



Published in final edited form as:

*Oral Maxillofac Surg Cases*. 2019 September ; 5(3): . doi:10.1016/j.omsc.2019.100113.

## Burkitt lymphoma of the maxilla in a HIV positive male – Presentation and review of diagnostic laboratory tests

William Alvarez<sup>a,1</sup>, Li Han Lai<sup>b,1</sup>, Shakira J. Grant<sup>c</sup>, Daniel E. Sabath<sup>d</sup>, Jasjit Dillon<sup>e,\*</sup>

<sup>a</sup>Tufts University. Former Resident, Department of Oral and Maxillofacial Surgery, University of Washington, Seattle, WA, USA

<sup>b</sup>Department of Oral and Maxillofacial Surgery, University of Washington, Seattle, WA, USA

<sup>c</sup>Division of Hematology-Oncology, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

<sup>d</sup>Departments of Laboratory Medicine and Medicine, University of Washington, Seattle, WA, USA

<sup>e</sup>Oral and Maxillofacial Surgery, Harborview Medical Center, Department of Oral and Maxillofacial Surgery, University of Washington, Seattle, WA, USA

### Abstract

Burkitt lymphoma (BL) is a highly aggressive, B cell non-Hodgkin lymphoma (NHL) that is rare outside Africa. We report a case of HIV-associated BL originating in the right maxillary sinus in a 31-year-old Hispanic male living in Washington, USA. We also highlight the diagnostic challenges in arriving at the diagnosis when the patient initially presented with a painless right facial swelling. Rapid diagnosis and treatment are critical because BL is one of the fastest-growing tumors. Treatment involves brief duration of high intensity chemotherapy and central nervous system prophylaxis. It is important for oral and maxillofacial surgeons to recognize this disease and understand the necessary steps to treat this aggressive tumor.

### Keywords

Burkitt lymphoma; Lymphoma; Human immunodeficiency virus; Maxillary sinus; Cervical lymph node

## 1. Introduction

Burkitt lymphoma (BL) is a highly aggressive, B cell non-Hodgkin lymphoma (NHL), characterized by the translocation and deregulation of the *MYC* gene on chromosome 8q14. Three distinct clinical forms of BL have been described; these include endemic, non-

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\*Corresponding author. Department of Oral & Maxillofacial Surgery, 4West Clinic, Harborview Medical Center, University of Washington, 325 Ninth Ave. Box 359893, Seattle, 98104, USA. dillonj5@uw.edu (J. Dillon).

<sup>1</sup>The first two authors contributed equally to this work.

### Disclosure

Dr. Dillon is the recipient of an Oral and Maxillofacial Surgery Foundation and Osteoscience Foundation grant. Neither have a conflict of interest with this manuscript.

endemic (sporadic), and immunodeficiency-associated [1]. The endemic form commonly occurs in children residing in equatorial Africa and New Guinea. The jaw or facial bones are most commonly involved, in approximately 50–60% of cases. Non-endemic BL occurs in the United States and Western Europe, accounting for <1% of adult NHL cases [2,3]. Non-endemic BL most commonly involves the abdominal organs, including the ileum, cecum and stomach amongst other sites. Lastly immunodeficiency-associated BL, which is most commonly due to human immunodeficiency virus (HIV), has a heterogeneous clinical presentation. Sites most commonly involved include the bone marrow, central nervous system and lymph nodes.

Anatomically, BL involving the head and neck region, most frequently involves cervical nodes, while extra-nodal site involvement in the head and neck region occur in less than 25% of reported cases [4]. We present a case of HIV-associated BL originating in the right maxillary sinus, highlighting the diagnostic challenges in arriving at the diagnosis in a patient presenting with painless right facial swelling.

## 2. Report of a case

A 31-year-old Hispanic male was referred to the Oral & Maxillofacial (OMS) outpatient clinic at University of Washington (UW) for evaluation of persistent right mid-facial swelling. A telephonic or in-person Spanish interpreter was utilized during all the encounters. Three months prior to his presentation, he developed progressive swelling and altered sensation of the right cheek, which was attributed to pressure effect due to sleep position. His symptoms progressed in the following weeks to involve trismus and painful mastication with solid foods. He first underwent an evaluation by his dentist, who extracted the patient's right wisdom teeth (ADA #1 and 32) due to concerns of dental infection. Despite this intervention, symptoms of midfacial swelling persisted. At a 2-week dental follow up visit, an incision and drainage of the right posterior maxillary buccal space and extraction of tooth #2 were performed. A course of clindamycin was also prescribed. Despite these interventions, the midfacial swelling appeared minimally improved with persistence of right facial paresthesia.

