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CASE REPORT Open Access

An unusual case of lymphoma — a case of extranodal NK/T-cell lymphoma, nasal type

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Abstract

Background: There is a great geographic variation of extranodal natural killer (NK)/T-cell lymphoma, nasal type (NNKTL) prevalence, with a much higher prevalence in the Asian and South American populations. According to our knowledge and searches, only one other case report/study of NNKTL has been published in South Africa.

Case presentation: We present a southern-African 31-year-old male residing in a township in the south of Johannesburg, South Africa. He presented with signs and symptoms similar to those of benign upper airway diseases. Further work-up of persisting signs and symptoms yielded a diagnosis of NNKTL. He was treated with the SMILE (steroids — dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) chemotherapy regimen, and sandwich radiotherapy was planned. He had a partial response to chemotherapy but unfortunately demised due to overwhelming sepsis prior to radiation therapy.

Conclusion: Making a diagnosis of NNKTL in resource-limited settings is challenging as the diagnosis requires not only the demonstration of NK-cell markers but also to have a positive Epstein-Barr virus (EBV) in situ hybridization (EBER-ISH). Collaboration of smaller centres with larger and better equipped centres is required to diagnose and document NNKTL more accurately in the African setting.

Keywords: Epstein-Barr virus (EBV), Natural killer (NK) cells, Lymphoma, Extranodal NK/T-cell lymphoma, Nasal type (NNKTL), Diagnosis, Treatment

Background

Epstein-Barr virus (EBV), also known as human herpesvirus 4 (HHV-4) is a ubiquitous virus, affecting 90% of the world's population in its latent form [1]. It belongs to the virus family Herpesviridae, subfamily Gammaherpesvirinae [2].

Viruses are responsible for 15–20% of all cancers in humans [3]. EBV is one of these oncogenic viruses, associated with both lymphomas and epithelial cancers in humans [1]. It infects B lymphocytes and epithelial cells [1]. It also infects unusual targets such as T lymphocytes and natural killer (NK) cells [1]. In the epithelial cells the virus undergoes lytic replication where it causes nasopharyngeal cancer, gastric cancer and breast cancer amongst others [1]. Infection of the lymphocytes is by latency where it causes a variety of haematolymphoid malignancies, the most well recognized being Burkitt lymphoma; Hodgkin lymphoma; posttransplant lymphoproliferative disorders and extranodal NK/T-cell lymphoma (NNKTL) [1].

There are two main EBV genotypes named type 1 and type 2 [1]. There is geographic variation in the distribution of the two EBV genotypes [4]. EBV type 1 is found mainly in Southeast Asia; Chinese; European and American populations, while the type 2 genotype is found mainly in African populations [4]. It is also important to note that the two genotypes have different biological

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properties, with type 1 predominantly affecting B lymphocytes and type 2 affecting epithelial cells [1].

The World Health Organization (WHO) classification makes a clear distinction between two histopathological subtypes of NK-cell malignancies, i.e. aggressive NK-cell leukaemias and NNKTL [5].

NNKTL predominantly affects Asian and South American populations [5]. Approximately, 3–10% of non-Hodgkin lymphoma (NHL) in Asia and South America is composed of NNKTL, whereas this tumor accounts for is < 1% of NHL in Western countries [6]. Literature on NNKTL in Africa is lacking [7]. A 10-year African retrospective study (2007–2017) of NNKTL in Tunisia showed that they accounted for 0.78% of all NHL in their setting [7]. This is in contrast to other EBV-related lymphomas in Africa such as endemic Burkitt and Hodgkin lymphomas, both of which are more common [8].

A case of NNKTL is presented in this paper. According to our knowledge and searches, only one other case report/study of NNKTL has been published in South Africa by Tlholoe et al. from the Department of Periodontology and Oral Medicine, University of Limpopo, Medunsa Campus [9].

