www.sada.co.za / SADJ Vol. 80 No.1

Extranodal NK/T-cell Lymphoma, Nasal Type: Report of a Case and Review of the South African Literature

SADJ FEBRUARY 2025, Vol. 80 No.1 P42-P45

A Odendaal[1], A Afrogheh[2], W Mahomed[3], SE Adam[4], J Grobbelaar[5], J Opperman[6]

CASE PRESENTATION

A 76-year-old African female was referred to the Ear, Nose and Throat (ENT) clinic at Tygerberg hospital in Cape Town, South Africa, with history of a progressively enlarging painful right-sided nasal mass with nasal obstruction. Her medical history was significant for controlled hypertension and type 2 diabetes mellitus. Clinical examination revealed swelling of the right nasolabial region with associated cellulitis and a necrotic right nasal mass with crusting (Figure 1). Flexible endoscopy of the left nasal cavity showed septal perforation.

Haematological tests revealed anaemia and leucocytosis with elevated levels of urea, creatinine, c-reactive protein and erythrocyte sedimentation rate (ESR). A surgical biopsy of the nasal mass was performed under local anaesthesia. A pus swab was also obtained for microbiological culture which identified Staphylococcus aureus and Streptococcus gordonnii. Subsequently treatment with the antibiotic, Clindamycin, was initiated. The patient was then discharged from the hospital, pending histology results. Histological examination of the biopsy obtained under local anaesthesia showed a small specimen with fragmentation artifacts and necrosis. A repeat biopsy was recommended.

On follow-up, the patient's condition had worsened. She presented with delirium, dehydration and a significant increase in the size of the nasal mass. The patient was subsequently taken to the operating theatre. Intraoperative exploration of the right nasal cavity disclosed a foul smelling necrotic tissue involving the anterior third of the nasal floor and septum, with extension into the oral cavity and destruction of the anterior maxillary alveolar cortex (Figure 2). Given the clinical history of diabetes mellitus, an invasive fungal infection (Mucormycosis) was highly suspected. However, biopsy from the right nasal region showed superficial mucosa with ulceration and dense chronic inflammation with no evidence of fungal organisms.

Further laboratory investigations were undertaken, including antineutrophil cytoplasmic antibodies (ANCA) test, serum angiotensin-converting enzyme (ACE) test, and syphilis serology, to rule out the destructive midface lesions, polyangiitis with granulomatosis (Wegener's granulomatosis), sarcoidosis and syphilis respectively. All test results were negative.

A representative biopsy taken in theatre for histological examination revealed a diffuse infiltrate of small atypical lymphoid cells with perineural- and perivascular (angiocentric) distribution (Figure 3a). The malignant lymphoid cells infiltrated the walls of the blood vessels, resulting in vascular destruction (angio-destruction) and necrosis (Figure 3b). The Natural Killer (NK) cell marker, CD56, was positive and EBER In Situ Hybridization (EBER-ISH) confirmed the presence of EBV DNA in the malignant lymphoid cells. Based on the histological features and positivity for CD56 and EBER-ISH, a diagnosis of Extranodal Natural Killer (NK)/T-cell Lymphoma, Nasal Type (ENKTL-NT) was established. The patient was subsequently referred to the oncology clinic for further management. Sadly, chemotherapy initiation was not feasible due to the patient's poor performance status. The patient was then transferred back to her base hospital for palliative care, and passed away a few weeks later.

DISCUSSION

In 1897, McBride et al. for the first time described a rapidly invasive and destructive granuloma-like lesion of the nasal cavity with an aggressive and lethal clinical course.[1] The disease was termed "lethal midline granuloma". [2,3] In the late 20th century, it was shown that the lesional cells had NK-cell (CD56) and T-cell (CD3) phenotype, and the tumour was named ENKTL-NT.[4-6] In 1990, Epstein-Barr virus (EBV) DNA was demonstrated in the lymphoma cells and ENKTL-NT is now recognized as an EBV-associated malignancy.[7] EBV, also known as human herpesvirus 4 (HHV-4) is an oncogenic virus, associated with some lymphomas and epithelial cancers in humans.[8] EBV infects B lymphocytes and epithelial cells.[8] It also infects T lymphocytes, however, the mechanism with which EBV infects NK/T-cells remains unclear. Infection of the lymphocytes is by latency where it causes a variety of haematolymphoid malignancies, the most well recognized being Burkitt lymphoma; Hodgkin lymphoma; plasmablastic lymphoma and ENKTL-NT. There is geographic heterogeneity in the prevalence of ENKTL-NT. In Asia and South America,

