Cutis laxa autosomal recessive type II or wrinkly skin syndrome?

Sir,

Cutis laxa (CL) is a rare disorder of connective tissue caused by abnormality in the elastic fibers. Three groups have been recognized based on the mode of inheritance—autosomal recessive (AR), autosomal dominant (AD), and X-linked. ARCL is further categorized into type I, type II, and type III. Features of ARCL type II overlap with those of Wrinkly skin syndrome (WSS). We present a case of CL type II and highlight the difference between the two conditions.

A 5-year-old boy was referred to our center with a diagnosis of loose skin. The patient's mother complained of hanging skin over abdomen, excessive mobility of joints with difficulty in walking, and change in gait. The child was the product of nonconsanguineous marriage and both antenatal period and labor at term were uneventful. An elder sibling (sister) aged 7 years and both parents were healthy. The birth weight was 1.5 kg, head circumference: 36 cm and length: 50 cm. There was history of two still births prior to birth of elder sibling. There was no history of easy bruisability, spontaneous fractures, visual or hearing problems, or abnormal involuntary movements in the patient or in the other family members. The developmental milestones were delayed. Orchidopexy was done for undescended testes at 5 years of age.

On physical examination, weight and height were 12.5 kg (<3rd percentile) and 95 cm (<3rd percentile), respectively. The head circumference was 46.5 cm (<3rd percentile). He had an elongated face with low-set eyes and depressed nasal bridge. The facial skin was thin and inelastic, and prominent veins were visible in the temporal region and also on cheeks. The skin over the abdomen, hands, and feet was wrinkled with decreased elasticity and recoil [Figures 1 and 2]. Both anterior and posterior fontanelles were closed at the time of presentation. He had bilateral inguinal hernias with infantile penis. Musculoskeletal examination revealed a waddling gait with scoliosis and flat feet. His arm span was 101 cm. Upper segment to lower segment ratio was 0.83. Joint examination revealed hypermobile joints at the wrist (thumb sign or Steinberg's sign positive, wrist sign negative), metacarpophalangeal joints, and ankles and knees. Ocular examination revealed myopia. Cardiopulmonary examination did not show any abnormality.

