The Usefulness of Straight Chemotherapy for Dermal Exposed Anaplastic Lymphoma Kinase Fusion-Positive Anaplastic Large-Cell Lymphoma with Intracranial Invasion

Abstract
Anaplastic large-cell lymphoma (ALCL) is characterized as extranodal lymphoma and usually chemosensitive disease with overall survival rate of 70%-90%. Prognosis is roughly distinguished by the existence of anaplastic lymphoma kinase (ALK) fusion in tumor cells with higher frequencies observed in the pediatric population, and the outcome of ALK fusion-positive ALCL is relatively good when appropriate treatment is completed. Here, we report a case of dermal-exposed ALK fusion-positive ALCL with intracranial invasion. The patient received straight chemotherapy (ALCL99 protocol) without any plastic or resection surgery. The dermal dehiscence was rapidly healed with controllable local infection, and the tumor was regressed without relapse. Therefore, straight chemotherapy has clinical relevance and is a useful treatment strategy for ALK fusion-positive ALCL with dermal dehiscence.

Keywords: Anaplastic large cell lymphoma, anaplastic lymphoma kinase fusion intracranial, skin exposure

Introduction
Anaplastic large-cell lymphoma (ALCL), predominantly occurred in male, presents a broad range of age and is manifested by extranodal disease. ALCL is usually chemosensitive disease and is relatively favorable prognosis with overall survival (OS) rate of approximately 70%-90%, which is distinguished by anaplastic lymphoma kinase (ALK) fusion in tumor cells according to the WHO 2016 classification. The present standard therapy for pediatric ALCL employed multi-agent combination chemotherapy.\(^1,^2\)

The frequency of ALK fusion in ALCLs varies around 40%-85% according to the age, with higher frequencies observed in the pediatric population.\(^3,^4\)

Although some reports showed the efficacy of multi-agent chemotherapy for ALCL regardless of skin dehiscence caused by skin involvement or cutaneous origin,\(^5\) we firstly report a case of an ALK fusion-positive ALCL with intracranial invasion and dermal exposure treated with straight chemotherapy.

Case Report
A 15-year-old male was admitted to a previous hospital due to basketball-induced head injury. At the initial radiographic examination, the patient was incidentally diagnosed with having an asymptomatic forebrain mass lesion (day 0). The mass was soft with mild tenderness and no mobility [Figure 1a]. The forebrain mass lesion has been increasing in size with dermal exposure; therefore, biopsy was conducted on day 14. In the time, plating for 2 cm diameter skull bone defect underneath was also conducted with titanium. Because the mass was growing rapidly, dermal dissection occurred, and the lesion was infected locally [Figure 1b, day 30]. Therefore, he was transferred to our institution on day 40. Laboratory tests indicated infectious inflammatory status: with a white blood cell (WBC) count of 10,000/µL and C-reactive protein (normal range: ≤0.14 mg/dL) and serum amyloid A (normal range: <8 µg/mL) elevated to 11.15 mg/dL and 1756 µg/mL, respectively. Computed tomography revealed the forebrain lesion, which was presented as a...
subcutaneous extension with destruction of the skull bone and replaced by the mass [Figure 1c]. Magnetic resonance imaging (MRI) revealed that the tumor was heterogeneously enhanced with intracranial invasion, with a maximum diameter of 65 mm [Figure 1d]. The invasive mass showed dural hypertrophy and compressed brain parenchyma. Fluorodeoxyglucose positron-emission tomography (FDG-PET) showed high uptake (maximum standard uptake value = 10.6) in the right forebrain lesion with another lesion of the left iliac bone [Figure 1e and f]. Serum levels of the tumor markers alpha-fetoprotein and N-telopeptide, which are the marker of endodermal sinus tumors and embryonal carcinomas or bone neoplasm, were not elevated. However, serum interleukin (IL)-2 receptor level was highly elevated (9576 U/mL, normal range: 145–519 U/mL).

