Lung hypoplasia and patellar agenesis in Ehlers-Danlos syndrome

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ABSTRACT

A 22-year-old male patient was admitted with severe cough associated with purulent expectoration, left-sided chest pain and breathlessness. There was a history of recurrent respiratory ailments since childhood. The patient appeared younger than his chronological age. His face and ears were both dysmorphic. Clinically, the patient was diagnosed with Ehlers-Danlos syndrome (EDS). Computed tomography of the thoracic region revealed hypoplasia of the left lung and hyperplasia of the right lung. Both the patellae were absent. However, ultrasonography of his abdomen, echocardiography and other routine blood and urine examination showed no gross abnormalities. Although other respiratory tract abnormalities with EDS are not uncommon, unilateral lung hypoplasia and patellar agenesis in EDS make this case unique.

Keywords: Ehlers-Danlos syndrome, lung hypoplasia, patellar agenesis

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INTRODUCTION

Ehlers-Danlos syndrome (EDS) comprises a clinically heterogeneous group of connective tissue disorders resulting from some defect in the synthesis or structure of the fibrillar collagen. Beighton et a1 proposed a simplified classification of EDS into six major types, according to some major and minor diagnostic criteria.[1] In addition to various forms of defects of the skin and joints, some internal organs, such as the lungs, may be affected in EDS. However, we present a rare variety of EDS associated with hypoplasia of one lung, as well as patellar agenesis.

CASE REPORT

A 22-year-old male patient was admitted to the Department of Chest Medicine, Kolkata, India, with severe cough associated with purulent expectoration, left-sided chest pain and breathlessness of about one week's duration. There was a history of chronic cough, occasional chest pain as well as dyspnoea on exertion since his childhood. The patient has three brothers and three sisters, and he was the second child. All his siblings were apparently normal. There was no history of consanguineous marriage. His mother had taken anti-tuberculous drugs during her second pregnancy (no

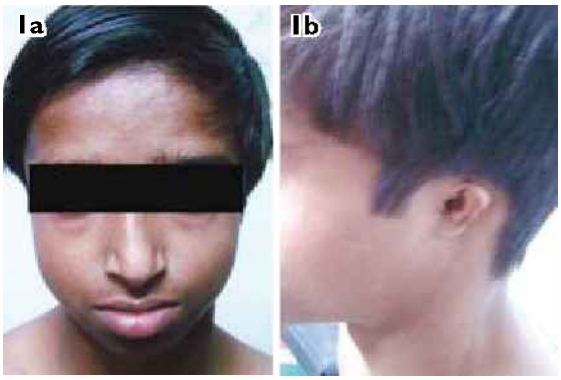
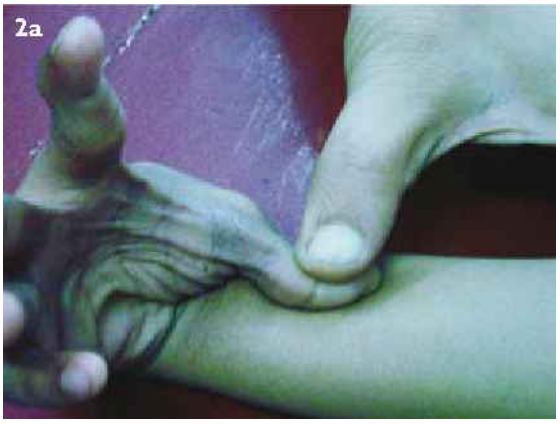


Fig. 1 Photographs show the (a) dysmorphic face, and (b) ears of the 22-year-old patient.



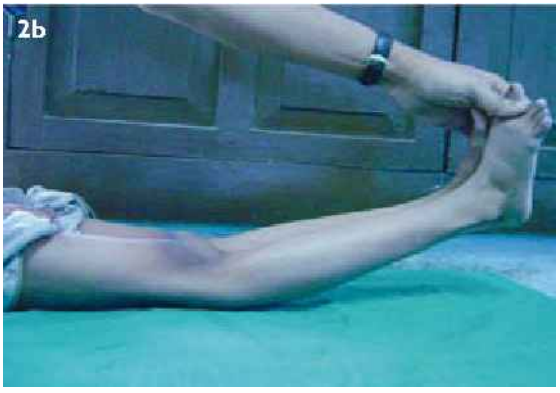


Fig. 2 Photographs show the patient's (a) hypermobile thumb, and (b) hypermobile knee joints.

