

CE Credit - Case Report(s) & Topic Review

Subtle Angioid Streaks Point to Underlying Paget's Disease

Ashley Price, OD^{1,2}; Lisa Schifanella, OD, MS^{1,2}; Cheryl Polinsky, OD^{1,2}

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ABSTRACT

Paget's disease of the bone (PDB) is a chronic and progressive abnormal remodeling of bones throughout the body and can result in several complications, including deafness and potential paraplegia. Fifty percent of patients with the ocular finding of angioid streaks within the retina are found to have an associated systemic condition, with PDB being one of them.¹ This case review highlights the clinical findings of angioid streaks, as well as the necessary laboratory testing, imaging, and referrals required for the detection and management of PDB.

CASE PRESENTATION

A 70-year-old Caucasian woman presented to the clinic for her doctor-directed follow-up for intermediate-stage non-exudative macular degeneration in both eyes. She had no visual nor ocular complaints. Her ocular history included bilateral pigment dispersion syndrome without glaucoma and cataract surgery in both eyes, with vision correctable to 20/20 in each eye. Her medical history included type 2 diabetes, hypertension, and fibromyalgia. Current medications included methotrexate, meloxicam, and atenolol. She also reported a history of a fractured ankle as well as bone pain in her wrists, hip, and back.

Preliminary testing was unremarkable and anterior segment findings were stable in both eyes compared to her visit 6 months prior. These findings included krukenburg spindles on both corneas, as well as transillumination defects at 10:00 in each iris

Posterior segment findings regarding her macular degeneration were also stable, with intermediate drusen and pigment mottling centrally in both eyes with no evidence of choroidal neovascular membrane (CNVM) formation in either eye. However, it was noted that radiating outward from each optic nerve head (ONH) were

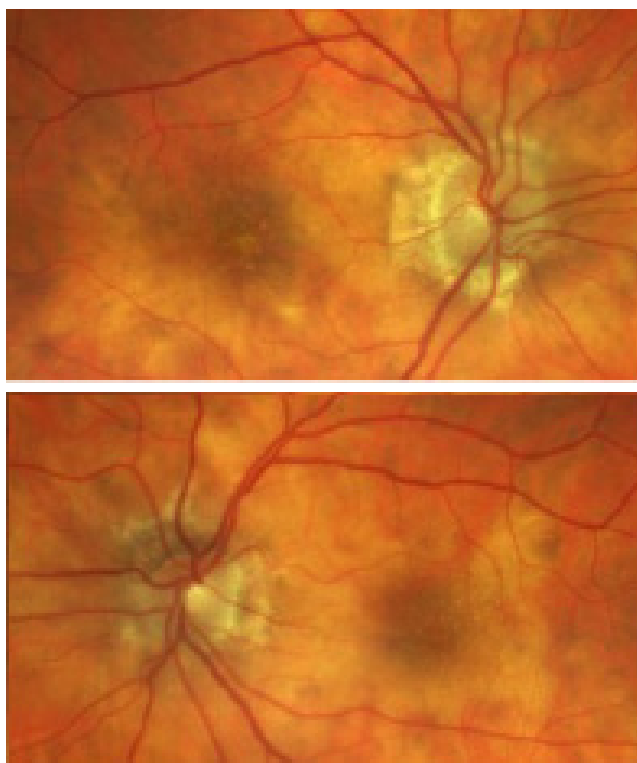


Figure 1 & 2: Angioid streaks radiating from both ONH.

very subtle, lightly colored, branching, linear lines deep to the retina (Figures 1-2). Fundus autofluorescence (FAF) images, along with optical coherence tomography (OCT), highlighted the changes to Bruch's membrane within the retina seen in her angioid streaks. (Figures 3-4). Based on the patient's demographics, including race, age, and history of bone pain and fractures, suspicions were high for PDB. Pseudoxanthoma elasticum (PXE), an inherited connective tissue disorder, was also considered because of its high association with angioid streaks. Laboratory testing was performed, including serum alkaline phosphatase to

¹Tuscaloosa Veterans Affairs Medical Center; ²University of Alabama at Birmingham School of Optometry

