

The editor-in-chief is world expert on the subject and does not accept publication of this paper unless the comments are incorporated:

1-Pseudoxanthoma elasticum (PXE) is a genetic metabolic disease with autosomal recessive inheritance caused by mutations in the ABCC6 gene and the diagnosis is by gene test or skin biopsy (Mansour AM, Shields JA, Annesley WH Jr, el-Baba F, Tasman W, Tomer TL. Macular degeneration in angioid streaks. Ophthalmologica. 1988;197(1):36-41). A quick screen does not rule out subtle pseudoxanthoma elasticum. A skin biopsy or gene test does.

2-The various systemic disease associations:

Systemic associations of **angioid streaks**.

Mansour AM. Int Ophthalmol Clin. 1991 Summer;31(3):61-8.

3-The evolution of the streaks:

Evolution of angioid streaks.

Mansour AM, Ansari NH, Shields JA, Annesley WH Jr, Cronin CM, Stock EL. Ophthalmologica. 1993;207(2):57-61.

4-Histology: Marked thickening and mineralization of Bruch's membrane losing its elasticity

Mansour AM. Marked thickening of Bruch's membrane in a 17-year-old patient with angioid streaks. Eye (Lond). 1998;12 (Pt 5):898-900.

Please include these references and the comments that PXE can be subtle and needs biopsy of the neck skin or gene testing.

Case study

Angioid Streaks and Systemic Pathologies. Is This Association Always There?

ABSTRACT

Aims: To describe Angioid Streaks and Systemic Pathologies

Presentation of Case: T.A.N., male, 32 years old, lawyer, born in Rio de Janeiro, attends the routine ophthalmologic appointment without specific ophthalmologic complaints.

In her previous pathological history, **he** claims not to have systemic comorbidities. Denies diabetes, eye trauma, previous eye surgeries and any eye pathologies. Denies previous ophthalmologic procedures, daily use of eye drops and family members with a history of glaucoma.

Discussion: The patient in the report, up to the time of the consultation, claimed not to be

aware of any systemic pathology and did not present any ocular complaints, not even knowing the findings of his fundus examination. Systemic associations should always be considered when diagnosing Angioid Streaks on funduscopy. Patients with Pseudoxanthoma Elasticum must have their follow-up done in parallel with the dermatology service. Patients with hemoglobinopathies should be immediately referred for diagnostic clarification with the medical clinic team

Conclusions: It is essential that specialists are familiarized with the peculiar appearance, their potential to produce retinal and subretinal complications and, especially, remember that this finding in funduscopy can be unique without being associated with systemic diseases.

Keywords: Blood dyscrasia; Angioid streaks; Elastic pseudoxanthoma; Choroid neovascularization; Retinography.

1. INTRODUCTION

Angioid streaks (AS) are dehiscence of the elastic layer of Bruch's membrane secondary to an abnormal fragility of its elastoid component. AS can be idiopathic in most cases or associated with a systemic condition, such as Pseudoxanthoma Elasticum, Paget's Disease of Bone or with hemoglobinopathies. No **gender** predilection is described. White people are the most affected.¹⁻⁴

They are characterized by ruptures in a mineralized and degenerated Bruch's membrane, being generally linear and similar in appearance to a blood vessel and, therefore, called angioids. They usually form around and radiate from the optic disc towards the retinal periphery.^{2,4-6}

AEs have a wide spectrum of manifestations and early diagnosis is of paramount importance, as late complications of the disease can irreversibly compromise the visual prognosis, despite the evolution of antiangiogenic therapies.^{3,6,7,8}

Clinically, AS are characterized by irregular lines with a thickness similar to the caliber of a retinal vessel, with a grayish, black or reddish subretinal location. Usually EAs are bilateral, but background changes can be asymmetric.^{1,4,6,7}

With age, the number, width and length of AEs can increase and complicate with subretinal hemorrhage and, consequently, with a decrease in visual acuity, especially if it has a subfoveal location.^{2-5,7}

