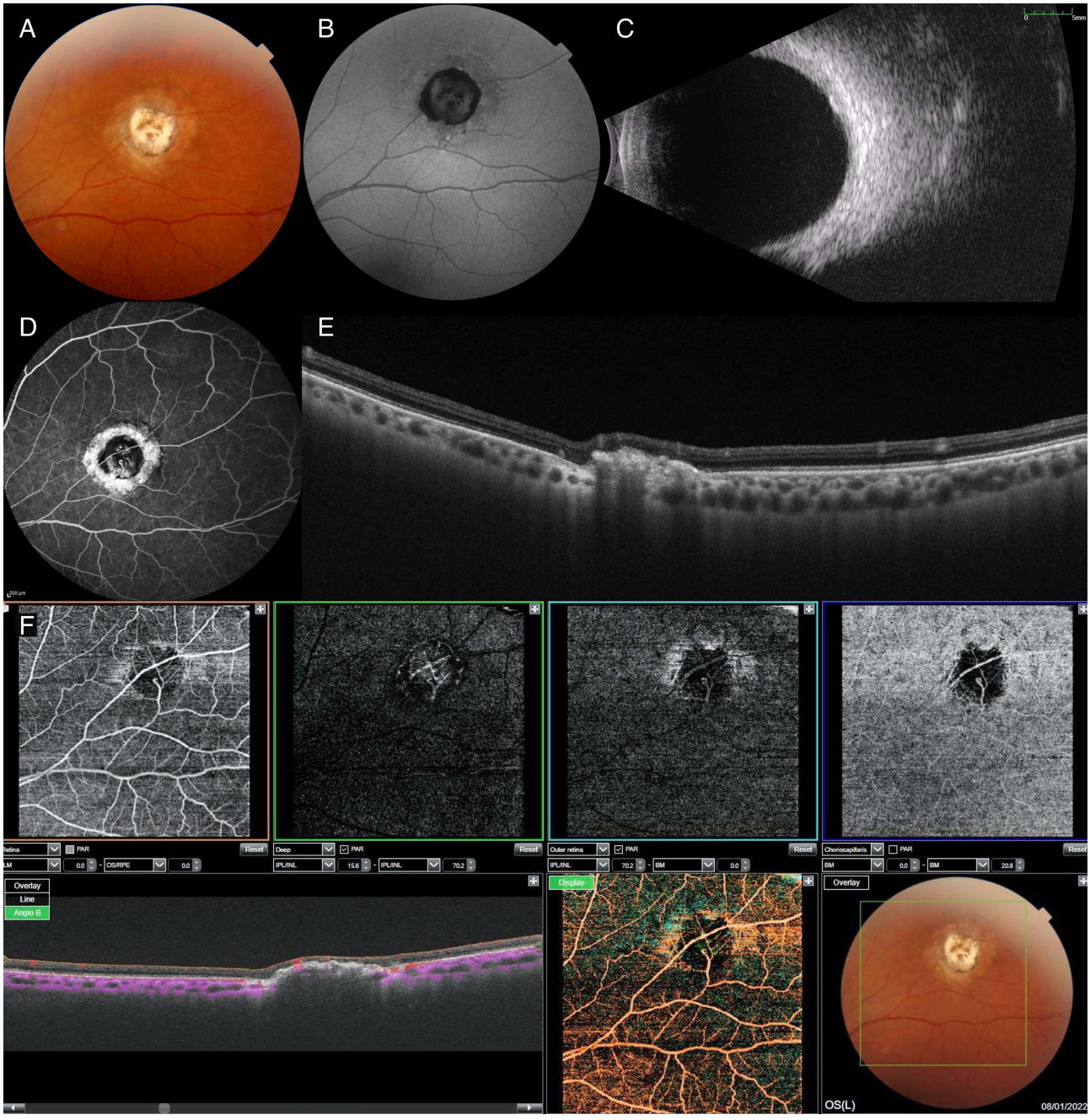

Figure 2 Multimodal imaging in sclerochoroidal calcification (SCC). (**A**) Color fundus photograph shows the SCC lesion in the superotemporal periphery. (**B**) Fundus autofluorescence demonstrates mixed hypoautofluorescence and hyperautofluorescence. (**C**) B-mode ultrasonogram shows an acoustically solid lesion. (**D**) Fluorescein angiography shows central hyperfluorescent calcific deposits, peripheral window defect, and chorioretinal shunt vessel. (**E**) Swept source optical coherence tomography shows the SCC lesion in rocky configuration and disrupted outer retinal layers. (**F**) Swept source optical coherence tomography angiography demonstrates mixed hypo- and hyperreflectivity in the superficial and deep retinal slabs and hyporeflectivity in the outer retinal and choriocapillaris slabs which is probably due to shadowing from calcium. Also, a chorioretinal shunt vessel is visible in all slabs.

