



Case series

Choroidal hemangioma in Sturge Weber syndrome: Case series with confirmed tissue diagnosis

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ABSTRACT

Introduction: Sturge-weber syndrome (SWS) is a rare condition that presents with a typical facial port-wine stain, neurological manifestations such as seizures, and ocular involvement by glaucoma and/or choroidal hemangioma. In this series we demonstrate the histopathological details of the primary ocular involvement as well as the late blinding secondary ocular changes.

Presentation of cases: Seven cases were included with the diagnosis of choroidal hemangioma in association with SWS (6 enucleations and one evisceration). Male to female ratio was 4:3. Age at enucleation/evisceration ranged from 25 to 68 years with a median of 42 years. Five cases had history of glaucoma (71.4%). Diffuse hemangioma was found in all (4 cavernous and 3 mixed cavernous/capillary type). Conjunctival and episcleral hemangiomas were found in 3/7. Iris neovascularization and retinal detachment were confirmed in 5/7 cases each (71%).

Discussion: Our demographic and histopathological findings parallel what was previously concluded in the literature about the lack of gender predilection in SWS, and the most common ocular presentations of glaucoma and choroidal hemangioma, which is mostly diffuse in nature. The hemangioma type was found to be mostly cavernous followed by mixed capillary and cavernous. We demonstrated late associated ocular changes such as cataract, iris neovascularization, exudative retinal detachment, retinal pigment epithelium hyperplasia/metaplasia, and optic nerve atrophy, all of which aid in the poor visual outcome in these patients.

Conclusion: Sturge-weber syndrome is a rare but visually disabling disease due to the associated ocular manifestations of glaucoma and choroidal hemangioma. Multidisciplinary approach because of the diverse presentation of this condition by pediatrician, neurologist, and ophthalmologist is essential with an attempt to preserve vision.

1. Introduction

Sturge-weber syndrome (SWS) is a rare, sporadic phacomatosis syndrome with no gender predilection [1]. The most common clinical manifestations of SWS include port-wine stains, seizures, glaucoma, and

choroidal hemangiomas [2,3,4]. Histopathological examination of eyes in patients with SWS has shown that choroidal hemangiomas can present in up to 40% of cases [5]. Choroidal hemangiomas can be circumscribed or diffuse [6]. The diffuse choroidal hemangioma (DCH) is the type typically associated with SWS [6]. Many reports are found in

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the literature associating DCH with SWS [6]. In our paper, we report 7 cases of choroidal hemangioma associated with SWS with histopathological confirmation.

2. Methods

This is a retrospective consecutive case series of SWS patients with a histopathologically confirmed tissue diagnosis of choroidal hemangioma at 2 tertiary hospitals in Riyadh, Saudi Arabia and Baltimore, United States between January 1971 and December 2020. Data was collected through a retrospective review of the medical records for the demographic information (gender, age at time of presentation), medical record number, pathology number, initial clinical presentation (affected side, symptoms), past medical and surgical history, family history, clinical examination findings, age at time of surgery, indication and type of surgery, gross examination and histopathological findings. The histopathological diagnosis was further confirmed by review of the slides by experienced ophthalmic pathologists in both tertiary academic centers.

The study adhered to the standards set forth by the Health Insurance Portability and Accountability Act, and the Declaration of Helsinki for research involving humans. General informed written consent was obtained from all patients including permission for anonymous use of their clinical information for publications. The Research registry of the case series was done with the following identifying number:

researchregistry7299. Descriptive statistics were presented in the form of percentages and frequencies. This case series is prepared according to the PROCESS criteria for case series [7].

3. Results

A total of seven cases of SWS-associated choroidal hemangiomas were evaluated. Summary of the demographic and clinical information of the cases is listed in Table 1. The male to female ratio was 4:3. The age at enucleation/evisceration was variable and ranged from 25 to 68 years with a median age of 42 years. The right eye was affected in 5/7 cases (71.4%). The past ocular history of five cases was positive for glaucoma (71.4%); four of which were secondary glaucoma, and one was congenital glaucoma. Two patients had a history of retinal detachment (28.6%); 1 of which was traumatic while the other was caused by the choroidal hemangioma. Six cases underwent enucleation due to a blind painful eye (85.7%) while one case underwent evisceration due to a large, disfigured globe with no light perception (NLP) in the affected eye. The average diameter of the 6 enucleated globes was 23.55 mm (Range 22–24.7 mm). The histopathological examination of all cases confirmed the diagnosis of choroidal hemangiomas with associated conjunctival/episcleral hemangioma in 3 cases. DCH was found in 100% of the cases. The typical endothelial-lined vascular spaces of variable size, with congestion and engorged adjacent blood vessels representing a predominant cavernous pattern was seen in 4 cases while mixed

Table 1
The clinicopathological correlation of findings in 7 cases of SWS with choroidal hemangiomas.

