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Letter to the Editor

Central nervous system relapse of systemic *ALK*-rearranged anaplastic large cell lymphoma treated with alectinib

1. Introduction

Anaplastic large cell lymphoma (ALCL) is a rare subtype of non-Hodgkin's lymphoma characterized by the proliferation of large, pleomorphic T-cells expressing the CD30 (previously Ki-1) surface antigen [1]. Approximately 60–85% of systemic ALCLs harbor rearrangements of the anaplastic lymphoma kinase (*ALK*) gene, resulting in production of an oncogenic tyrosine kinase fusion protein [2,3]. Response to anthracycline-based chemotherapy is generally favorable, though relapses to frontline treatment are common (˜40% five-year failure-free survival for ALK + ALCL) and carry a poor prognosis [4,5]. Salvage therapy using selective ALK inhibitors such as crizotinib [6–9] and ceritinib [10] can induce sustained remission in the setting of relapsed disease, though to our knowledge, treatment of central nervous system (CNS) relapse with ALK-targeted therapy has been described only once before [11].

Alectinib is a highly-selective, second-generation, oral ALK inhibitor known to evade the P-glycoprotein efflux transporter at the blood-brain barrier [12]. We present a case of systemic ALK + ALCL that relapsed to the cerebellum after complete metabolic response to anthracycline-based chemotherapy. The patient has achieved a durable second remission (> 12 months ongoing) with high-dose methotrexate (HD-MTX) followed by continuous alectinib monotherapy.

2. Case description

2.1. Initial presentation and frontline treatment

A 36-year-old man with a non-contributory past medical history presented with hematuria, urinary obstruction, low-grade fevers, night sweats, and 30 pounds of unintentional weight loss over the preceding two months. Computed tomography (CT) revealed bladder wall thickening, hydronephrosis, and diffuse inguinal and pelvic lymphadenopathy (Fig. 1**a–c**). The serum lactate dehydrogenase (LDH) level was elevated (392 units/L). Bladder and inguinal lymph node biopsies revealed proliferation of medium to large atypical lymphoid cells with prominent nucleoli, vesicular chromatin, and irregular nuclear borders that were positive for CD30 and negative for CD5/CD20 (Fig. 1**d–f**). *ALK* break-apart fluorescence *in situ* hybridization (FISH) confirmed *ALK* gene rearrangement. The patient was diagnosed with ALK + ALCL and was classified as high-intermediate risk based on an International Prognostic Index of 3.

The patient immediately underwent one cycle of CHOP chemotherapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 up to 2 mg, and prednisone 100 mg QD for 5 days) followed by five cycles of CHOEP chemotherapy (adding etoposide 100 mg/m^2 days 1–3). Positron emission tomography–computed tomography (PET-CT) scan demonstrated complete metabolic response. The patient improved clinically and was able to return to construction work one month later.

2.2. CNS relapse and salvage therapy

Three months after frontline therapy, the patient returned to the emergency room with interval development of severe, stabbing headaches, gait unsteadiness, diplopia, and emesis. Magnetic resonance imaging (MRI) revealed an irregular, enhancing left cerebellar mass (3.3x2.3x2.2cm) with a hemorrhagic center and significant peri-lesional edema (Fig. 1**g–h**). Dexamethasone was initiated. Stereotactic biopsy confirmed the diagnosis of relapsed ALCL. Suboccipital craniectomy was performed the following day to decompress the posterior fossa.

The first cycle of HD-MTX was initiated one week after biopsy. After two cycles of HD-MTX, the patient was administered his first dose of alectinib (600 mg Q12 h). The patient completed two more cycles of HD-MTX with a plan to continue alectinib. The alectinib dose was lowered after one month (450 mg Q12 h) to address persistent myalgias. A follow-up MRI acquired nine months into treatment demonstrated scant hemorrhage and gliosis in the left cerebellar hemisphere without gross evidence of tumor (Fig. 1g). The patient was discharged on alectinib and dexamethasone. The patient was undergoing work up for consolidation with stem cell transplantation.