or bilateral and manifests as unifocal or multifocal discrete yellow placoid lesions with irregular borders. There is frequently a halo of retinal pigment epithelium (RPE) atrophy surrounding the lesion.[6,20] The typical localization of the SCC lesions is usually in the superotemporal midperipheral fundus.[11,20,39] SCC can also occur inferotemporally. It has been suggested that SCC develops at the site of the insertions of oblique muscles, presumably due to chronic tractional forces exerted on the adjacent sclera.[4,18,20] However, SCC has been reported to occur in the macula, around the optic disc, and nasally as well. Visual acuity is usually not affected unless there is CNV or subretinal fluid. Additionally, in cases with macular localization or progression into the macula during follow-up, visual acuity may be altered.[11,20,39,41,42]

Systemic work-up is important in patients with SCC. Although most of the SCC cases are idiopathic, renal, endocrinologic, and skeletal pathologies leading to abnormal calcium and phosphorus metabolism should be excluded in all patients. While idiopathic cases tend to be seen in elderly patients, SCC associated with a systemic disorder is usually seen at younger ages. Both idiopathic SCC and those associated with systemic disorders usually appear as bilateral and multiple lesions.[6,8,20] However, unilateral and unifocal involvement can also occur.

In the first case series regarding SCC conducted by Sivalingam et al in 1991, 14 eyes of 7 patients were included.[4] Mean patient age was 69 years old and five patients (71.4%) were male. All the cases were asymptomatic and SCC was detected during routine ophthalmologic examination. All patients had bilateral multiple lesions and the average lesion count per eye was found to be 2.5. All SCC lesions were located near or above the superotemporal arcade. All patients had normal serum calcium, phosphate, and parathyroid hormone level; therefore, the cases were labelled as idiopathic SCC.[4]

Another case series by Honavar et al included 38 eyes of 27 patients with SCC.[18] Mean patient age was found to be 70 years. Of 27 patients, 12 (44%) were male and 15 (56%) were female. None of the patients had visual symptoms at the time of diagnosis. While 16 (59%) patients had unilateral presentation, 11 (41%) had bilateral disease. Mean lesion count per eye was found to be 2. The most common localization harboring the lesion was found to be the superotemporal quadrant (56%). Systemic work-up revealed hypomagnesemia in 6 patients, Gitelman syndrome in 4, and primary hyperparathyroidism in one.[20]

Fung et al reported 13 eyes of nine patients with a mean age of 74 years.[36] Five patients (55.5%) were male. All the patients were white. Mean visual acuity was found to be 20/33. Five (55.5%) patients showed unilateral presentation. The most common lesion localization was the superotemporal quadrant (70.5%). Systemic work up or blood calcium and phosphorus levels were not mentioned.[39]

Schachat et al published a case series composed of 19 patients with SCC. Mean patient age was 76 years. Eight patients (42.1%) were male and 11 (57.9%) were female. SCC was bilateral in 16 (84%) patients and unilateral in 3 (16%). The most common localization of the lesions was midperiphery and no quadrant was specified. Systemic work-up was done in nine patients of which one had hypercalcemia and the other had a history of surgical removal of parathyroid adenoma.[11]

In 2015, two consecutive papers on SCC were published by the Shields group.[38,39] In the first paper, OCT findings were evaluated in 67 eyes of 46 patients.[38] The mean age of the patients was 68 years and 57% were female. Almost all the patients were white (%98) and only one patient was of Hispanic origin. Twenty-one patients (45.7%) showed bilateral presentation and 25 patients (54.3%) were unilateral. Lesions were mostly located in the superotemporal quadrant (85%).[41] In the second paper by the same group, 179 eyes of 118 patients were included.[39] The mean age was 69 years and 60% were female. White patients comprised 98% of the whole cohort. SCC was unilateral in 57 patients (48%) and bilateral in 61 (52%) patients. Lesions were mostly found in the superotemporal quadrant (69%). Hyperparathyroidism was found in nine patients (27%), 5 of which had parathyroid adenoma. One patient (2%) had Bartter syndrome and six (11%) had Gitelman syndrome. Abnormal serum calcium was found in 21% of the patients, abnormal magnesium in 24%, and abnormal potassium in 7%.[42]

Associated Systemic Diseases

In this literature review, the most common systemic association seen with SCC was primary hyperparathyroidism. Primary hyperparathyroidism is characterized by the abnormally high amount of parathyroid hormone (PTH) production by the chief cells of the parathyroid gland. PTH is responsible for providing an equilibrium of serum calcium/phosphorus levels and when there is an imbalance due to excessive hormone production, serum calcium level increases resulting in metastatic calcification.[46] Secondary hyperparathyroidism which is usually caused by chronic kidney disease occurs secondary to elevated serum calcium levels and compensatory increased PTH production.[6] The second most common

systemic association of SCC was found to be renal tubular metabolic alkalosis syndromes such as Gitelman and Bartter syndromes. These two distinct clinical conditions are associated with hypokalemia and metabolic alkalosis. While Bartter syndrome usually starts at an earlier age, Gitelman syndrome tends to be seen in late childhood. The classical clinical manifestations of Bartter syndrome are polyuria, polydipsia, failure to thrive, and tendency for dehydration. Gitelman syndrome is characterized by muscle weakness, fatigue, and carpopedal spasm. The relationship between these syndromes and SCC is not yet fully understood.[20,46] Hypomagnesemia is also another important systemic association. Magnesium is known to have a role in the solubility of calcium pyrophosphate in the serum. When the serum magnesium level is low, calcium pyrophosphate deposition occurs in the joints as well as in the sclera and choroid. This mechanism is responsible for the tissue changes seen in calcium pyrophosphate deposition disease (pseudogout).[6,14,46] Besides, hypervitaminosis D causes hypercalcemia and results in calcification in sclera and choroid. Interestingly, one SCC patient in the literature was diagnosed with hypovitaminosis D. The authors did not bring an explanation to the coexistence of hypovitaminosis D and SCC.[44]

