Lymphomatoid Granulomatosis After Childhood Acute Lymphoblastic Leukemia: Report of Effective Therapy

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ABSTRACT. Lymphomatoid granulomatosis, a rare condition in children, affects the lungs primarily but may have significant extrapulmonary manifestations, especially in the central nervous system. We report a case of lymphomatoid granulomatosis with onset after the completion of chemotherapy for childhood acute lymphoblastic leukemia. Two months after treatment ended, the 7-year-old girl developed splenomegaly, cervical adenopathy, and bilateral interstitial pulmonary infiltrates. She improved on cefotaxime but experienced a seizure 1 month later. A computed tomography scan of the head was normal, but her pulmonary infiltrates had become nodular. A computed tomography–guided biopsy of 1 of the nodules revealed cellular interstitial pneumonitis. One month later, she had persistent pulmonary infiltrates, marked splenomegaly, and new seizures. Magnetic resonance imaging of the head revealed cerebral nodules. Itraconazole was begun, and the pulmonary infiltrates resolved. Five months after her initial symptoms, she developed tonic pupil and a decreased level of consciousness. Dexamethasone was initiated. Needle biopsies of the brain were carried out, yielding the diagnosis of severe chronic inflammatory changes focally consistent with granuloma. The child redeveloped splenomegaly and fever, and then suffered an acute decompensation with hypoxemia, tachypnea, splenomegaly, and cardiac gallop. Open-lung biopsy revealed lymphomatoid granulomatosis. Lymphoma-directed therapy was initiated, and the patient had complete resolution of pulmonary and cerebral nodules 5 months later. No intrathecal chemotherapy was administered, and radiation therapy was not necessary. Neuropsychological testing obtained after completion of therapy revealed an improvement in attention, coordination, and fine motor speed over time. She is now in good health and attending school.

CASE REPORT

A 5-year-old girl was diagnosed with ALL in September 1992. No central nervous system disease was detected. Lymphoblasts were of early B cell lineage, with only 3% CD3-positive cells in the diagnostic marrow. Treatment according to Children’s Cancer Group protocol 1881, regimen A, was completed in November 1994. No cranial radiation was given. Subsequent off-therapy bone marrow aspiration and cerebrospinal fluid (CSF) examinations were normal.

The onset of bilateral otitis media and pansinusitis was noted on January 30, 1995. At that time, the patient was febrile to 38°C, the spleen was palpable to 2 cm below the costal margin, and right cervical adenopathy was noted. A chest radiograph revealed diffuse bilateral interstitial pulmonary infiltrates. Complete blood count results were as follows: hemoglobin, 14.2 g/dL; platelets, 274 × 10^9/L; white blood cells, 4.5 × 10^9/L, with 13% basophils and no blasts. The patient improved on therapy with cefotaxime, and her splenomegaly resolved. On February 22, 1995, she experienced a partial complex seizure. A computed tomography (CT) scan of the head and CSF analysis were normal. The pulmonary infiltrates had become nodular, and a CT-guided needle biopsy of a nodule was obtained on March 12, 1995. The biopsy specimen was sent for consultation, and the diagnosis of cellular interstitial pneumonitis with features of lymphocytic interstitial pneumonitis was made.

By March 24, 1995, the patient had developed marked splenomegaly and additional seizures. Bone marrow and CSF were obtained; no evidence of leukemia or infiltrative process was noted. An MRI scan of the head revealed multiple gadolinium-avid cerebral nodules at the junction of the cerebral gray and white matter in a general distribution (Fig 1). Given the persistence of the nodular pulmonary infiltrates, empiric itraconazole was started. Over the next several weeks, continued improvement and resolution of the pulmonary infiltrates was noted (Fig 2).
However, on June 5, 1995, the patient acutely developed a tonic pupil on the left (dilated pupil and slow reaction to light and darkness, with photophobia), followed 3 days later by a decreased level of consciousness, bulbar speech, and drooling. Complete blood count revealed: hemoglobin, 10.9 g/dL; platelets, $168 \times 10^9$/L; and white blood cells, $2.5 \times 10^9$/L (46% neutrophils, 44% lymphocytes, 10% monocytes). CSF revealed: protein, 79 mg/dL; glucose, 50 mg/dL; red blood cells, 1/mm$^3$; and white blood cells, 7/mm$^3$ (100% lymphocytes). Dexamethasone (50 mg/m$^2$/day divided into 6-hour intervals) was administered, with improvement of neurologic symptoms. The dexamethasone was then quickly tapered to 10 mg/m$^2$/day. On June 9, 1995, a fine-needle aspiration of the spleen was obtained that was nondiagnostic. Four stereotactic needle biopsies of a brain nodule conducted on June 13, 1995 showed an atypical lymphoid infiltrate (Fig 3). The majority of lymphocytes were positive for CD3 with virtually no cells positive for L26 (CD20). Strong positivity for CD68 was present within macrophages. The biopsy specimens were referred for outside consultation yielding a diagnosis of severe chronic inflammatory changes focally consistent with granuloma. Additional stains for acid-fast organisms and toxoplasmosis were negative. Ultrastructural findings showed no evidence of significant demyelination or viral infection. Full clinical recovery was noted by June 17, 1995, and dexamethasone was tapered. On July 18, 1995, the patient redeveloped splenomegaly and fever. Neck pain, hesitant speech, and yawning followed, and she was again treated with dexamethasone. This was slowly tapered, but on August 22, 1995, she suffered an acute decompensation with hypoxemia, tachypnea, poor color, splenomegaly, diffuse rales, and cardiac gallop. An echocardiogram revealed poor cardiac function with a shortening fraction of 20%. An MRI of the head revealed new frontal and parietal lesions, similar in character to those previously seen. A CT of the abdomen revealed new wedge-shaped densities in the kidneys, consistent with vascular occlusion. The following day an open-lung biopsy was obtained, which demonstrated an atypical angiocentric lymphoproliferative process, suggestive of lymphomatoid granulomatosis (Fig 4). The perivascular atypical lymphocyte population was positive for CD45, CD3, and CD20, the majority being CD3-positive. Pathology consultation confirmed the immunohistologic diagnosis of lymphomatoid granulomatosis. Cultures of lung tissue were negative for routine bacterial and acid-fast organisms, fungi, and viruses. Polymerase chain reaction analysis of frozen lung biopsy tissue showed no clonal rearrangement of the immunoglobulin heavy chain (IgHJH), T cell receptor $\beta$-chain, and T cell receptor $\gamma$-chain genes. Serology for Epstein-Barr virus (EBV) was negative. Serologies and cultures for cytomegalovirus were indicative of past infection, with no evidence of current activation. Serologies for histoplasmosis, cryptococcus, and blastomyces were likewise negative. EBV in situ hybridization analysis, conducted on tissue from the lung biopsy with intact RNA, was negative.