2.3. Sustained remission and infectious complications

Several weeks after discharge, the patient returned to the hospital with shortness of breath and a productive cough. Chest CT revealed numerous soft tissue density cavitary pulmonary nodules. Sputum cultures, pleurocentesis, and lung nodule biopsy were performed to diagnose infection by *Nocardia asteroides*. A MRI of the head demonstrated multiple new, variably-sized enhancing parenchymal lesions involving the supra- and infra-tentorial compartments. Triple-therapy with amikacin, imipenem, and sulfamethoxazole-trimethoprim was initiated. Ceftriaxone subsequently replaced imipenem after cultures showed resistance to imipenem. A lumbar puncture was performed around this time, which revealed no evidence of lymphoma and negative fungal studies. Radiographic improvement of the CNS and pulmonary lesions was apparent after approximately one month of triple therapy, and the patient was discharged on dual-therapy of ceftriaxone and sulfamethoxazole-trimethoprim. The patient has since been tapered off of dexamethasone and ceftriaxone, and his clinical symptoms have resolved. He will remain on sulfamethoxazole-trimethoprim for one year followed by sulfamethoxazole-trimethoprim prophylaxis indefinitely.

At the time of writing, the patient has returned to full functional performance and has eclipsed 12 months of sustained remission on

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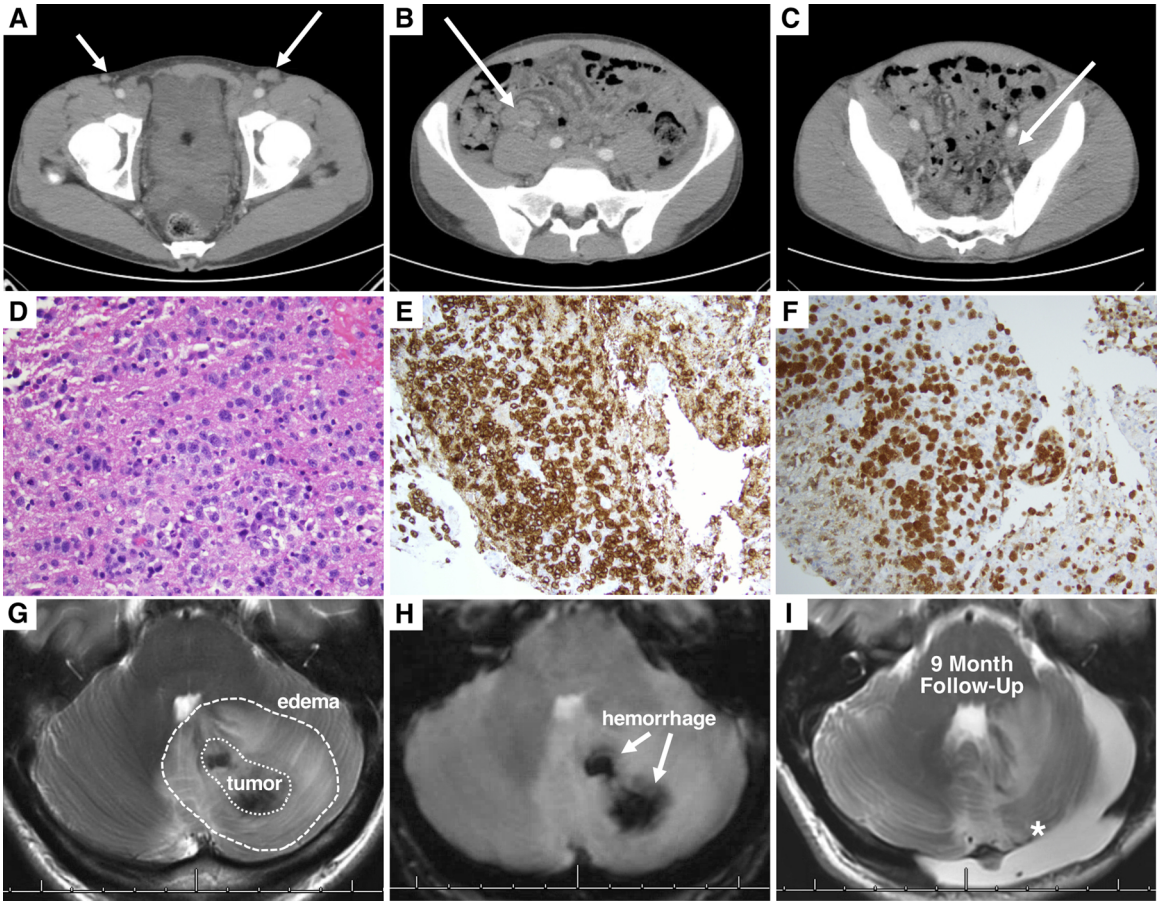