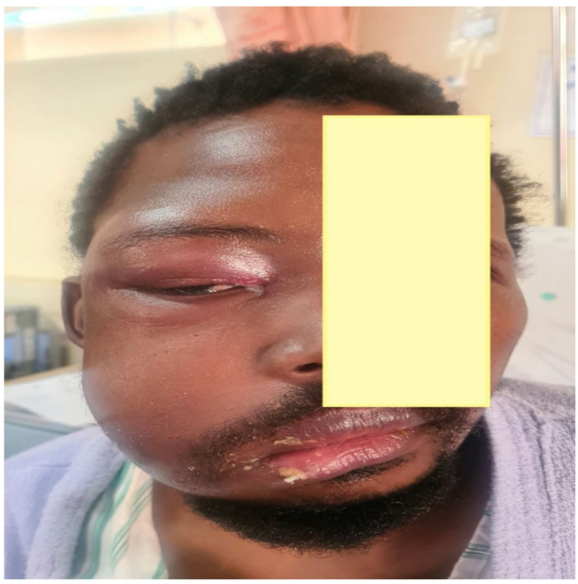

Fig. 1 Right facial swelling and cellulitis

Case presentation

We present a Southern-African 31-year-old male residing in a township in the south of Johannesburg, South Africa. He was negative for human immunodeficiency virus (HIV) infection.

He presented to a primary healthcare facility with a 1-week duration history of bilateral nasal congestion and a 6-month history of headache where he was assessed as having sinusitis. He was treated with a short course of antibiotics and antihistamines. He had no improvement on these treatments, and over the next 6 weeks, his face swelled on the right, and he developed bilateral purulent nasal discharge and loss of vision in his right eye. He had B symptoms in the form of weight loss and drenching night sweats. He had no peripheral lymphadenopathy and no abdominal masses or hepatosplenomegaly. He was ultimately referred to the Otolaryngology Department at the Chris Hani Baragwanath Academic Hospital (CHBAH). On clinical examination, he was noted to have an ulcerated and necrotic lesion on his right inner cheek complicated by cellulitis of his right face (see Figs. 1 and 2). The Waldeyer ring lymph nodes were not enlarged. Additionally, he had a diffuse papular rash on his upper limbs.

An incisional biopsy of the lesion was done. It revealed a high-grade NHL (see Fig. 3). Immunohistochemistry of the lesion was negative for CD20, CD3, CD4, CD8, CD15, CD30 and ALK 1 (anaplastic large cell kinase 1). CD56 showed membranous staining in the tumour cells

