

Pulmonary Emphysema in Cutis Laxa: A Report of Two Cases

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Abstract

Cutis laxa is a rare connective tissue disorder characterized by progressive looseness of skin, associated with abnormalities of other organs and structures such as lung. Early development of emphysema is usually seen in autosomal recessive forms with death in the early childhood. The autosomal dominant form is usually purely cutaneous and is exceptionally involved in the development of emphysema. In this article, we report two cases of autosomal dominant cutis laxa, both of them had emphysema.

Keywords: Cutis laxa; Dyspnea; Emphysema

Introduction

Congenital connective tissue disorders (Marfan, Ehlers-Danlos, cutis laxa) are rare causes of pulmonary emphysema. Cutis laxa syndrome (CL) represents a group of rare, congenital or acquired heterogeneous diseases, the common denominator of which is the alteration of the elastic tissue likely to cause lesions in any organ containing elastic tissue (skin, lungs, vessels). Early development of emphysema is usually seen in autosomal recessive forms with death in the early childhood [1,2]. The autosomal dominant form is exceptionally involved in the development of emphysema especially since it is a young, non-smoking person with no alpha1-antitrypsin deficiency. Elastic fibers are extracellular matrix (ECM) structures which are consisting essentially of microfibrils of fibrillin and elastin. They constitute a structural and mechanical support of the different tissues [3]. In addition, elastic fibers are needed for the regulation of the bioavailability of several growth factors, including transforming growth factor- β (TGF β) [4]. The most common molecular abnormalities of the autosomal dominant form of Cutis Laxa are the frameshift mutations found in exons 30, 32 and 33 at the 3' end of ELN. These mutations are responsible for the production of elastin in a normal quantity but whose function is impaired [5]. HU and all have demonstrated, through research on mice with an ELN gene mutation, that lung compliance was increased in mutated mice [5]. In addition to impaired ventilatory mechanics, the expression of mutant elastin was also associated with increased TGF β signaling and consequently activation of cell apoptosis pathways. Several studies have shown that these mechanisms were strongly involved in the development of emphysema [5-7]. A better understanding of these mechanisms may lead to specific treatments for emphysematous disease in the context of cutis laxa and in the most common forms of emphysema in chronic obstructive pulmonary disease. Only a few rare cases have been reported in the literature. We describe two new cases of autosomal dominant cutis laxa, both of them had emphysema.

1st observation

First observation is about a 14-years-old child, third in a family of three siblings, born from a non-consanguineous marriage and whose

parents were in an apparently good health, sent by his paediatrician to explore dyspnea on effort. He had a history of recurrent episodes of dyspnea since childhood treated with inhaled corticosteroids with an increase in the frequency and severity of these episodes in recent months. However, early development was normal. On examination, the face had a senile appearance with extremely wrinkled skin and pendulous ears (Figure 1A-C), the respiratory rate was 20 breaths per minute. The oxygen saturation was 98% at ambient air. The thorax was tympanic at the percussion. Cardiac auscultation revealed a diastolic mitral murmur. Pulmonary auscultation revealed a decrease in right vesicular murmurings. The chest X-ray showed chest hyperinflation with signs of emphysema in the right chest (Figure 2A). Thoracic computed tomography showed giant bullous emphysema of the right upper lobe and right postero-basal segment. There was also a total destruction of the middle lobe (Figure 2A and B). An alpha1 anti-trypsin deficiency was suspected but the dosage was normal. Cardiac echocardiography, required to search for manifestations and cardiac repercussions of the disease, showed mitral valve prolapse with moderate regurgitation and signs of pulmonary hypertension. Spirometry confirmed the presence of an obstructive pulmonary disease with a 41% FEV1/ FVC ratio.

2nd observation

The 24-years-old sister also had an appearance suggestive of cutis laxa. She had consulted for chest pain and abrupt installation dyspnea. The examination had shown, apart from the old appearance with a loose and stretchable skin, a tympanic thorax on percussion with diminution of vesicular murmurings, especially on the right. The chest X-ray showed obvious thoracic distension and right partial pneumothorax. Arterial gasometry had not shown hypoxemia. The evolution was spontaneously favorable with complete resolution of pneumothorax. A CT scan performed at a distance from the acute episode revealed centrolobular emphysema. After 8 years of follow-up, the patient did not describe a worsening of dyspnea. Control spirometry did not show a decline in respiratory function (FEV1/CVF ratio: 55%; FEV1 0.75L (22%)). However, an accentuation of the cutaneous lesions was noted responsible for a major aesthetic damage (Figure 1C-E)

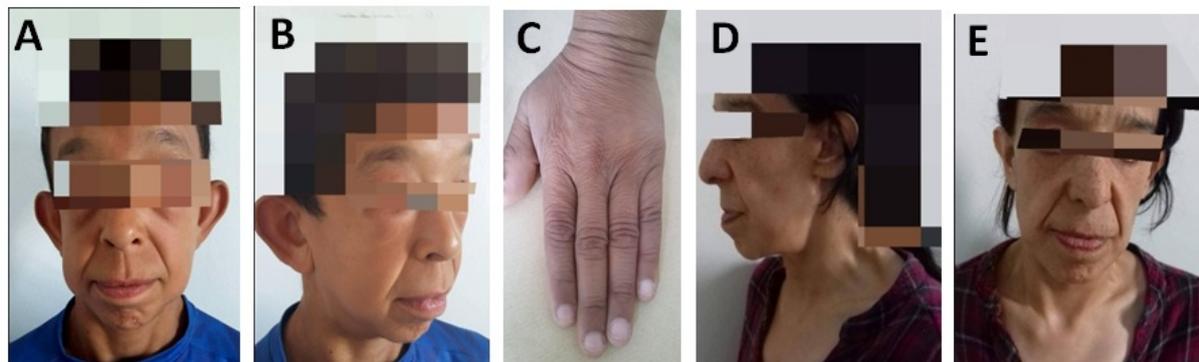


Figure 1: Phenotypic presentation in cutis Laxa. A, B: Wrinkled skin and pendulous ears; C: crumpled hands; D, E: Flaccid folds predominating in the loose regions at the folds and the facial features.

