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Delayed diagnosis of Shwachman diamond syndrome with short telomeres and a review of cases in Asia

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ABSTRACT

Inherited bone marrow failure syndrome (IBMFS) including Shwachman Diamond Syndrome (SDS) can present initially to the hematologist with myelodysplastic syndrome (MDS). Accurate diagnosis affects choice of chemotherapy, donor selection, and transplant conditioning. We report a case of delayed diagnosis of SDS in a family with another child with aplastic anemia, and review reported cases of SDS in Asia. This highlights the gap in identifying inherited bone marrow failure syndromes in adults with hematologic malignancies.

1. Introduction

SDS is an autosomal recessive disease characterised classically by exocrine pancreatic insufficiency and chronic neutropenia, but considerable phenotypic variation has been described even among siblings. In 90% of cases, SDS is caused by mutations in the Shwachman-Bodian-Diamond syndrome (*SBDS*) gene that produces a protein with critical roles in ribosome biogenesis, mitotic spindle stabilization, and normal chromosomal segregation. While many pathogenic variants in the SBDS gene have been described, no correlation has been found between genotype and phenotype [1]. Three other causal SDS genes, *DNAJC21, EFL1*, and *SRP54* have been reported. These genes have roles in the assembly of ribosomal subunits, the ribosomal subunit maturation, and ribosomal biogenesis respectively [2]. The epidemiology of SDS in Asia is not well studied and we performed a comprehensive review of reported cases to understand the clinical features and genetic variants here. A total of 65 cases have been described, most of which are from Japan. Those with clinical data are summarized in Table 1 [3–13]. Similar to previous reports, clinical manifestations including hematological abnormalities, pancreatic dysfunction, and short stature were common. The reported genetic mutations affecting patients in Asia were similar to their Western counterparts.

Individuals with SDS are at increased risk for developing myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Our review identified case reports of three patients who presented with MDS or AML without a prior diagnosis of SDS in Asia [9,14,15]. Similarly, SDS continues to be underdiagnosed internationally. Lindsley et al. found that 7 of 241 young adults with MDS enrolled in the Center for International Blood and Marrow Transplant Research (CIMBTR) repository had *SBDS* mutations, and 5 of these patients did not have a diagnosis of SDS before transplant [16]. Other studies utilizing gene panel testing to screen for genetic predisposition to AML/MDS in young patients presenting with MDS identified *SBDS* gene mutations in 1 out of 110 patients and 2 out of 197 patients [17,18]. While underlying SDS is rare in young adults presenting with MDS/AML, the growing use of next-generation sequencing technologies may facilitate identification.

2. Case report

Our patient was a 19 year old male patient who presented with a one-month history of fever, dyspnea, and skin abscesses. His full blood count showed pancytopenia and 14% blasts. Bone marrow aspirate was markedly hypocellular (10% cellularity) with features of dyserythropoiesis and dysmegakaryopoiesis and 3% blasts (Fig. 1). Flow cytometry detected 2.8% blasts that are CD34+ partial CD117+ and CD33+. Trephine was markedly hypocellular with rare hypolobated megakaryocytes and 8% CD117+ CD34+ myeloblasts. Cytogenetics with bone marrow karyotype showed a complex monosomal karyotype as follows, 42–45,XY,add(5)(q15),add(5)(q31),add(6)(q13), der(8)ins(8;?)(q13;?),del(9)(q21q22), dic(14;22)(p11.2;p12),tas(21;16)(q22.3;p13.3), add(17)(q21),-18,-21,+der(?)t(?;8)(?;q13),+r, +1–2mar[cp21]. These findings were compatible with primary hypocellular MDS or IBMFS evolving into MDS.

Physical examination revealed a relatively small head (3rd

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Table 1
Cases of Shwachman-diamond syndrome reported in Asia.

Country	Sex	Age at diagnosis	Pancreatic insufficiency	Hematological abnormalities	Skeletal abnormalities	Height (SD)	Body weight (SD)	*SBDS* mutations	Status at reporting
Japan	M	3mo	+	Pancytopenia	-	− 2.1	−1	183–184TA > CT/258 + 2T > C	NA
Japan	F	8y	+	Pancytopenia	+	−2	−1.5	183–184TA > CT/258 + 2T > C	NA
Japan	F	5mo	+	Pancytopenia	–	−3	−2	428C > G/258 + 2T > C	NA
Japan	M	1mo	+	Pancytopenia	–	−3	−1.8	183–184TA > CT/258 + 2T > C	NA
Japan	M	12y	+	Thrombocytopenia	–	−3	−1	183–184TA > CT/258 + 2T > C	NA
Japan	F	5y	+	Pancytopenia	+	−2.9	−1.4	183–184TA > CT/258 + 2T > C	NA
Japan	M	2mo	+	Pancytopenia	+	−2	NA	183–184TA > CT/258 + 2T > C	NA
Japan	M	8y	+	Pancytopenia	–	−2	−1.5	258 + 2T > C/259–1G > A	NA
Japan	M	6mo	+	Neutropenia	–	−3.1	−2.1	183–184TA > CT/unknown	NA
Japan	M	9mo	+	Pancytopenia	–	−3.6	−3.4	183–184TA > CT/258 + 2T > C	NA
Japan	M	6mo	+	AML	+	−4.8	−1.8	258 + 2T > C/292–295delAAAG	Alive
Japan	M	2y	+	MDS– > AML	+	−2.8	−1.8	258 + 2T > C/unknown	Dead
Japan	M	1mo	+	MDS– > AML	+	−2.3	−1.4	183–184TA > CT/258 + 2T > C	Dead
Japan	M	4y	+	Pancytopenia	+	−1.3	−1.1	183–184TA > CT/258 + 2T > C	Alive
Japan	M	2y	+	–	–	−3.5	−1.7	183–184TA > CT/258 + 2T > C	Alive
Japan	F	8y	+	Pancytopenia	+	−3.5	−1.3	183–184TA > CT/258 + 2T > C	Alive
Japan	M	5mo	+	Pancytopenia	–	−3	−3.5	183–184TA > CT/258 + 2T > C	Alive
Japan	F	15mo	+	Neutropenia	–	−5.2	−6.6	183–184TA > CT/258 + 2T > C	Dead
Japan	F	2y7mo	+	MDS	–	−1.2	−2.3	183–184TA > CT/258 + 2T > C	Alive
Japan	F	4mo	–	Neutropenia	+	−7.5	NA	79T > C / 183TA > CT	Alive
Korea	F	3y6mo	+	Neutropenia	+	< 3%	< 3%	183–184TA > CT/258 + 2T > C	Alive
Korea	M	13y9mo	+	Bicytopenia (WBC/PLT)	+	< 3%	< 3%	183–184TA > CT/258 + 2T > C	Alive
Korea	M	15y6mo	+	bicytopenia (WBC/PLT)	+	3%	10%	258 + 2T > C homozygous	Alive
India	M	4y	+	Pancytopenia	–	NA	NA	258 + 2T > C homozygous	Dead
China	M	8y	+	Bicytopenia (WBC/RBC)	+	< 3%	3%	183–184TA > CT/258 + 2T > C	Alive
China	M	1y3mo	+	Neutropenia	+	NA	< 3%	183–184TA > CT/258 + 2T > C	Alive
China	F	6mo	+	Pancytopenia	+	NA	NA	183–184TA > CT/258 + 2T > C	Alive

Abbreviations: M, male; F, female; y, year; mo, month; WBC, white blood cell; RBC, red blood cell; +, present; -, absent; NA, not available; SD, standard deviation; *SBDS*, Shwachman-Biodan-Diamond syndrome; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia.