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Rhizomelic Chondrodysplasia Punctata With Maternal Systemic Lupus Erythromatosus

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We report Rhizomelic Chondrodysplasia Punctata (RDCP), a rare, autosomal recessive disorder with rhizomelic shortening of limbs, congenital cataracts and seizures but without any biochemical abnormality. The mother of the baby developed Systemic Lupus Erythromatosus (SLE) with Ro/SSA antibodies 11 months after delivery. Ro/SSA antibodies may generate calreticulin antibodies causing characteristic skeletal changes.

Key words: *Anti Ro/SSA, Punctate epiphyseal calcification.*

The classic form of rhizomelic chondrodysplasia punctata (RCDP) a rare, autosomal recessive peroxisomal disorder is characterized by proximal shortening of the limbs, cataracts, distinct facial appearance, growth failure, psychomotor retardation and seizures[1]. Common radiological features are punctate epiphyseal calcifications, metaphyseal abnormalities, coronal clefts in vertebral bodies [1]. RCDP is usually lethal with 60% deaths occurring by age 1 year. [2] The characteristic biochemical profile has been previously described [3]. Recently, patients with RCDP phenotype but without abnormal peroxisomal function have been reported usually secondary to teratogen exposure or maternal diseases [4]. We report a neonate with features of RCDP without biochemical abnormality but whose mother was diagnosed having SLE 2 months prior to delivery.

CASE REPORT

This male baby was the first child of healthy unrelated Indian Hindu parents born at term by spontaneous vaginal delivery. His mother and father were 25 and 29 years old, respectively. There was no history of spontaneous abortions or antenatal teratogen exposure. His birthweight was 2459 g (10-25th percentile), length was 42.5 cm (<10th percentile), and head circumference was 33 cm (50th percentile). His upper segment to lower segment ratio was 1.8:1. He was a disproportionately

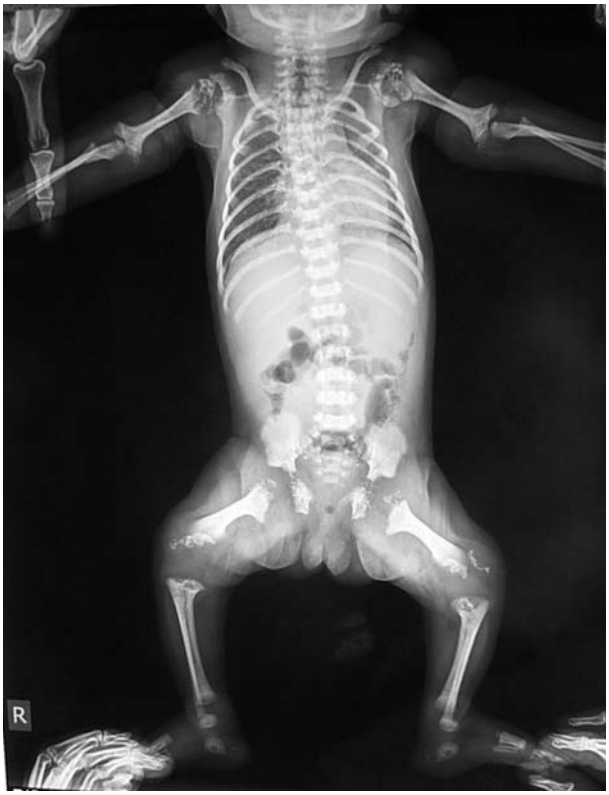

FIG. 1 *Skiagram showing punctate epiphyseal calcification of shoulder, elbow, hip and knee joints with metaphyseal flaring of humerus.*

short infant. He had proximal shortening of both upper and lower limbs, midfacial hypoplasia with a depressed nasal bridge. and anteverted nares with a short neck with nuchal fullness, a barrel-shaped chest. There were no skin lesions. Ophthalmological examination showed cataract in both eyes.

