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Case presentation

Generalized acquired cutis laxa type 1: a case report and brief review of literature

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Abstract

Cutis laxa, clinically characterized by loose and pendulous skin related to loss of elastic tissue, is a rare heterogeneous condition. It is classified into congenital and acquired types. We report a case of generalized acquired cutis laxa type 1 in a young man following pruritic urticarial plaques. We have done a brief review of literature.

Keywords : Cutis laxa; acquired cutis laxa; type 1 cutis laxa; Marshall syndrome; Post-inflammatory elastolysis and Cutis laxa

Introduction

Cutis Laxa [CL], also known as dermatochalasia, dermatomegaly, generalized elastolysis, generalized elastorrhexis, dermatolysis, chalazoderma or pachydermatocele, encompasses a rare group of disorders of the elastic tissue [1]. It is an etiologically heterogeneous condition, which may be inherited, or acquired as type 1 or type 2 forms. Type 1 acquired cutis laxa commonly begins in adulthood, although there have been isolated reports of onset in childhood. The cutaneous involvement may be localized or generalized, with variable systemic involvement. Acquired cutis laxa type 2, also known as Marshall syndrome and Post-inflammatory elastolysis and Cutis laxa (PECL), occurs in infancy or early childhood. The cutaneous involvement is predominantly localized and rarely generalized without any systemic involvement. The localized variant in both the acquired forms (type 1 & 2) may be cephalic and rarely, acral [1]. Skin lesions in both forms are characterized by ill-defined areas of loose, pendulous and redundant skin, giving the patient an old aged look [1]. Here we present a case of a young man who presented with a prematurely aged appearance following multiple episodes of pruritic urticarial plaques.

Case synopsis

A 25-year-old male, born of non-consanguineous parentage, presented with excessive wrinkling and sagging of the skin of lower face, bilateral ear lobes, neck and upper trunk, developing over a period of 18 months (Figures 1a, 1b and 1c). On enquiry, the patient elaborated that he had recurrent episodes of itchy, reddish, raised skin lesions, which first appeared over the face and slowly progressed to affect the submandibular area and upper chest. The lesions used to subside spontaneously over a period of 5 to 10 days, leaving behind loose and wrinkled skin.

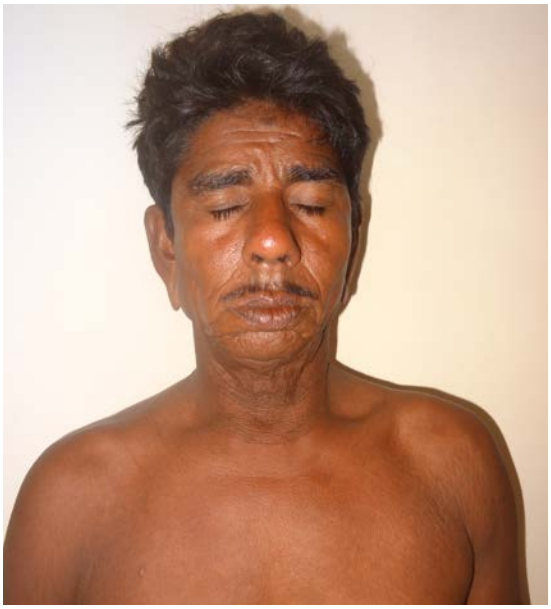


Figure 1a. Lower face and neck showing loose wrinkled skin, giving an aged look. **Figure 1b.** "Laughing Buddha" like pendulous ears. Note loose sagging skin with deep wrinkles on lower face. **Figure 1c.** Erythematous edematous plaques on chest (arrow)

The patient denied ingestion of over-the-counter or prescribed drugs, or history of skin allergy to any food and/or food preservatives prior to the onset of lesions. Living and working mostly in an indoor environment ruled out chances of photo-aggravation to sunlight.

He did not give any history of malar rash, vesicular, pustular, or nodular lesions over the skin or mucous membrane. There was no history of fever, anorexia, weight loss, myalgia, arthralgia, giddiness, headache, dyspnea, sore throat, vomiting, diarrhea, or burning micturition. Past medical, surgical, and family history were non-contributory.

