Case Report

Aase–Smith syndrome type II

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ABSTRACT

Aase-Smith syndrome type II is rare in childhood and there are few reported cases. Here, we report an 8-month-old boy with congenital red cell aplasia and triphalangeal thumbs. In addition to thumb anomalies, he presented with growth failure, hypertelorism and novel osseous radiologic abnormalities, large fontanelles and micrognathia as extraordinary. Some clinical symptoms had complete clinical remission with deflazacort treatment.

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Diamond-Blackfan anemia (DBA) is a rare form of pure red cell aplasia, typically presenting in infancy. Hematologic findings often include macrocytosis, elevated fetal hemoglobin and increased erythrocyte adenosine deaminase levels. Associated physical findings have been reported in over 40% of patients. A common facial appearance with "tow-colored hair, snub nose, wide-set eyes, thick upper lip, and an intelligent expression" was reported by Cathie and has since been called "Cathie face".[1,2] Aase-Smith syndrome is a rare, autosomal recessive inherited disorder characterized by anemia with some joint and skeletal deformities, first described by Aase-Smith in 1969.[3] Aase-Smith syndrome type I, shows congenital severe joint contractures, hydrocephalus with Dandy-Walker anomaly and cleft palate, and Aase-Smith syndrome type II shows triphalangeal thumbs and congenital hypoplastic anemia.[4] Steroids are generally useful for treatment of anemia, but have some known adverse reaction. In our patient, we used deflazacort to possibly reduce the steroidal adverse effects. In this paper, we report an 8-month-old boy with Aase-Smith syndrome type II and reviewed the literature.

Case Report. An 8-month-old boy presented with anemia, micrognathia and triphalangeal right thumb. In the medical history of the patient, he received 2 transfusions of packed red cells resulting from an abrupt fall of hemoglobin levels (3.3 g/dL and 4.1 g/dL) at 3 and 5 months old. General appearance was of pallor and lethargy. Physical examination revealed head circumference 40 cm (3% percentile), height 56 cm (3% percentile), weight 5.1 kg (3% percentile), micrognathia, anterior fontanelles 6x5 cm, hypertelorism and triphalangeal right thumb. Other physical signs were normal. Laboratory examination revealed hemoglobin (Hb) level 4.2 g/dl, platelets count $431x10^9$ /L, white blood cell count $11.5x10^9$/L, red cell distribution width 14, and mean corpuscular volume 91 fl. Peripheral blood smear revealed 76% lymphocytes, 12% neutrophils, 8% monocytes and 4% eosinophils. Red blood cell (RBC) morphology showed macrocytosis and anisocytosis. Reticulocyte count was 1%; prothrombin time and partial thromboplastin time were within normal range. Sickling, RBC enzymes were normal and Hb electrophoresis showed high fetal Hb levels (7%). Direct Coombs' test was negative. Serum levels of iron, ferritin and erythropoietin are elevated. Results

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of routine biochemical blood tests and routine urinalysis were normal. Virological studies were uninformative. A bone marrow aspirate showed normocellular bone marrow, erythroid hypoplasia with mild dyserythropoiesis, and hyperplasia of the myeloid series (M/E:8) (**Figure 1**). Hand x-ray roentgenography revealed right first finger has 3 phalanx and similar fork to second finger, metacarpophalangeal joint has subluxation on the left first finger and medial deviation on the interphalangeal joint (**Figure 2**). Chromosomal analysis was normal. Physical examination and hematologic evaluation of the parents showed normal results. The findings were consistent with Aase-Smith syndrome type II and he was transfused with 15 cc/kg packed red cells and received deflazacort at the dose of 2 mg/kg/day, which was subsequently tapered to 0.5 mg/kg/day. Thereafter, red cell counts increased, and Hb level stabilized (Hb 10-11 gr/dL) over a 7-month follow-up, without any need for additional treatment. The patient remained corticosteroid-dependent (0.5 mg/kg on alternate days).

