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Retinal arterial macroaneurysms with supravalvular pulmonic stenosis syndrome can be associated with coronary and major systemic arterial disease

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ABSTRACT

Purpose: To report novel life-threatening coronary and systemic arterial disease associated with Retinal Arterial Macroaneurysms with Supravalvular Pulmonic Stenosis (RAMSVPS) syndrome, previously known as Familial Retinal Arterial Macroaneurysms (FRAM).

Observations: A 29-years old woman with longstanding poor vision in her right eye presented with acute myocardial infarction and subclavian bruit. Her polyangiogram showed peculiar ostial coronary aneurysms, left anterior descending coronary artery stenosis, occlusion of the left subclavian artery, stenosis of both renal arteries, irregularities in the mesenteric artery and tapering of the aorta. Takayasu arteritis was initially presumed, however fundus examination revealed beading and macroaneurysms along major retinal arteries, intraretinal exudation and hemorrhages, retinal arterial sheathing and stenosis, Coats'-like features and submacular gliosis in the right eye, vitreous hemorrhage in the left eye, and persistent hyaloid artery remnant in both eyes. These features evoked RAMSVPS syndrome. Genetic testing identified the same homozygous *IGFBP7* c.830-1G > A mutation reported with RAMSVPS syndrome, rectifying the systemic diagnosis.

*Conclusion **and importance**:* RAMSVPS syndrome can be associated with more life-threatening coronary and widespread major arterial disease than previously recognized. It is crucial for ophthalmologists to recognize RAMSVPS syndrome and refer patients for a thorough cardiovascular evaluation. Likewise, a careful retinal examination and the possibility of an *IGFBP7* mutation should be considered in the setting of systemic arterial or cardiac disease.

1. Introduction

Familial Retinal Arterial Macroaneurysms (FRAM) was first recognized and described by Dhindsa and Abboud in 2002,[1] as a familial condition featuring a characteristic retinal phenotype, namely 1) arterial beading and macroaneurysms along major arterial trunks, a hallmark feature, 2) segmental arterial narrowing and sheathing, 3) persistent remnant of the hyaloid artery, 4) Coats'-like features, and 5) recurrent episodes of macroaneurysmal exudations and hemorrhages often leading to subretinal gliosis.[1,2] In 2011, a founder mutation in the insulin-like growth factor binding protein 7 (*IGFBP7*) with upregulation of BRAF/MEK/ERK pathway was identified as its underlying cause, and supravalvular pulmonary stenosis was recognized in all affected patients who underwent echocardiography as part of their systemic evaluation.[3] Until recently, the only systemic association reported with FRAM was supravalvular pulmonic stenosis, which prompted to rename the condition Retinal Arterial Macroaneurysms with Supravalvular Pulmonic Stenosis (RAMSVPS) Syndrome.[4] However, identification of additional affected patients, extended follow up of previously reported patients, and more extensive systemic evaluations of known cases identified additional aortic valvular, splenic and cerebral arterial involvement in a few patients.[4]

This case report expands the clinical spectrum of RAMSVPS syndrome further by describing previously unrecognized coronary and major systemic arterial involvement.

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2. Case report

This report was approved by the Institutional Review Board of King Khaled Eye Specialist Hospital (KKESH) and adhered to the tenets of the Declaration of Helsinki. In February 2011, a 40-year-old Saudi female presented to the Retina clinic at KKESH with a history of poor vision in the right eye since childhood and decreased vision in the left eye for six years which had prompted left panretinal photocoagulation (PRP) at a local eye care facility. Her past medical history was significant for acute myocardial infarction at the age of 29 years for which she was admitted at another institution. Review of medical reports from that institution indicates that, at presentation, a left subclavian bruit was evident. Cardiac catheterization demonstrated a 90% stenosis of the left anterior descending (LAD) coronary artery with "interesting ostial aneurysms of 1st and 2nd diagonal branches" (Fig. 1), but other coronary arteries were described as normal. A polyangiogram had revealed total occlusion of the left subclavian artery, mild stenosis of both renal arteries at their origin, mild irregularities in the mesenteric artery and tapering of the aorta as it reached its bifurcation. The cerebral and carotid arteries were described as normal. An extensive rheumatological workup was negative except for a mildly elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) titer. The diagnosis of Takayasu arteritis (TA) was initially entertained, and the patient was started on a short course of oral prednisone (60 mg daily) which rapidly normalized the ESR and CRP titers. Two months later, after an uneventful coronary artery bypass grafting surgery, TA was put into question and steroids were stopped. During the same hospitalization, the patient underwent an ophthalmologic examination prompted by complaints of long-standing poor vision in the right eye. Bilateral "macular scarring" and "retinal hemorrhages" in the left eye were documented and attributed to possible old chorioretinitis but no specific treatment was pursued. Five years later, the patient experienced sudden decreased vision in the left eye and underwent left PRP at another facility but these records were unavailable for review.

