Primary Anetoderma and Acquired Cutis Laxa Associated with Glomerulonephritis in a 37-year-old Filipino Male: A Case Report

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ABSTRACT

A 37-year-old Filipino man presented with a 9-month history of sagging skin progressing cephalocaudally from the chin and neck to the axillae, side of the trunk, and pelvic area. This was followed by a 2-month history of increasing serum creatinine levels associated with periorbital and bipedal edema, generalized weakness, decreased appetite, vomiting, and headache. Subsequently, skin-colored, non-tender sac-like plaques appeared on the abdomen, inguinal, and intergluteal areas. Histopathology of the latter lesions showed increased spaces between collagen bundles in the dermis. Staining with Verhoeff-van Gieson revealed focal sparse elastic fibers in the papillary dermis compared to that of the reticular dermis consistent with anetoderma. Further work-up revealed normal ANA titer and low serum C3. Kidney biopsy showed IgG deposition in the tubular basement membrane and trace C3 deposition in the glomerular mesangium, giving a diagnosis of rapid progressive glomerulonephritis. On subsequent follow-up, the sac-like plaques became lax and presented as generalized wrinkling of the skin, raising the question whether cutis laxa and anetoderma are occurring in a spectrum instead as distinct entities. Based on the current review of literature, this is the first reported case of primary anetoderma co-occurring with cutis laxa in a patient with glomerulonephritis. Deposition of immunoglobulins along the elastic fibers could have activated the complement system, mediating the destruction of the elastic fibers, resulting to cutis laxa and anetoderma. This case also considers the possibility of anetoderma and type I acquired cutis laxa occurring either in a spectrum or as distinct diseases in a single patient. Further investigations may identify an ultrastructural pattern that can help differentiate the two entities.

Key Words: anetoderma, cutis laxa, glomerulonephritis

INTRODUCTION

Primary anetoderma is an uncommon elastic tissue disorder that occurs on areas of previously normal skin, presenting as atrophic depression or saccular outpouchings. It may be associated with various systemic disorders and laboratory abnormalities. Cutis laxa (CL) is a rare, inherited or acquired, disorder that presents with loose, inelastic skin, giving a prematurely aged appearance. We describe a case of anetoderma co-occurring with acquired cutis laxa in association with a renal disorder. Furthermore, we discuss the possibility of both diseases occurring as a spectrum instead of distinct entities.

CASE DESCRIPTION

A 37-year-old Filipino man presented with a 9-month history of sagging skin on the neck, axillae, and side of the trunk (Figure 1). No preceding inflammatory dermatosis or intake of medication such as penicillamine or isoniazid

