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Thymic Dysplasia with Normal Immunoglobulins (The Nezelof Syndrome)*

(A Case Report)

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The Nezelof syndrome is a form of immunodeficiency disease firstdescribed in 1964.[1] It is characterized by cell mediated immunodeficiency with lymphopenia and a dysplastic thymus Immunoglobulin levels seem to be normal or near normal with evidence of some antibody production. Plasma cells are present in the expected locations. Although the clinical and patologic findings resemble those of severe combined immunodeficiency the clinical course and symptoms are less fulminant.[2] About 35 cases have been reported in literature, some surviving beyond 3-4 years of age.[3, 4]

Case Report

An 11 month old white male was admitted to Hacettepe Children's Hospital with the chief complaints of diarrhea, fever and cough. He was the product of an uneventful pregnancy and delivery. Neonatal period was normal. The patient was breastfed without additional food or vitamins. He had not received any immunizations. He had bilateral purulent otitis at the age of 7 months and developed pneumonia four weeks prior to his admission. During the course of treatment with antibiotics he developed a maculopapular rash which was tentatively diagnosed

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as measles and was hospitalized elsewhere for 2 weeks. Ten days after his discharge, fever and cough recurred which prompted his admission to our clinic.

Family history revealed that his unrelated parents were in good health. Four sisters and two brothers between 5 and 14 years of age were likewise healthy. The patient's development was essentially normal until 10 months of age. Physical examination revealed the patient's weight to be 5.2 kg (<3rd percentile) and height 69 cm. (at 3rd percentile). He had a moderate degree of dehydration with a body temperature of 37.8° C. A seborrheic dermatitis was noted on the scalp. He also had bilateral purulent conjunctivitis, otitis media, oral moniliasis, bilateral scattered fine rales over both lung fields and an enlarged liver measuring 4 cm below the right costal margin. The tonsils were small.

Laboratory Findings: Urinalysis was normal. Hemoglobin was 10 gm/dl., W. B. C. was 8,400 per cmm with 56 percent polymorphonuclears and 44 percent lymphocytes. The red cells were normocytic, normochromic and the platelets were adequate in number.

Total proteins were 6 gm/dl. A serum electrophoresis showed albumin to be 38.7 %, alpha-l-globulin 17.7 %, beta globulin 12.7 % and gamma globulin 28.3 %. A chest film showed bilateral bronchopneumonia. A throat culture yielded staph. aureus and a stool culture grew out nonpathogenic E. Coli, a blood culture was negative. Diarrhea continued despite antibiotics and supportive treatment. On the sixth day of admission the hemoglobin was 7.8 gm/dl and there was no change in the appearance of the chest film. 50 ml of plasma was transfused. The next day scattered petechial lesions appeared over the trunk. The platelet count was 58.000/cmm and the possibility of disseminated intravascular coagulation due to sepsis was considered and 500 units of heparin was administered every 6 hours. On the 10th day the platelet count was 44,000/cmm. The hemoglobin was 10.9 gm/dl and the W. B. C. was 18,400/cmm. 50 ml of plasma and 25 ml. of fresh blood were transfused. On the 11th day of admission the hemoglobin was 14.8 gm/dl, the hemotocrite 42 %, the platelets 60,000/cmm. The following day his condition deteriorated and the patient expired. A post mortem blood culture grew out pyocyaneus.

Special Studies-Material and Methods

The patient was included in a special study group of malnourished infants for the evaluation of his immune status.[5] Skin tests were done by intradermal injection of P. P. D. (Refik Saydam Merkez Hıfzıssıhha Enst. 5T. Units/dose), SKSD (Lederle labs. 50 U SK and 12.5 U SD/do-

se), PHA-P (Burroughs-Wellcome labs. 10 microgram/dose) and Candida (Hollister Stier labs, 50 PNU/dose) antigens. An induration over 5 mm. was considered as positive at the 48th hour reading. The micro method of Scheidegger for immuno-electrophoresis[6] and the radial immunodiffusion technique of Fahey and Mc Kelvey for immunoglobulins[7] (with Behring-Werke plates) were used. In vitro stimulation of the lymphocytes was done with PHA, candida and allogeneic lymphocytes (MLC) according to a previously published method,[8] Incorporation of H3Tdr into DNA was measured and the results were expressed as CPMx10^3/per million lymphocytes. A healthy subject's lymphocytes were treated in the same manner and served as control. The cultures were harvested on the 3rd day for PHA, on the 5th day for MCL and on the 7th day for Candida.