The patient was then referred to the University of Washington Oral and Maxillofacial Surgery (UW OMS) outpatient clinic. Upon presentation, he reported persistent paresthesia over his right cheek but minimal pain. He denied fever, night sweats, dyspnea, dysphonia, changes in vision, or malaise. He endorsed unintentional weight loss of an unspecified quantity over the past 2 weeks, the latter largely attributed to the inability to eat solid food due to trismus. His past medical history was significant for HIV, diagnosed 2 years prior to presentation and managed with antiretroviral therapy (abacavir, dolutegravir and lamivudine). HIV RNA was undetectable in the most recent viral load assay, and the CD4 count was 509 cells/ $\mu$ L. He had allergies to penicillin. Socially, he reported smoking tobacco, approximately half pack per day for 14 years, and he drank 1–2 alcoholic drinks weekly.

Physical examination revealed an alert and oriented Hispanic male in no acute distress. His vital signs were normal. There was hypoesthesia with 3 out of 5 directional sensation at the

right infraorbital nerve distribution. He had obvious right midfacial induration without overlying erythema. His extraocular movements were intact. The inferior border of the mandible was palpable. There was a palpable and tender cervical lymphadenopathy along the right sternocleidomastoid muscle levels I and II (Fig. 1).

Intraorally, a non-fluctuant induration of about 4 cm in size was palpable from the right posterior maxilla extending to the buccal area of tooth #3. The previous incision and drainage site was well-approximated with chromic gut sutures. There was no purulence on palpation. Tooth #3 had a grade 3 mobility. The tongue, floor of mouth, and remainder of the oral cavity and pharynx were normal. His mouth opening was about 30 mm. Evaluation of the panoramic radiograph showed evidence of recent extraction socket #32; however, extraction sockets #1 and 2, as well as the floor of right maxillary sinus, were not well-visualized due to overlying soft tissue shadowing (Fig. 2).

Given his persistent swelling in the setting of paresthesia and normal vital signs, concerns for a non-odontogenic pathology were considered. An urgent computer tomography (CT) scan maxillofacial and neck with contrast was obtained. The CT scan showed a soft tissue mass involving the right maxillary sinus and masticator space with erosive changes of the pterygoid plate and maxillary sinus extending into the pterygopalatine fossa, the Vidian canal, and into the foramen rotundum. There was extension to the orbital floor with abutment of the inferior rectus (Figs. 3–5). A right level IIb necrotic lymph node, of about 3 cm, was also noted (Fig. 6).

The patient was urgently referred to the Harborview Oral & Maxillofacial Clinic for further diagnostic evaluation and treatment. A fine needle aspiration of the right level IIb cervical lymph node was performed. Preliminary microscopic review showed a mass of blue staining cells. Several deep core biopsies of the maxillary mass were also obtained. Samples were sent fresh and in formalin for histopathologic evaluation and also to microbiology.

A biopsy measuring 1.0 × 0.6 × 0.3 cm was received for histological examination. Hematoxylin and Eosin (H&E) stained sections showed a monomorphic infiltrative population of medium-sized lymphoid cells with occasional interspersed macrophages. The neoplastic cells had irregular nuclei with clumped chromatin and multiple nucleoli, minimal cytoplasm and angulated cell borders (Fig. 7). There was high mitotic and apoptotic activity, and nearly 100% of neoplastic cells were Ki-67 positive (Fig. 8). BCL2 was negative in the neoplastic population (Fig. 9). In situ hybridization for EBV-encoded RNA was uniformly positive (Fig. 10). Flow cytometry demonstrated an abnormal mature B-cell population having abnormal expression of CD10, CD20 (decreased), CD38 (increased), CD45 (decreased), and  $\lambda$  light chain restriction with normal expression of CD19 without significant CD5 accounting for 93.5% of the total white cells. Interphase fluorescence in situ hybridization (iFISH) using a *MYC* breakapart probe (Visys/Abbott) showed no evidence of *MYC* rearrangement. However, iFISH using a *MYC-IGH* fusion probe (CytoCell) was positive for a *MYC-IGH*/t(8; 14) translocation.

