A Possible Immune Reaction Producing Spontaneous Remission in Leukemia

By Luther L. Burkett, Murray L. Fields and Lemuel W. Dice

LONG PERIODS of latency, spontaneous remissions and nonsurgical “cures” in a variety of malignancies have stimulated speculation and experimentation concerning immunity in cancer, a subject recently reviewed generally,\(^1,2\) and in reference to specific immune mechanisms\(^3,4\) of tumor inhibition and rejection. Acceptance of an immune theory in spontaneous cancer control demands demonstration of tumor-specific antigens, which has been accomplished in carcinogen-induced and transplanted tumors. Such direct evidence in spontaneous neoplasia is yet meagre, although differing antigenicity of normal and leukemic tissue of human source has been reported,\(^5\) and specific antigens have been found in spontaneous mouse leukemia\(^6\) and in human renal carcinoma.\(^7\) Other evidence has been indirect and has consisted of the local or reticuloendothelial accumulation of cells concerned with immune reactions, i.e., plasma cells and lymphocytes. The following case is of interest in this regard because of the sequential development of a brisk bone marrow plasmocytosis with Bence Jones proteinuria and spontaneous remission in acute leukemia.

METHODS

Blood counts were done by standard technics\(^8\) and platelet counts by the Rees-Ecker method.\(^9\) Bone marrow aspirates were prepared with a Wright-Giemsa stain; differential counts included 500 nucleated cells. Serum electrophoresis was performed on filter paper, using the Beckman-Spinco apparatus, and scanned with the Spinco Analytrol after staining with bromphenol blue. Urines were screened for Bence Jones protein by the method of Putnam et al.\(^9\) Positive urines were then subjected to thermal testing by the procedure of Jacobson and Milner.\(^10\)

CASE REPORT

A 49-year-old negro male was found to be severely anemic in December, 1959 after delayed healing of a traumatic ulcer of the left leg. Films of blood and bone marrow referred to one of us (L. W. D.) showed a predominance of blasts and red cell precursors in both, suggesting erythroleukemia (table 1, fig. 1A). Five blood transfusions were given and he was transferred to the Veterans Administration Hospital, Memphis, Tennessee on January 21, 1960.

Physical examination revealed oral temperature 101 F., a few crepitant rales at the right lung base, and two clean ulcers over the left thigh and lower leg. Sternal tenderness, lymphadenopathy, and hepatosplenomegaly were not found.

Blood count showed pancytopenia (table 1) with a differential white cell count of 29 per cent segmented neutrophils, 69 per cent lymphocytes and 2 per cent monocytes; no immature white cells or nucleated red cells were seen. Bone marrow was of normal cellu-
larity with a slight increase in myeloblasts and progranulocytes and moderate increase in plasma cells (18 per cent) (table 1, fig. 1B).

Two of three urine specimens were positive for Bence Jones protein. Serum electrophoresis showed decreased albumin and increased, peaked gamma fraction (fig. 2). Sia test was negative and a cryoglobulin was not demonstrable.

Chest x-ray revealed an infiltrate in the right lower lung field having the appearance of pneumonitis. Abnormal radiolucencies in the proximal humeri and femora were suspected from initial bone films, but later x-rays were considered normal. A lymph node
Table 1

<table>
<thead>
<tr>
<th>Date</th>
<th>WBC/cu. mm</th>
<th>% blasts</th>
<th>Nucleated</th>
<th>RBC/100 WBC</th>
<th>Hematocrit %</th>
<th>Reticulocytes %</th>
<th>Platelets/cu. mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec. 29, 1959</td>
<td>—</td>
<td>65</td>
<td>53</td>
<td>50/100</td>
<td>11.0</td>
<td>1.4</td>
<td>50/100</td>
</tr>
<tr>
<td>Jan. 22, 1960</td>
<td>900</td>
<td>0</td>
<td>0</td>
<td>68,000</td>
<td>26</td>
<td>1.4</td>
<td>68,000</td>
</tr>
<tr>
<td>Feb. 16, 1960</td>
<td>3400</td>
<td>0</td>
<td>0</td>
<td>254,000</td>
<td>39</td>
<td>5.2</td>
<td>254,000</td>
</tr>
<tr>
<td>Mar. 22, 1960</td>
<td>5600</td>
<td>0</td>
<td>0</td>
<td>242,000</td>
<td>39</td>
<td>2.0</td>
<td>242,000</td>
</tr>
<tr>
<td>Sept. 19, 1960</td>
<td>92,000</td>
<td>97</td>
<td>2</td>
<td>84,000</td>
<td>9</td>
<td>2.4</td>
<td>84,000</td>
</tr>
</tbody>
</table>

