

IN-DEPTH REVIEW

Association Between Pseudoxanthoma Elasticum and Bleeding

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ABSTRACT

Pseudoxanthoma Elasticum (PXE) is a rare genetic disease caused by a mutation of the ABCC6 gene, resulting in calcification of elastic fibers of the skin, eye and other organs and tissues that contain elastin. Because calcified arteries can bleed, hemorrhage from various organs is a reported complication of PXE. We conducted a literature review of all English language published articles reporting bleeding in patients with PXE. In this literature review, we identified 51 papers. Of those, 30 (59%) included at least 1 case of bleeding. Within these 30 papers, bleeding was reported in a total of 130 patients. Of the cases of bleeding, 113 occurred in the gastrointestinal tract, 12 occurred in the brain, 2 in the skin, 1 in the nose, 1 in the gums and 1 in the uterus. Clinicians and patients should be made aware of the risk of these significant complications, to facilitate preventive measures, prompt recognition and treatment.

INTRODUCTION

Pseudoxanthoma Elasticum (PXE) is a rare genetic disease caused by a mutation of the ABCC6 gene. This results in calcification of elastic fibers of the skin, eye and other organs and tissues that contain elastin. The internal elastic lamina of arteries can be affected, resulting in vascular complications including bleeding. Ringpfeil et. al. described mutations in the ABCC6 transporter protein inherited in a an autosomal recessive pattern in PXE.¹ Consequently, any organ containing elastic tissue can be affected, with skin² and eyes³ being the most common. Skin lesions are characterized by yellow xanthoma-like patches, papules and folds (figure 1A,1B). Mucosal lesions have also been described, particularly on the oral mucosa (figure 2). and the classic eye characteristics are angioid streaks in the retina (figure 3)⁴ though any elastic-

containing tissue can be affected. Heart valves can be involved, resulting in mitral valve prolapse⁵ and myocardial infarctions at an early age⁶. The latter complication occurs as a consequence of calcification of the coronary arteries.

PXE can be identified at any age and has been reported in ages as young as age 4.⁷ It is associated with numerous complications including characteristic skin lesions (Figure 1A, 1B) and angioid streaks in the retina (Figure 3). Serious vascular complications including myocardial infarction and stroke at a young age have been reported⁸. Because calcified arteries can bleed, hemorrhage from various organs is a reported complication of PXE. We therefore conducted a literature review of all English language published articles reporting bleeding in patients with PXE.

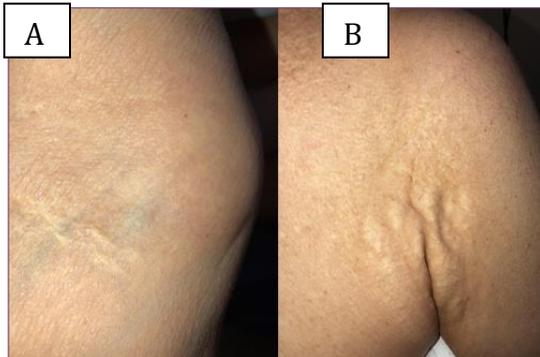


Figure 1. A) Yellow xanthoma-like papules typical of PXE B) Papules become confluent to form redundant folds in the axilla.

METHODS

A PubMed search was conducted using these terms: bleed, hemorrhage, haemorrhage, and pseudoxanthoma elasticum. Review articles were not included, nor were articles that did not include original cases of bleeding or hemorrhage. For reasons of scope, we did not include retinal bleeding in this review. For each report, we recorded the year of publication, number of subjects with PXE, the number with a bleeding event, the site of bleeding, and other complications among those with bleeding.



Figure 2. Yellow papules and patches on the lower lip.

RESULTS

Using the search terms outlined above, we identified 51 papers. Of those, 30 (59%) included at least 1 case of bleeding.⁹⁻³⁸ (The 21 remaining papers were excluded because they were review articles or did not include cases.) Within these 30 papers, bleeding was reported in a total of 130 patients. Of the cases of bleeding, 113 occurred in the gastrointestinal tract, 12 occurred in the brain, 2 in the skin, 1 in the nose, 1 in the gums and 1 in the uterus (see Table 1).