Cutaneous examination showed wrinkled skin of the lower face, neck, and upper trunk. The earlobes appeared pendulous bilaterally. The skin over the platysma and sides of the neck appeared hanging in loose redundant folds. Similar ill-defined areas of wrinkled skin were noted over the shoulders and upper chest. Of note, few erythematous edematous plaques with well-defined margins were noted over the upper chest. He had an aged facial appearance with down slanting of palpebral fissures. Systemic examination was within normal limits.

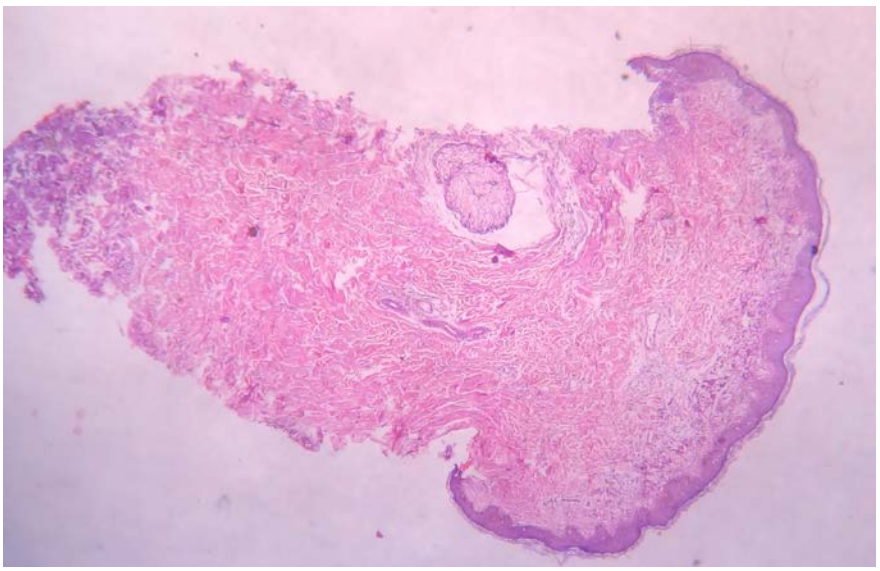
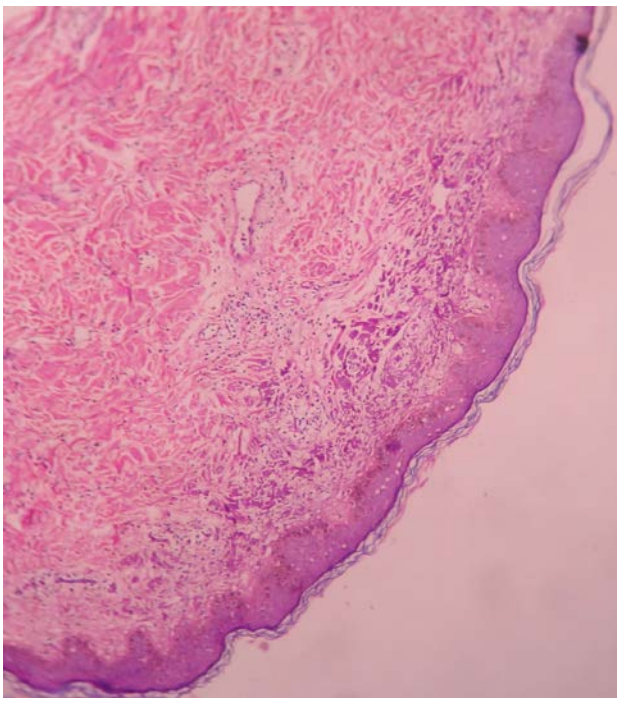
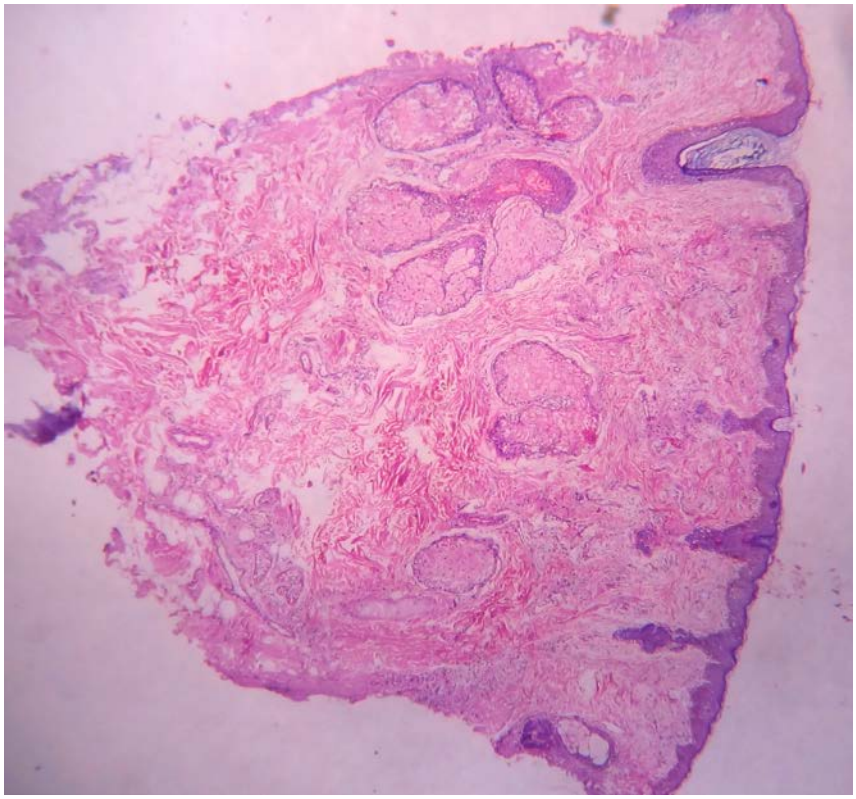