Fig. 1. (A–C) Presenting computed tomography (CT) scan. Axial slices revealing inguinal and pelvic lymphadenopathy (arrows). (D–F) Pelvic lymph node biopsy revealing anaplastic large cell lymphoma (D) with extensive CD30 (E) and ALK (F) immunostaining. (G–H) Magnetic resonance imaging (MRI) demonstrating relapsed disease to the cerebellum. (G) T2-weighted gadolinium-enhanced axial slice revealing cerebellar tumor with peri-lesional edema. (H) T2*-weighted axial slice demonstrating hemorrhage in the tumor bed. (I) Follow-up MRI scan (T2-weighted with contrast) acquired nine months after initiating treatment. An occipital pseudomeningocele and craniotomy defect are apparent (*). There is no evidence of tumor recurrence.

alectinib monotherapy. His most recent head MRI (acquired 9 months after initiating treatment) showed expected sequelae of suboccipital craniectomy with no evidence of tumor recurrence (Fig. 1i). We note that consolidation therapy with autologous or allogenic stem cell transplantation was initially considered but was deemed inappropriate in the setting of disseminated nocardiosis.

3. Discussion

We present an unusual case of systemic *ALK*-rearranged ALCL that relapsed to the cerebellum after responding favorably to anthracycline-based chemotherapy. Extranodal manifestations of ALK + ALCL typically involve the skin, bone, marrow, and soft tissues; CNS involvement is very uncommon [13–15]. CNS relapse of ALCL is extraordinarily rare [16] and has been described only in case reports [11,17–19].

Salvage approaches for relapsed/refractory ALCL include high-dose chemotherapy, autologous stem cell transplant, and recently, brentuximab vedotin [20,21]. In recent years, several promising reports have documented the use of ALK inhibitors in relapsed/refractory ALK + ALCL, which selectively inhibit the oncogenic tyrosine kinase [22]. In a phase II study by the Children's Oncology Group (NCT00939770), crizotinib, a first-in-class ALK inhibitor, was administered to children with relapsed/refractory ALK + ALCL. Of 20 patients treated at the recommended phase II dose (280 mg/m^2), 80% had complete response [9]. Gambacorti-Passerini and colleagues have reported impressive short-term (5–6 month follow-up) [7] and long-term (> 3 year follow-up) [6] responses among patients with relapsed/refractory ALK + ALCL treated with crizotinib. Richly et al. [10] reported durable responses to ceritinib, a second-generation ALK inhibitor, in three adults with relapsed ALK + ALCL enrolled in the phase II expansion cohort of the ASCEND-1 trial (NCT01283516). One case series from a phase II, non-randomized, non-controlled study (UMIN000016991) [23] involving the treatment of relapsed/refractory ALK + ALCL with alectinib has been published in abstract form [24], documenting complete responses in 6/10 patients.

The rationale for treating CNS-localized ALK + ALCL with alectinib is that it is known to penetrate the CNS [12]. Clinical evidence demonstrating the superior CNS activity of alectinib was obtained in a phase III trial comparing alectinib to crizotinib in patients with advanced, ALK + non-small-cell lung cancer [25,26]. To our knowledge, there is one published case describing the use of alectinib for treatment of ALK + ALCL involving the CNS. Reed et al. [11] reported a 27-year-old man with ALK + ALCL involving the cerebrospinal fluid at presentation who developed intolerable chemotherapy side effects and was treated with alectinib at relapse. The patient had a complete response within 2 months of alectinib therapy and was bridged to allogenic stem cell transplantation after 6 months.

We report the second case of CNS-localized, ALK + ALCL treated successfully with alectinib. Novel aspects of our case include the diagnosis of CNS involvement at relapse, CNS presentation as a discrete cerebellar mass, and the sustained response without stem cell transplantation. The durable remission observed in the case (> 12 months and ongoing) suggests that CNS-penetrant ALK inhibitors can be effective in treating ALK + ALCL involving the CNS.

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