The patient was diagnosed with Lymphomas Malin B (LMB) intermediate-risk, HIV associated Burkitt lymphoma of the right maxillary sinus with locoregional extension. The

Hematology/Oncology service was contacted, and he was admitted for urgent staging workup within 24 hours of the biopsy results. Initial staging evaluation included contrast enhanced CT imaging of the chest, abdomen and pelvis, which were negative for distal nodal or extra-nodal sites of involvement. According to Murphy/St. Jude's classification [1, 8], the patient was a stage 1A, indicating a single extra-abdominal tumor mass. Diagnostic bone marrow biopsy with aspirate, and lumbar puncture for cerebrospinal fluid analysis, showed no lymphomatous involvement. The hematologic findings were not remarkable in terms of the white blood cell counts. The serochemical value of alkaline phosphatase was normal. The lactate dehydrogenase was slightly elevated at 212 units/L. The EBV test results were also negative. Following additional pre-treatment evaluation of left ventricular ejection fraction (LVEF) with an echocardiogram and electrocardiogram, he was initiated on anthracycline based therapy with dose-adjusted etoposide (50 mg/m<sup>2</sup>/day), vincristine (0.4 mg/m<sup>2</sup>/day, no cap), doxorubicin (10 mg/m<sup>2</sup>/day), as a continuous infusion on days 1, 2, 3, 4 (96-h total); cyclophosphamide (750 mg/m<sup>2</sup>) on day 5; rituximab 375mg/m<sup>2</sup> on day 1 and prednisone (60 mg/m<sup>2</sup> twice daily) on days 1, 2, 3, 4, and 5. This chemotherapy regimen is also known as DA-EPOCH-R. Central nervous system (CNS) prophylaxis was provided with intrathecal methotrexate. A total of 6 cycles of DA-EPOCH-R was planned, with intrathecal methotrexate administered as CNS prophylaxis.

The patient completed 6 cycles of chemotherapy in August 2018 and tolerated well with minimal side effects. His labs (BMP and CBC) were all normal. A 1-week post-treatment CT scan was obtained and showed treatment response with interval decrease in size of the mass at right maxillary sinus and masticator space (Figs. 11–13). There was also resolution of previously noted right level IIb necrotic lymph node (Fig. 14). No new pathologic lymph node enlargement was noted. However, on a 3-month post treatment follow-up visit with Hem/Onc team, the patient noted itchiness at right eye. A CT scan was subsequently obtained and showed progression of the soft tissue mass at right maxillary sinus and masticator space with increased osseous erosion of the lateral wall of right maxillary sinus. No cervical lymphadenopathy was seen. The patient underwent right maxillary sinus antrostomy and biopsies and showed marked inflammation without evidence of neoplasm or fungal infection. He is currently being monitored closely by the Otolaryngology team.

### 3. Discussion

BL in the HIV-positive population accounts for approximately 20–40% of all HIV associated NHL cases [6]. Ziegler and Levine et al. classified the cases of the American Burkitt Lymphoma Registry (ABLR), using Murphy/St. Jude's system [1,8] as follows: stage I—single tumor mass (extra-abdominal 1A or abdominal 2A); stage II—2 separate tumor masses on the same side of the diaphragm; stage III—involvement of more than 2 separate masses or disease on both sides of the diaphragm; stage IV—pleural effusion, ascites, or involvement of the central nervous system (malignant cells in the cerebrospinal fluid) or bone marrow.

BL is generally associated with a translocation of the *MYC* gene on chromosome 8 to any of the immunoglobulin loci, most commonly the *IGH* locus on chromosome 14, but also the *IGK* locus on chromosome 2 and the *IGL* locus on chromosome 22. These rearrangements

result in increased expression of *MYC* protein, which is thought to be responsible for neoplastic transformation. This case was initially thought to lack a *MYC* rearrangement based on using a *MYC* breakapart iFISH probe, but interestingly was found to have a typical *MYC-IGH* translocation using a *MYC-IGH* fusion iFISH probe. While unusual, this phenomenon has been reported and depends on the specific *MYC* breakapart probe that is used [1].