Case/ gender	Specimen/eye	Past ocular history	Choroidal lesion description	Other significant findings
1/F	Enucleated RE	- Long standing loss of vision of unknown etiology - Corneal ulcer	Diffuse hemangioma (mixed cavernous and capillary) Location: posterior to equator and surrounding the disc for a radius of 4-5 mm.	Cornea: healed bacterial ulcer, Iris: coloboma, surgical, PI, PAS Lens: dislocation, cataract Retina: total RD with pigment migration RPE: osseous metaplasia
2/M	Enucleated RE	- Traumatic RD - S/P failed RD repair surgery	Diffuse hemangioma (mixed) Location: temporally with infiltration by lymphocytes and plasma cells.	Iris: neovascularization, PAS Lens: anterior subcapsular cataract Retina: cystic degeneration, gliosis, epi-retinal membrane RPE: osseous metaplasia ON: marked atrophy
3/M	Enucleated RE	- Congenital cataract - Trauma - Chronic glaucoma	Diffuse cavernous hemangioma Location: extending to the mid-periphery temporally	Iris: neovascularization with anterior fibrovascular membrane Lens: cataract Retina: total RD RPE: osseous metaplasia ON: atrophy
4/F	Enucleated RE	- Secondary glaucoma - S/P 5 glaucoma procedures	Diffuse cavernous hemangioma Location: temporally and peripapillary	Conjunctiva: Episcleral vascular hemangioma Lens: cataract ON head: atrophy with laminar ectasia
5/M	Enucleated LE	- Chronic keratitis - Neovascular glaucoma	Diffuse cavernous hemangioma Location: extending posteriorly from the midperiphery on either side.	Conjunctiva: limbal and episcleral vascular malformation (hemangioma) Cornea: band keratopathy Iris: neovascularization, occluded pupil, PAS Lens: cataract (partial resorption) Retina: chronic RD, proliferative vitreoretinopathy RPE: hyperplasia, drusen, fibrous & osseous metaplasia ON: atrophy, subdural hemorrhage
6/M	Enucleated RE	- Total secondary RD - S/P lesion treatment by diathermy - Secondary glaucoma - Corneal ulcer	Diffuse cavernous hemangioma Location: extending from the ora serrata on one side to the mid-periphery on the other side.	Conjunctiva: vascular hemangioma Cornea: band keratopathy Iris: neovascularization, PAS, ectropion uvea Lens: resorption of cataract Retina: chronic RD, proliferative vitreoretinopathy RPE: hyperplasia, fibrous & osseous metaplasia ON: marked diffuse atrophy
7/F	LE contents (Evisceration)	- Congenital glaucoma - S/P 4 glaucoma procedures	Diffuse hemangioma (mixed) Location: choroid & CB	Cornea: decompensation, attenuated endothelium Iris: mild neovascularization Retina: atrophy of ganglion and nerve fiber cell layers, cystic degeneration, outer segments of photoreceptor layer not preserved indicating RD. CB: involvement by hemangioma RPE: hyperplasia, and fibrous metaplasia; Intraocular hemorrhage

M: male; F: female; RE: right eye; LE: left eye; S/P: status post; PI: peripheral iridotomy; PAS: peripheral anterior synechia, RD: retinal detachment, RPE: retinal pigment epithelium, ON: optic nerve, CB: ciliary body.

cavernous and capillary-like proliferations were seen in 3. The clinicopathological correlation and other interesting histopathological findings for all cases are also summarized in [Table 1](#). A brief description of the cases is provided below, and the natural history of the disease is described with more details for the last case (Case 7), as an example of such visually disabling intraocular lesions.