At presentation to KKESH in February 2011, the patient had no further cardiac symptoms and no history of prior anti-inflammatory or immune modulating therapy. Her blood pressure was controlled with anti-hypertensive medications. Family history indicated parental consanguinity. Ophthalmic exam revealed best corrected visual acuity of 20/300 in the right eye and 20/60 in the left eye. Intraocular pressures were 15 and 13 mmHg in the right and left eye, respectively. External and anterior segment examinations were normal in both eyes. The lens in the right eye was clear but a tiny axial posterior subcapsular cataract and a Mittendorf dot was present at the posterior lens surface of the left eye. Fundus exam of the right eye showed multiple macroaneurysms along the major retinal arteries, some of which were surrounded by intraretinal lipid exudation and/or had overlying retinal hemorrhages. A sheathed inferotemporal retinal artery harboring several sclerosed macroaneurysms and several peripheral temporal sclerosed retinal arteries were seen. Significant macular and perimacular retinal pigment epithelial disturbances including atrophy, pigment hyperplasia and gliosis were present. No retinal neovascularization was noted. A posterior hyaloid artery remnant was seen at the optic nerve head (Fig. 2A). Fundus exam of left eye showed an attached retina with PRP scars. The macular area had no detectable pigmentary disturbances or fibrosis. The pre-macular posterior hyaloid surface was detached. Along the inferior arcade was a thick elevated fibrous proliferation. A traction-induced vitreous hemorrhage was present at this site. Significant sheathing of the inferotemporal retinal blood vessels was present. No active retinal neovascularization was seen. A persistent Cloquet canal was visible (Fig. 3).

Fundus fluorescein angiography (FA) of the right eye disclosed: 1) beading of the pre-papillary portion of the central retinal artery; 2) multiple macroaneurysms along major arterial trunks, associated in some areas with either localized pre-retinal blockage corresponding to the retinal hemorrhages, or adjacent capillary remodeling which leaked in the late frames of the angiogram; 3) peripheral Coats'-like features featuring large areas of retinal capillary dropout, saccular dilations and telangiectasis; 4) segmental narrowing of few retinal arterioles; 5) hypofluorescent patches in the macula with late staining corresponding to the pigmentary disturbances and gliosis; 6) intact retinal venous tree; and 7) no retinal neovascularization (Fig. 2B). In the left eye, the FA was hazy but epi-papillary leakage, significant attenuation of the retinal arteries in the inferior half of the retina and 360° hypofluorescent patches corresponding to the PRP scars could be seen.

The constellation of above fundus features raised the suspicion of RAMSVPS syndrome. Genetic testing, after obtaining patient's consent, identified a homozygous *c.830-1G > A* mutation in intron 4 of *IGFBP7*, confirming the diagnosis of RAMSVPS syndrome (Fig. 4). Repeat echocardiography to detect if supravalvular pulmonary stenosis was present, ruled out the latter. The coronary graft was patent with no residual obstruction nor further aneurysmal changes in the coronary arteries.