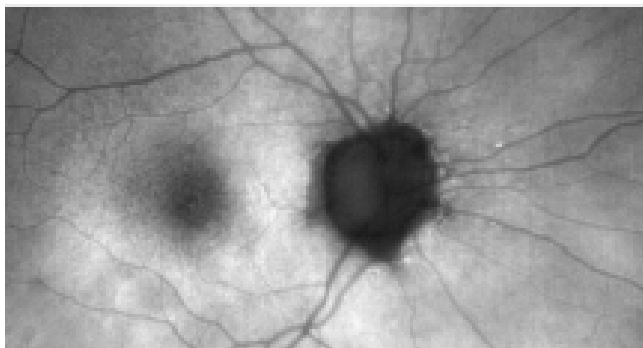


Figure 3 & 4: Hypoautofluorescent and hyperautofluorescent changes around ONH signifying presence of angioid streaks.



Figure 5: OCT of ONH through angioid streak with red brackets highlighting the structural changes between RPE-Bruch's membrane complex.

evaluate for PDB and a dermatology consultation to evaluate for PXE. Serum alkaline phosphatase results were elevated at 156, with the reference range being from 46 to 118. This elevated result was suggestive of PDB. A radiograph of the head was ordered (Figures 6-7), which also highlighted "extensive hyperostosis of the calvarium" pointing to PDB. The dermatology consultation revealed no evidence of PXE. Results of her laboratory testing and radiographs were communicated to her rheumatologist. The rheumatologist instituted treatment for PDB with 5mg of zoledronic acid via intravenous administration. Zoledronic acid is a

bisphosphonate delivered by infusion one time or yearly that works by slowing down the rate of bone turnover to aid in symptom relief in PDB.² Ocular treatment for the angioid streaks included polycarbonate lenses to protect her eyes from trauma and possible choroidal hemorrhage, as well as implementing the use of an Amsler grid daily for at-home monitoring for possible CNVM formation. At the time of this writing, the patient continues to be treated by rheumatology for PDB, and her vision has remained stable at 20/20 in each eye with no CNVM formation.



Figure 6 & 7: Radiographs of the cranium showing calcification and thickening.

DISCUSSION

Angioid (meaning "vessel-like") streaks, first named by Knapp in 1892, were considered to be of vascular origin until 1917, when Kolfer determined that the true level of angioid streak change was within Bruch's membrane.³ At the histologic level, angioid streaks represent tiny breaks or dehiscence within Bruch's membrane. Calcium accumulation thickens Bruch's membrane and makes it brittle, resulting in the tiny breaks. Bruch's membrane plays an important role in separating the retinal pigmented epithelium (RPE) and choriocapillaris, ultimately separating retinal and choroidal blood flow. Bruch's membrane also serves to regulate the transportation of nutrients and waste between the two layers.⁴ Because of the tiny breaks in a brittle Bruch's membrane, the weak membrane is susceptible to rupture, which allows blood from a choroidal hemorrhage to rise through the breaks (subretinal hemorrhage) or allows vessels from the choroid to rise through the breaks and form a choroidal neovascular membrane (CNVM). Indeed, 15% of patients with angioid streaks develop profound vision loss secondary to subretinal hemorrhaging after mild head trauma, while 86% of angioid streak patients develop a CNVM.¹ Typically, angioid streaks are bilateral, radiating outward from both optic nerve heads, with variation in color depending on the background fundus. The angioid lines appear jagged or irregular.⁵ Angioid streaks do not regress and can grow in both length and width over time.¹

Angioid streaks typically present in the 6th decade of life with no predilection for gender or race.⁴ The first systemic condition associated with angioid streaks was Pseudoxanthoma elasticum (PXE). PXE causes defective elastic fibers within connective tissue due to an autosomal recessive mutation of ABCC6 gene.¹ Typical findings for PXE include yellow papules most commonly seen on the neck and axillary cubital areas, often referred to as “plucked chicken” neck.¹ The altered elastic tissue can impact many major organs throughout the body, including the eye and cardiovascular system.¹ In regards to other ocular findings, diffuse pigment mottling of the retina called peau d’orange is a common finding in PXE patients.¹