Statistical analysis of patients with sufficient data revealed no differences between the idiopathic SCC and SCC occurring with systemic disease with respect to age, laterality, and unifocal vs multifocal involvement in this review. However, there was a positive correlation between systemic involvement and parameters including younger patient age, bilaterality, and multifocality.

Imaging Studies in SCC

In the majority of cases, the diagnosis of SCC can be made by indirect ophthalmoscopy. Ancillary testing methods used include A and B mode USG, FAF, FA, ICGA, OCT, OCTA, and CT. The common findings observed in each imaging modality are given in Table 2. There has been a paradigm shift in the use of these ancillary testing methods during the past 15 years. OCT and FAF have been increasingly used alongside the ubiquitous methods including USG, FA/ICGA, and CT. Currently, the most commonly used non-invasive tests include OCT, FAF, and USG.

Table 2 Imaging Features in Sclerochoroidal Calcification

USG	• Acoustically solid lesions located at the level of sclera and choroid with posterior shadowing having either a plaque-like or thicker nodular (tumor-like) appearance (B-mode) • Posterior shadowing in nodular lesions; posterior shadowing may be less/absent in plaque-like lesions (B-mode) • High reflectivity (A-mode)
FAF	• Mixed patchy hyperautofluorescent areas scattered among hypoautofluorescent areas representing calcified regions and RPE atrophy, respectively
FA	• Hyperfluorescence starting in the early venous phase, hyperfluorescence due to staining in the late phases usually with no leakage • Choroidal neovascular membrane if present
ICGA	• Hypocyanescence of the lesion in all the phases with mild late hypercyanescence • Increased cyanescence due to choroidal vascular hyperpermeability and multiple, scattered hypocyanescent areas due to circulation impairment in the macula
OCT	• Hyperreflective flat or elevated scleral mass causing back shadowing • Disruption and thinning of overlying choroid and outer retinal layers • Retinal atrophy overlying the lesion • Flat, rolling (dome shaped smooth surface), rocky (jutted appearance, steep contoured lesion), table-mountain (elevated table-top-like appearance)
OCTA	• Decreased reflectivity in the outer retina and choriocapillaris slabs due to masking effect of the lesion • Choroidal neovascular membrane if present • Retinochoroidal anastomosis if present
CT	• Hyperdense sclerochoroidal lesions due to calcium content in the posterior eyewall

Abbreviations: CT, computed tomography; FAF, fundus autofluorescence; FA, fundus fluorescein angiography; ICGA, indocyanine green angiography; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; RPE, retinal pigment epithelium; USG, ultrasonography.