During the following years, the left eye developed progressive posterior subcapsular cataract and epimacular membrane. Phacoemulsification with posterior chamber intraocular lens implantation, pars plana vitrectomy, membrane peeling and intraocular SF6 gas injection, performed 6 years after initial presentation, restored BCVA to 20/80. No exudative or hemorrhagic episodes were observed. In the right eye,

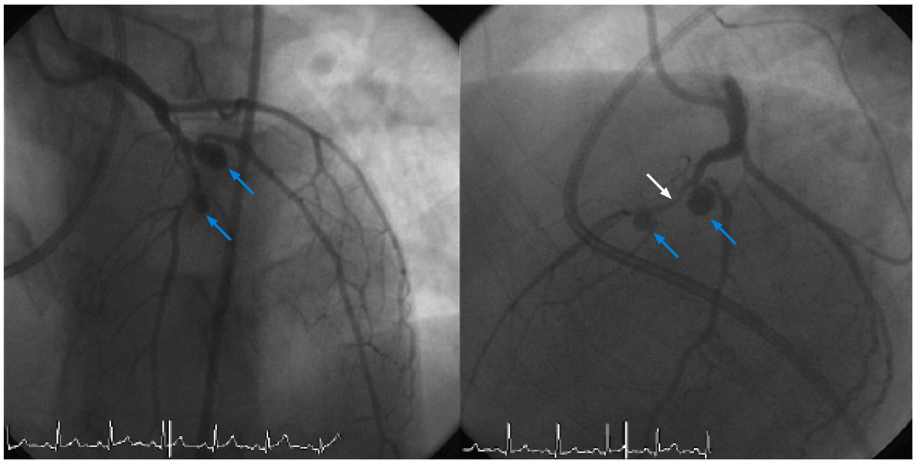

Fig. 1. Coronary angiography of a 29-year-old female with Retinal Arterial Macroaneurysms with Supravalvular Pulmonic Stenosis (RAMSVPS) syndrome presenting with myocardial infarction. A 90% stenosis of the left anterior descending coronary artery (white arrow) and unusual ostial aneurysms of 1st and 2nd diagonal branches (blue arrows) are seen. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

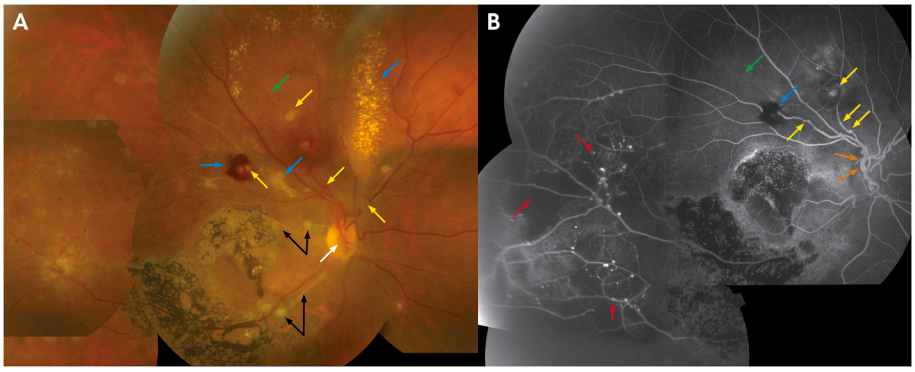

Fig. 2. Color fundus photo and fluorescein angiography of the right eye showing features of Retinal Arterial Macroaneurysms with Supravalvular Pulmonic Stenosis (RAMSVPS) syndrome. **(A)** The right fundus color photograph and **(B)** fluorescein angiogram show typical features of RAMSVPS syndrome: Beading of the central retinal artery (orange arrows) with macroaneurysms along major retinal arteries (yellow arrows); Intraretinal lipid exudation and/or retinal hemorrhages (blue arrows); Segmental retinal arterial narrowing (green arrows); Sclerosed macroaneurysms and sheathed retinal arteries (black arrows); Coats'-like features including capillary dropout, retinal telangiectasis and saccular dilations of the retinal capillaries (red arrows); Persistent Cloquet canal (white arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