Authors' information

1. Anneze Odendaal; *BChD.* Department of Oral Medicine and Periodontology, Faculty of Dentistry, University of the Western Cape, Cape Town, South Africa.
2. Amir Afrogheh; *BChD*, *MSc*, *MChD*, *PhD*. Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, University of the Western Cape and National Health Laboratory Service.Extraordinary Senior Lecturer, Division of Anatomical Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
3. Wasim Mahomed; *MBChB*. Division of Otorhinolaryngology, Department of Surgery, Stellenbosch University, Cape Town, South Africa
4. Shaun Edward Adam; *MBChB*, *MMed*, *FCORL* (SA). Division of Otorhinolaryngology, Department of Surgery, Stellenbosch University, Cape Town, South Africa.
5. Johan Grobbelaar; *MBChB*, *MMed*, *FCORL* (SA). Division of Otorhinolaryngology, Department of Surgery, Stellenbosch University, Cape Town, South Africa.
6. Johan Opperman; *BChD*, *BSc*, *MDS*. Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, University of the Western Cape and National Health Laboratory Service.Extraordinary Senior Lecturer, Division of Anatomical Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

Reprint requests:
Name: Amir Afrogheh, *BChD*, *MSc*, *MChD*, *PhD*
Department of Oral and Maxillofacial Pathology
National Health Laboratory Service
Tygerberg Hospital, Cape Town, South Africa
Email: amir.afrogheh@nhls.ac.za

Key words:
NK/T-Cell Lymphoma, South Africa, Nasal cavity, CD56, EBV

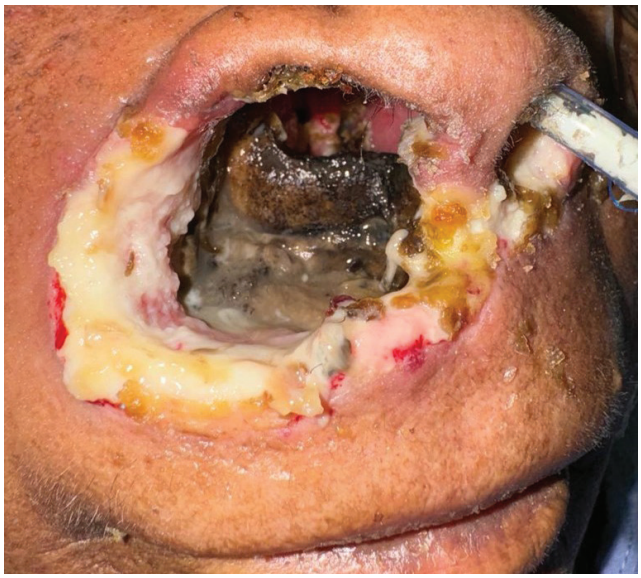


Figure 1: The image shows a necrotic mass with crusting, obstructing the right nasal cavity.

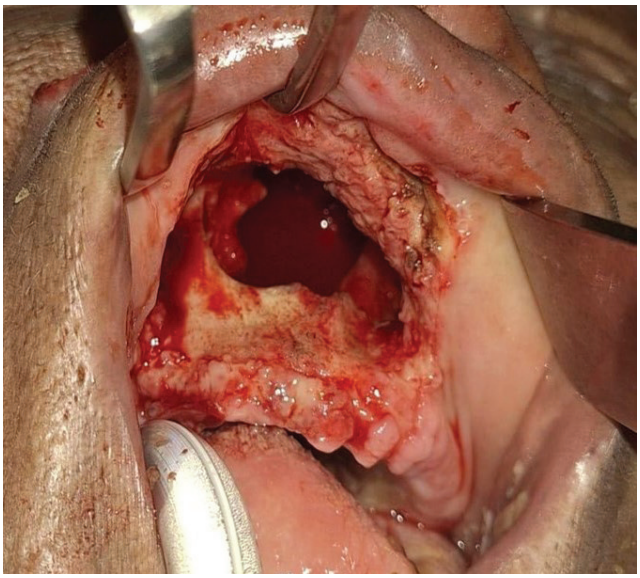


Figure 2: Intraoperative exploration shows perforation of the anterior floor of the nasal cavity and the anterior maxillary bone.