Figure 2a. Histopathology from plaque showing mild perivascular infiltration in upper and mid dermis. Upper dermis is remarkable for elastotic degeneration. (H&E x 40) **Figure 2b.** Histopathology from plaque showing focal atrophic epidermis with flattening of rete ridges, mild perivascular infiltration in upper and mid dermis, and elastotic degeneration in upper dermis. (H&E x 100)

A sample for histological examination was collected from both erythematous plaque and wrinkled skin. Histopathology from an erythematous plaque showed a sparse superficial perivascular lymphocytic infiltrate in the papillary dermis beneath an apparently normal epidermis (Figures 2a and 2b). In addition, the upper dermis was notable for numerous, short, wavy, fibrillar to slightly granular material with eosinophilic appearance present between normal pink bundles of collagen. Histopathology from wrinkled skin showed scant perivascular mononuclear cell infiltrate in the upper and mid dermis (Figures 3a and 3b). Verhoeff–Van Gieson stain (VVG) of both samples showed a decreased number of elastic fibers in in the upper and mid dermis. Fragmentation of the fibers was also present. (Figure 4a and 4b).



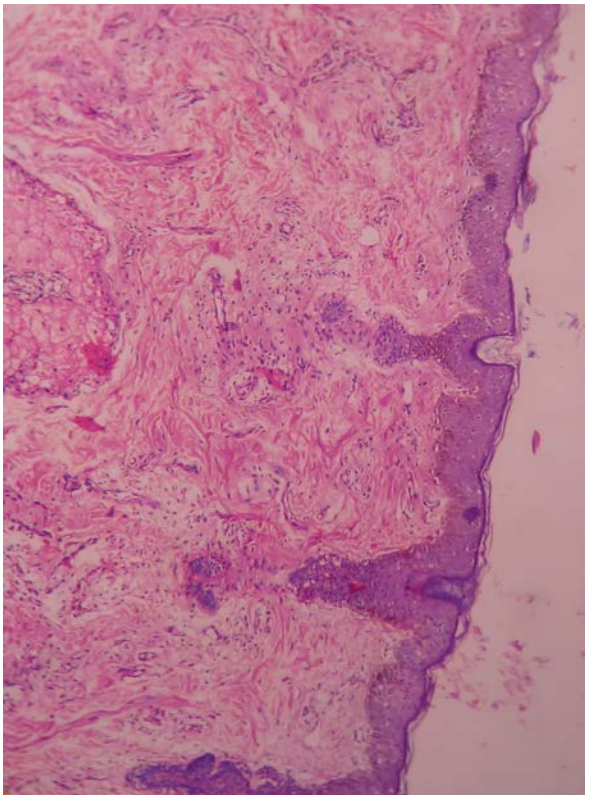
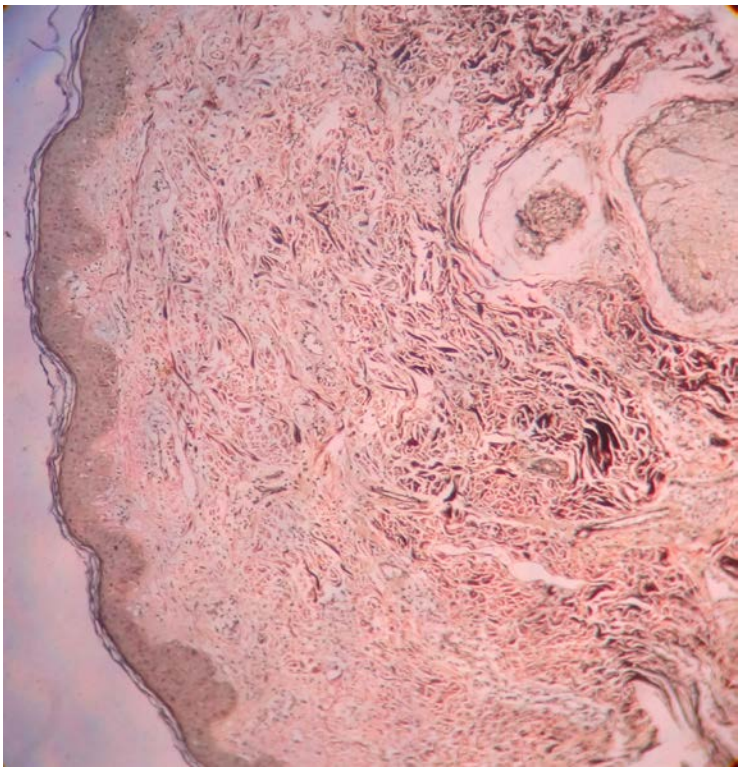


Figure 3a. Histopathology from wrinkled skin on face shows scant perivascular mononuclear cell infiltration in upper and mid dermis. (H&E x 40) **Figure 3b.** Histopathology from wrinkled skin on face shows unremarkable epidermis, dilated superficial blood vessels and scant perivascular mononuclear cell infiltration in upper and mid dermis. (H&E x 100)



