Granulomatous Dermatitis With Pseudoxanthomma Elasticum–Like Changes

Report of a Case in a Patient With Cystic Fibrosis

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Background: There is scant literature that documents pseudoxanthoma elasticum (PXE)–like histologic changes in the setting of inflammatory skin diseases. This article documents granulomatous dermatitis with PXE-like changes in a patient with cystic fibrosis. This is the first report of its kind, to our knowledge.

Observations: A 33-year-old woman with cystic fibrosis developed a papular eruption on the flexural surfaces of the upper and lower extremities, which was initially treated with prednisone. A punch biopsy showed granulomatous inflammation and associated PXE-like changes. The combined histologic and clinical findings were most consistent with granuloma annulare. There was no family history of PXE or clinical manifestations of PXE. The rash gradually resolved itself over the next several months.

Conclusions: There are few publications that document PXE-like changes in association with various inflammatory skin conditions. Thus, the clinical significance of this finding remains uncertain. This case and previous reports are discussed in the context of current molecular and genetic knowledge. It is hoped that greater awareness of this phenomenon will promote further investigation and elucidation of the clinical and biologic significance of PXE-like changes observed in biopsies of inflammatory skin disorders.

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PSEUDOXANTHOMMA ELASTICUM (PXE) is a genetic disorder that primarily affects the skin, eyes, and cardiovascular system.1 It is caused by a homozygous or compound heterozygous mutation in the adenosine triphosphate–binding cassette, subfamily C, member 6 gene (ABCC6). Recent research has shown that heterozygote carriers of the ABCC6 gene also sometimes manifest the characteristic histologic and clinical phenotypic abnormalities of PXE.2

This article documents an intriguing example of PXE-like histologic changes that accompany granulomatous dermatitis in a patient with cystic fibrosis. Although Bowen and colleagues3 have recently documented PXE-like changes that accompany various inflammatory dermatoses in the biopsies of 13 patients, there are only a few reports that document these changes in the setting of granulomatous dermatitis.3 Moreover, to our knowledge, this is the first reported example of PXE-like changes in a patient with cystic fibrosis.

A 33-year-old white woman with advanced cystic fibrosis (homozygous ΔF508) was seen by her primary care physician for a nonpruritic erythematous papular eruption that involved the flexural surfaces of the knees, elbows, axillae, and groin. The lesions had developed while she was being treated intravenously with meropenem and ceftazidime for a pulmonary infection. She reported no fever, arthralgias, or constitutional symptoms associated with the eruption.

The history of the patient was remarkable for a vasculitic syndrome associated with antibiotic administration, for which she had received prophylactic prednisone concurrently with antibiotics. However, with this most recent course of antibiotics, corticosteroids had not been administered. After she reported the eruption to her primary care physician, she received oral prednisone. Although some improvement was noted, the lesions persisted. She was referred to the Dermatology department for evaluation approximately...
4 weeks after the onset of the rash. At that time, erythematous papules were observed on the flexural surfaces of her knees and right groin, along with mild erythema over her antecubital fossae and right axilla (Figure 1).

According to the patient, the papular nature and flexural distribution of the new eruption differed from her previous vasculitic reaction. The absence of associated arthralgia and constitutional symptoms further argued against a recurrent vasculitic drug reaction. Because of the complex medical condition of the patient and her impending lung transplantation procedure, a 4-mm punch biopsy from a right inguinal papule was obtained to rule out an infectious or neoplastic process and further address concern for a drug-related cause. The cutaneous lesions gradually resolved during the next few months without any additional treatments.

Microscopic examination revealed histiocytic dermal inflammation associated with destruction of collagen and elastic tissue, variable numbers of neutrophils and eosinophils, and focal deposition of stromal mucin. Less-inflamed portions of the dermis showed frayed and thickened elastic fibers associated with calcium deposition, which recapitulated the characteristic histologic findings of PXE (Figure 2). A von Kossa stain highlighted the calcified elastic tissue. There was no evidence of vasculitis, and no acid-fast microorganisms or fungal elements were identified via Ziehl-Neelson or Gomori methenamine silver stains, respectively.

Together, the histologic and clinical findings were most consistent with granuloma annulare, accompanied by secondary PXE-like changes. The histologic differential diagnosis included a granulomatous drug eruption, but this diagnosis was not favored clinically. Granulomatous inflammation is not a histologic feature of PXE; thus, PXE-like histologic changes were unexpected and motivated us to report this case. Although there is limited information in the medical literature with regard to the clinical significance of PXE-like histologic changes in biopsies of inflammatory skin disorders, Bowen and colleagues documented heterozygous mutations in the ABCC6 gene in tissue from 2 of 6 patients with apparently incidental PXE-like histologic changes.3

**COMMENT**

There is limited literature with regard to PXE-like changes associated with inflammatory skin diseases. A recent publication documented 13 patients without the clinical phenotype of PXE who manifested PXE-like histologic alterations in the lesional skin of various inflammatory skin diseases.3 The patients were elderly women with a range of histologic diagnoses. Of the 13 biopsies, 12 had been obtained from the lower extremities. In 1 patient, the biopsy was obtained from the palm with a histologic diagnosis of granuloma annulare. The other diagnoses mentioned in that report were lipodermatosclerosis, lichen sclerosus, morphea profunda, erythema nodosum, septal panniculitis, basal cell carcinoma, and fibrosing dermatitis not otherwise specified. The polymerase chain reaction was used for DNA amplification, and sequencing of exons 24 and 28 of the ABCC6 gene from paraffin-embedded tissue was performed on tissue from 6 of these patients. Heterozygous PXE-associated ABCC6 mutations were identified in 2 of the 6 specimens.3