3.1. Case 1

A known case of SWS since childhood with facial hemangioma on the right side presented with non-traumatic loss of vision of unknown etiology in the right eye (RE) at the age of 6 years then was lost to follow up until her recent presentation at the age of 32 years with corneal ulcer in the same eye. Following evaluation of that painful blind eye, enucleation was suggested, and the patient agreed on the procedure. The histopathological examination of that globe revealed diffuse choroidal mixed hemangioma with total chronic retinal detachment (RD) showing pigment migration ([Fig. 1A](#)).

3.2. Case 2

A 68-years old white male presented with painful blind RE. He was diagnosed with SWS and underwent excision of large ipsilateral right upper lid and forehead hemangioma by the Plastic surgery department. He also gave history of trauma, RD, and unsuccessful reattachment surgery in the same eye. On examination the vision in that eye was recorded as NLP. The cornea was clear with peripheral iris bombe, and cortical material occluding the pupil and obscuring any fundus details.

The patient underwent enucleation by the treating ophthalmologist after discussion of all possibilities and outcome. His intraocular pressure (IOP) in the RE was 40 mmHg and the pre-operative diagnosis was phacoanaphylactic uveitis. At that time his mixed choroidal hemangioma was not diagnosed until the enucleated globe was examined histopathologically, which also showed osseous metaplasia ([Fig. 1B](#)).

3.3. Case 3

A young African American male with history of SWS who lost vision in the RE since childhood, presented at the age of 29 years with chronic glaucoma, high IOP, and pain over few years. His case was discussed and based on the above history, enucleation was performed, which showed DCH of the cavernous type ([Fig. 1C](#)), iris neovascularization, fibrovascular membrane, and optic nerve atrophy ([Fig. 1D](#)).

3.4. Case 4

A 34-years old female with history of SWS and long standing RE glaucoma, which was treated surgically in the same center by repeated 5 glaucoma drainage procedures, finally presented with blind painful RE and uncontrolled IOP. The patient accepted the decision for enucleation, which was performed by the same treating surgeon. The enucleated globe showed diffusely thickened choroid by numerous vessels of DCH (cavernous type) in addition to episcleral hemangioma.

