J Korean Med Sci 1998; 13: 201-6
ISSN 1011-8934

Short-rib Polydactyly Syndrome, Beemer-Langer Type, with Bilateral Huge Polycystic Renal Dysplasia
: An Autopsy Case

Short rib-polydactyly syndrome (SRPS) is a group of lethal skeletal dysplasia of an autosomal recessive inheritance characterized by markedly narrow ribs, micromelia, and multiple anomalies of major organs. We report a case of type IV SRPS with uncommon associations of polydactyly and bilateral polycystic kidneys, in a 28 week old female fetus. She was born dead to a 28 year old mother, showing a hydropic change, narrow thorax, and shortened limbs with postaxial heptasyndactyly of both hands and feet. Radiologic examination revealed short horizontal ribs, curved short tubular limb bones, small ilia and scapula, and a mild vertebral abnormality. Postmortem examination disclosed pulmonary hypoplasia, pancreatic cysts, hepatic fibrosis, and left persistent superior vena cava. In addition this case had bilateral huge polycystic renal dysplasia that was seldom described in any type of SRPS. Histologic sections of the vertebrae disclosed abnormal enchondral ossification with irregular and retarded hypertrophic zone.

Key Words : *Short rib-polydactyly syndrome, Beemer-langer type; SRPS IV; Kidney, polycystic; Bilateral polycystic renal dysplasia*

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Received : August 19, 1997
Accepted : November 22, 1997

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INTRODUCTION

Short rib-polydactyly syndrome (SRPS) is a very heterogeneous group of osteochondrodysplasias and includes at least 4 types: 1. SRPS I (Saldino-Noonan) 2. SRPS II (Majewski), 3. SRPS III (Verma-Naumoff), 4. SRPS IV (Beemer-Langer) according to the current International classification of osteochondrodysplasias in 1992 (1). SRPS I to IV are a group of genetic disorders that are inherited in autosomal recessive mode, showing the key features of chondrodysplasias such as short ribs, short limbs, and polydactyly. They are clinically manifested as the extreme, lethal forms of dwarfism. The delineation of its subtypes was difficult due to their shared dysmorphic features. There have been 3 main types i.e., types I-III of SRPS since they were defined by the International nomenclature of constitutional diseases of bone in 1978 (2). They were characterized by a marked limb reduction, polysyndactyly, short horizontal ribs with narrow constricted thorax and hypoplastic lungs, and early lethality. SRPS, Beemer type was later delineated as type IV by Beemer et al., which was distinguished from the previous 3 types by showing no polydactyly and the presence of short and bowed long bones and mild platyspondyly (3).

In general, SRPS is well-known to be associated with multiple systemic congenital anomalies, including pulmonary hypoplasia and variable combinations of renal, cardiovascular, genital, gastrointestinal, and brain anomalies. Of those, kidney and urinary tract anomalies are more frequently found. They are normal or small-sized kidneys with cystic dysplasia, hypoplasia, polycystosis, agenesis, urethral atresia etc. (4-11). However, bilateral huge polycystic renal dysplasia combined with intrahepatic fibrosis and large pancreatic cysts have never been described in the literature to our knowledge.

CASE REPORT

A female stillborn was delivered after 28 weeks of gestational period under the clinical impression of Potter's syndrome because ultrasonic examination had revealed a growth retardation with hydrops and bilateral huge polycystic kidney. The parents were nonsanguineous, and the mother was 28 years old. During the gestational period, oligohydramnios was found. External examination showed a hydropic and dysmorphic fetus, weighing 812 g and measuring 33 cm in crown-to-heel length (Fig. 1A). With nuchal edema, the head appeared large in comparison to the rest of the body, measuring