ENKTL-NT accounts for 3–10% of non-Hodgkin lymphomas (NHL), whereas in the western countries, the prevalence is less than 1%.[9-12]

The latter may be explained by the fact that, the Asian and South American population may have the susceptibility gene for ENKTL-NT.[13] Another explanation for the difference may be the existence of specific EBV strains or variants.[13] Environmental factors could also possibly play a role in the pathogenies of ENKTL-NT. A Japanese group has documented an increase in the incidence of ENKTL-NT following exposure to pesticides and chemical solvents.[14] Not much is known about the prevalence of ENKTL-NT in Africa. A 10-year retrospective study from Tunisia showed that ENKTL-NT accounted for 0.78% of all NHL.[15] The latter is in contrast to other EBV-related lymphomas in Africa such as endemic Burkitt and Hodgkin lymphomas, that show higher prevalence rates.[16] To the best of our knowledge there are only two reported cases of ENKTL-NT from South Africa (Table 1).[17,18] In general, ENKTL-NT is commonly seen in middle aged patients (40–50 years old) with male-to-female ratio of 2:1.[13] Review of ENKTL-NT case reports from South Africa, indicates that ENKTL-NT may be seen in elderly and young adult patients (Table 1). EBV is strongly associated with HIV-associated plasmablastic lymphoma. However, in contrast to HIV-associated plasmablastic lymphoma, HIV-infection appears to not be a risk factor for the development of ENKTL-NT (Table 1). Clinically patients with ENKTL-NT present with an ulcerating and necrotic nasal lesion with crusting (Figure 1). Most often patients present with advanced stage disease, with invasion and destruction of neighbouring anatomical structures, especially the palate (Figure 2). The most frequent symptoms are nasal obstruction and nasal discharge. There is often facial swelling with associated cellulitis, which in conjunction with leucocytosis, raised c-reactive protein and ESR levels, deceptively suggests an infective (bacterial or fungal) process (Table 1).

Table 1: Reported cases of ENKTL-NT from South Africa

Author	HIV status	Age and sex	Clinical presentation and symptoms	Blood test results	Risk factors	Treatment	Outcome	CD56/ EBER
Mankgele *et al.* (2022) (ref 18)	Negative	31, Male	Necrotic lesion of right inner cheek extending into sinonasal space Swelling and cellulitis, nasal discharge, loss of vision, weight loss and night sweats	None reported	None reported	Chemotherapy and planned radiotherapy	Partial response to chemo, passed away prior to planned radiotherapy due to overwhelming sepsis	CD56 and EBER positive
Tlholoe *et al.* (2013) (ref 17)	Negative	74, Male	Extensive necrosis and ulceration of midface Fever, nasal obstruction and nasal discharge	Leucocytosis, elevated ESR and c-reactive protein	None reported	Planned chemotherapy	Died prior to initiation of chemotherapy	CD56 positive EBER-Not done
Odendaal *et al.* (current case, 2025)	Negative	76, Female	Necrotic and ulcerative lesion of right nasal cavity with crusting and maxillary bone destruction Nasal obstruction, nasal discharge, swelling and cellulitis	Anaemia, leucocytosis, elevated ESR and c-reactive protein	Diabetes and hypertension	Palliative care	Died soon after referral to base hospital	CD56 and EBER-positive

