Primary adrenal extranodal NK/T-cell lymphoma: A case report and literature review

Satoshi Ichikawa⁎, Kei Saito, Noriko Fukuhara, Hisayuki Yokoyama, Koichi Onodera, Yasushi Onishi, Ryo Ichinohasamab, Hideo Harigae

a Department of Hematology, Tohoku University Hospital, Sendai, Japan
b Department of Hematopathology, Tohoku University Hospital, Sendai, Japan

ARTICLE INFO

Keywords:
Primary adrenal extranodal NK/T-cell lymphoma
L-asparaginase
Allogeneic hematopoietic stem cell transplantation
Graft-versus-lymphoma effect
Lymphomatous meningitis

ABSTRACT

A 37-year-old man was admitted to our department following the detection of bulky tumors in his bilateral adrenal glands. A biopsy resulted in the diagnosis of extranodal NK/T-cell lymphoma, nasal type (ENKL). After debulking by chemotherapy, allogeneic hematopoietic stem cell transplantation (alloHCT) was performed. Relapses in the liver and adrenal glands were identified 2 months post alloHCT, for which temporary administration of L-asparaginase resulted in complete metabolic response. However, multiple relapses in the central nervous system and lethal lymphomatous meningitis successively developed. Primary adrenal ENKL could tend to present as bulky lesion and follow an aggressive clinical course.

1. Introduction

Extranodal NK/T-cell lymphoma, nasal type (ENKL), is a rare subtype of aggressive non-Hodgkin lymphoma characterized by extranodal presentation and association with infection by Epstein-Barr virus (EBV) in the World Health Organization classification [1]. Typically, ENKL presents as an aggressive tumor, infiltrating the upper aerodigestive tract, with the nasal cavity being the prototypical site of involvement ("nasal ENKL"); however, cases of ENKL with extranasal involvement ("extranasal ENKL") do exist. ENKL is usually resistant to anthracycline-containing chemotherapies owing to the expression of the multidrug resistance gene (MDR1) and its P-glycoprotein product [2]. ENKL is relatively sensitive to radiation [3]. Recent clinical trials have shown that nasal ENKL can be managed using radiation, together with non-anthracycline chemotherapy [4, 5]. However, advanced or relapsed/refractory ENKL has a poor prognosis, with a median survival rate as low as 4 months [6]. Extranodal ENKL is reported to have poorer prognosis when compared to nasal ENKL [7-9], one of the reasons for this being the frequent presentation of ENKL at advanced stages. Extranodal presentation is also listed as one of the adverse factors for survival in the prognostic index for NK lymphoma (PINK), a recently proposed prognosis prediction model for ENKL [10].

Herein, we report a case of ENKL presented as bulky bilateral adrenal tumors, which followed an aggressive clinical course despite early intervention with allogeneic hematopoietic stem cell transplantation (alloHCT). Among the various presentations of extranasal ENKL, primary adrenal ENKL is considered rare and has only been sporadically reported in literature.

2. Case presentation

A 37-year-old man suffering from fever and abdominal pain for 2 weeks was presented to our department following the detection of bulky bilateral tumors in his adrenal glands by computed tomography (CT, Fig. 1a). At presentation, the patient had fever and abdominal distention. His performance status was two. Laboratory testing showed moderate liver dysfunction with elevation of lactic dehydrogenase (394 IU/L), ferritin (996 ng/mL), and soluble interleukin-2 receptor (4155 U/mL). The EBV viral load in the plasma was elevated (5.1 × 10⁴ copies/μg DNA). Positron emission tomography (PET), combined with CT, revealed bilateral bulky adrenal tumors with markedly increased uptake of fluorodeoxyglucose (FDG), appearing to directly involve the pancreas and kidney (Fig. 1b, c). Some increased FDG-uptake sites without abnormalities on CT were also observed (Fig. 1c). Biopsy of the left adrenal tumor revealed diffuse proliferation of large malignant cells, detected to be CD2+, surface CD3−, CD5−, CD7+, CD56+, CD4−, CD8−, TCRαβ−, TCRγδ−, CD30−, CD19−, and CD20− using flow cytometry. Immunohistochemistry (IHC) showed positive results for cytoplasmic CD3, CD7, CD56, TIA-1, and granzyme B. The Ki-67 labeling index was high (95%). In situ hybridization demonstrated the presence of EBV.
of EBV-encoded small RNA (EBER). Based on the abovementioned findings, a diagnosis of ENKL was established. The patient was classified as being at high risk according to PINK and PINK with EBV-DNA (PINK-E) [10].

