Spontaneous Remission of Papilledema and Sixth Nerve Palsy in Acute Lymphoblastic Leukemia

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Spontaneous regression of hematologic malignancies is not uncommon and occurs in a wide variety of lymphomas and leukemias. In contrast, spontaneous remission of neurologic symptoms produced by these tumors is exceedingly rare. We report a patient with central nervous system acute lymphoblastic leukemia who experienced at least one spontaneous remission of papilledema and sixth nerve palsy. This represents, to our knowledge, the first case of spontaneous remission of neuro-ophthalmologic signs in a patient with acute leukemia. We conclude that meningeal leukemia may have a protracted course, and that spontaneous remission of neuro-ophthalmologic findings should not be so readily ascribed to a benign process in a patient with preexisting leukemia.

Key Words: Spontaneous remission—Acute lymphoblastic leukemia—Leptomeningeal metastasis—Papilledema—Sixth nerve palsy.

CASE REPORT

The patient presented in August 1984 at age 16 with leg pain, a 5-lb weight loss, and fatigue. Phys-
ical examination was significant for left anterior cerebral adenopathy. Neurologic examination, including funduscopic, was normal. On complete blood count the hemoglobin was 6 g/dl, white blood cell count was 2,500/mm$^3$, and platelets were 67,000/mm$^3$. Chest radiograph showed hilar and mediastinal adenopathy. Plain films of the lumbosacral spine were normal. Ultrasound of the abdomen was normal. A bone marrow biopsy showed ALL. All cells were CALLA-positive (common ALL antigen, positive in greater than 80% of pediatric ALL cases), and the TdT marker (terminal deoxynucleotidyl transferase, present in immature ALL cells) was positive. Cerebrospinal fluid (CSF) examination showed normal protein, white blood cell count of 0/mm$^3$, and red blood cell count of 0/mm$^3$. She underwent induction chemotherapy with vincristine, prednisone, and L-asparaginase, followed by 2 years of maintenance with vincristine, methotrexate (oral, intravenous, and intrathecal), and 6-mercaptopurine. Chemotherapy was well tolerated, and follow-up bone marrow and lumbar puncture in November 1986 showed continued remission.

She did well until January 1988, when she developed horizontal diplopia and mild headache. Examination revealed visual acuity 20/20 OU, a right sixth nerve palsy (16 prism diopters of esotropia in the primary position), and bilateral papilledema with fine, flame-shaped hemorrhages inferio­rly. There was no evidence of an infiltrative process on funduscopic examination. Computed tomography (CT) of the head and orbits was negative. CSF analysis showed white blood cell count of 334/mm$^3$ (72% lymphocytes, 12% atypical lymphocytes, and 14% immature cells). Flow cytometry was unrevealing. The lymphocytes were 17% CALLA-positive, with a few cells demonstrating weak, scattered TdT positivity (see Table 1). CSF cryptococcal antigen, Lyme antibody, viral cultures, fungal cultures, and acid-fast bacteria cultures were negative. Serum Epstein-Barr virus, herpesvirus, cytomegalovirus, and Lyme titers were negative. The purified protein derivative of tuberculin (PPD) test was negative. She received one dose of cytosine arabinoside (ara-C) and intrathecal methotrexate. A repeat lumbar puncture that month showed an opening pressure of 25 cmH$^2$0 and a white blood cell count of 73/mm$^3$ (90% lymphocytes, 7% suspicious cells) with 21% CALLA and negative TdT markers. Myelin basic protein level was normal. The patient was placed on Diamox 250 mg b.i.d. for 2 months. A repeat lumbar puncture in June 1989 showed an opening pressure of 25 cmH$^2$0 and a white blood cell count of 45/mm$^3$ (84% lymphocytes, 5% immature cells, and 5% atypical cells). CALLA and TdT markers were negative. In August 1989, examination showed the papilledema had resolved, and there was no ocular motility defect. Follow-up funduscopic examination in January 1990 remained normal.