The list of commonly recognized associated conditions now also includes Ehlers-Danlos, PDB, and sickle cell anemia. The incidence of angioid streaks varies based on the associated systemic condition. Almost all PXE patients have angioid streaks, and PXE represents the most commonly associated systemic disease for angioid streaks (59-87%).¹ The second most common association is PDB, representing 2% of angioid streak cases, while angioid streaks are present in 8-15% of PDB patients.⁶ Only 0.9-6% of sickle cell patients have angioid streaks, and the number is even lower for Ehlers-Danlos.⁶ In fact, the existence of a link between Ehlers-Danlos and angioid streaks is debated in the literature, with many considering the link only coincidental.^{1,5} Newest research suggests angioid streaks are linked to many other conditions, including hereditary spherocytosis, macular degeneration, thalassemia, Marfan syndrome, acromegaly, epilepsy, and others.^{5,6,7} Although systemic associations have been supported with research, 50% of cases of angioid streaks remain idiopathic. Those patients with an identified associated systemic disease tend to develop angioid streaks at an earlier age, depending on said condition, and have an increased likelihood of CNVM development.⁵

Table I: Systemic associations related to angioid streaks and appropriate steps for diagnosis^{1,3,4,5,6,7}

Systemic Disease	Diagnosis
Pseudoxanthoma Elasticum	Dermatology consultation
Ehlers-Danlos	Physical exam, dermatology consultation, genetic testing, cardiology consultation
PDB	Alkaline phosphatase lab, radiographs
Sickle Cell	Hemoglobin electrophoresis

Table II: Common signs and symptoms in PDB^{2,6,8,9}

Signs or Symptoms of PDB
Bone pain
Bone fractures
Bone deformity
Spinal canal stenosis
Deafness
Hydrocephalus
Sarcoma

PDB is characterized as a chronic, progressive abnormal remodeling of bone throughout the body. In PDB, there is an increase in both bone formation by osteoblasts and bone reabsorption by osteoclasts, resulting in a woven bone matrix that is weak and prone to fracture. Any bone in the body is susceptible to such changes, but the spine, pelvis, and skull are the most common. The risk of developing PDB is highest for Caucasian males of increasing age with an associated family history of PDB. It is believed that anywhere from 15-30% of patients with PDB have a positive family history, and a positive family history is associated with earlier age of diagnosis and increased severity of disease.⁸ Genetic researchers have found a link between PDB and a genetic autosomal dominant mutation in the gene SQSMT1 that codes for a protein important in nuclear kappa B signaling.¹ However, the pathogenesis is not fully understood.² Research suggests that 80% of patients with this mutation develop PDB by the seventh decade.⁶ There are currently 15 other potential genetic loci affected in PDB.⁵ In addition, environmental risks have also been linked to PDB, including deficiency in vitamin D and vitamin C, as well as a history of skeletal trauma, toxin exposure, and/or previous slow viral infection like measles.¹ Besides bone fractures, PDB patients often have radiographic evidence of bone enlargement and altered bone shape. Such physical changes in bones throughout the body can lead to complications, including deafness, obstructive hydrocephalus, spinal cord stenosis, and even paraplegia. However, fewer than 10% of patients with PDB receive medical intervention for PDB, while an estimated 75% of PDB patients are asymptomatic. In fact, PDB is often found incidentally on radiographs. The most common symptom reported in symptomatic PDB patients is bone pain in 73%, followed by deafness in 8.9% and fractures in 8.5%.²

Around 8-15% of patients with PDB will develop angioid streaks. A characteristic finding in PDB is calcification of elastic tissue throughout the body, including the elastic layer found in the middle layer of Bruch’s membrane.⁵ This calcification creates a brittle, weak barrier prone to the complications mentioned above: subretinal hemorrhage with minor trauma and CNVM. In addition, PDB is linked with optic nerve atrophy, the exact mechanism of which is not yet understood.⁵