Choroidal neovascularization (CNV) is characterized by the presence of subretinal fluid, hard exudates or blood around the AS. The incidence of CNV in AS can be up to 86%, and bilateral involvement is seen in up to 71% of cases. CNV and subsequent disciform scar formation cause decreased vision in patients with AS.^{3,7,8,9} The chances of developing CNV are high if the AS are wide, long in length and if they affect an area within 1 disc diameter of the fovea.^{5,9,10,11}

Optical coherence tomography (OCT) reveals retinal, subretinal and sub-EPR changes in the NCV, as well as hyperreflectivity at the level of Bruch's membrane due to calcification. Angio-OCT can be used to demonstrate CNV.^{3,7,12-14}

AS are usually asymptomatic and do not need treatment. However, these eyes are more likely to develop subretinal hemorrhage even after minor trauma.^{12,17,17,18} All patients with AS should be screened for systemic associations and testing family members can provide clues about some systemic pathology.¹⁵⁻¹⁷

The main complication is CNV, which can cause sub and intraretinal hemorrhage, with diffuse exudation and often leading to the formation of a disciform scar with severe loss of vision. If CNV is detected, treatment options include laser photocoagulation, photodynamic therapy (PDT) and anti-angiogenic agents (anti-VEGF) such as ranibizumab, aflibercept, and bevacizumab (off-label).^{2,5,9,19,20-22} All anti-VEGF agents seem to be effective in interrupting the activity of CNV, reducing scar formation, which provides a better prognosis for patients who develop this complication.^{8,11,13,22,23}

2. Case Report

T.A.N., male, 32 years old, lawyer, born in Rio de Janeiro, attends the routine ophthalmologic appointment without specific ophthalmologic complaints.

In her previous pathological history, **he** claims not to have systemic comorbidities. Denies diabetes, eye trauma, previous eye surgeries and any eye pathologies. Denies previous ophthalmologic procedures, daily use of eye drops and family members with a history of glaucoma.

Visual acuity with best correction of 20/20 in both eyes (AO).

Biomicroscopy was within normal limits.

Intraocular pressure: 14/13 mmHg (14:30).

Bilateral fundus showed regular optic discs, physiological cup/disc ratio in both eyes, vascular arches without alterations, lesions with a gray appearance around and emerging from optic discs similar to retinal blood vessels going towards the periphery. No retinal hemorrhages and no CNV. Applied retinas, without AO detachment areas. (Figures 1 and 2)

Only the findings described in the image compatible with angioid streaks. no other changes



Figure 1- Right eye



Figure 2 – Left eye

Therefore, we opted for follow-up at the retinal clinic for regular follow-up in order to monitor the patient closely to detect possible complications early. The patient, in parallel, was referred to the internal medicine service to complement his systemic assessment, and no comorbidity has been detected so far. Despite screening for systemic pathologies, such as pseudoxanthoma elastica, hematologic malignancies, Ehlers Danlos and Paget's disease, no diagnosis of systemic comorbidities was reached.

3. Discussion

AS can be idiopathic and an underlying cause is not diagnosed in up to 50% of cases, with the most important systemic associations being Pseudoxanthoma Elasticum, Sickle Cell Anemia, Paget Disease of Bone and Marfan Syndrome.^{7,20,21,23}

AS in sickle cell disease are seen in about 1-2% of cases, usually after the 3rd decade. AEs have been reported in sickle cell trait, homozygous sickle cell disease, sickle cell thalassemia and sickle cell hemoglobinopathy. Age at onset is variable and most commonly presents around the fifth decade of life, but may manifest at a younger age in patients with comorbidities.^{8,17,24-26} The patient in the report, up to the time of the consultation, claimed not to be aware of any systemic pathology and did not present any ocular complaints, not even knowing the findings of his fundus examination.

The orientation of the AS may be related to the lines of traction of the intrinsic and extrinsic ocular muscles around a fixed location. Bruch's membrane fragility and opacification is secondary to degeneration of its elastic portion and calcium deposition in it.^{3,16,20-22} Histopathological examination in AS reveals Bruch's membrane thickening and calcification, with well-demarcated dehiscence. similar to cracks in its collagen and elastic layer.^{20-22,24,27} AS are usually asymptomatic and the decrease in visual acuity is mainly related to foveal involvement with dehiscence of Bruch's membrane, causing foveal subretinal bleeding.