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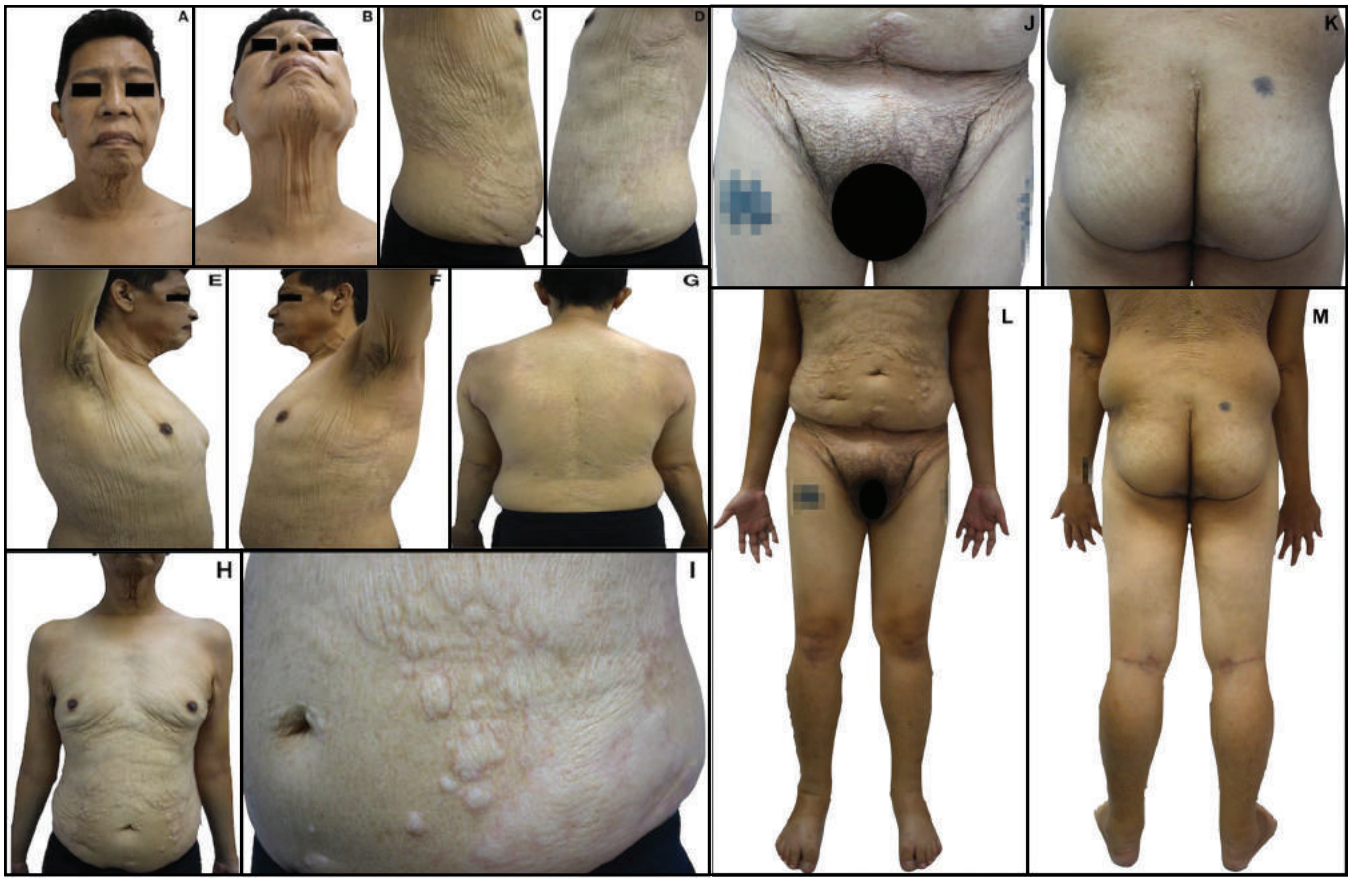

Figure 1. (A, B) The front view of this 37-year-old patient emphasized the sagging skin on the anterior neck, with noticeable wrinkling on the side and on the chin. The other parts of the face were relatively spared. **(C-H)** There was diffuse wrinkling of the skin on the side of the trunk, bilateral axillae, and at the back. There were also multiple, well-demarcated, irregularly shaped, hypopigmented, nontender, flaccid plaques with erythematous border, with some coalescing into larger plaques, located on the anterior and side of the trunk, periumbilical area, and at the back. **(I)** This was a close-up shot of the saccular outpouchings on the abdomen which was positive for the buttonhole sign. **(J, K)** Distinct saclike plaques were also present in the hypogastric area and in the gluteal cleft. Diffuse wrinkling was evident on the pelvic and the inguinal area. The genitals were not involved. **(L, M)** Aside from the grade 3 bipedal edema, the distal upper and lower extremities were spared.

