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Genetics Corner: A Neonatal Case of Shwachman-Diamond Syndrome with Prominent Skeletal Anomalies Diagnosed by Whole Exome Sequencing

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> *“IInitial echocardiogram revealed a small patent ductus arteriosus, moderate to severe elevation of pulmonary pressures, mild dilatation of the right ventricle, and mild hypertrophy of the right ventricle that later resolved on repeat echocardiogram. Chest x-ray findings were significant for a small thoracic cage concerning for asphyxiating thoracic dystrophy. Genetics consultation was requested.”*

Case History:

This is a 16-day-old male born at 36w4d via repeat C-section to a 38-year-old G9P3 mother. Prenatal history was significant for polyhydramnios, maternal UDS positive for marijuana use, and concern for cigarette smoking. Mother has a history of 4 spontaneous abortions and 2 ectopic pregnancies. GBS status was unknown. Prenatal labs were otherwise unremarkable. He was admitted to the referring hospital for one day and required CPAP due to acute respiratory distress and concern for cardiomegaly with a Grade III-IV murmur. Initial echocardiogram revealed a small patent ductus arteriosus, moderate to severe elevation of pulmonary pressures, mild dilatation of the right ventricle, and mild hypertrophy of the right ventricle that later resolved on repeat echocardiogram. Chest x-ray findings were significant for a small thoracic cage concerning for asphyxiating thoracic dystrophy. Genetics consultation was requested.

Genetic Evaluation:

A genetics consult was requested. The initial genetic consult was conducted when the infant was 16 days old. The dysmorphic features were noticed. The baby has frontal bossing, down slanting of the palpebral fissures, and deep-set eyes. The left ear helix appears thin and misshapen, broad nasal bridge, micrognathia, redundant skin fold, decreased chest diameter (see Figure 1), and sacral dimple. The X-ray suggests the possibility of asphyxiating thoracic dystrophy (see Figure 2, 3).

> *“Genetic consultations were requested. The initial genetic evaluation considered 1) Kagami-Ogata syndrome and 2) Asphyxiating thoracic dystrophy or Jeune syndrome. The chromosome microarray was normal, the skeletal dysplasia gene panel was non-diagnostic, and the uniparental disomy (UPD) study for chromosome 14 was negative.”*

The family history was significant for recurrent pregnancy losses in parents. A 13-year-old sister was born with a pelvic kidney but was otherwise healthy. A paternal uncle died at age 2 of liver failure of unknown etiology. A paternal half-aunt and both of her children have a mental illness, as did the paternal grandmother. A maternal first cousin, once removed, also had recurrent pregnancy losses and a son with birth defects and autism. There was no other family history of skeletal dysplasia, other birth defects, early infant deaths, intellectual disability, or known genetic disorders. Parents were of Caucasian ancestry.