Immediately following confirmation of the phenotype of NK/T-cell lymphoma by flow cytometry, we initiated chemotherapy using the SMILE regimen (dexamethasone, methotrexate, ifosfamide, L-asparaginase [L-asp], and etoposide) [11], which resulted in marked decrease of the tumors, achieving a partial response. Moreover, the EBV-DNA in the plasma was also decreased to an undetectable level. Six weeks after the initiation of chemotherapy, the patient received allogeneic peripheral blood stem cell transplantation from a human leucocyte antigen-identical sibling donor, which was preceded by a conditioning regimen with fludarabine (125 mg/m²) and melphalan (140 mg/m²). Prophylaxis for graft-versus host disease (GVHD) consisted of cyclosporine and short-term methotrexate. The clinical course of the patient was initially favorable without severe regimen-related toxicities or acute GVHD. Engraftment of neutrophils was established on day 15, and complete donor chimerism of peripheral blood was confirmed. However, 2 months post transplantation, PET/CT showed a relapse in the liver and left adrenal gland (Fig. 1d). Although the tumor did not decrease with abrupt interruption of cyclosporine administration, temporary administration of L-asp resulted in rapid tumor regression. On day 98, PET/CT confirmed complete metabolic response (Fig. 1e), which was maintained until death.

Facial palsy and hearing loss subsequently developed around day 120 and around day 140, respectively. Magnetic resonance imaging (MRI) revealed the presence of mass bilateral lesions in the internal acoustic meatuses and the fourth ventricle (Fig. 2a), which were considered relapsed lesions of ENKL. Although these lesions decreased after radiation treatment, further relapse in the cervical spinal cord was subsequently confirmed, which afflicted the patient with severe back pain and weakness of the upper limbs. Despite additional radiation for the cervical lesion, back pain had worsened, which led to the development of paraplegia that was not relieved with intravenous high-dose administration of methotrexate. A spinal tap revealed the massive infiltration of lymphoma cells (1775 cells/μL) in the cerebrospinal fluid (CSF; Fig. 2b) with EBV-DNA being significantly increased (4.7 × 10³ copies/μg DNA) in CSF, confirming a diagnosis of lymphomatous meningitis. Whole-body CT revealed no apparent relapsed lesions. Thereafter, the patient received the best supportive care, and died 3 weeks later.

3. Discussion

Advanced ENKL can involve various organs in addition to the prototypical nasal cavity. According to the 2016 WHO classification of lymphoid malignancies [1], the preferential lesion sites of ENKL are the skin, soft tissue, gastrointestinal tract, and testes. More recently, in a multicenter retrospective research, Yamaguchi et al. reported clinical features of 47 cases of extranasal ENKL and described the distribution of the extranodal sites involved at diagnosis in each case [7]. According to this study, frequently involved sites were the skin (18 cases), gastrointestinal tract (14 cases), liver (16 cases), spleen (11 cases), and
### Table 1

| Reference | Age/sex | B symptoms | Lymph node/bilaterality ([mm]) | Other lesions | Immunophenotype | Diagnosed measure | Treatment | Survival | Outcome |
|-----------|---------|------------|-------------------------------|--------------|----------------|------------------|----------------|----------|---------|
| [1]       | 40/F    | No         | 108 (L 75, R 31)              | No           | n/a            | Surgical resection | Autopsy | 77%     | mo       |
| [2]       | 67/M    | No         | 466                           | n/a          | +/− +           | CT-guided neck CT | +                       | 75%     | +       | +       |
| [3]       | 17/M    | Yes        | 394                           | n/a          | +/− +           | CT-guided neck CT | +                       | 95%     | +       | +       |

Other lesions:
- Bone marrow/peripheral blood (15 cases).
- Involvement of adrenal glands was also documented in 4 cases, and all had multiple organ involvements with unknown primary lesion sites. Although disseminated ENKL involving adrenal gland are not uncommon, only 5 cases of primary adrenal NK/T-cell lymphoma with the presence of EBER and pathologically cytotoxic molecules, which are considered to be mandatory for diagnosis, have been reported in literature [12-16]. The clinicopathological features of these five cases, and those of the present case, are described in Table 1. Among the six cases, bilateral adrenal lesions were present in five but adrenal insufficiency was only documented in one case. B symptoms were documented in three cases. All the cases showed bulky lesions (diameter ≥ 50 mm), with the present case presenting the largest bilateral lesions among all. Half of the cases were accompanied by multiple site involvements. Immuno-phenotypically, all except one case exhibited an NK-cell phenotype (CD56 positive), and all the cases showed a high Ki-67 labeling. There has been a single report describing long-term survival after aggressive treatment, including high-dose therapy and autologous hematopoietic stem cell transplantation. Two cases were diagnosed as ENKL, postmortem. Based on the findings mentioned above, primary adrenal ENKL tends to present with bilateral adrenal tumors accompanied by multiple other lesions and B symptoms, following an aggressive clinical course.