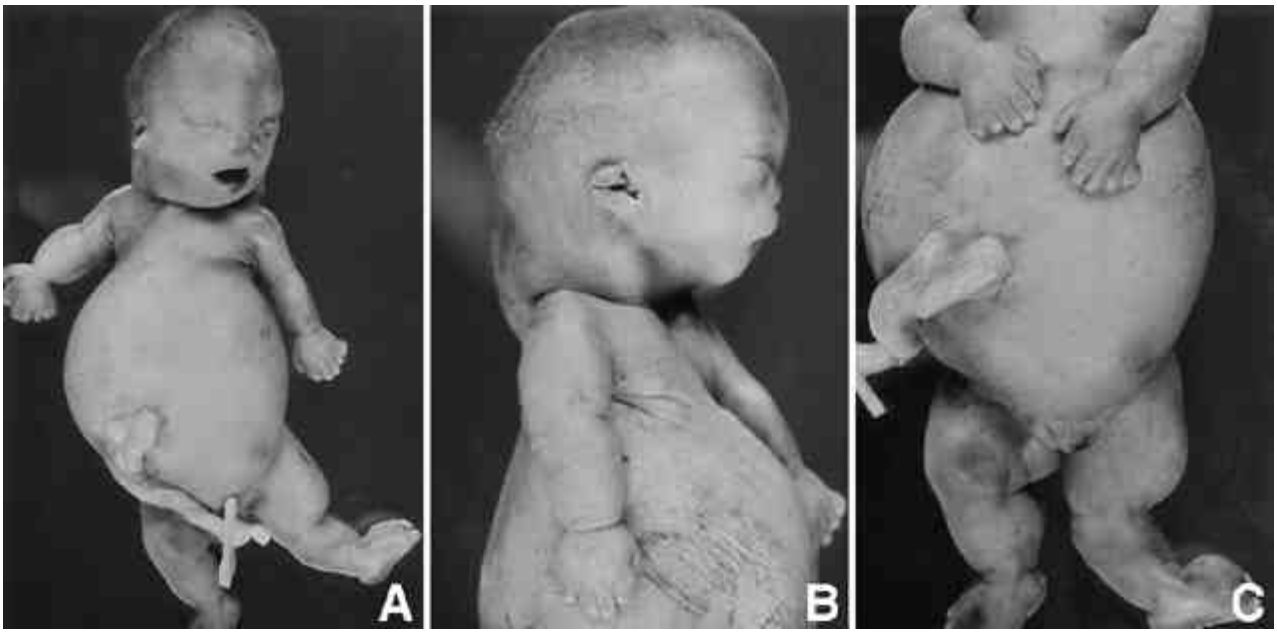

Fig. 1. A: Postmortem photograph shows a hydropic female fetus with a large head, narrow thorax, protuberant abdomen, and short extremities with postaxial polysyndactyly. B: Lateral view of the large head showing flat face, squashed nose, micrognathia, low-set ears, and hydropic bulging of posterior neck. C: Postaxial polysyndactyly of both hands and feet, with left genu valgum and talipes valgus deformities.

27 cm in circumference, and showed a flat face, broad nasal bridge with a squashed nose (Fig. 1B), and shallow middle-indentation of the upper gum. The ears were low-set and the eyes showed long intercanthal distance and both elongated mongolian slants. The thorax was short and narrow, measuring 19 cm in circumference, and the abdomen was very distended, measuring 28 cm in circumference. The external genitalia were normal. Four limbs were short and revealed postaxial polysyndactyly, with syndactylism of the short and thick 5th, 6th, and 7th fingers and of the 2nd and 3rd toes (Fig. 1C). The left leg showed genu valgum deformity.