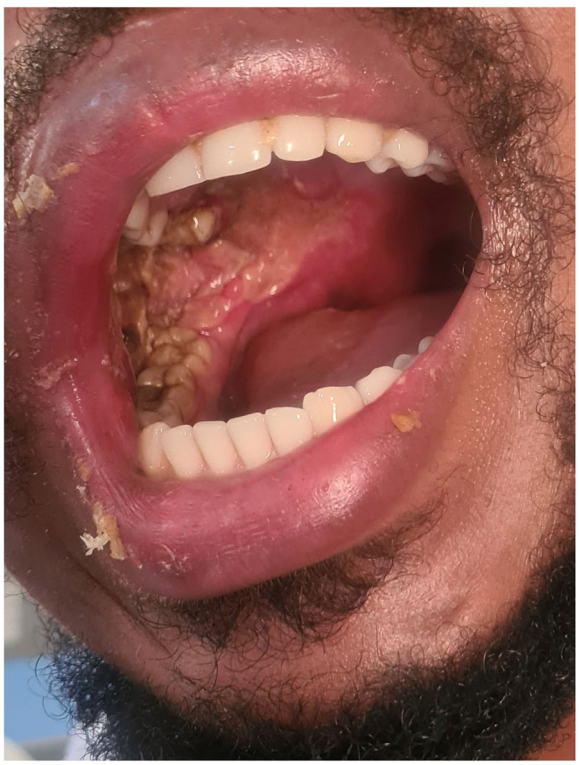

Fig. 2 Right inner buccal ulcerative and necrotising lesion

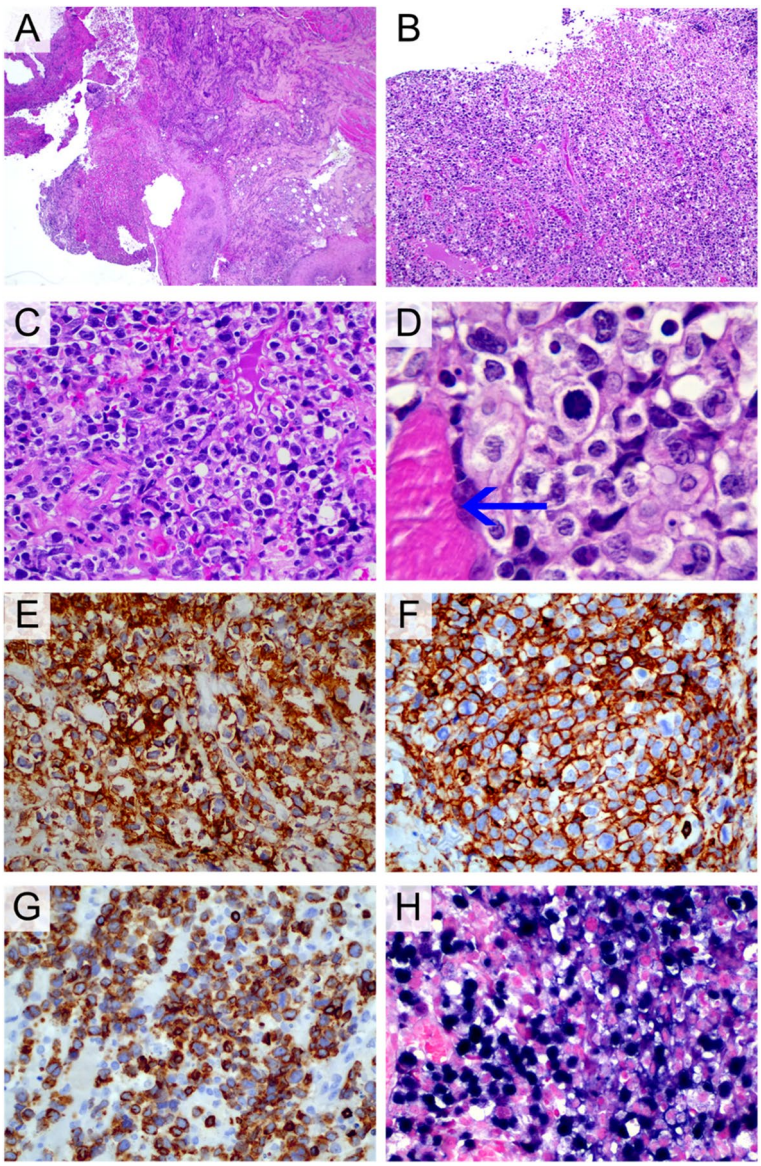

Fig. 3 Histology of the lesion. **A** Low-power photomicrograph of ulcerated nasal mucosa and submucosa (×40). **B** Photomicrograph of ulcerated mucosal surface and underlying lymphoid infiltrate (×100). **C** Dense atypical lymphoid infiltrate at high power (×400). **D** Malignant lymphoid infiltrate between skeletal muscle fibres (blue arrow) at high power (×1000). **E** Immunohistochemistry (IHC) shows membrane positivity of tumour cells for CD45 (×400). **F** CD56 (×400). **G** IHC shows cytoplasmic positivity for CD3 (×400). **H** EBV in situ hybridisation shows strong nuclear positivity in tumour cells (×400)

(see Fig. 3). EBV in situ hybridization (EBER-ISH) nuclear staining was positive (see Fig. 3). The tumour cells were negative for detection of clonal T-cell receptor gamma chain gene rearrangement.

