The Turkish Journal of Pediatrics 1995; 37: 383-389

A CASE OF ADENOSINE DEAMINASE – NEGATIVE SEVERE COMBINED IMMUNODEFICIENCY WITH NEUROLOGICAL ABNORMALITIES*

*İlhan Tezcan MD***, *Fügen Ersoy MD****, *Melda Çağlar MD****
*Özden Sanal MD****, *Esin Kotiloğlu MD*****, *Sabiha Aysun MD****

SUMMARY: Tezcan İ, Ersoy F, Çağlar M, Sanal Ö, Kotiloğlu E, Aysun S. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). A case of adenosine deaminase-negative, severe, combined immunodeficiency with neurological abnormalities. Turk J Pediatr 1995; 37: 383-389.

Presented here is a 17-month-old adenosine deaminase-deficient, severe combined immunodeficient patient with chest symptoms, oral ulcer, neurologic manifestations, head lag, spasticity and developmental delay in motor functions. Antibiotics, systemic antifungal agents, intravenous immunoglobulins and partial exchange transfusions with irradiated fresh red cells were given. No other mode of therapy for adenosine deaminase (ADA) deficiency was available at that time. Amelioration of neurologic manifestations within one month of therapy with irradiated fresh red cell exchange transfusions suggests that these manifestations may have resulted from accumulated toxic metabolites. However, no improvement was seen in the course of infection and oral ulcer, and the patient died of respiratory failure on the 48th day of admission. *Key words: adenosine deaminase deficiency, severe combined immunodeficiency, neurological abnormalities.*

Severe combined immunodeficiency (SCID) is the early-onset clinical syndrome characterized by the absence of both T- and B-cell immunity. Approximately 20 to 25 percent of all cases with SCID occur due to deficiency of adenosine deaminase (ADA), a purine salvage enzyme[1-5]. In ADA deficiency, adenosine, deoxyadenosine and their metabolites accumulate, and their toxic effects appear preferentially in the lymphoid system. Although the clinical phenotype of ADA deficiency demonstrates varying pictures from early-onset SCID to partial ADA deficiency with slight immune function abnormalities, the majority of affected infants cannot be grossly distinguished from patients with classical SCID due to other causes[2, 6]. Patients with ADA deficiency may also have abnormalities in non-lymphoid tissues including costochondral junctions, to a lesser extent the kidney and adrenal gland, and very rarely the central nervous system[1, 2, 7-9].

We present here an ADA-deficient SCID infant with neurological manifestations.

* From the Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

** Associate Professor of Pediatrics, Hacettepe University Faculty of Medicine.

*** Professor of Pediatrics, Hacettepe University Faculty of Medicine.

**** Assistant Professor of Pediatrics, Hacettepe University Faculty of Medicine.

Case Report

A 17-month-old girl, the first child of non-consanguineous parents, was admitted to Hacettepe Children's Hospital, Immunology Division, because of fever, cough, irritability and spasticity.

The medical history revealed that she was the product of an uncomplicated full-term pergnancy with a birth weight of 3.3 kg. BCG and three doses of DTP-OPV were administered. An axillary lymphadenopathy developed one week after the BCG vaccination.

Her developmental milestones were not appropriate for age. She could not sit without support and had no head control. Spasiticity of the extremities and developmental delay in motor functions were the principal complaints. She developed pneumonia at the age of 15 months and was put on antibiotic treatment at another institution. However, she began to suffer from persistent cough, recurrent fever and oral candidosis until her referral, and antibiotic combinations administered in the hope of ameliorating recurrent bouts of pneumonia were of no benefit.

On admission, her axillary temperature was 36.5 °C, and her weight, height and head circumference were below the 5^{th} percentile. She had respiratory difficulty with perioral cyanosis, tachypnea and intercostal retractions. Oral examination disclosed a mucosal ulcer measuring 2 x 2 cm on the palate, and several monilial patches were found. Neurological evaluation showed that she could follow light and objects with normal eye movements, and the fundi were normal. She had marked head lag, irritability, spasticity in the extremities and increased deep tendon reflexes. She was also retarded in language, motor functions and social performance.

