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Primary anetoderma as a possible preclinical cutaneous clue of Behçet's disease: evidence suggesting early microvascular-driven dermal elastolysis

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Abstract

Anetoderma is a rare elastolytic dermatosis characterized by focal loss of dermal elastic fibers leading to localized flaccid, atrophic, or herniated skin lesions. Although it may occur as a primary disorder or secondary to inflammatory dermatoses, infections, or trauma, immune-mediated vascular injury and dysregulation of extracellular matrix remodeling are increasingly recognized as key pathogenetic mechanisms. Behçet's disease (BD) is a multisystem inflammatory vasculitis driven by neutrophil hyperactivation and endothelial dysfunction, but elastolytic dermatoses have not been included among its classical cutaneous manifestations. We report a 27-year-old man who developed multiple asymptomatic atrophic lesions on the trunk and upper back. Histopathologic examination revealed preserved epidermal architecture and marked loss of elastic fibers in the papillary and mid dermis on Verhoeff-Van Gieson staining, consistent with primary anetoderma. Approximately 3 years later, the patient developed recurrent oral aphthosis, genital ulcers, papulopustular lesions, and a positive pathergy test, fulfilling the International Criteria for Behçet's Disease. The temporal sequence observed in our patient raises the hypothesis that primary anetoderma may represent a rare early cutaneous manifestation or a preclinical marker of microvascular inflammation in BD. Neutrophil-driven proteolysis and increased matrix metalloproteinase (MMP) activity may contribute to focal dermal elastolysis. Further observations are needed to clarify whether this association reflects a pathogenetic link or a coincidental finding.

Introduction

Anetoderma is a rare elastolytic dermatosis characterized by localized flaccid or herniated areas of atrophic skin, resulting from the focal loss of elastic fibers within the dermis. It may occur as a primary condition arising on previously normal skin or as a secondary phenomenon following inflammatory dermatoses, infections, trauma, or drug exposure. Increasing evidence suggests that immune-mediated vascular injury and the dysregulation of extracellular matrix remodeling play a pivotal role in its pathogenesis.¹

Behçet's disease (BD) is a chronic, relapsing, multisystem inflammatory disorder currently classified as a variable-vessel vasculitis. It is pathogenetically driven by profound immune dysregulation, neutrophil hyperactivation, and severe endothelial dysfunction.² Although mucocutaneous manifestations are considered hallmark features of the disease, elastolytic dermatoses have not traditionally been recognized among the typical dermatologic spectrum of BD.

To the best of our knowledge, the occurrence of primary anetoderma preceding the onset of BD has not been previously reported in the dermatologic literature. Herein, we describe a patient in whom primary anetoderma preceded the onset of the classical clinical manifestations of BD by approximately 3 years. While definitive causality cannot be established from a single observation, this intriguing temporal sequence raises the hypothesis that anetoderma may represent a rare, early cutaneous clue of underlying, subclinical microvascular inflammation in BD.

Case Report

A 27-year-old man was referred to our dermatology clinic for the evaluation of multiple asymptomatic atrophic lesions involving the trunk and upper back. According to the patient's history, the lesions had appeared 3 years earlier as small, soft, depressible macules that progressively evolved into slightly herniated atrophic plaques.

Clinical examination revealed multiple skin-colored, round-to-oval flaccid macules and plaques with a finely wrinkled surface and a characteristic sac-like appearance (herniation-like phenomenon). Upon palpation, the lesions were remarkably soft and displayed the typical "buttonhole" sign, where the finger easily sinks into the underlying focal dermal defect (Figure 1). Histopathologic evaluation demonstrated no significant epidermal or dermal architectural abnormalities, with preserved epidermal stratification and no evident cytologic atypia. The dermis appeared unremarkable on routine hematoxylin-eosin staining, without obvious fibrosis, sclerosis, or significant inflammatory infiltrates in fully developed lesions. However, special elastic stains (Verhoeff-Van Gieson) demonstrated a marked reduction to near-complete loss of elastic fibers within the papillary and mid-reticular dermis, with relative preservation of collagen bundles, a finding pathognomonic for anetoderma (Figure 2).¹ No significant vascular thrombosis was observed at the time of biopsy.

Approximately 3 years after the initial onset of these elastolytic lesions, the patient developed recurrent oral aphthosis (≥ 3 episodes per year), severe genital ulcerations, and papulopustular skin lesions. A pathergy test was performed and yielded a strongly positive result. Based on these compelling clinical findings, the diagnosis of BD was firmly established according to the International Criteria for Behçet's Disease.³ The patient obtained a score of 5 points (oral aphthosis, genital aphthosis, skin lesions, positive pathergy), robustly fulfilling the diagnostic threshold for BD.

