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Case Report

The Difficult Differential Diagnosis for A Pediatric Patient with Shwachman-Diamond Syndrome; A Case Report and Literature Review

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ABSTRACT

Shwachman-Diamond syndrome (SDS) is a rare autosomal recessive disease characterized by bone marrow dysfunction, exocrine pancreatic insufficiency and skeletal abnormalities. Persistent or intermittent neutropenia caused by bone marrow hypoplasia is the most common hematological abnormality in SDS. It can be difficult to diagnose the disease that usually occurs in early childhood. SDS should be kept in mind in the differential diagnosis of neutropenic patients. If the signs of pancreatic insufficiency are not observed, the diagnosis may be missed. The article wanted to present a patient with pancreatic insufficiency and SDS with the biallelic mutation who presented with neutropenia in a newborn.

Keywords: Shwachman-Diamond syndrome, Neutropenia, Biallelic mutation, Bone marrow transplantation

INTRODUCTION

Shwachman-Diamond syndrome (SDS), a rare autosomal recessive disorder first defined in 1964, is a multi-system syndrome characterized by exocrine pancreatic insufficiency, neutropenia, and skeletal changes.[1-3] Permanent or intermittent neutropenia caused by bone marrow hypoplasia is the most common hematologic abnormality in SDS.[1,4] The diagnosis of SDS is based on a clinical phenotype, but it is difficult to diagnose in children with general symptoms such as bronchiolitis, diarrhea, and anemia. Therefore, SDS should be considered in the differential diagnosis in children with diarrhea, low weight gain, skeletal anomalies, and neutropenia.[4]

The purpose of this report was to present a differential diagnosis for SDS in a patient with diarrhea, neutropenia, exocrine pancreatic insufficiency, and skeletal changes, and discuss the follow-up condition of this patient after bone marrow transplantation.

CASE REPORT

A two-month-old male patient was referred to our hospital with the symptoms of cough, respiratory distress, and diarrhea. The patient presented with neutropenia and anemia, as well as acute bronchiolitis. The physical examination of the patient revealed that his body weight (BW) was 4200 g (<3 P), height 58 cm (25 P), and head circumference 38.5 cm (3-10 P). The patient had abdominal swelling and proportional shortness in the extremities. In a lung examination, bilateral crepitant rales were detected. There was no organomegaly.

The patient weighing 3200 g at the 38th week of gestation was born from a 24-year-old mother. He had neutropenia, recurrent infection attacks, and diarrhea in the neonatal period. In his family history, there was second-degree consanguinity between the parents, but there were no similar diseases. The results of the laboratory tests were as follows: hemoglobin (HGB) 7.6 g/dL, hematocrit (HCT) 23%,

