case reports

Lymphomatous Meningitis From Anaplastic Lymphoma Kinase+ Anaplastic Large T-Cell Lymphoma Treated With Lorlatinib: A Case Report

Smitha Mellacheruvu, MD[1,2]; Mark N. Sayegh, MD[1]; R. Alejandro Sica, MD[3]; Haiying Cheng, MD, PhD[2]; Maria Laureana Santos-Zabala, MD[4]; Jacob H. Gebrael, MD[5]; Ulrich Hermanto, MD, PhD[6]; and Norman L. Rosen, MD[1]

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Background

Anaplastic large cell lymphoma (ALCL) accounts for approximately 2% of adult non-Hodgkin lymphoma, and is the second or third most common lymphoma with T-cell histology in adults.[1,2] According to the revised 2016 WHO classification, four distinct entities of ALCL are currently recognized: (1) ALCL, anaplastic lymphoma kinase (ALK)+ (2) ALCL, ALK–, (3) primary cutaneous ALCL, and (4) breast implant–associated ALCL.[3] All cases of ALK+ ALCL have a rearrangement in the ALK gene located on chromosome 2p23. The t (2;5) translocation yields an abundantly expressed chimeric protein containing the oligomerization motif of nucleophosmin 1 and the kinase domain of ALK.[4-6] The nucleophosmin-ALK homodimer cross-phosphorylates itself, leading to persistent kinase activation.[7,8] On the basis of this additional genetic evidence, the WHO recognized ALK+ ALCL in 2008.[9] Typical features of most ALCL tumors include the presence of hallmark cells, which are large cells with kidney-shaped nuclei and a perinuclear eosinophilic region, along with the universal expression of the CD30 antigen.[10]

ALK+ ALCL is associated with a better prognosis than ALK– ALCL, and the International Prognostic Index, originally proposed for non-Hodgkin lymphomas, is an effective tool to predict outcomes.[11] Although ALCL frequently involves lymph nodes and occasionally involves extranodal sites, it rarely occurs in the CNS,[12] and in the literature, ALCL of the CNS is limited to case reviews.[13-18] A few case reviews suggested that although ALK positivity and younger age appear to be favorable prognostic factors for primary ALCL of the CNS, it is generally much more aggressive than systemic ALCL or primary CNS lymphoma.[17,18] Herein, we report a case of multiply relapsed ALK+ ALCL with secondary lymphomatous meningitis with a dramatic response to lorlatinib.

Case Report

A 61-year-old Indian man presented in July 2017 with persistent upper abdominal pain for several weeks. He had a history of diabetes mellitus, ichthyosis, chronic kidney disease, and stage III ALCL (CD30-positive, ALK+); ALCL was diagnosed in 2004 and treated with six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone. Computed tomography (CT) of the abdomen and pelvis done in July 2017 revealed extensive intra-abdominal lymphadenopathy, and biopsy revealed ALK+ ALCL (Fig 2A).

He was started on brentuximab vedotin (BV) and a positron emission tomography (PET)-CT scan after six cycles revealed a complete response. After nine cycles of BV, the patient refused to continue further treatment and declined consolidative autologous stem-cell transplantation (ASCT). Two months after the last dose of BV, he presented with scalp nodules, which were biopsy-confirmed to be ALK+ ALCL. Two cycles of salvage chemotherapy with gemcitabine, dexamethasone, and cisplatin were given followed by ASCT with carmustine, etoposide, cytarabine, and melphalan conditioning. After ASCT, complete response was documented by PET-CT. Patient refused BV maintenance.

Nine months after ASCT, he developed a right orbital mass (Fig 1A) and hypermetabolic nodes on PET-CT. He received radiation therapy (RT) to the right orbital mass with complete radiographic response (Fig 1B) and subsequently started on crizotinib. The patient started experiencing headaches 11 months after initiating crizotinib. Although the initial brain magnetic resonance imaging (MRI) and PET-CT were negative, he was admitted 8 weeks later with severe headaches, dizziness, and unsteady gait, along with severe fatigue, and his performance status was Eastern Cooperative Oncology Group 4. He had also developed an erythematous, patchy area on the nape of his neck, oozing serous fluid, suspicious for lymphomatous

