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Research Letter

Clinical features in adults with acquired cutis laxa: a retrospective review

Dear Editor, Acquired cutis laxa (ACL) is a rare dermatological condition with numerous proposed aetiologies including medications, malignancy, infection, enzyme disorders, autoimmunity and renal disease, and although the pathogenesis of inherited CL is somewhat understood, little is known about ACL.[1] ACL is presumed to be a sequela of environmental exposures leading to elastic fibre destruction.[2] ACL typically presents in adulthood, and diagnosis is based on history and clinical examination followed by histopathology revealing reduction in elastic fibres or elastic fibre fragmentation.[2,3] Patients have localized or generalized wrinkled skin, and disease is either insidious or associated with preceding inflammation.[1,2] This study aimed to better understand potential presentations and triggers of ACL.

Following approval by the Institutional Review Board at Mass General Brigham (MGB), patients diagnosed with CL from January 1989 to April 2021 at MGB hospitals were identified using the Research Patient Data Registry. Inherited CL was excluded. Data were then extracted from medical records.

Ten adults (6 of 10 females) with ACL were identified with an average age at diagnosis of 40 (range 21–69) years (Table 1). As expected, skin laxity was seen in all patients. A majority was found to have additional cutaneous features such as dyspigmentation or pruritus (Table 1). Leading areas of involvement were upper extremities (6 of 10), lower extremities (5 of 10), face (5 of 10) and abdomen (5 of 10). Nine of ten patients underwent skin biopsy. Six patients received genetic testing (three whole-exome sequencing, one whole-genome microarray, two CL panels, one Ehlers Danlos panel, one cystic lung disease panel, one connective tissue disease panel, one single-gene analysis), three of which returned positive. All three patients had associated systemic manifestations: pulmonary disease (alpha-1 antitrypsin); abdominal hernia, obstructive lung disease and coagulopathy (*GGCX*); and refractory hypertension, visual deficits and leucopenia (*LTPB4*/*ALDH18A*).

Almost half the patients (4 of 10) were presumed to have developed ACL in association with medications, two of these being selective serotonin reuptake inhibitors (SSRIs).[3] Suspected drugs were escitalopram, sertraline, amoxicillin and a levonorgestrel-releasing intrauterine device (IUD). Two patients were suspected to have developed ACL associated with medical comorbidities, leucocytoclastic vasculitis and multiple myeloma. Half (5 of 10) sought treatment. One patient with focal disease noted improvement following 5 months of topical therapy (clobetasol, tacrolimus). Three noticed moderate improvement with lasers, surgery, or both. The data underlying this article cannot be shared publicly due to the Health Insurance Portability and Accountability Act. This project was approved by the Institutional Review Board at Mass General Brigham (#2021P000222).

Drugs (penicillin, penicillamine, isoniazid) have been associated with ACL; herein we add a second case of SSRI-associated CL, the first also reported from MGB.[3] No cases following IUD placement or antibiotic therapy have been reported, although our patient on antibiotics was empirically being treated for *Borrelia burgdorferi*, which has been associated with ACL.[1–3] In line with previous reports, clinical evidence of CL may develop gradually, as in the case of our patients receiving SSRI therapy, or suddenly, as in the case of the patient following IUD placement. It is recommended to discontinue the potentially offending medication to prevent further damage; however, degenerative dermal changes resulting from CL are generally irreversible.[4] Monoclonal gammopathy and leucocytoclastic vasculitis have both been previously associated with ACL diagnoses.[2,5] Although larger studies are warranted, providers should be aware of these potential associations and thoroughly review medications.

Reports of gene mutations in cases of ACL are exceedingly rare.[1–3,6] However, our cohort identified three patients. We hypothesize these cases might have arisen in adulthood in individuals with underlying genetic mutations associated with CL who subsequently were exposed to another environmental insult.[6] If a case of potential ACL arises, we recommend careful review of patient history and comorbidities. Thorough systemic investigations based on symptomatology should be considered for all patients with ACL, given the increased likelihood of associated systemic involvement, including cardiovascular, pulmonary and gastrointestinal disorders.[2] Notably, patients with or without systemic involvement may have genetic susceptibility for CL development. Genetic analysis with a CL panel should be considered, and those with unexplained systemic symptoms may warrant whole-exome sequencing should initial analyses return normal.

In line with prior studies, few patients in our series reported improvement following immunomodulators, with one patient improving following topical clobetasol and tacrolimus.[2] Similarly, procedural approaches may provide modest benefit in some patients, although patients should be counselled that multiple treatments may be necessary and disease progression will not be impacted.[2,7] While the retrospective nature and size of our study are limitations, ACL is extremely rare, with few reported series. Further studies are warranted to explore ACL aetiology and genetic susceptibility.