Blood

Bone Marrow

<table>
<thead>
<tr>
<th></th>
<th>Blasts</th>
<th>Progranulocytes</th>
<th>Other granulocytes</th>
<th>Lymphocytes</th>
<th>Monocytes</th>
<th>Plasma cells</th>
<th>RBC precursors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.5</td>
<td>1.5</td>
<td>66.0</td>
</tr>
<tr>
<td></td>
<td>8.6</td>
<td>4.2</td>
<td>13.6</td>
<td>19.8</td>
<td>2.8</td>
<td>18.0</td>
<td>33.0</td>
</tr>
<tr>
<td></td>
<td>3.2</td>
<td>3.2</td>
<td>24.6</td>
<td>11.6</td>
<td>4.4</td>
<td>1.8</td>
<td>51.2</td>
</tr>
<tr>
<td></td>
<td>80.2</td>
<td>1.4</td>
<td>0.8</td>
<td>7.8</td>
<td>0.4</td>
<td>1.0</td>
<td>8.6</td>
</tr>
</tbody>
</table>

obtained by supraclavicular fat pad biopsy showed reticuloendothelial hyperplasia. Other abnormal laboratory findings included a serum bilirubin of 1.9 mg./100 ml. with a direct fraction of 1.0 mg./100 ml., serum alkaline phosphatase of 7.0 Bodansky units, thymol turbidity of 6.25 units, a trace of albumin in the urine and 1–3 red cells in the urine sediment per high power field. Normal or negative studies included direct Coombs test, serologic tests for syphilis, serum glutamic oxaloacetic transaminase, serum calcium and inorganic phosphorus, stool Guaiac test, blood culture, gastric analysis and electrocardiogram.

Therapy consisted of chloramphenicol 0.5 Gm. and novobiocin 0.5 Gm. every 6 hours for 6 days followed by procaine penicillin 600,000 units and streptomycin 0.5 Gm. intramuscularly twice daily for 8 days; 500 ml. of blood were administered on the second day and 1000 ml. on the 15th day. Gradual defervescence over a period of 9 days resulted and the right lower lung infiltrate cleared. Ulcerations of the left leg rapidly healed. In spite of improvement the spleen became palpable two fingerbreadths below the left costal margin and remained palpable throughout the further course of 3 months hospitalization, although decreasing in size. Blood picture also gradually improved (table 1) and bone marrow aspirate on February 16, 1960 was considered normal except for erythroid hyperplasia (table 1). Serum electrophoresis on March 29, 1960 showed increase in albumin and decrease in gamma fraction which was less peaked (fig. 2). Later urines were negative for Bence Jones protein. He was discharged on April 15, 1960.

The patient reentered the hospital 5 months later on September 19, 1960 with complaints of sore throat for 1 week and fever and dyspnea for 3 days. In the interval he had remained well except for slight weakness. Examination revealed oral temperature 102.2 F., enlarged anterior cervical nodes, and fine crackling rales in both lung bases; the liver was palpable two fingerbreadths below the left costal margin and remained palpable throughout the further course of 3 months hospitalization, although decreasing in size. Blood picture also gradually improved (table 1) and bone marrow aspirate on February 16, 1960 was considered normal except for erythroid hyperplasia (table 1). Serum electrophoresis on March 29, 1960 showed increase in albumin and decrease in gamma fraction which was less peaked (fig. 2). Later urines were negative for Bence Jones protein. He was discharged on April 15, 1960.

Despite therapy with tetracycline, procaine penicillin, whole blood, metaraminol and intravenous hydrocortisone, he expired in shock the following day. Postmortem examination revealed leukemic infiltration in marrow from the sternum, rib and lumbar vertebra and in lungs, heart, spleen, liver, lymph nodes, kidneys and pituitary gland.
Fig. 1C.—Bone marrow 9/19/60: myeloblastic leukemia.

DISCUSSION

Questions posed by the sequence of events in this patient are could the picture of a plasmocytic dyscrasia have represented an immunologic reaction induced by the leukemia, and could it have produced the spontaneous remission which immediately followed? Lacking confirmation by precise immunologic methods, definite conclusions can not be drawn, although the temporal relationship of events is suggestive, particularly when considered in the light of previous experimental and clinical observations. Local and reticuloendothelial plasmocytic reactions have been noted in animals with transplanted or carcinogen-induced tumors,11,12 and the intensity of the reaction has been correlated with tumor inhibition and destruction.13,14 Although carcinoma is a recognized cause of bone marrow plasmocytosis,15 its occurrence and prognosis have not been correlated. However, Berg16 has found an improved prognosis in patients with breast cancer who had local inflammatory reaction consisting predominantly of plasma cells.