Lymphoma-directed chemotherapy was initiated on August 31, 1995 and consisted of intravenous cyclophosphamide, intravenous vincristine, oral prednisone, and intravenous methotrexate. The patient exhibited immediate and continued clinical improvement, and by January 16, 1996, complete resolution of nodules in the cerebrum and chest was noted. Cardiac function returned to normal. The spleen, still palpable, was markedly diminished in size. Chemotherapy ended on March 20, 1996, by which time the splenomegaly had resolved.

Neuropsychological testing was performed in February 1997, 11 months after completion of treatment for lymphomatoid granulomatosis. Testing revealed a decrease in overall intelligence quotient scores compared with baseline testing completed during treatment for her ALL in 1992. Follow-up neuropsychological testing was administered in March 1998, showing an improvement in attention, fine motor speed, and coordination, although still showing deficits compared with same-aged peers.
At her last medical follow-up in August 2000, the patient continued to be in good health. She had been off anticonvulsants for 41 months. She attends school in a mainstream class and receives special education services as needed under the “other health impaired” classification. Stimulant medication (methylphenidate) for attention problems has been beneficial.

**DISCUSSION**

The initial published series of 40 patients with lymphomatoid granulomatosis by Liebow et al included only 1 child, aged 8.5 years. A subsequent series added 116 cases, with 12 of 152 patients (8%) <20 years old. Although the primary pulmonary manifestations of this disorder are central to the diagnosis, extrapulmonary manifestations, as were present in our patient’s case, may be quite significant. Involvement of the nervous system (67%), skin (39%), kidney (32%), spleen (18%), liver (12%), heart (11%), and lymph nodes (8%) has been described.

The T cell origin of the disorder was first suggested by Nichols et al and was elegantly confirmed by Lipford and colleagues in 1988. A subsequent study of 4 patients confirmed T cell predominance but suggested that the process was dependent on an
EBV-associated B cell lymphoproliferative phenomenon. A more recent series of 16 cases determined the proliferation index of B cells, T cells, and histiocytes in lymphomatoid granulomatosis lesions, using combined immunohistochemistry for CD20, CD3, CD68, and CD57 with DNA topoisomerase II as a marker of proliferation. The authors found a significantly higher proliferation index in B cells compared with the other cell populations. The average B cell proliferation index in the high-grade (grade III) lesions was similar to that in large cell non-Hodgkin’s B cell lymphomas.

It should be emphasized that our patient had no evidence of EBV infection, based on serology and in situ hybridization of pathologic lung tissue. Our patient demonstrates that, as has also been shown in the posttransplant lymphoproliferative disorders, EBV need not be present to incite this illness.

Fauci and colleagues described their experience with 15 patients with lymphomatoid granulomatosis, one who was 16 years old. Thirteen patients received therapy with cyclophosphamide and prednisone; 7 had long-lasting complete remissions. Of those who did not respond to therapy and subsequently died, the majority developed malignant lymphoma. Fauci et al noted that early treatment with immunosuppressive therapy markedly decreased the previously high mortality rate (65%–90%) of lymphomatoid granulomatosis.

We confirm that cyclophosphamide and corticosteroid-based therapy is effective, and note that corticosteroids alone produced only temporary benefit in our patient. Central nervous system benefits obtained without such directed therapy as cranial radiation or intrathecal chemotherapy were remarkable in this case, and well documented by serial neuropsychological testing and MRI.

Our patient’s diagnosis was delayed in this case because of a number of factors: 1) the patient responded to empiric antibiotic therapy; 2) limited material was obtained from the needle biopsies, making histopathologic review difficult; and 3) the biopsies were all obtained when the patient was being treated with glucocorticoid therapy, which may have obscured the diagnosis early in the patient’s course. Awareness of the features of this syndrome in the appropriate clinical context may lead to earlier recognition and prompt institution of appropriate therapy. Childhood lymphomatoid granulomatosis should be considered in the clinicopathologic diagnosis of upper respiratory tract symptomatology with concurrent nodular pulmonary infiltrates and central nervous system manifestations, especially in the setting of past diagnosis of and treatment for ALL with apparent long-term remission.

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