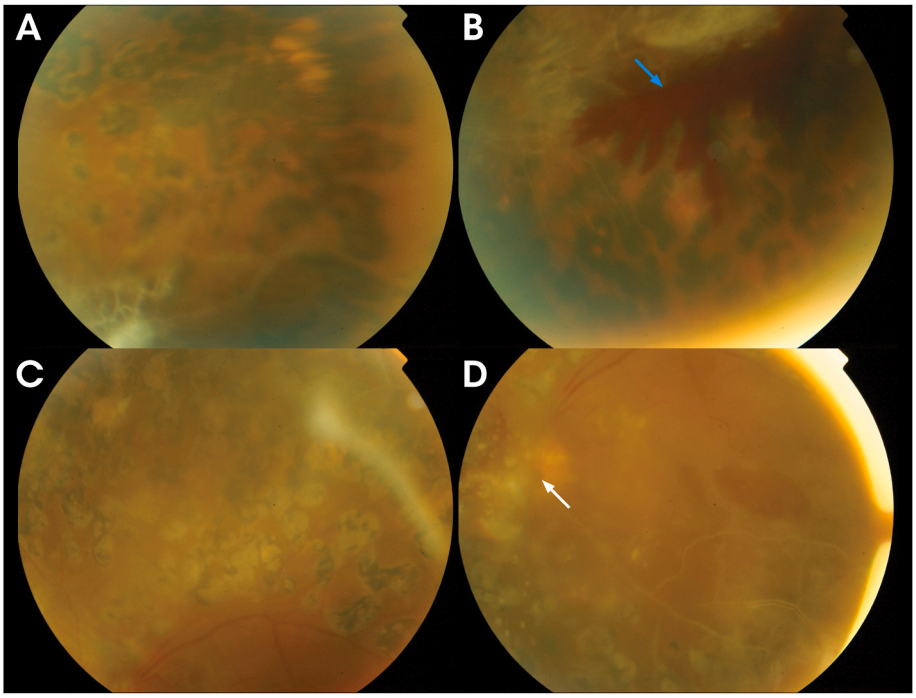

Fig. 3. Color fundus photograph of the left eye at presentation. **(A–C)** The left retina had received panretinal photocoagulation. **(B)** A fibrovascular proliferation with traction induced vitreous hemorrhage is present (blue arrow). **(D)** The pre-macular posterior hyaloid is detached. A Cloquet canal is visible (white arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

however, recurrent episodes of macroaneurysmal leakage with intraretinal lipid deposition were noted. Laser photocoagulation applied to the macroaneurysms in repeated sessions over a 2-year period, halted the leakage and allowed exudates to regress. BCVA remained at 20/300 at final follow up, 9 years later (Fig. 5).

3. Discussion

RAMSVPS is a recently recognized syndrome. To date, it has only been reported in young patients, aged 1–37 years, from consanguineous families in the Arabian Peninsula.[1–6] Its genetic association with a splicing mutation in *IGFBP7* was established in 2011.[3] A recent comprehensive study of 30 patients followed for an average of 8.5 years, detailed its characteristic retinal features and expanded its systemic spectrum.[4] Retina arterial beading and macroaneurysms along major trunks were hallmark findings in 100% of cases; persistent hyaloid artery remnant, retinal arterial narrowing or sheathing, and Coats'-like features occurred in 90, 42 and 42% of cases, respectively, and recurrent episodes of macroaneurysms leakage or bleeding causing preretinal, intraretinal or subretinal hemorrhages with subsequent submacular gliosis was observed in 35% of cases.[4] Systemic associations included 1) pulmonary (valvular or supravalvular) stenosis, observed in 65% of cases evaluated with echocardiography, requiring surgical intervention in 47%, or leading to death in 13% of these young patients, and prompting to change the syndrome's name form FRAM to RAMSVPS syndrome to highlight this potentially fatal association; 2) coexisting aortic supravalvular stenosis was observed in 22% of cases, 3) splenic artery involvement was documented in one case and 4) cerebral vascular involvement was noted in 3 cases leading to a stroke in a 14-year-old and death from cerebral hemorrhage in another patient.[4]