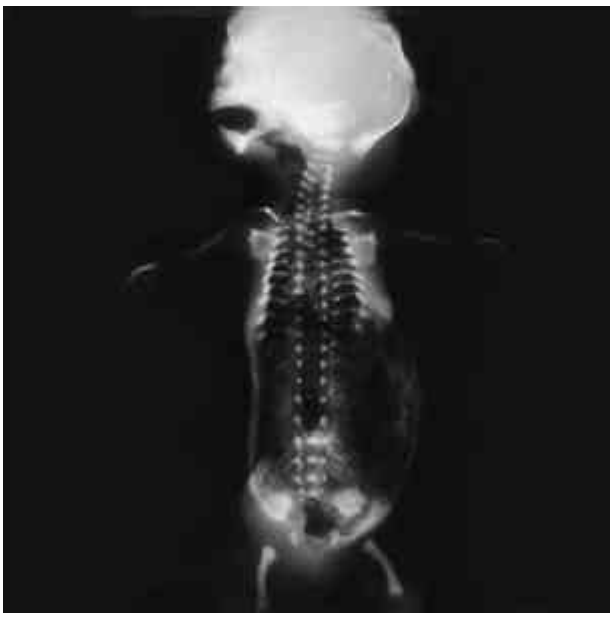

Fig. 2. Postmortem radiograph shows short horizontal ribs, small and flat lower lumbar and sacral vertebrae*, high-positioned clavicles, small scapulae, small ilia, short long tubular bones, with bilateral bowing of radius, ulna, and femur (*: They are remaining ones after removal of the cervical and upper lumbar vertebrae).

Postmortem radiograph (Fig. 2) showed short horizontal ribs, mild platyspondyly, small scapulae with high positioned clavicles, small iliac wings, shortened tubular bones with bowing of the femurs, radii, and ulnae, relatively normal tibiae longer than the fibulae, absence of conspicuous metaphyseal spicules, and short tubular bones of both hands and feet with postaxial polysyndactyly.

On gross examination of the internal organs, both lungs were evidently hypoplastic and the heart revealed left persistent superior vena cava, patent ductus arteriosus, and patent foramen ovale. The enlarged abdominal cavity was filled with huge kidneys, a large bilobed pancreas, and the centrally displaced stomach, intestine, and liver (Fig. 3). Both ureteropelvic junctions and ureters were narrowed and the urinary bladder was very hypoplastic. The uterus was bicornuate and attached with both salpinges. The enlarged right and left kidneys mea-

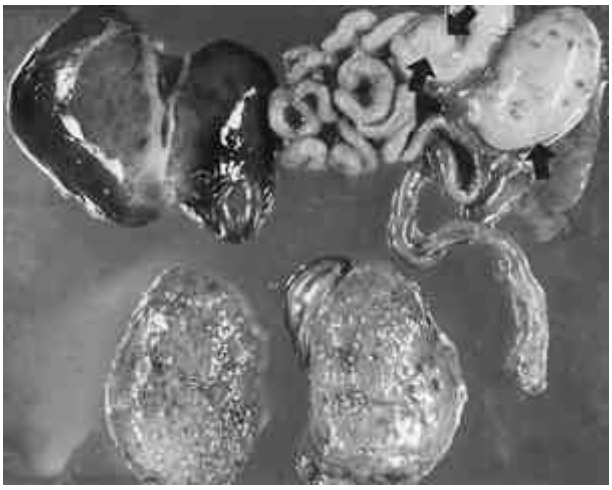

Fig. 3. Comparison of the sizes of abdominal viscera including both kidneys, liver, gastrointestinal tract, and pancreas (arrows). Note bilateral renal enlargement in comparison to others.

sured $6.5 \times 4 \times 3$ cm and $7 \times 4.5 \times 3$ cm, showing bosselated capsular surface. Cut section revealed relatively uniform round cysts involved both cortex and medulla (Fig. 4). Microscopically, the cysts were of cortical and medullary tubular origins, the linings of which showed flattened or cuboidal epithelial cells with the loose edematous or myxoid stroma (Fig. 5). There were some scattered primitive cortical nephrons and tubules surrounded by primitive myxoid stroma, but no dysplastic cartilage