A skeletal survey showed rhizomelic shortening of extremities. Bony stippling was noted in shoulder, elbow, hip and knee joints with metaphyseal flaring in humerus and femur (***Fig.* 1**). The pelvis appeared normal, but the spine exhibited minimal ossification and coronal clefts of the vertebral bodies.

Cranial and abdominal ultrasonography and echocardiography were normal. CT Brain revealed stippled anterior arch of foramen magnum. A diagnosis of rhizomelic chondrodysplasia punctata was made. Red blood cell plasmalogen content was performed as dimethylacetals (DMAs). The mean levels of C16:0DMA/C16:0 fatty acid, C18:0 DMA/ C18:0 fatty acid, VLCFA and phytanic acid levels were within the reference range.

Cataract extraction was done. Genetic assay could not be done due to financial constraints. Genetic counseling was given to the parents. The infant was discharged from the nursery at 10 days of age and is receiving regular physiotherapy.

Two months later, the mother had joint pain of the hands and the feet and photosensitive malar rash. Maternal serology results were diagnostic of SLE with positive antinuclear antibody with a 1:640 titer in a speckled pattern; positive for extractable nuclear antigen with an anti-SM level of 42.10 EU/mL [reference:<20 EU/mL] and anti-RNP level of 192.50 EU/mL [reference: <20.01 EU/mL]; positive for anti- SSA[Ro] 155.4 EU/ mL (reference:<25.1 EU/mL). Other antibodies were negative with normal C4 complement level. The mother was started on low dose prednisolone 10 mg/day.

DISCUSSION

Chondrodysplasia punctata (CDP) is characterized by punctuate calcification of cartilage. It includes peroxisome biogenesis disorders (Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum disease, and RCDP Type1), maternal conditions and teratogen exposure. CDP has four main types, the autosomal dominant (Conradi-Hunermann's type), autosomal recessive (rhizomelic type), the X-linked dominant form (Happle) and the X-linked recessive form.

There are three types of RCDP. RCDP Type 1 involves mutations in the PEX7 gene [3]. RCDP Types 2 and 3 are phenotypically similar to RCDP Type 1, but result from deficiencies of dihydroxyacetone phosphate acyltransferase and alkyldihydroxyacetone phosphate synthase, respectively[1].

Though our patient presented with many characteristic features of RCDP but he differed from other patients in that there was no abnormality of red blood cell plasmalogens and phytanic acid levels. Antenatal history of teratogens like rubella infection, and warfarin or dilantin use was negative. There are case reports of maternal autoimmune diseases like SLE and phenylketonuria with CDP in their babies [5-9]. Our patient is the eleventh reported RDCP patient born to a mother with SLE. Only 3 have had the characteristic skin lesions of neonatal lupus erythematosus (NLE) and none had congenital heart block.

The proposed mechanism for stippling in CDP-associated maternal lupus is immune mediated by maternal autoantibodies crossing the placenta in early to midgestation. These antibodies inhibit a high-affinity calcium-binding protein of endoplasmic reticulum, calreticulin. Anti Ro/SSA is an autoantigen complex that may include calreticulin. Auto-antibodies to calreticulin and Ro/SSA are involved in the pathogenesis of congenital heart block and the cutaneous lesions of SLE and may be responsible for the skeletal changes by inhibiting calcium binding. Animal model studies showed that immunization of mice with Ro resulted in the production of anti-Ro, anti-La, and anti-calreticulin antibodies [10] Our patient's mother was positive for Ro/ SSA. Alternatively maternal autoantibodies affect the infant's vitamin K metabolism [8] resulting in bleeding into the epiphyseal cartilage, which produces the stippled appearance.

Autoantibodies may be the largest single risk factor for the development of CDP in the neonate but the presence of autoantibodies cannot be the only determining factor to predict the occurrence of CDP, because the incidence of CDP in infants of mothers with SLE is very low. Management of these babies is mainly supportive. Cataract extraction and physiotherapy may help. Genetic counseling is necessary. Monitoring growth and development, seizure control, vision, hearing, contractures and orthopedic complications need regular assessment on follow up.

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