Acquired Angioedema With Lymphoproliferative Disorder: Association Of C1 Inhibitor Deficiency With Cellular Abnormality

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A patient with a lymphoproliferative disorder, angioedema, and an acquired deficiency of the inhibitor of the activated first component of complement was studied. The patient's complement profile revealed depletion of the first component of complement, which has not been seen in angioedema of the hereditary type. There was no evidence for C1-depleting activity in the patient's plasma. The majority of the patient's peripheral blood mononuclear cells resembled B cells in their membrane receptor properties and in that they carried easily detectable immunoglobulin, predominantly IgM. However, these cells were unusual in that they phagocytosed both latex particles and C3-coated erythrocytes. Morphological study of the cells infiltrating the patient's lung revealed immature, atypical, and plasmacytoid lymphocytes and immunoblasts. Both the patient's peripheral blood mononuclear cells and a suspension of cells from the pulmonary infiltrate were capable of depleting the first component of complement and its inhibitor from homologous plasma. Normal ABO-compatible cells did not possess this property. The data suggested that the patient's abnormal lymphoid cells may have interacted with the complement system to produce a biochemical defect and a clinical syndrome closely resembling angioedema of the hereditary type.

ABNORMALITIES in serum complement have been observed in a variety of human pathologic states, usually associated with immune complex disease. In addition, a variety of inherited human complement disorders have been described involving deficiencies of individual complement components or control proteins in the complement pathways. One such disease, hereditary angioedema, is characterized by a marked deficiency of the inhibitor of the activated first component of complement (C1 INH). C1 INH deficiency results in secondary depletion of the fourth (C4) and second (C2) components, but serum levels of the first complement component (C1) and the terminal complement components (C3-9) remain normal.

One previous patient with angioedema and acquired C1 INH deficiency has been reported in detail. We report a second patient with a lymphoproliferative disorder, acquired C1 INH deficiency, and angioedema. The mononuclear cell...
abnormality has been characterized and its relationship to the complement alterations examined. Evidence is presented to suggest that the patient's abnormal lymphoid cells may interact directly with the complement system.

**MATERIALS AND METHODS**

**Complement Studies**

Fresh-frozen guinea pig serum (Rockland, Gilbertsville, Pa.) and goat anti-C1 INH antisera (Miles Laboratories, Kankakee, Ill.) were obtained as indicated. Partially purified guinea pig C2 and human Cl were prepared by modification of established methods. Cells coated with hemolytic antibody and the fourth component of complement (EAC4), and the first component of complement (EAC1) were prepared as previously described and utilized to prepare the additional complement intermediates, EAC14 and EAC142. Individual complement components and Cl INH, the inhibitor of activated Cl, were quantitated by effective molecule titration, utilizing the appropriate complement intermediate. C3-9 serum levels were also determined by effective molecule titration, using the intermediate EAC142 and human serum diluted in ethylenedinitrilotetraacetic acid buffer.

**Cell Studies**

Mononuclear cells were separated from heparinized human peripheral blood by Ficoll-Hypaque density gradient centrifugation. The E10, EAC11, and EA12 rosette methods were utilized to assess the cell surface receptors of T cells, B cells, and monocytes, respectively, in the mononuclear cell population. B cells were also quantitated by the binding at room temperature to mononuclear cell membrane immunoglobulin of fluorescinated antihuman antisera monospecific for the immunoglobulin class (Behring Diagnostics, Somerville, N.J.). Phagocytic activity of mononuclear cells was assessed by suspending $1 \times 10^6$ cells in 1 ml of Medium 199 (Microbiological Associates, Bethesda, Md.). Latex particles 1.0 μm in diameter (Difco, Detroit, Mich.) were added at 37°C for 30 min. Smears were then prepared and stained with Sudan Black.

