A Qualitative Study of Normal Leukocyte Antigens of Human Leukemic Leukoblasts

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SUMMARY

Twelve leukocyte antigens have been determined by the method of cytotoxicity in vitro on leukoblasts from 38 patients with acute leukemia, using two batteries of isoimmune human sera. None of these antigens was absent in this leukemic population. The presence of the leukocyte antigens 1, 3, 4, 6, and 7 of the Hu-1 system (5) was confirmed by absorption experiments. In 17 patients, the leukocyte group defined on leukoblasts during the acute phase of the disease was found to be identical to that determined on lymphocytes from the same patients during the remission period. No qualitative antigenic alterations of these alloantigens were found on the leukoblasts from patients with acute leukemia.

INTRODUCTION

Carcinogenesis may be associated with modifications of normal antigens of the tumor cell. The loss of normal hetero-specific antigens has been described in the malignant cells of several solid tumors (9, 26, 38), and also in acute leukemia (23, 32). An hypothesis for the mechanism of carcinogenesis is based on the concept of “antigenic deletion” (9, 11).

In the mouse, alterations of histocompatibility antigens in tumors has been evoked to explain the abnormal growth capacity of some tumor homotransplants, some of which are able to cross strong histocompatibility barriers (24).

In man, little is known of the alloantigenic structure of malignant cells. Leukocyte antigens, which are closely related to histocompatibility in man (7), represent, for the time being, the most important antigens of nucleated cells. They have already been detected, not only on peripheral leukocytes and platelets, but also in a number of other normal tissues (13, 22) and on human cancer cell lines in culture (21, 22). Most of these antigens are part of a single system, called Hu-1 (5, 6), which resembles the histocompatibility-2 system in the mouse.

We have adapted the methods of tissue typing to the determination of leukocyte antigens on leukoblasts from patients with acute leukemia, and we now report a systematic qualitative analysis of these antigens.

MATERIALS AND METHODS

Cell Suspensions. Leukoblast suspensions were obtained from 38 untreated patients with acute leukemia, including 23 acute lymphoblastic leukemias, 12 acute myeloblastic leukemias, and 3 hemoytoblastic leukemias which were not classifiable by cytologic and cytochemical reactions (peroxidase, esterase, and periodic acid-Schiff). From 22 of these patients with hyperleukocytosis, pure leukoblast suspensions could be obtained from defibrinated peripheral blood by means of erythrocyte sedimentation in 25% dextran (Poviet Production, Amsterdam, M.W. 200,000, 5 gm %) or fluid gelatin (Plasmagel, Roger Bellon, France, 3 gm %). The leukocyte-rich supernatant was centrifuged, the cells resuspended in Hanks’ solution (Institut Pasteur, Paris) and adjusted to a concentration of 5 x 10⁶ per ml. In the remaining 16 cases, leukoblast suspensions were obtained from bone marrow aspirated by sternal puncture and collected in sodium citrate; the white cells, separated after erythrocyte sedimentation in dextran, were washed twice in Hanks’ solution and resuspended at the same concentration as mentioned above. All the cell suspensions contained at least 85% leukoblasts as counted on smears stained with May Grünwald Giemsa. Leukocyte suspensions were later obtained again from 17 of these patients when they were in complete remission following chemotherapy. At the time of the test, all these patients were under maintenance treatment (Methotrexate i.m., 15 mg/sq m/week, and 6-mercaptopurine p.o. 90 mg/sq m/day). The peripheral blood lymphocytes were obtained as described elsewhere (15) by an iron carbomyl method (33), then resuspended in Hanks’ solution and adjusted to a concentration of 5 x 10⁶ per ml. Whole leukocyte suspensions were prepared in the same way except that the iron carbomyl treatment was eliminated.

Immune Sera. Leukocyte antigens were detected by means of batteries of human immune sera containing known antileukocyte antibodies. These 78 sera were selected from among the sera of multiparous women, multiple transfused patients, and volunteers immunized by skin grafts and leukocyte or platelet injections. Two batteries of sera were used successively: the first one, named A in the tables, consisted of 50 immune sera, the reactivity and specificity of which were extensively studied by leukoagglutination and lymphocytoxicity methods on a panel of cells from 133 normal individuals (6). The other battery, named B, consisted of 35 sera (7 of them being common with battery A), the specificity of which was established by cytotoxicity on lymphocytes and complement fixation on plate-.
lets from normal individuals (5). The correlation between the reactions of these two sets of sera, A and B, was made by reacting both of them on the same 100 individuals by the lymphocytecytotoxicity techinic.