Considering the poor prognosis of patients with advanced or relapsed/refractory ENKL, alloHCT could be a treatment option if patients have a good general condition [2, 17]. Retrospective analysis of 82 ENKL cases, receiving alloHCT, in the database of the Center for International Blood and Marrow Transplant Research [18], the 3-year progression-free survival was 34% after a median follow-up of 36 months. No relapses were observed within 2 years of alloHCT, which was considered to be achieved owing to the graft-versus-lymphoma (GVL) effect. In the present case, although premature relapse was experienced early following alloHCT, complete metabolic response of systemic disease was achieved after a short course of administration of l-asp, which was maintained until death. This robust response may be due to the GVL effect. Conversely, we assumed that the central nervous system (CNS) relapse had escaped the GVL effect and developed a fatal lymphomatous meningitis. The efficacy of CNS prophylaxis is not established in ENKL, and it remains unknown whether CNS relapse, in the present case, could have been affected by inadequate CNS prophylaxis prior to transplantation.

In summary, we report a case of primary adrenal ENKL with bilateral bulky tumors, for which alloHCT was performed. A GVL effect was observed; however, it was not effective against a CNS relapse and thus led to the development of lethal lymphomatous meningitis. Further accumulation of clinical experience is necessary to understand primary adrenal ENKL and for the development of improved therapeutic interventions against this disease.

### Declaration of Competing Interests

The authors declare that there are no conflicts of interest relevant to this study.

### References

[1] S. Swerdlow, E. Campo, N. Harris, E. Jaffe, S. Pileri, H. Stein, WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, IARC Press, Lyon, 2016.

[2] M. Yamaguchi, R. Suzuki, JSH practical guidelines for hematological malignancies, 2018: II. Lymphoma-9. Extranodal NK/T-cell lymphoma, nasal type, Int. J. Hematol. 109 (4) (2019) 371–376.

[3] N. Yoshikawa, T. Inomata, T. Shinbo, M. Takahashi, Y. Uesugi, Y. Narumi, Extracranial natural killer/T cell lymphoma, nasal type (ENKL), Int. J. Hematol. 109 (4) (2019) 371–376.

[4] M. Yamaguchi, K. Tobinai, M. Oguchi, N. Ishizuka, Y. Kobayashi, Y. Isobe, K. Itoh, N. Usui, I. Wasada, T. Kinoshita, K. Ohshima, Y. Matsuno, T. Terauchi, S. Nawano, S. Ishikura, Y. Kagami, T. Hotta, K. Oshimi, The authors declare that there are no conflicts of interest relevant to this study.
T-cell lymphoma: Japan clinical oncology group study JCOG0211, J. Clin. Oncol. 27 (33) (2009) 5594–5600.

[5] S.J. Kim, D.H. Yang, J.S. Kim, J.Y. Kwak, H.S. Eom, D.S. Hong, J.H. Won, J.H. Lee, D.H. Yoon, J. Cho, T.K. Nam, S.W. Lee, Y.C. Ahn, C. Suh, W.S. Kim, Concurrent chemoradiotherapy followed by L-asparaginase-containing chemotherapy, VIDL, for localized nasal extranodal NK/T-cell lymphoma: CISL08-01 phase II study, Ann. Hematol. 93 (11) (2014) 1895–1901.

[6] R. Suzuki, Treatment of advanced extranodal NK/T-cell lymphoma, nasal-type and aggressive NK-cell leukemia, Int. J. Hematol. 92 (5) (2010) 697–701.

[7] M. Yamaguchi, R. Suzuki, K. Miyazaki, J. Amaki, J. Takizawa, N. Sekiguchi, S. Kinoshita, N. Tomita, H. Wada, Y. Kobayashi, N. Nitsu, T. Ando, T. Maeda, B. Saito, H. Matsuoka, R. Sakai, N. Kubota, Y. Masaki, Y. Kameska, N. Asano, M. Ouchi, N. Katayama, Improved prognosis of extranodal NK/T-cell lymphoma, nasal type of nasal origin but not extranasal origin, Ann. Hematol. 98 (7) (2019) 1647–1655.

[8] J.C. Jo, D.H. Yoon, S. Kim, B.J. Lee, Y.J. Jang, C.S. Park, J. Huh, S.W. Lee, J.S. Ryu, C. Suh, Clinical features and prognostic model for extranasal NK/T-cell lymphoma, Eur. J. Haematol. 89 (2) (2012) 103–110.

