

Imaging of in vivo pseudoxanthoma elasticum via multiphoton microscopy and optical coherence tomography



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INTRODUCTION

Pseudoxanthoma elasticum (PXE) is an autosomal recessive disorder of abnormal elastic tissue deposition and calcification.¹ PXE primarily affects the elastic fibers in the dermis of the skin, Bruch membrane of the eye, and the media and intima of mid-sized arteries. The skin findings may present as small yellow, orange, or cream-colored papules, resembling plucked-chicken skin or cobblestone. The skin on the neck and skin flexures may be lax and redundant because of the impaired elastic features, causing a degree of psychosocial distress. Histologic changes of the skin consist of fragmented and disorganized elastin fibers in the mid and deep reticular dermis with overlying calcium deposits.

The diagnosis of PXE is primarily clinical with histologic confirmation. Multiphoton microscopy (MPM) is a noninvasive imaging technique that allows visualization of skin components. MPM is based on optical signals generated through nonlinear light-matter interactions. MPM can easily contrast keratinocytes, collagen, and elastin fibers to a depth of 200 μm . Optical coherence tomography (OCT) is an imaging technology that uses near-infrared light and the reflective properties of tissue to generate real-time, noninvasive cross-sectional images of biological tissues to a depth of 1 to 2 mm. OCT makes it possible to visualize structures in the skin such as the epidermis, dermoepidermal junction (DEJ), dermis, hair follicles, sweat glands, and blood vessels. Here we investigate the ability of MPM and OCT to provide a noninvasive diagnosis of skin in a patient with PXE.

Abbreviations used:

DEJ: dermoepidermal junction
MPM: multiphoton microscopy
OCT: optical coherence tomography
PXE: pseudoxanthoma elasticum

CASE REPORT

We present the case of a 65-year-old woman with a long-standing, biopsy-proven diagnosis of PXE. She had subtle yellowish skin papules coalescing into plaques on the lateral neck with skin laxity of the axilla (Fig 1), face, neck, and groin. Noncutaneous history of PXE was significant for angioid streaks, atrophic retinal break of the right eye, angina pectoris, myocardial infarction, peripheral artery disease, coronary artery disease, vitreous degeneration, and bilateral posterior vitreous detachment.

Noninvasive imaging with MPM and OCT was performed to visualize any irregularities in dermal elastin and/or calcium deposits. The patient consented to the imaging procedure, which was approved by the Institutional Review Board. We imaged an area of lax skin on the right axilla with dynamic OCT (VivoSight Dx, Michelson Diagnostics Ltd, London, UK) and MPM tomography (MPTflex, JenLab GmbH, Jena, Germany) and processed images using the freely available ImageJ software (National Institutes of Health, Bethesda, MD).

Multiphoton microscopy

Specifications and settings of the MPM tomography system and methods are outlined in prior work.²⁻⁴

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Fig 1. PXE in the patient's scanned, right axilla. Note the lax and redundant skin.

The patient's images showed an abundance of chopped, fragmented, and irregular elastin bundles in the lower part of the visualized papillary dermis about 30 μm below the DEJ with clearance of elastin bundles in the reticular dermis (Fig 2). Calcium deposits were undetectable via visual inspection of MPM images.

Optical coherence tomography

OCT imaging of the lax axilla skin displayed large areas of hyporeflective, homogeneous areas of attenuation, or signal loss, in the mid dermis (Fig 3). In contrast to normal skin, which attenuates the image at about 0.7 to 0.9 mm, the depth of the PXE image exhibits relative superficial attenuation of 50% at 0.3 mm and near complete attenuation at a depth of about 0.53 mm. The observed changes may be associated with the noted abundance of elastin at and above this level on histology.

DISCUSSION

PXE is a systemic condition with multiple phenotypes, making it difficult to diagnose clinically. Noninvasive imaging with MPM was able to capture a dermatologic feature of PXE consistent with fragmented and irregular dermal elastin. Although these findings are not specific for PXE, we find that MPM can be a useful diagnostic tool. The contrast mechanisms of MPM are based on second harmonic generation from collagen fibers and 2-photon-excited fluorescence from nicotinamide adenine dinucleotide plus hydrogen, flavin adenine dinucleotide, keratin, melanin, and elastin fibers. MPM images of age-controlled normal skin from a non-sun-exposed area (Fig 3) leverage the contrast

between the autofluorescence from elastin and the second harmonic generation from collagen in the dermis, revealing the harmony of normal dermal collagen and elastin and making such MPM images of PXE clearly characteristic of the condition.

Based on our literature search, no prior reports of in vivo MPM of PXE have been performed. Ex vivo MPM analysis of PXE has demonstrated similar findings showing higher densities and larger amounts of elastin in the dermis with direct comparison to histopathologic images.^{5,6}

OCT imaging of PXE has shown dermal clusters of hyporeflective aggregates with peripheral clefts, which our images do not show.⁷ Another imaging modality known as *reflectance confocal microscopy* (RCM) has been used to image perforating PXE in a prior study, showing a disorganized arrangement at the DEJ and hyperreflective, amorphous material in the papillary dermis which resembled eggs in a basket.⁸ Reflectance confocal microscopy images of our patient's axilla, however, demonstrated no such findings.