Herein we describe the first case of genetically confirmed RAMSVPS syndrome associated with aneurysms and stenosis in the coronary artery that led to myocardial infarction in a young adult. Stenotic changes in the aorta, subclavian, mesenteric and renal arteries were also discovered. These involvements expand the systemic and potentially life-threatening associations with *IGFBP7* mutation and highlight the

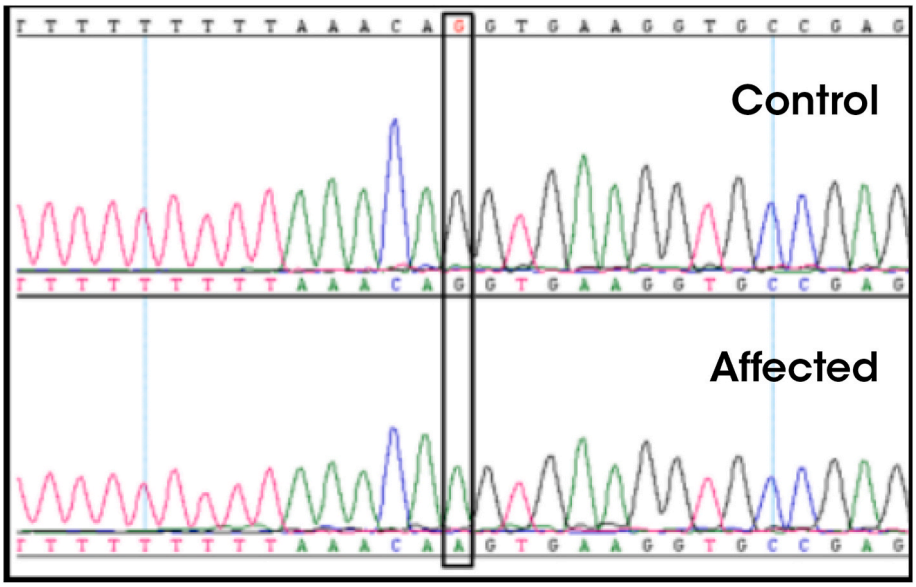

Fig. 4. Chromatogram showing the *IGFBP7* mutation. Sequence chromatogram of a control sample versus the affected patient with RAMSVPS syndrome showing the insulin-like growth factor-binding protein 7 (*IGFBP7)* splicing mutation (c.830-1G < A). This mutation was absent from 300 Saudi controls.

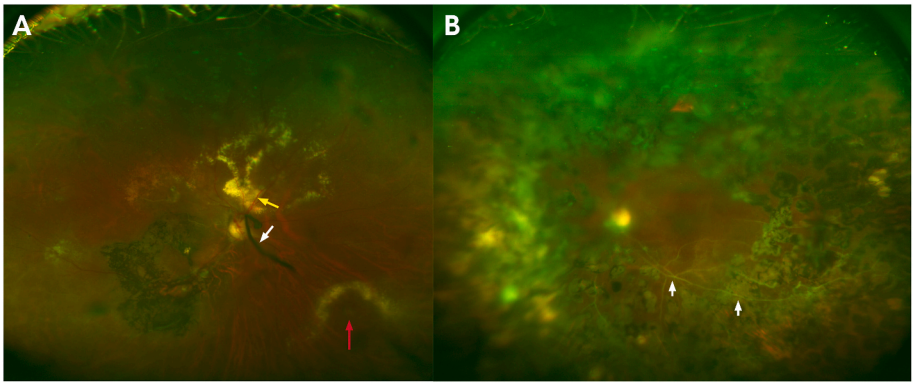

Fig. 5. Color fundus photographs of the both eyes after 9 years of follow-up. **(A)** The right fundus showing leakage with intraretinal lipid deposition stemming from macroaneurysms along the superonasal (yellow arrow) and inferonasal (red arrow) arteries. A persistent Cloquet canal is noted (white arrow). **(B)** Fundus photograph of the left eye one year after vitrectomy shows a clearer media, an attached retina and panretinal photocoagulation scars. Significant sheathing of the inferotemporal retinal blood vessels is present (white arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

importance of genetic testing and a thorough cardiovascular evaluation in patients with retinal features evoking RAMSVPS syndrome. During the revision of this manuscript, another patient with RAMSVPS syndrome and giant coronary aneurysm was reported.[6] This suggests that the coronary manifestations in RAMSVPS syndrome may not be anecdotal.

