Rapidly ulcerated swelling in the hard palate of a HIV-positive pregnant woman

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CLINICAL PRESENTATION

A 40-year-old pregnant woman was referred to our service with a chief complaint of an ulcerated and painful swelling on the left hard palate and a normal-colored swelling in the right hard palate, with an evolution time of 15 days. The patient's dental history was noncontributory, but she reported a previous diagnosis of untreated human immunodeficiency virus (HIV) infection, discovered during pregnancy examinations at 5 weeks' pregnancy. CD4+ T-cell count was 5 cells/mm^3 (1%) and the HIV RNA level was greater than 500,000 copies/mL. Complete blood count was normal, except for hemoglobin level of 9.1 g/dL, white blood cell count of 3.2/mcL, and platelet count of 103,000/mcL. The patient also denied any history of trauma. Intraoral evaluation revealed a swelling in the left and right hard palates measuring 20 × 45 mm and of firm consistency. According to the patient, the lesion was presented for and rapidly increased in size in the last 15 days, accompanied by nasal obstruction, persistent fever, and epistaxis. Analgesic treatment with acetaminophen and ibuprofen was performed. The patient reported night sweats, increase in nausea, dizziness, vomiting, and constipation prior to the consultation.

Clinical examination revealed a massive lesion with an ulcerated reddish surface that affected the left side of the palate and a normal-colored swelling in the right hard palate, extending to the posterior palatal seal area (Figure 1). Contrast-enhanced computed tomography (CT) revealed a homogeneously enhanced lesion, with areas of different densities, destroying or obliterating the left sinonasal structures and invading the hard palate, mostly apparent on the right side of the palate (Figure 2).

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DIFFERENTIAL DIAGNOSIS

A wide range of differential diagnoses can be considered for lesions causing concomitant destruction of the sinonasal structures and swelling of the hard palate. Biopsy is always mandatory, most likely along with other diagnostic tests because a wide variety of lesions have a similar clinical presentation. However, clinical and radiographic features may guide the diagnostician to formulate precise diagnostic hypotheses. Based on the clinical appearance and CT findings of the current case, our clinical suggestions included salivary gland tumors (SGTs), sinonasal epithelial tumors (e.g., Epstein-Barr virus [EBV]–positive carcinoma), lesions associated with HIV positivity (e.g., plasmablastic lymphoma), and lymphomas (e.g., nasal T-/natural killer (NK)–cell lymphoma and diffuse large B-cell lymphoma [DLBCL]). Although it is extremely rare in the maxillary sinus, Kaposi sarcoma was also considered in the differential diagnosis because of the immunosuppression status of the patient.

SGTs are generally considered the main differential diagnosis for palatal swelling. A varied number of benign and malignant SGTs may be considered, but due to the aggressive behavior and the rapid evolution time of the lesion in this patient, malignant lesions, such as adenoid cystic carcinoma and adenocarcinoma NOS (not otherwise specified), were mainly considered.[1] These lesions commonly affect females in the sixth decade of life and, intraorally, is mostly observed in the palate (most commonly lateral to the midline of the posterior palate).[2] Nevertheless, in our experience, the involvement of the palate as the primary site with extension to the sinonasal region is uncommon and takes time to occur.[1,3] In addition, the extensive appearance of the lesion on the CT scan, showing a massive destruction of the sinonasal region, led us to consider a sinonasal lesion as a diagnostic possibility.

The first hypothesis for sinonasal lesion included epithelial tumors. EBV-positive carcinoma was our first consideration because 40% to 50% of all sinonasal cancers are histologically described as squamous cell carcinomas.[4] These lesions are commonly observed in male patients from 50 to 60 years of age.[5] However, their features did not match the characteristics of the lesion in our patient. The possibility of this being a Schneiderian papilloma had to be considered.

