



Pallister-Killian Syndrome

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CASE PRESENTATION

A 27-year-old gravida 6, para 2 woman was referred to our fetal care center at 26 3/7 weeks' gestation because of the presence of multiple fetal anomalies.

The maternal and pregnancy histories were notable for substance use (tetrahydrocannabinol, alcohol, methamphetamines), depression, herpes labialis (on suppressive therapy), exercise-induced asthma, and normocytic anemia. She established late prenatal care at 25 1/7 weeks' gestational age (GA) at which time, anatomic ultrasonography showed sonographic age of 23 3/7 weeks' gestation (estimated fetal weight [EFW], 2nd percentile), polyhydramnios (amniotic fluid index [AFI], 28.6 cm), omphalocele, shortened femurs (measuring 17 2/7 weeks' gestation), concave chest, and stomach positioned above the diaphragm. These findings prompted referral to our fetal care center for further evaluation and multidisciplinary consultation.

Anatomic ultrasonography at our institution at 26 3/7 weeks' gestation revealed multiple congenital anomalies including left-sided congenital diaphragmatic hernia (CDH) containing liver, bowel, and stomach (lung-to-head circumference ratio [LHR], 0.95); small omphalocele containing liver and bowel; severe shortening of the long bones especially the femurs (9 weeks behind dates); right hand deformity; severe polyhydramnios (maximum vertical pocket, 11 cm); small chest cavity; generalized skin thickening; flattened facial profile; interocular distance suggesting hypertelorism; fetal growth restriction (EFW <2nd percentile); and elevated umbilical artery Dopplers (4.7–6.3). Fetal magnetic resonance imaging (MRI) performed the same day showed a large left-sided CDH containing the left hepatic lobe and stomach associated with rightward displacement of the heart and severely diminished fetal lung predictors (LHR 0.76 and observed/expected [O/E] LHR 29.5%). Although severe fetal growth restriction makes predictive interpretation more challenging, calculated total fetal lung volume (TFLV) was 4.3 mL (normal TFLV at this GA is 34.8 mL [range 22.5–44.2 mL]), O/E TFLV was 12%, and no significant left fetal lung tissue was identified. Additional fetal MRI findings included a small omphalocele containing liver; deformity of the right hand; generalized prominence of the extra-axial spaces; and widely spaced eye globes and thick coarseness of the facial soft tissues (Fig 1). Fetal

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ABBREVIATIONS

AFI	amniotic fluid index
CDH	congenital diaphragmatic hernia
EFW	estimated fetal weight
GA	gestational age
LHR	lung-to-head circumference ratio
MRI	magnetic resonance imaging
O/E	observed/expected
PKS	Pallister-Killian syndrome
TFLV	total fetal lung volume