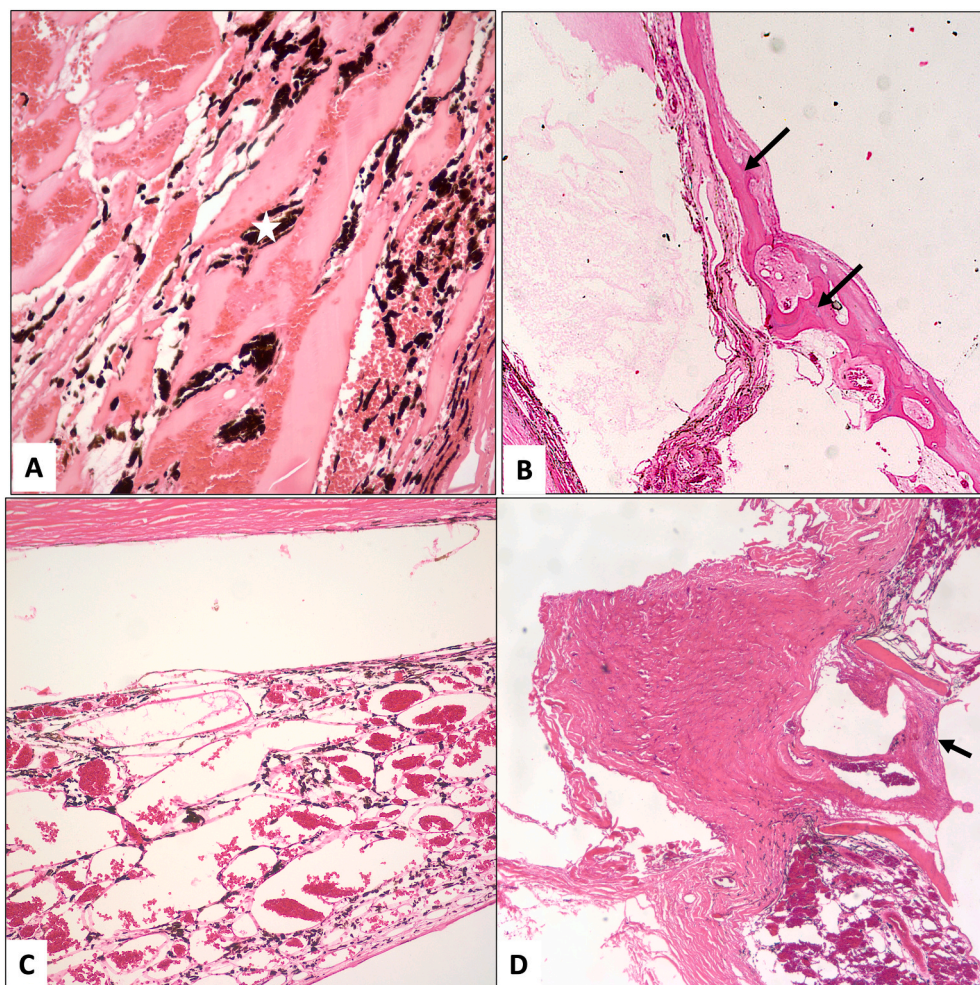


Fig. 1. A: An illustration of cavernous choroidal hemangioma with retinal pigmented epithelium hyperplasia (white star) in case 1 (Original magnification $\times 200$ Hematoxylin and eosin). B: The histopathological appearance of the enucleated globe posteriorly in case 2 showing diffuse cavernous choroidal hemangioma with bone formation (black arrows) (Original magnification $\times 50$ Hematoxylin and eosin). C: The appearance of the diffuse cavernous hemangioma in case 3 (Original magnification $\times 100$ Hematoxylin and eosin). D: The peripapillary hemangioma with optic nerve head (black arrow) involvement in the same case (Original magnification $\times 40$ Hematoxylin and eosin).

3.5. Case 5

A 67-years old African American man with history of SWS presented with blind painful left eye (LE) secondary to long-standing neovascular glaucoma. His ipsilateral facial hemangioma was stable and cosmetically acceptable. The patient was referred to an ophthalmologist who discussed the situation with the patient and the decision was to go for enucleation of the LE. The eye findings confirmed the presence of cavernous DCH, iris neovascularization with occluded pupil, peripheral anterior synechia in addition to other findings as per [Table 1](#). This patient had also limbal and episcleral hemangioma.

3.6. Case 6

A 41-years old male, who is a known case of SWS, presented with 20 years history of RE non rhegmatogenous RD secondary to his diagnosed choroidal hemangioma. The patient was initially consented for diathermy treatment, but this failed to flatten the retina despite the drainage of the subretinal fluid at the time of the diathermy. This was followed by a recent corneal ulcer in addition to the further advanced secondary glaucoma. On examination, he had extensive elevated hemangioma on the right side of the face, hazy cornea, and dilated conjunctival and episcleral blood vessels representing conjunctival hemangioma. The prognosis was discussed with the patient, who agreed to have this eye enucleated. A DCH of the cavernous type was confirmed histopathologically.

3.7. Case 7

A 2-year-old girl with a history of SWS and congenital glaucoma in the LE was referred from her primary treating center for uncontrolled IOP. The child had a history of trabeculectomy in the LE at the age of one month then the family has fallen off from follow-up. The child was born after full-term uneventful pregnancy with no significant perinatal history. The parents denied any family history of ocular diseases and described her development as normal compared to her siblings. The child had a previous history of seizure for which she was admitted in the intensive care unit for 7 days at the age of two months and since then she has been on maintenance dose of Tegretol with no recurrence of seizures. Brain computed tomography (CT) scan was performed at that time which showed no intracranial tumors or vascular malformations. At the initial ophthalmic examination, the child was able to fix and follow in the RE but not in the LE. IOP by applanation tonometry was 15 mmHg in the RE and 50 in the LE. The horizontal corneal diameter was 10.5 mm and 13.5 in RE and LE, respectively. Examination of the LE showed a buphthalmic globe with large clear cornea, deep anterior chamber and updrawn pupil to the site of previous trabeculectomy. Fundus exam of the LE showed 0.4 cup-disc ratio with no signs of choroidal hemangioma. Examination of the RE was unremarkable with healthy disc and normal fundus exam. Retinoscopy showed a refraction of +3.50 + 1.00 × 90 in the RE and -9.00 + 2.00 × 180 in the LE. The child was noted to have a port-wine stain over the left side of her face and trunk which was present since birth. The patient underwent cyclotherapy twice in the LE at the age of 2 for IOP control. At the age of 7 years, the IOP was not controlled despite repeated cyclotherapy and maximum medications with significant cup-disc ratio progression. The child also experienced right-sided hemiparesis and focal seizure secondary to intracranial hemorrhage. Brain CT scan and cerebral angiography confirmed the presence of arteriovenous (AV) malformation in the left side of the brain. At the age of 9 years, the IOP continued to be high on full anti-glaucoma medications with counting finger visual acuity, 0.8 cup-disc ratio and ischemic retina without clinical evidence of choroidal hemangioma. The patient underwent glaucoma implant surgery in the LE which was complicated by massive chorioretinal effusion and total retinal detachment resulting in NLP vision. She continued to follow up as blind non-painful eye with controlled IOP and