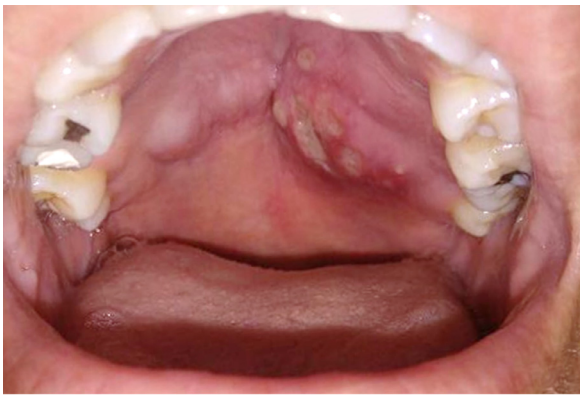

Fig. 1. The clinical presentation on the first visit, showing ulcerated swelling in the left hard palate and normal-colored swelling in the right hard palate, close to the hard and soft palate junction, with an evolution time of 15 days.

Schneiderian papillomas usually occur in male patients in the sixth decade of life and display a nonaggressive behavior.[6] However, our patient did not meet the age and gender criteria, and the lesion demonstrated aggressive behavior that is not consistent with a Schneiderian papilloma.

Infectious diseases are usually included in the differential diagnosis of sinonasal lesions, including bacterial and fungal sinusitis. These entities are a common complication of upper respiratory infection or allergic inflammation. It has been observed that around 6% to 7% of pediatric patients with respiratory problems are presented with bacterial or fungal sinusitis. Mostly common there is no gender predilection, and patients demonstrate nasal discharge and/or cough and fever as the main clinical manifestations.[7,8]

HIV-associated tumors had to be considered because of our patient's nontreated HIV-positive status,

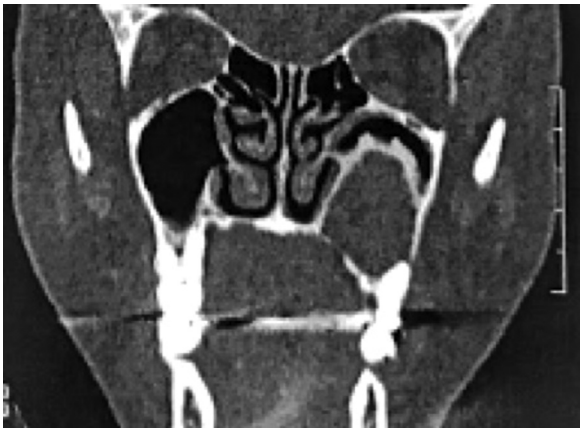

Fig. 2. Contrast-enhanced computed tomography (CT) image, in coronal section, showing a homogeneously enhanced lesion with different density, causing extensive destruction, from the cranial base to the hard palate and in both sides of the hard palate.

diagnosed during routine pregnancy examination. Non-Hodgkin lymphoma is the most common malignancy in HIV-positive patients. Clinically, plasmablastic lymphoma affects male patients in the adult age group.[9] This lesion, on CT scans, commonly shows bone lysis, heterogeneous contrast medium uptake, and unilateral and/or heterogeneous opacity, as seen in the current case. Plasmablastic lymphoma commonly creates nasal obstruction, anosmia, mucopurulent rhinorrhea, and epistaxis.[10] In addition, Kaposi sarcoma was also considered. This entity commonly affects skin and is not frequently found in the head and neck region. In the nasal mucosa, the lesion is rare, with less than 10 cases reported in the literature. Clinically, the lesion shows a history of chronic sinus congestion and recurrent nasal obstruction. Radiographically, a mass is seen occupying the nasal cavity and causing erosion of the adjacent structures, consistent with our findings in this case.[11]

On the basis of the aggressive clinical aspects of this case, other lymphomas were also considered, particularly the NK-/T-cell lymphoma subtype and DLBCL. NK-/T-cell lymphoma is an uncommon, aggressive, malignant neoplasm, strongly associated with EBV infection.[12,13] The lesion commonly affects male patients in the fifth decade of life.[13] With regard to clinical aspects, this lesion is observed as a destructive lesion, located in the sinonasal midline and commonly extending to the hard palate. In addition, the lesion causes nasal obstruction, nasal discharge, and epistaxis.[13,14] Although NK-/T-cell lymphoma generally occurs in the midline and in our patient only the left sinonasal region was affected, the aggressiveness and the location strongly suggested this diagnosis.[14] DLBCL is considered the most common sinonasal lymphoma.[15] It affects males in the seventh decade of life.[15,16] Clinically, patients demonstrate nasal obstruction, rhinorrhea, and bloody discharge, as well as B symptoms, such as fever and weight loss.[15] On the basis of these features and the clinical behavior of the lesion, we considered DLBCL as a strong possibility. However, the age and gender factors of DLBCL did not fit the characteristics of the lesion in the current case.