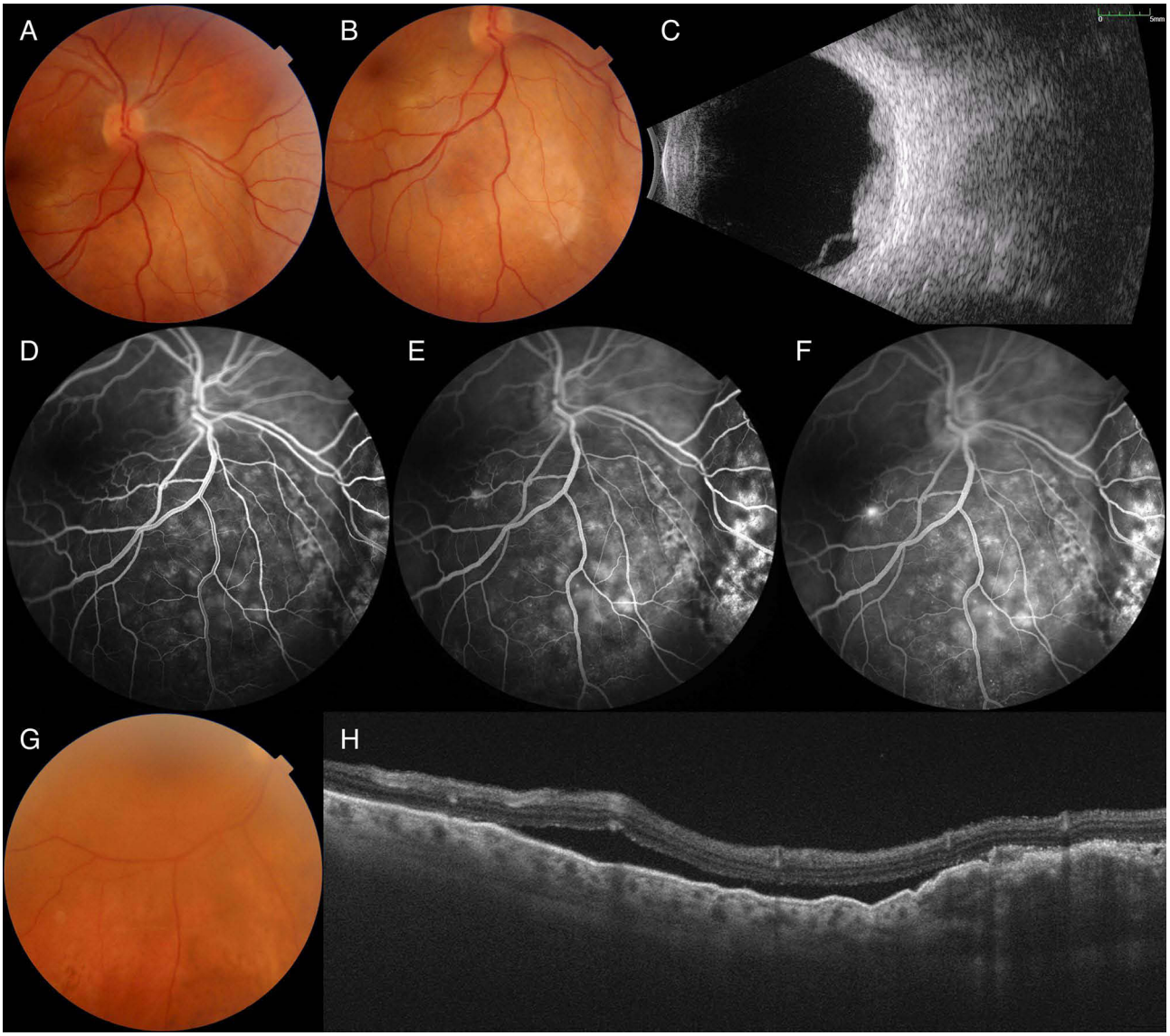

Figure 3 Multimodal imaging in choroidal metastases. (**A** and **B**) Color fundus photographs show multiple metastatic breast cancer lesions inferior and nasal to the optic disc in the right eye. (**C**) B-mode ultrasonogram demonstrates multiple acoustically solid lesions with exudative retinal detachment. (**D**–**F**) Fluorescein angiogram shows increasing globular hyperfluorescence throughout the angiogram at 30 seconds, 3 minutes, and 5 minutes (from left to right) in the tumor, respectively. (**G**) Color fundus photograph of choroidal metastasis in a patient with breast cancer shows metastatic lesion inferior to the inferior vascular arcade. (**H**) Swept source optical coherence tomography reveals lumpy bumpy appearance of the tumor, subretinal highly reflective dots, and associated subretinal fluid.

A and B-Mode Ultrasonography

SCC causes acoustically solid, hyperechoic appearance with posterior shadowing in B-mode USG due to its high calcium content (Figure 2C). SCC may appear as plaque-like or nodular tumor-like (up to 4–6 mm in diameter) lesion on B-mode ultrasonography.[17] On A-mode USG, the lesion displays high reflectivity.[4]

Fundus Autofluorescence

SCC gives rise to a mixed hyperautofluorescent and hypoautofluorescent appearance in FAF (Figure 2B). Calcific lesions display hyperautofluorescence; however, surrounding RPE atrophy may eventually lead to a hypoautofluorescence appearance.[38,39] Total chorioretinal atrophy may lead to scleral hyperautofluorescence.

Fluorescein Angiography

The lesion usually shows hyperfluorescence in the early venous phase with increased hyperfluorescence in the late frames. In the late frames, there is usually no leakage (Figure 2D).[4,10] FA also eloquently demonstrates CNV developing

