Extranodal NK/T Cell Lymphoma, Nasal Type: An Unusual Entity – A Guide to Diagnosis for the General Pathologist

M Foy, G Turner, F Pezzella, K Fasanmade, N Mungalsingh

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Abstract

Extranodal NK/T cell lymphoma, nasal type (ENKTLNT), is an angiodestructive T-cell non-Hodgkin's lymphoma associated with latent Epstein Barr virus (EBV) infection.[7]

On biopsy, it can present as a poorly differentiated necrotic lesion, requiring a methodical histopathological assessment. The final diagnosis is confirmed by the demonstration of a cytotoxic T-cell phenotype and the presence of EBV in the malignant cells.[7,3]

We present the case of a 66-year-old male with an ulcerated maxillary lesion in which we review the histological features of these lymphomas and discuss the general histopathological approach to the diagnosis.

INTRODUCTION

ENKTLNT is a rare neoplasm associated with EBV. It is found most commonly in the upper aerodigestive tract and usually presents as an ulcerated, necrotic, locally aggressive lesion.[7]

The location, histological features and a characteristic immunoprofile help confirm the diagnosis.[7, 8]

CASE REPORT

A 66-year-old man with a past medical history of thyroid disease, pernicious anaemia and necrotising fasciitis, developed facial and dental swelling with weight loss of several months duration. He presented to the Oral and Maxillofacial surgeons with a large, indurated, soft tissue mass, centred on the right buccal mucosa and extending onto the palate and jaws. Necrosis, cavitation and ulceration were also present (figure 1). There were no raised edges to the ulceration which had a definite border.

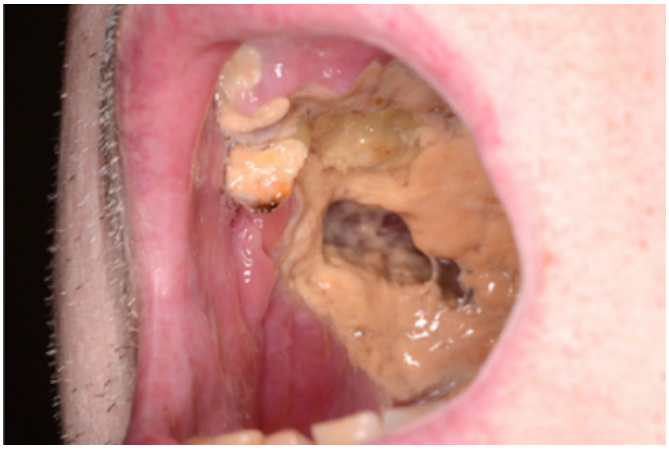
CT, MRI and PET scans confirmed the lesion involved the left and right sides of the face, extending from the middle turbinate to below the thyroid cartilage. It infiltrated the right maxillary alveolus and antrum, the hard palate and the lateral wall of the oropharynx.

There was bilateral cervical lymphadenopathy but no distant metastatic disease was identified.

The oral lesion was clinically suspicious for squamous cell carcinoma and was biopsied.

Figure 1

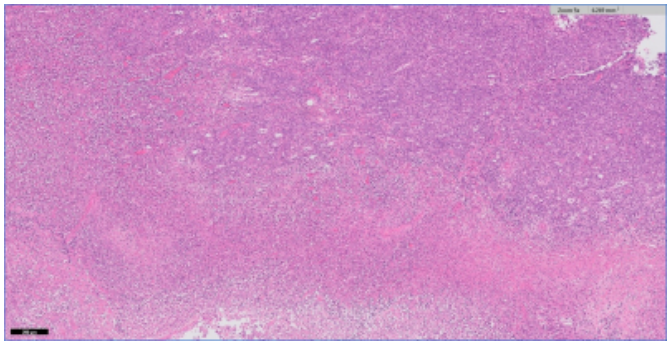
Ulcerated and necrotic oral lesion



The histology of the biopsy revealed an ulcerated, poorly differentiated tumour, diffusely infiltrating the mucosa and underlying skeletal muscle. Extensive areas of necrosis were also present (figure 2).

Figure 2

Low power Haematoxylin and eosin (H&E) stained section showing the infiltrative lymphoid malignancy replacing the palatal mucosa with a band of surface ulceration and necrosis



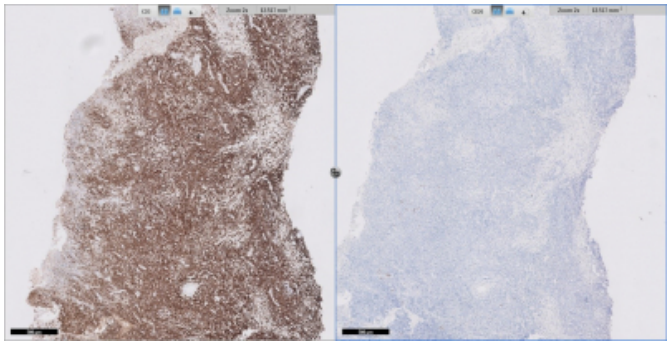
The tumour was arranged in sheets of large neoplastic cells with a high nuclear to cytoplasmic ratio, hyperchromatic nuclei and frequent mitoses.