The in vitro proliferative responses of mononuclear cells to phytohemagglutinin (PHA-M, Difco, Detroit, Mich.) and pokeweed mitogen (PWM, Grand Island Biological Co., Grand Island, N.Y.) were examined by culturing $1 \times 10^6$ cells in 1 ml of 10% autologous plasma-Medium 199 for 3 days in a humid atmosphere of 5% CO2 in air. The degree of proliferative response was assayed as described previously.

**Preparation of Enriched T- and B-Cell Suspensions**

Peripheral blood mononuclear cells collected by Ficoll-Hypaque density gradient centrifugation were allowed to form E rosettes. Following 1 hr incubation at 4°C, the rosettes were suspended gently. The suspension was then diluted with chilled Medium 199 in a ratio of two volumes of the rosette suspension to one volume of the medium. Five parts of the diluted rosette suspension were then layered on three parts Ficoll-Hypaque gradient. The tubes were spun at 700 g for 35 min at 10°C. Cells in the upper layer of the gradient were found to be predominantly T cells (95% ± 4%), whereas those in the pellet were predominantly B cells (91% ± 8%). Sheep red cells in the pellet were lysed by hypotonic shock and both the B and T cells were washed with Medium 199 before use.

**Adsorption Studies**

Washed mononuclear cells obtained from the peripheral blood of both normal volunteers and patient B.T. were employed. Suspensions of washed cells obtained from tissues were also utilized. Six $\times 10^6$ cells were incubated with 0.2 ml plasma, serum, or partially purified Cl on a rotator at 37°C for 30 min. Cells were centrifuged at 4°C and the cell-free supernatant either placed at –70°C or assayed immediately for Cl and C1 INH.
Morphological Studies

Tissue for light microscopic studies was fixed in Bouin’s solution, embedded in paraffin, cut at 5 μ, and stained with either hematoxylin and eosin, methyl green pyronin, or periodic acid-Schiff. Tissue obtained from a lung biopsy was also fixed in Zamboni’s fixative for transmission electron microscopy. Tissue was postfixed in 1% osmium tetroxide in cacodylate buffer and embedded in epoxy resin. Thick sections for survey were stained with alkaline toluidine blue, and thin sections were stained with lead hydroxide and uranyl acetate.15

Patient Summary

B.T. was a 73-yr-old man admitted to the Hospital of the University of Pennsylvania on December 4, 1974, because of laryngeal edema. He had two children and no surviving siblings. There was no familial or past history of angioedema. He was well until March 1974, when he developed fever, malaise, weight loss, and increasing hoarseness. He was admitted to the University Hospital for these symptoms in June 1974, at which time significant physical findings consisted of enlarged submandibular glands, temperatures varying between 100°F and 102°F, mild pallor, and a slightly enlarged liver. A biopsy of the enlarged salivary gland revealed periductal and periacinar collections of atypical histiocytes; atypical lymphocytes with indented and lobulated nuclei and plasmacytoid lymphocytes; as well as larger histiocytic cells with round vesicular nuclei, prominent nucleoli, and eosinophilic cytoplasm. This latter population of cells was called “immunoblasts”18 by the pathologists. There were also plasma cells, fibrosis, and destruction of focal areas of gland parenchyma.

The patient manifested continued malaise and fever. His final admission 5 mo later was precipitated by two attacks of laryngeal edema and stridor. The first attack led to his admission to another hospital where an emergency tracheostomy was performed. He was discharged after improvement, but 1 mo later developed a second attack, was brought to our emergency ward and immediately admitted.

The patient appeared chronically ill. He had marked laryngeal stridor and angioedema of the face. The tongue was swollen, and the larynx and vocal chords were edematous. Bibasilar inspiratory rales were present in his lungs. He appeared somewhat pale. The temperature was 101°F; the remainder of his physical examination was not remarkable.

