Immunological Basis of Close-Contact Sensitization to Osteosarcoma

Arnold Powell, Alice M. Sloss, and John T. Makley

Abstract

Normal persons with a history of close contact with cancer patients often given positive responses in tests for specific tumor immunity. The present study was designed to establish the immunological relevance of such reactivity. Leukocyte adherence inhibition analysis was used to test responses of osteosarcoma (OS)-positive donors to extracts of OS. The test system proved highly specific in that positive leukocyte adherence inhibition responses were detected in 35 of 39 OS patients while only 6 to 7% of the controls were positive. Thus, the test system appears useful in the detection of OS. Two persons reactive presumably because of exposure to OS tissue gave booster-like leukocyte adherence inhibition responses on each reexposure. Reactivity was abrogated by treatment of their leukocytes with a goat anti-T-cell immunoglobulin G. Thus, the reactivity of cells from normal donors exposed to OS probably has an immunological basis, since the test system was highly specific, reflected anamnestic reactivity, and depended on lymphocytes (probably thymus dependent). These findings suggest that an OS-associated antigen can be transmitted horizontally, but the relation of immunity to risk remains obscure.

Introduction

Tests for specific tumor immunity have revealed that positive responses often occur in individuals exposed to cancer patients but who themselves have no signs of the disease. This acquired reactivity has been noted in breast carcinoma, malignant melanoma, neuroblastoma, and OS. However, the immunological specificity of the test procedures has not yet been rigorously established. The only defining criterion used has been reactivity in the test system.

The purpose of this presentation is to establish that reactivity of close contacts actually reflects immunization. The criteria include proof of specificity of the test system, existence of anamnestic reactivity, and the involvement of lymphocytes.

Materials and Methods

The test system used in these studies was LAI determined by the hemacytometer method described elsewhere in this symposium (1). Cells were isolated from peripheral blood by the Hypaque-Ficoll method. Antigens were tumor extracts obtained by the 3 M KCl method.

Results

Specificity of the Test System. To establish specificity of the test system, 3 conditions must be satisfied: (a) OS extract consistently must elicit positive LAI responses from cells of known OS patients; (b) the same reactive cells must prove unreactive to extracts of non-OS tissues; and (c) the OS extracts shown to give positive responses with cells from OS donors must have no effect on cells from non-OS donors.

Chart 1 summarizes experiments which establish conformity of the LAI system with the 3 criteria for specificity. Positive reactions occurred in 90% of the trials in the specific combination, while the 2 control situations gave false positives 6 and 7% of the time, respectively. These findings establish the specificity of the system and satisfy the first criterion for an immunological mechanism. It appears that the LAI system is a reliable means for detecting OS.

Positive responses were noted in 4 of 10 mothers of OS patients, 1 of 9 fathers, and 1 of 16 siblings and other close associates. The 2 orthopedic surgeons responsible for most of the OS cases at this hospital were strongly positive, while 2 surgeons lacking such contact were negative. Two of 4 laboratory workers gave strong responses. These 2 workers are responsible for processing tumor tissue in the preparation of extracts.

Criterion 2: Anamnesis. The 2 laboratory workers responding to OS were followed by LAI testing for about 10 months. In Chart 2, it can be seen that the first time Subject AMS was tested she gave a negative response to OS. On about Day 50, she processed a fresh OS, and 1 week later her LAI response was significant. On Day 100, she was reexposed, and 1 week later she exhibited a strong LAI. Her reactivity diminished over a period of nonexposure but was strongly augmented following a new exposure on Day 168. Her LAI reaction to OS diminished thereafter but remained positive.

Subject AP showed a similar pattern, but no preexposure analysis was available. Each of his exposures was of longer duration than those of AMS, but on each occasion of reexposure his LAI response was elevated. Again, reactivity fell off during periods of noncontact with OS material.

These patterns are strongly suggestive of anamnesis in that, on each of the 6 occasions when a booster reaction might have occurred with these 2 subjects, it did indeed occur. Thus, the second criterion for immunity appears to have been satisfied.

Criterion 3: Lymphocytes. The involvement of lymphocytes in the LAI analysis of sensitivity to OS has been dealt with in our previous contribution to this workshop. A goat anti-T-cell IgG completely inhibited the LAI response of cells from the above 2 donors to OS. This fact, taken...
Close-Contact Sensitization to OS

Chart 1. LAI responses of various donors to various antigens. OS/OS, OS extract tested against cells from OS patients preoperatively; OS/NON-OS, extracts of sarcomas, carcinomas, or normal tissues tested against cells of preoperative OS patients; NON-OS/OS, OS extract tested against cells of normal donors or donors with a wide variety of malignant tumors.

Together with data showing the T-lymphocyte dependency of the LAI assay, satisfies the third criterion.

Discussion

The 3 conditions set forth to define an immune response have been met. The test system is highly specific, anamnestic reactivity was demonstrated, and lymphocytes are necessary. Thus, sensitization of normal persons through close contact with OS patients or OS tissue seems to reflect an immunized status.

These studies imply that OS-associated antigens may be transmitted horizontally from person to person. This does not prove by any means, however, that OS is a contagious disease. Such a conclusion cannot reasonably be drawn from these studies. It is not possible, as yet, to relate resistance to cancer to immunological status of the host. Thus, it remains to be seen whether vicariously sensitized individuals are at a greater than ordinary risk or are, in fact, protected against OS.

References


Discussion

Dr. Thomson: How do you account for the positive responses of the laboratory technicians?

Dr. Powell: I think where it comes from is the fact that in some of our preparations we have Waring-blended our material. We have also placed the material in an ultracentrifuge, which I think creates aerosols all over the laboratory. I think these are 2 situations in which aerosols are generated, and I think we have breathed it in. I do not know if this is a normal mode of acquisition, but I think something along these lines may account for our having become immunized. The second point I want to make is that, while we have shown reactivity here, we do not know if we have done ourselves any good or if we have done ourselves any harm; this has yet to be shown. That does not mean that precautions should not be taken, but I do not think we ought to panic over the existence of data of this sort. I am not sure that what we have shown here can be extrapolated to other kinds of tumors. We are talking only about OS in this case, and, as far as I know, it may be the only tumor in which it exists to any large extent. I do not know, except that it has been reported elsewhere.

Dr. Thomson: I have been doing experiments with melanoma and colon carcinoma tissues for 6 years now, and I certainly have not become sensitized; none of us in our lab has. And yet, even with other cell-mediated immunity techniques, people have found that we still do not react.
Immunological Basis of Close-Contact Sensitization to Osteosarcoma

Arnold Powell, Alice M. Sloss and John T. Makley


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/39/2_Part_2/658

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.