Cytotoxic Techinic. The techinic used throughout this study was that of cytotoxicity in vitro in the presence of rabbit complement (37). Rabbit serum, which appears to be the most efficient source of complement in this human cytotoxic system (14, 35), is also spontaneously toxic for human leukocytes (31, 34, 36) and even more so for lymphocytes of chronic lymphocytic leukemia (30, 28) and for malignant leukoblasts, in our experience. The toxicity for fresh leukoblasts must be removed by exhaustive absorption of rabbit serum with human cells. In this study, pools of fresh rabbit sera were absorbed twice, at 0°C, for 1 hour each time, with equal volumes of cells from a pool of saline-washed human blood cells from donors with different ABO groups. A third absorption was made for 30 min in the cold with 1 volume of washed and packed leukemic white cells (obtained from patients with acute leukemia or chronic lymphocytic leukemia) for 3 volumes of rabbit serum. Once absorbed, the rabbit complement was kept at −70°C until used. Each pool of complement was titrated by a standard system with human antiserum on human lymphocytes (14). The complement must contain by titration at least fifty 100% cytolytic units per ml for use in our cytotoxic techinic. One one-hundredth ml of immune serum, 0.05 ml of cells at a concentration of 5 × 10⁶/ml, and 0.05 ml of rabbit complement are mixed and incubated for 2 hours at 37°C. The percentage of dead cells in each tube is counted after trypan blue staining. For the detection of leukocyte antigens, the immune sera are tested at a 1:2 dilution. A test is considered positive when the percentage of stained cells exceeds 20%, there being less than 10% of stained cells in negative controls in which the immune serum was replaced by Hanks solution. The leukoblasts appear more sensitive to immune lysis than do lymphocytes. The absence of toxicity of normal human serum in the reaction was controlled by including in the batteries a number of individual sera and a pool of 450 serum samples from healthy blood donors with different erythrocyte groups.

Leukocyte Antigens. The leukocyte antigen nomenclature used in the tables is that of Dausset (5, 6). The leukocyte antigens were defined for each cell suspension from the simultaneous reactivity of sera having the same range of specificity. All details concerned with criteria of definition of these antigens, their correlation in the Hu-1 system, their relationships with histocompatibility antigens, and their correspondence with other nomenclatures are found in a previous publication (5). Battery A makes it possible to define 10 antigens (antigens 1 to 10). Antigens 1, 3, and 7 are each determined by 7 sera, antigen 2 by 4 sera, antigens 4, 5, and 8 by 3 sera, antigen 6 by 2 sera, and antigens 9 and 10 by 1 serum; the specificity of the 12 remaining sera is unidentified as yet. With the battery B, 2 additional antigens (antigens 11 and 12) can be identified. In this battery, antigens 5 and 10 are each determined by 5 sera, antigens 1 and 4 by 4 sera, antigens 6 and 8 by 3 sera, antigen 11 by 2 sera, and antigens 3, 7, and 12 by 1 serum; the specificity of 6 sera remains uncertain as yet. It is to be noted that, at the present time, these 12 antigens are not to be considered as definitive entities, and that each of them may consist of several antigenic factors.

Absorption Studies. In order to absorb the antileukocyte antibodies with leukoblasts, selected sera were inactivated for 30 min at 56°C, then diluted to the last dilution causing 100% lysis in a positive standard lymphocyte suspension. One-half ml of serum diluted in this manner was mixed with 1 to 5 × 10⁸ packed leukemic cells. These cells had been isolated as described above and washed 3 times in phosphate-buffered saline. After 90 min incubation at 37°C, the cells were spun down at low speed, and the supernatant centrifuged at 10,000 × g for 30 min to eliminate the remaining cell fragments. Absorbed and unabsorbed sera were then tested again against a normal lymphocyte suspension by the cytotoxic techinic. Controls were made by mixing the leukemic cells with sera not reacting with them. In a few instances the nonspecific absorbing capacity of some leukoblast suspensions, especially myeloblasts, had to be corrected by reducing the number of cells used for absorption.

RESULTS

Detection of Leukocyte Antigens on Leukoblasts with Cyto-toxic Techinic. The reactivity of the sera from the two batteries, A and B, has been studied on leukoblast suspensions from 26 patients with a cytotoxic techinic. The leukemic cells from 11 patients were tested with the 50 sera of battery A; the leukoblasts from the 15 other patients were tested with the 35 sera of battery B. Each serum studied reacted with at least one of the leukoblast suspensions tested. This demonstrates that all 78 sera can individually detect normal leukocyte alloantigens corresponding to their individual antileukocyte antibody specificity.

The 12 leukocyte antigens determined by the reactivity of the sera of these 2 batteries (see Methods) were detected on the limited number of leukoblast suspensions studied. Table 1 illustrates the antigenic pattern of 23 leukoblast suspensions, 11 studied with complete battery A and 12 studied with battery B. Each antigen is represented in this leukemic population.

