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Prolonged Complete Response in a Pediatric Patient With Primary Peripheral T-Cell Lymphoma of the Central Nervous System

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Abstract

We describe a child with a 2-week history of progressive headaches, blurry vision, and intermittent vomiting. Magnetic resonance imaging (MRI) of the brain showed a deep left hemispheric lesion with extension into the corpus callosum. Histology and immunophenotyping of the lesion was consistent with peripheral T-cell lymphoma, not otherwise specified. Chemotherapy was initiated and a complete remission was achieved. This case illustrates that a chemotherapeutic regimen used in adults with central nervous system (CNS) lymphoma can achieve durable remissions in pediatric patients with peripheral T-cell lymphoma, not otherwise specified of the CNS.

Keywords

CNS tumors; NHL; therapy

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an exceedingly rare, aggressive malignancy that arises from the CNS, specifically the brain parenchyma, spinal cord, cranial nerves, and/or meninges [1]. PCNSL accounts for ~2% of all primary brain tumors, with 2% of this subset having T-cell origin [2, 3]. Children with acquired and congenital

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DECLARATION OF INTEREST

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immunodeficiency are at increased risk for PCNSL; however, immunocompetent children still represent the majority of patients.

Although the majority of PCNSL are of B-cell origin, this paper will focus on the more rare, aggressive peripheral T-cell PCNSL [4, 5]. In pediatrics, most T-cell lymphomas have an immature phenotype, presenting as either a lymphoblastic lymphoma or leukemia. Peripheral T-cell lymphoma refers to the mature immunophenotype rather than the site of involvement and comprises a heterogeneous group of hematologic tumors, which constitutes ~10% of all non-Hodgkin's lymphoma (NHL) in adults. Most pediatric peripheral T-cell lymphoma cases are CD30+/anaplastic lymphoma kinase (ALK)-positive, categorizing them as anaplastic large-cell lymphoma (ALCL), according to World Health Organization (WHO) classification [6]. Peripheral T-cell lymphoma not otherwise specified (NOS) is a diagnosis of exclusion and includes the remainder of mature T-cell forms that are not classifiable as a specific disease entity by WHO [6, 7]. This category of neoplasms comprises over 25% of all peripheral T-cell and other NK/T-cell lymphomas [6].

Due to the limited number of pediatric cases of PCNSL, inclusive of B-cell and T-cell, there have been no prospective treatment studies performed in children; therefore, treatment and prognosis have been extrapolated from adult studies. Age, performance status, and administration of methotrexate (MTX) have been correlated with better outcomes in adults [4, 8]. However, despite aggressive treatment regimens with chemotherapy, whole-brain radiation therapy (WBRT), and/or stem cell transplant, PCNSL, specifically of T-cell origin, portends a poor prognosis.

We present a 12-year-old female with PCNSL, categorized as peripheral T-cell lymphoma NOS, who achieved a durable complete remission (CR) after treatment with a chemotherapeutic regimen used for adult central nervous system (CNS) lymphoma.

CASE REPORT

A healthy 12-year-old female presented initially to an outside hospital with a 2-week history of progressively worsening headaches, blurry vision, vomiting, and dizziness. Her past medical history was negative for frequent infections, including otitis media and pneumonia, rash, joint pain, fatigue, weight loss, and/or hematologic disorders. The family history was positive for inflammatory bowel disease and psoriatic arthritis on the paternal side, however was negative for rheumatoid arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus (SLE), pediatric malignancy, hematologic disorders, or immunologic deficiencies. Magnetic resonance imaging (MRI) of the patient demonstrated a left frontal mass with cerebral edema. She received highdose steroids and underwent a near-complete resection. Pathology of the mass, including immunohistochemistry, was inconclusive and showed a macrophage-rich lesion with necrosis, myelin loss, microcalcifications, and inflammation. T-cell receptor gene rearrangement studies were not performed at this time. The patient was evaluated for many infectious diseases (fungal, bacterial, viral, human immunodeficiency virus [HIV]), as well as a workup for rheumatologic (SLE, neurosarcoidosis, autoimmune conditions) and immunologic (primary immunodeficiencies, common variable immune deficiency) etiologies, with all results being negative.