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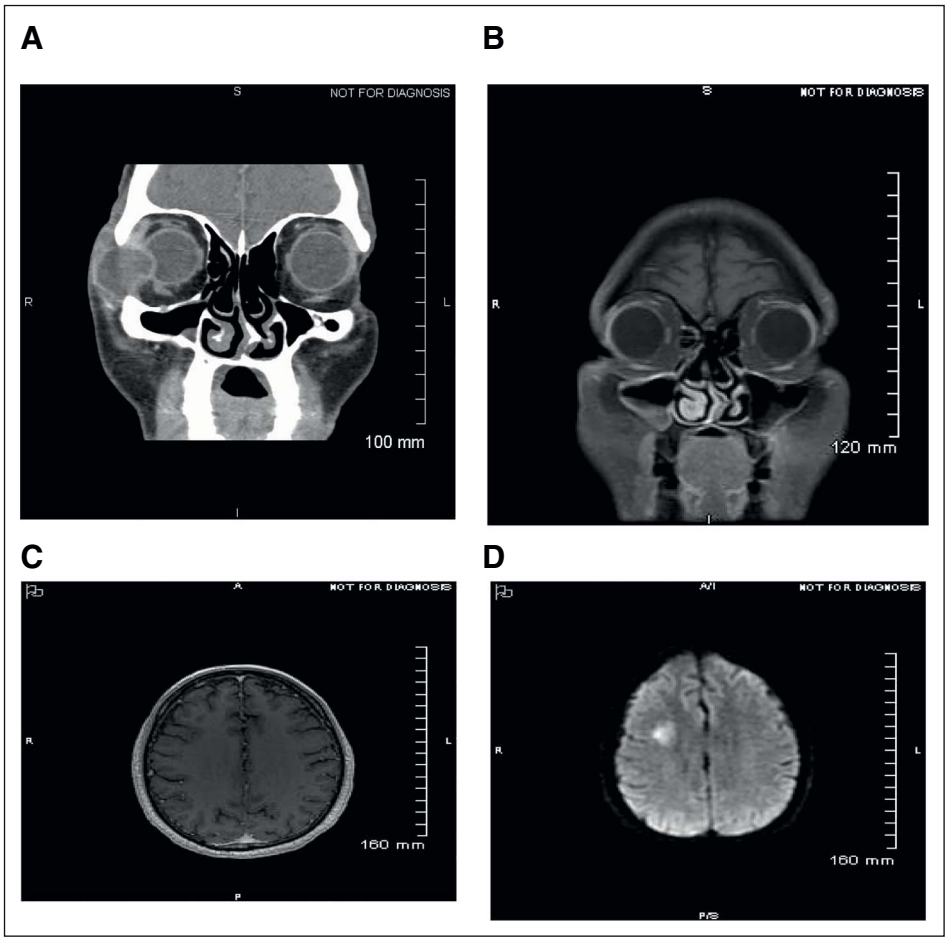

FIG 1. (A) Pretreatment computed tomography orbits with contrast-coronal image showing right orbital lymphoma 2.4 cm × 1.2 cm × 2.1 cm abutting the anterior aspect of the right lateral orbital rim just inferior to the right lacrimal gland and extending into the anterior portion of the extraconal orbit. (B) Post-treatment magnetic resonance imaging brain with and without contrast—post-contrast coronal sequence through the orbits showing no involvement by lymphoma. (C) Fluid-attenuated inversion recovery sequence showing mild increased signal change in the white matter of the right frontal lobe. (D) Diffusion-weighted image through the same area showing restricted diffusion suspicious for early lymphomatous involvement.

infiltration; however, a biopsy was not obtained. MRI brain done at that time showed an abnormal signal intensity within the right frontal lobe, which was suspicious for lymphoma (Figs 1C and 1D). CSF analysis revealed xanthochromia, a protein level of 1,530 mg/dL (normal 15-45 mg/dL), a glucose level of 35 mg/dL (normal 40-70 mg/dL), and a WBC count of 240/mm^3. Cytology was consistent with involvement by ALK+ ALCL (Figs 2B-2D)

At that time, he refused to consider intrathecal chemotherapy or RT. Because of his refusal of these options, MRI spine was not pursued. He did not want to pursue high-dose methotrexate or cytarabine. Since he developed CNS progression on crizotinib and since lorlatinib has been effective in treating CNS metastases including leptomeningeal carcinomatosis from ALK+ non–small-cell lung cancer (NSCLC),[19-22] we offered him lorlatinib off-label. After obtaining informed consent, it was started at 100 mg once daily with the resolution of headaches and oozing of the cutaneous lesion after just two doses. He developed hallucinations and slurry speech 3 days after starting lorlatinib, which resolved on temporary interruption for 2 days. Lorlatinib was resumed with a dose reduction to 50 mg once daily with resolution of all his symptoms over the next few weeks. Informed consent was obtained from the patient to publish this case report.