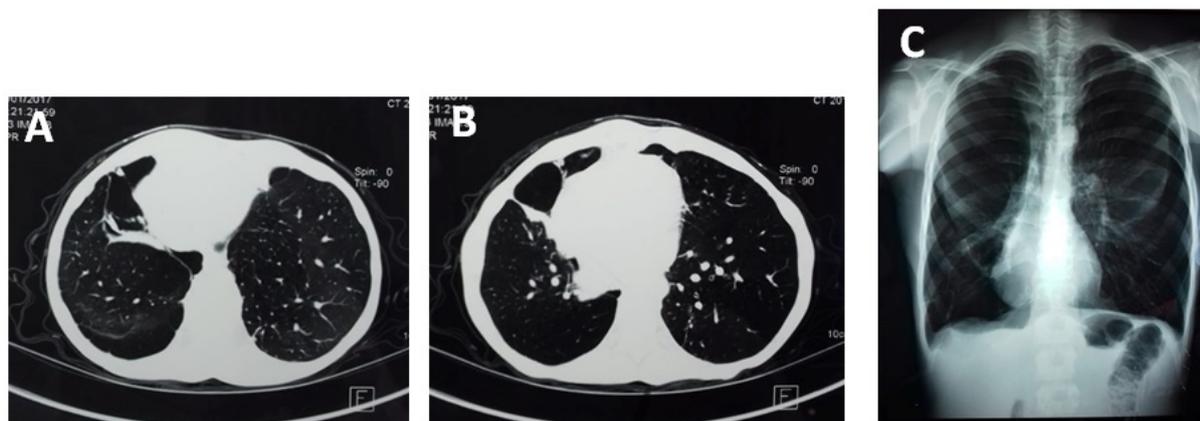


Figure 2: Emphysema in Cutis Laxa A, B: Giant Bullous emphysema of the right upper lobe and right postero-basal segment; C: chest hyperinflation with signs of emphysema in the right chest.

Discussion

Emphysema in adolescents is unusual, even in cases of homozygous alpha1-antitrypsin deficiency (AATD). Alpha1-antitrypsin is a serine protease inhibitor. Its most important physiologic function is the protection of pulmonary tissue from aggressive proteolytic enzymes. AATD is an inherited disease responsible of emphysema [8]. In the cases presented in our observation, Emphysema was associated with a clinical diagnosis of cutis laxa. This is a group of clinically and genetically heterogeneous conditions, characterized by skin hyperlaxity with abnormally stretchy and loose skin in the presence of numerous flaccid and crumpled folds predominant in the loose regions at the folds and the facial features, the origin of the old appearance suggestive of the disease [9]. This characteristic semiological appearance results from various connective tissue abnormalities and can be either congenital or acquired. Hereditary forms include autosomal dominant CL (ADCL), autosomal recessive CL (ARCL), Urban-Rifkin-Davis syndrome (URDS), macrocephaly-alopecia-CL-scoliosis syndrome (MACS), arterial tortuosity syndrome (ATS) and CL linked to chromosome X (CLLX) [9].

The mode of transmission can be autosomal recessive with the most severe clinical manifestations [1,2]. This form is the most severe, as it often involves cardiopulmonary damage in particular emphysema, diaphragmatic abnormalities, arterial malformations and aneurysms [1,10,11]. Joint laxity and muscular hypotonia are also observed. Patients die of pulmonary or cardiac complications in early childhood [2,12].

On the other hand, in the autosomal dominant form, cutaneous involvement can occur from birth or occur later in early adulthood [13,14]. Patients have loose, inelastic and redundant skin that usually worsens with age [2,15]. Previously, the autosomal dominant form of CL was considered benign skin disease with few systemic lesions [14]. However, later research showed that emphysema [16-18], and aortic aneurysms [2], were also part of the phenotypic profile of this syndrome and could lead to significant morbidity and mortality.

To prevent these complications, cardiac echocardiography and pulmonary function tests are recommended [9]. There is marked intrafamily variability of cutaneous manifestations and other visceral involvement [5]. About 30% of patients with ADCL have new mutations with no family history [2,9]. The genetic abnormality responsible during this form is a gene mutation (elastin gene ELN)

[19]. The brother and sister reported in our observation both had a cutis laxa and a clinical presentation that was compatible with the dominant autosomal form.

Conclusion

Cutis Laxa syndrome is a group of rare diseases of the elastic tissue, which may be acquired or hereditary, characterized by a cutaneous hyper laxity associated with variable systemic manifestations. Its early diagnosis allows a better management of the patient and his entourage. This management has four components: research, monitoring and treatment of associated extra-skin manifestations, identification of the mode of transmission that may allow genetic counselling, psychological support for the patient and his family and plastic surgery for correction of cutaneous manifestations.

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