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The factors associated with the early diagnosis of nasal NK/T-cell lymphoma with prominent ocular symptoms and general nasal NKTL

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ABSTRACT

Aim: This study explored the clinical features of nasal natural killer/T-cell lymphoma (NKTL) in patients with prominent ocular symptoms and those with general nasal NKTL to improve the early diagnosis of nasal NKTL.
Method: A retrospective cohort study was performed with 278 patients with nasal NKTL admitted to the First Affiliated Hospital of Zhengzhou University between January 2011 and December 2017. Of these cases, 56 presented with nasal NKTL and prominent ocular symptoms, and 222 presented with general nasal NKTL.
Results: No significant differences in gender and age distribution were found between patients with general nasal NKTL and those with nasal NKTL and prominent ocular symptoms ($p > 0.05$). Cases of nasal NKTL and prominent ocular symptoms were usually complicated with B symptoms(48.2% vs 32.9%, $p < 0.05$). Patients with nasal NKTL and prominent ocular symptoms were more likely to progress to stage III disease ($p < 0.01$). The median time from first onset to diagnosis was 2.5 months. Most patients with general nasal NKTL had a longer history (69.6% vs 45.0%, $p < 0.01$). The misdiagnosis rate of the first visit of patients with general nasal NKTL was 29.3%, and that of patients with prominent ocular symptoms was 51.8%; this difference was significant ($p < 0.01$). Patients with nasal NKTL and prominent ocular symptoms showed a higher positive rate of EBV DNA ($p < 0.01$), which was significantly associated with staging ($p < 0.01$).
Conclusions: Compared with patients with general nasal NKTL, the early diagnosis of patients with prominent ocular symptoms is difficult and easy to misdiagnose. Patients with nasal NKTL and prominent ocular symptoms mostly present with advanced disease stages, and most patients have B symptoms and a high positive rate of EBV DNA.

1. Introduction

Nasal extranodal natural killer/T-cell lymphoma (NKTL) is a highly invasive and heterogeneous non-Hodgkin's lymphoma (NHL) that accounts for 40–74% of all cases of nasal lymphomas [1,2]. According to the pathological review of the Beijing Lymphoma Collaboration Group, extranodal NKTL is the second most common type of lymphoma after diffuse large B-cell lymphoma (DLBCL) in China [3]. It accounts for 5–10% of all malignant lymphomas in China and > 10% of all NHLs in East Asia and Latin America but < 1% of all NHLs in North America and Europe [1].

In 1897, McBride first described the rapid destruction of necrotising granulomatous on the nose and the midline of face; therefore, this disease was previously referred to as “lethal midline granuloma (LMG)” or “gangrene granuloma” [4,5]. Nasal NKTL is characterised by its significant necrosis, vascular centre growth, cytotoxic phenotype, and close relationship with Epstein-Barr virus (EBV) [6]. According to previous literature, the inappropriate expression of EBV latent genes combined with environmental and genetic factors might cause viral-associated malignancies [7]. In addition, a high load of circulating EBV DNA is associated with poor quality of life among patients with extranodal NKTL [7]. The main clinical manifestations of this disease are unilateral nasal congestion, suppurative and/or bloody rhinorrhoea, repeated epistaxis or chronic sinusitis, and other local signs [8].

Recently, an increasing amount of literature has studied the epidemiological characteristics of nasal NKTL as well as its pathogenesis, treatment, and prognosis; however, the early diagnosis of nasal NKTL remains difficult. Because of the lack of specificity among the clinical symptoms of nasal NKTL, patients often do not pay attention during the early stage of this disease, and much time passes between disease onset and time of treatment. In addition, pathologically confirmed cases of the intraocular involvement of nasal NKTL are rare [9], and few studies

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have investigated this condition. When most patients with prominent ocular symptoms first seek treatment, their clinicians often ignore the possibility of nasal NKTL, which delays the early treatment of this disease. The purpose of this paper was to study the early clinical features of nasal NKTL among patients with prominent ocular symptoms and compare them with patients with general nasal NKTL to further understand the characteristics of nasal NKTL in central and western China.