Laboratory studies were as follows: the hemoglobin was 9.9 g/100 ml. The WBC count was 11,700/cu mm, with 85% mature granulocytes. The 15% mononuclear cells appeared normal and mature by light microscopy. The platelet count was 240,000/cu mm. The sedimentation rate was 68 mm/hr (Westergen). The following values were normal or negative: blood sugar, blood urea nitrogen, serum electrolytes, serum creatinine, urinalysis, serum transaminase, alkaline and acid phosphatases, rheumatoid factor, LE cell preparation, cold agglutinins, and anti-nuclear antibodies. Numerous cultures of the blood, urine, and sputum revealed no pathogens. Bone marrow aspirate was normocellular, with a normal M:E ratio; no abnormal cells were seen. The chest x-ray showed patchy infiltrates in both lower lung fields. X-rays of the GI tract were normal. Isotopic liver and spleen scan showed mild splenomegaly. Serum protein electrophoresis revealed 5.5 g of protein with slight hypogammaglobulinemia (0.78 g), and an immunoelectrophoresis showed increased IgM with a small anodal IgM band. Serum quantitative immunoglobulin (Ig) determinations using quantitative immunodiffusion plates (Meloy Laboratories, Springfield, Va.) revealed IgG 540 mg/100 ml (normal = 548-1768), IgA 72 mg/100 ml (normal = 78-322), and IgM 712 mg/100 ml (normal = 78-153). In order to assess whether the increased IgM in his serum was due to an increase in pentameric (normal IgM) or monomeric IgM, 3.5 ml of serum were fractionated by upward flow by Sephadex G-200 chromatography (5 x 100 cm).8 All antigenically detectable IgM (Ouchterlony analysis) eluted in the void volume coincided with 900,000 molecular weight IgM. The patient’s serum complement profile is summarized in Table 1.

The patient continued to deteriorate, with increasing fever, worsening anemia, further weight loss, and increasing pulmonary infiltrates. On January 2, 1975 an open lung biopsy was performed. The lung tissue showed soft whitish nodules 1-2 mm in diameter. Microscopically the peribronchial, perivasculare, septal, and subpleural interstitial spaces were infiltrated with a mixed population of lymphocytes, plasma cells, immunoblasts, and atypical histiocytes (Fig. 1).
The infiltrate was essentially the same as that seen in the salivary gland, with fewer atypical lymphocytes and histiocytes. Methyl green pyronin stain for RNA showed that many of the cells were strongly positive. In addition to the infiltrate, there was interstitial fibrosis and organizing bronchiolitis obliterans. Cultures were sterile.

Electron microscopic studies revealed that the lymphoid infiltrate was composed mostly of cells with eccentric oval-shaped nuclei, finely dispersed chromatin, and prominent nucleoli (Fig. 2). The cytoplasm contained abundant rough endoplasmic reticulum containing slightly granular electron-dense material (Fig. 3).

Therapy was begun with cyclophosphamide and corticosteroids. The patient showed an initial improvement, but over the next 4 mo deteriorated and died of respiratory failure secondary to the underlying disease, with superimposed pulmonary infections with *Pneumocystis carinii* and *Candida albicans*. No alteration of his complement profile was noted with therapy, but no attacks of angioedema occurred during his hospitalization. Because of a decline in the number of circulating
Fig. 2. Low-power electron microscopic view of the lymphoid cells infiltrating the pulmonary parenchyma. Three plasmacytoid lymphocytes are seen; they are characterized by a round nucleus with finely dispersed chromatin and a prominent nucleolus. The cytoplasm contains abundant rough endoplasmic reticulum. Bar represents 1 μm.

Fig. 3. A higher magnification of the plasmacytoid lymphocytes illustrated in Fig. 2. The prominent rough endoplasmic reticulum and immature nucleus are apparent. Bar represents 1 μm.
mononuclear cells with corticosteroid and cyclophosphomide therapy, additional morphological studies of these cells were not undertaken.

At autopsy the infiltrate described previously was still present in the lungs but slightly less prominent and had a patchy distribution. A similar infiltrate was present in the supravclavicular, tracheal, and hilar lymph nodes. However, the nodal architecture was preserved. There was no involvement of the parotid gland, liver, spleen, bone marrow, or abdominal lymph nodes.