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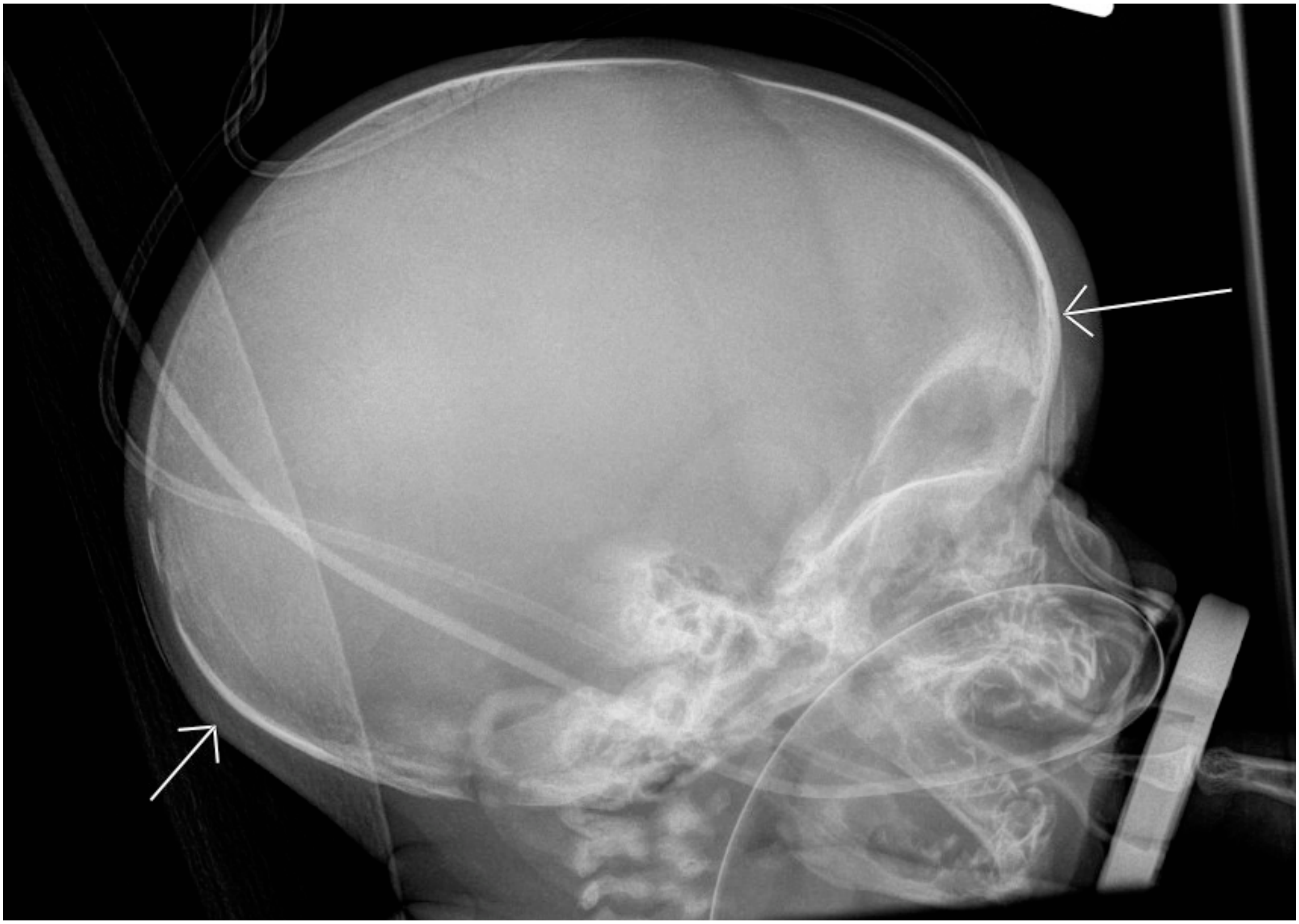


Figure 1. Mild scaphocephalic shape of the skull.

The initial differential diagnoses included 1) Kagami-Ogata syndrome; 2) Asphyxiating thoracic dystrophy, or Jeune syndrome 3) Chromosome abnormality.

Chromosome microarray analysis was normal, and a skeletal dysplasia gene panel was non-diagnostic. The patient was readmitted three months later due to 3 episodes of seizure-like activities. Genetics was again consulted. This time, uniparental disomy 14 testing was completed to evaluate for Kagami-Ogata syndrome and was negative. Trio Whole Exome Sequencing (WES) was then recommended.

> ***"Chromosome microarray analysis was normal, and a skeletal dysplasia gene panel was non-diagnostic. The patient was readmitted three months later due to 3 episodes of seizure-like activities."***

At five months of age, he failed to thrive and was being assessed for G-tube placement.

> ***"The whole exome sequencing (trio) was performed and detected compound heterozygosity for two likely pathogenic genetic variants in the SBDS gene, consistent with a diagnosis of Shwachman-Diamond syndrome. "***

Whole exome sequencing (WES) revealed that the patient has two different pathogenic variants (mutations), one on each copy of the *SBDS* gene (see Figure 4). The maternally inherited variant c.258+2T>C is predicted to disrupt the GT donor site and interfere with normal splicing. This variant has been reported in the homozygous and compound heterozygous states in individuals with Shwachman-Diamond Syndrome. The paternally-inherited variant, c.183_184delinsCT, is predicted to result in premature protein termination (p.Lys62*). This variant has been reported in many patients with Shwachman-Diamond Syndrome when found with another pathogenic variant. Currently, in ClinVar, 11 pathogenic and 11 likely pathogenic variants are curated.

Whole Exome Sequencing Result

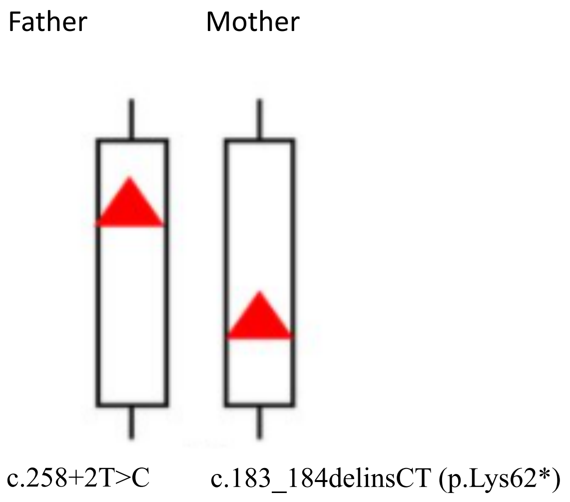


Figure 3: Compound heterozygotes with two likely pathogenic variants in SBDS were detected; parental testing confirmed one variant was inherited from each parent.

