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

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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]. Extranasal 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. Extranasal 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 (5.1×10^4 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 $CD3^-$, $CD5^-$, $CD7^+$, $CD56^+$, $CD4^-$, $CD8^-$, $TCR\alpha\beta^-$, $TCR\gamma\delta^-$, $CD30^-$, $CD19^-$, 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

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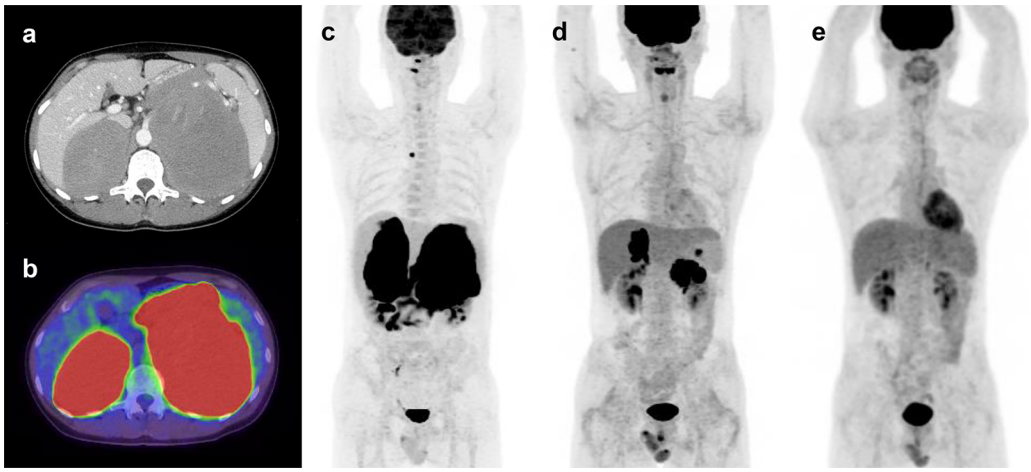

Fig. 1. Radiological findings. At diagnosis, computed tomography (CT) (a) and Positron emission tomography (PET)/CT (b) revealed the presence of bilateral bulky adrenal tumors with direct invasion toward the pancreas. The maximum standardized uptake value (SUVmax) was high (left 23.1, right 24.0). PET (c) also revealed the presence of some other lesions that were not obvious in CT. Systemic relapse was detected 2 months post transplantation (d), and was well controlled after short-term administration of L-asparaginase (e).

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/m^2) and melphalan (140 mg/m^2). 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 × 10^3 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

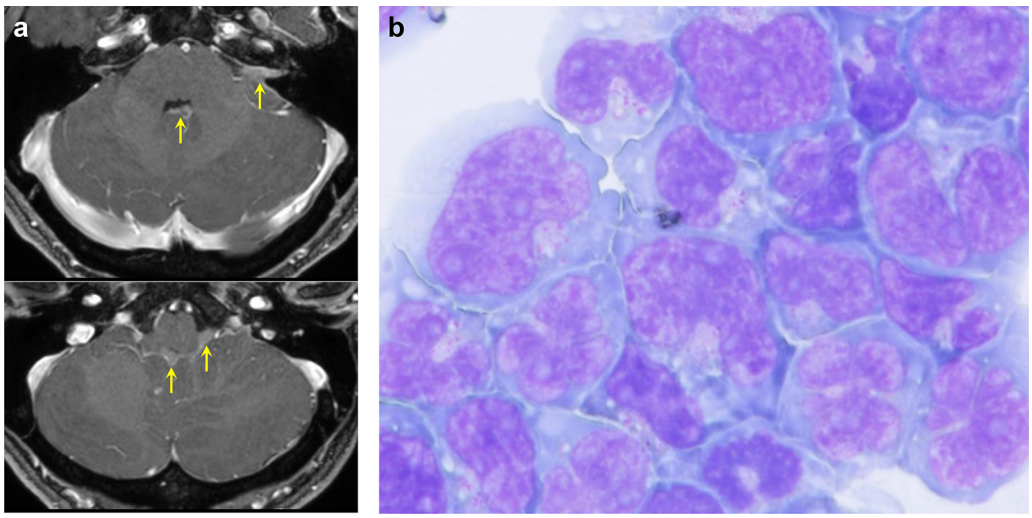

Fig. 2. Findings of the central nervous system (CNS) infiltration. (a) Images obtained with magnetic resonance imaging (MRI) at the time of exacerbation of hearing loss (gadolinium-enhanced T1-weighted images). Arrows show lesion sites. (b) The massive infiltration of lymphoma cells in the cerebrospinal fluid (May-Giemsa staining, × 100).

Table 1
Reported cases of primary adrenal extranodal NK/T-cell lymphoma.

Reference	Age/ Sex	B symp-toms	Adrenal insufficiency	LDH [IU/L]	sIL-2R [U/mL]	Laterality (max tumor diameter [mm])	Other lesions	Diagnostic measure	Blood EBV-DNA	Immunophenotype CD2	CD3	CD4	CD8	CD30	CD56	GzB	TIA-1	EBER-ISH	Ki-67 LI	Therapy	Outcome
[12]	40/F	No	No	n/a	n/a	Bilateral (L 75, R 31)	Soft tissue	Surgical resection	n/a	+	ε+	–	–	–	+	+	n/a	+	70%	GLIDE, HDT + ASCT	Survival, > 1 y
[13]	79/F	No	Yes	1038	1185	Bilateral (L 55, R 57)	No	Autopsy	n/a	n/a	+	–	–	–	–	–	+	+	77%	–	Early death
[14]	67/M	No	No	n/a	n/a	Bilateral (n/a)	CSF, BM	CT-guided needle biopsy	n/a	+	–	–	–	n/a	+	+	+	+	n/a	DEX	Early death
[15]	35/M	Yes	No	666	n/a	Left (50)	No	Surgical resection	n/a	dim	dim	n/a	n/a	n/a	+	+	+	+	75%	hyperCVAD/ MA, CHOP	Death, 3 mo
[16]	17/M	Yes	No	4480	34,900	Bilateral (L 50, R 48)	Liver, lung, BM, spleen, etc.	Autopsy	detected	n/a	–	n/a	n/a	n/a	+	+	+	+	n/a	–	Early death
This case	37/M	Yes	No	394	4155	Bilateral (L 138, R 101)	Nasal cavity, pancreas, paravertebra	CT-guided needle biopsy	detected	+	+	–	–	–	+	+	+	+	95%	SMILE, Sib/ PBSCT	CNS relapse, Death, 10 mo

Abbreviations; BM, bone marrow; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CNS, central nervous system; CSF; cerebrospinal fluid; DEX, dexamethasone; EBER, EBV-encoded RNA; GLIDE, gemcitabine, L-asparaginase, ifosfamide, dexamethasone, etoposide; GzB, granzyme B; HDT + ASCT, high-dose chemotherapy with autologous hematopoietic stem cell transplantation; hyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; Ki-67 LI, Ki-67 labeling index; LDH, lactic dehydrogenase; MA, methotrexate, cytarabine; n/a, not available; Sib/PBSCT, HLA-identical sibling donor peripheral blood stem cell transplantation; sIL-2R, soluble interleukin-2 receptor; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide.

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. Immunophenotypically, 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.

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