Pathological findings

We performed the pathological diagnosis from the biopsy sample. Microscopically, some large cells with horseshoe-shaped nuclei in the eosinophilic region near the nucleus and mononuclear inflammatory cells in the background were observed [Figure 2a]. Immunohistochemistry revealed the presence of CD30 positive large tumor cells on the cell membrane and in the Golgi apparatus [Figure 2b]. These tumor cells showed ALK-1 expression in the cytoplasm and nucleus [Figure 2c]. In contrast, CD3, CD5, and CD20 were negative (data not shown). Fluorescent in situ hybridization (FISH) analysis using ALK break-apart probe connecting 2p. 23 lesion and including ALK gene revealed ALK rearrangement [Figure 2d].[6] Ki-67 index was 80%. Together, the tumor was diagnosed as ALK fusion-positive ALCL.

Treatment

The tumor tissue was exposed with infectious skin ulcer; therefore, we washed and sterilized the legion [Figure 3a, day 40] and treated with antibiotics (meropenem and clindamycin) for the local infection without any plastic or resection surgery. Furthermore, we conducted immediate chemotherapy which was performed at day 59 based on the evaluation of skin disruption as a controllable local infection. Chemotherapy was immediately administered for six courses based on the ALCL99 protocol [Figure 4].[7] Granulocyte-colony stimulating factor treatment was required because of chemotherapy-related febrile neutropenia; grade 3 according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, (Department of Health and Human Services, Washington, DC US), wound infection was successfully controlled. While only 2 days...
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after induction chemotherapy, the mass size decreased rapidly. As epithelialization progressed, bones and intracranial tissue were not exposed. The tumor was mostly disappeared, which was partially scarred at the end of the first course of chemotherapy [Figure 3b]. Finally, six courses of the chemotherapy regimen were successfully completed, and the skin dehiscence was completely epithelialized [Figure 3c]. MRI and FDG-PET revealed that systemic tumors were completely disappeared. On the duration of follow-up period (as long as 20 months) after the end of chemotherapy term, he keeps complete remission status, checked with a set of serum IL-2 receptor level and FDG-PET imaging.

Discussion

ALCL, a rare subtype type of lymphoma, is histologically characterized by frequently cohesive proliferation of large pleomorphic blasts and continuous expression of the cytokine receptor CD30 on the tumor cells. ALK-1-positive ALCL predominantly affects young males, and the outcome is relatively good when appropriate treatment is completed. The ALCL99 protocol, which was conducted as an international joint clinical trial in Europe and Japan, is the present standard therapy for pediatric ALCL. The ALCL99 protocol employed multi-agent combination chemotherapy. Among the registered patients, the 2-year event-free survival rate was 74.1% and the 2-year OS rate was 92.5%.

Although pediatric patients with ALCL have generally favorable prognosis, approximately 30% of the cases were relapsed and required further treatments. ALK-1 inhibitors pathologically have potential to play a central role in the molecular targeting therapy for ALK fusion-positive ALCL; the first-generation ALK-1 inhibitor crizotinib has been reported to be effective against ALK fusion-positive ALCL by the Children’s Oncology Group trial (ADVL0912 trial). The overall response rate for the treatment was 89% (8/9), with 78% (7/9) exhibiting complete response.

Here, we diagnosed ALK fusion-positive ALCL using FISH, which can be effective when complete remission is not observed in the patient by just standard chemotherapy. We firstly report a case of dermal exposed ALCL with intracranial invasion, who received straight chemotherapy (ALCL99 protocol) without any plastic or resection surgery and the dermal dehiscence was rapidly healed with controllable local infection. Intervention delay of chemotherapy might have caused critical neurological damage if this patient got tumor debulking and debridement surgery preceding to the induction chemotherapy. These kinds of risks come up to the surface, especially for chemosensitive tumors including ALCL. Surgical intervention with general anesthesia also holds its complication risks.

Therefore, straight chemotherapy has clinical relevance and is a useful treatment strategy for ALCL with dermal dehiscence.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initial will not be published and due efforts...
will be made to conceal his identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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