Reminder of important clinical lesson

Extranodal natural killer/T cell lymphoma, nasal type presenting as a palatal perforation and naso-oral fistula

Vijaya Raj Bhatt,¹ Bibek Koirala,¹ Terenig Terjanian²¹Department of Medicine, Staten Island University Hospital, Staten Island, New York, New York, USA;²Division of Hematology and Oncology, Department of Medicine, Sanford R Nalitt Institute for Cancer and Blood Related Diseases, Staten Island University Hospital, Staten Island, New York, New York, USA

Correspondence to Dr Vijaya Raj Bhatt, vrbhatta@gmail.com

Summary

Extranodal natural killer/T cell lymphoma (ENKL), nasal type, a rare disease presenting with vague non-specific symptoms, can impose great diagnostic difficulties and may masquerade several infectious, rheumatological or neoplastic conditions. Here, the authors report a case of ENKL presenting as a palatal perforation, naso-oral fistula and fever in a 21-year-old man, which was initially misdiagnosed as bacterial osteomyelitis, invasive fungal infection and Wegener's granulomatosis. The case report underlines the possibility of ENKL occurring at a young age, its rapidly progressive and locally destructive nature, associated diagnostic challenges and the importance of immunophenotyping in establishing the diagnosis.

BACKGROUND

Palatal ulceration and perforation in a young adult can be a rare presentation of a number of conditions including infections, for example, bacterial osteomyelitis, invasive fungal infection and syphilis,^{1–3} inflammatory diseases particularly Wegener's granulomatosis,⁴ neoplasms, for example, mucoepidermoid carcinoma, squamous cell carcinoma and lymphoma,^{5–9} necrotising sialometaplasia of the palate,¹⁰ cocaine-induced injury,¹¹ intranasal prescription narcotic abuse¹² and rhinolith.¹³ Here, we present a case of a previously healthy young man with palatal perforation with an elusive diagnosis.

CASE PRESENTATION

A 21-year-old previously healthy male immigrant from Guatemala presented to the emergency department with a 2-month history of pain and foul-smelling discharge from his hard palate, which was worsening over the last few days. It was associated with a low-grade fever, chills and sweating along with occasional regurgitation of food and fluids through his nostrils. Although he was not a smoker, he confessed snorting cocaine a few times during 4 months prior to his presentation. He denied drinking alcohol or having multiple sexual partners.

On examination, he was a well-built male with a blood pressure of 116/90 mm Hg, heart rate of 70/min, respiratory rate of 18/min and temperature of 100°F. He had multiple tattoos in his skin. His oral cavity showed a 2.5 cm×2.5 cm ulcer on the roof of the hard palate covered with foul-smelling purulent debris and poor oral hygiene (figure 1). The rest of his physical examination was normal.

INVESTIGATIONS

Laboratory evaluation revealed a white count of 6700/μl, haemoglobin of 14.4 g/dl, platelet of 2 21 000/μl and normal glucose, electrolytes, renal and liver functions. CT scan of maxillofacial sinus with intravenous contrast

showed destruction of the right side of the hard palate and inferior and superior turbinates with a tract from the nasal cavity into the oropharynx (figure 2). Other findings included septal deviation to the left, opacification of the right ethmoid, maxillary and left sphenoid and ethmoid sinuses. CT scan of the head was negative. Nasal endoscopy showed right naso-oral fistula, necrotic tissue in right nasal cavity and right pansinusitis. Palatal biopsy was performed and sent for histopathological examination and culture.

TREATMENT

With the possibility of bacterial osteomyelitis, the patient was started on intravenous clindamycin and ticarcillin-clavulanate. Patient was doing well until day 4, when he spiked a temperature of 102.3°F and complained of severe headache. Voriconazole was added due to the possibility of invasive fungal infection. Urine and blood cultures as well as ELISA for HIV antibodies were negative. The culture of biopsy specimen was negative. Histopathologic examination revealed ulcerated oral mucosa exhibiting acute sialoadenitis and extensive necrosis with focal perivascular inflammatory infiltrate of small vessels and a medium-sized artery, consistent with Wegener's granulomatosis. At this point, the results of immunophenotyping on the biopsy specimen were pending. Antibiotics were withheld, and although anti-neutrophil cytoplasmic antibody (ANCA) test turned out to be negative, it was decided to start a trial of oral prednisone. His tuberculin test came back positive (10 mm) but the chest x-ray was unremarkable. A decision was made to treat the patient for latent tuberculosis with isoniazid and pyridoxine in case any additional immunosuppressant was required.

OUTCOME AND FOLLOW-UP

The patient continued to have a low-grade fever and repeat oral culture grew *Proteus mirabilis* and *Enterobacter aerogenes*.

Figure 1 Clinical photography of oral cavity showing ulcer on the roof of hard palate covered with purulent debris.

Figure 2 CT scan image (coronal section) of maxillofacial sinus showing erosion of the right side of the hard palate and opacification of the right maxillary and ethmoid sinuses.