RESULTS

Patient B.T.'s serum complement profile is shown in Table 1. Although C3–9 levels and C3 determined antigenically by radial immunodiffusion (not shown) were normal, C1 was 8% and C2 and C4 <4% of normal. C7 INH was 6% of normal. In addition, C7 INH was undetectable as a protein by Ouchterlony analysis. However, C7 INH and C4 levels in the patient's two asymptomatic children were within the normal range. These studies suggested that the patient had acquired C7 INH deficiency, and the mechanism of C7 INH and C1 depletion was explored.

In order to determine whether the profound C1 depletion was caused by circulating anticomplementary activity in B.T. serum causing C1 consumption, B.T. serum was incubated with equal volumes of buffer or normal sera for 30 or 50 min at 37°C and sedimented at 40,000 g for 15 min. The supernatants were harvested and assayed for C1 activity. Sera from two normal individuals served as controls. Incubation of the normal sera with buffer or with each other reduced the C1 titer to that predicted by dilution (Fig. 4A). Similarly, incubation of B.T. serum with normal serum reduced the C1 titer to a level predicted by dilution alone. The results were similar whether incubation was for 30 or 50 min and when B.T. serum was incubated with three different normal control sera.

A supernatant extract obtained from the lung biopsy was also examined for C1-depleting activity. A minced suspension of the lung biopsy was suspended in 0.15 M NaCl at room temperature for 30 min, sedimented, and the supernatant extract harvested. The extract had an optical density of 1.100 at 280 mμ and contained 500 μg/ml protein by Folin analysis. C1 consumption was assessed as above after incubation with normal human serum and partially purified C1 as complement substrate. Incubating equal volumes (0.5 ml) of the lung extract with serum or C1 at 37°C for 50 min did not result in C1 depletion (Fig. 4B).

In the absence of evidence for serum or soluble complement-depleting activity, we studied the patient's peripheral blood mononuclear cells separated on a Ficoll–Hypaque gradient. The percentages of the mononuclear cell types in B.T. peripheral blood are shown in Table 2. The percentage of E-rosetting cells was significantly lower than normal, whereas 70% of the mononuclear cells in B.T. peripheral blood formed EAC rosettes (compared to 16% ± 5% in normals). Approximately half of the EAC were found within, as well as surrounding B.T. mononuclear cells. A similar percentage of B.T. cells was also capable of ingesting latex particles (69% compared to 8% of normal cells). These phagocytic cells also stained with Sudan Black, a property associated with monocytes. However, the percentage of B.T. peripheral blood mononuclear cells possessing the monocyte surface receptor for the Fc portion of
ACQUIRED ANGIOEDEMA

Fig. 4. (A) Bars indicate C1 titer following incubation of either two normal sera or normal serum with B.T. serum. No C1-depleting activity was detected in B.T. serum. (B) Bars indicate C1 titer following incubation of lung biopsy extract with normal human serum (NHS) or partially purified C1. No C1-depleting activity was detected in the extract.

Table 2. Characterization of Peripheral Blood Mononuclear Cells

<table>
<thead>
<tr>
<th>Technique Used</th>
<th>Patient</th>
<th>Controls*</th>
</tr>
</thead>
<tbody>
<tr>
<td>E rosettes</td>
<td>31</td>
<td>63 ± 5</td>
</tr>
<tr>
<td>EAC rosettes</td>
<td>70†</td>
<td>16 ± 5‡</td>
</tr>
<tr>
<td>Surface Ig</td>
<td>62</td>
<td>23 ± 9</td>
</tr>
<tr>
<td>Whole§</td>
<td>51</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>IgM</td>
<td>16</td>
<td>17 ± 7</td>
</tr>
<tr>
<td>IgG</td>
<td>4</td>
<td>2 ± 2</td>
</tr>
<tr>
<td>IgA</td>
<td>15</td>
<td>11 ± 5</td>
</tr>
<tr>
<td>EA rosettes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latex particle ingestion</td>
<td>69¶</td>
<td>8¶</td>
</tr>
</tbody>
</table>