A biopsy of the papular skin lesions was done that showed a resolving lichenoid reaction pattern.

A staging computed tomography (CT) scan showed a right-sided, contrast- enhancing soft tissue mass lesion with the epicentre in the right maxillary antrum measuring 39 × 61.1 × 52.4 mm. The mass was limited medially by the nasal septum. Superiorly, it eroded the lamina papyracea, extended into the medial orbital space and was inseparable from the medial rectus muscle with resultant proptosis. There was also involvement of the right ethmoid air cells and frontal sinuses. The mass was limited inferiorly by the hard palate and floor of the maxillary antrum. It extended posteriorly along the right pharyngeal wall with obliteration of the right torus

tubarius and fossa of Rosenmuller. There was also a left cervical lymph node at the level of C3 measuring 17.3 × 10.5 mm. No other lesions were detected on the staging CT scan (see Fig. 4 — CT scan coronal view in our patient with NNKTL — blue arrow showing right buccal mass extending into sino-nasal space, orange arrow showing occlusion of the osteomeatal complex, red arrow showing right orbital extension).

EBV polymerase chain reaction (PCR) was also done but there was no result due to a sample processing error. A final diagnosis of NNKTL was made, T4N1M0, stage 3.

The patient was treated supportively, and specifically with chemotherapy using the SMILE regimen — steroids (dexamethasone), methotrexate, ifosfamide, L-asparaginase and etoposide as well as sandwich radiation therapy planned.

He had a partial response to chemotherapy but unfortunately demised due to overwhelming sepsis prior to radiation therapy.

Discussion

NK cells target tumour cells and bacteria or virus-infected cells and kill them by cytolysis [10]. NK cells and T cells share a common ontogeny, and thus, both express CD2 and CD7 [10]. Unlike T cells, NK cells are negative for surface CD3 but express cytoplasmic CD3. NK cells also express CD56, CD57 and CD16, with CD56 being the most consistently expressed [10].

NNKTL is characterized by distinct extranodal distribution [1]. It is a relatively rare NHL. It was first described in 1897 by McBride who observed destruction of the midline (nose and face) and coined the term "lethal midline granuloma" [11]. In the late twentieth century, it was called nasal T-cell lymphoma [6]. Later, the tumour cells were found to have the NK-cell marker CD56; hence, the term NNKTL was adopted [6]. The association of NNKTL and EBV was described by Harabuchi et al. in Japan in 1990 [12].