One month postoperatively, she presented to our hospital with worsening right-sided weakness, demonstrated by difficulty curling her toes, limited dorsiflexion, and worsening gait. Neurologic examination confirmed right-sided weakness and gait showed right-sided circumduction with foot drop. MRI was performed, which demonstrated a recurrence of the deep left hemispheric lesion with extension into the corpus callosum. Mild mass effect was noted with midline shift to the right. There were also multiple new enhancing T2 bright lesions in the gray matter of the cerebral hemispheres bilaterally (Figure 1).

An open brain biopsy was performed, and pathology was consistent with the initial pathology of macrophage infiltrates, perivascular lymphocytic cuffing, and patchy necrosis. Pathology slides were circulated to experts nationally. The complete panel of immunohistochemical stains included CD20, CD3, CD5, CD4, CD8, CD30, ALK, T-cell receptor (TCR) gamma, TCR beta F1, S100, CD68, GFAP, NF, Toxo, herpes simplex virus 1 (HSV1), HSV2, cytomegalovirus (CMV), CD56, granzyme B, perforin, and Epstein-Barr virus (EBV) by in situ hybridization. Special stains periodic acid–Schiff (PAS), Gomori methenamine silver (GMS), and acid-fast bacilli (AFB) were negative. Immunohistochemical stains of the neoplastic cells showed abundant CD8-positive cells, partial loss of CD5, and dual expression of TCR gamma and beta F1 (Figure 2). This has been reported in other, both EBV negative and positive [9, 10]. CD30, ALK-1, and EBV-encoded RNA (EBER) stains were negative; however, polymerase chain reaction (PCR) was positive for clonal T-cell receptor gene rearrangement, leading to the diagnosis of peripheral T-cell lymphoma NOS of the CNS by the National Cancer Institute pathology reference laboratory. Metastatic workup was negative and included ophthalmologic examination, bone marrow assessment, lumbar puncture, and whole-body positron emission tomography/computed tomography (PET/CT) scan. Lactate dehydrogenase (LDH) was normal at presentation to our hospital, 181 units/L. The patient was registered on the Children's Oncology Group (COG) rare tumor registry study ANHL 04B1. The purpose of this study is to explore the biologic and pathologic features of rare pediatric NHL and develop a bank for future therapeutic protocol development.

Therapy was initiated with protocol CALGB 50202 used in adults with CNS lymphoma [11]. She was placed on high-dose dexamethasone (2.5 mg/m² 4 times a day [qid]) due to cerebral edema and mass effect. Induction chemotherapy consisted of high-dose methotrexate (HDMTX) (8 g/m² q 2 weeks) and temozolomide (TEM) (150 mg/m² q 4 weeks). After 4 months of therapy, MRI showed an unconfirmed CR (disappearance of all disease on imaging with confirmatory imaging required at least 4 weeks later) [12]. Consolidation therapy followed with 2 cycles of high-dose cytarabine (Ara-C) (2 g/m² q12h for 8 doses/cycle) and etoposide (ETOP) (40 mg/m² continuous over 96 h/cycle). Currently, our patient is >1 year since the completion of therapy and remains in a durable confirmed CR, with minimal neurologic sequelae. She continues to have limited right great toe dorsiflexion, 4/5 distal lower extremity strength, and mild right-sided gait circumduction. She remains in physical and occupational therapy for continued improvement.

DISCUSSION

We report the first pediatric patient with peripheral T-cell lymphoma NOS of the CNS who was successfully treated with chemotherapy alone using an adult PCNSL regimen. To date, there are only 2 case reports in the literature that describe pediatric patients with peripheral T-cell lymphoma NOS of the CNS [13, 14]. One patient was surgically resected, had a complete remission, and was lost to follow up after 6 years, and the other pediatric patient died 1 month after initiation of chemotherapy [13, 14].

PCNSL are extranodal and are confined to the brain, eyes, and/or leptomeninges [13]. In patients under 19 years of age, PCNSL are exceptionally unusual, accounting for <1% of all cases [2]. Due to the rarity of this condition, performing a prospective therapeutic study is nearly impossible.

