**CASE REPORTS**

**Lethal Midline Granuloma in a 15-Year-Old Girl: A Diagnostic Dilemma**

**ABSTRACT**

**Objective:** To report a case of lethal midline granuloma and discuss the diagnostic and treatment dilemma and management.

**Methods:**
- **Design:** Case Report
- **Setting:** Tertiary Government Hospital
- **Patient:** One

**Results:** A 15-year-old girl under treatment for pulmonary tuberculosis presented to the Emergency Room for epistaxis and a nasopalatine lesion. She was managed as a case of nasopalatine osteomyelitis for one month and discharged on antibiotics. She returned due to bleeding after being lost to follow up for 3 more months. Hemostasis, debridement and biopsy yielded atypical cells, possibly lymphoma. Immunohistochemistry confirmed the diagnosis of NK-cell lymphoma. Unfortunately, she expired prior to initiation of chemotherapy.

**Conclusion:** Clinicians must have a high index of suspicion for lethal midline granuloma in chronic, non-healing midline lesions. Multiple biopsies confirm the diagnosis and earlier initiation of treatment may improve prognosis.

**Keywords:** Granuloma, lethal midline; Lymphoma, extranodal NK-T-cell

Lethal midline granuloma is a rare clinical entity that usually occurs among middle-aged men in the Southeast Asian and South American region with only a few documented cases in the Philippines. With informed consent from her parents and her assent, we report its presentation in a young girl and discuss the diagnostic and treatment dilemma and management involved.

**CASE REPORT**

A 15-year-old girl presented to the ear, nose, throat (ENT) emergency room (ER) of the Northern Mindanao Medical Center with a chief complaint of epistaxis and a nasopalatine lesion. Nine months prior to admission, she noted nasal pruritus and occasional discomfort of the hard palate. No consultations were made and no medications were taken.

Two months before admission, she was brought to a local health center for nonproductive cough associated with undocumented fever and weight loss. Direct sputum smear microscopy...
was positive for acid-fast bacilli and Category I Anti-tuberculosis (TB) treatment was started using the Directly Observed Treatment-Short Course (DOTS) protocol with good compliance. She did not reveal that she already had a nasopalatine lesion at this time.

She developed increasing nasal congestion over the next month and had epistaxis the day before, prompting consult and subsequent admission. She had no previous hospitalization or surgery and no history of any heredofamilial disease.

Baseline vital signs were within normal limits. She was asthenic with a BMI of 11.41 kg/m². Clinical examination revealed an extensively ulcerated and necrotic lesion on the hard and soft palate with a perforation that communicated with the nasal cavity. (Figure 1) Diagnostic nasal endoscopy revealed a perforation of the inferior to mid- nasal septum with erosion and ulceration of the nasal floor and inferior turbinate and minimal purulent discharge. The rest of the physical exam findings were unremarkable.

She was anemic (RBC 2.46 x10⁶/μL, hemoglobin 5.5 g/dL, hematocrit 17.4%) with leukocytosis (WBC 15.93 x10³/μL), neutrophilia (89%) and lymphocytopenia (7.1%). Contrast-enhanced computed tomography (CT) scan showed central, lobulated, soft tissue densities in both nasal cavities with partial lysis of the septum, hard palate and turbinates. (Figure 2 A, B)

Initial aerobic wound culture showed light growth of Pseudomonas putida, sensitive to multiple antibiotics. Blood cultures were negative. Nasopalatine swab was negative for acid-fast bacilli (AFB) and potassium hydroxide (KOH) stain. Sputum AFB, GeneXpert and TB culture were negative. The patient was initially managed as a case of nasopalatine osteomyelitis. Clindamycin was started, anti-TB meds were continued, and she was co-managed by the pediatric infectious disease service.

Repeat wound culture a month later showed heavy growth of Stenotrophomonas maltophilia, sensitive to trimethoprim/sulfamethoxazole. Repeat blood cultures were negative. Repeat
Histopathology of the intraoperative biopsy specimens showed atypical cells, suggestive of lymphoma. (Figure 6A) Immunohistochemical stains (CD3, CD20, cytokeratin, synaptophysin, chromogranin) were negative except for CD56, confirming diagnosis of NK-cell lymphoma. (Figure 6B) She was referred to Family and Community Medicine for counseling and supportive care and to Pediatric Oncology for chemotherapy but expired due to sepsis and bleeding.

DISCUSSION

Lethal Midline Granuloma is a rare clinical entity. McBride first described the term in 1897, after which it was also known as Stewart’s Granuloma and Polymorphous Reticulosis. These previous terminologies were generic and confusing because the entity described is actually a heterogeneous group of disorders. Hence, it was subsequently recommended that the label ‘Lethal Midline Granuloma’ be used as a descriptive designation until a specific diagnosis is obtained.