*Data expressed as ± 2 SD or results with parallel normal control (experiment with latex particle ingestion).
†Fifty per cent of EAC rosetting cells have ingested red cells.
‡None of the EAC-rosetting mononuclear cells have ingested red cells.
§Antiserum raised against all immunoglobulin (Ig) classes.
¶All phagocytic cells when stained with Sudan Black were positive.
Table 3. In Vitro Proliferative Response of Peripheral Blood Mononuclear Cells in Presence of Mitogens

<table>
<thead>
<tr>
<th>Cell Source</th>
<th>Unstimulated Cultures (cpm)*</th>
<th>S/t in presence of PHA</th>
<th>PWM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>326 62 3 109 57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal Control</td>
<td>372 125 7 62 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal Range†</td>
<td>80-210 6-20 46-80 4-22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Three days' culture.
†Stimulation index: ratio of counts per minute (cpm) of stimulated cultures over cpm of stimulated cultures.
‡Fifty normals obtained in our laboratory.

IgG (binding EA indicator cells) was not significantly increased (15% versus 11% for normal). In addition, the majority of B.T. mononuclear cells carried surface immunoglobulin of the IgM class, suggesting identity as B lymphocytes. B.T. peripheral blood mononuclear cells also responded well to pokeweed mitogen, and somewhat less effectively to the mitogen phytohemagglutinin (Table 3). Thus, the majority of the mononuclear cells in B.T. blood appeared to have some characteristics of monocytes and other properties suggesting B lymphocytes.

The possible interrelationship between the mononuclear cell and serologic abnormalities was next assessed. The capacity of B.T. peripheral blood mononuclear cells to deplete C1 and C1 INH at 37°C from homologous ABO compatible sera was studied (Table 4). B.T. cells depleted 55% of C1 and 50% of C1 INH activity from control No. 2 serum, while the normal cells did not deplete either C1 or C1 INH. In addition, B.T. cells depleted 72% of C1 from control No. 3 serum. However, neither B.T. cells nor control No. 2 cells depleted C1 or C1 INH from control No. 1 serum. Thus, B.T. cells were capable of depleting C1 and C1 INH activity from some, but not all, compatible sera.

Three additional experiments were performed to examine the interactions between normal mononuclear cells and homologous serum C1 and C1 INH. First,
three additional normal sera were incubated with homologous ABO-compatible mononuclear cells at 37°C. Less than 20% depletion of C1 was observed in each case. Second, normal serum (0.2 ml) was incubated, with increasing concentrations of normal ABO-compatible mononuclear cells (6, 18, and 30 x 10⁶ cells) at 37°C for 30 min. No C1 or C1 INH depletion was observed, even when the number of mononuclear cells was fivefold greater (30 x 10⁶ cells) than that of the B.T. cells used in the comparative experiments described above (Fig. 5). In addition, since B.T. peripheral blood mononuclear cells resembled B cells primarily, rather than T cells, we examined the capacity of B cell-enriched populations obtained from normal blood to deplete C1 from plasma (autologous and homologous) and from a solution of partially purified C1. Normal B or T cells did not deplete partially purified C1 or deplete C1 from autologous or homologous plasma (Table 5). Thus, it appeared that the C1-depleting activity of B.T. mononuclear cells could not be accounted for on the basis of an increased percentage of normal B lymphocytes, but rather appeared to be due to a unique characteristic of B.T. mononuclear cells.