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mean corpuscular hemoglobin (MCH) 32 pg, mean corpuscular volume (MCV) 95 fL, white blood cell count 4000/µL, the total number of neutrophils 400/µL, platelet count 217,000/µL, and reticulocyte percentage 1.5%. The biochemical test results were normal. Fat was found +2 in the stool. The percentages of lymphocytes, neutrophils, and monocytes in the blood smear were 80, 10, and 10, respectively, and platelets were sufficiently clustered. Bone marrow aspiration was heterogeneous normocellular. Normal myeloid and erythroid serial development pressures were seen. The myeloid series was decreased compared with the erythroid series. No atypical cells or bone marrow dysplasia was observed. The fecal elastase test result was 117 µg/g, and the sweat test was normal. The extremity and chest radiographs revealed irregularity and enlargement at the level of the costochondral junction, increased sclerosis in both the radius and distal ulnar metaphyses, and an ovoid-shaped vertebral corpus (Figure 1, 2). Ultrasonography and computed tomography of the abdomen showed that the pancreas body and tail section were hypoplastic. Serum amylase was detected as 12 U/L (25-125 U/L), serum lipase 4/L (8-78 U/L), vitamin D level 10.9 ng/mL, vitamin E 3.7 mg/L (6.6-14 mg/L), and vitamin A 115 mcg/L (200-430 mcg/L). Cystic fibrosis mutation analysis was normal. In the mutation analysis of SDS, biallelic heterozygous mutations were detected in the 7q11.21 gene (SBDS):c.258+2T>C. The SDS diagnosis was made, and 5 µ/kg of granulocyte colony-stimulating factor (G-CSF) was started. An adequate response was achieved when the dose of G-CSF was increased to 10 µ/kg. Enzyme replacement therapy was added to the treatment plan due to the presence of a pancreatic exocrine disorder. During the follow-up, diarrhea decreased, but the total neutrophil count was still about 420/mm^3. When the patient was aged 11 months, he was followed up with persistent severe neutropenia, recurrent infection attacks, and thrombocytopenia that required platelet transfusion. Therefore, hematopoietic stem cell transplantation (HSCT) was performed from the bone marrow of his fully compatible healthy sister. A conditioning regimen including fludarabine 30 mg/m^2 (-8-3 days), busulfan 2.5 mg/kg (-5-3 days) and thymoglobulin 10 mg/kg (-5-3 days) were used. Cyclosporine 3 mg/kg and mycophenolate mofetil (MMF) 1200 mg/m^2 were given for graft versus host disease (GVHD) prophylaxis (Table 1). CD34+ cells (10.9 x10^6/kg) were infused. Neutrophil and thrombocyte engraftment was achieved on +15th and +20th days. On the 16th day, the full donor myeloid chimerism was recorded using polymerase chain reaction/short tandem repeat loci analysis. No signs of acute or chronic GVHD and other transplant-related complications were observed in the follow-up in the 4 years after HSCT with full donor chimerism. The pancreatic insufficiency improved and he did not need pancreatic enzyme replacement after age 4 years. In the final physical examination, BW was 13.4 kg (<3P) and height was 100 cm (<3P) and the laboratory test results were 13.6 g/dL for HGB, 40% for HCT, 9020/µL for the white blood cell count, 2680/µL for the total neutrophil count, and 215,000/µL for the platelet count.