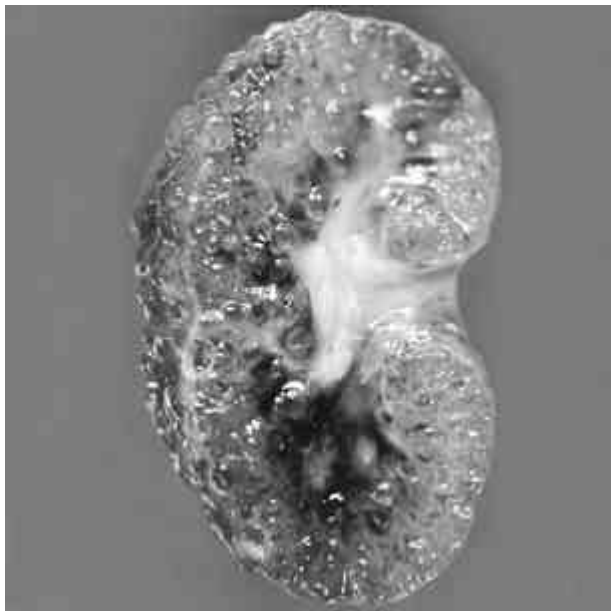

Fig. 4. Cut section of the kidney shows diffusely scattered uniform round cysts in both renal cortex and medulla.

was found. The pancreas showed an enlarged and bilobed appearance and the variable-sized cysts were scattered in the parenchyma, the largest measuring $4 \times 3 \times 2$ cm. Histologically, the lining was composed of flattened ductal epithelial cells and the surrounding stroma was diffusely fibrotic and edematous with mononuclear cell infiltration (Fig. 6). The liver showed portal fibrosis with

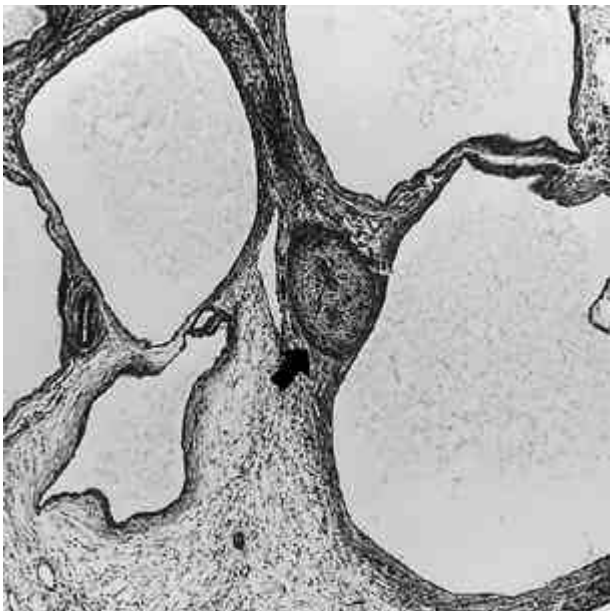

Fig. 5. The kidneys histologically reveal cystic dilatations of the cortical and medullary tubules, with immature mesenchymal proliferation around small primitive ducts (arrow) but no dysplastic cartilage (H&E, ×40).

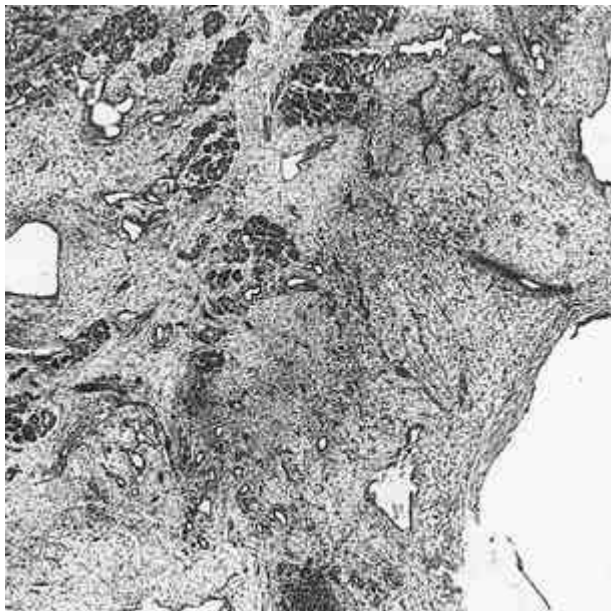

Fig. 6. Histologic sections of the pancreas disclose variable cystic dilatations of the ducts and diffuse parenchymal fibrosis (H&E, ×10).