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Table 1 Characteristics of patients diagnosed with acquired cutis laxa

Age at diagnosis (years), sex, race/ethnicity, years since CL diagnosis	Comorbidities	Cutaneous manifestations[a]	Areas of skin involvement	Systemic involvement	Treatment and outcome	Specialists other than Dermatology	Genetic testing (results)	Suspected inciting event or medication
52, M, Black, 8	Sjogren syndrome, cutaneous lupus, HTN, type 2 diabetes mellitus	Skin laxity-associated paraesthesia, hyperpigmentation	Cheeks, forearms, hands, buttocks, thighs	None	None	Rheumatology, gastroenterology, endocrinology, genetics	*LMNB2* gene (negative)	
29, M, White, 1	Leucocytoclastic vasculitis with renal involvement, chronic idiopathic urticaria	Skin laxity, associated striae	Face, neck, axillae, abdomen	None	None	Allergy, rheumatology	None	Leucocytoclastic vasculitis
23, F, White, 2	None	Skin laxity	Breasts, thighs, hips, legs	None	None	Rheumatology, genetics, gastroenterology, breast oncology, infectious diseases	WES, CL panel, Ehlers Danlos panel[b] (negative)	Amoxicillin
69, F, White, 5	Asthma, irritable bowel syndrome, carpal tunnel, spinal stenosis, panic disorder	Skin laxity and wrinkling	Lower face, upper extremities, bilateral thighs	Obstructive pulmonary disease	None	Pulmonology, cardiology, haematology/oncology, genetics	Cystic lung disease panel[c] [MZ carrier at *SERPINA1* (alpha-1 antitrypsin)]	
54, M, White, 1	Frontal fibrosing alopecia, lichen planus, anxiety, hypothyroidism, lumbosacral radiculopathy, peripheral venous insufficiency, GERD	Skin laxity	Face, upper and lower extremities	None	None	None	None	
45, F, White, 12	Asthma, sinusitis, pulmonary disease with eosinophilia and elevated IgE	Skin laxity, hypopigmentation (specifically on neck)	Neck, upper extremities (most pronounced on shoulders, antecubital fossa), upper chest, back, abdomen	None	Prednisone, dapsone, ciclosporin, PUVA (no improvement), Fraxel laser (improved)	None	None	Escitalopram

(*Continued*)

Table 1 (Continued)

Age at diagnosis (years), sex, race/ethnicity, years since CL diagnosis	Comorbidities	Cutaneous manifestations[a]	Areas of skin involvement	Systemic involvement	Treatment and outcome	Specialists other than Dermatology	Genetic testing (results)	Suspected inciting event or medication
34, M, Black, 4	HTN, multiple myeloma	Skin laxity	Face (most pronounced on upper/lower eyelids), neck, upper extremities, back, abdomen	None	Bilateral upper blepharoplasty, rhytidectomy, midface lift, neck lift (minimal improvement)	Genetics, otolaryngology, haematology/oncology	Whole-genome microarray (negative)	Multiple myeloma
25, F, White, 7	None	Skin laxity, pruritus, oedema, erythema	Right upper back	None	Clobetasol, tacrolimus (improved)	None	None	Levonorgestrel-releasing intrauterine device
21, F, White, 2	Raynaud phenomenon	Skin laxity	Neck, proximal upper extremities, back, abdomen	Obstructive pulmonary disease, abdominal hernia, coagulopathy	Bilateral brachioplasty and neck lift (improved), Fraxel laser for abdomen (improved)	Genetics, cardiology, pulmonology, plastic surgery, ophthalmology	WES (compound het. GGCX c.2017C>T, p.R673X, c.763G>A, p.V255M mutations)	Sertraline
45, F, Asian, 8	None	Skin laxity	Chest, back, abdomen, lower extremities	Refractory HTN, bilateral renal artery stenosis, leucopenia, iron deficiency anaemia, visual deficits	NB-UVB, prednisone (no improvement)	Vascular surgery, cardiology, pulmonology, genetics, gastroenterology, nephrology	WES, CL panel, CTD panel (het. LTBP4 mutation c.1307G>A, R436H, het. ALDH18A1 c.1222G>A, R41H mutation)	

CL, cutis laxa; CTD, connective tissue disease; GERD, gastroesophageal reflux disorder; het., heterozygous; HTN, hypertension; IgE, immunoglobulin E; NB-UVB, narrowband ultraviolet B; PUVA, psoralen with ultraviolet light A; WES, whole-exome sequencing.
[a]Associated with areas of CL skin involvement as listed in column only unless otherwise noted. [b]Cutis laxa panel: *ALDH18A1*, *ATP6V0A2*, *EFEMP2*, *ELN*, *FBLN5*, *LTBP4*, *PYCR1*; Ehlers Danlos panel: *ADAMTS2*, *ATP7A*, *B3GALT6*, *B4GALT7*, *CHST14*, *COL12A1*, *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*, *CRTAP*, *FKBP14*, *FLNA*, *P3H1*, *PLOD1*, *SLC39A13*. [c]Cystic lung disease panel: *EFEMP2*, *ELN*, *FBLN5*, *FLCN*, *LTBP4*, *SERPINA1*, *TSC1*, *TSC2*.

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