

Images in Allergy

Loeys-Dietz Syndrome Presented with Giant Bullae and Asthma

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A 29-year-old Japanese man was referred to our institution for a gradual increase in dyspnea on effort. He had asthma since his infancy and also had alcohol-induced asthma, allergic rhinitis, atopic dermatitis, and 3 episodes of pneumothorax in his early 20s. He experienced dyspnea and cough particularly during the low atmospheric pressure and in winter. Since the age of 26 years, he gradually developed dyspnea on effort despite treatment with high doses of inhaled corticosteroid and bronchodilators. He worked in retail, had never smoked, and had no pets and no remarkable family history except for 2 maternal uncles who underwent surgeries for aneurysms of the aortic root. He was 171 cm tall, weighed 38.5 kg, and had arachnodactyly, flat feet, hyperextension of the joints (Figure 1, A and B), pectus carinatum, keratoconus, and high palate, which were suggestive enough of hereditary connective tissue disease. Chest auscultation was diminished bilaterally. A chest X-ray showed bilateral pulmonary hyperinflation and a giant bulla, and on chest computed tomography, low-attenuation areas were extensively observed (Figure 1, C to E). Laboratory evaluation showed blood eosinophilia (379/ μ L), high serum total IgE (850 IU/mL), and elevated specific IgE against dust mite (>100 UA/mL), Japanese cedar, cat, and dog (0.36–0.74 UA/mL). A pulmonary function test revealed severe airflow limitation with forced expiratory volume in 1 second (FEV₁)/forced vital capacity 21.8% and FEV₁ 0.74 L (17.5% predicted), which was increased to 0.86 L after switching from a dry powder to metered-dose inhaler. An echocardiogram revealed mild dilation of the root of the aorta. Characteristic appearance, atopic condition, and a severe emphysematous change of the lungs at a young age prompted genetic testing. Finally, the diagnosis of Loeys-Dietz syndrome (LDS), type 4 with a mutation in transforming growth factor (TGF)- β 2 coding gene (NM_003238), was made.

In 2005, LDS was first described by Loeys et al,¹ who examined 10 families with aortic aneurysms, generalized arterial

tortuosity, hypertelorism, and bifid/broad uvula or cleft palate. Notably, approximately 75% of the cases show new mutations in TGF- β receptors and the TGF- β signaling pathway, while they are autosomal-dominantly inherited.¹ In Marfan syndrome, which has major phenotypical overlaps with LDS, TGF- β signaling is upregulated *via* mutations of the fibrillin 1 gene, and an emphysematous change of the lungs probably due to developmental impairment of distal alveolar septation is observed. As it could be critical like this patient, pulmonary involvement or emphysematous changes occurring in a patient with LDS potentially because of upregulation of the TGF- β signaling pathway should be well acknowledged. Concomitant allergic diseases, including asthma, atopic dermatitis, and food allergies, are important features of LDS, which underscores a role of TGF- β signaling in the immune system and allergic diseases. In one study, 26 among 58 patients with LDS (45%) had clinician-diagnosed asthma.² Patients with LDS with upregulation in the TGF- β signaling pathway had higher levels of serum IgE, type 2 cytokines, and eosinophil counts than nonallergic controls. Conclusively, clinicians should consider LDS in patients with asthma or allergic predisposition who show the above-mentioned characteristic physical features. Furthermore, the possibility of emphysematous changes should be noted, which could lead to severe airflow limitation and require careful management.

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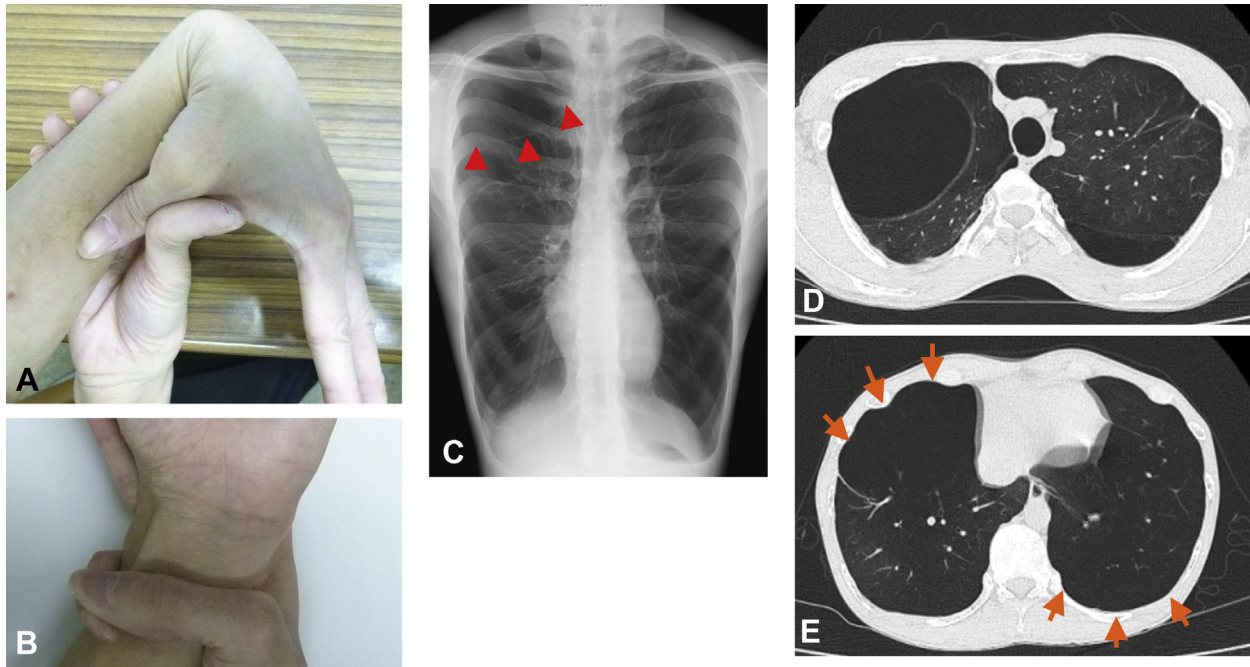


FIGURE 1. **A**, The wrist joint can be hyperflexible and the thumb can reach the distal part of the forearm. **B**, The thumb and the fifth finger can overlap each other, indicating hypermobility and arachnodactyly (wrist sign). **C**, Chest radiograph shows hyperinflation of the bilateral lungs and a giant bulla in the right upper lung field (arrow heads). **D**, High-resolution computed tomography scan reveals a giant bulla in the upper lobe of the right lung. **E**, Lung structure destruction and subsequent extensive lower attenuation areas are prominent in the lower lung field (arrows).