The antigenic pattern of lymphoblasts does not appear to differ strikingly from that of myeloblasts.

The systematic analysis of the repartition of leukocyte antigens in leukemic patients as compared with normal individuals is not possible due to the small number of patients studied. Nevertheless, the frequency of reactivity of most of the sera of battery A tested on 26 leukoblast suspensions was slightly higher than that observed on normal lymphocytes. This may be the expression of the greatest sensitivity of leukoblasts to immune lysis. In any case, no common characteristic antigenic pattern or phenotype can be found in untreated leukemic patients as compared with 100 healthy individuals tested simultaneously.

Absorption of Antileukocyte Antibodies by Leukoblasts. Table 2 shows the results of a few qualitative absorption experiments performed as described in Methods. Leukoblast suspensions obtained from 8 patients were used to absorb the cytotoxic activity of 7 human immune sera. The absorption of antileukocyte antibodies was obtained successfully by leuko-
Table 1

<table>
<thead>
<tr>
<th>Typing</th>
<th>Patient</th>
<th>Acute leukemia type</th>
<th>Leukocyte isoantigens</th>
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<td>B.A.Z.</td>
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</tr>
<tr>
<td>B</td>
<td>F.A.V.</td>
<td>ALL</td>
<td></td>
</tr>
<tr>
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<td>M.A.R.</td>
<td>ALL</td>
<td></td>
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<td>G.I.L.</td>
<td>AML</td>
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</tr>
<tr>
<td>B</td>
<td>A.R.I.</td>
<td>ALL</td>
<td></td>
</tr>
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</table>

Leukocyte antigens determined on leukoblasts from 23 patients with acute leukemia. ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; AHL, acute hemocyto- blastleukemia.

Table 2

<table>
<thead>
<tr>
<th>Serum No.</th>
<th>Specificity</th>
<th>Before absorption</th>
<th>Absorbed with blasts</th>
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<tr>
<td>A 9</td>
<td>anti 1</td>
<td>85 64</td>
<td>1 2 3 4 5 6 7 8 9 10 11 12</td>
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</tr>
<tr>
<td>A 45</td>
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<tr>
<td>A 4</td>
<td>anti 4</td>
<td>73 6 nd</td>
<td></td>
</tr>
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<td>A 35</td>
<td>anti 5</td>
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</tr>
<tr>
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<td>?</td>
<td>100 27 5 40 74 7</td>
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</tr>
<tr>
<td>BER.</td>
<td>?</td>
<td>100 93 5 22 nd</td>
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</table>

Absorption of isoimmune sera with leukoblasts. Numbers indicate the percentage of cells stained by trypan blue when absorbed serum is retested on normal positive lymphocytes. nd, not done; Ag, antigen.

blasts bearing the corresponding antigen. Within the limits of our experimental conditions, and as far as antigens 1, 3, 4, 6, and 7 are concerned, it confirms that leukoblast cells possess antigens present on normal lymphocytes. Quantitative absorption experiments are under study, and preliminary results have shown that the amount of antigen 1 on leukoblasts is not significantly different from that of normal lymphocytes.

Comparison Between Cytotoxic Tests Performed on Leukoblasts and Lymphocytes from the Same Patient in Remission.

Leukocyte groups were determined in 17 patients, on their leukoblasts before treatment, and then on their morphologically normal leukocytes or lymphocytes during the complete remission. The results of the cytotoxic tests performed with the 36 sera of battery B on leukoblasts and lymphocytes from 8 patients (6 acute lymphoblastic leukemias and 2 acute myeloblastic leukemias) are shown in Table 3. It can be seen that the leukocyte antigens remain unchanged. It should be noted that occasional variations in the reactivity of some immune
Comparison between leukocyte antigens determined on the leukoblasts and the lymphocytes from the same patient. Bl, leukoblasts; Ly, lymphocytes; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia.

<table>
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<tr>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<th>9</th>
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<td>-</td>
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<td>-</td>
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<td></td>
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DISCUSSION

The twelve leukocyte antigens studied, as determined with human isoimmune sera by the method of cytotoxicity in vitro, can be detected on leukoblasts from patients with acute leukemia. Some differences exist between tissue typing performed on leukemic cells and on normal lymphocytes. In animals, leukemic cells are known to be more sensitive to immune lysis than sarcoma and epithelial cells or normal lymphocytes (12-25). Similarly, human malignant leukoblasts (14) appear to be more sensitive than normal lymphocytes to the cytolytic activity of heterophile antibodies present in fresh rabbit serum used as a source of complement. Titers of human isoimmune sera, observed in the presence of nontoxic, exhaustively absorbed rabbit complement, are generally higher with leukoblasts than with normal lymphocyte suspensions. The greater sensitivity of leukemic cells to immune lysis may be due to particular properties of the cell membrane, or to differences in surface antigen concentration. As antileukocyte antibody specificities are determined by testing normal lymphocytes, the rise of the level of sensitivity of cytotoxic tests performed on leukemic cells might be responsible for the appearance of additional antileukocyte antibody specificities in some immune sera which are not monospecific for one leukocyte antigen. This possibility has been eliminated by the simultaneous use of several antisera for the detection of each leukocyte antigen, and by absorption of antisera determining antigens 1, 3, 4, 6, and 7.

