

Extranodal NK/T cell lymphoma nasal type: A case report and literature review

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Abstract: Extranodal NK/T cell lymphoma nasal type (ENKTL) is a rare malignancy. Due to its non-specific early symptoms and highly aggressive nature, the diagnosis and treatment of ENKTL remains clinically challenging. Combination of chemotherapy and radiotherapy is the standard treatment for stage I/II ENKTL. Herein, we report a case of primary ENKTL first presented in left-side nasal cavity and then in right-side larynx. More than four years after the initial diagnosis of nasal ENKTL, his left nose was ulcerated due to swelling and it was highly suspected that the lesion was local recurrence. Following up for 22 months after the diagnosis of laryngeal ENKTL, there was no sign of local recurrence of laryngeal lesions after six cycles of GDP program and three-dimensional radiotherapy. The final diagnosis was primary laryngeal ENKTL, and local recurrence of nasal cavity was highly suspected. From the initial diagnosis, after the application of CHOP, DDGP/DGP sequential chemotherapy and simultaneous radiotherapy, nasal and laryngeal tumors were successfully controlled. We also review the relevant literature to discuss the treatment of NKT, hoping to provide some clinical enlightenment.

Keywords: extranodal NK/T cell lymphoma nasal type (ENKTL), nasal cavity, larynx

1. Introduction

Extranodal NK/T cell lymphoma nasal type (ENKTL) is a rare aggressive non-Hodgkin lymphoma, which has been reported predominately in East Asia and Latin America. ENKTL is derived from NK cells or cytotoxic T cells and is closely related to EB virus (EBV) infection [1]. ENKTL almost occurs in non-nodal sites, and 80% of it occurs around the upper respiratory tract, such as nose, nasopharynx, oropharynx and the Waldeyer's ring [2]. Its symptoms are usually non-specific, including stuffy nose, runny nose, sore throat and so on. Histomorphologically, tumor infiltrates often present with angiodestruction, zonal necrosis resulting in the destruction of midline facial structures. The typical immunophenotypes commonly expressed by tumor cells are CD2+, surface CD3+, cytoplasmic CD3ε+, CD56+ and cytotoxic molecules (such as perforin, **granzyme B**, and TIA1+) [3].

The treatment strategy of ENKTL is determined according to its stage and prognostic factors. The standard treatment of stage I/II ENKTL includes radiotherapy, chemotherapy or a combination of them. For stage III/IV and relapsed/ refractory ENKTL, in addition to radiotherapy and chemotherapy, more aggressive approaches such as hematopoietic stem cell transplantation (HSCT), targeted therapy and immunotherapy are needed [4-6].

Here we report a case of primary ENKTL occurs metachronously in nasal cavity and larynx, in order to provide reference for the diagnosis and treatment of ENKTL.

2. Case report

2.1 First diagnosis and treatment

A 26 year old Chinese male patient had left-side nasal congestion and runny nose for half a month, which failed to respond to antibiotic treatment in primary care. After we admitted the patient, a

nasopharyngeal CT was arranged, which revealed a neoplasm in the left-side nasal cavity. Biopsy of the neoplasm was arranged immediately, and the pathological result was ENKTL. Immunohistochemistry (IHC) analysis demonstrated that tumor cells were CD2+, CD3+, CD3ε+, CD43+, CD56+, GrB+, TIA1+ and weakly positive for EBER, negative for CD20 and CD79a, and Ki67 60% (Figure 1, Table 1). Plasma EBV DNA was negative. After essential workup procedures including chest and abdominal CT, bone marrow biopsy, the patient was clinically diagnosed as nasal cavity ENKTL, stageIE, low-risk group. Following 5 cycles of chemotherapy with CHOPE regimen (cyclophosphamide 750mg/m² day 1, vincristine 2mg day 1, doxorubicin 40mg/m² day 1, prednisone 100mg day 1~5, and etoposide 100mg/m² day 1~3), partial response (PR) was achieved. Concurrent radiotherapy of nasal cavity (50Gy, 25F) was performed along with the 6th and 7th cycles of CHOPE chemotherapy, with the 8th cycle of CHOP chemotherapy performed after radiotherapy. Ultimately, after 8 cycles of chemotherapy and concurrent radiotherapy, the patient's condition was stable and the final outcome is complete response (CR). This good recovery has been maintained for three years.