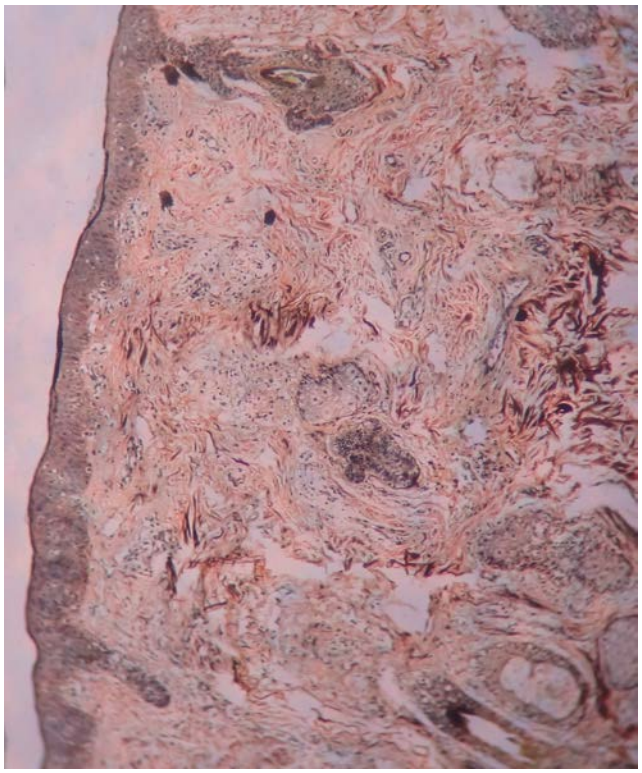


Figure 4a. Verhoeff–Van Gieson stain showing loss of elastic fibers in upper and mid dermis in sample from erythematous plaque. Lower dermis shows good number of elastic fibers. (x 100) **Figure 4b.** Verhoeff–Van Gieson stain showing loss of elastic fibers in upper and mid dermis in sample from wrinkled skin on face. Note focal retention of elastic fibers in mid dermis. (x 100)

Laboratory investigations including complete hemogram, blood glucose, serum electrolytes, hepatic and renal profile, lipid profile, thyroid profile, and antinuclear antibody did not reveal any abnormality. Venereal Disease Research Laboratory (VDRL) test and serology for Human immunodeficiency virus (HIV) were non-reactive. Chest X-Ray and ultrasonography of abdomen did not reveal any abnormality. Electrocardiogram of heart suggested no abnormality. Based on clinico-pathological correlation, we established a diagnosis of generalized acquired generalized cutis laxa type 1 without any systemic involvement. Mutational analysis, serum elastase, serum elastase inhibitor, and lysyl oxidase activity could not be explored because of financial constraints. Considering possibility of systemic elastolysis, patient has been kept under regular periodic follow up.

Discussion

All healthy individuals, under normal circumstances develop increased skin laxity with an advancing age because of accelerated dermal photodegradation [1]. Physiologically this can also occur in individuals undergoing excessive weight loss following obesity. Rarely the skin may appear lax and loose because of localized or generalized defects in the elastic tissue resulting from other causes, which are termed as localized or generalized elastolysis, respectively [1]. A simplified classification of elastolytic disorders has been presented in Table 1. Cutis Laxa [CL] is classified into congenital and acquired forms. Review of literature revealed 200 reported cases of CL, with more than 50 cases being acquired secondarily [1]. All forms of CL are clinically characterized by loose, pendulous, sagging skin with reduced elasticity and resilience, giving the affected patient a premature aged look [1]. ‘’Bloodhound’’ facies is a term designated to patients with CL presenting with a hooked nose and a long upper lip. Elongation of the philtrum and down slanting of palpebral fissures are other typical facial changes. All these are attributed histologically to sparse and fragmented elastic fibers. Cutaneous findings are present at birth in most heritable forms of CL but may develop later in life in autosomal dominant as well as acquired variants [1].

Table 1. Classification Of Elastolytic Disorders [5,6]

[A] Localized Elastolysis :
(1) Anetoderma

- Primary
- Secondary
- Perifollicular elastolysis

(2) Mid-Dermal Elastolysis

(3) Blepharochalasis

(4) Acrodermatitis chronica atrophicans due to Borrelia

(5) Granulomatous slack skin due to lymphoma

(6) Others – Elastic tissue nevi

[B] Generalized Elastolysis (Cutis Laxa, CL) :
(1) Inherited

- Autosomal Recessive CL- Types IA, IB, IIA, IIB, III
- Autosomal Dominant CL
- X-Linked Recessive CL
- Adult Late-Onset CL
- Urban–Rifkin–Davis syndrome (URDS),
- Macrocephaly-alopecia-CL-scoliosis (MACS) syndrome
- Arterial tortuosity syndrome (ATS)

(2) Non Inherited

- Transient neonatal cutis laxa
- Neonatal cutis laxa with Marfan phenotype
- Acquired Cutis Laxa Type 1
- Acquired Cutis Laxa Type 2 (Marshall's syndrome, Post-inflammatory elastolysis and cutis laxa).