DIAGNOSIS

All of the above clinical differential diagnoses were considered, but a histopathologic examination was mandatory and an intraoral incisional biopsy was performed. Microscopically, the specimen showed a diffuse lymphoid infiltrate composed of small- to medium-sized neoplastic cells with irregular nuclei, inconspicuous nucleoli, and moderate pale cytoplasm, with scattered mitotic figures (Figures 3A and 3B). In addition, a significant amount of reactive plasma cells and lymphocytes were observed (Figure 3C), as well as fibrinoid changes around the blood vessels (Figure 3D). Because of the lymphoid predominance in various areas of the lesion, lymphoma was considered

first. Immunohistochemically, the neoplastic lymphoid cells showed positivity for CD3, granzyme B, and perforin. The cellular proliferative index, assessed by Ki67-nuclear expression, was very high. EBV in situ hybridization, using an EBV-encoded small nuclear RNA 1/2 probe, showed strongly positive reactions in the nuclei of the tumor cells (Fig. 4). Reactions against CD20 and CD56 were negative. The final diagnosis was extranodal NK-/T-cell lymphoma, nasal type.

MANAGEMENT

After the diagnosis was determined, a multidisciplinary team was set up to evaluate the case. All management options, including continuing the pregnancy with therapies and interventions, as well as elective termination, were reviewed. Continuing the pregnancy without oncologic management was not recommended. The patient elected to undergo preterm delivery of the fetus; and with the approval of the obstetrician, delivery was performed after 31 weeks of pregnancy. Subsequently, the patient was evaluated at the Medical Oncology and Hematology Department and a treatment protocol was established. The team proposed treatment with CHOP (cyclophosphamide, adriamycin, vincristine, prednisolone) chemotherapy followed by radiotherapy. However, the patient died 15 days after delivery, 275 days after diagnosis and follow-up.

DISCUSSION

Extranodal NK-/T-cell lymphoma, nasal type, is an aggressive tumor mainly arising in the nasal cavity and sinuses.[17,18] This tumor presents large areas of necrosis usually affecting the palate and extending to the oral cavity,[17] as seen in the current case. According to epidemiologic studies, the incidence of extranodal NK-/T-cell lymphoma varies worldwide, and it appears that higher numbers of patients are affected by this disease every year.[19] Extranodal NK-/T-cell lymphoma, nasal type, represents around 45% of all lymphomas occurring in the nasal cavity; however, they are exceedingly rare in HIV-positive patients. In this report, we have presented an additional case of NK-/T-cell lymphoma in a HIV-positive pregnant woman.

Clinically, patients commonly present with nonspecific nasal symptoms (i.e., nasal discharge, epistaxis, and nasal obstruction), facial edema, hemifacial pain, and dysphagia, commonly associated with the aggressiveness of the tumor.[17,20] Frequently, NK-/T-cell lymphomas are presented as destructive lesions, causing facial disfiguration; however, they may occur as swellings in the oral cavity, as in the case presented here. Our patient experienced nasal obstruction, persistent fever, and epistaxis and received analgesic therapy with different drugs for 2 weeks prior to the visit to our department. NK-/T-cell lymphomas may exhibit systemic dissemination,[21] which was not observed in our patient.