Another question posed by the case reported is the significance of the Bence Jones proteinuria. “Abnormal” serum and urinary proteins are generally considered to be products of malignantly transformed plasma cells or lymphocytes. However, recent widespread use of serum electrophoresis and ultracentrifugal analysis has disclosed paraproteinemia in association with neoplasms other than myeloma and primary macroglobulinema.17-19 Bence Jones protein has also been found in the urine of patients with carcinomas, bone tumors and leukemia.20-22 Since it is unlikely that the neoplastic cells in these cases produced the paraproteins, it is possible that “abnormal” proteins may result from stimulation by antigenic components of certain neoplasms, rather than
SPONTANEOUS REMISSION IN LEUKEMIA

A /25/60

I 7 0.6
1.0 0.9
3
Gm /IOOmI
3.1 0.3 0.7 0.9 2 5 Gm /IOOmI

Total Protein: 7.3 Gm /lOOml. Total Protein: 7.5 Gm./lOOml

Fig. 2.—Serum electrophoresis.

from malignant change in their cells of origin, a postulate recently offered by Osserman and Takatsuki.17

Previously reported cases of breast carcinoma23 and lymphoma24 have demonstrated both paraproteinemia and intense plasmocytic reactions in blood and bone marrow. Unfortunately the effect of the reaction on the course of the disease can not be assessed definitively in either case because of excisional biopsy in the former and urethane therapy in the latter. It would be of great interest to evaluate future cases of a similar nature for evidence of remission and improved prognosis.

SUMMARY

A patient is described in whom four phases of illness were recognized: (1) erythroleukemia, (2) brisk bone marrow plasmocytosis with Bence Jones protein in the urine suggesting multiple myeloma, (3) normality physically and of blood and bone marrow, with the exception of slight splenomegal., (4) myeloblastic leukemia with death from Pseudomonas septicemia.

Local and reticuloendothelial plasmocytic reactions have been observed in experimental animals and in man with malignant disease, and this occurrence has been related to tumor inhibition and improved prognosis. Paraproteinemia and paraproteinuria have been noted in malignancies other than those arising from plasma cells or lymphocytes.

It is suggested that the plasmocytosis and abnormal protein in the case reported, as well as in other similar cases previously reported, may have represented an immune reaction induced by the malignancy and responsible for its remission.

SUMMARIO IN INTERLINGUA

Es describite le caso de un patiente in qui quatro phases de maladia eseva recognoscite: (1) Erythroleucemia, (2) plasmocytosis del medulla ossee con proteïna de Bence Jones in le urina (lo que suggestionava myeloma multiple), (3) normalitate physic e del sanguine e medulla ossee, con le exception de un
leve grado de splenomegalia, e (4) leucemia myeloblastic con morte per septicemia a Pseudomonas.

Plasmocytic reactiones local e reticuloendothelial ha essite observate in animales experimental e in humanos con morbo maligne, e iste occurrentia ha essite relationate con inhibition de tumor e melioration del prognose. Para-proteinemia e paraproteinuria ha essite notate in malignitates altere que illos resultante de plasmocytos o lymphocytos.

Es postulate le possibilitate que le plasmocytosis e le proteina anormal in le caso hic reportate e etiam in altere simile casos previamente reportate representava un reaction immunologic que esseva inducite per le malignitate e que esseva responsabile pro su remission.

REFERENCES


Luther L. Burkett, M.D., Chief of General Medicine and Hematology Section, Medical Service, Veterans Administration Hospital, Memphis, Tennessee; Assistant Professor of Medicine, University of Tennessee, College of Medicine, Memphis, Tenn.

Murray L. Fields, M.D., Chief of Radioisotope Service, Veterans Administration Hospital, Memphis, Tennessee; Assistant Professor of Medicine, University of Tennessee, College of Medicine, Memphis, Tenn.

Lemuel L. Diggs, M.D., Professor of Medicine, University of Tennessee, College of Medicine, Memphis, Tennessee; Consultant in Hematology, Veterans Administration Hospital, Memphis, Tenn.
A Possible Immune Reaction Producing Spontaneous Remission in Leukemia

LUTHER L. BURKETT, MURRAY L. FIELDS and LEMUEL W. DIGGS