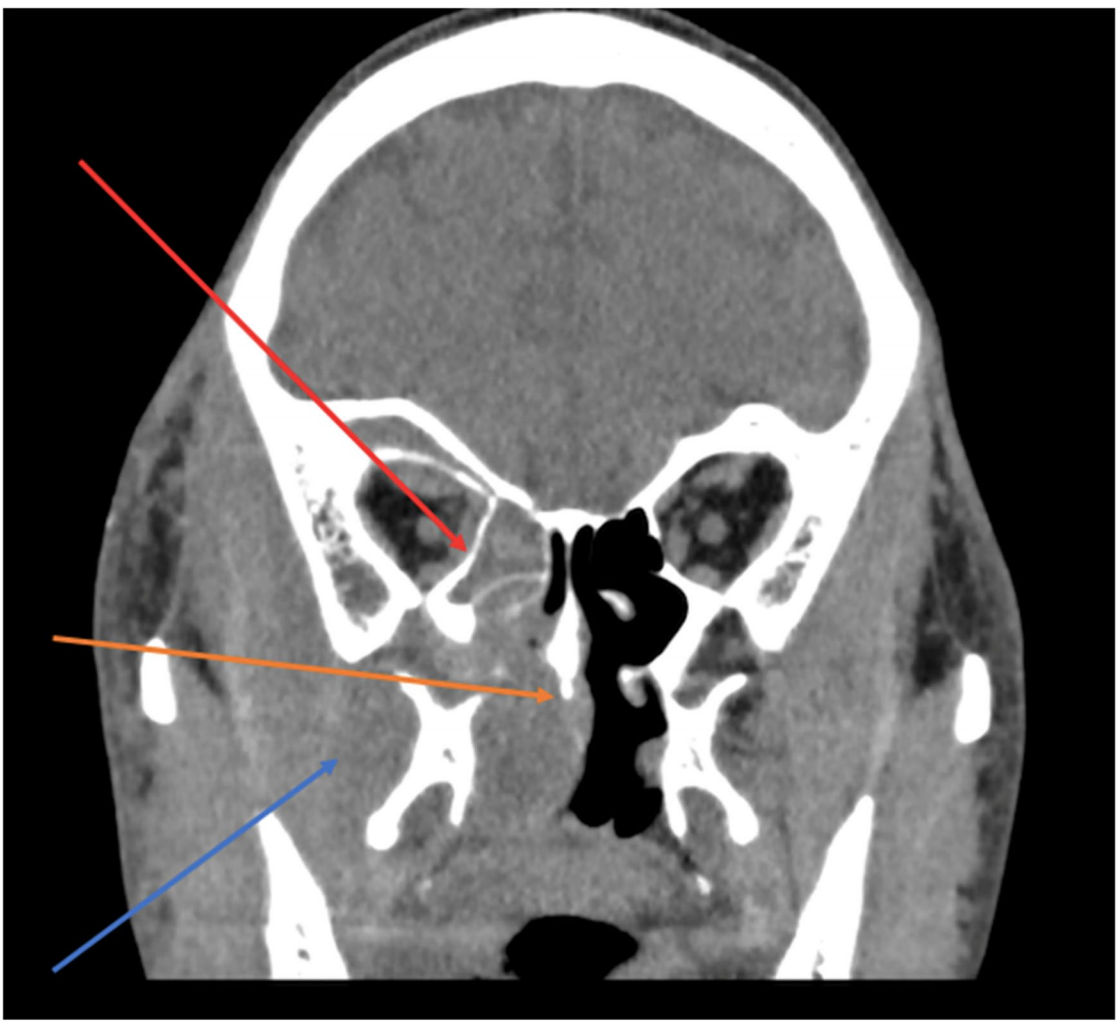

Fig. 4 CT coronal view - right buccal mass extending into the right orbit and right sinonasal spaces

As discussed earlier, there is a geographic variation of NNKTL prevalence. Much is still being unveiled about the reasons for the variation [6]. It has been postulated that certain human leukocyte antigen (HLA) types have the disadvantage of presenting EBV-associated proteins to T cells, similar to HLA-B46 that is a risk factor for nasopharyngeal cancer, which is also an EBV-associated cancer [6]. Another postulation for the geographic variation is that of the differences in EBV strains and their potential to cause NNKTL [6]. Environmental factors may also play a role in the differences [6]. Some authors have postulated that the low documented NNKTL figures in Africa are also due to lack of requisite immunohistochemical and molecular diagnostic techniques to diagnose NNKTL [8].

The NNKTL lymphoma cells comprise a polymorphous population of atypical small, intermediate and large lymphocytes, admixed with eosinophils; histiocytes and plasma cells [6]. The tumour infiltrate is angio-centric and angio-invasive, with resultant coagulative necrosis [5].The presence of EBV in the tumour cells is detected most reliably by EBER-ISH, which is a diagnostic requisite [5].

NNKTL is initially found as a necrotic granuloma in the nasal cavity, palate and nasopharynx [6]. The symptoms of this stage of the lymphoma are nasal congestion and/or bloody rhinorrhoea [6]. Other symptoms include fever, weight loss, sore throat, swelling of the buccal area or orbits and a hoarse voice [6]. Although usually locally aggressive, NNKTL may spread to the skin, salivary glands, bone marrow, testes and gastrointestinal tract [5]. Tumour-associated haemophagocytic lymphohistiocytosis (HLH) can also occur [5]. There is no difference in distribution between the genders, and the lymphoma develops around the ages of 40 to 50 years [6].