The pathogenesis of extranodal NK-/T-cell lymphoma, nasal type, remains unknown, although it is strongly associated with EBV infection.[17,21,22] EBV-positive tumors are commonly associated with a poor prognosis because of the high local recurrence rate and extension to other extranodal areas, usually with systemic manifestations, such as weight loss and fever.[17,22,23] The prognosis for our patient was poor, and she died after her baby was born. Li et al.[24] described an association between the overexpression of the tumor suppressor p53, probably associated with gene mutation activated by the presence of EBV, and the lesion's aggressiveness. HIV infection is, indeed, a risk factor for the development of lymphomas. The role of HIV infection in NK-/T-cell lymphoma is unknown, but it possibly facilitates rapid progression of the disease.[23,24] NK-/T-cell lymphoma associated with HIV infection is rare, particularly in the head and neck region, with only 6 cases reported in the literature so far (Supplemental Table S1).

Biopsy is usually necessary to confirm the diagnosis of extranodal NK-/T-cell lymphoma, nasal type, because of the presence of intense inflammation and large areas of necrosis, and this lesion can be a diagnostic challenge.[17,19,23] The association of histologic and immunohistochemical features with the detection of EBV RNA is crucial to confirm the final diagnosis.[22] This lymphoma demonstrates areas of atypical small- to medium-sized cells, which are nonspecific for a diagnosis. Vascular areas with perivascular cuffs are commonly seen, with possible penetration of these cells into the lumen, forming vascular thrombi, as well as penetration of these cells across the vessel wall, often causing fibrinoid necrosis of the vessels. In addition, areas with marginal pseudoepitheliomatous hyperplasia of the nasal mucosa, fibrosis, and necrosis may be observed.[17,20] Immunohistochemically, the lymphoid cells are CD2+ and CD56+, and CD3+.[18] In addition, the cytotoxic proteins granzyme B and perforin are also expressed by T cells. The tumor cells are always positive for EBV.[17,22]

CT is the main modality used in the diagnosis of extranodal NK-/T-cell lymphoma, nasal type. CT shows the lesion's margin and possible extension to adjacent structures and allows for staging the tumor by defining the tumor site and the presence of osteolysis, which explains the palatal swelling.[17,21] Moreover, pretreatment evaluation, determination of response to