A more serious but rare complication of PDB is osteosarcoma, an aggressive form of bone cancer. The 5-year survival rate for osteosarcoma is estimated at around 10%, with the mean survival rate being only 27.8 months.¹⁰ Osteosarcoma has a high rate of metastasis, most commonly to the lung. The longer the duration and increased severity of PDB are associated with a higher risk for osteosarcoma. Importantly, osteosarcoma can be seen as the presenting finding in PDB patients due to the large percentage of PDB patients who are asymptomatic and not yet diagnosed with PDB.¹⁰ While the estimated rate of osteosarcoma in PDB patients is relatively low at 0.03%, because of the associated poor prognosis, it is an important consideration for patients with PDB.⁴

Diagnosis of PDB can be greatly aided by laboratory testing and/or radiographs. Serum alkaline phosphatase (ALP) is considered the first-line choice for screening for suspected PDB with a sensitivity of 57.7% and specificity of 88.9%.⁵ ALP can be attained relatively easily with a blood draw and is a cheaper alternative to radiographs. Elevated ALP reflects elevated bone turnover and/or liver dysfunction, but it is not specific to PDB. In PDB, the overactivity of the osteoblasts leads to overproduction of ALP, resulting in the high levels of ALP in the bloodstream.¹¹ To supplement an elevated ALP test, radiographs are used to look for PDB-specific changes. Radiographs of the abdomen alone diagnose 89% of PDB cases, while 93% of PDB cases are found with a combination of radiographs of the abdomen, upper tibia, and skull.² Radiologic findings of all three areas mentioned demonstrate cortical thickening, osteolytic areas, and bone expansion/deformity. PDB can be further assessed for the extent of the disease with radionuclide bone scans with intravenous radiolabeled bisphosphonate.⁵ The radionuclide pools in areas with an increased rate of bone remodeling, thus allowing for the localization of affected bone tissue.²

MANAGEMENT

An interdisciplinary approach to care is vital for PDB patients. After diagnosis with ALP serum levels and radiographs, most PDB patients are managed by rheumatology. Typically, only those symptomatic with bone pain will receive medical intervention. First-line therapy for pain management is a one time or yearly bisphosphonate infusion, typically zoledronic acid.² While the bisphosphonate infusions help with bone pain and potentially slow the rate of bone remodeling, the infusions have not been shown to prevent bone fractures, deafness, or blood loss during orthopedic surgery. The infusions only help to relieve bone pain and potentially slow the rate of bone remodeling.⁴ Bisphosphonate infusions have a low rate of side effects, but flu-like symptoms can occur.² Importantly, there is no current evidence that bisphosphonate infusions stop progression or reverse damage from PDB.⁹

As mentioned above, an important and potentially fatal complication of PDB is osteosarcoma. A consultation with oncology can be considered to rule out osteosarcoma in PDB patients.

Because of the woven or mosaic appearance of bone in those affected by PDB, patients are at an increased risk of fracture with minor falls. Physical therapy can be useful to assess PDB patients for fall risk and to help with fall prevention.

Ocular treatment for patients with PDB focuses on preventing subretinal hemorrhages and early detection of CNVM. As mentioned, 15% of angioid streak patients suffer profound vision loss secondary to subretinal hemorrhaging after minor trauma to the eyes. PDB patients can lower their risk of potential trauma sequelae to the eyes with polycarbonate lenses and safety glasses for high-risk activities.^{1,5} It is recommended that PDB patients be fitted with polycarbonate lenses due to their high impact resistance quality. To detect and treat CNVM formation early, it is recommended that PDB patients have regular comprehensive eye exams and monitor the vision in each eye between exams with a home Amsler grid. Like CNVM in exudative macular degeneration, angioid streak-related CNVMs are typically treated with anti-VEGF injections. CNVM formation tends to be seen along or near the angioid streaks. Bilateral CNVM occurs within 18 months in many angioid streaks patients. Greater angioid streak width and length, as well as closer proximity to the macula, are associated with a higher risk of CNVM development.¹² Legal blindness is the result in 50% of the cases of untreated macular CNVM secondary to angioid streaks, further highlighting the importance of closely monitoring patients with angioid streaks.³ CNVM can reactivate after treatment in the same location or develop in a different location.⁴ Although the mechanism of formation of CNVM is similar between angioid streaks and exudative macular degeneration at the level of Bruch's membrane, the decline of visual function from CNVM from angioid streaks is faster. This quick decline is thought to be because of the high likelihood of reactivation with angioid streak-related CNVM.⁴ Response and outcome to angioid streak associated CNVM treatment varies significantly among patients with worse visual prognosis in younger patients.⁴