Ishi et al. first recognized the presence of tumor cells expressing CD3 and termed the disease ‘nasal T-cell lymphoma.’ However, Suzumiya et al. noted that tumor cells in nasal lymphoma stained positive with cytoplasmic CD3 and CD56, but not T-cell receptors, suggesting an NK-cell origin. The combined term ‘Extranodal NK/T-cell Lymphoma’ was adopted to take this into account.

The differential diagnosis includes squamous cell carcinoma, other lymphomas, Wegener granulomatosis, infections or idiopathic which is then labeled as Idiopathic Midline Destructive Disease.

The NK/T-cell lymphoma type of lethal midline granuloma is strongly associated with Epstein-Barr virus infection with a higher prevalence in

nasopalatine swab was also negative for AFB but positive for budding cells and pseudohyphae. A biopsy only showed granulation tissue with focal mild acute and chronic inflammation and necrosis. After three weeks, a more extensive biopsy with debridement and sequestrectomy under general anesthesia also showed chronic inflammation on histopathology. She was discharged on antibiotics and was subsequently lost to follow-up.

After 3 months, she presented at the ER for bleeding. The lesion had progressed anteriorly with necrosis and loss of the philtrum, columella, inferior and middle turbinates and nasal septum. (Figure 3, 4 A, B) She underwent emergency debridement and ligation of bleeders with pre- and post-operative blood transfusions. (Figure 5)
South-East Asia, Central and South America, and it commonly occurs
in middle-aged persons and affects males more frequently.2 Due to its
rarity, exact incidence is unknown. At the Northern Mindanao Medical
Center, this is only the second documented case.6

According to Gourin,7 the patient will initially present with nasal
congestion, epistaxis and pain. As the disease progresses, necrosis,
tissue loss and bleeding are noted. Secondary infection with bone
sequestration is frequent, thus purulent discharge is expected. Systemic
symptoms such as fever and weight loss are present only in advanced
stages.7

The working impression for this case was osteomyelitis vs. TB due to
the patient’s history of an ongoing TB infection along with the clinical
appearance of the lesion on initial presentation. Exhaustive diagnostics
for TB as well as other cultures and preliminary biopsies were either
equivalent or inconclusive. Due to lack of clinical improvement, repeated
biopsies were needed with more tissue from multiple sites and a
greater portion of clinically normal-looking tissue. However, the patient
was lost to follow-up for three months. Even when adequate biopsy
specimens had been obtained, the unavailability of immunostaining
in our institution and the expense of sending the specimens to
another institution caused additional delays in clinching the diagnosis.
Definitive diagnosis requires some combination of histopathological,
immunohistochemical, and molecular studies, often only after repetitive
biopsies have been obtained.3

Histologically, NK-cell lymphoma is characterized by polymorphic
inflammatory infiltrates.5 Necrosis favors the entrance of infectious
processes that can lead to sepsis.6 On immunostaining, the malignant
tumor cells express CD2, cytoplasmic CD3 and CD56. In some instances,
they may also express cytotoxic granular-associated proteins, granzyme
B, perforin and T cell-restricted intracellular antigen (TIA-1).2

Nasal NK/T cell lymphoma has a long natural history with an average
of 29 months reported in all races.5 It has a very high mortality reaching
almost 100% if untreated due to sepsis, hemorrhage or intracranial
spread.5 It is usually responds to radiation and chemotherapy with
the best clinical outcomes achieved when treatment is started early
in the course of the disease. The chemotherapeutic regimens used in
published case reports are CHOP (cyclophosphamide, doxorubicin,
vincristine, and prednisone), SMILE (steroid [dexamethasone],
methotrexate ifosfamide, L-asparaginase and etoposide)10 and
AspaMetDex (L-asparaginase, methotrexate and dexamethasone).11
Other treatment options include autologous or allogenic hematopoietic
stem-cell transplantation (HSCT) for advanced cases when remission
is achieved.12 Local recurrence occurs in 50% of cases and overall
prognosis is poor, with a 5-year survival rate of 10% to 45% depending
on the series.13

Our unfortunate experience taught us that clinicians must have
a high index of suspicion for chronic, non-healing midface
lesions as they are often incorrectly diagnosed as infection. Repeat
biopsies must be done with access to advanced diagnostics such as
immunohistochemical staining in order to clinch the diagnosis. The
patient’s financial situation is a serious consideration in the diagnostic
delay, therefore we must advocate for better health care access and
universal coverage. Although the prognosis is poor, aggressive
treatment of secondary infections and subsequent chemoradiotherapy
give the best possible chance of survival.

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