prior to the onset of skin manifestations was noted. This was followed by a 2-month history of increasing serum creatinine levels associated with periorbital and bipedal edema, generalized weakness, decrease appetite, vomiting, and headache. There was no history of alopecia, malar rash, photosensitivity, myalgia, arthritis, leg pain, stroke, and livedo reticularis, making the diagnosis of systemic lupus erythematosus less likely. Patient was referred to nephrology and was diagnosed with nephrotic-nephritic syndrome. Kidney biopsy with immunofluorescence showed IgG deposition in the tubular basement membrane and trace C3 deposition in the glomerular mesangium consistent with rapid progressive glomerulonephritis. In the interim, there was appearance of skin-colored, non-tender sac-like papules and plaques on the abdomen, inguinal, and intergluteal area, prompting referral to the dermatology department in our institution. On digital pressure on the saccular outpouchings, the examining finger sunk without resistance into a distinct pit with sharp borders. The bulge reappeared when the pressure from the finger was released. A punch biopsy was done, which revealed increased spaces between collagen bundles in the dermis (Figure 3A). Staining with Verhoeff-van Gieson (Figure 3B) revealed focal sparse elastic fibers in the papillary dermis compared to that of the reticular dermis consistent with anetoderma. Further work-up revealed a high ASO titer, a normal ANA titer, and low serum C3. After two months, the patient followed up and presented with increased wrinkling of the skin (Figure 2). The initial sac-like plaques on the abdomen became inelastic such as what is found in cutis laxa (Figure 2F). Work-up for other autoimmune diseases and systemic involvement was planned but the patient was lost to follow-up.