Multiple skin diseases require biopsy for diagnosis, and PXE is one such diagnosis that would benefit from histologic confirmation. MPM offers an alternative noninvasive diagnostic method that spares the patient from an invasive biopsy. The main limitation of this modality is that MPM has yet to be widely adopted. It is expensive, imaging time is lengthy, imaging depth maximizes at 200 μm , its field of view is minimal, and scanning curved skin surfaces is challenging due to the large, 1.5-cm lens. OCT offers another method of dermal imaging at a maximum depth of 1 to 2 mm for some devices, covering the deeper parts of the dermis in a shorter amount of time but at a much lower resolution. Therefore, it cannot yet be used as a reliable means of diagnosis.

The differential diagnosis of PXE includes cutis laxa, solar elastosis, mid-dermal elastolysis, PXE-like papillary dermal elastolysis, and fibroelastolytic papulosis, which are all consequences of altered elastin fibers. PXE-like histologic findings have also been reported in diseases like lipodermatosclerosis, morphea profunda, erythema nodosum, granuloma annulare, lichen sclerosis, tumefactive lipedema, and basal cell carcinoma. Optical imaging in dermatology is in early developmental stages, and we aim to advance the process and help establish guidelines in diagnostic optical imaging of these diseases.

This report describes the findings of MPM and OCT imaging of PXE in vivo, offering what is known as an *optical biopsy*. We show PXE can adequately be imaged in vivo with MPM and OCT to aid in diagnosis, setting the stage to avoid unnecessary

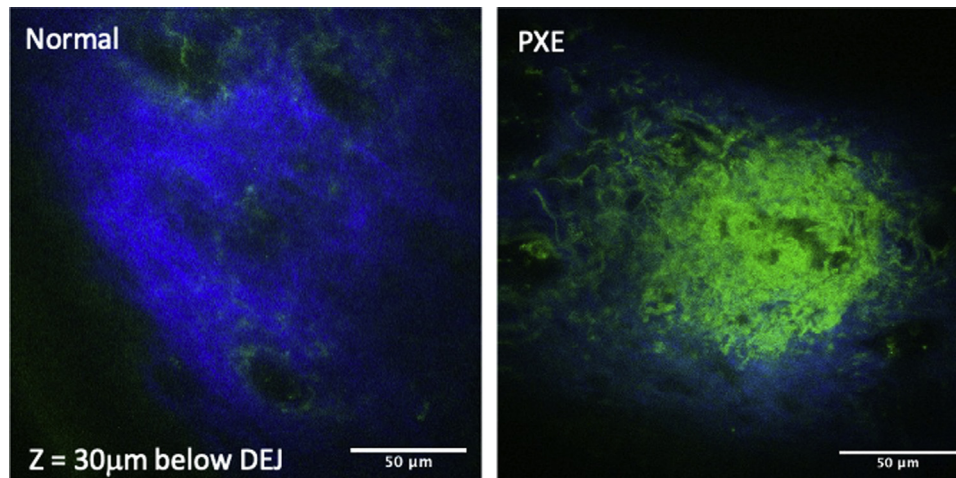


Fig 2. MPM images of normal skin (**left**) vs PXE (**right**), 30 μm below the DEJ. PXE is characterized by dense bundles of fragmented elastin (*bright green*) surrounded by organized collagen (*blue*). Normal, non-sun-exposed skin of a different patient controlled for age shows organized collagen and harmonized elastin.

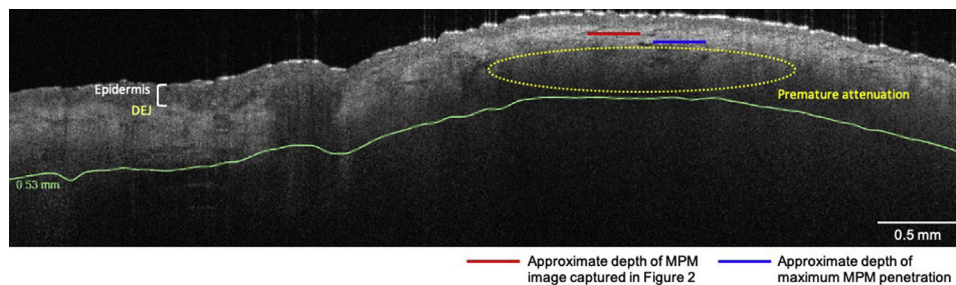


Fig 3. OCT cross-section of PXE shows homogenous areas of premature signal loss (*yellow, dotted circle*), with 50% of total attenuation at 0.3 mm below the skin surface and near-complete attenuation at about 0.53 mm. The approximate depth of the MPM image at 30 μm below the DEJ is marked by the red line, and an approximation of the maximum depth MPM can penetrate is marked by the blue line.

procedures when a diagnosis is uncertain as new versions of these improved technologies are being developed.

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