Figure 3. Angioid streaks of the retina

DISCUSSION

Figure 4 shows calcified elastic fibers in the skin biopsy of a patient with PXE. Retinal bleeding is very common, but bleeding at other sites can also occur and is the subject of this review. There were many sites of

bleeding identified in this literature review, including the brain⁹, skin³⁵, nose³⁵, uterus³⁵ and gums,¹³ but gastrointestinal bleeding was particularly common^{11,15,28,30}, followed by cerebral hemorrhage^{12,14}. Because of the bleeding tendency, certain management

Table 1

Year	Author	Site of Bleeding	Other complications	Number in study	Number with bleeding
2020	Sunmonu NA	Brain	stroke	1	1
2021	Lanfranco S	Brain	stroke	1	1
2016	Dibi A	gastrointestinal	vascular disease	2	2
2014	Drue HC	brain		1	1
2008	Adam AM	gums		1	1
2008	Bock A	brain		1	1
2007	Goral V	gastrointestinal		1	1
2006	Antiga E	gastrointestinal		1	1
2005	Golliet-Mercier N	gastrointestinal		1	1
2004	Makharia GK	gastrointestinal		1	1
2002	Ospedale S	gastrointestinal/intercranial	gastric artery aneurysm/ischaemic attack	29	2
1996	Spinzi G	gastrointestinal		2	2
2000	Costopanagiotou E	gastrointestinal		1	1
1992	Yap EY	gastrointestinal	aneurysms of the gastric arteries	1	1
1991	Yamamura H	gastrointestinal		1	1
1990	Slade AK	gastrointestinal		1	1
1988	Jacyk WK	gastrointestinal		7	1
1988	Kundrotas L	gastrointestinal		1	1
1988	Belli A	gastrointestinal	vascular abnormalities	2	2
1982	Drost H	gastrointestinal		1	1
1982	Morgan AA	gastrointestinal		1	1
1980	Keim HJ	gastrointestinal	total gastrectomy and partial jejunal resection	1	1
1973	Olbromska W	gastrointestinal		1	1
1973	Van Waes L	gastrointestinal		1	1
1968	Gignoux R	gastrointestinal	total gastrectomy	1	1
1966	Dhers A	gastrointestinal		3	3
2000	van den Berg JS	gastrointestinal, skin, nose, uterus		100	17 gastrointestinal; 2 skin; 1 nose; 1 uterus
1967	Grant AK	gastrointestinal		3	3
2004	Bercovitch L	gastrointestinal		306	66
1988	Neldner KH	gastrointestinal and brain		100	8

strategies can be used to minimize that adverse outcome. For example, the avoidance of blood thinners, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) should be considered given these risks. Other activities known to be associated with gastrointestinal bleeding such as heavy alcohol consumption, cigarette smoking, and dual antiplatelet therapy should be avoided. Periodic checks of the stool for blood should be considered as part of the routine examination of patients with PXE. Because of the known risk of retinal bleeding and intracranial hemorrhage, trauma to the head should be avoided, and certain sports such as boxing or soccer may not be ideal for patients with PXE.

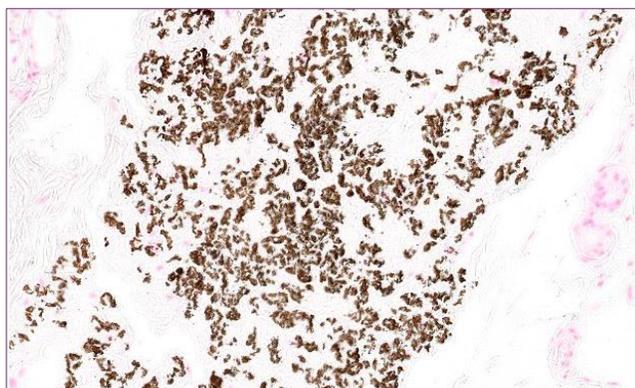


Figure 4. Calcified elastic fibers in the dermis of a patient with PXE

CONCLUSION

In summary, PXE is associated with bleeding from many sites. While retinal bleeding is most common, there are many reports of gastrointestinal followed by bleeding in the brain. Clinicians and patients should be made aware of the risk of these significant complications, to facilitate preventive measures, prompt recognition and treatment.

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