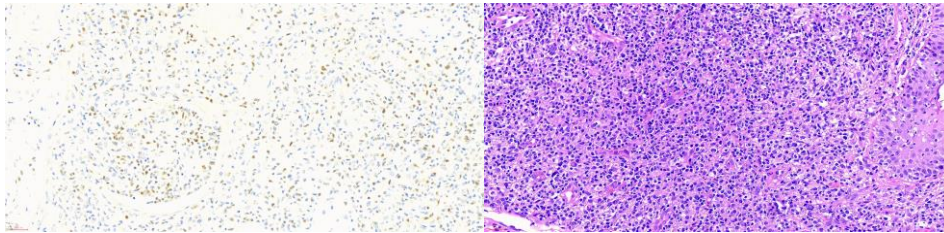


Figure 1: Histological immunopathology of the ENKTL patient (EBER, original magnification 40). (A) From the nasal cavity in 2015, (B) from the larynx in 2019.

Table 1: The IHC of the nasal cavity and Larynx.

	CD2	CD3	CD3ε	CD5	CD7	CD43	CD56	GrB	TIA1	EBER	Ki67	CD20	CD79a
Nasal cavity	+	+	+			+	+	+	+	Weak	60%	-	-
Larynx	+		+	Weak	+	+	+	Weak	+	+	35%	-	-

Weak: weakly positive.

2.2 Primary / recurrent larynx ENKTL

Exactly three years later in the spring, he developed pain in the right-side throat. Nasopharynx and neck MRI revealed changes in the left-side nasal cavity after radiotherapy and a neoplasm in the right-side oropharynx (Figure 2). The patient then underwent laryngoscopy, which reported the presence of neoplasm in the right-side laryngeal zone, ventricular zone and laryngeal ventricle. The neoplasm in the right-side ventricular band was biopsied and the result was also ENKTL. The IHC showed that the tumor cells were mainly CD2+, CD3ε+, CD7+, CD43+, CD56+, TIA1+, and weakly positive for CD5 and GrB, negative for CD20 and CD79a, and Ki67 35%. CISH: EBER+ (Figure 1, Table 1). EBV DNA was still negative. After completing comprehensive workup examinations including chest and abdominal CT, bone marrow biopsy, we detected no recurrence in nasal cavity, then considered that the patient's laryngeal lesion was primary, so we diagnosed he with laryngeal ENKTL, stage IE, low-risk group.

At this time, he was 29 years old and did not have any chemotherapy contraindications. Considering the accumulative toxicity of anthracycline in the previous 8 cycles of chemotherapy, as well as the consensus that non-anthracycline-based-pegaspargase-including regimens are more effective, we suggested the more effective DDGP regimen (dexamethasone, cisplatin, gemcitabine, and pegaspargase). However, the patient only received GDP (gemcitabine 800mg/m² day 1 day 8, dexamethasone 15mg/m² day 1~5, and cisplatin 20mg/m² day 1~4) chemotherapy for economic reasons, and the efficacy was PR after 2 cycles. During the third cycle of chemotherapy, the patient was unable to receive gemcitabine chemotherapy on the 8th day because of continuous low blood platelets, so concurrent radiotherapy of the larynx (55Gy, 25F) was started immediately under our recommendation. During radiotherapy the subsequent course of chemotherapy was carried out. During the 6th cycle, he developed fever and upper respiratory tract infection, which improved after active anti-infective treatment, but the patient refused gemcitabine chemotherapy on the 8th day. At that time, CR has been achieved and he was discharged from the hospital. Then came the outbreak of COVID-19 and a nationwide lockdown, so he did not have regular follow-up or continued treatment.