Laboratory examination revealed a leukocyte count of 3800/mm^3 with lymphopenia (980/mm^3), IgG 52.4 mg/dl (N: 605-1430), IgM 19.7 mg/dl (N: 66-228), and IgA 21 mg/dl (N: 30-107). Delayed-type hypersensitivity skin tests to PHA, Candida, tetanus and PPD were negative. Lymphocyte subpopulations were CD_3 16%, CD_4 14% CD_8 5%, CD_{20} 6% and CD_{56} 2%. Lymphocyte proliferation assays showed no response to mitogenic lectins. [Patient: 394 cpm to phytohemagglutinin (PHA); 636 cpm to concanavalin A (Con A); Control: 140202 cpm to PHA, 156967 cpm to Con.A]. ADA activity in red cells was zero and her parents' ADA activities were within heterozygous ranges. Purine nucleoside phosphorylase (PNP) enzyme activities were found to be normal. Chest x-ray showed interstitial infiltration, and thymus shadow was not evident. Roentgenograms of the bones revealed no abnormality, and computerized axial tomography (CT) of the cranium showed cerebral cortical atrophy. Other laboratory findings were within normal ranges. Besides administration of intravenous immunoglobulin, antibacterial and systemic antifungal agents, partial exchange transfusions with irradiated fresh red cells were performed as other specific modes were not available. Within one month

of her hospitalization she gained head control and her muscle tone gradually decreased. However, there was no improvement in either her immunologic laboratory findings or her susceptibility to infections. Despite all therapeutic attempts, the mucosal ulcer on the palate enlarged and respiratory difficulty worsened. Eventually, she died of respiratory failure on the 48th day of admission.

A partial necropsy examination excluding the central nervous system was performed according to the family's wishes. Necropsy findings were as follows: The thymus was not identified grossly. Although all available soft tissues in the expected localizations of the thymus were examined microscopically, no thymic structure was seen. Lymphoid follicles in the cortical regions of the lymph nodes, in the white pulp of the spleen and in the intestinal mucosa were sparse and mostly of primary type without germinal centers (Figs. 1 and 2). There were multiple foci of central coagulative necrosis surrounded by sparse mononuclear inflammatory reaction and parenchymal cells with intranuclear inclusions in the lung, liver, tongue, esophagus, adrenal glands and ovaries (Fig. 3). An immunohistochemical study revealed that these inclusions were Herpes Simplex Virus type I (DPC-Monoclonal antibody; avidin-biotion peroxidase technique). Thin, fibrous bands around parenchymal cell cords in the outer cortex of the adrenal glands, diffuse fatty change in the liver and focal interstitial mononuclear cell infiltrates in the kidney were also observed.

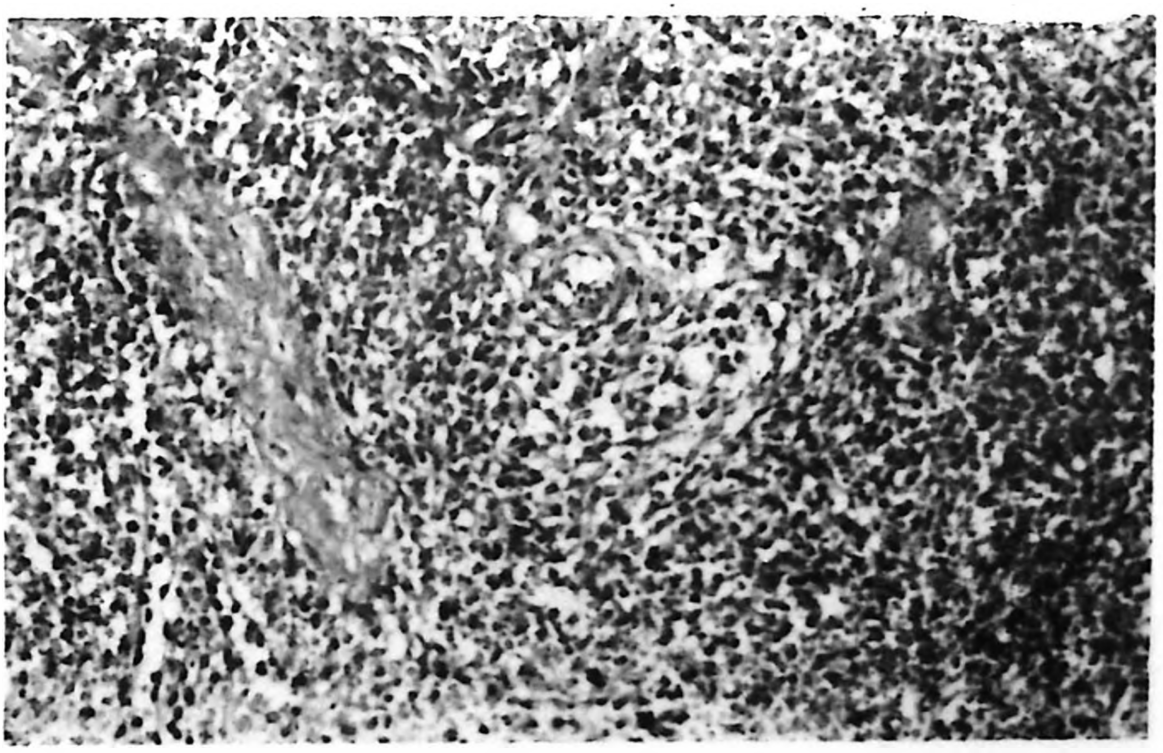

Fig. 1: Sparse lymphoid cells around the central arteriole in the spleen (HE, X 66)