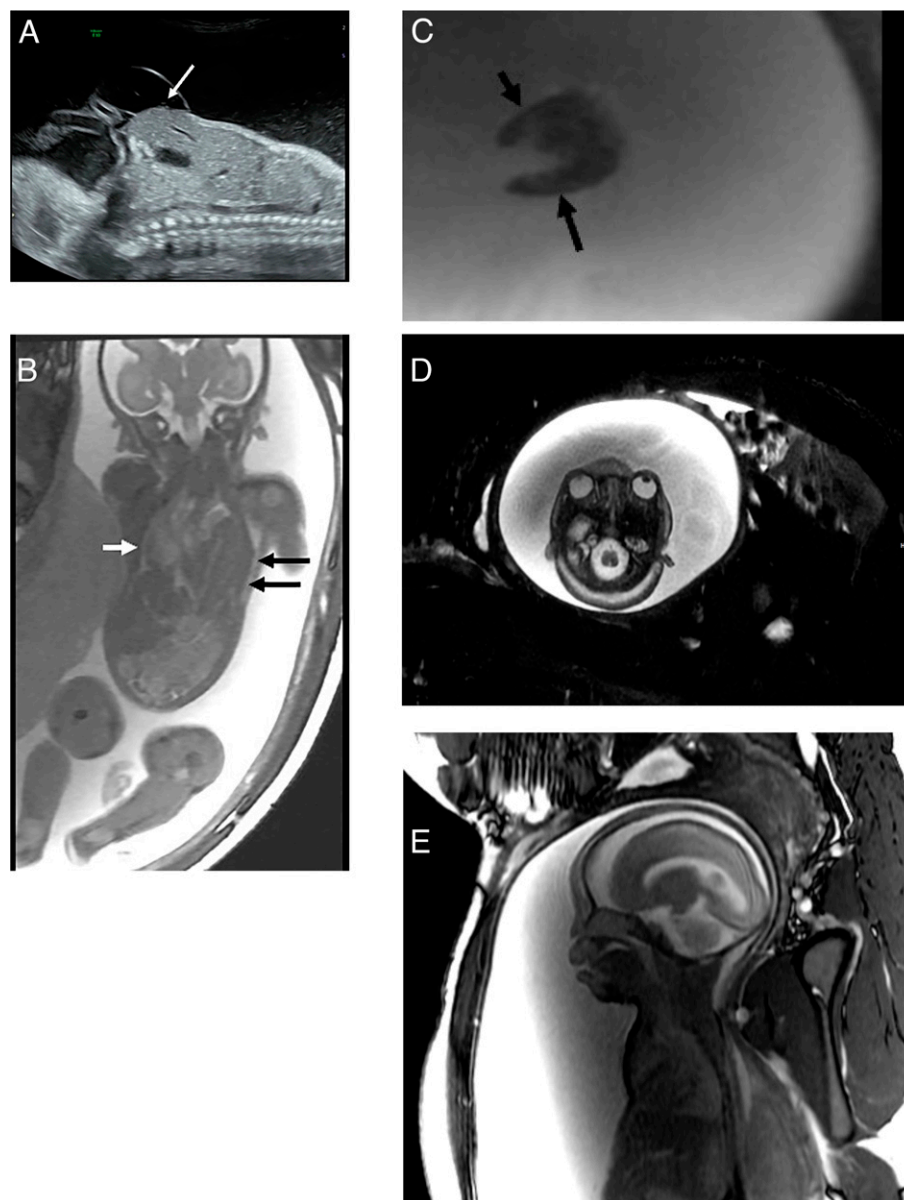


Figure 1. A. Fetal ultrasonography at 26 3/7 weeks' gestation showing a small abdominal omphalocele (arrow). Fetal magnetic resonance imaging scan at 26 3/7 weeks' gestation showing congenital diaphragmatic hernia with liver (black arrows) herniated into left chest and heart displaced into right chest (white arrow) (B); deformed hand (arrows) (C); widely spaced eye globes (D); coarse facial features and prominence of extra-axial spaces (E).

echocardiography at 26 3/7 weeks' gestation showed normal cardiac structure and function with mild hypertrophy of both ventricles. Cell-free DNA screening showed low risk (<1/10,000) for trisomies 21, 18, and 13 and monosomy X as well as low risk for triploidy; a female fetus was predicted. The couple received urgent genetic counseling given the imaging findings and were offered late amniocentesis but declined.

EXPERT OPINION

Given the multiple anomalies, the case was presented at our multidisciplinary fetal care conference to solicit the

input of our colleagues from maternal-fetal medicine, neonatology, genetics, and pediatric surgery. From fetal lung predictors for CDH alone, mortality and/or need for extracorporeal membrane oxygenation were estimated to be high. The additional anomalies also predicted a low likelihood of survival. If the infant's respiratory function could be supported, surgical management would remain challenging given both the CDH and omphalocele. The initial focus would be to approach the CDH from the chest because the omphalocele prevented an abdominal approach. There was high suspicion for an underlying genetic etiology. Medical

genetics would be consulted postnatally with a plan to send a microarray and reflex to exome sequencing if necessary.

The expectant parents were extensively counseled by specialists in neonatology, pediatric surgery, and medical genetics. Social work involvement was vital during counseling and throughout the prenatal course. In-depth discussions focused on delivery room management of the CDH and omphalocele as well as escalation of resuscitative efforts to possibly include chest compressions and intravenous medications should their daughter not respond to initial interventions. The option of solely comfort care was also explained in detail. The couple opted for a trial of intensive care with full attempts at resuscitation.