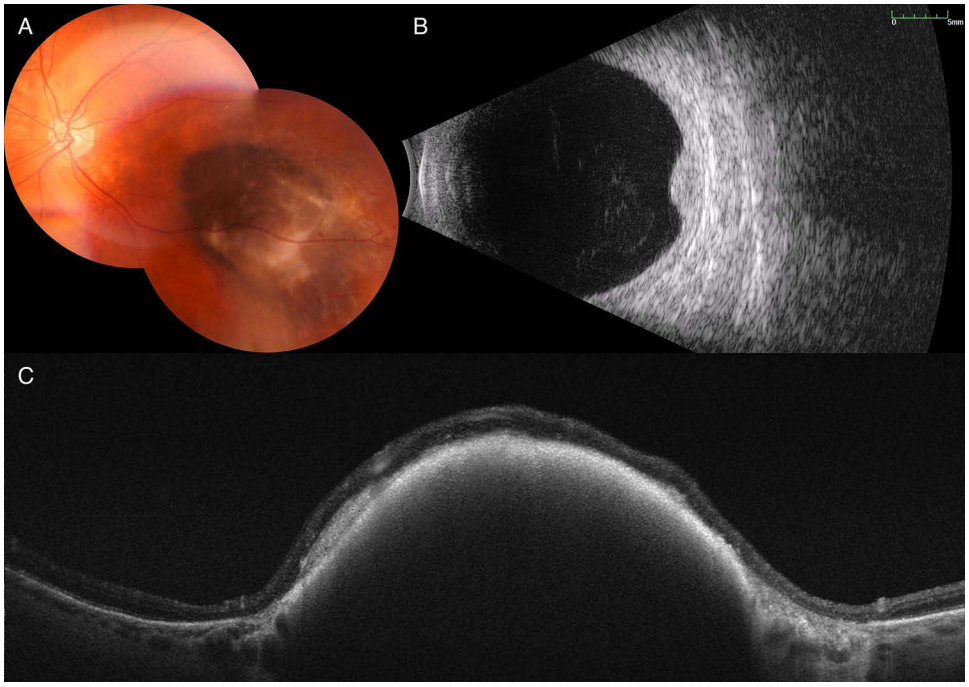

Figure 4 Multimodal imaging in dormant choroidal melanoma. (**A**) Composite color fundus photograph shows choroidal melanoma located inferotemporal to the fovea. (**B**) B-mode ultrasonogram demonstrates the acoustically solid lesion with no posterior shadowing. (**C**) Swept source optical coherence tomography shows retinal thinning, loss of retinal lamination, subretinal hyperreflective deposits, and hyperreflective anterior wall of the mass with choroidal compression.

in the context of SCC. The degree of hyperfluorescence is usually less than that seen in common masquerading lesions including choroidal metastases and melanoma.

Indocyanine Green Angiography

There have been few papers on the ICGA findings of SCC. Lassandro et al reported hypocyanescence in early phases and mild hypercyanescence towards late phase.[56] In another study, SCC lesions remained hypocyanescent during all the phases of ICGA.[20] In two other papers, choroidal hyperpermeability giving rise to hypercyanescence with scattered hypocyanescent lesions due to impairment in choroidal circulation were noted in the macular area.[52,54]

Optical Coherence Tomography

SCC lesions are typically seen on OCT as hyperreflective, irregular lesions giving rise to posterior shadowing (Figure 2E). SCC starts in the sclera and gradually compresses the overlying choroid. This process causes attenuation and thinning of choroid on OCT. Outer retinal layers including outer nuclear layer, ellipsoid zone, and RPE are also found to be affected over some SCCs.[28,32,34,39,52]

With the developments in the OCT technology, enhanced depth imaging OCT (EDI-OCT) enabled the clinicians to visualize the internal tumor features down to sclera better. Hasanreisoglu et al classified the EDI-OCT appearances in SCC into 4 subtypes based on mountain-like patterns. Type 1 "flat" lesion was described as the thinnest subtype with no disturbance in the overlying RPE or sensory retina.[41] Type 2 "rolling" lesions were thicker than type 1 and characterized by a dome shaped smooth lesion. Type 3 "rocky-rolling" lesions were thicker compared with type 2, had irregular and jutted surface characteristics and produced marked disruption of the overlying outer retina. Type 4 "table-mountain" subtype had abrupt elevation at both edges with a central plateau of relatively preserved central choroid and retina.[41]

Of these subtypes, type 3 was the thickest and type 4 was the largest in basal diameter. Type 3 had the most profound effect on the overlying choroid, RPE, and outer retinal layers. The retinal layers were undisturbed in type 1 lesions and outer retinal abnormalities were found in all other types. Type 4 showed the least outer retinal abnormalities compared to type 2 and 3 lesions. The choroid was thinned in all subtypes of SCC.[41]