Congenital CL can be inherited as an autosomal dominant, autosomal recessive, or X-linked disorder, with the autosomal recessive variant being the most common and severe type. The age of onset of autosomal recessive and X-linked disorder is mostly at birth. However, it may be delayed in the autosomal dominant variant. The mild dominant form results from mutation in the elastin gene, with elastolysis limited to the skin and the patient having a normal life span [2]. The severe recessive form results from mutation in fibulin 5 and fibulin 4 genes, with internal organ involvement and death in the first few years of life [3,4].Another less severe recessive variant is caused by mutation in the ATP6V0A2 gene [5]. X-linked recessive cutis laxa, has been associated with abnormalities of copper metabolism leading to decreased activity of lysyl oxidase, an enzyme involved in the cross linking of elastin and collagen. It is caused by mutations in the copper-transporting ATPase, alpha polypeptide (ATP7A) [6]. Congenital CL has variable prognosis with death being reported in infancy. CL can rarely be an acquired sequelae following a primary event. This acquired form is subdivided into type 1 and 2 and has been summarized in **Table 2**. Type 1 acquired CL may be a localized or generalized condition which mostly has an adult onset although onset in children has been reported. The cutaneous changes, preceded by certain dermatoses (**Table 3)**, commonly begin in the head and neck region as ill defined areas of loose skin which progress in a cephalo-caudal direction with elastolysis extending beyond the areas of inflammation. Consistent with the features of generalized acquired type 1 cutis laxa, our patient had the disease onset in adulthood. In our case, there was a preceding pruritic urticarial eruption, which eventually progressed to develop cutis laxa.

Table 2. Acquired cutis laxa type 1 and type 2

Salient feature	**Acquired cutis laxa type 1**	**Acquired cutis laxa type 2 [Marshall syndrome, Postinflammatory elastolysis and Cutis laxa (PECL)]**
Age of onset	Begins in adulthood.	• Associated with sweet syndrome-infancy or childhood (1.5 - 4 years) • Associated with neutrophilic dermatosis-young adults
Race	No racial predilection	Mostly reported in African and North American children
Sex	No sex predilection	Females are more commonly affected
Family history	May be present	Absent
Extent of involvement	Localized (face or acral area) or generalized	Localized (face or acral area) or generalized
Preceding inflammation	Skin laxity preceded by an inflammatory phase of erythematous plaques in approximately 50% cases.	Skin laxity preceded by Sweet syndrome or neutrophilic dermatosis (not meeting criteria of Sweet syndrome) in almost all cases.
Clinical features	Characterized by pendulous, coarsely wrinkled areas of skin- affects face and particularly ear lobe and spreads in a cephalocaudal manner. Palm and sole involvement is rare.	Characterized by two stages- eruptive phase and elastolysis phase. • Eruptive phase- lasts several months to several years. Lesion starts as juicy, bright red papules and plaques that expands peripherally over a period of 1-2 weeks to form a 2-10 cm round or oval plaque with an active bright red cordlike border. Appearance of lesions is frequently associated with systemic symptoms that include malaise, fever, and leukocytosis. • Elastolysis phase- As the lesions resolve, skin becomes wrinkled and hyperpigmented. Mild cases may have a peau d'orange

