Decreased Lymphocyte Adenosine Deaminase Activity in Tumor Patients

Joseph Uberti, Robert M. Johnson, Robert Talley, and James J. Lightbody
Department of Biochemistry, Wayne State University School of Medicine, Detroit 48201 (J. U., R. M. J., J. J. L.), and Division of Oncology, Henry Ford Hospital, Detroit, Michigan 48201 (R. T.)

SUMMARY

Adenosine deaminase has been measured in the lymphocytes of individuals with various types of solid tumors. The mean activity was found to be significantly lower when compared with control individuals of a similar age.

INTRODUCTION

It has been postulated that the immune system plays an important role in the defense against the development of autochthonous tumors (2). We have focused our attention on the possibility that biochemical alterations in the immune system (either genetically or environmentally caused) may be responsible for the development of some neoplasms.

It has been reported that approximately 50% of the children with combined immune deficiency disease were deficient in adenosine deaminase (8). Various explanations have been suggested as to the function of adenosine deaminase in the immune response (4, 9). The present study was undertaken to determine the adenosine deaminase levels in patients with solid tumors as compared with normal individuals of similar ages. The results indicate that the mean adenosine deaminase levels in such patients are significantly lower than in the normal controls.

MATERIALS AND METHODS

Lymphocyte Purification. The lymphocyte fraction was prepared in an identical manner for all groups studied. The procedure for the purification of lymphocytes has been previously published and will be described only briefly (6). Heparinized peripheral blood was centrifuged at 150 x g for 10 min. The plasma and buffy coat were removed and re-centrifuged at 400 x g for 10 min. The leukocyte pellet was resuspended in Tissue Culture Medium 199 purified on a Ficoll-Hypaque gradient (specific gravity, 1.077) using the method of Boyum (1). The resultant lymphocyte fraction was resuspended in phosphate-buffered saline (0.9% sodium chloride-0.05 M potassium phosphate, pH 7.4). The purified lymphocyte fraction was washed 2 additional times in phosphate-buffered saline. The erythrocyte contamination averaged 10% for all groups. The remaining 90% were leukocytes of which approximately 95% were small lymphocytes and monocytes and 5% were polymorphonucleocytes. No difference in leukocyte subpopulations could be determined between patients and controls. The lymphocyte suspension was treated sonically for 30 sec with a Kontes sonic oscillator. Microscopic examination was used to assure complete cell disruption. The extracts were then centrifuged at 37,000 × g for 10 min and the supernatant was used immediately for enzyme analysis.

Adenosine deaminase activity was measured by the spectrophotometric method of Hopkinson et al. (5). The absorbance of the reaction mixture was determined at 293 nm in a 1-cm light path. The reaction mixture was incubated at 37° for 30 min. Assays were done in triplicate. Protein was determined by the method of Lowry et al. (7). No significant differences in protein on a per cell basis was observed in any of the groups. Adenosine deaminase activity was expressed as the amount (nmoles) of adenosine converted per mm per mg of protein. The Student t test was used to determine significance between the means of the different groups. A p value of less than 0.05 was considered significant.

RESULTS

Twenty-eight patients (mean age, 59; range, 42 to 75) with various types of solid tumors were investigated for leukocyte adenosine deaminase levels. Twenty-one normal individuals of similar age (mean age, 52; range, 46 to 63), who were in the hospital for annual physicals, were used as controls. An additional group of controls consisted of 32 young adults with a mean age of 23. No difference in adenosine deaminase values between the 2 control groups was apparent. None of the patients were undergoing any type of chemotherapy or radiation therapy at the time the blood samples were taken. Seven % had undergone chemotherapy and 36% radiation therapy from 10 yr to 8 months prior to the enzyme analysis. There was no correlation between the time interval between either of these treatments and adenosine deaminase levels. Seventy-five % had undergone surgery for removal of a primary tumor between 6 months to 11 yr prior to acquisition of the blood. Again, there was no discernable correlation between the adenosine deaminase levels and time from previous surgery. Metastasis had occurred in 89% of the patients ranging from minimum to extensive. Again, no correlation could be determined be-

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Comparison of adenosine deaminase values between norm and cancer patients

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Mean ± S.D.</th>
<th>p</th>
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<tbody>
<tr>
<td>Normal younger adults (mean age 23)</td>
<td>37.1 ± 11.8 (14.4-69.0)</td>
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<tr>
<td>Normal older adults (mean age 52)</td>
<td>38.6 ± 11.9 (20.8-61.5)</td>
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<tr>
<td>Patients (mean age 59)</td>
<td>25.6 ± 13.2 (4.5-55.9)</td>
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* Comparison between normal older adults and patients.

ACKNOWLEDGMENTS

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REFERENCES


DISCUSSION

Recent reports from numerous laboratories (3, 4, 8, 9) have suggested that alterations in nucleotide metabolism can result in an impaired function of both the afferent and efferent arms of cellular immunity. Consequently, any change in purine or pyrimidine concentrations within the lymphocytes may result in a reduced immune response directed against tumor antigens on neoplastic cells. The nucleotide alterations may result from external sources such as chemotherapy or environmental changes or result from genetic defects in enzymes associated with nucleotide metabolism. Possible examples are the absence of adenosine deaminase in some (T cell immune deficient) children and the absence of nucleoside phosphorylase in others. High levels of adenosine can inhibit cell division (4), which is essential for the immune response. Increased levels of adenosine may also diminish cellular immunity (9).

The results reported here are similar to those reported earlier for acute lymphocyte leukemia (10). A large variation in lymphocyte adenosine deaminase levels appears to exist within the general population with a large overlap between cancer patients and controls. However, the mean values are clearly lower in patients with disseminated and solid tumors.
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