There are benign histopathological and phenotypical mimickers of extranodal NK/T-cell lymphomas that need to be differentiated from the lymphoma. These include chronic active EBV infection, mosquito-bite hypersensitivity, lymphomatoid gastropathy and NK-cell enteropathy [5].

Regardless of the initial site of presentation of NNKTL, a nasal panendoscopy must be performed, and biopsy of suspicious lesions is taken [6]. Bone marrow biopsies must include EBER-ISH to exclude bone marrow involvement. Positron emission tomography-computed tomography (PET/CT) is the recommended imaging modality [6]. In settings where PET/CT is not readily available, magnetic resonance imaging (MRI) or computed tomography (CT) can be used.

Measurement of serum-free circulating EBV deoxyribonucleic acid (DNA) by PCR is an accurate surrogate biomarker of lymphoma load [12].

The extranodal pattern of disease of NNKTL renders the Ann-Arbour staging system of limited use in prognostication and treatment guidelines. Rather, a TNM staging was suggested by Yan et al. in 2015. This TNM staging system was found to be very effective in stratification of tumour burden and survival risk [13].

NNKTL are radiosensitive [5]. Recurrence is high with radiation alone, so chemoradiation is the recommended standard of treatment [6]. Anthracycline-based regimens with radiotherapy showed unsatisfactory results to a multidrug resistance phenotype of NNKTL cells [6]. Different chemotherapy regimens can be used including DeVIC (dexamethasone, etoposide, ifosfamide and carboplatin), SMILE and others with limited success [6]. A multicentre study by Yang et al. in 2015 looked at a prognostic nomogram for overall survival in previously untreated patients with NNKTL. The finding was that the overall survival (OS) rate was 60.3% [14]. The role of stem cell transplantation is unknown but may be beneficial in the relapsed setting [15, 16].

Conclusion

The early signs and symptoms of NNKTL are similar to those of benign upper airway diseases. Persisting signs and symptoms should prompt the clinician to look for more sinister pathology. Making a diagnosis of NNKTL in resource-limited settings is challenging as the diagnosis requires not only the demonstration of NK-cell markers but also to have a positive EBER-ISH. Collaboration of smaller centres with larger and better equipped centres is required to diagnose and document NNKTL more accurately in the African setting. Mortality remains high in these patients. Different treatment regimens which are affordable in the African setting should be explored.

Abbreviations

EBV: Epstein-Barr virus; NK: Natural killer; NNKTL: Extranodal NK/T-cell lymphoma, nasal type; SMILE: Steroids — dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide; HHV-4: Human herpesvirus 4; NHL: Non-Hodgkin lymphoma; WHO: World Health Organization; HIV: Human immunodeficiency virus; EBER-ISH: EBV in situ hybridization; PCR: Polymerase chain reaction; CHBAH: Chris Hani Baragwanath Academic Hospital; HLA: Human leukocyte antigen; CT: Computed tomography; PET/CT: Positron emission tomography-computed tomography; MRI: Magnetic resonance imaging; DeVIC: Dexamethasone, etoposide, ifosfamide and carboplatin; HLH: Haemophagocytic lymphohistiocytosis; DNA: Deoxyribonucleic acid.

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Authors' contributions
MM wrote up the case report. LQ, VP, YP FW, AL and MP supervised the case report. YP provided and annotated the histology images. AL provided the patient photographs. The author(s) read and approved the final manuscript.

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Availability of data and materials
Data pertaining to the case is available upon reasonable request.

Declarations

Ethics approval and consent to participate
Permission for the case report was reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee.

Consent for publication
Written permission for the case report was sought from the patient.

Competing interests
The authors declare that they have no competing interests.

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