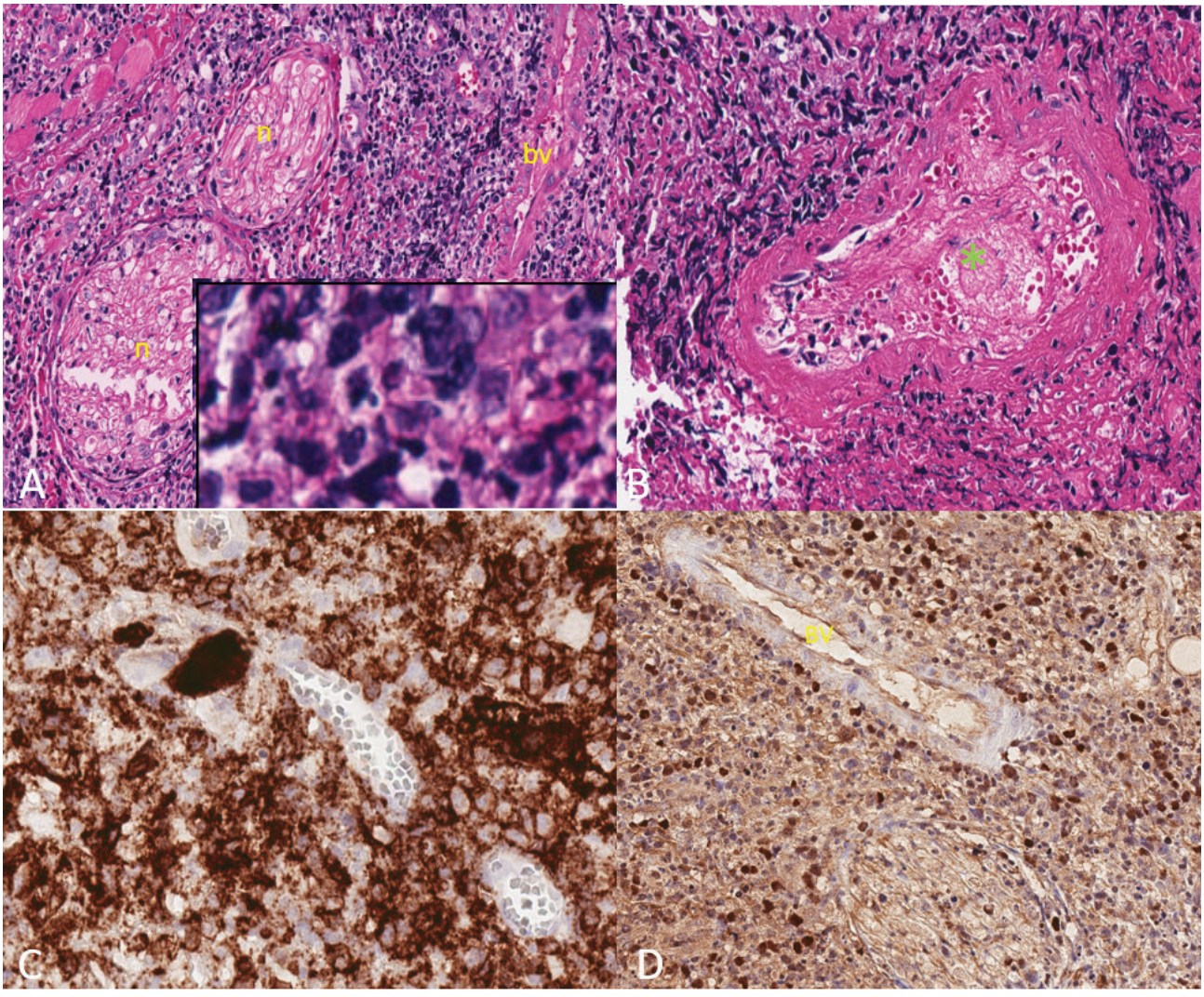
Histologically, a diffuse infiltrate of small atypical lymphoid cells with irregular folded hyperchromatic nuclei (triangular-shaped) is seen in ENKTL-NT. The lymphoma cells show a perivascular arrangement (angiocentricity) with infiltration and destruction of blood vessels (angio-destruction) (Figures 3a and 3b). Therefore, prominent necrosis is usually observed in ENKTL-NT.