A comprehensive laboratory evaluation was performed to investigate potential autoimmune conditions known to be associated with anetoderma. Antinuclear antibodies, extractable nuclear antigen antibodies,

Anti-double-stranded DNA antibodies, anti-cardiolipin antibodies, and anti- β 2 glycoprotein I antibodies were all negative. Complement levels were within normal limits.

The patient was initiated on a therapeutic regimen of azathioprine (2 mg/kg/day) combined with a short course of oral prednisone (initial dose 0.5 mg/kg/day followed by gradual tapering), strictly adhering to the current European League Against Rheumatism recommendations for the management of Behçet's syndrome with mucocutaneous involvement.⁴ Following treatment, the patient achieved complete clinical remission, defined by the total absence of recurrent oral or genital ulcerations, the resolution of inflammatory skin lesions, and a lack of systemic disease activity for more than 12 months under stable therapy. At the time of the most recent dermatologic follow-up, the disease had remained in sustained remission for approximately 1 year on azathioprine maintenance therapy.

Importantly, the elastolytic lesions in our patient developed on previously normal-appearing skin and were not preceded by any clinically evident inflammatory dermatoses, trauma, infections, or drug exposure. Furthermore, histopathology did not demonstrate the dermal fibrosis or residual dense inflammatory infiltrates that are typically observed in secondary, post-inflammatory anetoderma. These robust clinical and histological findings strongly support the diagnosis of primary anetoderma rather than a secondary elastolytic process.

Discussion

Primary anetoderma has been well-documented in association with various autoimmune disorders, particularly systemic lupus erythematosus and antiphospholipid antibody syndrome, suggesting that subclinical vascular injury and immune-mediated elastolysis are fundamental contributors to its development.^{5,6}

BD is intrinsically characterized by neutrophil hyperactivation, endothelial dysfunction, and the inflammatory involvement of small and medium-sized vessels.⁷ Activated neutrophils in BD release copious amounts of reactive oxygen species and potent proteolytic enzymes capable of severely damaging both vascular and dermal structures. Furthermore, increased levels of matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, have been consistently reported in the serum of patients with BD, strongly correlating with disease activity and extracellular matrix degradation.⁸

MMPs are critical zinc-dependent endopeptidases involved in connective tissue remodeling and possess the unique capability of degrading structural dermal proteins, including elastin. Excessive

metalloproteinase activity, coupled with a localized reduction in specific tissue inhibitors, may therefore precipitate focal dermal elastolysis. From a pathogenetic perspective, the chronic microvascular inflammation and neutrophil-driven proteolysis inherent to BD could create a highly permissive microenvironment for the localized degradation of elastic fibers within the dermis. Persistent endothelial activation may chronically facilitate leukocyte recruitment and the subsequent release of elastolytic enzymes, ultimately culminating in the focal loss of elastic tissue that is the histological hallmark of anetoderma.

The clinical observation that anetoderma preceded the overt clinical onset of BD in our patient suggests that subtle, subclinical vascular inflammatory processes may already be active during the prodromal phases of the disease. Consequently, elastolytic changes in the dermis could represent an unrecognized cutaneous expression of early microvascular damage, occurring well before the full systemic phenotype of BD becomes clinically evident.

Conclusions

In conclusion, we report a highly unusual observation of primary anetoderma preceding the onset of BD. While we acknowledge that this association may be coincidental, the strict temporal sequence and the strikingly overlapping pathogenetic mechanisms – specifically involving vascular inflammation, neutrophil hyperactivation, and MMP-mediated extracellular matrix degradation – suggest a highly plausible pathophysiologic link that warrants further systematic investigation. The astute recognition of unusual elastolytic dermatoses may therefore provide dermatologists with critical early clues to underlying, yet-to-be-diagnosed systemic inflammatory diseases.

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Figure 1. Clinical presentation of primary anetoderma. A) Lateral view of the right shoulder and upper arm showing multiple skin-colored, flaccid, well-demarcated atrophic plaques with a characteristic herniated, sac-like morphology. B) Posterior view of the upper trunk and back demonstrating the bilateral and symmetrical distribution of asymptomatic, finely wrinkled atrophic macules. The lesions are remarkably soft upon palpation, exhibiting a positive “buttonhole” sign.



Figure 2. Histopathological features of anetoderma. A) Hematoxylin-eosin staining (original magnification $\times 400$) reveals preserved epidermal stratification with no architectural abnormalities or cytologic atypia. The dermis appears unremarkable, without evident fibrosis or significant inflammatory infiltrates in the established lesion. B) Special elastic stain demonstrating a marked reduction to near-complete loss of elastic fibers within the papillary and mid-reticular dermis, with relative preservation of collagen bundles, confirming profound focal dermal elastolysis.