Discussion. Aase-Smith syndrome belongs to the clinical-hematologic framework of DBA and consists of the association of triphalangeal thumbs with congenital erythroid aplasia.[5] Triphalangeal thumbs were reported in 19 patients (bilateral in 14, and unilateral in 5) in whom the course of anemia was not different from that of the entire DBA group.[2,6] Other features may be hydrocephalus with Dandy-Walker anomaly, cleft palate, and multiple contractures of the joints, and narrow shoulders.[2] In addition to thumb anomalies, hypertelorism and novel osseous radiologic abnormalities, large fontanelles and micrognathia was found in our patient. The syndrome generally occurs in males and was originally described in 2 male siblings. The genetic basis of the disease is not known clearly. Inheritance is probably autosomal recessive. The disease which previously mapped to human chromosome 19q13, is frequently associated with a variety of malformations. Draptchinskaia et al[7] reported that the breakpoint occurred in the gene encoding ribosomal protein S19. Furthermore, they identified mutations in ribosomal protein S19 in 10 of 40 unrelated DBA patients, including nonsense, frameshift, splice site and missense mutations, as well as 2 intragenic deletions. Our case did not show a family history of Aase-Smith syndrome but we recommended genetic counseling. Anemia is a major clinical problem in these patients. The anemia is caused by underdevelopment of the bone marrow, which is where blood cells are formed. D'Avanzo et al[8] reported 2 patients with Aase-Smith syndrome and showed that in vitro growth of erythroid colonies was normal in one patient and totally absent in the other. In both patients, treatment with glucocorticoids induced remission of anemia. These results suggest that the different growth patterns of erythroid colonies observed in the 2 patients could reflect the defect of erythroid differentiation occurring at discrete maturational levels.[8] In some cases steroids may be useful for treatment of anemia.[6,8] D'Avanzo et al[8] also reported a patient with Aase-Smith syndrome presenting with hemolytic anemia and showed favorable effect of splenectomy. Their study suggests that haptoglobin levels are important in DBA patients for evaluation of chronic hemolysis and low haptoglobin serum levels may provide a rationale for splenectomy.[5] The presence of a cell-derived soluble inhibitor of erythropoiesis has been reported in some DBA patients but its pathogenetic relevance remains obscure.[9]

Steroids are generally used for treatment of anemia in Aase-Smith Syndrome, but it has some known adverse reactions. Steroids have profound effects at multiple stages of calcium metabolism, resulting in decreased bone formation and enhanced bone resorption leading to accelerated osteoporosis.

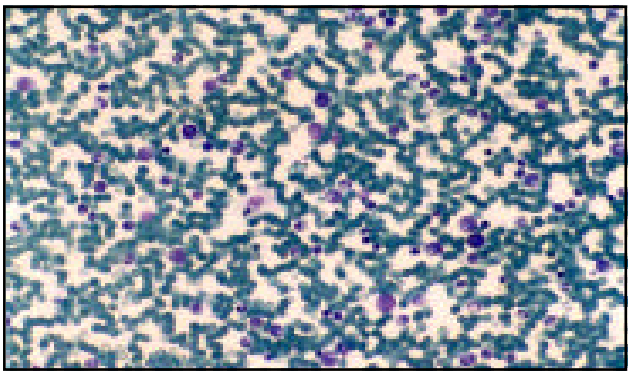

Figure 1 - A bone marrow smear demonstrating erythroid hypoplasia and hyperplasia of the myeloid series (May-Grunwald- Giemsa stain X 20).

Figure 2 - Hand x-ray roentgenography .

Glucocorticoid-induced osteoporosis occurring primarily in trabecular bone has been thoroughly recognized, but the true incidence of osteoporosis in patients receiving glucocorticoid therapy is unknown. Development and severity of glucocorticoid induced osteoporosis are dependent on the particular glucocorticoid used. For this reason we chose deflazacort for possible reduction of some adverse effects. Deflazacort, an oxazolinic derivative of prednisolone, is recently reported to be less harmful to cancellous bone mass than other equally effective corticosteroids.[10,11] However, further prospective trials are needed to determine if deflazacort may provide a promising alternative to existing systemic corticosteroid therapy.

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