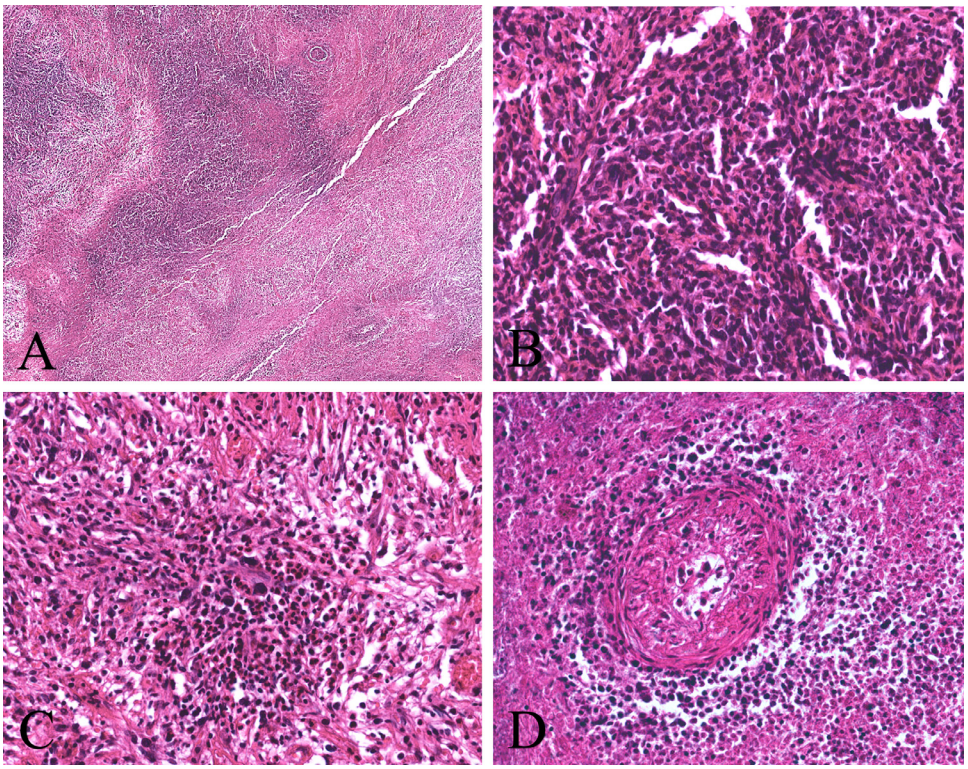

Fig. 3. Histopathologic features of a swelling in the hard palate of a HIV-positive pregnant woman. **A, B,** The tumor showing diffuse lymphoid infiltrate with an evident angiocentric and angiodestructive growth pattern. Tumor cells were ovoid, with scattered eosinophilic cytoplasm arranged in a solid pattern (hematoxylin and eosin [H&E]; original magnification × 5 [**A**] and × 40 [**B**]). **C,** Prominent polymorphous reactive infiltrate, composed of variable numbers of plasma cells and lymphocytes (H&E; original magnification × 40). **D,** Perivascular destructive infiltrates with fibrinoid changes of blood vessels and extensive areas of necrosis were also observed (H&E; original magnification × 40). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05690.*

treatment, and stringent follow-up are crucial to the management of this disease.[21]

The diagnosis of extranodal NK-/T-cell lymphoma, nasal type, should be followed by accurate staging of the tumor before any treatment. Staging is achieved on the basis of findings from physical examination to identify superficial lymph nodes, hepatomegaly, or splenomegaly; chest radiography; abdominal ultrasonography; chest and abdominal CT; bone marrow biopsy; gastrointestinal endoscopy; and, possibly, lumbar puncture in the presence of a lesion in the skull base.[21,22] It is important to define the best treatment approach and the patients prognosis.

Treatment of extranodal NK-/T-cell lymphoma, nasal type, remains complex. Previous studies have reported that surgery is ineffective because it is usually followed by rapid progression of the lesion. Thus, surgery is recommended only for diagnostic purposes.[17,23] The best treatment approach involves chemotherapy and radiotherapy, that is, CHOP followed by radiotherapy of the involved field, and showed results of a better prognosis. Because of the lesion's aggressiveness, most pregnant patients, as in the current case, should be treated with intensive chemotherapy, usually with CHOP regimen, as well as rituximab. However, these drugs can have teratogenic effects and may result in abnormal fetal formation. Thus, patients diagnosed in the first trimester may be considered for more conservative management, including localized radiation therapy, to control cervical disease.[25] In the case presented here, no treatment could be provided because the patient died shortly after delivery. In general, nasal-type NK-/T-cell lymphoma has a poor prognosis, with 5-year overall survival rates ranging from 37% to 45%, according to current research.[17]

CONCLUSIONS

The diagnosis of extranodal NK-/T-cell lymphoma, nasal type, is challenging because of the rarity of this lesion and its ability to mimic other conditions. Because oral manifestations might be the only signs of the disease, the dentist should be aware of the features of this disease to help with early diagnosis. The occurrence of extranodal NK-/T-cell lymphoma, nasal type, is,