These hemorrhages do not show evidence of CNV and usually resolve spontaneously.^{7,24-29} The patient denied any previous ophthalmological complaints, having always undergone regular ophthalmological follow-up with the use of refractive correction by glasses, which did not prompt the patient to seek help from a doctor more immediately. In more advanced and severe cases, a fibrovascular or neovascular tissue can form at the edge of Bruch's membrane dehiscence and grow under the retina or RPE, with reduced central vision secondary to involvement of the foveal region by an AS that ruptured and led to the alteration of the choriocapillary.^{20,22,27-30} CNV is a common cause of visual decline and metamorphopsia, affecting most patients with AS.^{21,29,31-34} This complication was not yet present in the patient in the present report, which gave him a better prognosis. However, his regular ophthalmological follow-up was intensified to every 6 months in order to detect possible retinal changes that could cause permanent visual sequelae in the patient. Systemic associations should always be considered when diagnosing AS on funduscopy. Patients with Pseudoxanthoma Elasticum must have their follow-up done in parallel with the dermatology service. Patients with hemoglobinopathies should be immediately referred for diagnostic clarification with the medical clinic team.^{26,29,34,35} The patient in the present report denied any history of systemic comorbidities, and when AE was diagnosed through the fundus examination, referral to the internal medicine service was promptly performed. A detailed anamnesis is essential, as he denied any previous systemic pathology and family members with important pathologies. Therefore, the clinical history should always try to rule out systemic associations and a comprehensive ocular examination should be performed. The visual prognosis of patients with untreated CNV or the presence of a disciform scar tends to be limited.^{12,19,,24,36}

4. Conclusion

AS occur due to alterations in the elastic layer of Bruch's membrane, showing a notorious association with Pseudoxanthoma Elasticum, Paget's Disease of Bone, Sickle Cell Hemoglobinopathies, Marfan Syndrome and Ehlers-Danlos Syndrome. Ocular complications include exudative maculopathy, retinal hemorrhages and foveal involvement. The formation of CNV greatly worsens the visual prognosis of these patients, since there may also be the formation of disciform scars in the macula.

Therefore, it is essential that specialists are familiarized with the peculiar appearance of AS, their potential to produce retinal and subretinal complications and, especially, remember that this finding in funduscopy can be unique without being associated with systemic diseases, as well as strong association with certain pathologies that, if diagnosed late, can cause sequelae in affected individuals, which are often irreversible.

searches and review the study. All authors read and approved the final manuscript."