Coronary artery aneurysms are primarily associated with atherosclerosis.[7] Other causes may include systemic vasculitis, congenital heart disorders and percutaneous coronary intervention.[8] None of these associations were presented in our patient.

IGFBP7 has a highly specific developmental role in the cardiovascular system. Its expressed protein, an angiocrine factor called angiomodulin, is a developmental central nervous system (CNS) vascular-specific marker expressed by developing CNS vasculature.[9] CNS vascular networks are formed by activating 1) vascular endothelial growth factor A (VEGF-A) signaling which drives cerebral angiogenesis, 2) Wnt7a, Wnt7b and norrin pathway which induces/maintains blood brain barrier and 3) angiocrine factors which are tissue-specific factors produced by endothelial cells that influence CNS-specific vascular developments and maintenance. Previous studies suggested the ability of *IGFBP7* to block VEGF-induced angiogenesis by interfering with VEGF expression as well as VEGF signaling rather than inducing apoptosis.[10] Blocking angiomodulin in the zebrafish ortholog resulted in a remarkable defect of vascular sprouting and patterning, proving the gene's role in vasculogenesis and angiogenesis.[11] Further studies demonstrated that in the retinal vasculature, *IGFBP7* is specifically expressed in the endothelium of large smooth muscle vasculature but not smaller capillaries.[3] Interestingly, this corresponds to the location of the retinal arterial beading and maroaneurysms in RAMSVPS syndrome along the major arteries, and not at more distal arterioles. Macroaneuryms likely appear as a result of reduced mechanical integrity and structural defects in the arterial vessel wall where the pressure is highest.[3]

Since patients with RAMSVPS syndrome do not make a normal IGFBP7 transcript, the condition provides an opportunity to observe the consequences of germline mutations in *IGFBP7* on vasculogenesis and angiogenesis in the systemic vasculature as well. Remarkable parallels between the retinal and systemic arterial features are observed. Firstly, in terms of location, macroaneurysms tend to develop at the proximal portion of arteries. This is observed in the retina, at the ostial portion of the coronary artery branches as seen in our patient, and in the carotid and middle cerebral arteries as previously described.[4] Secondly, the sheathing and stenosis of the retinal arteries observed in our patient and reported in 41% of cases of RAMSVPS syndrome,[4] recall the segmental stenosis of the coronary, subclavian, renal and mesenteric arteries observed in our patient, and the segmental stenosis of the cerebral and splenic arteries previously reported.[4] Thirdly, the retinal capillary non-perfusion observed in our case and described in 42% of cases of RAMSVPS syndrome, resembles the "significant paucity and

non-visibility of left middle cerebral artery branches" illustrated on the cerebral angiography of a 14-year old patient with RAMSVPS syndrome who developed a stroke and left middle cerebral artery infarction.[4]

Although our patient did not demonstrate pulmonary stenosis, her retinal features presented the full spectrum of RAMSVPS syndrome. The recurrent episodes of aneurysmal exudations in the right eye noted during follow-up and the history of recurrent hemorrhages in the left eye are also characteristic. Ablative treatment with laser photocoagulation is generally successful for leaky aneurysms, although repeated sessions are often needed. Anti-vascular endothelial growth factor (*anti*-VEGF) agents have been reported to decrease exudation from retinal arterial macroaneurysms,[12,13] but their role in RAMSVPS syndrome is unclear. Hemorrhagic episodes due to macroaneurysm rupture rarely require laser, since aneurysm occlusion and fibrosis often follows bleeding. However, pars plana vitrectomy may be required if bleeding extends under the macular center or if vitreous hemorrhage precludes good vision.