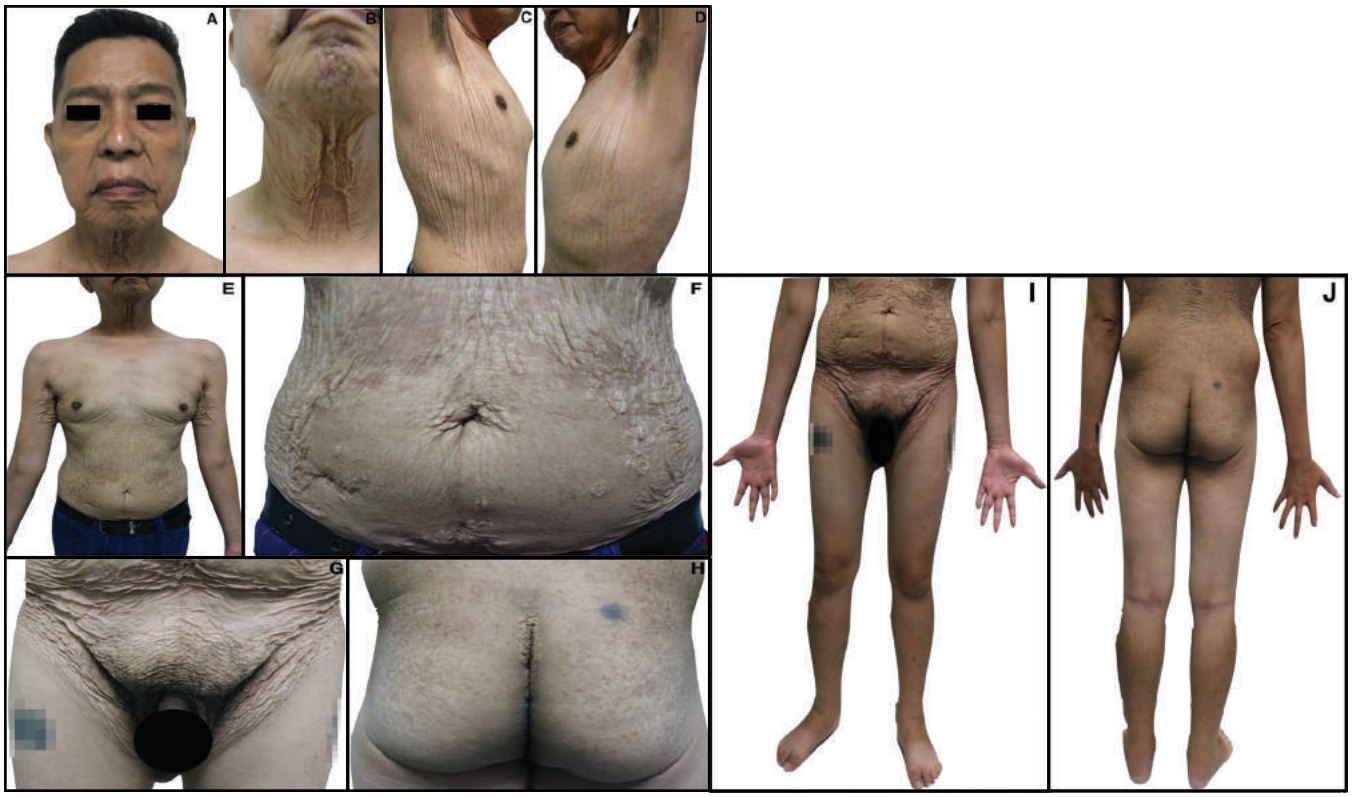

Figure 2. **(A-D)** After three months, patient presented with increased sagging and wrinkling of the skin. **(E)** The wrinkling of the skin from the axillae to the medial arms were more pronounced. **(F)** The initial sac-like plaques on the abdomen became lax, exhibiting a diffuse prune-like texture with erythematous border. **(G)** Diffuse wrinkling became more evident on the pelvic and the inguinal areas. The genitals remain uninvolved. **(H)** The previous hypopigmented, flaccid plaques remained at the intergluteal cleft albeit less firm. **(I, J)** The distal upper and lower extremities remained unaffected.

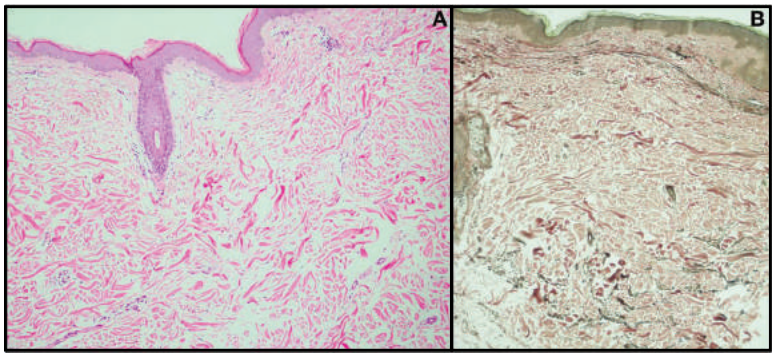

Figure 3. **(A)** Histopathology (H&E) showed increased spaces between collagen bundles in the dermis (X20). **(B)** Staining with Verhoeff-van Gieson revealed focal sparse elastic fibers in the papillary dermis consistent with anetoderma (X20).

DISCUSSION

Cutaneous elastic tissue disorders may be divided into those with increased elastic tissue and those in which elastic tissue is reduced.[1] The latter subcategory can be localized, as in anetoderma, or generalized, as in cutis laxa. Cutaneous lesions may affect any part of the body, mostly the head, neck, trunk, and upper extremities. Although the histological pattern of elastolysis for some diseases (mid-dermal elastolysis, pseudoxanthoma-like papillary dermal elastolysis, and upper dermal elastolysis) can be specific and diagnostic, the pattern of elastolysis for other elastic tissue disorders may be variable.[2]

Primary anetoderma is a rare skin disease associated with autoimmune disorders commonly with antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies).[1] Based on the Philippine Dermatological Society - Health Information System (PDS-HIS), there were only 21 cases of anetoderma from 2011–2019. Only one was diagnosed with primary anetoderma. More men

were affected contrary to common reports in literature.[2] The true prevalence and incidence are still unknown. Lesions usually appear on the upper part of the trunk and proximal part of the extremities, presenting as papules that may be sunken, atrophic, saclike, and bulging. On histology, there is sparse or complete loss of elastic tissue in the papillary, mid, or deep dermis.[2]