Frequently, the initial presentation of BL is that of a painless mass, although clinical symptoms may vary based on the involved site. In the head and neck region, patients may present with signs and symptoms of nasal obstruction, rhinorrhea, facial swelling, unilateral tonsillar enlargement, dental pain, and cervical lymphadenopathy. These nonspecific symptoms may present a diagnostic challenge to providers, resulting in a delay or misdiagnosis of BL involving extra nodal sites in the head and neck region, which ultimately results in a delay of chemotherapy administration. This is demonstrated in our case, where an initial diagnosis of dental infection and later presumed odontogenic abscess was made, resulting in dental extractions and incision and drainage.

This case highlights the need to expand the differential diagnostic considerations in a young HIV positive patient presenting with atypical facial swelling and hypoesthesia in the absence of obvious dental pathology. Additional etiologies such as malignancy, especially BL, should also be considered. The prompt diagnosis and initiation of chemotherapy for BL is critical due to the highly aggressive tumor biology demonstrated by BL, with an estimated doubling time of 24–48 hours [5]. Despite the aggressive biology, 2-year survival rates following intensive chemotherapy regimens have been estimated at 80–90%, with 5-year overall survival rates estimated at 60% for patients age 20–39 years, declining further with advanced age [7]. Delay in treatment of BL could result in further locoregional extension and distal spread which may result in worse survival. Prompt diagnosis and treatment implementation for DL is therefore encouraged.

## Funding

This project was supported in part by the Research and Training Fund of the Department of Oral and Maxillofacial Surgery, University of Washington School of Dentistry.

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**Fig. 1.** 31-year-old male, HIV, presents with right mid-facial swelling with overlying paresthesia and palpable firm enlarged right cervical lymph node.



**Fig. 2.** Panoramic radiograph showed evident extraction socket #32 but poorly visualized extraction sockets #1 and 2 and floor of left maxillary sinus.

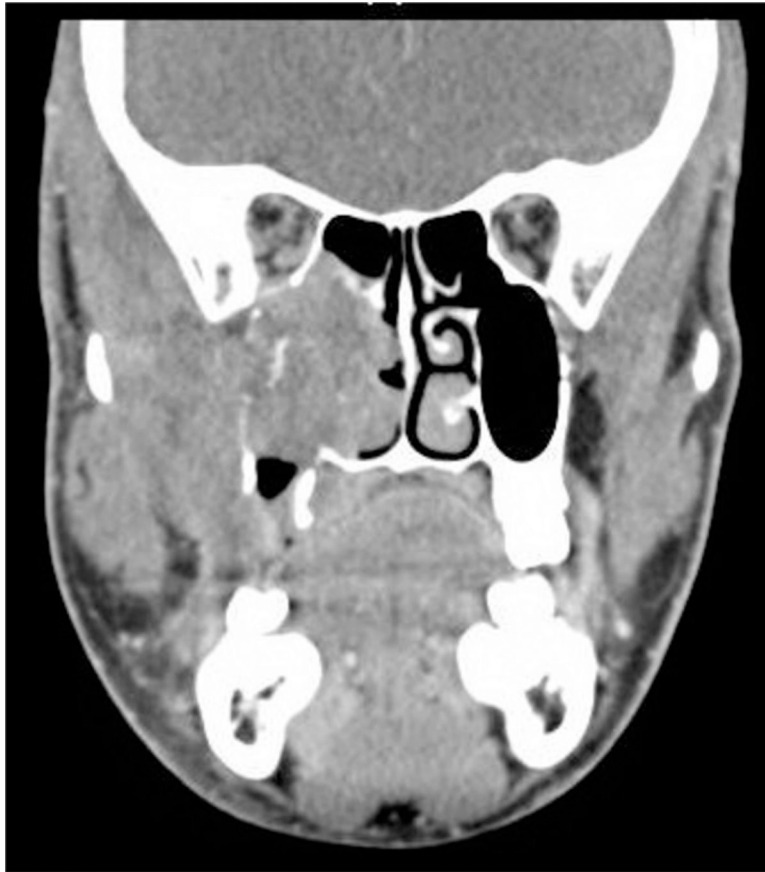




**Fig. 3.** CT neck with contrast soft tissue window, axial cut, showed soft tissue mass in left maxillary sinus and masticator involving the pterygoid plates, maxillary sinus walls, pterygoid fossa, Vidian canal, and foramen rotundum.