In April 1991 she first presented to the Hospital of the University of Pennsylvania with headaches, sore throat, rhinorrhea, right retro-orbital pain, and numbness over the right lower face. On examination visual acuity was 20/20 OU. Lumbar puncture revealed an opening pressure of 33 cmH$^2$O; protein, 34 mg/dl; and white blood cells, 62/mm$^3$ (89% lymphocytes, 4% histiocytes, and 7% suspicious cells). Also, 50% of cells were TdT-positive. CALLA was negative. Cerebrospinal fluid VDRL, Lyme, viral, and acid-fast bacteria studies were negative. MRI of the brain had gadolinium enhancement was unremarkable. A repeat lumbar puncture in June 1991 showed an opening pressure of 28 cmH$^2$O and a white blood cell count of 73/mm$^3$ (90% lymphocytes, 7% suspicious cells) with 21% CALLA and negative TdT markers. Myelin basic protein level was normal. The patient received one dose of ara-C (cytosine arabinoside) and intrathecal methotrexate. She did well until January 1988, when she developed horizontal diplopia and mild headache. Examination revealed visual acuity 20/20 OU, a right sixth nerve palsy (16 prism diopters of esotropia in the primary position), and bilateral papilledema with fine, flame-shaped hemorrhages inferiorly. There was no evidence of an infiltrative process on funduscopic examination. Computed tomography (CT) of the head and orbits was negative. CSF analysis showed white blood cell count of 334/mm$^3$ (72% lymphocytes, 12% atypical lymphocytes, and 14% immature cells). Flow cytometry was unrevealing. The lymphocytes were 17% CALLA-positive, with a few cells demonstrating weak, scattered TdT positivity (see Table 1). CSF cryptococcal antigen, Lyme antibody, viral cultures, fungal cultures, and acid-fast bacteria cultures were negative. Serum Epstein-Barr virus, herpesvirus, cytomegalovirus, and Lyme titers were negative. The purified protein derivative of tuberculin (PPD) test was negative. She received one dose of cytosine arabinoside (ara-C) and intrathecal methotrexate. A repeat lumbar puncture in February 1988 revealed a white blood cell count of 43/mm$^3$ (97% mature lymphocytes, 3% histiocytes). CALLA and TdT markers were negative. By March 1988 she was asymptomatic. The sixth nerve palsy and papilledema had resolved and diagnosis of a viral syndrome was made.

In May 1989 she developed horizontal diplopia and blurred vision. Bilateral sixth nerve palsies and papilledema were present. Visual acuity was 20/20 OU. Lumbar puncture revealed an opening pressure of 33 cmH$^2$O; protein, 34 mg/dl; and white blood cells, 62/mm$^3$ (89% lymphocytes, 4% histiocytes, and 7% suspicious cells). Also, 50% of cells were TdT-positive. CALLA was negative. Cerebrospinal fluid VDRL, Lyme, viral, and acid-fast bacteria studies were negative. MRI of the brain had gadolinium enhancement was unremarkable. A repeat lumbar puncture in June 1991 showed an opening pressure of 28 cmH$^2$O and a white blood cell count of 73/mm$^3$ (90% lymphocytes, 7% suspicious cells) with 21% CALLA and negative TdT markers. Myelin basic protein level was normal. The patient received one dose of ara-C (cytosine arabinoside) and intrathecal methotrexate.

### Table 1: Cerebrospinal fluid results and cell marker positivity

<table>
<thead>
<tr>
<th>CSF sample</th>
<th>WBCs/mm$^3$</th>
<th>Abnormal cells (%)</th>
<th>CALLA+ (%)</th>
<th>TdT+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/88*</td>
<td>334</td>
<td>26</td>
<td>17</td>
<td>—</td>
</tr>
<tr>
<td>2/88</td>
<td>43</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5/89*</td>
<td>62</td>
<td>7</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>5/89</td>
<td>73</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6/89</td>
<td>45</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4/91*</td>
<td>1,200</td>
<td>40</td>
<td>87</td>
<td>60</td>
</tr>
</tbody>
</table>

- CSF, cerebrospinal fluid; WBCs, white blood cells; CALLA, common acute lymphoblastic leukemia antigen; TdT, terminal deoxynucleotidyl transferase.
- *Patient received one dose of ara-C (cytosine arabinoside) and intrathecal methotrexate.
- Patient placed on Diamox 250 mg b.i.d. for 2 months.
- Patient diagnosed with central nervous system relapse of acute lymphoblastic leukemia.
opening pressure exceeding 55 cmH₂O; protein, 59 mg/dl; and white blood cell count of 1,200/mm³ (16% lymphocytes, 44% monocytes, and 40% atypical lymphocytes). Cells were 87% CALLA-positive and 60% TdT-positive. Biopsy of the left posterior auricular mass showed malignant lymphocytes. CT scans of the chest, abdomen, and pelvis revealed a small right pleural soft tissue density representing leukemic mass or adenopathy. Peripheral blood smear and bone marrow biopsy from both iliac crests were normal. A diagnosis of CNS relapse of ALL was made. The patient received whole-brain radiation therapy followed by systemic DATVP (daunorubicin, ara-C, 6-thioguanine, vincristine, and prednisone) and intravenous and intrathecal methotrexate. CSF cytology remained positive, and intrathecal therapy with ara-C was given from May through July 1991. Following reinduction chemotherapy, she received craniospinal radiation. The headaches and enlarged blind spots improved with this therapy, and her papilledema resolved with mild residual left optic nerve atrophy. In August 1991 she was accepted for allogeneic bone marrow transplant at another institution.