> ***"SDS is a rare autosomal recessive, multisystem disease. SDS presents with exocrine pancreatic insufficiency, impaired hematopoiesis, and a predisposition for the development of leukemia. Skeletal, immunologic, hepatic, and cardiac disorders have been described. (1)"***

Discussion:

SDS clinical presentations:

SDS is a rare autosomal recessive, multisystem disease. SDS presents with exocrine pancreatic insufficiency, impaired hematopoiesis, and a predisposition for the development of leukemia. Skeletal, immunologic, hepatic, and cardiac disorders have been described. (1)

Neutropenia is the most common hematologic abnormality affecting 88–100% of patients with SDS. Anemia has also been described in 42%–82% of patients. Thrombocytopenia has been reported in 24%–88% of patients. Patients with SDS have an increased risk for myelodysplasia and malignant transformation, particularly the development of acute myelogenous leukemia. Patients with SDS are susceptible to recurrent bacterial, viral, and fungal infections. Neutropenia is likely a contributing factor. SDS can present with exocrine pancreatic dysfunction of varying severities. This dysfunction is caused by the absence of acinar cells in early infancy leading to malabsorption, steatorrhea, failure to thrive, and low levels of fat-soluble vitamins A, D, E, and K. Patients with SDS have normal sweat chloride tests. This feature distinguishes them from patients with cystic fibrosis whose pancreatic defect involves the exocrine pancreatic ducts. Several case reports have described SDS associated with neonatal cardiac issues. (2, 3)

> ***"Patients with SDS have normal sweat chloride tests. This feature distinguishes them from patients with cystic fibrosis whose pancreatic defect involves the exocrine pancreatic ducts."***

The Skeletal Phenotype in Patients with SDS

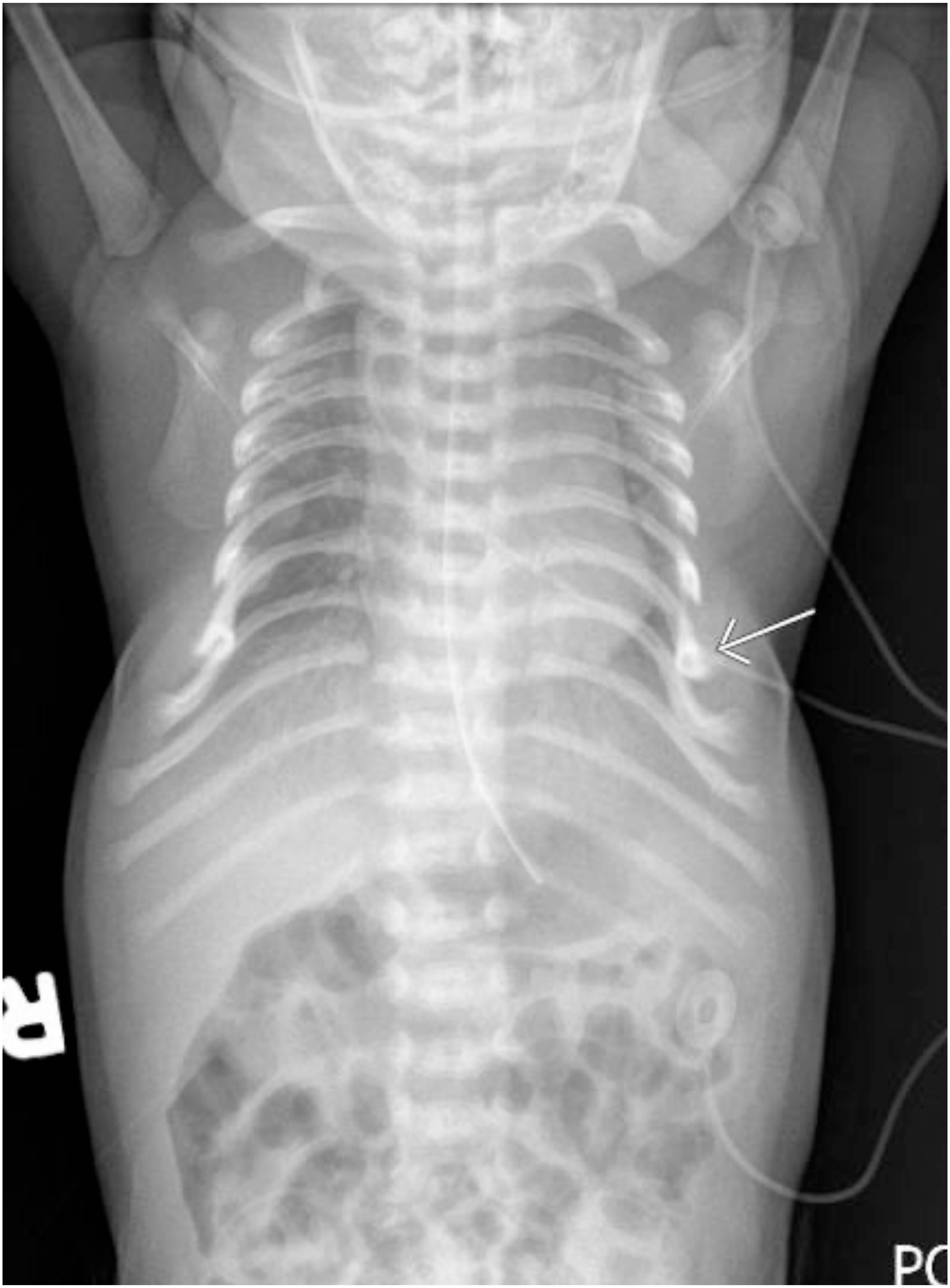
While pancreatic exocrine and bone marrow dysfunctions are considered universal features of SDS, the associated skeletal dysplasia is variable and not consistently observed. (4) The primary skeletal defect is abnormal growth plate development. The metaphyses are profoundly affected. Metaphyseal dysostosis has been reported in roughly 50% of the patients, is usually asymptomatic, and most commonly involves the femoral head. (5, 6) The knees, humeral heads, wrists, ankles, and vertebrae may also be affected. Rib-cage abnormalities are found in 30%–50% of patients, including narrow rib cage, shortened ribs with flared anterior ends, and costochondral thickening. Case reports have described respiratory failure in newborns due to these rib cage abnormalities. (2)