We also examined the capacity of the cells obtained at lung biopsy and from the lung lesion at autopsy to interact with C1 and C1 INH. Controls consisted of equal numbers of cells obtained from a normal lymph node and normal lung at autopsy (Table 6). The cells obtained at lung biopsy depleted 75% of C1 from normal serum, while the cells obtained from the lung lesion at autopsy depleted 67% of C1 and 80% of C1 INH activity from a second normal serum. In addition, the lung lesion cells depleted 90% of partially purified C1. Normal lung and lymph node cells did not possess this activity.
Table 5. Adsorption of Cl by Normal B and T Cells

<table>
<thead>
<tr>
<th>Cl Source</th>
<th>Cells Used for Adsorption</th>
<th>Cl Titer (U/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purified</td>
<td>Normal (W) unfractionated</td>
<td>23,000</td>
</tr>
<tr>
<td>Purified</td>
<td>Normal (W) B cells</td>
<td>20,000</td>
</tr>
<tr>
<td>Purified</td>
<td>Normal (W) T cells</td>
<td>25,000</td>
</tr>
<tr>
<td>Purified</td>
<td></td>
<td>22,000</td>
</tr>
<tr>
<td>Normal plasma (R)</td>
<td>Homologous unfractionated</td>
<td>96,000</td>
</tr>
<tr>
<td>Normal plasma (R)</td>
<td>Homologous B cells</td>
<td>110,000</td>
</tr>
<tr>
<td>Normal plasma (R)</td>
<td>Homologous T cells</td>
<td>120,000</td>
</tr>
<tr>
<td>Normal plasma (R)</td>
<td></td>
<td>100,000</td>
</tr>
<tr>
<td>Normal plasma (W)</td>
<td>Autologous unfractionated</td>
<td>104,000</td>
</tr>
<tr>
<td>Normal plasma (W)</td>
<td>Autologous B cells</td>
<td>120,000</td>
</tr>
<tr>
<td>Normal plasma (W)</td>
<td>Autologous T cells</td>
<td>150,000</td>
</tr>
<tr>
<td>Normal plasma (W)</td>
<td></td>
<td>105,000</td>
</tr>
</tbody>
</table>

DISCUSSION

Hereditary angioedema is an inherited disorder characterized by intermittent attacks of subcutaneous and mucosal angioedema with particularly frequent episodes of laryngeal edema. The disorder is secondary to a deficiency of the normal circulating inhibitor of activated Cl, CT INH inhibitor. Deficiency of CT INH is associated with the unopposed action of Cl on its natural substrates C4 and C2, with reduction of C4 and C2 serum levels. The onset of angioedema is associated with the generation of kinin-like activity in plasma; this may be due to a fragment of C2 or to the uninhibited action of Hageman factor.

We describe here a patient with a lymphoproliferative disorder with associated intermittent attacks of angioedema and laryngeal edema and acquired CT INH deficiency. Only two family members have been available for study. The presence of normal levels of C4 and CT INH in these two asymptomatic children and the absence of a family history of angioedema argue against the diagnosis of hereditary angioedema. Furthermore, the presence of only 8% of hemolytically active Cl in B.T. plasma (Table 1) is inconsistent with that diagnosis. In CT INH deficiency of the hereditary type, the titer of Cl is normal, as

Table 6. Adsorption of Cl and CT INH by Cells Obtained From Lung Lesion

<table>
<thead>
<tr>
<th>Serum</th>
<th>B.T. Cell Source</th>
<th>Cl Titer* (U/ml)</th>
<th>CT INH Titer* (U/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 2</td>
<td>Lung lesion (autopsy)</td>
<td>40,000</td>
<td>6,000</td>
</tr>
<tr>
<td>Control 2</td>
<td>Normal lung (autopsy)</td>
<td>90,000</td>
<td>22,000</td>
</tr>
<tr>
<td>Control 2</td>
<td>Lymph node (autopsy)</td>
<td>100,000</td>
<td>20,000</td>
</tr>
<tr>
<td>Control 2</td>
<td></td>
<td>120,000</td>
<td>30,000</td>
</tr>
<tr>
<td>Control 1</td>
<td>Lung lesion (biopsy)</td>
<td>25,000</td>
<td>—</td>
</tr>
<tr>
<td>Control 1</td>
<td></td>
<td>100,000</td>
<td>—</td>
</tr>
<tr>
<td>C1</td>
<td>Lung lesion (autopsy)</td>
<td>2,500</td>
<td>—</td>
</tr>
<tr>
<td>C1</td>
<td>Normal lung (autopsy)</td>
<td>18,000</td>
<td>—</td>
</tr>
<tr>
<td>C1</td>
<td>Lymph node (autopsy)</td>
<td>20,000</td>
<td>—</td>
</tr>
<tr>
<td>C1</td>
<td></td>
<td>25,000</td>
<td>—</td>
</tr>
</tbody>
</table>