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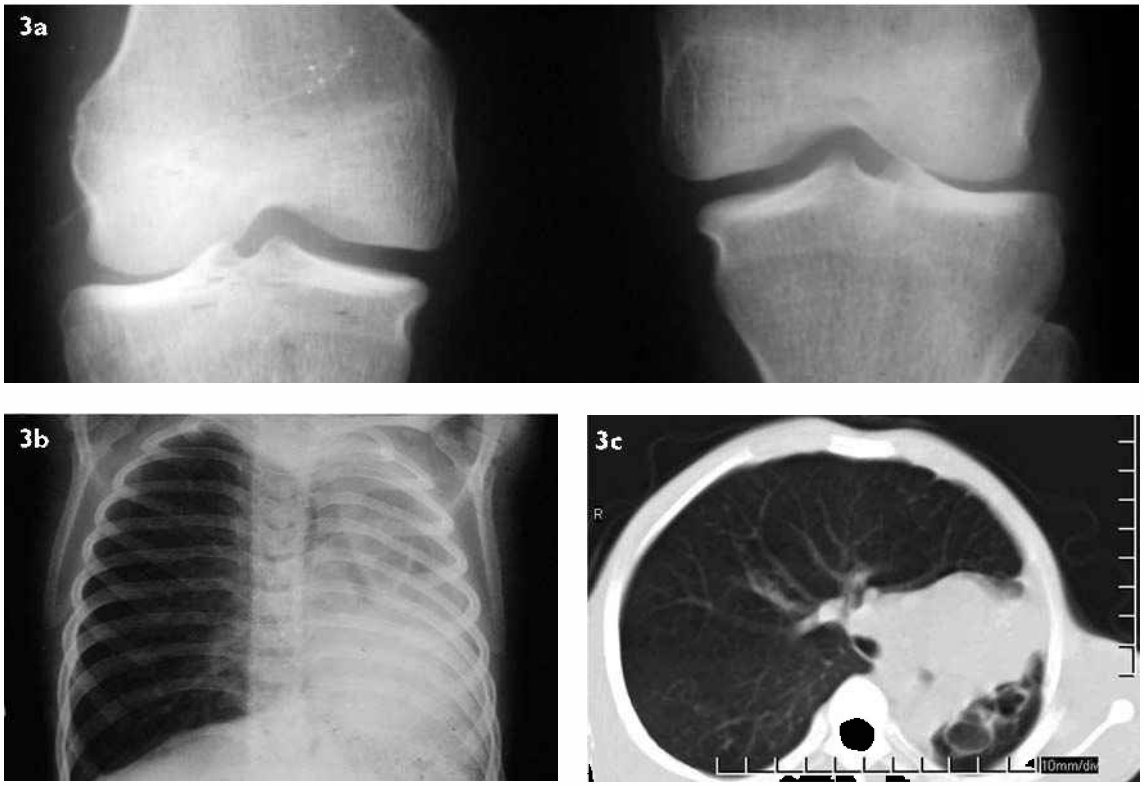

Fig. 3 (a) Radiograph of both knees shows the absence of patella bilaterally. (b) Chest radiograph shows obvious left lung opacification, hyperinflation of the right lung and shifting of the mediastinum to the left side. (c) Axial CT image of the thorax shows a small hypoplastic left lung, with a small narrow left bronchus without any further branching.

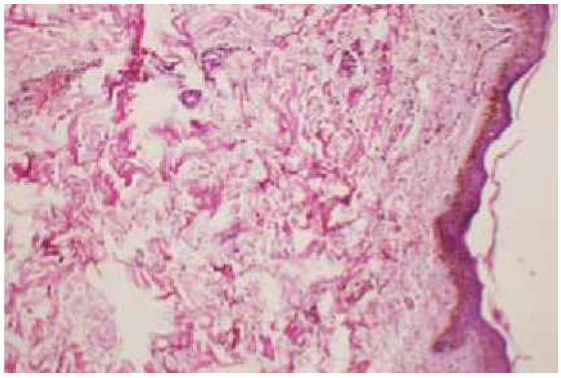

Fig. 4 Photomicrograph of the skin biopsy shows a thin papillary dermis and fragmented collagen fibres in the reticular dermis (Haematoxylin & eosin, × 100).

details were available) and had a history of prolonged labour with premature rupture of the membrane during delivery.