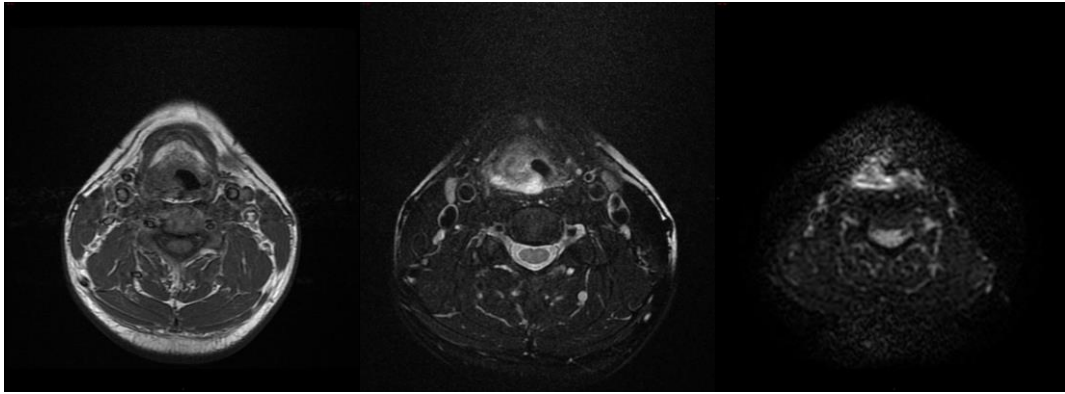


Figure 2: MR images from the patient's larynx were taken in 2019. (A) T1, (B) T2, (C) DWI.

2.3 Subsequent treatment and follow-up

Four months later, the patient found a mass in the left-side nasal cavity which began to fester, resulting in the swelling of right-side face, so he sought treatment again. Because our hospital admitted the COVID-19 patients, he was unable to be admitted in our hospital and thus transferred to another hospital. CT scan of the paranasal sinus was performed, showing changes of the left nasal cavity with the formation of local ulcers. The pathology of nasal mass showed necrotic tissue. However, considering the previous diagnosis of ENKTL, the doctor in charge diagnosed the patient with recurrent nasal cavity ENKTL, so he received one cycle of chemotherapy with Gemox regimen.

After that, our hospital was opened to the public, and the patient was accepted by us. Rebiopsy of nasal lesion was performed, which identified no traces of recurrence again. In the absence of pathological confirmation of recurrence, we recommended he to be rebiopsied in a more authoritative hospital. Still, only numerous necrotic tissue was found. Meanwhile, nasal secretions were cultured showing *Enterococcus faecalis* infection, and corresponding antibiotics were given according to the drug sensitivity test. Considering the highly possibility of recurrence, pegaspargase was added and P-Gemox regimen (pegaspargase 2,500IU/m² day 1, gemcitabine 1,250mg/m² day 1, and oxaliplatin 80mg/m² day 1) was used for the second and third cycle of chemotherapy. At that time, the ulceration of left-side nasal cavity has been healed, but the nasal wing was partially missing and the midline structure of the face was damaged. There were no symptoms such as local redness, swelling, heat and pain, so the patient refused further treatment.

When all treatments were completed, the patient experienced 2 rounds of radiotherapy and 17 cycles of chemotherapy. It has been 5 years and 3 months since the initial diagnosis. Now the 31-year-old patient is regularly followed up with the treatment effect of CR. We earnestly hope that the patient can have a longer survival time.

3. Discussion

The combination of chemotherapy and radiotherapy is the standard treatment for stage I/II ENKTL. Many regimens of chemotherapy have been demonstrated effective, including AspaMetDex, MESA, MEDA, GELOX, PGEMOX, DDGP, GDL, GOLD, GLIDE[7]. Compared with chemotherapy, the integration of radiotherapy improved loco regional control as well as long-term survival, which makes radiotherapy an essential component for the treatment of stage I/II ENKTL [8]. However, the optimal timing of radiotherapy has not been elucidated. Without clinical trials showing superiority of one combination over another, both sequential and concurrent radiochemotherapy are acceptable [2].