Results

The absolute lymphocyte count varied between 4,400 and 3,700 cmm. All skin tests (for PPD, SKSD, PHA and Candida) were negative. Immunoglobulins (per dl) were as follows: IgG 1230 mg, IgA 104 mg, IgM 182 mg, B_1C 51 mg. In vitro lymphocyte studies showed a low PHA and candida , but a normal MLC response. In the patient CPM with PHA stimulated and unstimulated were 27,900 and 2,400, the stimulation index (SI) was 11.5. In the control CPM with PHA stimulated and unstimulated were 189,000 and 294, SI was 643. For candida the SI for the patient and the control were 0.1 and 10.8, respectively.

Necropsy Findings: The thymus weighed 2.0 gm (normal for the same age: 10 gm). Cortico-medullary differentiation and Hassal's corpuscles were absent with a reduced number of lymphocytes (Figure 1). In the spleen, cuffs of lymphocytes were present around many arterioles giving a follicular appearance. There were no germinal centers. The small mesenteric lymph nodes revealed marked depletion of lymphocytes mainly in the thymic dependent areas and poorly developed lymphoid follicles some of which showed ill defined germinalcenters and scattered plasma cells (Figures 2 and 3). The villi of the small intestine were blunted and the mucosa was surprisingly well preserved without any evidence of autolysis. There were numerous plasma cells in the tunica propria. Peyer's patches and lymphoid follicles of the mucosa were recognized in the intestinal tract; they revealed however, no germinal centers. Histologic examination of both tonsils showed cryptic ulcers and lymphoid follicles with germinal centers (Figure 4). Diffuse bronchopneumonia with multiple abcesses, severe, fatty degeneration of the liver with nonspecific reactive hepatitis and interstitial nephritis were also found.

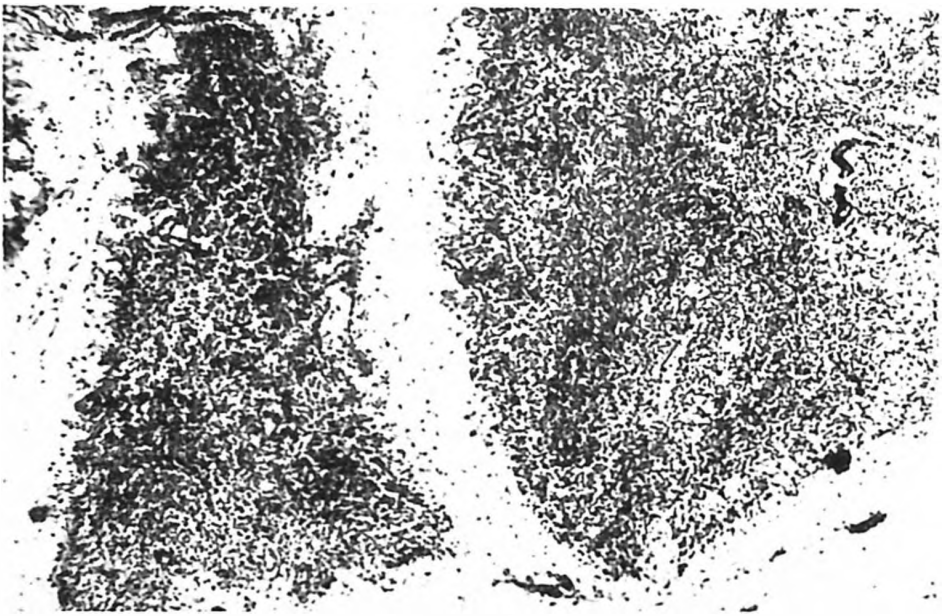

Figure 1

Thymus showing no corticomedullary differentiation and absence of Hassal's Corpuscles (hematoxylen-eosin x 40).