The patient looked younger than his age. His face and ears were dysmorphic (Fig. 1). There was easy bruisability and moderate hyperelasticity of the skin folds, but no loose folds. All the small and large joints were hypermobile (Fig. 2). Joint hypermobility was confirmed by using the Beighton scale[1] (Tables I & II). There was no patella in both knee joints (Fig. 3a). Secondary sexual characters were poorly developed, and there was sparse axillary and pubic hairs. His voice was feminine in nature. His height was 126 cm, and body weight was 17 kg. His head circumference was 49 cm, and the chest circumference was 55 cm. There was mild kyphoscoliosis as well as a little flattening of the chest wall of the left side. However, there were no obvious clinical signs of any nerve or spinal cord injury.

The posteroanterior radiograph of the chest showed left lung opacification, hyperinflation of the right lung and gross shifting of the mediastinum towards the left side (Fig. 3b). Radiographical features of the long bones suggested a normal chronological age. However, there was mild osteopenia. Ultrasonography of the abdominal organs was normal. Echocardiography showed that the heart was within normal limits. A very small hypoplastic left lung with small narrow left bronchus without any further branching was found on computed tomography (CT). Hence, this was a case of lung hypoplasia, and not lung aplasia (Fig. 3c). Pulmonary function studies showed a 68% predicted forced vital capacity and a 41% predicted forced expiratory volume in the first second. The fundus of both eyes showed tilted discs with peripapillary atrophy. There was associated myopia in both eyes. Histopathological examination of the skin showed thinning of the papillary dermis and the presence of fragmented collagen fibres. The epidermis was flattened (Fig. 4).

Table I. Major and minor criteria of Ehlers-Danlos syndrome Type 4.[1]

Criteria for Ehlers-Danlos syndrome Type 4*	Status in the present case
Major	
• Generalised joint laxity (as per Table II).	Present
• Severe muscle hypotonia at birth.	Not known
• Scoliosis at birth, progressive.	Scoliosis present
• Scleral fragility and rupture of occular globe.	Not found
Minor	
• Tissue fragility including atrophic scars.	Present
• Easy bruising.	Present
• Arterial rupture.	Not known
• Marfanoid habitus.	Not present
• Microcornea.	Not done
• Radiologically – osteopenia.	Mild
• Family history – affected siblings.	Nothing suggestive

* One or more major criteria establish the clinical diagnosis.

Table II. Beighton scale of joint hypermobility.[1]

Criteria	Points	Score for the present case
• Passive dorsiflexion of the little fingers beyond 90°.	1 per hand	2
• Passive dorsiflexion of the thumbs to the flexor aspect of the forearm.	1 per hand	2
• Hyperextension of elbows beyond 10°.	1 per elbow	0
• Hyperextension of knees beyond 10°.	1 per knee	2
• Forward flexion of the trunk with knees fully extended so that palms can rest flat on the floor.	1	0
Total score	9 (maximum)	6*

* A score of ≥ 5/9 defines hypermobility.

DISCUSSION

The present case was diagnosed as EDS, which was described in detail by Ehlers in 1901 and Danlos in 1908.[2] In this condition, the essential defect is a quantitative deficiency of fibrillar collagen, which is usually due to mutations in the collagen-modifying genes. EDS has been classified into ten clinical types.[3] In addition to joint hyperextensibility, most of the clinical features of Type 7 (subtype-c) were fulfilled by the present case. EDS Type 7C is an "autosomal recessive" type of disorder, which is characterised by growth retardation, characteristic facies with micrognathia, skin fragility and laxity.[3,4] Beighton et al proposed a simplified classification of EDS into six major types, according to several major and minor diagnostic criteria.[1] The presence of one or more major criteria was necessary for clinical diagnosis. However, the presence of one or more minor criteria is helpful to diagnose a specific type, although they are not sufficient to establish the diagnosis in the absence of a major criteria. Based on to this recent classification, the present case may be considered a Type 4 (vascular type) or Type 6 (kyphoscoliosis type) (Tables I & II).