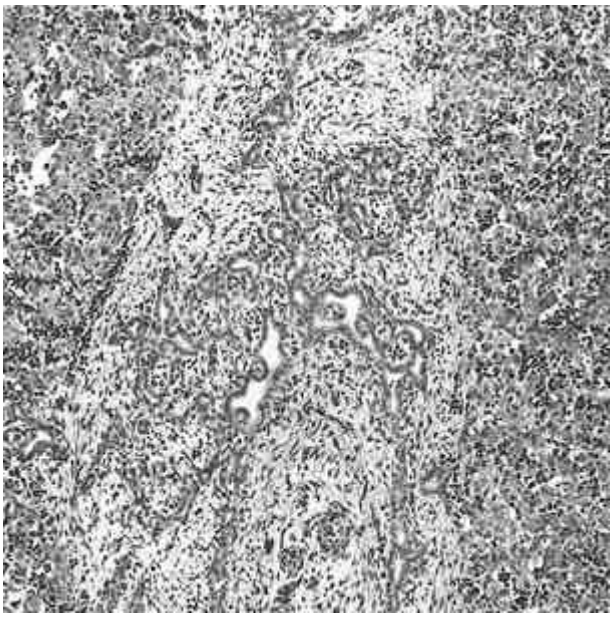

Fig. 7. The liver shows portal fibrosis and marked bile duct proliferation, with diffuse extramedullary hemopoiesis (H&E, × 100).

Fig. 8. The vertebral abnormality is found as irregular chondro-osseous junction and disorganized physeal growth zone in contrast to normal resting cartilage (H&E, ×200).

numerous dilated bile ducts and fibrous tissue proliferation, and a prominent extramedullary hematopoiesis (Fig. 7). The brain was grossly unremarkable, but the histologic sections disclosed germinal matrix hemorrhages around the posterior part of lateral ventricles. Histopathologic examination of the vertebrae showed the disorganized physeal growth zone with dysplastic chondrocytic proliferation, serrated chondro-osseous borders, and an irregular wide zone of provisional calcification (Fig. 8), with no abnormal findings in the resting zone.

DISCUSSION

In general, SRPS is diagnosed by the main features of distinct short-rib thoracic cage hypoplasia and significant shortening of the limbs and additional important manifestations such as perinatal or early neonatal death, polysyndactyly, median cleft lip and palate, genital abnormalities, epiglottic hypoplasia, and other visceral anomalies (11, 12). The diagnosis of SRPS in this case seems to be obvious because there were polysyndactyly, short horizontal ribs with narrow constricted thorax and hypoplastic lungs, generalized systemic abnormalities, and early lethality. Subtyping of SRPS is, however, generally difficult because the characteristic features are considerably overlapped in the four main types. Possible explanations for the overlapping among SPRS subtypes include: different allelic mutations at the same locus, double heterozygosity for different mutations at the same locus, and variable expressivity of the same mutation (13, 14). Further studies particularly of familial cases will help to elucidate the genetic heterogeneity and variability of expression in SPRS.

Although the clinical and radiological findings of lethal SRPS are remarkably overlapped in the different types of short rib syndrome, most authors agree that the Majewski type (type II) is clearly different from SRPS types I and III. The recently separated Beemer-Langer type, type IV SRPS was once considered as a variant of the Majewski type (type II). However, it became independent because Beemer-Langer type (type IV) shows no short ovoid tibia that is a diagnostic finding of type II. In general, type II is characterized by polydactyly, short and ovoid configuration of the tibiae, and phalangeal hypoplasia, whereas type IV shows a mild platyspondyly, small iliac wings, bowing of the tubular bones, and greater length of the tibia (15). Beemer-Langer type (type IV) was originally reported not to be associated with polydactyly, but later, Yang et al. (1991) described a case of Beemer-Langer type with polydactyly (10). In summary, the cardinal features of Beemer-Langer type became very clear; macrocephaly, flat face, hypertelorism, median cleft lip, short ribs and bowed limbs, and uncommon polydactyly (9). The skeletal manifestations in this syndrome and the generalized systemic abnormalities involving all organ systems seem to suggest a defect in the regulation of cellular differentiation during early embryogenesis (7, 16).