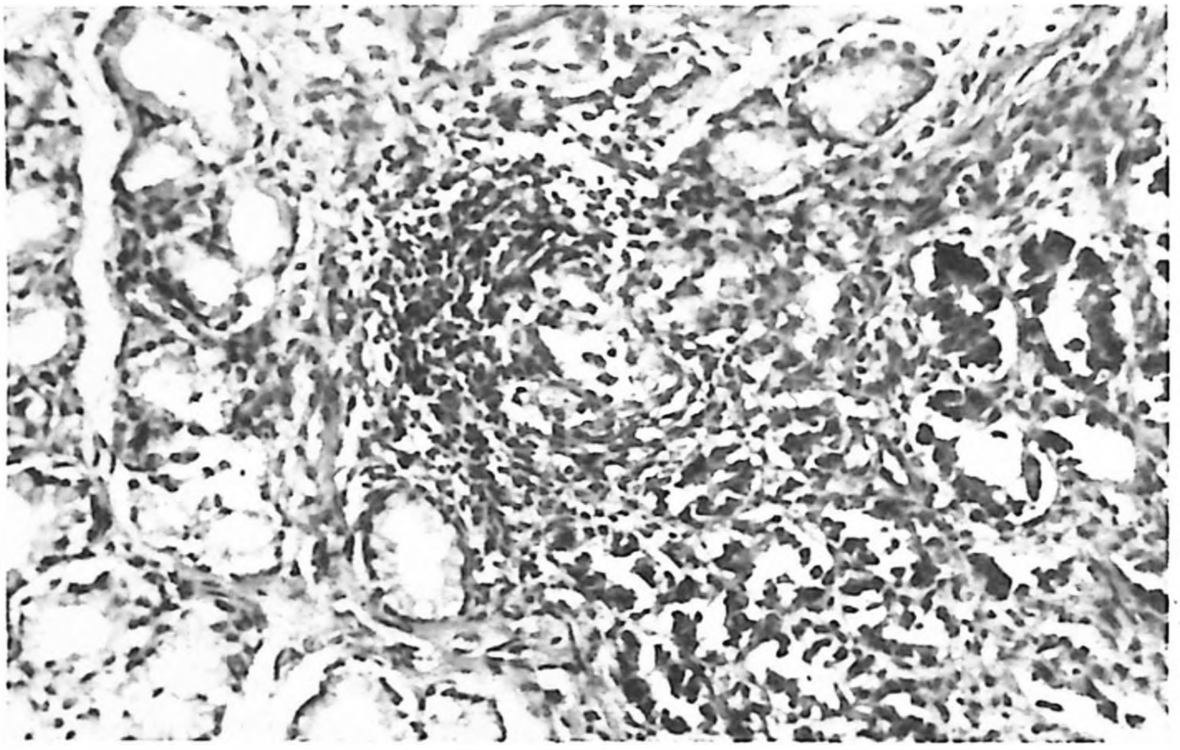

Fig. 2: Small lymphoid follicle in the intestinal mucosa (HE, X 66).