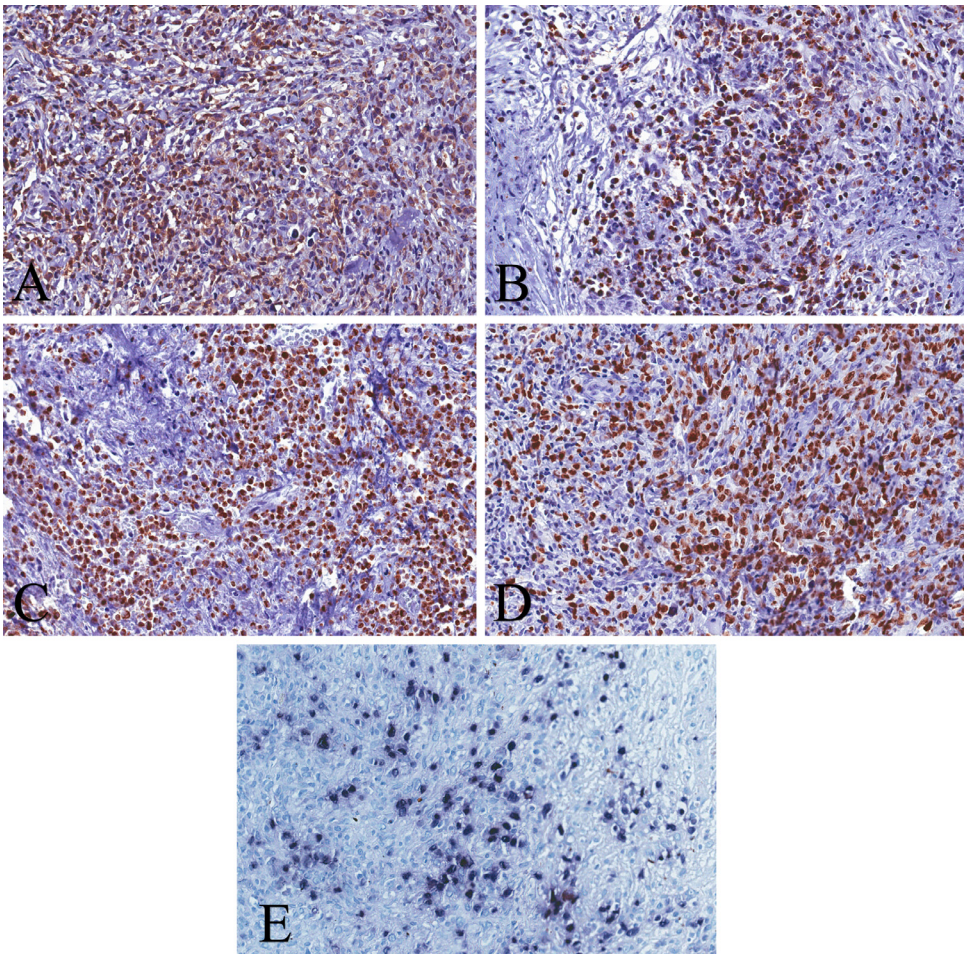

Fig. 4. Immunohistochemical findings. **A,** Tumor cells were positive for CD3 in the membrane (3,3′-diaminobenzidine [DAB]; original magnification × 40). **B,** Granzyme B in the nuclei (DAB; original magnification × 40). **C,** Perforin in the cytoplasm (DAB; original magnification × 40). **D,** Ki-67 labeling index was approximately 70% of staining in the nuclei (DAB; original magnification × 40). **E,** Most nuclei of EBV-infected cells were strongly positive on in situ hybridization.

however, exceedingly rare in the context of HIV infection and acquired immunodeficiency syndrome (AIDS).

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.oooo.2019.12.026.

REFERENCES

1. Fonseca FP, Sena Filho M, Altemani A, Speight PM, Vargas PA. Molecular signature of salivary gland tumors: potential use as diagnostic and prognostic marker. *J Oral Pathol Med*. 2016;45:101-110.
2. He S, Li P, Zhong Q, et al. Clinicopathologic and prognostic factors in adenoid cystic carcinoma of head and neck minor salivary glands: a clinical analysis of 130 cases. *Am J Otolaryngol*. 2017;38:157-162.
3. Coca-Pelaz A, Rodrigo JP, Bradley PJ, et al. Adenoid cystic carcinoma of the head and neck—an update. *Oral Oncol*. 2015;51:652-661.
4. Doescher J, Piontek G, Wirth M, et al. Epstein-Barr virus infection is strictly associated with the metastatic spread of sinonasal squamous-cell carcinomas. *Oral Oncol*. 2015;51:929-934.
5. Bell D, Hanna EY. Sinonasal undifferentiated carcinoma: morphological heterogeneity, diagnosis, management and biological markers. *Expert Rev Anticancer Ther*. 2013;13:285-296.
6. Benevenuto de Andrade BA, Piña AR, León JE, et al. Primary nasal mucosal melanoma in Brazil: clinicopathologic and immunohistochemical study of 12 patients. *Ann Diagn Pathol*. 2012;16:344-349.
7. Wald ER, Applegate KE, Bordley C, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. *Pediatrics*. 2013;132:e262-e280.
8. Smith A, Thimmappa V, Shepherd B, et al. Invasive fungal sinusitis in the pediatric population: systematic review with quantitative synthesis of the literature. *Int J Pediatr Otorhinolaryngol*. 2016;90:231-235.