		appearance.
Sites	Localized lesions are noted around the eyes (blepharochalasis) or on palms and soles (acral type). Generalized lesions begin in the earlobes and face, and progress cephalocaudally.	Head, neck, and upper trunk region.
Elastolysis	Elastolysis and skin laxity is noted beyond the margins of the primary inflammatory event.	Lesions are limited to sites of previous inflammation.
Systemic elastolysis	Frequent	Rare
Systemic involvement	Pulmonary : emphysema, pneumothorax, fibrosis. Cardiovascular : cardiomegaly, congestive heart failure, cor pulmonale, ectasia of the aorta and/or aortic aneurysms. Gastrointestinal : diverticula, inguinal, hiatal and/or umbilical hernias. Urogenital : hernias, urogenic diverticulae, uterine prolapse and/or cystocele.	Generally absent
Associated conditions	Medications, malignancies, Infections, Connective tissue diseases, Renal diseases, alpha-1 antitrypsin deficiency, Mastocytosis, Amyloidosis, Dermatitis herpetiformis, Interstitial granulomatous dermatitis, Sarcoidosis, and Celiac disease (Table 3)	Sweet syndrome, Neutrophilic dermatosis (not fulfilling criteria of Sweet syndrome), Leukocytosis with eosinophilia,
Histopathology	The histopathological features in early phase are dominated by mild fragmentation, or degeneration of elastic fibers, accompanied by a neutrophilic or lymphocytic infiltrate. In some cases, early lesion may show features of primary inflammatory condition. In late phases, predominance of histiocytes as infiltrating cells, phagocytosis of abnormal elastic fibers and marked depletion of elastic tissue are noted.	Eruptive phase shows dermal edema, capillary dilatation, and perivascular infiltrate of neutrophils, and eosinophils. Swelling and granular degeneration of elastic fibers can be seen, even in early lesions. In late phases, lymphohistiocytic infiltrate and nearly complete loss of elastic tissue in the upper and mid dermis are observed.

Table 3. Conditions associated with Acquired CL type 1 [2,6]

[1] Drugs - Penicillin, Penicillamine, Isoniazid, Selective Serotonin Reuptake Inhibitor

[2] Cutaneous disorders –

- Inflammatory Dermatoses : Urticaria, Angioedema, Discoid lupus erythematosus, Lupus erythematosus profundus, Erythema multiforme, Necrobiosis lipoidica, Sarcoidosis, Dermatitis herpetiformis, Mastocytosis, Interstitial granulomatous dermatitis, Amyloidosis,
- Hypersensitivity Reactions : Arthropod bite reactions, Drug eruptions.
- Neoplasm : Plasma cell dyscrasia, Multiple myeloma, Hodgkin's disease
- Infections : Toxocara canis, Borrelia burgdorferi, Treponema pallidum, Onchocerca volvulus
- Miscellaneous : Granulomatous slack skin, Klippel Trenaunay-Waber syndrome.

[3] Extracutaneous Inflammatory Disorders - Rheumatoid arthritis, Systemic lupus erythematosus, Nephrotic syndrome, Celiac disease, Sarcoidosis, Alpha-1 antitrypsin deficiency.

Although the localized variant has a pure cutaneous involvement, the generalized variant in addition to cutaneous changes has a wide spectrum of systemic involvement in the form of pulmonary emphysema, pneumothorax, aortic ectasia, cor pulmonale, inguinal and umbilical hernias, gastrointestinal and urogenic diverticulae, inflammatory arthritis, cutaneous mastocytosis, and developmental retardation [7,13-15]. Our patient did not have any of the above mentioned systemic manifestations. The type 2 acquired CL (Marshall Syndrome) can also have localized or generalized cutaneous changes, which usually manifests in infancy or childhood. There is a female predominance [8]. The lesions start as well-demarcated, asymptomatic or mildly pruritic erythematous papules and plaques that extend peripherally with a hyperpigmented center. The resolution of lesions occurs in several days and this is usually associated with elastolysis, clinically manifesting as wrinkling. The skin lesions appear in crops over a period of days to weeks and the appearance of new lesions is usually associated with constitutional symptoms of fever, malaise, and peripheral eosinophilia. A few scattered lesions may be noticeable or such lesions may become confluent and widespread. The face and neck are most commonly affected, but lesions may appear elsewhere on the skin, although they are unusual on the palms and soles. [9]