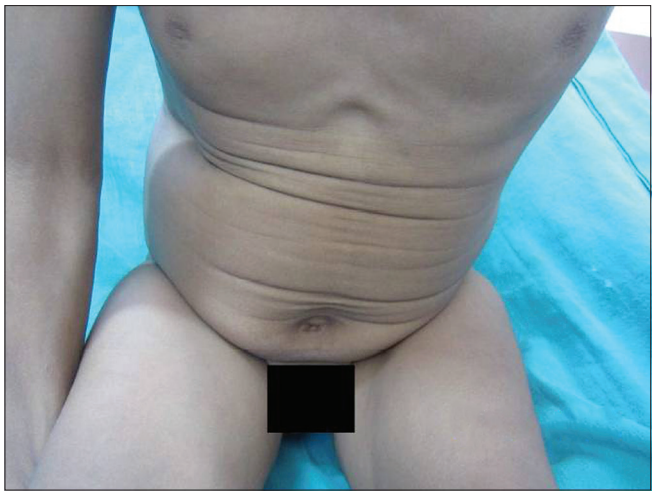

Figure 1: Wrinkling of skin over the abdomen

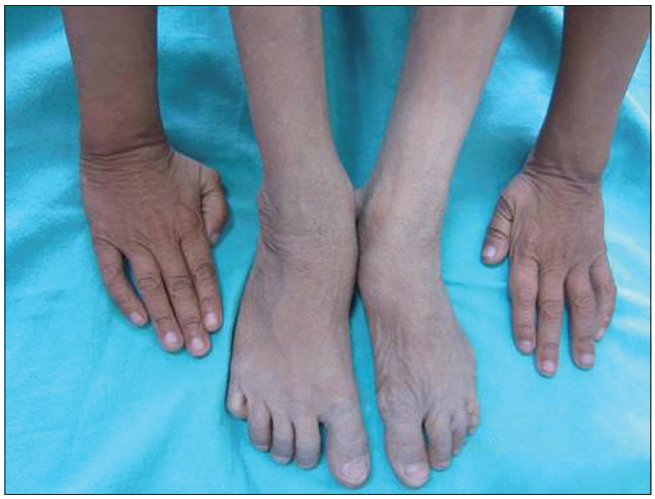

Figure 2: Dorsa of hands and feet showing wrinkled and inelastic skin

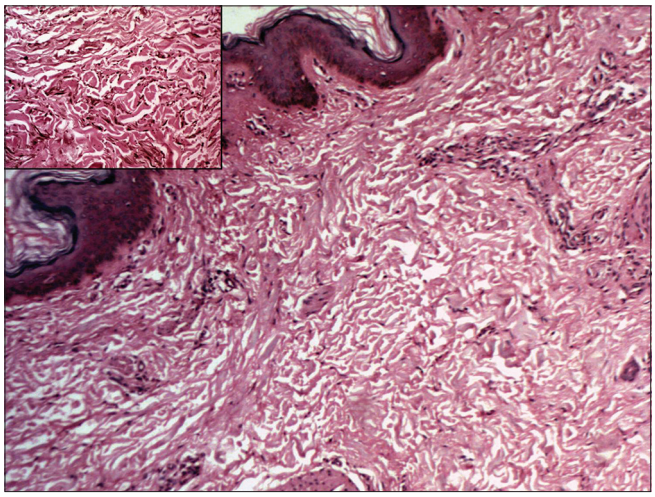

Figure 3: Photomicrograph of skin biopsy showing papillary dermal fibrosis (H and E, ×100). Inset shows elastin stain demonstrating uneven and granular staining pattern of elastic fibers in upper and middermis (Verhoff–van Gieson stain, ×400)

Table 1: Features observed in our case in comparison with ARCL II and wrinkly skin syndrome

Feature	ARCL II	WSS	Index patient
Generalized laxity	++	+	+
Facial laxity	++	++	+
Severity of laxity	++	+	+
Dysmorphic facies	++	+	+
Microcephaly	+	+	-
Delayed closure of fontanelle	++	+	-
Downward slanting of palpebral fissure	++	+	+
Delayed motor development	++	+	+
Mental retardation	+	+	+
Dwarfism/short stature	+	-	+
Spontaneous fracture	+	-	-
Hip dislocation	++	+	+
Joint laxity	++	+	+
Hernias	+	+	+
Scoliosis	+	-	+
Postnatal growth delay	++	++	+
Bladder diverticuli	Seen in other variants	-	+

AR: Autosomal recessive, CL: Cutis laxa, WSS: Wrinkly skin syndrome. -: Not seen, +: May be seen, ++: Common finding

Hematologic and biochemical profile were normal. Hematoxylin and eosin staining of skin biopsy done from the abdomen showed reduction in elastic fibers with breakage and granularity. Staining with Verhoeff–van Gieson demonstrated uneven and granular staining pattern of elastic fibers in upper and middermis [Figure 3]. Skeletal survey revealed scoliosis with spina bifida at S1. There was cranial migration of both femora suggestive of bilateral hip dislocation. Magnetic resonance imaging (MRI) of lumbosacral spine and pelvis confirmed these findings. Ultrasound of kidney and urinary bladder showed right hydroureteronephrosis with trabeculations in urinary bladder suggestive of diverticuli, which were confirmed on intravenous urography. Micturating cystourethrography showed bilateral grade IV/V vesicoureteric reflux. Echocardiogram, skull X-ray, and MRI of brain and cervical spine were all normal. Development quotient was 24, signifying severe global developmental delay. Based on these findings, a diagnosis of ARCL type II was made. As there is no specific treatment, the patient was managed symptomatically for the skeletal and urinary problems.

CL is a rare disorder of elastic fibers comprising congenital and acquired forms characterized by loose, redundant, and hypoelastic skin. Inherited patterns include autosomal dominant, AR, and X-linked forms. These occur due to defect in the synthesis of elastic fibers and usually present at birth or soon afterwards.

ARCL is the more severe form and consists of three distinct types.

ARCL type II is characterized by variable severity of CL, abnormal growth, and developmental delay and associated skeletal abnormalities. Wrinkled inelastic skin is seen especially on the dorsal acral surfaces and abdomen. Patients have dysmorphic facies with progeroid appearance.[1-3] Other features that may be seen are hip dislocation, pigeon breast, scoliosis, inguinal hernia, and flat feet.[4,5]

Based on the findings, our patient was diagnosed as ARCL type II, which has features overlapping with the WSS, an AR syndrome manifesting with wrinkled and inelastic skin involving the face, dorsa of hands and feet, and abdomen. Other clinical features seen in WSS (and ARCL) are outlined in Table 1. Histopathology in the former reveals normal or decrease in number and length of elastic fibers in the affected skin. There is a great deal of similarity between these two disorders. However, skin changes are more severe and generalized in CL. Facial dysmorphism is prominent in CL (as seen in our patient) and minimal in WSS. Also the presence of vesicoureteric reflux, hydronephrosis, and bladder diverticuli has been described in CL but has not been reported in association with WSS.

Mutations in the ATP6V0A2 gene have been found in families with ARCL.[6] This defect causes abnormal glycosylation leading to defect in the biosynthesis of N- and O-linked glycans. Similar mutation has been found in WSS suggesting the possibility that CL and WSS are phenotypic variants of the same disorder and reflect varying severity of the same disease. As a result, complete differentiation may not be always possible and cases with overlapping features may be seen as in our patient.

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Conflicts of interest

There are no conflicts of interest.

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