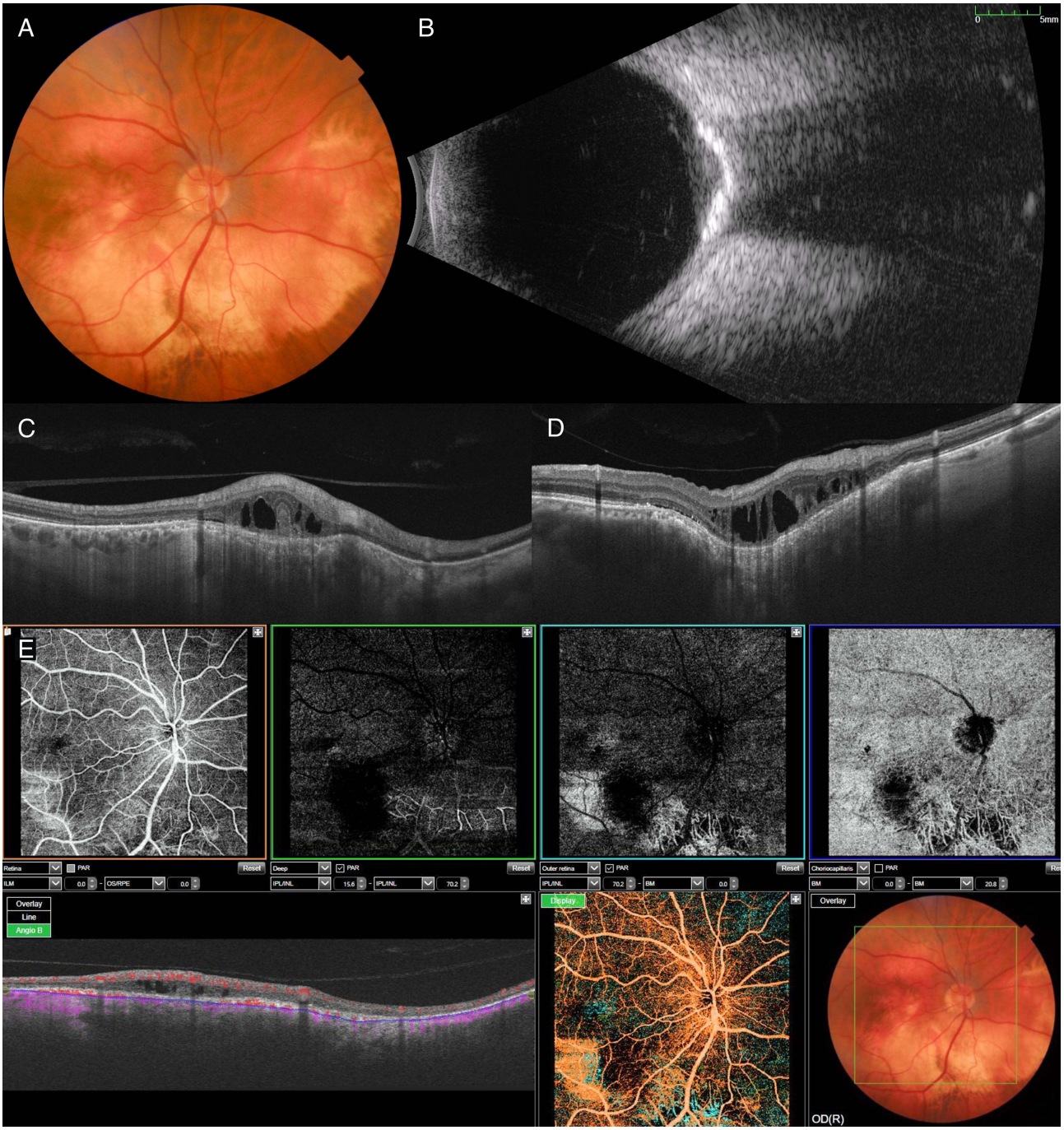

Figure 5 Multimodal imaging in choroidal osteoma. (**A**) Color fundus photograph shows choroidal osteoma inferior to the optic disc in the right eye. (**B**) B-mode ultrasonogram shows the dense acoustically solid lesion with posterior shadowing. (**C** and **D**) Swept source optical coherence tomography demonstrates choroidal thinning (**C** and **D**), focal choroidal excavation (**D**), retinal pigment epithelial (RPE) atrophy, and intraretinal schisis cavities (**C** and **D**). (**E**) Swept source optical coherence tomography angiography shows visible straight choroidal vessels as well as shadowing due to intraretinal fluid in the choriocapillaris slab. Fine branching vessels within the tumor area may represent intrinsic tumor vasculature. Choroidal vasculature is visible in the outer retinal slab due to unmasking from RPE atrophy.

Optical Coherence Tomography Angiography

There were 3 reports in the literature on OCTA findings in SCC at the time of this writing. In two studies, CNV associated with SCC was demonstrated using OCTA.[51,55] In the other case report, OCTA features of SCC were described in detail. In this case, the outer retinal and choroidal slabs demonstrated hyporeflectivity in the lesion area probably because of the shadowing effect of calcium. The superficial and deep retinal plexi showed a mixed iso-hyporeflective appearance