The cornerstone therapy for adults with PCNSL is HDMTX; however, as monotherapy, the progression-free survival (PFS) is about 12 months; PFS is 24 months if radiation therapy is added [11]. In a recent study in adults with PCNSL, Rubenstein et al. [11] showed that patients could achieve durable CR with chemotherapy alone, without the use of WBRT; CR rates were comparable to regimens that used WBRT. Forty-four newly diagnosed patients with PCNSL (mostly B-cell) were treated with HDMTX, temozolomide, and rituximab, and those who achieved a CR (66%) received consolidation therapy with Ara-C and ETOP. The overall 2-year PFS was 0.57, with a median follow-up of 4.9 years [11].

In a retrospective review of children with PCNSL, 12 patients were included (the only T-cell origin were 3 patients with ALCL). Then children received chemotherapy alone, while 2 received chemotherapy plus radiation therapy. The 5-year event-free survival in patients who received chemotherapy alone was $70 \pm 14.5\%$ [15]. The 3 patients with ALCL received chemotherapy alone, and survived without evidence of relapse >6 years from the review.

Another retrospective study of PCNSL in childhood included 29 total patients, most had B-cell lesions, 5 of whom had ALCL. Most patients ($n = 27$) received MTX-based regimens. The overall response rate (ORR) was 86%, CR 69%, and 2-year PFS 61%. Of the 18 patients who received chemotherapy alone, 67% of patients had a CR. Primary treatment with chemotherapy alone was associated with better ORR with an odds ratio (OR) of 0.125 ($P = .02$) [16].

In a recent review series of 17 pediatric patients with PCNSL (1 patient with peripheral T-cell lymphoma), 3 NHL-BFM protocols were used, and with the exception of the 5 patients diagnosed with ALCL, radiation therapy was held. The 3-year probability of overall survival for all patients was $63 \pm 12\%$, and $92 \pm 8\%$ for the immunocompetent patients. As seen in multiple adult cases, immunodeficiency in pediatric patients has correlated with worse overall survival when compared with their immunocompetent counterparts [15, 17, 18]. In this review series, all 5 patients with immunodeficiency died, mostly from infection or treatment-related toxicity, and 1 died from disease. No definitive conclusions can be drawn from these statistics; however, some theories regarding poor outcomes in immunodeficiency suggest that the CNS lymphoma is more aggressive and not as amenable to therapy in this patient cohort, possibly due to association with EBV. Additionally, these patients are

immunosuppressed even prior to initiation of chemotherapy, which places them at a higher risk of acquiring infections that can lead to mortality [18]. This series is one of the largest to date of patients treated with NHL-BFM protocols, supporting previous reviews mentioned above that patients with B-cell PCNSL can be successfully treated without irradiation [17].

Avoidance of WBRT in young children is important, given the well-described late effects of cranial irradiation in children: neurocognitive impairment, secondary malignancy, and endocrine abnormalities. Our case describes a pediatric patient with PC-NSL of T-cell origin treated with chemotherapy based on an adult lymphoma protocol who achieved a durable CR. These results provide an alternative treatment approach for pediatric patients with peripheral T-cell lymphoma of CNS origin using chemotherapy alone.

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FIGURE 1.

(A) At diagnosis: contrast-enhanced axial T1-weighted image through the centrum semiovale shows a large enhancing mass in the deep left hemisphere, with surrounding edema. (B) Relapsed images of patient: contrast-enhanced axial T1-weighted image shows progressive increase in the size of the deep left hemispheric mass. Multiple new enhancing tumor nodules have developed in both cerebral hemispheres (*arrows*), most appear cortically based. (C) Most recent MRI: contrast-enhanced axial T1-weighted image reveals essentially complete resolution of the deep left hemispheric mass, with development of cystic encephalomalacia in the region. All of the previously documented enhancing nodules have also resolved.

FIGURE 2.

(A) A high-power hematoxylin and eosin–stained section showing a dense atypical lymphoid infiltrate involving the white matter with admixed numerous macrophages. The lymphoid cells are relatively small, with condensed chromatin and mild cytologic atypia (400×). By immunohistochemistry the majority of the infiltrate is composed of T cells expressing CD8 (B) (400×), with partial expression of CD5 (C) (400×). (D) Molecular studies revealed clonal rearrangement for the T-cell receptor gamma locus using a single multiplexed PCR reaction.