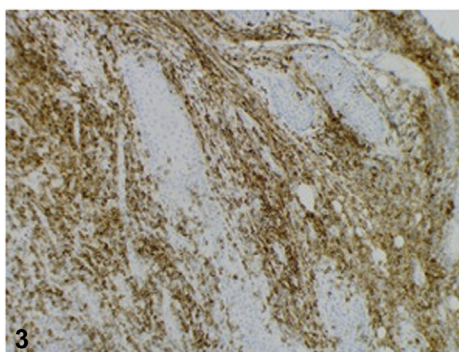


Centrofacial cutaneous and oral ulcerations associated with pansinusitis



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A 56-year-old Vietnamese woman presented with worsening chronic pansinusitis with progressive oral and cutaneous involvement. For the previous 8 months, she had undergone multiple endoscopic submucosal resections of the nasal turbinates. Despite debridement and many courses of oral and intravenous antibiotics, her clinical course worsened. Although further tests were pending, dermatology department was consulted. On the day of consultation, physical examination showed diffuse centrofacial edema, ulceration of the right alar

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groove (Fig 1), and necrosis of her soft palate (Fig 2). Punch biopsy of the skin adjacent to the ulcer was performed, and the dermal infiltrate stained CD56⁺ (Fig 3).

Question 1: Which is the most likely diagnosis?

- A. Rhinosporidiosis
- B. Nasal extranodal natural killer/T-cell lymphoma (ENKTL)
- C. Granulomatosis with polyangiitis
- D. Extranasal ENKTL
- E. Paracoccidioidomycosis

Answers:

A. Rhinosporidiosis — Incorrect. This is a chronic infection caused by the fungus *Rhinosporidium seeberi*. This could be included as a differential diagnosis due to the frequent involvement of the nasal turbinates and lack of improvement with antibiotic therapy; however, the tissue biopsy did not show fungal involvement.

B. Nasal ENKTL — Correct. The anatomic distribution of nasal ENKTL includes primary tumors of the upper aerodigestive tract and nose.¹⁻³ The signs and symptoms and diagnostic markers such as CD56⁺, Epstein-Barr virus, and cytotoxic proteins along with the presence of a midline oral lesion confirms the diagnosis. The cutaneous involvement is secondary to the primary tumor.

C. Granulomatosis with polyangiitis — Incorrect. Although nasal crusts and sores can be present in this condition, inflammation was not the primary observation; rather, necrosis was observed. Granulomatous tissue was not observed during biopsy.

D. Extranasal ENKTL — Incorrect. The anatomic distribution of extranasal ENKTL includes primary tumors in areas such as the skin, gastrointestinal tract, bone marrow, lung, and central nervous system.²⁻⁴ The patient first experienced aerodigestive sinus issues that progressed into secondary cutaneous involvement, thus ruling this diagnosis out.

E. Paracoccidioidomycosis — Incorrect. Lesions of the mouth and throat are present with the swelling of lymph nodes due to infection caused by the fungus *Paracoccidioides*. Oral and intravenous antibiotics should improve the condition. However, there was no evidence of fungal involvement in the tissue biopsy.

Question 2: Which patient demographic is most commonly affected by ENKTL?

- A. A 57-year-old man from Peru
- B. A 64-year-old woman from Malaysia
- C. A 23-year-old woman from Germany
- D. A 36-year-old man from the United States
- E. A 25-year old man from China

Answers:

A. A 57-year-old man from Peru — Correct. ENKTL predominantly affects middle-aged men in the fifth and sixth decades, and age is a vital prognostic factor, with patients older than 60 years tending to have poorer prognosis. Cases are rare in the United States and Europe and are more commonly seen in Asia and in the South and Central Americas.^{2,3}

B. A 64-year-old woman from Malaysia — Incorrect. Although the patient is from Asia and fits the age demographic, she is a woman. A male patient of a similar age would be more likely.

C. A 23-year-old woman from Germany — Incorrect. This patient is from Europe, where cases of ENKTL are rare. Moreover, the patient is a woman, and her age is much lesser than the typical age at which patients present with ENKTL.

D. A 36-year-old man from the United States — Incorrect. Although a male, this patient is from the United States, where cases of ENKTL are rare. Moreover, his age is much lesser than the typical age at which patients present with ENKTL.

E. A 25-year-old man from China — Incorrect. Although a male and from Asia, this patient is not the best answer choice, given the observed typical demographic profile of patients with ENKTL.

Question 3: Which gene product has been implicated in the Epstein-Barr virus–associated repression of microRNAs found in ENKTL?

- A. Survivin
- B. AURKA
- C. EZH2

D. RUNX3

E. C-MYC

Answers:

A. Survivin — Incorrect. Survivin inhibits caspase activation and thus downregulates apoptosis. It has been shown to be activated in up to 97% of ENKTL cases.¹

B. AURKA — Incorrect. AURKA promotes cellular proliferation and mitosis in ENKTL.¹

C. EZH2 — Incorrect. EZH2 acts as a transcriptional coactivator via a noncanonical pathway, which has been shown to be the mechanism by which EZH2 promotes cell growth in ENKTL.¹

D. RUNX3 — Incorrect. RUNX3 mediates the transcriptional activation of genes involved in lymphocyte activation, proliferation, and effector function, including interferon gamma, perforin, and granzyme B.¹

E. C-MYC — Correct. C-MYC is a transcriptional target of the Epstein-Barr virus proteins EBNA and LMP1 and has been implicated in global microRNA repression found in ENKTL. C-MYC regulates other

ENKTL-associated proteins such as EZH2 and RUNX3. Hence, when microRNA repression is induced, these proteins are subsequently overexpressed.¹

Abbreviation used:

ENKTL: extranodal natural killer/T-cell lymphoma

Conflicts of interest

None disclosed.

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