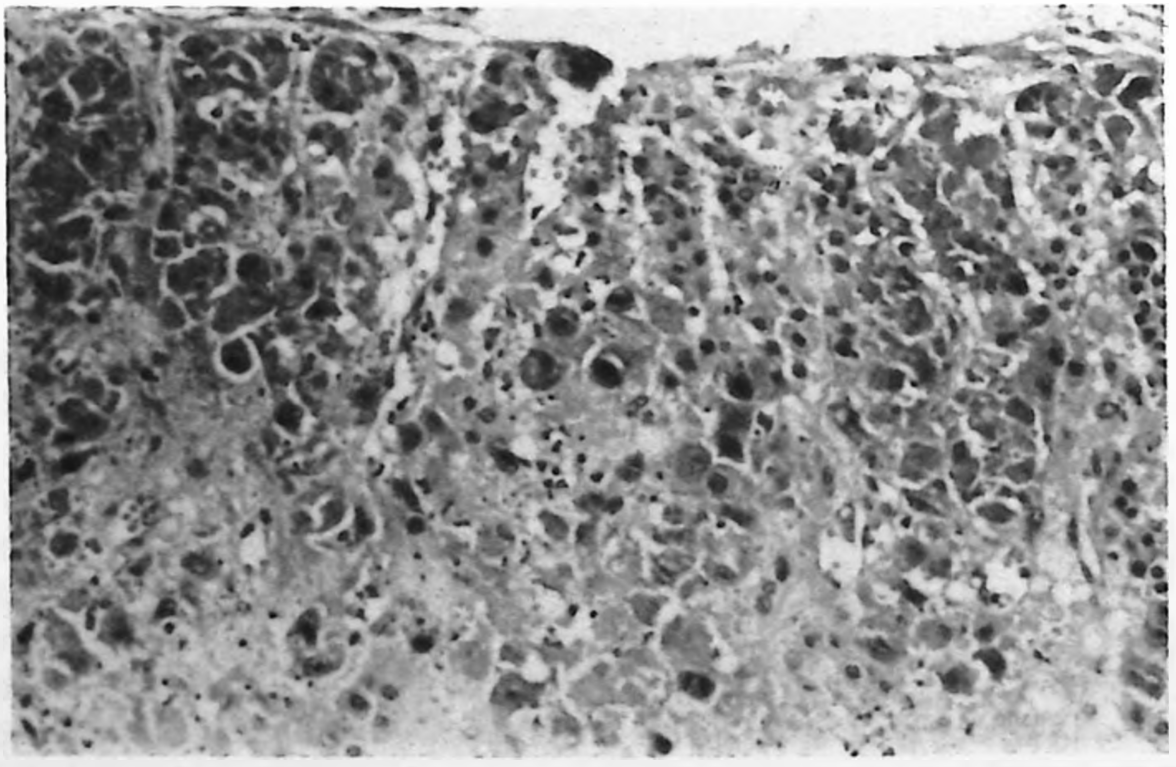

Fig. 3: Cortical cells with intranuclear inclusions in the adrenal gland (HE, X 66).

In the year following the patient's death, prenatal diagnosis was performed by the family. ADA activity determined in the erythrocytes isolated from the fetal blood taken via cordocentesis in the 21st week of pregnancy was very low. (9 µmol uricacid/h/gr Hb). Spontaneous abortion occurred two days after the cordocentesis. Autopsy could not be performed.

Discussion

When admitted to a local health center, the patient was diagnosed with cerebral palsy, and recurrent lung infections were thought to be due to aspirations caused by epiglottic dysfunction. Taking into consideration the history of recurrent lung infections, resistant oral candidosis and laboratory findings, the patient was diagnosed with SCID due to ADA deficiency. She had classical findings of SCID such as recurrent respiratory tract infections, failure to thrive and oral candidosis. Primary abnormalities specific for ADA-deficient SCID belong to the lymphoid system. In the thymus, diverse morphological findings are typically observed. However, sometimes the thymus cannot be observed grossly, as in our case.

Some pathologic alterations have also been reported in non-lymphoid tissues such as kidney, adrenal and chondro-osseous tissues[9]. In our case, we could detect only fibrosis in the adrenal cortex. Our patient also had neurologic manifestations such as head lag, spasticity, irritability and developmental delay. Neurologic abnormalities are uncommon in ADA-deficient SCID infants, but such abnormalities can be seen in mice after the injection of ADA enzyme inhibitor, deoxycoformycin[10]. A few reports have been published about ADA-deficient SCID infants with neurologic manifestations[8-11]. One of the cases described by Hirschhorn et al.[8] had spasticity of the upper extremities and the other had tremors in his hands and intermittent dystonic postures. Another case was reported in 1980[8]. This four-month-old could not follow light and had nystagmus, dystonic posture, athetoid movement, head lag and absent deep-tendon reflexes. These abnormalities improved considerably during the removal period of toxic metabolites by erythrocyte exchange transfusions. In ADA deficiency, toxic substrates such as deoxyadenosine and phosphorylated metabolites accumulate and may have some effects on the central nervous system, probably via purinergic receptors. Treatment with erythrocyte exchange transfusions provides intact enzyme and binding sites for the clearance of metabolites and may lead to improvement of neurologic manifestations.

Treatment of our patient with bone marrow transplantation, polyethylene gycol-modified ADA and somatic gene therapy was not available; therefore, red cell partial exchange transfusions were initiated[11-15]. Improvement of muscle spasticity, irritability and head control was observed after the initiation of transfusions. However, she did not respond with regard to immunologic

parameters, a finding consistent with some of the cases reported previously[2]. These neurologic abnormalities might have been secondary to a previous viral infection of the brain or an undefined event during the perinatal period. Amelioration of neurologic findings with eyrthrocyte transfusions suggests that these abnormalities may result from accumulated toxic metabolites acting via purinergic receptors in the central nervous system. Hirschhorn et al.[8] showed that a decrease in toxic metabolites accompanied the improvement of neurologic manifestations in an infant with ADA-deficient SCID.

It is difficult to explain why most ADA-deficient patients have no neurologic abnormalities. Although environmental factors and genetic heterogeneity may play a role, the main mechanism responsible for involvement of the central nervous system remains to be elucidated.

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