Consent

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

Ethical approval

Not applicable

References

- 1- Aleluia MM, Fonseca TCC, Souza RQ, Neves FI, da Guarda CC, Santiago RP, et al. Comparative study of sickle cell anemia and hemoglobin SC disease: clinical characterization, laboratory biomarkers and genetic profiles. *BMC Hematol*. 2017 Sep 15;17:15.
- 2- da Guarda CC, Yahouédéhou SCMA, Santiago RP, Neres JS, Fernandes CFL, Aleluia MM, et al. Sickle cell disease: A distinction of two most frequent genotypes (HbSS and HbSC). *PLoS One*. 2020 Jan 29;15(1):e0228399.
- 3- Lucas C, Aranha J, da Rocha I, Sousa D. Case Report: Pseudoxanthoma elasticum. *F1000Res*. 2020 Jan 9;9:9.
- 4- Setó-Torrent N, Iglesias-Sancho M, Arandes-Marcocci J, Fernández-Figueras MT. Pseudoxanthoma elasticum-like papillary dermal elastolysis in non-exposed skin. *An Bras Dermatol*. 2020 Mar-Apr;95(2):247-249.
- 5- Ashorobi D, Ramsey A, Yarrarapu SNS, Bhatt R. Sickle Cell Trait. 2021 Jul 23. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. PMID: 30725815.
- 6- Gonzalez ME, Votava HJ, Lipkin G, Sanchez M. Pseudoxanthoma elasticum. *Dermatol Online J*. 2009 Aug 15;15(8):17.
- 7- Zineb K. Ophthalmologic manifestations of pseudoxanthoma elasticum. *Oman J Ophthalmol*. 2018 Jan-Apr;11(1):88-89.
- 8- Maraite F, Bonnet S, Lepièce G. Pseudoxanthome élastique révélé par un néovaisseau choroïdien [Pseudoxanthoma elasticum revealed by choroidal neovascularization]. *Rev Med Liege*. 2019 Jul;74(7-8):401-405.
- 9- Karampelas M, Soumplis V, Karagiannis D, Parikakis E, Webster AR. An atypical case of choroidal neovascularization associated with pseudoxanthoma elasticum treated with intravitreal bevacizumab: a case report. *BMC Res Notes*. 2013 Dec 11;6:530.
- 10- Chatziralli I, Saitakis G, Dimitriou E, Chatzirallis A, Stoungioti S, Theodossiadi G, et al. ANGIOID STREAKS: A Comprehensive Review From Pathophysiology to Treatment. *Retina*. 2019 Jan;39(1):1-11.
- 11- Matonti F, Conrath J. Les stries angioïdes [Angioid streaks]. *J Fr Ophtalmol*. 2012 Dec;35(10):838-45.
- 12- García-López A, González-Castaño C. Membrana neovascular subretiniana asociada a estrías angioides tratada con bevacizumab intravítreo [Subretinal neovascular membrane in angioid streaks treated with intravitreal bevacizumab]. *Arch Soc Esp Oftalmol*. 2014 May;89(5):203-6.
- 13- Mangla A, Ehsan M, Agarwal N, Maruvada S. Sickle Cell Anemia. 2021 Apr 14. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. PMID: 29489205.

- 14- Ungureanu E, Geamanu A, Careba I, Grecescu M, Gradinaru S. Angioid streaks - a rare cause of neovascular glaucoma. Case report. J Med Life. 2014;7 Spec No. 4(Spec Iss 4):71-3.
- 15- Demirseren DD, Ugurlu N, Arman A, Emre S, Yavuz SO, Metin A. A case of pseudoxantoma elasticum. J Ocul Biol Dis Infor. 2013 May 5;5(3-4):83-5.
- 16- Murro V, Mucciolo DP, Giorgio D, Sodi A, Boraldi F, Quaglino D, et al. Coquille d'oeuf in young patients affected with Pseudoxantoma elasticum. Ophthalmic Genet. 2019 Jun;40(3):242-246.
- 17- Spaide RF. Peau d'orange and angioid streaks: manifestations of Bruch membrane pathology. Retina. 2015 Mar;35(3):392-7.
- 18- Tsang SH, Sharma T. Inborn Errors of Metabolism: Pseudoxanthoma Elasticum. Adv Exp Med Biol. 2018;1085:187-189.
- 19- Onishi AC, Nesper PL, Fawzi AA. Adaptive Optics Scanning Laser Ophthalmoscopy and Multimodal Imaging of Peau D'Orange in Pseudoxanthoma Elasticum. Ophthalmic Surg Lasers Imaging Retina. 2017 May 1;48(5):436-440.
- 20- Liaska A, Petrou P, Georgakopoulos CD, Diamanti R, Papaconstantinou D, Kanakis MG, et al. β -Thalassemia and ocular implications: a systematic review. BMC Ophthalmol. 2016 Jul 8;16:102
- 21- Georgalas I, Tservakis I, Papaconstantinou D, Kardara M, Koutsandrea C, Ladas I. Pseudoxanthoma elasticum, ocular manifestations, complications and treatment. Clin Exp Optom. 2011 Mar;94(2):169-80.
- 22- Drawz P, Ayyappan S, Nouraie M, Saraf S, Gordeuk V, Hostetter T, et al. Kidney Disease among Patients with Sickle Cell Disease, Hemoglobin SS and SC. Clin J Am Soc Nephrol. 2016 Feb 5;11(2):207-15.
- 23- Quaglino D., Boraldi F., Annovi G., Ronchetti I. A complexidade multifacetada de doenças genéticas: A Lesson from Pseudoxanthoma elasticum. In: Ikehara K., editor. Avanços no estudo das doenças genéticas. InTech; Rijeka, Croácia: 2011.
- 24- Valente-Frossard TNS, Cruz NRC, Ferreira FO, Belisario AR, Pereira BM, Gomides AFF, et al. Polymorphisms in genes that affect the variation of lipid levels in a Brazilian pediatric population with sickle cell disease: rs662799 APOA5 and rs964184 ZPR1. Blood Cells Mol Dis. 2020 Feb;80:102376.
- 25- Savastano MC, Minnella AM, Zinzanella G, Falsini B, Caporossi A. Successful long-term management of choroidal neovascularization secondary to angioid streaks in a patient with pseudoxanthoma elasticum: a case report. J Med Case Rep. 2014 Dec 22;8:458.
- 26- Mimoun G, Ebran JM, Grenet T, Donati A, Cohen SY, Ponthieux A. Ranibizumab for choroidal neovascularization secondary to pseudoxanthoma elasticum: 4-year results from the PIXEL study in France. Graefes Arch Clin Exp Ophthalmol. 2017 Aug;255(8):1651-1660.
- 27- Attaglia Parodi M, Romano F, Marchese A, Arrigo A, Llorenç V, Cicinelli MV, et al. Anti-VEGF treatment for choroidal neovascularization complicating pattern dystrophy-like deposit