> ***" After the diagnosis was made, almost one year after the initial genetics consult, the laboratory workup showed he had moderate pancreatic insufficiency with low pancreatic elastase. He is on supplemental pancreatic lipase (Creon), started by peds GI right after diagnosis, and has no hematological abnormalities."***

Neonatal SDS

While the diagnosis of SDS has classically relied on exocrine pancreatic dysfunction and bone marrow failure, a publication based on the North American SDS Registry reported that almost half of 37 individuals with genetically confirmed SDS did not have this classic combination of manifestations

The typical clinical, laboratory, and imaging features of SDS are often lacking in the first months of life, which may delay diagnosis. (7) A few cases of SDS presentation and molecular diagnosis have been documented in the first months of life (8, 9) and



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misdiagnosed as asphyxiating thoracic dystrophy. (9) Our case presented with prominent skeletal phenotype with an X-ray image suggesting asphyxiating thoracic dystrophy. After the diagnosis was made, almost one year after the initial genetics consult, the laboratory workup showed he had moderate pancreatic insufficiency with low pancreatic elastase. He is on supplemental pancreatic lipase (Creon), started by peds GI right after diagnosis, and has no hematological abnormalities.

> ***"After the diagnosis was made, almost one year after the initial genetics consult, the laboratory workup showed he had moderate pancreatic insufficiency with low pancreatic elastase. He is on supplemental pancreatic lipase (Creon), started by peds GI right after diagnosis, and has no hematological abnormalities."***

Practical Applications

1. Shwachman–Diamond syndrome (SDS, MIM 260400) is an autosomal recessive disorder characterized by exocrine pancreatic dysfunction, bone marrow failure, skeletal abnormalities, short stature, and a variety of other less common features.
2. Pancreatic exocrine and bone marrow dysfunctions are considered universal features of Shwachman–Diamond syndrome (SDS), whereas the associated skeletal dysplasia is variable and not consistently observed.
3. In addition to the pancreatic and bone marrow insufficiency, the skeletal manifestations should be considered an integral diagnostic feature of the syndrome and carefully assessed with a complete skeletal survey at presentation.
4. The typical clinical, laboratory, and imaging features of SDS are often lacking in the first months of life, which may delay diagnosis.
5. Skeletal dysplasia mimicking asphyxiating thoracic dystrophy with respiratory failure could be the major presentation in an infant with SDS.
6. Whole exome sequencing is a powerful tool for the early diagnosis of SDS for atypical presentations essential for the neonate.

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