The etiopathogenesis of acquired CL (ACL) remains unknown. A primary cascade of any inflammatory skin condition usually leads to invasion of neutrophils and monocytes-macrophages into the dermis. These inflammatory cells release elastase into the extracellular matrix and this enzyme acts on the amorphous component of elastic fibers leading to proteolysis and degradation [1,10]. Another pathological mechanism proposed is that the enzyme alpha1-antitrypsin is an elastase inhibitor itself that can prevent proteolysis of the elastic fibers. Thus the individuals with alpha1-antitrypsin deficiency can be susceptible to excessive proteolysis of elastic fibers. Immunopathogenic mechanisms have also been proposed in a few cases of acquired CL. Evidence in favor of this mechanism is the occurrence of acral or generalized CL in association with monoclonal gammopathies and observation of IgG, IgA and/or amyloid deposition in the lesional skin [1,11]. In addition, abnormal copper metabolism, deficiency of copper, decreased production of tropo-elastin, and genetic susceptibility for the development of CL have all been postulated [1,12,13].

The diagnosis of CL is based purely on history and clinical examination, which needs histopathologic confirmation. Along with routine hemotoxylin and eosin stains, special stains for elastic tissue (Verhoeff–van Gieson stain) need to be employed to highlight the pathological changes in the dermis. Histopathologically, it is characterized by a reduction in the number of elastic fibers and associated degenerative changes. The fibers may be deficient in the papillary dermis, reticular dermis, or both and may vary greatly in their diameters. Those seen in the reticular dermis may be shortened, tapered, and degenerated. Fragmentation of fibers with indistinct and hazy borders may be noted. In our patient, elastic fibers were decreased in number. In addition, there was fragmentation of the elastic fibers in the upper and mid dermis. Similar changes in the elastic tissue may occur in the alveolar walls, blood vessels, and elsewhere [1,16].Giant cells may be seen phagocytosing the elastic fibers. There are certain histopathological differences in ACL type 1 and type 2 and these have been summarized in Table 2. In acquired CL following an inflammatory skin condition, a variable amount of mixed infiltrate of neutrophils, eosinophils, and lymphocytes may be present in the superficial or deep dermis. Consistent with this description, we could appreciate a perivascular mononuclear cell and lymphocytic infiltrate in the dermis. Ultrastructural studies may reveal defective deposits of abnormal globular, amorphous, electron-dense elastin that may accumulate irregularly on the normal microfibrillar frame [1,16].

Most routine laboratory tests are normal. Serum elastase, serum elastase inhibitor, serum copper and ceruloplasmin, alpha1-antitrypsin, and lysyl oxidase levels might be helpful, even though they are not required for the diagnosis [7,16]. Systemic evaluation should be undertaken to investigate the involvement of internal organs [1,13,16]. Conditions in the differential diagnosis such as anetoderma, Ehlers– Danlos syndrome, Marfan syndrome, and pseudoxanthoma elasticum must be ruled out [1,16].

Although some forms of CL improve with time, others may worsen with age [1]. After confirming the diagnosis, it is important for the clinician to counsel and reassure the patient about the disorder as these patients are susceptible to significant psychological trauma owing to the untoward cosmetic appearance. Although there is no satisfactory treatment available for CL, the options should be discussed with the patient along with psychological and emotional support. Our patient has been counseled regarding the prognosis of the disease and is advised periodic follow-up to detect any manifestations of systemic elastolysis. The primary associated condition preceding acquired CL should be treated accordingly. The associated internal organ involvement may require appropriate care through a multidisciplinary approach. The non invasive treatment option that has been tried is the use of dapsone to control the inflammation. Results have been variable with no effect on the disease progression. However, a diminution of inflammation could be seen. Invasive techniques include botulinum toxin injections, thread lifts, and plastic surgery techniques, such as rhytidectomy, ear lobe reduction, blepharoplasty, and correction of lower eyelid laxity and upper eyelid ptosis

[1,7,12,16,17]. Patients need understand that all these modalities do not prevent the progression of the disease and have to be repeated periodically. We had discussed the options of cosmetic surgeries but the financial burden was the limiting factor for him. Moreover, unsuccessful repeated plastic reconstruction surgeries may become frustrating for the patient as well as the clinician. In future molecular therapies with introduction of elastin gene can be tried in cases of genetic abnormality, and this may provide some hope for the patients [1,16].

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