2. Data and methods

2.1. Clinical review

The medical records of all patients with nasal NKTL treated at the First Affiliated Hospital of Zhengzhou University between January 2011 and December 2017 were reviewed. All patients were diagnosed with nasal NKTL based on a pathological biopsy and immunohistochemistry exam. Statistical analyses of the patients' gender, age, clinical symptoms, EBV DNA, clinical stage, and imaging data were performed.

Based on patients' clinical data, all patients were staged using the 2002 American Joint Committee on Cancer (AJCC) Ann Arbor staging system.

2.2. Statistical analyses

After data collection, frequency (%) was used as a descriptive statistic. Univariate statistical analyses were performed on the data of patients with nasal NKTL and prominent ocular symptoms and those with general nasal NKTL. Between-group comparisons were performed using Chi-squared test and Fisher's exact test ($p < 0.05$). Results associated with $p < 0.05$ were considered significant. SPSS version 21.0 was used for all analyses.

3. Results

3.1. Patient characteristics

A total of 278 patients with nasal NKTL were selected, including 222 cases of general nasal NKTL and 56 cases of nasal NKTL with prominent ocular symptoms. Nasal congestion was the most common symptom among patients with general nasal NKTL (39.8%). Patients with nasal NKTL and prominent ocular symptoms were most often characterised based on a swelling of the eyelids (21.3%) (Table 1).

In terms of gender and age distribution, no significant difference was found between patients with general nasal NKTL and those with prominent ocular symptoms ($p > 0.05$). Compared with patients with general nasal NKTL, cases of prominent ocular symptoms were more likely to be complicated with B symptoms (48.2% vs 32.9%, $p < 0.05$). Patients with nasal NKTL and prominent ocular symptoms were more likely to progress to stage III disease (33.9% vs 10.4%, $p < 0.01$). Stage II disease was common among patients with general nasal NKTL (30.4% vs 39.6%, $p < 0.01$). The time from first onset to diagnosis was 0.5–32 months for all patients, with a median time of 2.5 months. Patients with nasal NKTL and prominent ocular symptoms showed a shorter medical history (69.6% vs 45.0%, $p < 0.01$) (Table 2).

Table 1
Clinical manifestations of the 278 patients with nasal NKTL.

Items	Nasal NKTL with prominent ocular symptoms (n = 56) (%)	General nasal NKTL (n = 222) (%)
Eye symptoms		
Eyelid swelling	38/178 (21.3)	
Eye pain	26/178 (14.6)	
Ocular exophthalmos	19/178 (10.7)	
Epiphora	12/178 (6.7)	
Visual decline/visual field defect	9/178 (5.1)	
Other symptoms		
Nasal congestion	22/178 (12.4)	172/432 (39.8)
Purulent/bloody nasal mucus	14/178 (7.9)	112/432 (25.9)
Nose/facial swelling	10/178 (5.6)	64/432 (14.8)
Fever	11/178 (6.2)	23/432 (5.3)
Headache	8/178 (4.5)	35/432 (8.1)
Anosmia	9/178 (5.1)	26/432 (6.0)

Table 2
Clinical features of patients with nasal NKTL.

Items	Nasal NKTL and prominent ocular symptoms (n = 56) (%)	General nasal NKTL (n = 222) (%)	*p*-Value
Gender			
Male	33 (58.9)	144 (64.9)	0.409
Female	23 (41.1)	78 (35.1)	
Age			
≤60	46 (82.1)	174 (78.4)	0.536
> 60	10 (17.9)	48 (21.6)	
B symptoms			
Positive	27 (48.2)	73 (32.9)	< 0.05
Negative	29 (51.8)	149 (67.1)	
EBV DNA			
Positive	41 (73.2)	101 (45.5)	< 0.01
Negative	15 (26.8)	121 (54.5)	
Ann Arbor staging			
I	7 (12.5)	61 (27.5)	
II	17 (30.4)	88 (39.6)	< 0.01
III	19 (33.9)	23 (10.4)	
IV	13 (23.2)	50 (22.5)	
Misdiagnosis rate	29 (51.8)	65 (29.3)	< 0.01
Time from first onset to diagnosis			
< 2.5 months	39 (69.6)	100 (45.0)	< 0.01
> 2.5 months	17 (30.4)	122 (55.0)	