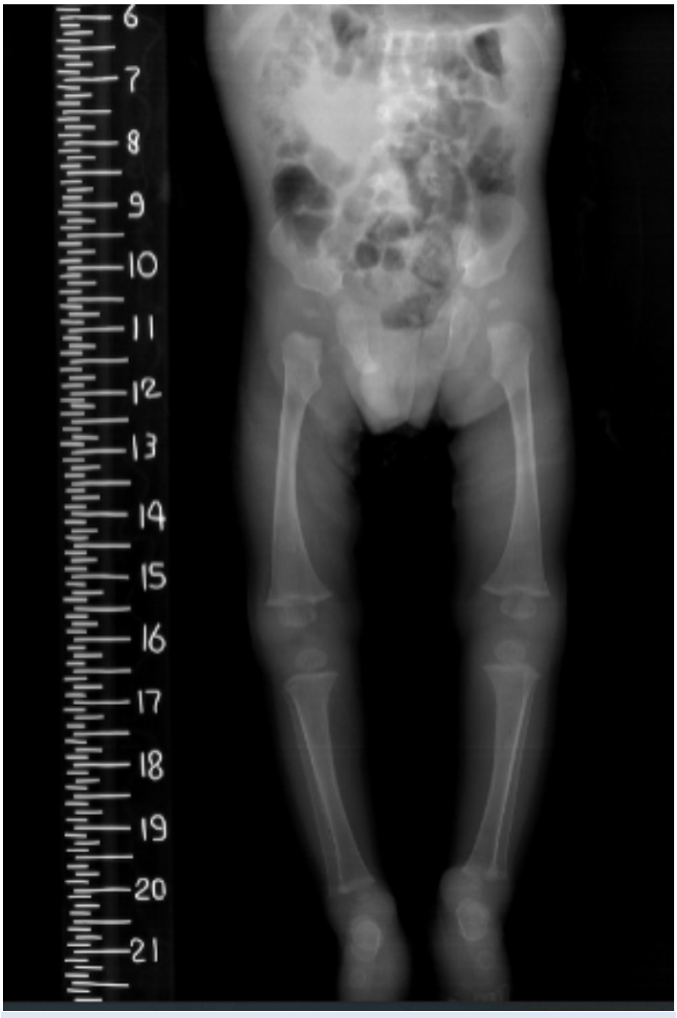

Figure 1. Limb shortening and epiphysis enlargement

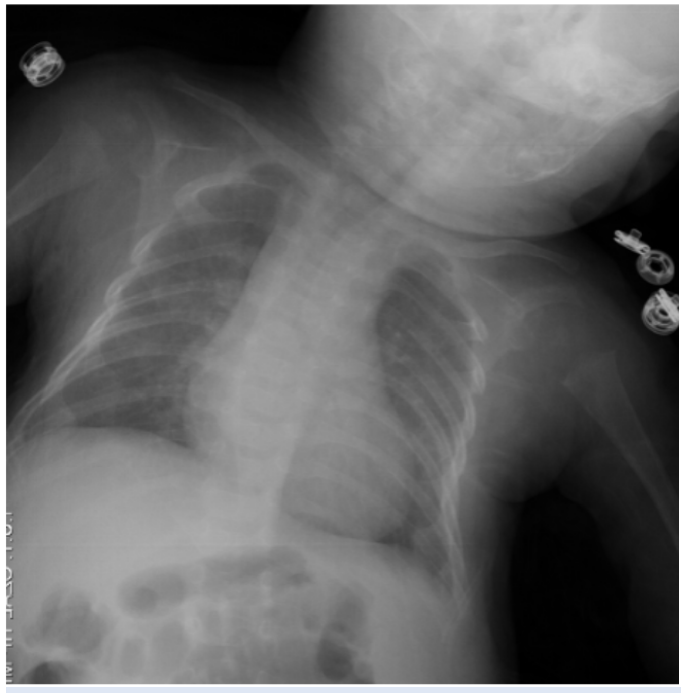

Figure 2. Irregularity and enlargement of the costochondral junction were detected on chest radiographs

Table 1. Transplantation characteristics	
Age at transplantation	**11 months old**
HLA matched sibling	Bone marrow
Myeloablative	Fudarabine 30 mg/m^2 (-8-3 days); Busulfan 2.5 mg/kg (-5-3 days); Thymoglobulin 10 mg/kg (-5-3 days)
CD 34+ cells	10.9x10^6/kg
GVHD prophylaxis	Cyclosporine 3 mg/kg Mycophenolate mofetil 1200 mg/m^2
Post transplant follow-up age	5 years old
The pancreatic insufficiency	No
Cytopenia	No
Recurrent infection	No
Growth retardation	Yes
Acute and chronic GVHD	No
AML and MDS transformation	No

HLA: Human leukocyte antigens, MDS: Myelodysplastic syndrome, AML: Acute myeloid leukemia, GVHD: Graft versus host disease

DISCUSSION

Shwachman-Diamond syndrome is a rare hereditary disease with serious clinical consequences, such as pancreas and bone marrow failure. Neutropenia is a common hematologic abnormality seen in patients affected by SDS, and chemotaxis defects also occur in neutrophils with reduced numbers. Apart from neutropenia, normochromic normocytic anemia is the second most common cytopenia. Increased fetal hemoglobin levels are accompanied by thrombocytopenia.[5,6] Although the treatment of patients with anemia and thrombocytopenia can be supported by red cell and platelet transfusions, very severe neutropenia (ANC <200/µL) remains an adverse prognostic factor because it is associated with a high mortality rate and risk of life-threatening infections.[7,8] The hematologic abnormality of our patient was severe neutropenia (ANC: 200/µL), and although there was initially no thrombocytopenia, mild thrombocytopenia and aplasia occurred three months later. Our patient had recurrent episodes of infection due to neutropenia. Erythrocyte suspension occurred due to anemia, resulting in the requirement of transfusion.

