NK/T cell Lymphoma as a Rare Cause of an Oronasal Fistula

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The study has not been presented previously in a congress or symposium.

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INTRODUCTION

Extranodal NK/T cell lymphoma (NKTCL) nasal type or previously known as lethal midline granuloma, is considered as one of the rarest differential diagnoses to cause an oronasal fistula (ONF). It is a belligerent malignancy of putative NK-cell origin, with a minority deriving from the T-cell lineage. About 80% of cases occur in the nose, nasopharynx, oropharynx, the Waldeyer ring, and parts of the upper aerodigestive tract, while 20% in non-nasal areas such as skin, gastrointestinal tract, testis, salivary gland, etc [1].

ONF is an internal fistula defined by an abnormal epithelialized track communicating the nasal cavity with the oral cavity in which it may be due to multiple causative factors and can be divided into congenital, infection, iatrogenic, and tumour causes. Tumours such as squamous cell carcinoma, adenoid cystic carcinoma, melanoma, acute lymphoblastic leukemia and lymphoma are known causes of ONF. Nevertheless, extranodal NKTCL itself is a rare encounter [2].
Symptoms of the NKTCL nasal type are varied and non-specific. It may include nasal discharge, nasal obstruction, epistaxis, and other sinonasal symptoms. Thus, it is frequently missed and treated as a viral or bacterial infection, which leads to a late diagnosis and increases morbidity and mortality. Therefore, an early diagnosis of the disease has to be made meticulously [3].

**CASE PRESENTATION**

A 32-year-old man with no known medical illness, presented with a two-day history of left epistaxis. It was associated with worsening bilateral nasal blockage, rhinorrhea and hyposmia for six months. He also complained of a painless ‘hole’ on the left side of his soft palate which started as an ulcer and has subsequently increased in size for the past three months. It was complicated by nasal regurgitation as well as hypernasal voice. The nasal regurgitation was reduced by taking food in small amounts while the epistaxis was minimal in amount and had resolved spontaneously.

The patient had an intermittent low-grade fever with night sweats and a significant weight loss of 20 kilograms in the past two months. He denied having any symptoms or contact with tuberculosis patients. He did not have odynophagia, dysphagia, hypernasality voice, stridor, shortness of breath, or neck swelling. There were no other complaints except for reduced hearing, especially over the left ear.

On examination, he was a moderately-built adult with good hydration, not anaemic nor septic looking. Vital signs were within normal limits with no signs of anaemia. He had no palpable cervical, axillary or inguinal lymph nodes. All cranial nerves were grossly intact except for the reduced sensation of smell in bilateral nostrils.

An intraoral examination revealed an irregular edge fistula over the left side of the soft palate connecting the oral and nasal cavity, measuring 3 x 3 cm (Figure 1). Upon palpation, the area was slightly tender but with no contact bleeding. Otherwise, the surrounding structures, including the bilateral tonsils, uvula and anterior pillars, were normal. The nasal endoscopy showed a fleshy mass occupying the left nasal cavity (Figure 2). His right nasal airway had a hypertrophied inferior turbinate with no mass seen, with the septum intact. Otoscopy showed a retracted left tympanic membrane with evidence of conductive hearing loss.

The laboratory test showed normal findings except for his lactic acid dehydrogenase (LDH) level, which was high at 419 units per liter (U/L). His EBV PCR was reported as positive (POS 2.7 LOG IU).

Biopsy of the left soft palate ulcer revealed lymphoproliferative neoplasm of T-cell lineage with a high proliferation index. Bone marrow aspiration revealed no infiltration. The Contrast-enhanced computed tomography (CECT) paranasal sinus showed focal irregularities in the soft palate with no
A focal enhancing lesion seen. An apparent exophytic hypodense lesion in the superior aspect of the soft palate which is projecting into the nasopharynx with the soft palate and uvula appearing bulky and irregular (Figure 3). There were subcentimeter cervical nodes seen with hepatosplenomegaly.

A final diagnosis of NKTCL, Stage 1b (T2N0M0) was made and the patient is currently undergoing chemotherapy (SMILE Protocol). Besides the ongoing therapy, the patient was given chlorhexidine mouth wash 10ml TDS with an oral moisturizer to keep a normal oral pH, therefore avoiding dental carries. On day 19 of his chemotherapy, the size of the ONF widened to 5 cm x 4 cm, but with more healthy-looking edges (Figure 4). The patient was planned for surgical closure of the ONF after completion of the chemotherapy. If surgical closure fails, a maxillary obturator prosthesis may be applied.

**DISCUSSION**

In this case, ONF developed following a persistent non-healing ulcer on the left soft palate and had worsened post biopsy of the ulcerated part. ONF is an abnormal epithelial communicating tract between the oral and nasal cavity. Thus, it impairs both oral and nasal functions, such as swallowing and speech, through nasal regurgitation of food and nasal speech respectively, besides having the risk of nasal infection as a result of food lodgement. It causes hypernasality due to escape of air during speech and also leads to regurgitation of food and fluid into the nasal cavity [4]. There are several causative factors that may contribute to ONF formation (Table 1).