An initial immunohistochemical panel showed that the malignant cells were positive for CD45, confirming a lymphoid lineage, and negative for a variety of cytokeratins, melanocytic, neuroendocrine and vascular markers, PD1, p63 and p16. Focal positivity for EMA was seen. The tumour cells were positive for CD3 and negative for CD20, indicating a T-cell lineage (figure 3).

These findings were suggestive of a T-cell non-Hodgkin's lymphoma.

Figure 3

Immunohistochemical staining of the tumour cells for the pan-T-cell antigen CD3 (strongly positive brown staining with DAB chromogen) compared to the B-cell marker CD20 (negative)



Further work-up following the referral of the case to the Regional Lymphoreticular Pathology Team showed that the neoplastic cells were also positive for CD2, CD30, CD43, CD25, Granzyme B and EBV (by EBER in situ hybridisation), with a few being weakly positive for CD4. They were negative for CD20, CD79a, CD5, CD7, CD8, CD10 and Alk1 (figures 4 and 5). Interestingly, they were also negative for CD56.

The proliferation index of the lesion (MIB1) was high (approximately 60%).

Figure 4

A higher powered image of the tumour cells showing an NK/T-cell phenotype with expression of Granzyme B in the cytoplasm (left pane) and aberrant CD30 expression on large atypical T-cells (right).

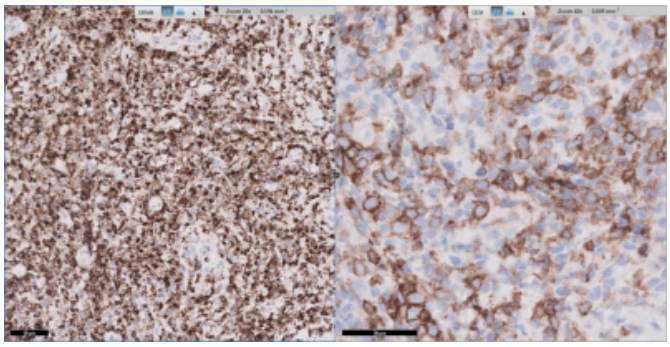
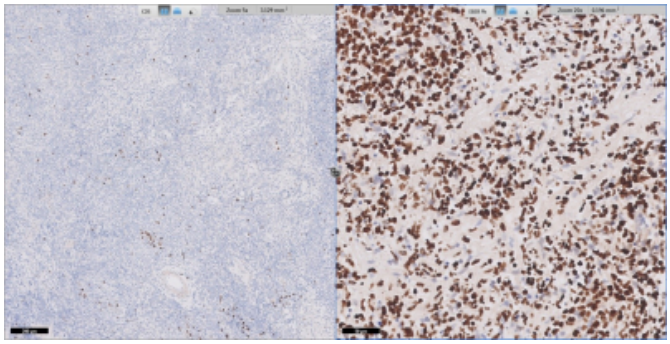


Figure 5

Higher power view showing complete loss of CD5 T-cell marker expression (right) but strong diffuse nuclear staining for EBV on EBER in situ hybridisation



The loss of CD5, CD7, CD8 and the scanty expression of CD4 confirmed an aberrant T-cell phenotype and Granzyme B positivity, despite negative CD56, confirmed a cytotoxic NK/T immunophenotype.

Therefore, the immunoprofile described and the EBER positivity suggested the diagnosis of extranodal NK/T cell lymphoma, nasal type.

Following the histopathological diagnosis and clinical staging, the patient underwent 6 cycles of DDGP chemotherapy with good clinical response. This will be followed by radiotherapy. He continues under the care of the

regional multidisciplinary team.

DISCUSSION

Extranodal NK/T cell lymphoma, nasal type (ENKTLNT), is rare, but the most common subtype of mature NK/T-cell neoplasms[3]. It is a characteristically angiodestructive lymphoma which shows prominent necrosis and is associated with evidence of latent EBV infection[7]. The latter is likely to have a role in its pathogenesis[3]

ENKTLNT is most commonly seen in adult males and is more prevalent in Asians and the indigenous populations of Mexico, Central and South America.[7, 3] It constitutes 3-10% of non-Hodgkin lymphomas in these areas and less than 1% elsewhere.[13]

These lymphomas are mostly extranodal and the most frequent site of presentation is the upper aerodigestive tract.[7] As illustrated in this case, the clinical lesion can be locally very aggressive and can extend to adjacent tissues, hence the previous term used to describe the clinical course of a 'lethal midline granuloma'.[7]

Clinically, the destructive nature of the lesion and its location suggest a number of differential diagnoses and a biopsy is therefore required to rule these out.[12]