*Activity of Cl or CT INH remaining in serum or preparation of partially purified Cl following adsorption with the indicated cell source.
ACQUIRED ANGIOEDEMA

there is no immunologic fixation of Cl or decrease in Cl titer from interaction with Cl INH. The depletion of Cl in B.T. plasma suggests another mechanism, possibly immunologic, for Cl and Cl INH depletion.

Incubation of B.T. serum with normal serum did not reveal Cl depletion as measured by effective molecule titration (Fig. 4). Thus, it was unlikely that B.T. serum contained sufficient Cl-depleting activity to account for the marked Cl depletion observed in B.T. serum. We, therefore, studied the mononuclear cell population in B.T. plasma, as well as the cells infiltrating his lung. The population of mononuclear cells in B.T. peripheral blood was clearly abnormal. The majority of cells were characteristic of B lymphocytes, as they carried easily detectable immunoglobulin on their surface and had the membrane receptor (forming EAC rosettes) for mouse complement (Table 2). They responded less effectively to PHA than normal and vigorously to pokeweed mitogen (Table 3), also suggestive of increased B lymphocyte activity. However, these cells were unusual in that they demonstrated both immune phagocytosis (ingestion of EAC) and nonimmune phagocytosis (ingestion of latex particles). These mononuclear cells, however, did not exhibit one typical characteristic of monocytes, a receptor for IgG, as witnessed by a normal percentage of EA rosette-forming cells.

EAC-bound cells are rarely phagocytosed by mononuclear cells having the complement receptor. Recent evidence in a mouse model suggests that phagocytosis of such complement-coated red cells relates to the state of activation of the mononuclear cells. This finding would suggest a heightened metabolic state of these cells in B.T. peripheral blood.

Microscopically, the lung tissue infiltrate appeared to be composed of immature atypical and plasmacytoid lymphocytes, histiocytes, and cells with large oval-shaped nuclei with prominent nucleoli and abundant cytoplasm (Fig. 1-3). These latter cells have been designated as immunoblasts. The presence of immunoblasts and plasmacytoid cells further suggested a B-cell disorder. In the absence of ultramicroscopic morphological studies of the peripheral blood mononuclear cells, it was unclear whether these blood cells were identical to a cell population infiltrating B.T. lung.

The disease process could not be designated a lymphoma because of the inability to identify a single malignant cell population. The absence of bone marrow involvement and a more uniform infiltrate made a diagnosis of Waldenström’s macroglobulinemia unlikely. Morphological features, i.e., vasculitis, which would suggest lymphomatoid granulomatosis, were not present. Immunoblastic lymphadenopathy also involves a proliferation of a B-cell population. The morphological criteria for the diagnosis of immunoblastic lymphadenopathy, however, were not entirely fulfilled in the autopsy lymph node from this case. There was only rare acidophilic interstitial material, and less proliferation of small vessels than has been described. Additionally, the infiltrate in B.T. lung was more predominantly plasmacytoid than that seen in immunoblastic lymphadenopathy. In the opinion of several consulting pathologists and hematologists, the pathologic process was felt to fit into the overall spectrum of the immunoproliferative disorders.