Acquired cutis laxa (CL) is an uncommon entity associated with multiple conditions (i.e., lymphoma, sarcoidosis, Sweet's syndrome, systemic lupus erythematosus, nephrotic syndrome, alpha-1 antitrypsin and complement deficiency, amyloidosis, infections such treponemal and Lyme disease) and drugs such as isoniazid and penicillin.[3] Type I acquired CL (generalized acquired elastolysis) presents subtly as ill-defined loose skin with reduced elasticity and resilience on the head and neck, which progresses cephalocaudally. The development of skin lesions is preceded by an inflammatory dermatoses in half of the reported cases.[4] It may also follow hypersensitivity reaction to insect bites or drugs, and neoplastic disorders.[5] In some patients, clinical manifestations are limited to the skin.[6,7] Type I CL is also associated with a high risk for systemic elastolysis, affecting the pulmonary (emphysema, cor pulmonale, and tracheobronchomegaly), cardiovascular (aortic aneurysm and valvular incompetence), gastrointestinal and urogenital (diverticula and hernia).[1,2,4] Type II acquired CL (also called post-inflammatory elastolysis and cutis laxa or Marshall syndrome) affects women more often and presents in the acute phase as localized, nonpruritic erythematous plaques that extend peripherally. It has a hypopigmented center and can be associated with fever, malaise, peripheral eosinophilia, and leukocytosis. Lesions resolve with central clearing, hyperpigmentation, and peripheral collarette of scales.[8] Organ involvement is rare.[9] The chronic phase presents with resolution of the plaques, forming wrinkled and loose skin with or without extension to normal skin. Skin lesions in both forms are similar and present with a prematurely aged appearance. The characteristic histologic feature is sparse and/or fragmented elastic fibers in the papillary and reticular dermis. Neutrophilic or lymphohistiocytic infiltrate with elastophagocytosis may be seen in earlier lesions.[2] At present, there were only ten unpublished cases of acquired cutis laxa reported in the PDS-HIS from 2011-2019, seven of which were type II acquired CL, while the other three were unspecified. Only one patient was younger than 18 years. The rest were adults with a male to female ratio of 1:4.

The pathogenesis of anetoderma is still uncertain. Increased breakdown of elastic fibers may be due to upregulation or inhibition of matrix metalloproteinase (MMP) elastolytic activity,[10-12] ischemia,[13] phagocytosis,[14] and autoimmune[15,16] as seen from its association with antiphospholipid antibodies. As in anetoderma, the pathophysiology of acquired CL remains unclear. Enhanced degradation of elastic fibers may be due to decreased synthesis of elastase inhibitors[17] and elastin gene expression,[18] and an increase in dermal fibroblast[19] and neutrophil elastase activity.[20-22] A decrease in synthesis of elastic fibers due to copper deficiency has also been implicated.[23,24] Deposition of immunoglobulins in elastic fibers have also been documented,[25-28] highlighting the immune mechanism for elastolysis.

In our patient, the only immune-related co-morbidity identified was glomerulonephritis. A search for recent published literature using NCBI, Pubmed, Google Scholar, and Herdin revealed only one case report of a hereditary renal condition (Alport's syndrome) observed to present with anetoderma.[29] However, there was no explanation with regards to its pathogenesis. In contrast, two studies associated acquired CL with a renal disease. Tsuji et al.[30] described a 41-year-old woman who developed laxity of the skin followed by edema of the face and legs. Laboratory studies showed normal ANA titers and low serum C3, as in our patient. Renal biopsy and immunofluorescence revealed C3 and IgG deposition in the mesangial matrix and along the glomerular basement membrane. The authors hypothesized that a common immunoglobulin could have caused both the acquired CL and the glomerulonephritis. Joss and colleagues[31] also reported a similar case in a 37-year-old man, with normal serum ANA and low C3. Renal biopsy showed deposition of C3 on the mesangial and capillary loop in addition to lambda light chains. In both cases, skin lesions predated the renal signs and symptoms. Acquired CL has also been reported to occur in relation to immunoglobulin heavy chain deposition, with both cases presenting first with the renal disease before appearance of skin laxity.[32,33]