It is interesting that during the patient's initial hospitalization, TA was presumed based on the finding of systemic arteries stenosis. TA is a non-atherosclerotic chronic granulomatous large vessels vasculitis affecting the aorta and the proximal parts of its branches as well as the pulmonary arteries.[14] It occurs predominantly in women of childbearing age, and is diagnosed based on several criteria[14] of which the patient presented at least three: 1) age at disease onset $\leq$40 years, 2) bruit over subclavian arteries and 3) occlusion of the left subclavian artery with mild stenosis of both renal arteries. Coronary artery aneurysms have been described in <10% of patients with TA,[15] and attributed to arterial wall inflammation leading to intimal weakness and aneurysmal dilation.[16] Retinal manifestations in TA present as either a hypertensive retinopathy secondary to renal artery stenosis or as a hypoperfusive retinopathy primarily involving the peripheral retinal vasculature.[17,18] Interestingly, the literature includes a report of a 3-year-old boy with TA and unilateral Coats' disease. The latter was associated with "fusiform dilation of retinal arterioles" and significant yellow exudates at the posterior pole.[19] Our careful review of the fundus photos shows, in addition, macroaneurysms on the large arterial trunks, suggesting that this may have been a case of RAMSVPS syndrome. In our patient, the diagnosis of TA was later dismissed by the rheumatologist, presumably because of insufficient diagnostic criteria. In the absence of a progressive vascular manifestations and no immunosuppressive therapy over 20 years of follow-up, TA is indeed unlikely. The genetic confirmation of *IGFBP7* mutation further supports the diagnosis of RAMSVPS syndrome. Yet, the similarity of the systemic arterial features of both conditions is interesting and opens the question to whether TA and RAMSVPS syndrome share yet undiscovered common genetic and pathophysiologic grounds. Until the time of this writing, a search of the of OMIM® "Online Mendelian Inheritance in Man" database and published TA literature shows no studies exploring the role of *IGFBP7* in TA.

To date, RAMSVPS syndrome has only been reported in patients from the Arabian peninsula.[1–6] However, it is plausible that some cases of RAMSVPS syndrome may have been mis-diagnosed as Coats' disease or as idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) because of shared retinal features. Coats' disease occurs predominantly in males, is usually unilateral, and mainly features more distally located retinal capillary saccular dilations and telangiectasia,[20] rather than proximal retinal arterial beading or aneurysms. These last two features help distinguish Coats' disease from RAMSVPS syndrome, even when the latter includes peripheral Coats'-like features. IRVAN may mimic RAMSVPS syndrome since it features macroaneurysms along the branching points of the first order retinal arteries and at optic nerve head arterioles, as well as episodes of macroaneurysmal exudations or hemorrhages.[21] However, IRVAN is associated with intraocular inflammatory signs which are notably absent in RAMSVPS syndrome. Neither Coats' disease or IRVAN are associated with systemic manifestations. However, since the serious systemic associations of RAMSVPS syndrome may not be known when patients present to ophthalmologists, a high index of suspicion for RAMSVPS syndrome is necessary when evaluating patients with bilateral Coats' disease or IRVAN. A timely cardiovascular investigation including echocardiography and genetic studies are in order. Anticipatory investigations of major systemic arterial systems are also recommended.

4. Conclusion

In conclusion, RAMSVPS syndrome can be associated with major potentially life-threatening coronary and systemic vascular disease which must be recognized. A thorough cardiovascular evaluation aiming at early detection and management of these complications is crucial in patients with RAMSVPS syndrome. Likewise, a careful retinal examination and the possibility of an *IGFBP7* mutation should be considered in the setting of cardiac or systemic cardiovascular disease.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could identify the patient.

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Authorship

All listed authors meet the ICMJE criteria. We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

We confirm that the manuscript has been read and approved by all named authors.

We confirm that the order of authors listed in the manuscript has been approved by all named authors.

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Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

IRB approval was obtained (required for studies and series of 3 or more cases)

Written consent to publish the case report was not obtained. This report does not contain any personal information that could identify the patient.

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Declaration of competing interest

No conflict of interest exists.

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