Note: (1) B symptoms: night sweating, fever of unknown cause over 38 °C for 3 days or more, weight loss of 10% or more within 6 months without another cause. (2) EBV: Epstein-Barr virus.

3.2. EBV DNA

The positive rate of EBV DNA among patients with nasal NKTL and prominent ocular symptoms was higher than that among patients with general nasal NKTL (73.2% vs 45.5%, $p < 0.01$). In addition, EBV-DBA was significantly associated with disease staging ($p < 0.01$), and a more advanced stage predicted a higher positive rate of EBV DNA (Table 3).

3.3. Misdiagnosis rate

Of the patients with nasal NKTL and prominent ocular symptoms, 29 (51.8%) first went to an ophthalmology clinic. The initial doctors provided symptomatic supportive treatments such as anti-inflammatory and hormone therapies, and the symptoms did not significantly improve. A total of 65 patients (29.3%) in the general nasal NKTL group were misdiagnosed. A significant difference was found with regard to the misdiagnosis rates between the two groups (51.8% vs 29.3%,

Table 3
EBV DNA and staging of patients with nasal NKTL and prominent ocular symptoms.

Staging	EBV DNA (−)	EBV DNA (+)
I/II	11	13
III/IV	4	28

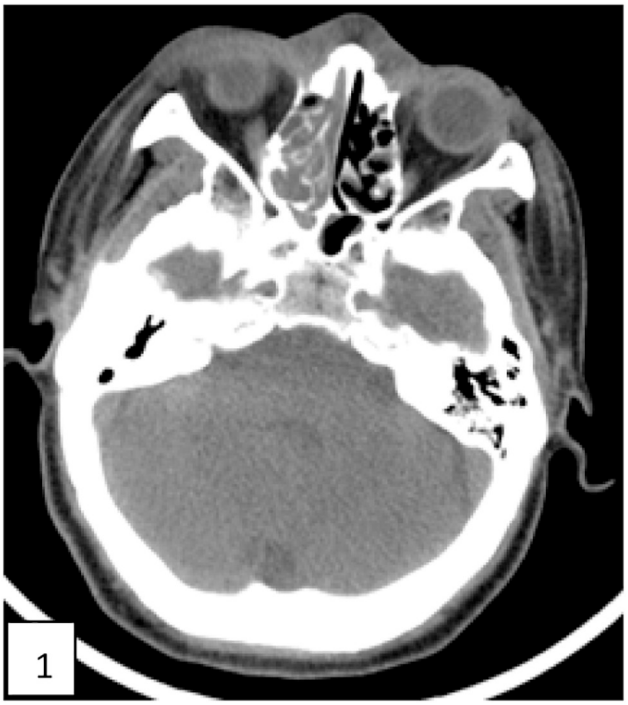

Fig. 1. Sinus CT showed that the soft tissues of the right eyelid were significantly thickened, and soft tissue density shadows were observed in the right nasal cavity, bilateral ethmoid sinus and sphenoid sinus.