The clinical symptoms of pancreatic insufficiency appear after more than 98% of the exocrine acinar capacity of the pancreas has been lost. Steatorrhea is seen in 90% of affected children with SDS in the first year of life. Fat-soluble vitamin deficiency (vitamins A, D, E, and K) is caused by steatorrhea and malabsorption.[6] Our patient presented with diarrhea, growth retardation, and therefore we considered the possibility of cystic fibrosis, which was the most common cause of pancreatic insufficiency. Stool elastase level and fat-soluble vitamins were low, and genetic evaluation for cystic fibrosis was negative. After the diagnosis of cystic fibrosis was excluded and anemia was added to neutropenia, the patient was evaluated with suspicion of SDS. The patient's extremity radiographs were evaluated and limb shortening was detected. Genetic testing was planned for SDS and pancreatic enzyme and vitamin supports were given for diarrhea.

The detection of cytogenetic abnormalities in the bone marrow is a marker of clonal evolution and malignant transformation.[5] It was stated that c.258+2T>C heterozygous mutations might be associated with severe cytopenia.[9] Our patient had these biallelic heterozygous mutations in the *SDS* gene located on chromosome 7q. Therefore, when the patient was aged 1 year, an allogeneic hematopoietic stem cell transplant was performed from his sister with full human leukocyte antigen compatibility. After the transplant, the patient was followed up for 4 years, during which his pancytopenia improved and he did not require transfusion. The patient had received neutropenic fever treatment four times before the transplant, and over the 4-year follow-up period, he was referred to the hospital twice with symptoms of fever. A decrease in the frequency of infections was observed after transplantation, which was linked to the resolution of neutropenia.

Patients with SDS may have malabsorption, recurrent infections, metaphyseal dysostosis, low birth weight, delayed bone age, delayed puberty, mucositis and periodontal infections, dental dysplasia, hepatomegaly, elevated liver enzymes, severe eczema, and cognitive and attention impairment. The clinical phenotype of SDS is extremely heterogeneous showing a wide range of abnormalities and symptoms; therefore, a definitive diagnosis still presents a challenge.[7,10-12] Although our patient had neutropenia and recurrent infection attacks in the neonatal period, the diagnosis of SDS was made late. Therefore, it is important to consider SDS in the differential diagnosis in patients with neutropenia, diarrhea, and recurrent infections.

In a literature review from 1988 to 2016, Cesaro et al.[13] evaluated the results of a total of 91 patients. They found that the prognosis was poor in non-transplant patients who transformed to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).[13] Myers et al.[14] determined that 33 of 36 patients presented with MDS or AML had previously been diagnosed as

having SDS. In another retrospective study, the same author in the same year reported the results of HSCT in 52 patients with SDS. Myers et al.[15] emphasized that transplant success declined after AML or MDS transformation. They found a 5-year survival of 72% in patients with bone marrow failure transplanted before MDS or ALL developed.[15] Our patient presented with neutropenia and recurrent infection attacks in the neonatal period. When it was learned that he had diarrhea, the patient was thought to have cystic fibrosis and the relevant tests were performed. Further tests were requested in the differential diagnosis of SDS when the patient's clinical status progressed and anemia developed.

In conclusion, if there is growth retardation in a child with diarrhea, steatorrhea, and neutropenia; skeletal abnormalities for SDS should be investigated and exocrine pancreatic insufficiency and bone marrow failure should be evaluated. SDS should be kept in mind in the differential diagnosis of patients with neutropenia. If a compatible donor is found, it will be appropriate to plan a bone marrow transplant before the development of MDS or leukemia.

Ethics

Informed Consent: Informed consent was obtained.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: D.Ç.A., A.A., Z.Ş.H., Ü.Ö., Design: D.Ç.A., A.A., Z.Ş.H., Ü.Ö., Data Collection or Processing: D.Ç.A., A.A., Z.Ş.H., Ü.Ö., Analysis or Interpretation: D.Ç.A., A.A., Z.Ş.H., Ü.Ö., Literature Search: D.Ç.A., A.A., Z.Ş.H., Ü.Ö., Writing: D.Ç.A., A.A., Z.Ş.H., Ü.Ö.

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