poor view to posterior pole secondary to dense cataract. Because of the large disfiguring appearance of the globe, the patient underwent evisceration at the age of 25 years (A timeline graph of the events can be viewed as a supplementary file).

Grossly, the specimen consisted of a corneal button with blood clot adherent posteriorly measuring 13 mm × 12 mm in diameters and intraocular contents, which aggregate to measure 25 mm in diameter submitted “en toto” in separate cassettes. On microscopic examination, the corneal button showed mild edema of the stroma, oblique stromal cornea scar corresponding to a previous surgical intervention, intact Descemet's membrane with moderately attenuated endothelium, and retro-corneal adherent red blood cells with iris tissue at one end of the specimen, which was showing mild neovascularization. The disorganized intraocular contents consisted mainly of uveal tissue including the choroid and the ciliary body. Part of the choroid and ciliary body showed numerous dilated spaces lined by a flat layer of endothelial cells with minimal stroma, some of which were filled with blood ([Fig. 2A](#)). The type of choroidal hemangioma was difficult to assess in an evisceration specimen; however, the engorgement of the pre-existing vessels being intermixed with the vascular tumor, the outlined vascular channels by immunohistochemical endothelial marker (CD 34), and in view of the history of SWS, the findings were consistent with diffuse hemangiomatosis of the mixed capillary and cavernous types ([Fig. 2B and C](#)). The retina was disorganized with marked atrophy of the ganglion and nerve fiber cell layers consistent with long-standing glaucoma. The outer segments of the photoreceptor layer were also not preserved indicating a degenerative process and previous retinal detachment. The internal limiting membrane was only seen along one portion of the folded retina. In other areas, there were areas of retinal pigment epithelium hyperplasia and fibrous metaplasia as well as localized outer retinal cystic degeneration ([Fig. 2D](#)). Intraocular hemorrhage was observed among the contents.

4. Discussion

SWS, also known as encephalo-trigeminal angiomas, is a rare, sporadic condition that occurs with an estimated incidence of 1 in 20–50,000 live births with no gender predilection as proved as well in our limited series [1]. Clinical manifestations of SWS include a wide variety of cutaneous, neurological, and ocular manifestations [2]. The most common cutaneous manifestation is port-wine stains (PWS), also known as nevus flammeus, that are present since birth [2]. Neurologically, seizures are the earliest and most common manifestation of SWS [2]. Other neurological manifestations include leptomeningeal angiomas, developmental delay, and mental retardation [2]. The two most common ocular manifestations include glaucoma; present in 30–70% of SWS patients, followed by choroidal hemangiomas; present in about 50% of SWS patients [3,4]. Other ocular manifestations include conjunctival or episcleral hemangiomas, which was found in 3/7 of our patients: 2 episcleral (cases 4 and 5), and 1 conjunctival (case 6), in addition to retinal vascular tortuosity, iris heterochromia and retinal detachment as a late sequela of the choroidal vascular lesion [3]. In our series, iris neovascularization and retinal detachment were confirmed histopathologically in 5/7 cases each (71%). Histological examination of eyes in patients with SWS has shown that choroidal hemangiomas can present in up to 40% of cases [5]. SWS is diagnosed clinically by the presence of the typical PWS and neurological features and/or glaucoma [2]. The diagnosis in all our cases was confirmed long time prior to the enucleation with confirmed glaucoma in 71% of the patients. Our presented case (#7) presented with both neurological features in the form of cerebral AV malformation, seizures, and glaucoma.

Choroidal hemangiomas are rare vascular hamartomas that are believed to have a congenital origin [8]. They are non-proliferative tumors as the endothelial cells lining their vascular channels do not proliferate, however, these tumors progressively enlarge secondary to venous congestion within the mass rather than cell proliferation [9].