**DISCUSSION**

Despite evidence for leptomeningeal metastasis of acute lymphoblastic leukemia, our patient had at least one spontaneous remission of papilledema and sixth nerve palsy over a 3-year period. A single dose of chemotherapy administered early in her central nervous system presentation failed to clear the cerebrospinal fluid pleocytosis. However, definitive therapy was not continued, since her neuro-ophthalmologic signs rapidly improved, and a benign process was considered responsible. When the papilledema and ocular motility defect returned 1 year later, Diamox was started for the unexplained increased intracranial pressure. Although it is conceivable that Diamox played some role in the second remission, the patient remained asymptomatic for nearly 2 years after the Diamox was discontinued. The persistent CSF pleocytosis and atypical cells would also exclude a diagnosis of pseudotumor cerebri (19). Thus, any role Diamox played in the prolonged remission was likely negligible.

We believe the clinical remissions observed in our patient reflect an inherent control of the host over tumor growth. Presumably, she was able to reverse some manifestation of the CNS leukemia but could not eliminate the entire tumor load. In instances where the host response is more robust, complete spontaneous regression would occur.

Spontaneous regression of hematologic malignancy is not uncommon and may occur in up to 20% of patients with low-grade non-Hodgkin’s lymphoma (3,8). Although the mechanism of spontaneous regression is unknown, a number of factors that enhance immunologic surveillance have been proposed. In Cole’s reviews (1,5), “operative trauma” was the most commonly cited mechanism, present in 46% of cases of spontaneous regression (2). Surgical removal of part of the tumor theoretically heightens the immune system’s response to the tumor that remains (2,5). The appearance of a second malignancy may coincide with or follow spontaneous remission of leukemia (3,20,21). Antigenic competition, whereby the immunologic response to one antigen enhances the immune system’s response to a second antigen (22), has been forwarded as a possible mechanism in these remissions (3). Viral infections have been implicated in a wide variety of lymphomas that have undergone spontaneous regression, including Burkitt’s lymphoma (6), non-Hodgkin’s lymphoma (7,8), and lymphosarcoma (23).

Dock (24) reviewed the therapeutic effect of infection on leukemia in 1904. Early reports documented spontaneous regression of leukemia following bacterial (3,10,11,25), viral (25), and unspecified infections (26). More recent cases of spontaneous regression in leukemia have followed a variety of infections. Complete and partial remissions of adult T-cell leukemia have followed cytomegalovirus pneumonia (12) and bacterial infections (13). Murakawa and coworkers (13) proposed that the bacterial infections induced expansion of an adult T-cell leukemia clone and secretion of cytokines, which further enlarged the clone. Antibiotic therapy suppressed cytokine production with subsequent shrinkage of the clone population. Stimulation of natural killer cell function by concurrent tuberculosis infection may have contributed to the 13-year disease-free survival of a patient with acute nonlymphoblastic leukemia (27). Multiple studies failed to identify a viral, bacterial, or fungal infection in our patient.

Spontaneous remission of neurologic signs and symptoms produced by CNS hematologic malignancies is rare and to our knowledge has never been reported in acute leukemia. CSF cytology in our patient remained negative or showed an equivocal number of suspicious cells and markers for more than 3 years before she was diagnosed with CNS relapse of ALL. Absence of malignant cells in the CSF, however, does not exclude a di-
agnosis of leptomeningeal metastasis (28). Initial CSF cytology may be negative in 15 to 46% of patients whose tumor has spread to the leptomeninges (29). Examination of CSF cytology shortly before death failed to identify nearly half of lymphoma or leukemia patients with autopsy-proven leptomeningeal tumor (28). Cytology of cisternal CSF may help detect patients with suspected leptomeningeal metastasis who have unremarkable lumbar punctures (29). It is unclear if cisternal puncture would have led to an earlier diagnosis in our patient.

This patient demonstrates that untreated CNS hematologic malignancies may have a protracted course. Spontaneous remission of neuroophthalmologic signs in a patient with preexisting leukemia may not represent a benign process, and careful surveillance of such patients is warranted.

REFERENCES