Although no other renal disease has been associated with anetoderma aside from the ones described by O'Malley et al.[32] and Tan et al.,[33] immunofluorescence studies on lesions of anetoderma showed dermal deposits of IgG, IgM, C3, and C4 in early inflammatory lesions.[34] Localization of C3 on elastic fibers was also noted, which could have served as chemotactic stimulus to macrophages.[35] A common working theory for these cases, including ours, is that excess immune reactants (i.e., heavy or light chains) may have been deposited in tissue surrounding elastic fibers, leading to complement activation and subsequent elastolysis. Reasons for the immunogenicity of elastic fibers remain elusive though there have been reports suggesting elastin to be the culprit.[36,37] Unfortunately, direct immunofluorescence and electron microscopy of the skin were not done since the patient was lost to follow-up. Documentation of immunoglobulins on the skin biopsy specimens could have helped identify further the cause of his acquired CL.

A unique feature noted in this patient was the initial presentation of skin lesions on the abdomen as herniating, sac-like papules that exhibited the buttonhole sign consistent with anetoderma. These progressed to a loose, pendulous, and generalized wrinkling of the skin, two months later, similar to that of cutis laxa. It begs the question whether

anetoderma and cutis laxa are distinct entities or are diseases occurring in a spectrum. Histologically and ultrastructurally, anetoderma and cutis laxa are identical, unlike mid-dermal elastolysis where the band-like loss of elastic fibers is in the mid-dermis only.[38,39] The continuous degradation and loss of the elastic fibers of the anetoderma lesions can lead to the clinical picture of cutis laxa with no elastic recoil. Further investigations are needed to substantiate our claim that both disease entities occur in a spectrum.

Another point to consider is whether the initial lesions were indeed of primary anetoderma or a type of acquired CL. Our patient developed lesions in multiple areas during adulthood that progressed cephalocaudally, which is typical in type I acquired CL. Although most type I acquired CL presents with systemic elastolysis, two patients did not have any systemic manifestation[6,7] as in our case. Type II acquired CL (Marshall syndrome), on the other hand, presents in infancy or childhood on sites of previous inflammation with localized, nonpruritic, erythematous plaques followed by wrinkling of the skin in the chronic phase. Reports of fever, malaise, peripheral leukocytosis and eosinophilia[4,7] are often noted. Furthermore, acute lesions of Marshall syndrome do not present with herniation or the buttonhole phenomenon, unlike in anetoderma. Looking at the clinical features and progression of the lesions, it is more likely that the diagnosis in our case is acquired cutis laxa type I, with co-occurrence of primary anetoderma (should these two entities be considered distinct and not occurring in a spectrum). Based on the current review of literature, this is the first reported case of primary anetoderma co-occurring with acquired cutis laxa in a patient with glomerulonephritis.

CONCLUSION

Anetoderma and acquired cutis laxa are uncommon elastic tissue disorders that have different associations. Whereas the former may be related to autoimmune diseases, acquired CL is often accompanied by internal manifestations that can have fatal consequences. The similarity of both diseases in this case was that deposition of immunoglobulins along the elastic fibers could have activated the complement system, mediating the destruction of the elastic fibers and ultimately resulting to cutis laxa and anetoderma. The same deposition process in tubular basement membrane and glomerular mesangium led to the development of glomerulonephritis in this patient. This case also considers the possibility of anetoderma and type I acquired CL occurring either in a spectrum or as distinct diseases in a single patient. Further studies may possibly identify an ultrastructural pattern that can help differentiate the two entities.

Statement of Authorship

Both authors participated in the data collection and analysis and approved the final version submitted.

Author Disclosure

Both authors declared no conflicts of interest.

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