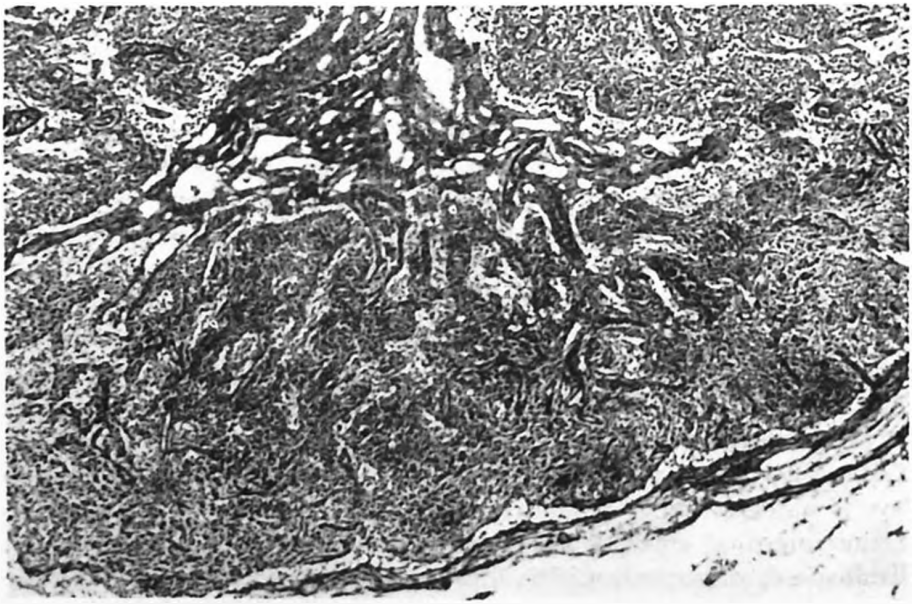

Figure 2

Mesenteric lymph node showing depletion of lymphocytes and poorly developed lymphoid follicles (hematoxylen-eosin x 40).

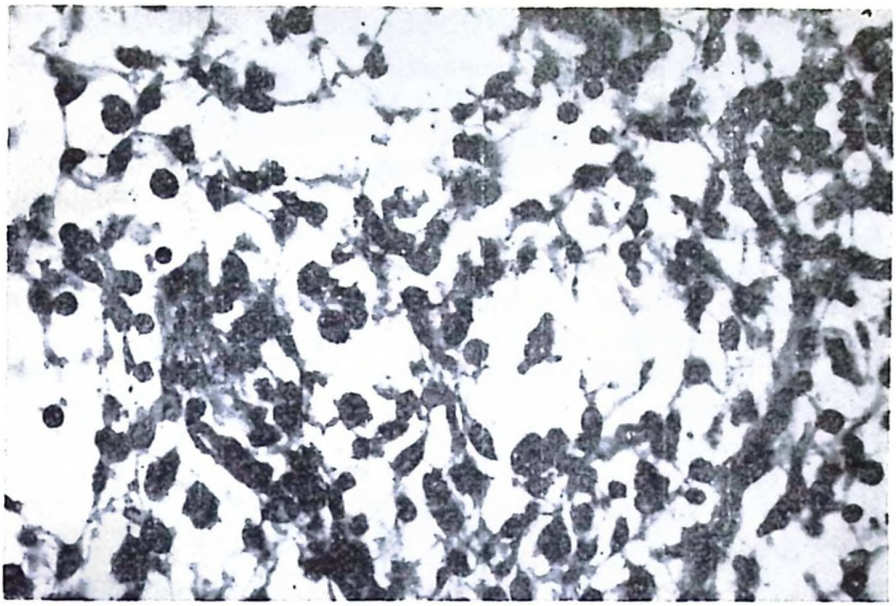

Figure 3

Higher magnification of lymph node showing presence of plasma cells interspersed with decreased number of lymphocytes (hematoxylen-eosin x 400).

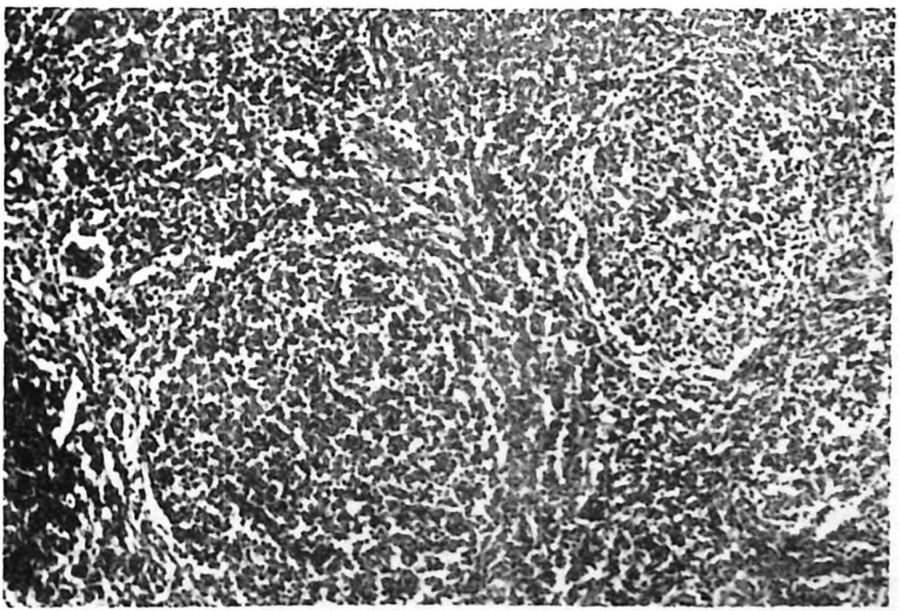

Figure 4

Tonsil showing rather well formed primary and secondary follicles and adequately populated lymphocytes (hematoxylen-eosin x 100).