Eleven months after starting lorlatinib for lymphomatous meningitis from multiply relapsed ALK– + ALCL, the patient continues to show excellent clinical response with an Eastern Cooperative Oncology Group performance status of 1.

Follow-up imaging shows resolution of abnormal signal in the frontal lobe; CSF analysis shows remission by cytology and flow cytometry, and PET-CT reveals systemic remission.

Discussion

Chemotherapy has been the predominant treatment for patients with ALCL; however, late relapses can occur. Chemotherapy has long-term side effects such as infertility and secondary malignancies, which are particularly important in the pediatric population.[23] Hence, there is a need to develop more efficacious and less toxic targeted approaches. On the basis of the two hallmark features of ALK+ ALCL, targeted therapies against CD30 and ALK are being tested both in the upfront and relapsed settings. CD30 is universally expressed in ALK+ ALCL and promotes activation of the CD30 signaling pathway.[24] BV is an antibody drug conjugate composed of a CD30-directed antibody linked to the antitubulin agent monomethyl auristatin E. It received US Food and Drug Administration (FDA) approval as a single-agent therapy for the treatment of systemic ALCL after failure of at least one prior multiagent

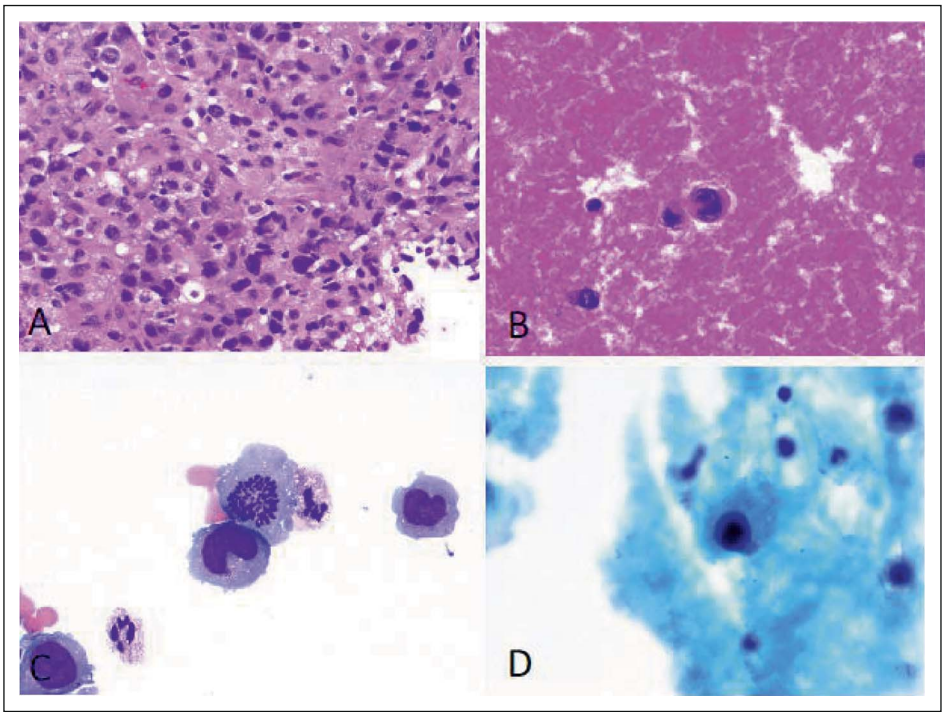

FIG 2. Anaplastic large cell lymphoma, ALK+. (A) Diffuse infiltrate of large, atypical cells, on retroperitoneal lymph node core biopsy, H&E 200×. CSF (B) Hallmark cells, cell block H&E. (C) mitosis and large, atypical cells, Wright stain. (D) Large atypical cells, Papanicolaou stain. By immunohistochemistry the neoplastic cells were positive for CD45+, variably expressed T-cell markers (CD5, CD4, and CD3), and strongly express CD30 with a subset expressing ALK-1. Concurrent flow cytometry revealed a large T-cell population coexpressing CD5+ and CD4+. ALK, anaplastic lymphoma kinase; H&E, hematoxylin and eosin.

chemotherapy regimen.[25-27] On the basis of superior survival without added toxicity in the ECHELON-2 phase III trial, BV + cytoxan, doxorubicin, and prednisone has also recently been approved for frontline treatment of ALCL, in which ≥ 10 percent of cells express CD30 by immunohistochemistry.[29] For relapsed or refractory systemic ALCL, BV alone has the potential to induce long-term remission in a subset of patients without any further anticancer therapy or ASCT. Our patient received single-agent BV for initial relapse and went into complete remission; however, his remission was very brief.