He was started on empiric moxifloxacin though the possibility of oral colonisation by these organisms could not be excluded. The patient complained of dysphagia and regurgitation of food through his nostrils. He was, therefore,

planned for a percutaneous endoscopic gastrostomy tube placement. The next day, however, he was found to be missing from the hospital. Subsequently, immunophenotyping of the biopsy revealed focal zones of neoplastic

Table 1 Differentiating common causes of palatal ulceration and/or naso-oral fistula

Causes	Diagnostic features
Bacterial osteomyelitis	Fever, foul-smelling purulent drainage, elevated white count; gram stain and culture of biopsy specimen from the affected area can show causative bacteria; responds to antibiotics. ²
Invasive fungal infection	Often seen in patients with uncontrolled diabetes/diabetic ketoacidosis, malignancy, extensive burns or immunosuppression (eg, neutropenia or steroid use). Can be rapidly progressive. Fever and elevated white count; histopathologic examination using fungal stains (eg, Gomori methenamine silver stain) or fungal culture can be positive. ¹
Tertiary syphilis	High-risk sexual behaviour, history of genital ulcer and/or other manifestations of syphilis; positive serology (VDRL, TPHA) and dark ground microscopy. ³
Wegener's granulomatosis	Systemic manifestations, for example, involvement of upper respiratory tract, lungs and kidneys; positive ANCA, abnormal chest radiograph and urine analysis; necrosis, granuloma formation and vasculitis of small-to-medium-sized vessels on biopsy. ¹⁹
Necrotising sialometaplasia	Single unilateral ulcer, often subsequent to surgical procedure or trauma; characteristic histopathological features: preservation of lobular architecture and squamous metaplasia of minor salivary gland ducts and acini. Immunophenotyping, for example, myoepithelial markers, basement membrane markers, E-cadherin and cytokeratins may be helpful. ¹⁰
Malignancy	Regional lymph nodes may be involved. Histopathological examination of biopsy positive for specific type of malignancy, for example, high-grade mucoepidermoid carcinoma shows intermediate basal and epidermoid cells in solid nests or cords. Neoplastic cells vary in size and shape and have prominent nucleoli and abundant mitotic figures. ⁹ ENKL requires immunophenotyping. ^{14 17}

lymphocytic infiltrate involving minor salivary glands with angiocentric growth pattern, positive for CD2, CD3 (dimly positive), CD30, CD56, MUM-1 and Epstein-Barr virus early RNA (EBER) and negative for CD4, CD5, CD8, CD10, CD15, CD20, CD79a, EMA, LCA, ALK-1 and BCL-6. Thus, a diagnosis of Epstein-Barr virus (EBV) positive, CD 30 positive extranodal natural killer/T cell lymphoma (ENKL) was made. Multiple attempts were made to communicate with the patient but regretfully, he was lost to follow-up.

DISCUSSION

ENKL is a rare but distinct entity of non-Hodgkin's lymphoma, mostly derived from natural killer cell lineage and occasionally cytotoxic T cell lines.¹⁴ It is characterised by ethnic preponderance (more common in East Asians and Latin Americans than Caucasians), consistent association with EBV infection, predilection for upper aerodigestive tracts, particularly nasal and paranasal areas (80% cases), mixed cellular infiltrate with angiocentricity, angioinvasion and necrosis on histological examination, and aggressive locally destructive nature.^{14–16} It affects males more commonly than females and has a median age of onset of 52 years.¹⁷ However, as highlighted by this case report, it can also occur in young adults. Initial symptoms are non-specific and include pain, obstruction, discharge, foul smelling and bleeding, which can masquerade sinusitis.¹⁸ These symptoms usually predate ulceration and local destruction by months to years.^{16 17} However, the disease can have a rapidly progressive course as in this patient, who presented with a relatively short history. Fever and weight loss are present only in advanced cases. Increased LDH levels and B symptoms are reported in less than half of all cases.^{16 17}

Several infectious, inflammatory and neoplastic conditions can cause destruction of palate and adjacent areas. Diagnosing the underlying cause could be very challenging as illustrated by this case and requires consideration of several factors as well as gram stain, fungal stain, culture and histopathologic examination of biopsy specimen (table 1). The diagnosis can be further complicated by isolation of normal oral flora. Therefore, it is important to continue the search for alternate diagnosis if a patient fails appropriate and adequate therapy for infectious aetiology. It is important to realise that the

angiocentric cellular infiltrate of ENKL can be mistaken for the vasculitic picture of Wegener's granulomatosis. Absence of other features of Wegener's granulomatosis should alarm a physician about this possibility. In addition, immunophenotyping can make the definite diagnosis of ENKL. ENKL is typically CD2+, CD56+, surface CD3–, cytoplasmic CD3epsilon+ and cytotoxic granule-associated protein (TIA-1, granzyme B and perforin) positive.^{14 17} EBV positivity, detected by in situ hybridisation, can further help identify neoplastic from non-neoplastic lymphocytes.¹⁶

Treatment of ENKL consists of radiotherapy or chemotherapy, either alone or in combination, depending on the extent of disease, age and comorbidity. ENKL often remains localised in the nasal primary site; regional nodal spread (15–30%) or systemic dissemination (<20%) is uncommon at the time of presentation. Early-stage localised nasal disease is highly curable whereas disseminated disease has very poor prognosis.¹⁴ This underlines the importance of early diagnosis and therapy.

Learning points

- ▶ Failure of standard therapy for bacterial osteomyelitis and invasive fungal infection in a patient with palatal ulceration and fever should trigger diagnostic work up for possible rheumatological and neoplastic conditions.
- ▶ The angiocentric cellular infiltrate seen in ENKL can be confused with the vasculitic picture of Wegener's granulomatosis. Therefore, the diagnosis of Wegener's granulomatosis should not be based solely on histopathological findings rather should also be supported by the ANCA positivity and other clinical features.
- ▶ Misdiagnosis of ENKL or delaying the treatment has serious consequences. Therefore, in the absence of conclusive diagnosis, we recommend immunophenotyping and EBER staining of the biopsy to rule out the possibility of ENKL.
- ▶ Fungal lesions, such as mucormycosis, are likely to produce an oronasal fistula, thus mimicking the destruction pattern of an ENKL. Therefore, in these cases, it is advisable to perform fungal staining and culture.

Competing interests None.

Patient consent Obtained.

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