PRENATAL COURSE

The pregnant patient presented several times over the next few weeks with abdominal pain due to worsening polyhydramnios (AFI 35 cm and then 44 cm). Amnioreduction was offered but the patient declined. She received betamethasone and tocolysis. At 30 5/7 weeks' gestation, she again presented with abdominal pain and contractions (AFI 47 cm), and this time consented to amnioreduction given the severity of her pain. Approximately 2 L of fluid was removed with notable symptomatic relief; an additional 30 mL of amniotic fluid was sent for cytogenetic studies including a karyotype. She was followed closely as an outpatient with serial ultrasonography. Her last ultrasonographic scan performed at 32 2/7 weeks' gestation before ultimately delivering at 32 5/7 weeks' gestation showed an AFI of 44.7 cm. At that time, the EFW was 1,149 g (<2nd percentile) mainly due to severely shortened long bones following a rhizomelic pattern (femur length measuring 20 6/7 weeks' gestation and humeral length measuring 21 2/7 weeks' gestation whereas biparietal diameter and head circumference measured at 34 and 35 4/7 weeks' gestation, respectively). Umbilical artery Dopplers were elevated with systolic/diastolic ratio of 3.9 to 5.4 (95th percentile systolic/diastolic ratio at 32 weeks' GA is 3.79) and the LHR was 0.87 (O/E LHR 26%–28%). The left-sided CDH was again seen with right mediastinal shift as was the omphalocele. There was mild skin edema but no other evidence of hydrops.

OUTCOME AND POSTNATAL COURSE

The pregnant patient presented in active labor at 32 5/7 weeks' gestation. She underwent urgent cesarean delivery in the context of multiple fetal anomalies and a desire for full resuscitation and intensive care support. The infant emerged hypotonic and apneic. The umbilical cord was immediately

clamped and cut. The infant was moved to the warmer, placed in a bowel bag to cover the omphalocele, and underwent intubation. A Repleg tube was inserted to aid with gastrointestinal decompression. Auscultation of the heart rate was difficult given the CDH, and the infant briefly received chest compressions in the delivery room. Electrical activity was noted on the cardiac monitors and, while auscultation continued to pose a challenge, a brachial pulse was palpable.

Upon arrival to the NICU, attempts at establishing access proved difficult given the limitations posed by the omphalocele. Both peripheral intravenous access and peripheral arterial access were unsuccessful. Intraosseous access obtained in the right tibia initially functioned but then infiltrated. An emergent umbilical venous catheter was placed through the omphalocele while pediatric surgery attempted femoral access that was unsuccessful.

The infant was placed on high-frequency oscillatory ventilation with a fraction of inspired oxygen of 1.0 and inhaled nitric oxide of 20 parts per million. She was given 1 dose of intratracheal surfactant. Her chest radiograph showed near total opacification of the thorax [Fig 2]. The endotracheal tube was noted to be high and subsequently advanced. Pre- and postductal oxygen saturations demonstrated a 60-point difference. The infant's heart rate slowly

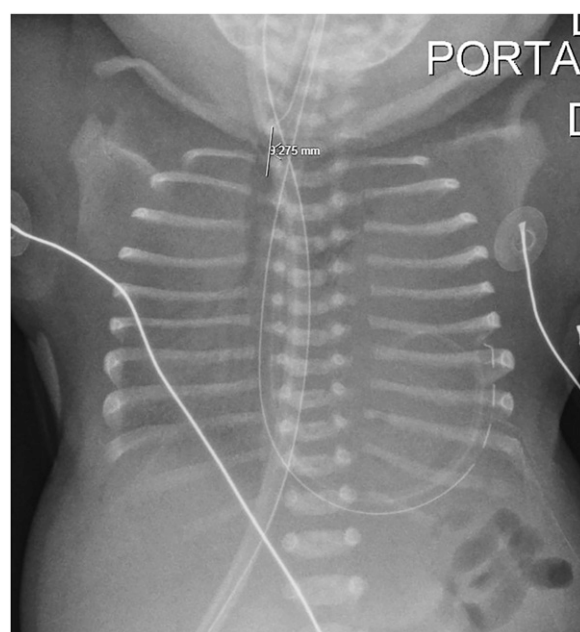


Figure 2. Chest radiograph at approximately 30 minutes of age. Endotracheal tube is in the cervical trachea (subsequently advanced 1 cm). Nasogastric/orogastric tube with tip and side-port projecting over the left lower thorax. There is complete opacification of the thorax with air bronchograms and the cardiomeastinal silhouette is completely obscured by the opacified lungs. Subcutaneous edema is noted as well as 11 ribs bilaterally.