Advancements in imaging technology have improved the ability to detect angioid streaks. Because angioid streaks are often subtle, they can easily be missed by a typical fundus photograph until complications such as subretinal hemorrhage or CNMV arise. However, the addition of fundus autofluorescent (FAF) photos to color fundus photography can allow for earlier detection of the subtle changes in a non-invasive manner. Autofluorescent photography captures the presence of lipofuscin within the RPE and thus provides clinicians insight into the health and metabolism of the RPE.^{1,4} FAF hypoautofluorescence represents RPE loss or death, while hyperautofluorescence signifies actively

dying RPE. Therefore, FAF photos allow for visualization of RPE atrophy and potential areas of future atrophy.^{1,6} FAF photos can allow for much easier visualization of the angioid streaks (Figures 3-4).

Another important and non-invasive imaging modality for angioid streaks is ocular coherence tomography (OCT), which allows visualization of the intricate layers of the retina, including Bruch's membrane. In angioid streaks, the adherence of the RPE and Bruch's membrane is altered because of the structural changes within Bruch's membrane. An OCT of angioid streaks may be able to image these structural changes which appear as undulations both in and out of the two layers, as seen in the red brackets of Figure 5. It is speculated that these structural changes are secondary to the pulling forces around the eye from the extraocular muscles.⁴ The areas of Bruch's membrane that have become calcified may also be visualized on OCT as hyperreflective spots. Furthermore, OCT is valuable for detecting fluid within the retina and for detecting CNVM formation.⁴ OCT-angiography (OCT-A) has also gained traction in the assessment of CNVM. OCT-A allows for non-invasive imaging of abnormal blood flow as seen in CNVM formation.⁴ This newer imaging technique confirmed previous research that CNVM formation follows the path of angioid streaks.⁴

Fluorescein angiography (FA) can also be utilized to evaluate for angioid streaks and associated CNVM formation, but FA is more invasive as it requires intravenous administration of fluorescein dye while fundus photos are taken. FA has its value when CNVM is suspected, and clinical examination of the fundus is difficult. Active CNVMs will leak on FA.¹ It is important to know that presentation of angioid streaks on FA is opposite to that of FAF. Areas of RPE atrophy will produce hyperautofluorescence, while actively dying RPE will be hypoautofluorescent. FA can be used as supplemental imaging, but it is not always necessary for monitoring of angioid streaks or CNVM formation, as the conditions are often more easily detected with other modalities (clinical examination, fundus photos, FAF, OCT).

CONCLUSION

Angioid streaks can be a subtle retinal finding surrounding both optic nerves. Although angioid streaks are potentially idiopathic, 50% of patients with angioid streaks have an underlying systemic condition. Thus, these patients require a thorough workup and timely referral to the relevant subspecialty. PDB remains an important differential for angioid streak patients, especially those with a history of fractures, bone pain, and hearing loss. When suspicious for PDB, clinicians can utilize serum alkaline phosphatase followed by radiologic testing to aid in the diagnosis, with prompt referral to rheumatology if positive. Around 75% of patients with PDB remain undiagnosed, but significant and even fatal complications such as deafness, paraplegia, and osteosarcoma can result from PDB, making detection

of angioid streaks and subsequent systemic testing and referrals an important task for eye care providers. Regardless of the systemic cause for angioid streaks, patients with angioid streaks should utilize ocular protection in the form of polycarbonate spectacles and safety glasses, regularly monitor their vision with an Amsler grid to allow for early detection of CNVM formation, and obtain annual comprehensive eye examinations.

The views expressed are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

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