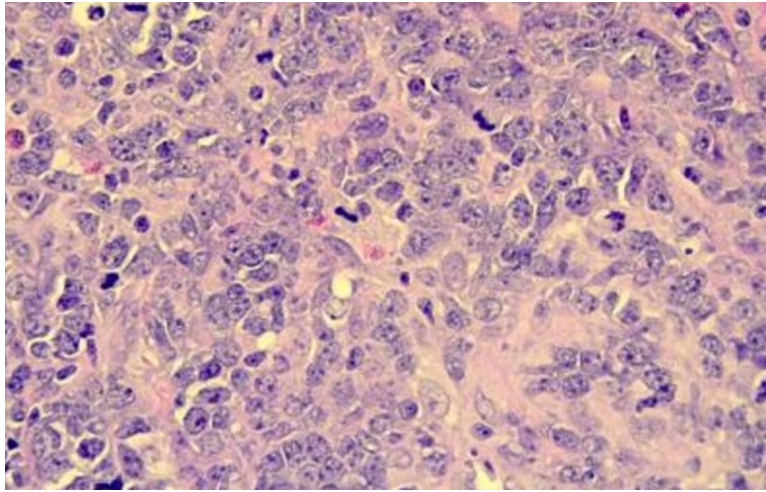
**Fig. 4.** CT neck with contrast soft tissue window, sagittal cut, showed soft tissue mass in left maxillary sinus and masticator involving the pterygoid plates, maxillary sinus walls, pterygoid fossa, Vidian canal, and foramen rotundum.



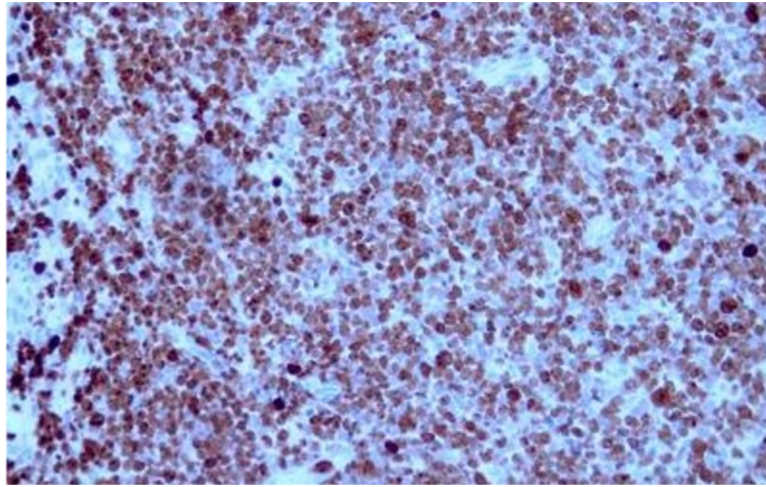
**Fig. 5.** CT neck with contrast soft tissue window, coronal cut, showed soft tissue mass in left maxillary sinus and masticator involving the pterygoid plates, maxillary sinus walls, pterygoid fossa, Vidian canal, and foramen rotundum.



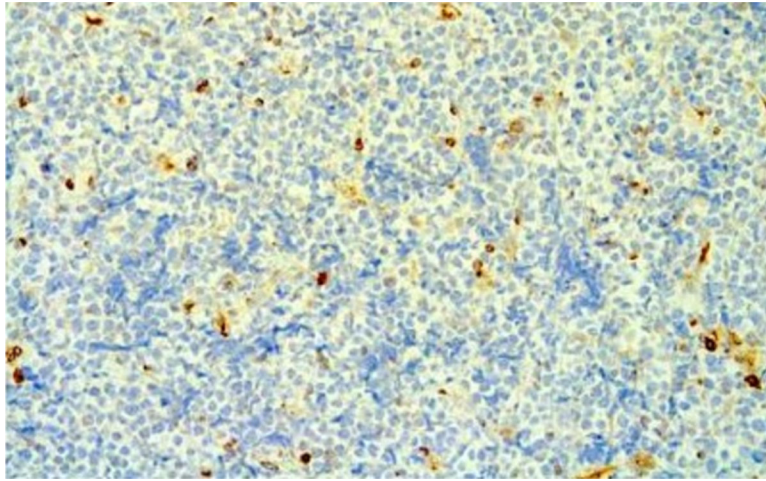
**Fig. 6.** CT Neck with contrast, soft tissue window, coronal cut, showed necrotic lymph node at right level IIb.