downtrended to less than 60 beats/min. Chest compressions were provided, and she was given a dose of intravenous epinephrine. She received 1 dose of sodium bicarbonate for profound metabolic acidosis and 60 mL of packed red blood cells for a hematocrit value of 21%. She was given fentanyl boluses for pain and sedation. The mother was brought to the bedside and counseled on the infant's condition. In discussion with the team and given the infant's poor prognosis, the family elected to stop resuscitative efforts. The infant underwent compassionate extubation and was placed in her mother's arms. She died approximately 30 minutes later at 2 hours of age.

Results of the karyotype from the amniocentesis were 48,XX,+i(12)(p10)x2[2]/46,XX[17]. Identification of the presence of 2 i(12p) chromosomes indicated that the fetus was

hexasomic for the short arm of chromosome 12. Mosaicism for an isochromosome of the short arm of chromosome 12 is clinically associated with Pallister-Killian syndrome (PKS). While most cases of PKS are the result of tetrasomy 12p, rare cases of hexasomy 12p have been reported. (1)(2)

The parents consented to have an autopsy. Notable findings on autopsy (Fig 3) included abnormal facies (prominent forehead, hypertelorism, sparse eyebrows, flattened nasal bridge, short nose, long philtrum, peaked upper lip, patchy cranial hair, short neck) and skeletal anomalies (short limbs with humerus and radius length fourth percentile for GA; femur, tibia, and fibula length <1st percentile for GA; fused right duplicated first toe; 11 ribs). The omphalocele included intestinal malrotation containing a