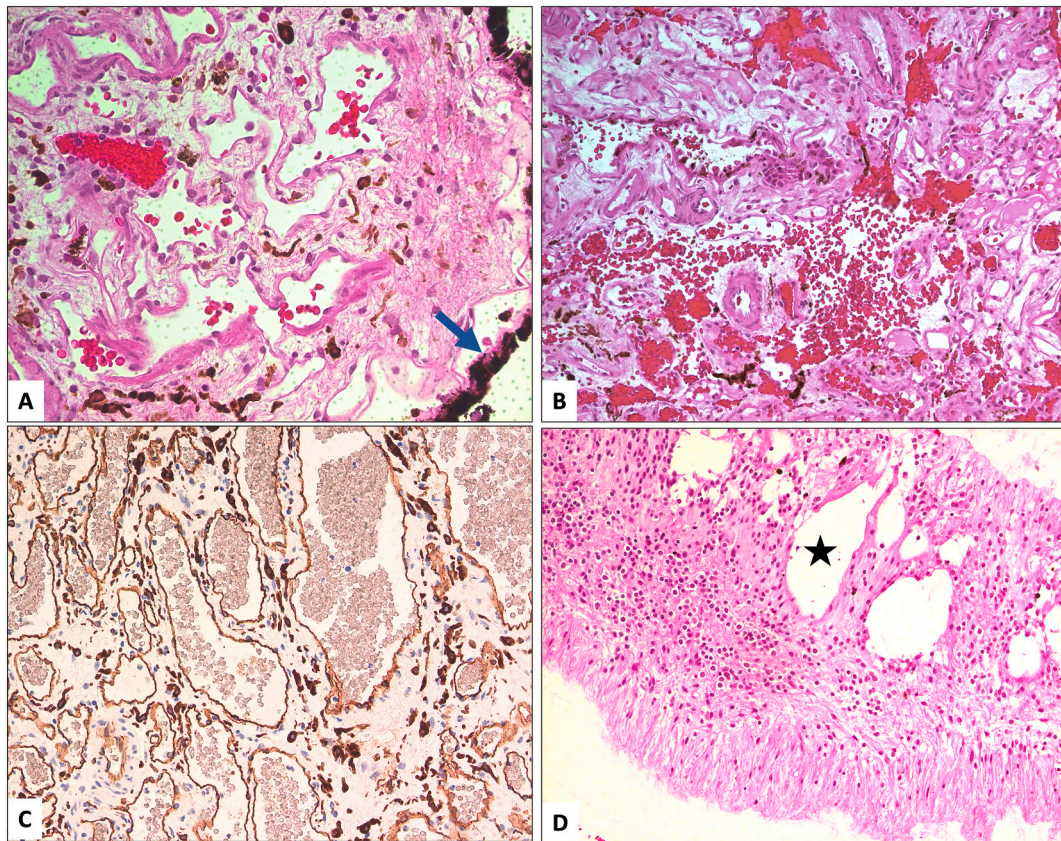


Fig. 2. A: The ciliary body (CB) in the eviscerated tissue of case 7 showing the ciliary body epithelium (blue arrow) and endothelial-lined vascular spaces with similar involvement of the choroid (Original magnification $\times 400$ Hematoxylin and eosin). B: A slightly lower magnification of the uveal hemangioma in another area showing mixed capillary and cavernous type (Original magnification $\times 200$ Hematoxylin and eosin). C: The vascular spaces, which are mostly cavernous in this area outlined by endothelial marker (Original magnification $\times 400$ CD34). D: The cystic degeneration of the detached retina (black star) (Original magnification $\times 200$ Hematoxylin and eosin). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Choroidal hemangiomas can present in two growth patterns: circumscribed and diffuse. Circumscribed choroidal hemangiomas present as isolated unilateral tumors with no systemic association [8]. DCH are typically ipsilateral to the facial cutaneous vascular malformation and cause choroidal thickening observed clinically as a diffuse, poorly defined red-orange mass surrounding more than half of the choroid [9]. This choroidal thickening was observed histopathologically in all enucleated globes (6/6), however choroidal thickening was difficult to assess in the eviscerated globe of case 7. DCHs involve more than one quadrant of the choroid and represent the pattern typically associated with SWS as confirmed in all our cases, however, few reports have documented the occurrence of circumscribed hemangiomas in patients with SWS [6]. DCH can result in vision loss secondary to refractive error, foveal distortion, or exudative retinal detachment, which was observed in 71% of the cases in our series [4]. The remaining cases lost vision due to other anterior segment pathologies such as neovascular glaucoma.