As evident in the present case report, it may prove difficult to diagnose ENKTL-NT in small biopsy specimens by histological examination, due to the small size of the lymphoma cells (which can mimic lymphocytes) and the presence of necrosis. Clinicopathological correlation, a high-index of suspicion and an appropriate panel of immunohistochemical markers can aid the pathologist in arriving at the correct diagnosis. In fact, the low prevalence of ENKTL-NT in Africa could be linked to misdiagnosis or lack of immunohistochemical and molecular diagnostic techniques required for the diagnosis of ENKTL-NT. The ENKTL-NT cells express T-cell markers, such as CD2, CD7 and cytoplasmic CD3 (CD3ε), as well as the NK-cell marker CD56 (Figure 3c). Although CD56 is a very useful marker in the diagnosis of ENKTL-NT, expression may be seen in some peripheral T-cell lymphomas.[19] Almost all cases of ENKTL-NT are positive for EBV DNA, which can be demonstrated by in situ hybridization (EBER-ISH) to confirm the diagnosis (Figure 3d). In addition, NK-cells express perforin and granzymes, proteins that target tumour cells/bacteria and kill them by cytolysis.

ENKTL-NT is radiosensitive ; however, recurrence is high with radiation alone, which is why chemoradiation is the recommended standard of treatment.[20] NK-cells express high levels of P-glycoprotein, leading to a multidrug resistance (MDR) phenotype.[20] Thus, Anthracycline-containing (CHOP, Cyclophosphamide, Adriamycin, Vincristine, Prednisolone; or CHOP-like) regimens, designed for conventional high-grade B-cell lymphomas, are MDR-dependent and ineffective.[20] Hence, various non-Anthracycline-containing regimens have been developed for ENKTL-NT. A central component of these regimens is asparaginase, which induces apoptosis of NK-cells in vitro.[20]

In general, the survival of patients with low stage disease has increased from < 50% in the early 2000s to > 80% in recent years.[21] The improved survival can be attributed to introduction of asparaginase-based chemotherapy and advanced radiological detection techniques. Significant changes in survival are also seen in patients with advanced-stage disease.[21] The median overall survival for advanced-stage disease has increased from a few months to more than

Figure 3 A and B: H&E staining reveals a diffuse infiltrate of atypical lymphoid cells exhibiting a perineural (n) and angiocentric (bv) distribution, accompanied by angio-destruction. Figure B highlights a transmural tumour infiltrate in a blood vessel (*) with necrosis. Figure 3C: Immunohistochemical analysis shows cytoplasmic positivity for CD56, while Figure 3D demonstrates in situ hybridization for EBV (EBER), with reactivity observed in the majority of tumour cell nuclei.



3 years. The better prognosis in advanced-stage disease is largely attributable to the introduction of asparaginase-based chemotherapy and PD-1/PD-L1 blockade immunotherapy.[21] Nevertheless, the prognosis appears to remain relatively poor for patients that reside in sub Saharan Africa (Table 1).

CONCLUSION

Clinicians should always consider ENKTL-NT in the differential diagnosis of ulcerative/necrotic midface lesions and must alert the pathologist to this possibility, to ensure early diagnosis and management, resulting in improved overall survival. A collaborative multicentre study in sub Saharan Africa may help better understand the true prevalence, prognosis, management and pathophysiology of ENKTL-NT in this region.