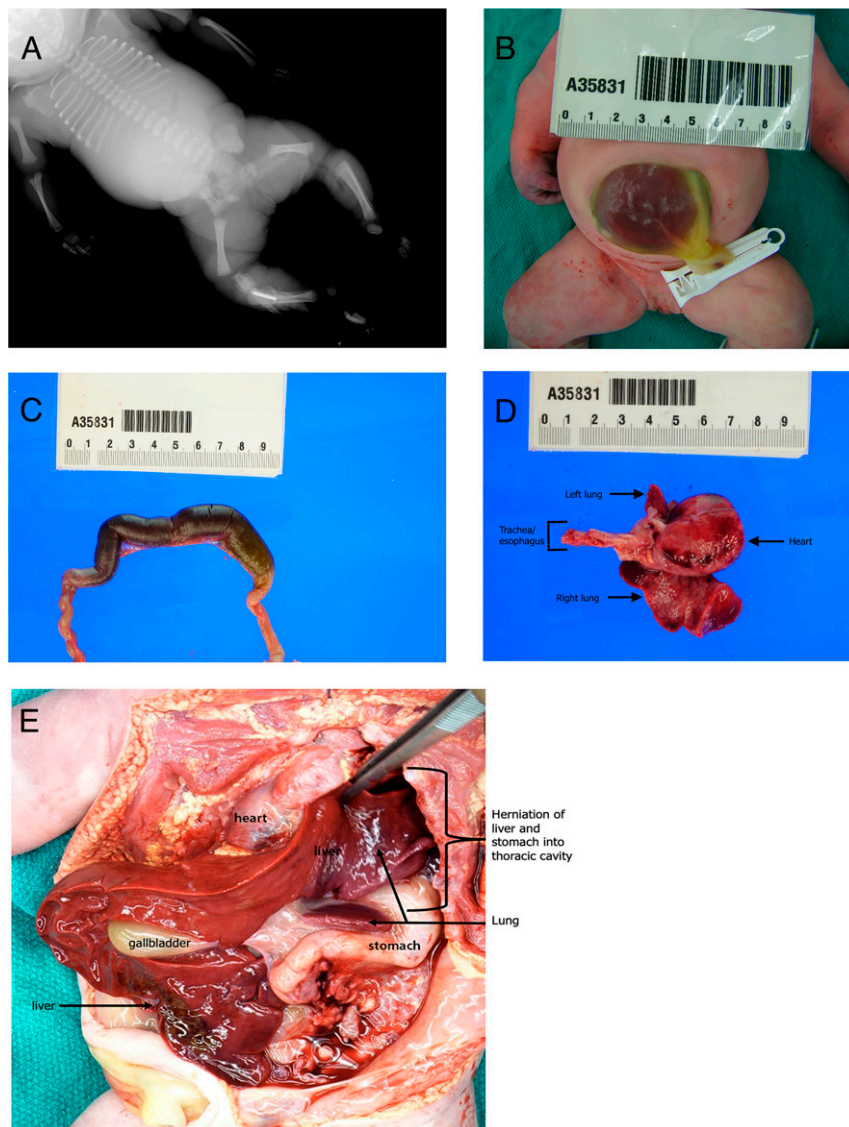


Figure 3. Gross autopsy photographs. A. Skeletal radiograph demonstrating rhizomelic limb shortening. B. Omphalocele. C. Intestinal malrotation containing 10 cm dilated loop of bowel. D. Lung hypoplasia. E. Congenital diaphragmatic hernia containing portion of stomach and liver.

10-cm segment of dilated bowel. The CDH included herniation of the spleen, a portion of the stomach, and a portion of the liver. The infant's hypoplastic lungs measured less than the 1st percentile for GA, and the cardiac atria were compressed. A tissue culture was performed, and chromosomes were analyzed. Chromosome analysis identified 2 copies of isochromosome 12 in 12 of 20 cells examined, resulting in mosaic hexasomy for chromosome 12p. The presence of this i(12p) was confirmed with fluorescence in situ hybridization and substantiated the abnormal amniocentesis result, consistent with a diagnosis of PKS.

DISCUSSION

PKS is a rare genetic syndrome caused by extra copies of the short arm of chromosome 12 (12p) with an estimated incidence of 5.1 per million live births; however, it is likely underdiagnosed. (3) PKS is due to a spontaneous mosaic duplication event most often resulting in tetrasomy 12p from the formation of an additional 12p isochromosome, (4) however, PKS may also be due to cases of trisomy and hexasomy 12p (as in our case). First described by Dr Pallister in 1977 (5) and subsequently by Drs Teschler-Nicola and Killian in 1981, (6) PKS is a multisystem developmental disorder with significant variability in phenotype owing to the mosaic distribution of the disease. While the mechanism leading to formation of the isochromosome 12p cell lines is still to be determined, most studies suggest maternal meiosis II nondisjunction as the likely mechanism of mosaic tetrasomy 12p. (7) More rarely, paternal nondisjunction has been reported as well. (8)(9) Similar to other autosomal aneuploidy syndromes such as trisomy 21, a maternal age effect is seen in PKS. (10) Reported cases of PKS have all been sporadic; recurrence risk is therefore close to that of the general population.

Prenatal diagnosis of PKS can be challenging because of the variability of associated features and difficulty detecting the isochromosome 12p. (11) The 3 most frequent prenatal ultrasonographic indicators in PKS, all of which were noted in our case, are polyhydramnios, CDH, and rhizomelic shortening. (12) A flat facial profile and thickened nuchal fold can also be seen on ultrasonography. (11) Additional common prenatal findings may include cerebral ventriculomegaly, and congenital heart disease. (13)

Tissue-limited mosaicism for isochromosome 12p is the hallmark of PKS, making diagnosis challenging. The percentage of mosaicism is higher in skin fibroblasts, amniocytes, or chorionic villi cells as opposed to lymphocytes. (13) Often, a buccal smear or skin biopsy is needed for

diagnosis after the neonatal period as euploid cells in the blood replace tetrasomic cells. (13)

Postnatally, multiple systems are affected in PKS. Common findings include atypical facial features, differences in pigmentation, intellectual disability, epilepsy, CDH, congenital heart disease, and limb differences. Characteristic facial features include prominent forehead, frontoparietal sparse hair with sparse eyebrows, hypertelorism or telecanthus, long philtrum, depressed nasal bridge, prominent cheeks, low-set and posteriorly rotated ears with ear pits and/or thickened helices, palate differences, accessory nipples, and short neck. (7) "Pallister lip," described as extension of the philtral skin into the vermilion border of the upper lip, is a classic feature. Facial features coarsen over time and the typical pattern of alopecia tends to resolve, making diagnosis more difficult with age.