A review of previous articles from 1982 to 1994 on

Table 1. Frequency of systemic malformations and polydactyly in 23 cases of SRPS reported in literature

Cases*	1-13	14	15	16	17-22	23	Total (%)
Sex (F:M)	8 : 5	F	F	M	?	F	11 : 6
Cardiovascular anomaly	5/13	−	−	+	3/6	+	10/23 (43%)
Gastrointestinal anomaly	5/11	−	+	+	3/6	−	10/21 (48%)
Kidney and UT anomalies	2/12	+	+	+	1/6	+	7/22 (32%)
Pre or postaxial polydactyly	1/13	−	−	+	3/6	+	6/23 (26%)

* : 1-13, Hennekam (1991); 14, Cideciyan (1993); 15, Lin (1991); 16, Yang (1991); 17, Lurie (1994); 23, present case.
Abbreviations: SRPS, short-rib polydactyly syndrome; UT, urinary tract.

the systemic malformations of a total of 23 cases of SRPS type IV including our case is summarized (Table. 1). The gastrointestinal anomaly is most frequently associated (48%) and the deformities of the cardiovascular and genitourinary systems are 43% and 32%, respectively. Pre- and postaxial polydactyly are associated in 26% of the cases. In the context of the early lethality of SRPS patients, the association of multiple systemic anomalies is well-known, including pulmonary hypoplasia, congenital heart defects, renal anomalies, gastrointestinal anomalies, and brain malformations. The urinary tract disorders in this syndrome have been reported to include cystic renal dysplasia, renal hypoplasia, renal agenesis, and hydronephrosis. According to the previous reports, the renal anomalies were found mostly in either normal or small sized kidneys and the most frequent histologic finding was cystic renal dysplasia (4, 5, 7-9, 11, 14, 17-19). The kidneys of our case were histologically compatible with cystic dysplasia, because diffusely scattered variable-sized round cysts were intermixed with areas of primitive mesenchymal proliferation around primitive ducts. However, the size of both polycystic kidneys in our case seemed to be unusually large for the general cystic dysplasia. With this bilateral polycystic change, intrahepatic fibrosis and pancreatic cysts were found and thus the infantile polycystic renal disease might be an important differential diagnosis in this case. The hepatic changes resembled those of congenital hepatic fibrosis associated with autosomal recessive or infantile type of polycystic kidney, but the microscopic features of the kidney in our case are not compatible with infantile polycystic kidney (Potter type I) which usually shows cylindrical dilatations of all collecting tubules, with no dysplastic component. Another differential diagnosis could be an Ivemark's syndrome which had bilateral dysplastic kidneys, multiple large hepatic cysts, congenital hepatic fibrosis, and dysplasia associated with a large pancreatic cyst. However, those patients don't have the skeletal findings such as short rib and polydactyly (11).

The renal anomalies have been reported in over 50% of SRPS cases, and are more frequently found in type I or III rather than type II or IV (5). Also, they have been less frequently associated with type IV (Beemer-Langer) than type II (Majewski) (9, 12, 19). Cystic renal dysplasia is a well-known associated anomaly of the SRPS, whereas the bile duct ectasia, hepatic fibrosis, and pancreatic cysts have been only rarely reported (11).

Our case is thought to be a rare case of Beemer-Langer type SRPS with bilateral huge polycystic renal dysplasia, which was simultaneously associated with pancreatic cysts and hepatic fibrosis. These combined anomalies seem to be worthy of note in the context of the pathogenetic relationship between SRPS and polycystic diseases.

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