The leukocyte group as defined on leukoblasts (myeloblasts or lymphoblasts) from patients with acute leukemia does not change when determined on morphologically normal lymphocytes from the same patient during the remission period. Similarly, no differences are observed in the antigenic pattern of myeloblasts, lymphoblasts, or hemocytoblasts, when com-
pared to that of the whole leukocyte suspension (containing polymorphonuclear leukocytes) from the same patient in remission. A few occasional variations in the reactivity of some immune sera, when tested on leukoblasts and then on lymphocytes from the same patient, were observed with very weak reactions, at the threshold of sensitivity of the technique. These rare variations do not affect the leukocyte antigen determination, since the reactivity of one antiserum is usually controlled by that of other antisera with the same specificity. This study failed to show any qualitative loss of leukocyte alloantigens in the leukoblasts tested. The 12 antigens studied here represent most of the antigens defined for the time being (5) but some antigens, such as antigens PGrLyF1 (3), 7a, 7b, and 9a (27), and 5a and 5b (16) have not been determined in our study. The list of leukocyte antigens is, of course, provisional: among the isimmune sera used in the present work were included several sera the specificity of which is still unknown.

The presence of the leukocyte antigens on human leukoblasts has several implications of clinical interest. The determination of the leukocyte group of a patient during the acute phase of the disease may make possible ultimately the choice of the best donors for leukocyte transfusions when needed in the case of bone marrow failure induced by chemotherapy; the value of leukocyte typing in the determination of homograft-histocompatibility is now well established for skin grafts (7) and kidney grafts (8); and selection of donors may also improve the efficiency of white cell transfusions.

Strong antileukocyte immunization can be elicited by allogetic leukocytes of chronic myelocytic leukemia (3). Similar immunization is to be expected upon injection of allogetic leukemic leukoblasts into patients, as in the course of active immunotherapy trials (20), and can later lead to posttransfusion shocks.

The in vitro sensitivity of leukemic leukoblasts to antileukocyte antibodies has been confirmed in vivo (C. Dresch and F. M. Kourilsky, unpublished data). Allogeneic malignant leukoblasts, labeled in vitro with 31Cr (10), disappeared very rapidly from the circulation when they were reinjected intravenously into leukemic patients with acute leukemia having posttransfusion antileukocyte antibodies. The kinetics of the disappearance of radioactivity from the peripheral blood in allogenic transfused patients was not significantly different from that observed in the autologous donor of leukoblasts.

The study of the distribution of leukocyte antigens in leukemic patients as compared with normal population is interesting, since an association between histocompatibility-2 locus and the genetic susceptibility to leukemias induced by Gross and Friend viruses in mice, have been demonstrated recently (17, 18). If such a situation exists in human leukemia, the repartition of leukocyte antigens, which represents, for the time being, the best serologic approach to histocompatibility antigens in man, could be different in patients with acute leukemia. The small number of patients studied in the present work does not allow any valid statistical analysis. Nevertheless, no particular phenotype appears to be specific for the patients with acute lymphoblastic or myeloblastic leukemia, whether they are going into remission or dying during the acute phase of this disease. The detailed analysis of the repartition of the leukocyte antigens was made in a population of 116 patients with acute leukemia in remission, as compared with 234 nonleukemic individuals (15), and showed no significant differences in the frequency and the repartition of leukocyte antigens between the two groups.

It was already known that leukoblasts react with leukocyte alloantibodies used in leukoagglutination (4). This present work shows that the leukoblasts of acute leukemia apparently do not lack any of the normal leukocyte antigens tested. This does not exclude quantitative alterations of antigenicity of these malignant cells. Boyse et al. (2) recently demonstrated that the presence of the thymus leukemia antigen in mice was associated with a diminution of the expression of histocompatibility antigen (H-2b) on thymus cells. Diminution of erythrocyte alloantigens ABH and I (1, 19) have been found in acute leukemia, especially in the myeloblastic forms. Such antigenic alterations may be the consequences of factors alien from the cell, like mycoplasmas (29), or related directly to antigenic modifications of the cell structure during malignancy.

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REFERENCES


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