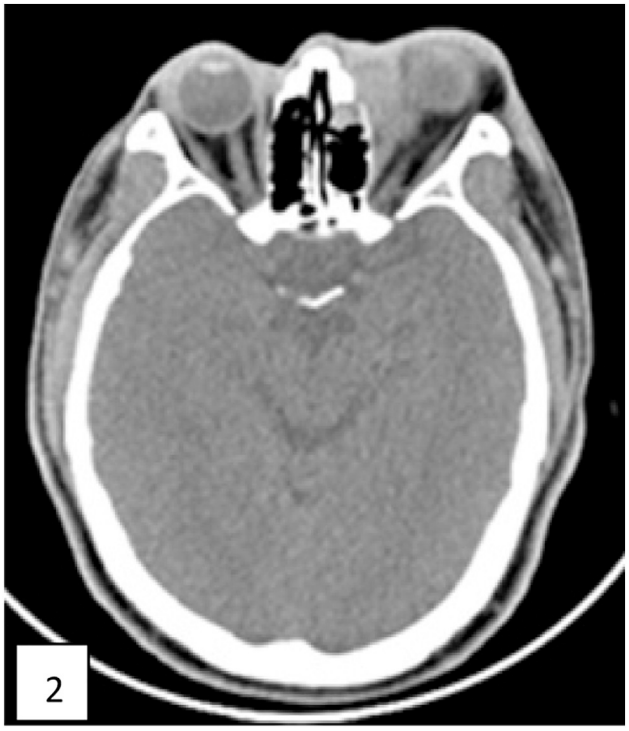

Fig. 2. Sinus CT showed soft tissue density shadows in the left ethmoid sinus with uniform density, and the lesion protruded into the left eye socket. No obvious damage was observed in the adjacent bone.

$p < 0.01$).

3.4. Imaging exhibitions

The CT findings of patients with nasal NKTL and prominent ocular symptoms included 38 cases of soft tissue swelling of the eyelids (Fig. 1); eight cases of soft tissue shadows with uniform density and non-smooth boundaries in the orbital socket adjacent to the nasal sinus (Fig. 2); five cases of sinus lesions invading the medial canthus (Fig. 3); five cases of sinus lesions invading the apex of the eye socket (Fig. 4). The CT findings of patients with general nasal NKTL revealed soft tissue density shadows and mucosa thickening in the nasal cavity and sinus as well as bone tissue destruction around the lesion and perforation of the hard palate or nasal septum in some patients.

4. Discussion

Most patients with nasal NKTL were men (2:1) with a median age of 50 years [10,11]. In this study, the male to female ratio of patients with nasal NKTL and prominent ocular symptoms was 1.4:1. The median age of all patients was 48 years old (range, 4–82 years), which is consistent with studies published by other single-centre institutions [12]. Although men were predominant, no difference in gender distribution was found between patients with nasal NKTL and prominent ocular symptoms and those with general nasal NKTL.

Patient with nasal NKTL and prominent ocular symptoms often presented with eye invasion and more obvious infection symptoms. In addition to the symptoms common to general nasal NKTL, these patients often showed swelling and pain of the eyelids, severe oedema of the conjunctiva, epiphora, ocular exophthalmos, and decreased vision or visual field defects. In foreign reports, patients with nasal NKTL and ocular symptoms showed swelling of the eyelids, swelling around the eye socket, ocular protrusion, photophobia, diplopia, blurred vision, decreased vision, and other conditions [9,13–16], which corroborates our results. In the central and western regions of China, patients with nasal NKTL and prominent ocular symptoms had a higher incidence of

