Severe lymphopenia in tuberculosis

A mere coincidence or a significant association?

E. Nazlı Gönç[1], Seza Özen[1], Ayhan Göçmen[1], Yeşim Zafer[1], İlhan Tezcan[1]

[1]*Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey*

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A variety of infectious agents can cause secondary immunodeficient states. We herein present a one-year-old patient, admitted to the hospital with severe lymphopenia, who was subsequently diagnosed as tuberculosis. After the antituberculosis (anti TB) therapy was started, the clinical condition and the immunologic findings of the patient improved. We have thus concluded that the transient lymphopenia of the patient was due to Mycobacterium tuberculosis. We suggest that immunodeficiency should be investigated more often in children with tuberculosis and that further studies will shed light on the pathogenesis of this aspect of the disease.

Key words: childhood, lymphopenia, tuberculosis.

The altered immune status in infectious diseases has been an attractive subject for many clinicians. Quantitative and qualitative abnormalities in white blood cells have been clearly demonstrated in various infections; lymphopenia and certain immune deficient states have been associated with a number of infectious agents such as brucella[1], Epstein-Barr virus[2] cytomegalovirus[3,4], human immunodeficiency virus (HIV)[5] and even Mycobacterium tuberculosis. However, in most of these, the mechanism of secondary immunodeficiency induced by infectious agents has not yet been well established.

Tuberculosis is still a common disease not only in developing countries but also in developed countries, where a resurgence has occurred. We herein present an infant with tuberculosis who developed severe lymphopenia.

Case Report

A one-year-old girl was admitted to Hacettepe University Children's hospital with the symptoms of persistent gastroenteritis, lethargy and high fever. During the previous two months, she had not gained any weight. She had received two diphtheria-pertussis-tetanus (DPT) and oral polio vaccines but no BCG vaccine had been given. She was the fifth child of parents with second degree consanguinity. Her two brothers had died at four and eight months of age of unknown causes. The socioeconomic status of the family was very low.

On admission, she was in a septic state. Her weight and length were below the third percentile. She had severe dehydration, ascites and marked hepatosplenomegaly.

On laboratory examination, severe lymphopenia (total white blood cell count: 9000/mm^3, peripheral smear: 98% polymorphonuclear leukocyte, 2% lymphocyte; absolute lymphoyte count: 180/mm^3) was detected. the liver enzymes and bilirubin levels were elevated. She had deep metabolic acidosis. C reactive protein was positive. The antibodies against hepatitis A, B and C, cytomegalovirus, Epstein-Barr virus, HIV, and the titers of agglutinins for salmonella and brucella were all negative. No infectious agents were recovered from repeated nasopharyngeal, urine, stool, blood and bone marrow cultures. The sweat chloride concentration, the alpha^1 antitrypsin level, and the chest X-ray were normal. Abdominal ultrasonography showed ascites, hepatomegaly with marked parenchymal heterogeneity and splenomegaly. Bone marrow revealed lymphopenia.

The plasma immunoglobulin levels were normal; IgA: 101 mg/dl (25-158 mg/dl), IgG: 599 mg/dl (452-1192 mg/dl), IgM: 101 mg/dl (50-200 mg/dl). The delayed hypersensitivity skin tests for

candida, phytohemagglutinin and purified protein derivative were negative. Adenosine deaminase and purine necleoside phosphorylase levels were within normal limits. The serum isohemagglutinin titer anti A was 1/128 and the titers of antibodies for trivalent polio vaccine were as follows: T1: 1/32, T2: 1/32, T3: 1/128. On the other hand, the lymphoycte subpopulations CD3, CD4, CD8 and CD19 were extrmely low (Table I). In vitro lymphocyte proliferative responses to mitogens, phytohemagglutinin and concanavalin-A were normal.