Histopathologically, choroidal hemangiomas are classified according to the type of vessels within the tumor as cavernous, capillary, or mixed [9]. The cavernous type is composed of large, thin-wall vascular channels lined by flat endothelium and separated by limited connective tissue whereas the capillary type is composed of small, capillary type vessels lined by flat endothelium and separated by loose connective tissue. The mixed type shows both cavernous and capillary types of blood vessels. In a clinicopathological study of choroidal hemangiomas, Witchel et al. examined 71 cases choroidal hemangiomas associated with SWS and all cases were of the diffuse growth pattern and mixed cell type [9]. As mentioned earlier all our cases had the typical DCH with the majority being cavernous in 4/7 of the cases. The remaining were mixed in nature including our case illustrated clearly in Fig. 2. Other common

interesting findings found in our series and documented for the first time histopathologically were the Retinal pigment epithelium (RPE) fibrous and/or osseous metaplasia with bone formation in hyperplasia in almost all cases (6/7), optic nerve atrophy in 5/7, and RPE hyperplasia in 3/7. These are secondary changes due to the long-standing presence of the primary vascular pathology and the eventual blindness since the median age for enucleation/evisceration was 42 years in our series and RPE metaplasia is known to be one of the phthisical changes in blind eyes. It was also noted that lens opacification (cataract) with or without resorption was found in all the 6 enucleated globes.

Many treatment options are available for DCH including low-dose radiotherapy, proton beam irradiation and photodynamic therapy [10,11]. The decision to treat is individualized based on the case and visual complaints of the patient, aiming for the prevention of ocular complications secondary to the presence of the choroidal hemangioma and the improvement of the final visual outcome [10]. It is difficult to assess the efficacy of such management options in our series because we have only included the cases of DCH that ended up with enucleation in 6 (and evisceration in one) blind painful eyes. This is one of the limitations of this study in addition to the retrospective nature of the case series. However, we were able to demonstrate by histopathologically the late ocular changes in these affected eyes. More recently, several papers have reported the multifactorial physiologically related pathogenesis of SWS based on interesting molecular findings [12]. Sporadic somatic mutations were found involving guanine nucleotide-binding protein, G alpha subunit q (*GNAQ*), and phosphatidylinositol 3-kinase (*PI3K*). These were found to be involved in the dysregulation and/or activation of the mitogen-activated protein kinase (MAPK) leading to the aberrant vascular lesions and further progression of the port-wine stains in the

skin [12,13]. Furthermore, *GNAQ R183Q* was found in all SWS cases with glaucoma and abnormal scleral tissue that has dysplastic vasculature, thus, was thought to regulate episcleral vessels of patients with SWS [13]. These markers are useful as early diagnostic tools and may give hope for better treatment modalities to prevent further progression of the disease [12,13].

5. Conclusions

Sturge-weber syndrome (SWS) is a rare sporadic phacomatosis condition with characteristic cutaneous, and neurological manifestations. One of these involves the eye in the form of DCH, which can be visually disabling because of secondary changes including exudative retinal detachment, neovascular glaucoma, cataract, and optic nerve atrophy. These ocular posterior segment complications are followed by the development of phthisical changes. Pediatricians, neurologists, and ophthalmologists should be fully aware of this rare syndrome to provide earlier counselling and management options for these patients.

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IRB is not required for case reports/series. However, information was obtained and reported in a manner that was compliant with the standards set forth by the Health Insurance Portability and Accountability Act, and the Declaration of Helsinki as amended in 2013.

Consent

General informed written consent was obtained from the patients including permission for anonymous use of photos and for reporting.

Author contribution

Hala A. Helmi: Review of charts, literature review and first draft of the manuscript.

Hind M Alkatan: Study design, and overall review/editing of the manuscript for submission as the corresponding author.

Rakan S. Al-Essa & Talal W Aljudi: Literature review and data collection.

Azza M.Y. Maktabi: Histopathological review of slides and images.

Charles G. Eberhart (Senior author): Final histopathological

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