Pseudoxanthoma elasticum is traditionally diagnosed by a set of major and minor clinical-pathologic criteria that were developed by a consensus conference in the early 1990s. The major criteria include: (1) characteristic skin involvement (yellow cobblestone-shaped lesions in flexural locations), (2) characteristic histopathologic features of lesional skin (altered and calcified elastic fibers, confirmed with a histochemical stain for calcium), and (3) characteristic ocular disease (angioid streaks, peau d’orange, or maculopathy) in adults more than 20 years of age. The minor criteria include: (1) characteristic histopathologic features of nonlesional skin (altered and calcified elastic fibers, confirmed with a histochemical stain for calcium), and (2) family history of PXE in first-degree relatives.4 Our patient meets only 1 of these criteria: characteristic histopathologic features of lesional skin (altered and calcified elastic fibers, confirmed with a histochemical stain for calcium), and (2) family history of PXE in first-degree relatives.4 Even though the flexural distribution of her eruption paralleled the distribution observed in patients with PXE, her lesions did not have the characteristic yellow cobblestonelike appearance. Furthermore, other than this recent transitory skin erup-

![Figure 1. Clinical presentation of erythematous papules distributed across flexural surfaces. A, Papules across the backs of both knees, and B, on right groin.](https://jamanetwork.com/)
tion, the patient did not manifest the other clinical features of PXE. In particular, she denied a history of visual disturbances or symptoms of cardiovascular disease, and she lacked a family history of PXE.

With the advent of molecular testing, direct genetic analysis for PXE is now possible. Currently available molecular tests for PXE have moderate sensitivity: they detect mutations in approximately 80% of affected individuals. Pseudoxanthoma elasticum has traditionally been classified as an autosomal recessive disorder, which requires homozygous or compound heterozygous mutations in the ABCC6 gene. Recently, however, there have been reports of heterozygous individuals with single ABCC6 mutations who fully manifest the characteristic clinical and histologic abnormalities of PXE. One of these reports documents 4 such cases. Other studies have shown that parents of children diagnosed with PXE, who themselves had not previously been diagnosed with the disease, can have mild ocular and/or cutaneous findings, such as the characteristic histopathology of PXE. Likewise, heterozygote carriers in families with a history of PXE have been shown to have dermal alterations very similar to, although less severe than, those of typical patients with PXE.

Thus, it is conceivable that our patient could have a heterozygous mutation within the ABCC6 gene. This would be an intriguing finding because the CFTR gene responsible for cystic fibrosis is also classified in the ABC cassette transporter gene family and is designated as ABCC7. An association between the two disorders cannot be explained on simple genetic grounds, however, because the genes reside on separate chromosomes: ABCC6 is on chromosome 16, whereas CFTR/ABCC7 is on chromosome 7. One could postulate a metabolic disturbance common to both conditions; however, we would expect to find additional reports of cystic fibrosis patients with PXE-like changes if this were the case. To the contrary, a search of English-language medical publications between 1939 and 2008 (http://www.ncbi.nlm.nih.gov/pubmed) did not identify any reports of PXE in patients with cystic fibrosis. We discussed with the patient the possibility of genetic testing for PXE, including polymerase chain reaction analysis on the skin biopsy specimen, but she declined further testing.

In summary, this report documents PXE–like changes in association with granulomatous dermatitis. To our knowledge, this is the first report of PXE-like histologic changes in the setting of cystic fibrosis. The clinical sig-

Figure 2. Skin biopsy. A, Scanning magnification that shows nodular and interstitial dermal inflammation (hematoxylin-eosin, original magnification ×20). B, Histiocytic infiltrate with necrobiosis (arrows) and thickened, hypereosinophilic elastic fibers (arrowhead) (hematoxylin-eosin, original magnification ×400). C, Calcified elastic fibers (arrows) (von Kossa, original magnification ×40).
The significance of PXE-like changes in biopsies of inflammatory dermatoses remains unclear owing to the small number of published reports, most of which lack long-term clinical follow-up. It is hoped that greater awareness of this phenomenon will promote further investigation to elucidate its clinical and biological significance.

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Author Contributions: Drs Olerud and George and Mr Tiger had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: McKenzie and Tran. Acquisition of data: McKenzie, Tran, Olerud, and George. Analysis and interpretation of data: Olerud and George. Drafting of the manuscript: Tiger, McKenzie, Olerud, and George. Critical revision of the manuscript for important intellectual content: Tran, Olerud, and George. Study supervision: McKenzie, Olerud, and George.

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REFERENCES


Archives Web Quiz Winner

Congratulations to the winner of our July quiz, Anisha Chandy, MBBS, Department of Dermatology, Christian Medical College, Vellore, India. The correct answer to our July challenge was elastosis perforans serpiginosa (EPS). For a complete discussion of this case, see the Off-Center Fold section in the August Archives (Diaz GJM, Berk D, Bruckner AL, Kim J. Annular and keratotic papules and plaques in a teenager. Arch Dermatol. 2009;145[8]:931-936).

Be sure to visit the Archives of Dermatology Web site (http://www.archdermatol.com) to try your hand at the interactive quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the Archives. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of The Art of JAMA II.