Table I. Absolute Lymphocyte Count and Lymphocyte Subpopulations Detected on the Given Dates

Date	Absolute lymphoycte count	Lymphocyte subpopulations			
		CD3	CD4	CD8	CD19
At admission	180/mm^3	1%	1%	1%	0%
After 3 weeks	960/mm^3	81%	58%	32%	0%
After 4 weeks	2640/mm^3	88%	61%	29%	0%
After 5 weeks	2150/mm^3	79%	57%	29%	6%
After 7 weeks	2980/mm^3	33%	25%	14%	20%
After 9 weeks	5200/mm^3	32%	21%	16%	62%
After 3 months	3900/mm^3	41%	30%	14%	49%
After 6 months	4100/mm^3	58%	34%	24%	32%

The metabolic acidosis and severe dehydration were corrected in itially. Her general status deteriorated in the subsequent three days. Ciprofloxacin and amikacin were started empirically for her septic state. She was then diagnosed with tuberculosis by the twice positive polymerase chain reaction (PCR) for Mycobacterium tuberculosis in ascites fluid and a positive BCG test[6]. The direct examination of ascites fluid and gastric aspirates for acid-fast bacilli and the cultures were all negative. The chest X-ray of the patient's father revealed unilateral costophrenic sinus obliteration, raising the possibility of pulmonary tuberculosis. Intermittent antiTB therapy with isoniazid and rifampicin was started both for the patient and her father. A month later, the clinical condition of the patient improved and there was an increase in the absolute lymphocyte count (Table I). After six months of well-controlled treatment, she gained weight and improved markedly in motor and mental activity. The spleen was no longer palpable, the liver was reduced in size and ascites disappeared. After six months of treatment, the repeated PPD test revealed an induration of 15 mm in diameter.

Discussion

The incidence of tuberculosis has declined steadily over the past century due to impraved socioeconomic conditions in developed countries, but in recent years the disease became a common problem both in developed and developing countries despite widespread application of the BCG vaccination[7-9].

In tuberculosis, quantitative[10-15] and qualitative[16,17] abnormalities in both B cells and T cells have been reported in the literature; however, the most prominent abnormality is a CD4 lymphopenia and reversal of CD4/CD8 ratio[13,15]. There are only two reports of a relative B cell lymphopenia[13,18]. Our case is the first presentation of severe B and T cell depletion. After the initiation of the antiTB therapy, the first improvement was in the T cell count, although B lymphopenia persisted for seven weeks.

A primary immunodeficiency was ruled out by the improvement of clinical and laboratory parameters with antiTB therapy. The normal circulating amounts of immunoglobulins, despite decreased B cells in peripheral blood, may reflect the activation of B cell clones in lymphoid organs before the development of the secondary immune defect[19]. On the other hand, it may also be speculated that a defect in the lymphocyte migration from lymphoid organs to the circulation might have been responsible for the lack of these cells in the periphery[20]. An alternative possibility for the lack of lymphocytes in the circulation may be the sequestration of these cells in tuberculous granulomas as suggested by Onwubalili et al.[13]. Normal immunoglobulin and isohemagglutinin levels, good specific antibody response and normal in vitro lymphocyte proliferation tests of our patient were also suggestive of efficient lymphoyctes, although not detected in the periphery.

No other infectious agents were detected in this patient except Mycobacterium tuberculosis. Delacourt et al.[21] claimed that the PCR is the most specific and sensitive method for the diagnosis of mycobacterium tuberculosis, especially in childhood. Many data establish the utility of the PCR test for the rapid detection of Mycobacterium tuberculosis[22,23]. The BCG test, which was found to be positive in our patient, has been previously reported to have higher sensitivity and specificity than the PPD test in diagnosis of tuberculosis. The BCG test is unaffected by age, nutritional status, or by type and localization of infection[6]. The

diagnosis of tuberculosis was strengthened by the improvement of the clinical signs and symptoms as well as of the lymphopenia with antiTB therapy. We were unable to recover Mycobacterium tuberculosis by traditional culture methods because a combination of broad spectrum antibiotics which also cover Mycobacterium tuberculosis had to be administered for the patient's severe septic state before the evaluation of tuberculosis. The malnutrition might also have contributed to the immunodeficient state of this patient.

We conclude that the transient lymphopenia of this case was associated with Mycbacterium tuberculosis. The abnormal lymphocyte traffic might have been responsible for this condition. We suggest that immunodeficiency should be investigated more often in children with tuberculosis. Further studies will shed light on the pathogenesis of this aspect of the disease.

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