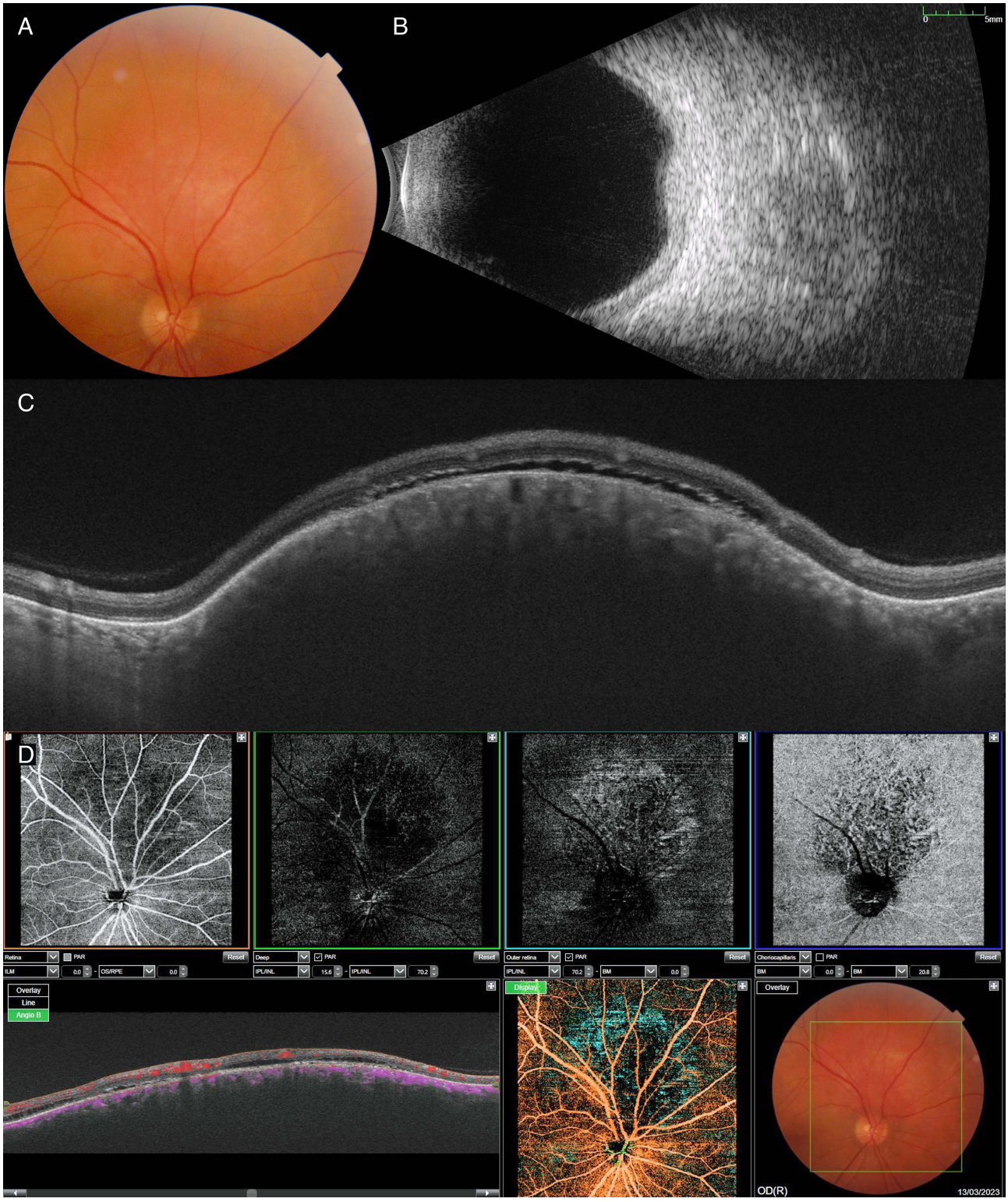

Figure 6 Multimodal imaging in circumscribed choroidal hemangioma. (**A**) Color fundus photograph shows the choroidal hemangioma superior to the optic disc in the right eye. (**B**) B- mode ultrasonogram demonstrates the acoustically solid tumor. (**C**) Swept source optical coherence tomography shows dome-shaped choroidal mass, expansion of choriocapillaris without compression, and subretinal fluid overlying the tumor. (**D**) Swept source optical coherence tomography angiography demonstrates interconnected tumor vessels in the choriocapillaris slab. Hyporeflectivity in the superficial and deep retinal slabs is due to compression from the tumor and focal hyperreflectivity in the outer retinal slab is due to retinal pigment epithelium atrophy.

presumably due to compression of vascular structures by the lesion (Figure 2F). This case also featured a chorioretinal anastomosis best demonstrated on B-scan angio.[60] The chorioretinal anastomosis may develop as a result of impediment of retinal venous outflow.

Computed Tomography

SCC lesions appear as hyperdense structures in the posterior eyewall consistent with the calcium content on CT.[4,18,36] In some cases, there is chorioretinal atrophy along or superior to the arcade without typical SCC lesions. CT displayed eyewall calcium in these cases further providing support to the hypothesis that SCC starts in the sclera and progresses to invade the choroid.[26,36]

Differential Diagnosis

Sivalingam et al reported that SCC lesions were usually referred with the diagnoses of choroidal osteoma, choroidal metastasis, amelanotic choroidal nevus, and choroidal granuloma.[4] In the series reported by Honavar et al,[20] the most common referring diagnoses were choroidal metastases (26%), choroidal melanoma (21%), choroidal nevus (11%), and choroidal lymphoma (3%). Other conditions that may mimic SCC include chorioretinitis, choroidal hemangioma, regressed retinoblastoma, and retinal astrocytic hamartoma.[6]

Choroidal Metastases

Choroidal metastases are typically seen as yellow-colored lesions with fairly distinct margins and exudative retinal detachment (Figure 3). They are usually located in the macula and posterior pole and are rarely seen outside the vascular arcades.[65] Choroidal metastatic lesions can be bilateral and multifocal and usually do not produce areas of RPE dropout. Patients usually present with vision loss, floaters, flashes, metamorphopsia, and pain. Some may also be asymptomatic. A history of malignancy is usually present but in 1/3 of the cases no primary cause is found at the time of detection of the choroidal mass.[66] Metastatic lesions usually do not display calcium which is a distinguishing feature from SCC.