REFERENCES

1. McBride, P., 1897. Photographs of a case of rapid destruction of the nose and face. *Laryngol, 12*, pp.64-66.
2. Williams, H.L., 1949. LXXXVII Lethal Granulomatous Ulceration Involving the Midline Facial Tissues. *Annals of Otology, Rhinology & Laryngology, 58*(4), pp.1013-1054.
3. Harabuchi, Y., Kataura, A., Kobayashi, K., Yamamoto, T., Yamanaka, N., Hirao, M., Onodera, K. and Kon, S., 1992. Lethal midline granuloma (peripheral T-cell lymphoma) after lymphomatoid papulosis. *Cancer, 70*(4), pp.835-839.
4. Ng, C.S., Chan, J.K. and Lo, S.T., 1987. Expression of natural killer cell markers in non-Hodgkin's lymphomas. *Human pathology, 18*(12), pp.1257-1262.
5. Ishii, Y., Yamanaka, N., Ogawa, K., Yoshida, Y., Takami, T., Matsuura, A., Isago, H., Kataura, A. and Kikuchi, K., 1982. Nasal T-cell lymphoma as a type of so-called "lethal midline granuloma". *Cancer, 50*(11), pp.2336-2344.
6. Yamanaka, N., Kataura, A., Minase, T., Sambe, S. and Ishii, Y., 1985. Midfacial T cell lymphoma: characterization by monoclonal antibodies. *Annals of Otology, Rhinology & Laryngology, 94*(2), pp.207-211.
7. Harabuchi, Y., Yamanaka, N., Kataura, A., Imai, S., Kinoshita, T. and Osato, T., 1990. Epstein-Barr virus in nasal T-cell lymphomas in patients with lethal midline granuloma. *The Lancet, 335*(8682), pp.128-130.
8. Ayee, R., Ofori, M.E.O., Wright, E. and Quaye, O., 2020. Epstein Barr virus associated lymphomas and epithelia cancers in humans. *Journal of Cancer, 11*(7), p.1737.
9. Liu, J., Song, B., Fan, T., Huang, C., Xie, C., Li, J., Zhong, W., Li, S. and Yu, J., 2011. Pathological and clinical characteristics of 1,248 non-Hodgkin's lymphomas from a regional cancer hospital in Shandong, China. *Asian Pac J Cancer Prev, 12*(11), pp.3055-3061.
10. International T-Cell Lymphoma Project, 2008. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *Journal of clinical oncology, 26*(25), pp.4124-4130.
11. Rüdiger, T., Weisenburger, D.D., Anderson, J.R., Armitage, J.O., Diebold, J., MacLennan, K.A., Nathwani, B.N., Ullrich, F. and Müller-Hermelink, H.K., 2002. Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. *Annals of Oncology, 13*(1), pp.140-149.
12. Lima, M., 2013. Aggressive mature natural killer cell neoplasms: from epidemiology todiagnosis. *Orphanet journal of rare diseases, 8*, pp.1-10.
13. Takahara, M., Kumai, T., Kishibe, K., Nagato, T. and Harabuchi, Y., 2021. Extranodal NK/T-cell lymphoma, nasal type: genetic, biologic, and clinical aspects with a central focus on Epstein–Barr virus relation. *Microorganisms, 9*(7), p.1381.
14. Xu, G.;Wang, H.; Xie, K.; He, G.; Du, Z. Analysis of clinicopathological features and prognostic factors of 62 nasal NK/T-cell lymphomas. J. Clin. Otorhinolaryngol. *2007*, 21, 932–934.
15. Missaoui, N., Mestiri, S., Bouriga, A., Abdessayed, N., Belakhdher, M., Ghammem, M., Abdelkefi, M., Mokni, M. and Hmissa, S., 2019. Extranodal NK/T-cell lymphoma in Tunisia: clinicopathological features, immunophenotype and EBV infection. *Journal of the Egyptian National Cancer Institute, 31*, pp.1-8.
16. Abubakar, M., Shuaibu, I.Y., Chitumu, D., Liman, A.A. and Suleiman, D.E., 2019. Extranodal NK/T cell lymphoma: diagnostic challenges in a resource-constrained setting. *Sub-Saharan African Journal of Medicine, 6*(1), pp.49-53.
17. Tlholoe, M.M., Kotu, M., Khammissa, R.A., Bida, M., Lemmer, J. and Feller, L., 2013. Extranodal natural killer/T-cell lymphoma, nasal type:'midline lethal granuloma.'A case report. *Head & face medicine, 9*, pp.1-5.
18. Mankgele, M., Goqwana, L., Philip, V., Waja, F., Lakha, A., Perner, Y. and Patel, M., 2022. An unusual case of lymphoma—a case of extranodal NK/T-cell lymphoma, nasal type. *The Egyptian Journal of Otolaryngology, 38*(1), p.114.
19. Li, W., 2022. The 5th Edition of the World Health Organization Classification of Hematolymphoid Tumors. *Exon Publications*, pp.1-21.
20. Tse, E., Zhao, W.L., Xiong, J. and Kwong, Y.L., 2022. How we treat NK/T-cell lymphomas. *Journal of hematology & oncology, 15*(1), p.74.
21. Tse, E. and Kwong, Y.L., 2013. How I treat NK/T-cell lymphomas. *Blood, The Journal of the American Society of Hematology, 121*(25), pp.4997-5005.
22. Yan, Z., Yao, S., Wang, Z., Zhou, W., Yao, Z. and Liu, Y., 2023. Treatment of extranodal NK/T-cell lymphoma: From past to future. *Frontiers in Immunology, 14*, p.1088685.