Multiple organ systems may be affected in patients with PKS. Neurologic manifestations of PKS include severe intellectual disability, epilepsy, and abnormal muscle tone (7) with hypotonia often noted in infancy and variable spasticity and hypertonia in older individuals. (10) Common abnormal MRI findings in patients with PKS include cerebral volume loss, malformations of cortical development, dysgenesis of the corpus callosum, white matter disease, and craniofacial malformations (abnormally shaped skull, hypertelorism, and maxillary hypoplasia). (4) Congenital heart disease, most commonly atrial or ventricular septal defects, can be seen in individuals with PKS. Other cardiac manifestations include bicuspid aortic valve, aortic dilation, patent ductus arteriosus, and patent foramen ovale. Later onset cardiomyopathy is rare but potentially life-threatening. (14)

Ophthalmologic findings in patients with PKS can include strabismus, nystagmus, and/or myopia, with 20% having significant visual impairment and diagnosed as legally blind. (15) Hearing loss of all forms is also common in PKS and is often bilateral. (10) Gastrointestinal involvement ranges from anatomic to functional. Intestinal malrotation, CDH, umbilical hernias, and displacement of the anus are common anatomic findings whereas functional manifestations can include feeding difficulties, dysphagia, constipation, and gastroesophageal reflux disease. (7) The most common genitourinary finding in PKS is cryptorchidism. (7) Musculoskeletal manifestations can include polydactyly, broad thumbs and first toes, joint contractures, and hip dislocations. (7)

Individuals with PKS often show a pattern of prenatal overgrowth followed by growth deceleration over the first few years of age. (7) Developmental delay is common and ranges from mild to profound, most often severe to profound. (7) Behavioral manifestations can include repetitive

hand and body movements as well as self-injurious behaviors. (10) Life expectancy has never been formally evaluated. One report cites individuals with PKS surviving into their 40s and 50s. (7) However, given the diagnostic challenges, more mild presentations, and individuals who may not have undergone genetics assessment, it is likely that there may be undiagnosed older individuals with PKS. (7)

Summary

This case of PKS fittingly demonstrates this rare, multisystem, sporadic disorder. PKS is due to mosaic supernumerary isochromosome 12p leading to a wide spectrum of possible clinical manifestations. Most often these manifestations include craniofacial, neurologic, cardiac, ophthalmologic, musculoskeletal, dermatologic, and growth and developmental anomalies. Suspicion for PKS should be raised if polyhydramnios, CDH, and/or rhizomelic shortening are seen on prenatal ultrasonography. Cytogenetic diagnosis is challenging with higher diagnostic rates using amniotic fluid or skin fibroblasts. As demonstrated in our case of PKS, coordination of complex care is imperative for fetuses with multiple anomalies of possible genetic etiology, so as to bridge uncertainties in both the prenatal and postnatal periods.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the role and risks of magnetic resonance imaging, as well as other non-ultrasonographic imaging techniques in assessing fetal anatomy.
- Know the importance and limitations of ultrasonographic findings of common fetal anomalies including congenital heart disease.
- Know the significance of polyhydramnios and the management of pregnancy when it is diagnosed.
- Know how specific fetal diagnoses, such as airway abnormalities, abdominal wall defects, myelomeningocele, or severe hydrocephalus might alter prenatal care and intrapartum management (eg fetal intervention “Exit” strategy).

- Plan appropriate therapy for an infant with extrapulmonary causes of respiratory distress.
- Recognize the clinical features of extrapulmonary causes of respiratory distress.
- Recognize the imaging features of extrapulmonary causes of respiratory distress.
- Know how mosaicism modifies clinical presentation.
- Recognize the diagnostic implications of single vs. multiple anomalies.

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