Choroidal Melanoma and Nevus

Choroidal melanoma and nevus are usually pigmented, but they can also be amelanotic in which case they may simulate SCC. Choroidal melanoma usually has distinct borders without RPE dropout, is associated with exudative retinal detachment, and lacks calcium on imaging studies (Figure 4). Choroidal nevus has similar features to choroidal melanoma, but it is usually smaller in size.[67]

Choroidal Lymphoma

The presence of multifocal creamy-yellow patches at the level of choroid is the most characteristic ophthalmoscopic finding. Also, obscuration of choroidal blood vessels by diffuse choroidal lymphoid aggregates is an important feature. Choroidal folds, lipofuscin deposits, optic disc swelling, and occasionally serous retinal detachments may be seen in choroidal lymphoma. All these features are not compatible with SCC.[68]

Choroidal Osteoma

Choroidal osteoma is usually seen in young individuals, mostly women. Ophthalmoscopically, choroidal osteoma appears as a yellow-white or orange-red mass depending on the pigmentary abnormalities on the surface. It presents as a unilateral, solitary, peripapillary oval or round lesion with distinct margins. The B-mode ultrasonogram shows calcification and associated posterior shadowing (Figure 5). Decalcification may occur in long standing osteomas. In contrast to SCC, many patients with choroidal osteoma show decrease in visual acuity from the posterior tumor location, decalcification, associated CNV, and hemorrhage associated with choroidal nonperfusion.[69,70]

Choroidal Hemangioma

Choroidal hemangioma is a benign vascular tumor of the choroid. It may manifest as circumscribed or diffuse choroidal hemangioma. Circumscribed choroidal hemangioma is sporadic and not associated with any systemic diseases. Diffuse choroidal hemangioma is usually seen in association with Sturge-Weber syndrome. Ophthalmoscopic examination of circumscribed choroidal hemangioma reveals unilateral, well-defined, non-pigmented, yellow or orange mass which may be accompanied by subretinal fluid and/or retinoschisis (Figure 6). B-mode USG shows an acoustically solid lesion. FA

demonstrates early hyperfluorescence within the tumor in the arterial phase. Choroidal melanoma and metastasis usually manifest later onset hyperfluorescence.[71]

Management and Follow-Up

SCC is a benign condition which generally does not require treatment unless it is complicated. It is typically found in the mid-peripheral region outside of the vascular arcades and seldom affects the fovea. Correct diagnosis of SCC and evaluation for systemic diseases altering calcium metabolism such as hyperparathyroidism, renal failure, Bartter syndrome, Gitelman syndrome, and metastatic bony lesions are extremely important to prevent or reduce ocular and systemic morbidity.

SCC usually remains stable; however, in a minority of cases, it may demonstrate slow progression and enlargement on long-term follow-up. In a case series published by Schachat et al, 10 patients were followed ranging from 7 months to 10 years and no change was observed in any of the patients.[11] Boutboul et al reported a case with familial chondrocalcinosis and SCC who was followed up for 24 years. The lesions were in the form of little placoid elevated lesions at the time of diagnosis but 24 years later, they appeared to evolve into tumorlike white choroidal lesions.[23] In another case report on idiopathic SCC, no change or progression was noticed in the first year follow-up examination. Nevertheless, the lesion was found to be larger 10 years later.[48]

CNV associated with SCC is the most common cause of vision loss in SCC. CNV is associated with subretinal fluid, subretinal hemorrhages, exudates, and hemorrhagic RPE detachments. The treatment modalities used for CNV varies. There have been cases in which argon laser photocoagulation (ALPC) was used,[15,17] while lately intravitreal anti-VEGF injections have become the other effective treatment option.[43,47,55,59] However, if CNV is far from the macula, close follow-up of patients with CNV remains as another option.[20,51,57]

Conclusion

SCC is a rare disease often confused with other amelanotic fundus tumors. SCC lesions usually appear as calcific lesions superotemporally. SCC manifests as an acoustically solid mass on B-mode USG with posterior shadowing and displays calcification on CT. On FA, SCC shows early venous onset of fluorescence and late hyperfluorescence. On OCT, the lesion has either a smooth or jutted appearance with scleral hyperreflectivity consistent with calcium content. There is posterior shadowing from the calcium content. On OCTA, SCC displays hyporeflectivity in the outer retina and choriocapillaris from posterior shadowing. Associated CNV and retinochoroidal anastomosis are also nicely demonstrated using OCTA. There is no treatment available to ameliorate the degenerative effects of SCC on the sclera and choroid. Secondary CNV can be observed or treated using laser photocoagulation, PDT, and/or intravitreal anti-VEGF injections if vision is affected. Although not statistically proven in this systematic review, unilateral cases in elderly patients usually do not require systemic work-up. However, bilateral SCC seen in younger patients generally warrant systemic investigation.

As a limitation, our review had a low threshold for risk of bias assessment for inclusions of manuscripts if they met the initial eligibility criteria. With respect to different papers on the same subject from the same research group, there was no way to exclude patients included concurrently in these papers. We acknowledge this shortcoming but exclusion of some of these papers might have resulted in loss of important data.

Disclosure

The authors report no conflicts of interest in this work.

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