9. Rodrigues-Fernandes CI, de Souza LL, Santos-Costa SFD, et al. Clinicopathological analysis of oral plasmablastic lymphoma: a systematic review. *J Oral Pathol Med*. 2018;47:915-922.
10. Lombard M, Michel G, Rives P, Moreau A, Espitalier F, Malard O. Extranodal non-Hodgkin lymphoma of the sinonasal cavities: a 22-case report. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2015;132:271-274.
11. Agaimy A, Mueller SK, Harrer T, Bauer S, Thompson LDR. Head and neck Kaposi sarcoma: clinicopathological analysis of 11 cases. *Head Neck Pathol*. 2018;12:511-516.
12. Vazquez A, Khan MN, Blake DM, Sanghvi S, Baredes S, Eloy JA. Extranodal natural killer/T-cell lymphoma: a population-based comparison of sinonasal and extranasal disease. *Laryngoscope*. 2014;124:888-895.
13. Tababi S, Kharrat S, Sellami M, et al. Extranodal NK/T-cell lymphoma, nasal type: report of 15 cases. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2012;129:141-147.
14. Ou CH, Chen CC, Ling JC, et al. Nasal NK/T-cell lymphoma: computed tomography and magnetic resonance imaging findings. *J Chin Med Assoc*. 2007;70:207-212.
15. Kanumuri VV, Khan MN, Vazquez A, Govindaraj S, Baredes S, Eloy JA. Diffuse large B-cell lymphoma of the sinonasal tract: analysis of survival in 852 cases. *Am J Otolaryngol*. 2014;35:154-158.
16. Huang Y, Jia B, Jiang S, et al. Different clinical characteristics and treatment strategies for patients with localized sinonasal diffuse large B cell lymphoma and extranodal NK/T cell lymphoma. *J Hematol Oncol*. 2017;10:7.
17. Al-Hakeem DA, Fedele S, Carlos R, Porter S. Extranodal NK/T-cell lymphoma, nasal type. *Oral Oncol*. 2007;43:4-14.
18. Sánchez-Romero C, Paes de Almeida O, Rendón Henao J, Carlos R. Extranodal NK/T-cell lymphoma, nasal type in Guatemala: an 86-case series emphasizing clinical presentation and microscopic characteristics. *Head Neck Pathol*. 2019;13:624-634.
19. Haverkos BM, Pan Z, Gru AA, et al. Extranodal NK/T cell lymphoma, nasal type (ENKTL-NT): an update on epidemiology, clinical presentation, and natural history in North American and European Cases. *Curr Hematol Malig Rep*. 2016:(11):514-527.
20. Coha B, Vucinic I, Mahovne I, Vukovic-Arar Z. Extranodal lymphomas of head and neck with emphasis on NK/T-cell lymphoma, nasal type. *J Craniomaxillofac Surg*. 2014;42:149-152.
21. Z Yan, Huang HQ, Wang XX, et al. A TNM staging system for nasal NK/T-cell lymphoma. *PLoS One*. 2015;10:e0130984.
22. Abdelwahed Hussein MR. Non-Hodgkin's lymphoma of the oral cavity and maxillofacial region: a pathologist viewpoint. *Expert Rev Hematol*. 2018;11:737-748.
23. Meng W, Zhou Y, Zhang H, et al. Nasal-type NK/T-cell lymphoma with palatal ulcer as the earliest clinical manifestation: a case report with literature review. *Pathol Oncol Res*. 2010;16:133-137.
24. Li T, Hongyo T, Syaifudin M, Nomura T, et al. Mutations of the p53 gene in nasal NK/T-cell lymphoma. *Lab Invest*. 2000;80:493-499.
25. Pereg D. 1, Koren G, Lishner M. The treatment of Hodgkin's and non-Hodgkin's lymphoma in pregnancy. *Haematologica*. 2007;92:1230-1237.

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