Similarly, as the oncogenic driver in the ALK+ ALCL, ALK fusion appears as an ideal therapeutic target.[30] Several generations of ALK inhibitors have been approved in the context of more prevalent ALK+ cancers, particularly ALK+ NSCLC. ALCL-inclusive trials and case series of patients with ALCL treated with the first-generation ALK inhibitor crizotinib have yielded positive results, particularly in the pediatric population.[31-33] The FDA has approved crizotinib for relapsed or refractory ALCL in children and young adults on the basis of the results from the ADVL0912 (ClinicalTrials.gov identifier: NCT00939770) study. Resistance mutations similar to those seen in other ALK+ cancers have been reported in both preclinical models[34,35] and in patients with ALCL.[33] Our patient relapsed within 12 months after ASCT, but responded to crizotinib for approximately 11 months, and then developed CNS progression. Possible reasons for CNS progression could have been acquired resistance to crizotinib and its poor penetration of the blood-brain barrier.[36]

Lorlatinib is a third-generation ALK tyrosine kinase inhibitor (TKI) that is more potent and has broad activity against ALK-resistant mutations.[19] Recently, FDA has approved lorlatinib in the frontline setting for patients with ALK+ metastatic NSCLC on the basis of data from the study B7461006 (ClinicalTrials.gov identifier: NCT03052608). Initially, lorlatinib was FDA-approved on the basis of a multicenter phase I/II study, for the treatment of patients with ALK+ metastatic NSCLC who were previously treated with one or more ALK TKIs.[20] Rapid responses were seen in patients with brain metastases. Leptomeningeal carcinomatosis from NSCLC represents a therapeutic challenge, mostly refractory to standard treatment, and is associated with a dismal prognosis. In this setting, case reports suggest a high efficacy of lorlatinib even after treatment failure of preceding ALK TKIs.[21] Researchers have demonstrated the efficacy of lorlatinib in nine ALK+ patients and two ROS1-positive patients with leptomeningeal carcinomatosis. The overall intracranial response rate, intracranial disease control rate, and median progression-free survival were 45%, 91%, and 9.3 months, respectively.[22]

Primary or secondary CNS involvement from ALK+ ALCL is limited to case series.[16-18] Protocols including high-dose methotrexate, high-dose cytarabine, RT, and intrathecal treatments seem to be effective in this population. However, our patient declined these options and favored oral targeted therapy at home. Given prior success in ALK+ malignancies refractory to ALK inhibitors as well as data in NSCLC with leptomeningeal metastases, we proposed lorlatinib as a salvage option. We observed a remarkable and rapid clinical response in our patient with a dismal performance status. Lorlatinib was well tolerated upon dose adjustment

for transient CNS side effects.[37] We are aware of an ongoing clinical trial testing the efficacy of lorlatinib in patients with refractory ALK+ lymphoma (A Study of Oral Lorlatinib in Patients With Relapsed ALK+ Lymphoma [CRU3] ClinicalTrials.gov identifier: NCT03505554). Our experience exemplifies the importance of rapid deployment of novel therapies as a salvage option on the basis of information extrapolated from clinical trials using the same molecular driver when conventional therapies are neither available nor acceptable to the patient.

AFFILIATIONS

[1]Department of Hematology and Oncology, St John's Riverside Hospital, Yonkers, NY
[2]Department of Oncology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY
[3]Division of Hematologic Malignancies, Department of Oncology, Montefiore Medical Center, Bronx, NY
[4]Department of Anatomic and Clinical Pathology, St John's Riverside Hospital, Yonkers, NY
[5]Department of Radiology, St John's Riverside Hospital, Yonkers, NY
[6]Department of Radiation Oncology, Montefiore Yonkers Radiation Oncology, Yonkers, NY

CORRESPONDING AUTHOR

Smitha Mellacheruvu, MD, St John's Riverside Hospital, 967 North Broadway, Yonkers, NY 10701; e-mail: smimella@montefiore.org.

AUTHOR CONTRIBUTIONS

Conception and design: Smitha Mellacheruvu, Mark N. Sayegh, R. Alejandro Sica
Provision of study material or patients: Ulrich Hermanto
Collection and assembly of data: Smitha Mellacheruvu, Mark N. Sayegh, R. Alejandro Sica, Maria Laureana Santos-Zabala, Jacob H. Gebrael
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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