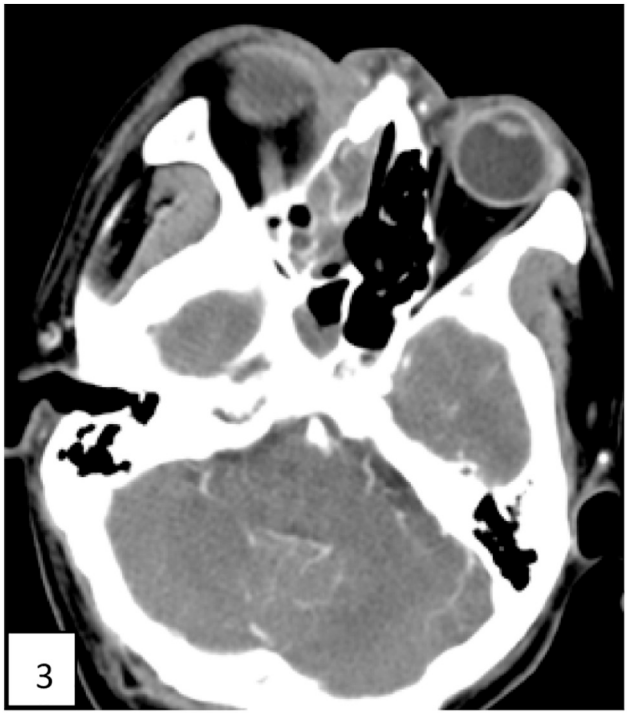

Fig. 3. Sinus CT showed soft tissue density shadows at the right ethmoid sinus and sphenoid sinus. The ethmoid sinus lesion protruded into the right medial canthus, and no obvious damage was observed to the surrounding bone.

B symptoms than those with general nasal NKTL (48.2% and 32.9%, respectively). Kiessling et al. [17] reported the rates of B symptoms in patients with nasal NKTL in other countries (42%, 25%, 24% and 23%), which are lower than the rate associated with patients with nasal NKTL and prominent ocular symptoms in our study.

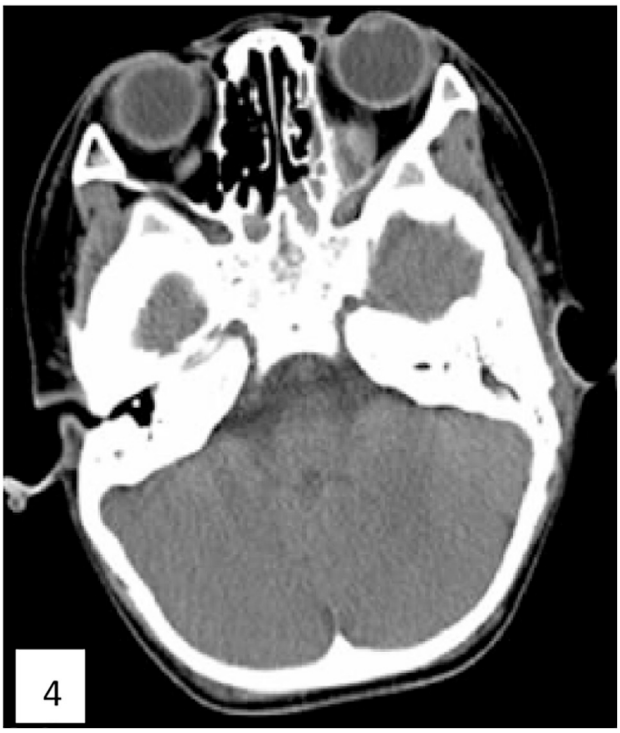

Fig. 4. Sinus CT showed soft tissue density shadows at the left sphenoid sinus and the left temporal apex, which oppressed the eye muscles and optic nerve.

EBV is a widespread lymphotropic gammaherpesvirus that infects > 90% of the world's population. At present, much literature has shown that EBV is of great significance regarding the diagnosis and disease monitoring of extranodal NKTL [18]. Plasma EBV DNA viral load is closely related to clinical staging, treatment response, and survival [18]. We studied the positive rate of EBV DNA in patients with nasal NKTL and prominent ocular symptoms in central and western China; the result was 73.2% (41/56), primarily because of the release of clonal EBV carried by tumour cells. A more advanced clinical stage denoted a higher positive rate of EBV DNA. Recent studies have shown that the susceptibility gene of extranodal NKTL is HLA-DPB1, which suggests that it has a different pathogenic mechanism from nasopharyngeal carcinoma or Hodgkin's lymphoma [19]. We will further investigate the significance of the HLA-DPB1 gene with regard to early diagnosis of this disease.