When B.T. peripheral blood mononuclear cells were incubated with homologous plasma at 37°C, Cl was depleted (Table 4). This result could not be
explained by an increased percentage of B cells in peripheral blood (Table 5, Fig. 5), but appeared to be due to the abnormal nature of these cells. Interaction of B.T. cells with homologous plasma also resulted in C1 INH depletion (Table 4). These data suggested that the abnormal mononuclear cells in peripheral blood may have interacted with human plasma to cause C1 and C1 INH depletion. Whether this was due to the large percentage of IgM, an efficient binder and activator of C1 on the surface of these cells is unknown. However, B.T. cells were unable to deplete uniformly C1 and C1 INH from all homologous sera. This failure was not due to low C1 or C1 INH concentrations in the individual sera. This may relate, however, to individual differences in the kinetics of C1 and C1 INH interactions with B.T. cells, to a requirement for this interaction not present in all normal sera, or to the presence of an inhibitor in some sera.

An extract from the pathologic lung tissue did not demonstrate C1-depleting activity (Fig. 4). However, cells obtained both at lung biopsy and at autopsy from B.T. lung infiltrate resembled the peripheral blood cells in their capacity to deplete C1 from homologous plasma, or from a preparation of partially purified C1 (Table 6). Cells obtained from the contralateral normal lung or from a normal lymph node did not have this activity. Furthermore, the infiltrating lung cells also depleted functional C1 INH from normal plasma.

These studies do not distinguish C1 INH-depletion secondary to C1 activation from a direct C1 INH binding to B.T. cells. The markedly depressed levels of C4 and C2 in the serum of B.T. suggest that a significant degree of activation of C1 had taken place in vivo. The absence of C1 INH as a protein in B.T. serum suggests removal, rather than just inactivation in vivo. Classically, C1 binding to an antibody-coated cell results in C2, C4, and C3 depletion without profound C1 INH depletion. The marked depletion of C1 INH in B.T. serum suggests a binding of C1 INH to B.T. cells relatively independent of C1. Subsequent binding and activation of C1 might result in C4 and C2 depletion without sufficient formation of a stable C42 complex to permit marked C3 cleavage and depletion. Recently, the interaction of C-reactive protein with protamine sulfate in human serum has also been shown to result in C1, C4, and C2 consumption with preservation of C3-9. C1 INH levels were not determined. Conceivably C1 could also be activated by B.T. cells in a manner resulting in depletion of both C1 and C1 INH activity, without C1 binding directly to the cell membrane surface or with cell-bound, uninhibited C1 dissociating from the cell surface. Such C1 in the absence of C1 INH might cause C4 and C2 cleavage without C3-9 depletion.

Three previous patient reports of C1 INH deficiency and angioedema have been described. All patients had a lymphoproliferative disorder and a similar serum complement profile to that of B.T. The first patient had lymphosarcoma and some evidence for C1-depleting activity in his serum, suggesting a humoral factor causing C1 depletion. The patient’s mononuclear cells were not studied. The two other patients were reported in abstracts; one had chronic lymphocytic leukemia and the other lymphocytic lymphoma. The mononuclear cell population was not characterized and the mechanism of C1 INH-depletion not examined. Therefore, whether a similar population of lymphoid cells in each of these patients was associated with the C1 INH-depletion, and whether this was the same cell population(s) implicated in B.T. are unknown.
ACQUIRED ANGIOEDEMA

CTI INH levels have been analyzed in patients with malignant disorders, including lymphocytic lymphoma and leukemia.26 While elevations in CTI INH are frequent, depletion has not been observed. Angioedema also appears to be a rare complication of lymphoproliferative or immunoproliferative disorders, further suggesting that complicating CTI INH depletion is quite uncommon.

This report describes the first detailed analysis of the abnormal cell population in a patient with a lymphoproliferative disorder and associated CTI INH deficiency and angioedema. Although the precise mechanism of CTI INH-depletion in this disorder remains to be defined, our studies suggest that an interaction between the abnormal cells and the complement system may, in part, underlie its pathogenesis.

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