Respiratory system involvement is not uncommon in EDS, which clinically presents with or without recurrent haemoptysis. Multiple scattered cavitary lesions of one or both lungs, parenchymal cysts, fibrous or fibro-osseous nodules (abnormal attempt to repair parenchymal or vascular tears), chronic pulmonary diseases or recurrent spontaneous pneumothorax, were reported in cases of EDS.[3-14] However, to the best of our knowledge, pulmonary hypoplasia or patellar agenesis in EDS has not been reported previously. Like clinical heterogenecity, EDS is also variable at the molecular level. Abnormalities in the expression or structure of the fibrillar collagen (Types I, III and V), as well as enzymatic abnormalities in the post-translational modification and processing of these collagens, have been identified in a number of EDS subtypes.[2] In about 50% of individuals with the classic type of EDS, mutations in the COL5A1 and COL5A2 genes are found. Mutations in the TNX-B gene cause an autosomal-recessive "classic-like" phenotype of EDS. The genetic defects underlying the hypermobility type of EDS is not well known. A phenotypic continuum may exist between classic and hypermobile EDS. Therefore, haploinsufficiency of the COL5A1 gene or heterozygous mutations in the TNX-B gene may be found in patients with the hypermobility type of EDS. Homozygous or compound heterozygous mutations in gene encoding enzymes involved in collagen biosynthesis have been documented in several autosomal-recessive forms of

EDS. Homozygous mutations in LH-1 (PLOD1) are noted in the cases of the kyphoscoliotic type of EDS. A deficient activity of procollagen-N-proteinase due to mutations in the ADAMTS-2 gene encoding, the enzyme is responsible for EDS Type 7C.[15] The EDS may be diagnosed by the clinical manifestations, but the presence of particular genetic and biochemical abnormalities, as well as molecular defects, are useful for identifying the specific subtype.

Lung development progresses through four stages, viz. pseudoglandular (7–17 weeks gestation), canalicular (17–26 weeks gestation), saccular (24 weeks gestation to birth) and alveolar (28 weeks to eight years of age).[16] There are three prerequisites for normal lung maturation: (a) sufficient intrathoracic space; (b) normal foetal breathing movements; and (c) sufficient amniotic fluid. The neonatal lung has abundant Type III and Type IV collagen, but little Type I collagen (found in mature lungs). Therefore, neonatal lungs are more plastic, and the cell shape and orientation can be changed accordingly. The rapid deposition of Type I collagen postnatally confers structural stiffness. Unilateral lung hypoplasia is often associated with impaired foetal breathing movements, pleural effusion with foetal hydrops, cystic adenomatoid malformation, defects in diaphragmatic activity, congenital diaphragmatic hernia or any respiratory anlage at a later stage of lung development.[17,18] Thus, prolonged premature rupture of the membranes may also lead to diminished lung growth postnatally. In EDS Type 7C, there is mainly a specific molecular defect in the processing of Type I procollagen to Type I collagen.[3,4] Type III and Type IV collagen are normally found in developing lungs. However, during postnatal maturation of the lungs, Type III and Type IV collagen fibres are replaced by a rapid deposition of Type I collagen.[16] Moreover, in EDS Type 7C, there is premature rupture of the placental membranes during birth,[3] which might be one of the causes of lung hypoplasia in this case.

Type I collagen is found in the tendon, aponeuroses and ligaments. The defect in Type I collagen in this case is responsible for the hypermobility of the joints. Another distinctive observation was that both the patellae were absent, which was not previously reported in any EDS case. Ocular signs may be due to hyperelasticity of the sclera. However, the cornea is normal in this case, although a precise geometrical pattern of the Type I collagen is normally found in the cornea for its transparency.[19] The defect in the lung and absence of the patella in the present case are unique. The defect in the synthesis or structure of collagen is probably organ-specific, depending on the mutation of other genes, and thus, may consequently produce a varied morphological abnormality.

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