The histological features of ENKTLNT consist of diffuse infiltrates of malignant lymphoid cells, which can vary in size from small to anaplastic and which are mitotically active.[7] An angiocentric and angiodestructive pattern is typically seen, with mucosal ulceration and prominent tissue necrosis. Mixed inflammation can also be present. [7, 12]

When assessing the biopsy, the general pathologist should use an 'everyday' general approach and consider the differential of inflammatory and other more common neoplastic conditions. [12]

Bacterial and fungal infections should be ruled out, bearing in mind that they can also be present as a secondary process within the necrotic lesion[12]. Non-infectious autoimmune vasculitic granulomatous inflammatory conditions, such as granulomatosis with polyangiitis, should also be considered. [12]

In this case, the histological features were clearly malignant, and showed a diffusely infiltrative poorly differentiated neoplasm.

The differential diagnoses of such a lesion in the upper aerodigestive tract include carcinoma, lymphoproliferative lesions and, more rarely, sarcomas and melanomas. [12, 3]

The most common carcinomas to consider are squamous cell carcinoma (SCC) and undifferentiated nasopharyngeal carcinoma.[12] Pseudoepitheliomatous hyperplasia can sometimes be seen in association with ENKTLNT, and care should be taken not to confuse the lesion with poorly differentiated SCC.[1, 7, 3, 12]

The main lymphoproliferative lesions to consider are diffuse large B cell lymphomas and ENKTLNT. Other EBV-related lymphoid malignancies should also be considered. [7, 3, 12]

The General Pathologist should therefore undertake an initial basic immunohistochemical panel to determine the lineage of the neoplastic cells (including B and T cell lymphoid markers). In doing so, they should be mindful of the need to preserve tissue for potential further investigations.

Once the initial assessment has been done and a non-Hodgkin T-cell lymphoma diagnosed, the case should be referred to a specialist Haematopathology team, as per local protocols, for further immunohistochemistry and ISH studies.

The most typical immunoprofile of ENKTLNT is positive for CD2, CD56, cytoplasmic epsilon CD3, cytotoxic molecules (such as Granzyme B, TIA 1 and perforin) and EBV . Variable expression of CD7, CD25 and CD30 is seen . ENKTLNT is usually negative for B cell markers, CD4, CD5, CD8 and CD43 [7, 3].

Most ENKTLNT have an NK phenotype but some cases show a cytotoxic T-cell phenotype instead.[7] While T-signature versus NK-signature may be useful for future potential targeted therapy, the differentiation between these has no prognostic implications.[4]

The case we presented showed a similar immunoprofile as described above, consistent with ENKTLNT, but was CD56 negative.

Negativity for CD56 is relatively infrequent in these lymphomas, but can occur in 24-25% of the cases.[9] Interestingly, some authors suggest that ENKTLNT which are CD56 negative have a more aggressive clinical course.[9, 10]

Despite CD56 being negative, the diagnosis of ENKTLNT was still favoured in this case due to the location and

histology of the lesion with positive cytotoxic markers (Granzyme B) and EBV.[7, 8]

A T-cell lymphoma with a CD3+/CD56- phenotype lacking cytotoxic markers and EBV expression would however be classified as a peripheral T-cell lymphoma NOS[7].

Once the final diagnosis of ENKTLNT is made, clinicopathological correlation and multidisciplinary teamwork are essential for staging and management decisions.

The prognosis has improved over the years, especially in localised disease, but it is still relatively poor, with high relapse rates.[7, 3, 11, 12]

In conclusion, ENKTLNT is a rare aggressive neoplasm of the upper aerodigestive tract with a characteristic immunoprofile. Although the final diagnosis will be ultimately made by a specialist haematopathologist, all general pathologists should consider it when faced with a poorly differentiated tumour in this location and act promptly and methodically, starting with a general, ‘everyday’ approach.

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Author Information

M. Victoria Foy, MD (Hons), DipRCPath
ST3 Histopathology, Wycombe Hospital
High Wycombe, United Kingdom

GDH Turner
Consultant Histopathologist, Department of Cellular Pathology, John Radcliffe Hospital
Oxford, United Kingdom

F Pezzella
Professor of Tumour Pathology, Consultant Pathologist, Department of Cellular Pathology, John Radcliffe Hospital
Oxford, United Kingdom

Kunmi Fasanmade, BDS, MBBS, FDSRCS, MRCS, FRCS(OMFS)
Consultant Oral and Maxillofacial/Head and Neck Surgeon, SDU Lead (Joint) in Oral and Maxillofacial, Orthodontics and Restorative Dentistry, Buckinghamshire Healthcare NHS Trust
Buckinghamshire, United Kingdom

Narendra Mungalsingh, BSc (Hons), BM, FRCPath
Consultant Histopathologist, Wycombe Hospital
High Wycombe, United Kingdom