Patients with nasal NKTL and prominent ocular symptoms had mostly progressed to an advanced disease stage (stage III). Patients with general nasal NKTL were primarily classified as stages I and II (67.1%), whereas patients with prominent ocular symptoms were more likely classified as stages III and IV (57.1%). Li et al. [20] examined 264 patients with nasal NKTL who were treated at West China Hospital of Sichuan University and identified more patients in stages I and II (86.0%); this result was similar to the staging distribution of patients with general nasal NKTL in our study.

The misdiagnosis rate at the first visit of patients with nasal NKTL and prominent ocular symptoms was 51.8% (29/56), which was significantly higher than the 29.3% (65/222) of the patients with general nasal NKTL. The reasons for this finding are as follows. 1) Because of their obvious eye symptoms, most patients went to an ophthalmology clinic first. 2) The first doctors failed to perform a systematic examination, which delayed diagnosis. 3) An inaccurate biopsy site and method resulted in inaccurate pathological results. 4) Most patients had a history of glucocorticoid use, which affected the accuracy of the pathological results. For these patients, necrotic or inflammatory tissue on the surface of the lesions should be removed to the fullest extent possible during biopsy, and the biopsy site, biopsy volume, and depth should be sufficient.

The median time from first onset to confirmed diagnosis was 2.5 months. Patients with general nasal NKTL had a longer history of disease before diagnosis. The nasal symptoms of most patients were relatively common; therefore, patients often did not attend to them, and these symptoms were usually significantly aggravated by the time of treatment. Patients with nasal NKTL and prominent ocular symptoms showed a brief disease history. Eye symptoms were the major manifestations, which seriously affected their personal appearance, work, and life; therefore, most patients visited their doctors early.

Imaging examination is also important for the early diagnosis of nasal NKTL. Ct of paranasal sinus can better display the location of the lesion and the invasion of the surrounding bone. This is essential for the early diagnosis, clinical staging and treatment of the nasal NKTL.

5. Conclusions

Our study confirms that patients with nasal NKTL and prominent ocular symptoms have several different characteristics from patients with general nasal NKTL. Patients with prominent ocular symptoms are difficult to diagnose at an early stage and are easily misdiagnosed. If their eye symptoms are considered to be caused by infections; their symptoms do not significantly improve or reappear after effective antibiotic application, local physiotherapy, or surgery; and the nasal cavity and sinus show extensive swelling, roughness and erosion, granulation hyperplasia, and greyish-white or caseous necrotic tissue on the surface of neoplasm, then they should be considered as having lymphoma in combination with clinical manifestations and auxiliary examinations.

Most patients with nasal NKTL and prominent ocular symptoms develop advanced stages of this disease (i.e., stages III and IV). For these patients, a clear diagnosis should be made as soon as possible, and standardised treatment should be performed early after diagnosis to inhibit disease progression and improve prognosis. For patients with general nasal NKTL, if the nasal symptoms reappear repeatedly, progressively aggravate, or last for > 3 months, then they should be examined early in the hospital to eliminate the possibility of malignant tumours. In addition, nasal NKTL is related to EBV DNA; therefore, EBV DNA can be used for diagnosis and follow up, especially in epidemic areas.

Finally, this study confirms the epidemiological and clinical features of patients with nasal NKTL and prominent ocular symptoms in the central and western regions of China.

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Disclosures

The Author(s) declare(s) that there is no conflict of interest. Participants provided informed consent and the consent was written. The authors alone are responsible for the content and writing of the article.

Ethics approval

All cases were approved by the Institutional Review Board and Ethics Committee of the First Affiliated Hospital of Zhengzhou University. All the subjects enrolled into the study gave written formal consent to participate.