associated with pseudoxanthoma elasticum. Graefes Arch Clin Exp Ophthalmol. 2019 Feb;257(2):273-278.

28- Gliem M, Birtel J, Herrmann P, Fimmers R, Berger M, Coch C, et al. Aflibercept for choroidal neovascularizations secondary to pseudoxanthoma elasticum: a prospective study. Graefes Arch Clin Exp Ophthalmol. 2020 Feb;258(2):311-318.

29- Rahman S, Srisuwananukorn A, Molokie RE, Gowhari M, Njoku F, Hussain FA, et al. Evaluation of point-of-care International Normalized Ratio in sickle cell disease. Res Pract Thromb Haemost. 2021 May 27;5(4):e12533.

30- Sasso BM, Cintra ML, de Souza EM. Pseudoxanthoma elasticum. Autops Case Rep. 2017 Dec 8;7(4):18-21

31- Boraldi F, Murro V, Lofaro FD, Mucciolo DP, Costa S, Pavese L, et al. Phenotypic Features and Genetic Findings in a Cohort of Italian Pseudoxanthoma Elasticum Patients and Update of the Ophthalmologic Evaluation Score. J Clin Med. 2021 Jun 19;10(12):2710.

32- Marconi B, Bobyr I, Campanati A, Molinelli E, Consales V, Brisigotti V, et al. Pseudoxanthoma elasticum and skin: Clinical manifestations, histopathology, pathomechanism, perspectives of treatment. Intractable Rare Dis Res. 2015 Aug;4(3):113-22.

33- Maalej A, Ouederni M, Khallouli A, Gabsi S. Stries angioïdes compliquées de néovaisseaux choroïdiens révélant un pseudoxanthome élastique : diagnostic et stratégie thérapeutique. À propos d'un cas [Angioid streaks complicated by choroidal neovascularization secondary to pseudoxanthoma elasticum: diagnosis and treatment. Case report]. J Fr Ophtalmol. 2012 Dec;35(10):803-8.

34- D'Marco L, Soto C, Dapena F. Pseudoxanthoma Elasticum and Cardiorenal Disease: A Case Report. Eur J Case Rep Intern Med. 2019 Dec 17;7(1):001260.

35- Naik RP, Haywood C. Diagnóstico do traço falciforme: implicações clínicas e sociais. Hematologia Am Soc Hematol Educ Program. 2015; 2015: 160-7.

36- Marchese A, Rabiolo A, Corbelli E, Carnevali A, Cicinelli MV, Giuffrè C, et al. Ultra-Widefield Imaging in Patients with Angioid Streaks Secondary to Pseudoxanthoma Elasticum. Ophthalmol Retina. 2017 Mar-Apr;1(2):137-144.