Discussion

Impairement of cellular immunity has been described in severe combined immunodeficiency (SCID), in thymic hypoplasia (Di George syndrome), in ataxia-telangiectasia, in the Wiskott-Aldrich syndrome and in immunodeficiency with short-limbed dwarfism.[9] In SCID, there is also an associated defect in immunoglobulins and antibody response. Breton and co-workers published a case of Swiss type agammaglobulinemia where normal serum levels of IgM with a deficient IgG and IgA had been observed.[10] In 1964 Nezelof and colleagues reported a 14 month-old boy with severe cellular immunodeficiency with normal serum levels of IgG, IgM and IgA. The patient expired at 18 months of at age and autopsy, a dysplastic thymus and depletion of lymphocytes of the lymphoid organs in the thymic dependent areas were found; however the plasma cells were present.[1] Since then similar cases have been reported and the entity was called "Nezelof's Syndrome".[3 11-14] Inheritance of this entity is autosomal recessive or x linked recessive but, as in our patient, occasionally a positive family history may not be obtained.[1,2] Usually the clinical picture is indistinguishable from SCID, but in most patients the Nezelof syndrome presents itself late in infancy.[2] The case presented in this report was well until 7 months of age at which time he developed purulent otitis media followed by bronchopneumonia, severe gastroenteritis and a gram negative (pseudomonas) septicemial leading to death. Absolute lymphocyte counts were within normal range, but the skin test responses were similar to those seen in other cases of Nezelof syndrome. In our patient serum immunoglobulins were normal, while the serum complement (C_3) level was low. Necropsy findings were also consistent with the diagnosis of the Nezelof syndrome. The thymus was dysplastic, the lymphoid cells in thymic dependent areas of lymphnodes, the spleen and the intestine were depleted, the plasma cells were present in the peripheral lymphoid tissues. Impairment of cellular immunityhas been reported in patients with kwashiorkor or protein calorie malnutrition.[15-17] Statistical analysis of a study carried out on marasmic children in our laboratories showed that serum immunoglobulins were significantly elevated and serum complement levels were significantly low in only severely malnourished cases.[5] In the same study marasmic children had normal absolute lymphocyte counts, normal PHA skin tests and normal in vitro PHA response. Lymphonode biopsies, following antigenic stimulation with diphteria-tetanus toxoid showed primary adn secondary follicles with germinal centers and normal appearing subcortical areas.

We would like to emphasize that marasmus is a common clinical entity in developing countries and its clinical picture at times may mimic primary immunodeficiency. In severe cases of marasmus, low levels of complement (C_3) may usually lead to infection with gram negative microorganisms.[18] However the serum immunoglobulin levels are usually normal or elevated. Cellular immunity tests show normal results as mentioned above. When in vitro lymphocyte response to PHA is abnormal along with a negative skin test in a marasmic child with normal immunoglobulins, one should eliminate the possibility of the Nezelof syndrome. The findings in our patient indicate that further immunologic studies of such patients may be rewarding in establishing the diagnosis of this disease entity.

Summary

Thymic dysplasia with normal immunoglobulins is a form of primary immunodeficiency occurring in infancy. Its clinical picture is indistinguishable from severe combined immunodeficiency with decreased or absent immunoglobulins. A similar picture to that seen in Nezelof syndrome may also be observed in patients with severe marasmus indicating that these two entities have to be differentiated occasionally. This report concerns an 11-month old boy with severe malnutrition, normal immunoglobulins, decreased serum complement (C_3) level and depressed cellular immunity. Surprisingly, post mortem examination revealed a small dysplastic thymus and small lymph nodes with marked depletion of lymphocytes in thymic dependent areas while plasmocytes were present. It is suggested that in marasmic infants with severely depressed cellular immunity and normal immunoglobulins the possibility of Nezelof syndrome should be considered with further appropriate immunologic investigations.

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