References

[1] Luo H, Quan X, Song XY, et al. Red blood cell distribution width as a predictor of

survival in nasal-type, extranodal natural killer/T-cell lymphoma[J]. Oncotarget 2017;8(54):92522–35.
[2] Guo Y, Lu JJ, Ma X, et al. Combined chemoradiation for the management of nasal natural killer (NK)/T-cell lymphoma: elucidating the significance of systemic chemotherapy[J]. Oral Oncol 2008;44(1):23–30.
[3] Wang GN, Zhao WG, Li L, et al. Prognostic significance of CD30 expression in nasal natural killer/T-cell lymphoma[J]. Oncol Lett 2017;13(3):1211–5.
[4] Aozasa K, Zaki MA. Epidemiology and pathogenesis of nasal NK/T-cell lymphoma: a mini-review[J]. Scientific World Journal 2011;11:422–8.
[5] Aozasa K, Takakuwa T, Hongyo T, et al. Nasal NK/T-cell lymphoma: epidemiology and pathogenesis[J]. Int J Hematol 2008;87(2):110–7.
[6] Kim HJ, Ko YH, Kim JE, et al. Epstein-Barr virus-associated lymphoproliferative disorders: review and update on 2016 WHO classification[J]. J Pathol Transl Med 2017;51(4):352–8.
[7] Chen R, Wang C, Zhou Y, et al. Prognostic implications of circulating Epstein-Barr virus DNA for extranodal natural killer/T-cell lymphoma, nasal type: a meta-analysis[J]. Cancer Manag Res 2018;10:2183–92.
[8] Hmidi M, Kettani M, Elboukhari A, et al. Sinonasal NK/T-cell lymphoma[J]. Eur Ann Otorhinolaryngol Head Neck Dis 2013;130(3):145–7.
[9] Yoo JH, Kim SY, Jung KB, et al. Intraocular involvement of a nasal natural killer T-cell lymphoma: a case report[J]. Korean J Ophthalmol 2012;26(1):54–7.
[10] Saleh KA, Razif, Gendeh BS. Nasal NK/T cell lymphoma mimicking an latrogenic lateral nasal wall infection: a diagnostic dilemma[J]. Med J Malaysia 2011;66(2):160–1.
[11] Coha B, Vucinic I, Mahovne I, et al. Extranodal lymphomas of head and neck with emphasis on NK/T-cell lymphoma, nasal type[J]. J Craniomaxillofac Surg 2014;42(2):149–52.
[12] Au WY, Weisenburger DD, Intragumtornchai T, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project[J]. Blood 2009;113(17):3931–7.
[13] Kanzaki A, Funasaka Y, Nakamizo M, et al. Extranodal natural killer/T-cell lymphoma, nasal type, with primary manifestation as an upper eyelid swelling[J]. J Nippon Med Sch 2016;83(4):177–9.
[14] Zuhaimy H, Aziz HA, Vasudevan S, et al. Extranodal natural killer/T-cell lymphoma presenting as orbital cellulitis[J]. GMS Ophthalmol Cases 2017;c4:7.
[15] Cimino L, Chan CC, Shen D, et al. Ocular involvement in nasal natural killer T-cell lymphoma[J]. Int Ophthalmol 2009;29(4):275–9.
[16] Turker B, Uz B, Isik M, et al. Nasal natural killer/T-cell lymphoma with skin, eye, and peroneal nerve involvement[J]. Turk J Haematol 2012;29(4):413–9.
[17] Kiessling SY, Soyka MB, Huber GF, et al. Delayed diagnosis of sinonasal lymphoma due to bilateral manifestation[J]. Eur Arch Otorhinolaryngol 2017;274(2):823–7.
[18] Zhang L, Li S, Jia S, et al. The DDGP (cisplatin, dexamethasone, gemcitabine, and pegaspargase) regimen for treatment of extranodal natural killer (NK)/T-cell lymphoma, nasal type[J]. Oncotarget 2016;7(36):58396–404.
[19] Qin C, Huang Y, Feng Y, et al. Clinicopathological features and EBV infection status of lymphoma in children and adolescents in South China: a retrospective study of 662 cases[J]. Diagn Pathol 2018;13(1):17.
[20] Li N, Zhang L, Song HL, et al. Prognostic impact of absolute lymphocyte count/absolute monocyte count ratio and prognostic score in patients with nasal-type, extranodal natural killer/T-cell lymphoma[J]. Tumour Biol 2017;39(5):1393384161.