[9] W.Y. Au, D.D. Weisenburger, T. Intragumtornchai, S. Nakamura, W.S. Kim, I. Sng, J. Vose, J.O. Armitage, R. Liang, T.C.L.P. International peripheral, clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the international peripheral T-cell lymphoma project, Blood 113 (17) (2009) 3931–3937.

[10] S.J. Kim, D.H. Yoon, A. Jaccard, W.J. Lim, H. Hong, Y. Park, K.M. Chang, Y. Maeda, F. Ishida, D.Y. Shin, J.S. Kim, S.H. Jeong, D.H. Yang, J.C. Jo, G.W. Lee, C.W. Choi, W.S. Lee, T.Y. Chen, K. Kim, S.H. Jung, T. Murayama, Y. Oki, R. Advani, F. d’Amore, N. Schmitz, C. Suh, R. Suzuki, Y.L. Kwong, T.Y. Lin, W.S. Kim, A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis, Lancet Oncol. 17 (3) (2016) 389–400.

[11] M. Yamaguchi, Y.L. Kwong, W.S. Kim, Y. Maeda, C. Hashimoto, C. Suh, K. Izutsu, F. Ishida, Y. Ito, K. Inamoto, T. Kodama, H. Kimura, R. Hyn, S. Nakamura, K. Oshimi, R. Suzuki, Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-cell tumor study group study, J. Clin. Oncol. 29 (33) (2011) 4410–4416.

[12] P. Dong, L. Wang, G. Shen, L. Li, Primary adrenal extranasal NK/T-cell lymphoma with subcutaneous involvement demonstrated on FDG PET/CT: a clinical case report, Medicine (Baltimore) 98 (11) (2019) e14818.

[13] T. Tsukahara, A. Takasawa, M. Murata, K. Okumura, M. Nakayama, N. Sato, T. Hasegawa, NK/T-cell lymphoma of bilateral adrenal glands in a patient with pyothorax, Diagn. Pathol. 7 (2012) 114.

[14] K.K. Dunning, K. Wudihansri, A.O. Safi, C.J. Holman, R.W. McKenna, S.E. Pambuccian, Adrenal extranodal NK/T-cell lymphoma diagnosed by fine-needle aspiration and cerebrospinal fluid cytology and immunophenotyping: a case report, Diagn. Cytopathol. 37 (9) (2009) 686–695.

[15] M.A. Thompson, M.A. Habra, M.J. Rabout, F.C. Holsinger, N.D. Perrier, S.G. Wagaenpach, M.A. Rodriguez, Primary adrenal natural killer/T-cell nasal type lymphoma: first case report in adults, Am. J. Hematol. 82 (4) (2007) 299–303.

[16] Y. Mizoguchi, K. Nakamura, S. Miyagawa, S. Nishimura, K. Arima, M. Kobayashi, A case of adolescent primary adrenal natural killer cell lymphoma, Int. J. Hematol. 81 (4) (2005) 330–334.

[17] M.A. Kharfan-Dabaja, A. Kumar, E. Ayala, M. Hamadani, P. Reimer, C. Gisselbrecht, F. d’Amore, E. Jantunen, T. Isida, A. Bazarbachi, F. Foss, R. Advani, T.S. Fenske, H.M. Lazarus, J.W. Friedberg, M. Aljurf, L. Solok, K. Tobinai, E. Tox, J.C. Burns, N.M. Reddy, R. Suzuki, S. Ahmed, A. Nademanee, M. Mothy, A.K. Gopal, M.A. Fanale, B. Pro, A.J. Moskowitz, A. Sureda, M.A. Perales, P.A. Carpenter, B.N. Savani, Clinical practice recommendations on indication and timing of hematopoietic cell transplantation in mature T cell and NK/T cell lymphomas: an international collaborative effort on behalf of the guidelines committee of the american society for blood and marrow transplantation, Biol. Blood Marrow Transplant 23 (11) (2017) 1826–1838.

[18] A.S. Kanate, A. DiGilio, K.W. Ahn, M. Al Malki, E. Ayala, E. Ball, Q. Bashir, A. Cashen, D. Couriel, J. Díez-Martin, E. Katsanos, Y. Linhares, S. Mori, R. Nash, A. Pawaorde, M.A. Perales, C.D. Phipp, C. Richman, B.N. Savani, M.Y. Shapiro, P. Stiff, R. Strair, T.S. Fenske, S.M. Smith, A. Sureda, M.A. Perales, P.A. Carpenter, M. Hamadani, Allogeneic haematopoietic cell transplantation for extranodal natural killer/T-cell lymphoma, nasal type: a CIBMTR analysis, Br. J. Haematol. 182 (6) (2018) 916–920.