Although non-anthracycline-based regimens especially regimens containing L-asparaginase have been demonstrated superior than anthracycline-based regimens, CHOPE was widely utilized in our department [9]. When this patient was first diagnosed with stage I primary nasal cavity ENKTL, 5 cycles of CHOPE chemotherapy followed by concurrent radiochemotherapy as well as consolidating chemotherapy was performed. After 2 cycles of CHOPE, PR has already been yielded. At the completion of chemo radiotherapy, there was no evidence of tumor on nasal cavity, indicating that CHOPE radiochemotherapy with radiotherapy was effective in our patient.

Three years after complete remission, when the neoplasm of his larynx was pathologically

diagnosed as ENKTL, we could not determine whether the laryngeal lesion was primary or related to the nasal lesion. Although initial workup showed no macroscopically tumor in larynx, microscopically tumor may exist that was missed by CT-scan, which demonstrated the importance of the initial staging. Therefore, (18)F-FDG PET/CT, as a valuable tool for diagnosis, staging, and treatment planning in ENKTL, should be recommended for early and timely use. [10, 11]. At that time, we considered that the lesion of his larynx was primary, although to date there was no report of both primary nasal cavity and laryngeal ENKTL. Anil Gungor et al. have reported a case of local infiltration from the anterior part of the inferior turbinate into the bilateral posterior nasal cavity and eventually into the larynx, although both nasal cavity and larynx were biopsied and confirmed ENKTL, laryngeal lesion was clearly related to nasal lesion, which defined as local invasion [12]. In our case, there was no evidence suggesting that laryngeal lesion was spread from nasal cavity.

No matter laryngeal lesion was primary or secondary, there is no difference in the subsequent treatment. At that time, there was a consensus on the treatment of ENKTL based on asparaginase/pegaspargase regimen, which can significantly improve the PFS (progression-free survival) and OS (Overall Survival) of newly diagnosed ENKTL patients with good tolerance [13, 14]. So we recommended DDGP regimen for chemotherapy [15, 16]. However, because of the high price of pegaspargase, the patient was subjected to a regimen without pegaspargase (GDP), which was also an effective regimen. Studies have shown that after the second cycle of the GDP scheme, the CRR (Complete remission rate) and ORR (objective response rate) are 30.6% and 91.7%, respectively [17]. In our patient, GDP was proved effective as PR was achieved after 2 cycles of chemotherapy. With a follow-up of 22 months since the diagnosis of laryngeal ENKTL, after 6 cycles of GDP regimen with sandwiched radiotherapy, the laryngeal lesion shows no signs of local recurrence.

Recurrence is a common condition frequently encountered in the treatment of malignant tumors, including ENKTL [18]. Four years and four months after the initial diagnosis of nasal cavity ENKTL, when his left-side nose festered with swelling, it was reasonable that the lesion was highly suspected as local recurrence. However, although the patient underwent three times biopsies of nasal lesion, it was never pathologically diagnosed as recurrence. Whether the lesion was only infection or infection with recurrence, it was hard to demonstrate. Whatever, the infection was cured with antibiotics, and considering from the worst scenario that the lesion was recurrence, the patient was treated with salvage chemotherapy, following which, there was no evidence of lump or infection. The P-Gemox regimen was proven to be effective and well-tolerated [19]. Its ORR and CRR are 80.0% and 51.4% respectively. 3 year PFS and OS rates were 38.6% and 64.7%, respectively [20]. Yet whether four cycles of chemotherapy (one cycle of Gemox and three cycles of P-Gemox) is enough warrants long-term follow-up.

In this report, we showed a case initially diagnosed with primary ENKTL of nasal cavity, and then diagnosed with primary ENKTL of larynx three years later, and finally highly suspected with local recurrence of nasal cavity. The combination of radiotherapy with either CHOPE or GDP chemotherapy were considered effective because complete remission was achieved following each treatment. However, complete remission does not guarantee long-term tumor-free survival. How to reduce recurrence and improve long-term survival warrants more corresponding researches.

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Informed consent: The patient's written consent has been signed/obtained.

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