As for this patient, the most common differential diagnosis according to the sign and symptoms is left nasal squamous cell carcinoma (SCC), followed by nasopharyngeal carcinoma (NPC) and olfactory neuroblastoma (ONB). The reason is, from the patient’s history, there is a progressive history of nasal blockage with epistaxis. The patients also complained of loss of appetite with significant weight loss. Examination of the left nasal cavity revealed a fleshy mass with ONF which is prone to the diagnosis of SCC as being the commonest sinonasal malignancy. However, due to the patient’s age and no history of potential carcinogenic inhalant exposure, the diagnosis is unlikely. From examination as well, the patient has no palpable cervical nodes or neck swelling to suggest NPC. According to the gender predominance, ONB favours females more than males. Hence, hyposmia or anosmia is not a strong indicator for diagnosing an ONB and is non-specific.

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**Figure 3.** Axial CT scan of paranasal sinus showing soft tissue mass occupying posterior 2/3rd of the left nasal cavity (red arrow) and posterior 1/3rd of the right nasal cavity (black arrow), extending posteriorly to the nasopharynx (yellow arrow), inferiorly involving uvula and palate (white arrow).

**Figure 4.** Oral cavity examination showed a smooth-edge fistula measuring 5cm x 4cm (black arrow).
Lymphoma Presented with Oronasal Fistula

NKTCL has an ethnic predominance of East Asians and Latin Americans. It is associated with Epstein-Barr virus (EBV) infection, with preference for involvement of upper-aerodigestive-tracts, particularly nasal and paranasal areas (80% of cases). It features a locally aggressive with a mix of necrotic cellular infiltrates and angioinvasion on histological examination. Males are more affected than females, with a median age of onset of 52 years [5]. Nonetheless, in this case report, it can also occur in young adults. The patient's initial symptoms are non-specific and include nasal obstruction with minimal epistaxis, which can mimic sinusitis symptoms. These symptoms usually precede ulceration and local destruction by months to years. However, the disease can have a rapidly progressive course, as in this patient, who presented with a relatively short history and significant weight loss, which is commonly presented in advanced cases of NKTCL. Similar to the less than half of cases reported, this patient also showed an increase in LDH levels with B symptoms as well.

NKTCL shows more local destructive behaviour as compared to other types of NHL. In this case, the initial ulcer over the soft palate was not in the midline, contrary to the commonly reported cases of NKTCL of maxillofacial or nasopharyngeal structures which tend to occur in the midline. The non-specificity of the symptoms of NKTCL based on the sites involved, therefore, may lead to delay in detection of the disease and a high probability of misdiagnosing with other conditions.

In the case of NKTCL, a diagnosis is not solely based on clinical manifestation. A combination of histopathology, imaging and even liver function parameters, i.e EBV PCR, LDH, are needed to confirm the diagnosis. The gold standard treatment for NKTCL is radiotherapy, but the treatment choice can be varied depending on the staging of the disease. Stage I and II are best treated with radiotherapy, chemotherapy or both, while stage III/IV is treated with the SMILE Protocol [6]. A novel regimen of steroids, i.e dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) showed promising remission in patients with NKTCL.

The ONF became wider despite day 19 of SMILE. The protocol can be explained by the reduction of the inflamed and oedematous edges of the ONF as a direct positive effect of the treatment protocol. For this patient, if the ONF persists after completion of the treatment, it is indicated to surgically close the defect with primary closure. Local flap from buccal pad of fat or palatal flap can be incorporated if unable to achieve primary closure. If surgical closure fails, a maxillary obturator prosthesis may be applied [7].

As for the patient's follow-up, it is recommended to have a multidisciplinary team involving hemato-oncology, oromaxillofacial surgery, and otorhinolaryngology outpatient clinic to closely monitor the patient's progress and tumour surveillance [8].

CONCLUSION

Diagnosis of a rare NKTCL as the cause of ONF is challenging. Hence, one must have a high index of

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**Table 1. Proposed causes of palatal perforation by Patil SR (6).**

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental</td>
<td>Cleft palate (Secondary to maternal alcohol consumption and cigarette smoking, folic acid deficiency, teratogenic drugs, viral infection, corticosteroid use and anticonvulsant therapy)</td>
</tr>
<tr>
<td>Drug related</td>
<td>Narcotics (cocaine, heroin etc.,)</td>
</tr>
<tr>
<td>Trauma</td>
<td>Iatrogenic, Thermal</td>
</tr>
<tr>
<td>Infection</td>
<td>Tertiary Syphilis, Tuberculosis, Leprosy, Typhoid, Mucormycosis, Actinomycosis, Aspergillosis, Paracoccidioidomycosis, Histoplasmosis, Naso-Oral Blastomycosis, Leishmaniasis, Diphtheria, Rhinoscleroderma</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Lymphoma, Carcinoma, Melanoma, Acute Lymphoblastic Leukemia</td>
</tr>
<tr>
<td>Collagen vascular</td>
<td>Wegener's granulomatosis, Systemic lupus erythematos</td>
</tr>
<tr>
<td>disease</td>
<td>Midline lethal granuloma</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Sarcoidosis, Crohn's disease</td>
</tr>
<tr>
<td>Granulomatous disease</td>
<td>Rhinoscleroderma</td>
</tr>
<tr>
<td>Other</td>
<td>Rhinoliths</td>
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suspicion with several differential diagnoses when encountering such cases. It is essential to involve a multidisciplinary team to help diagnose and treat NKTCL, especially in cases presenting with non-specific nasal and oral symptoms. The disease should be staged appropriately to help in deciding the best treatment protocol. Furthermore, the main presentation of this case was an ONF, which by itself is a rare complication of NKTCL.

CONFLICT of INTEREST

The authors declare no conflict of interest.

REFERENCES