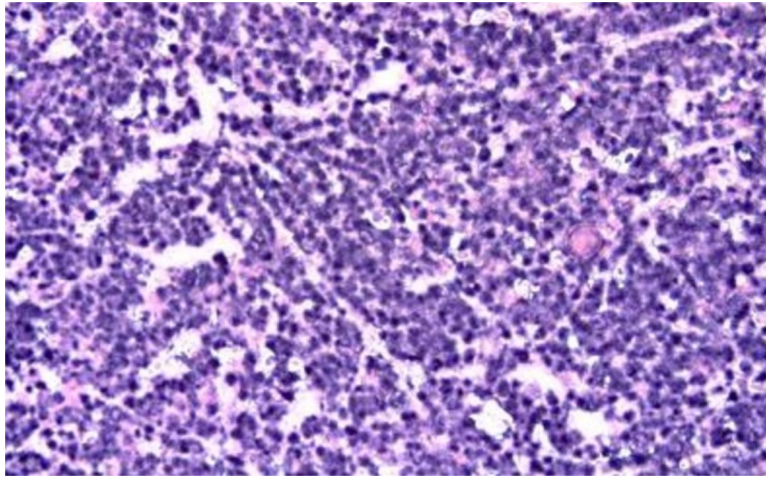
**Fig. 7.** Histology of excisional biopsy. Hemotoxylin/eosin stain (original magnification 600X).



**Fig. 8.** Histology of excisional biopsy. Ki-67 immunohistochemistry (original magnification 300X).

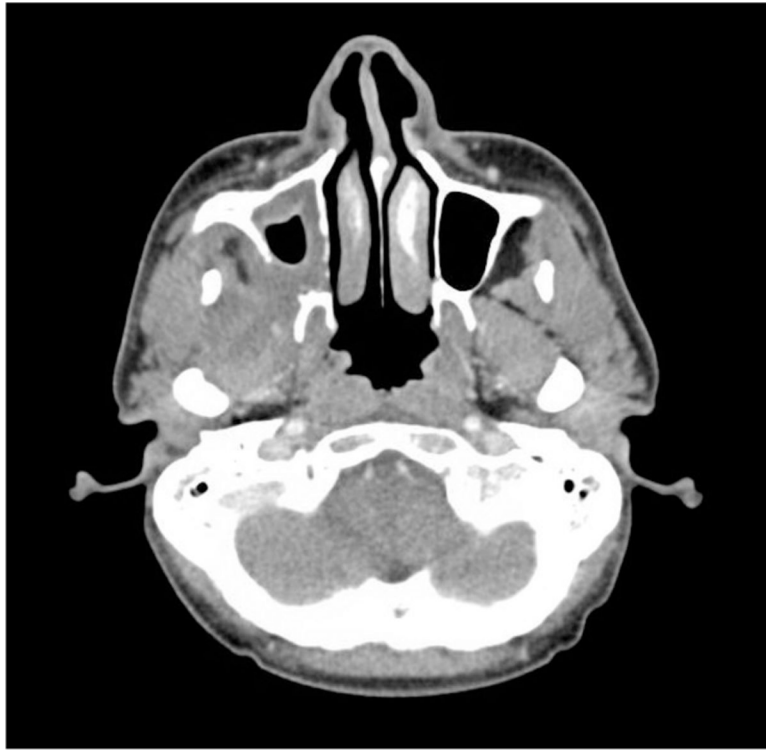


**Fig. 9.** Histology of excisional biopsy. BCL2 immunohistochemistry (original magnification 300X).

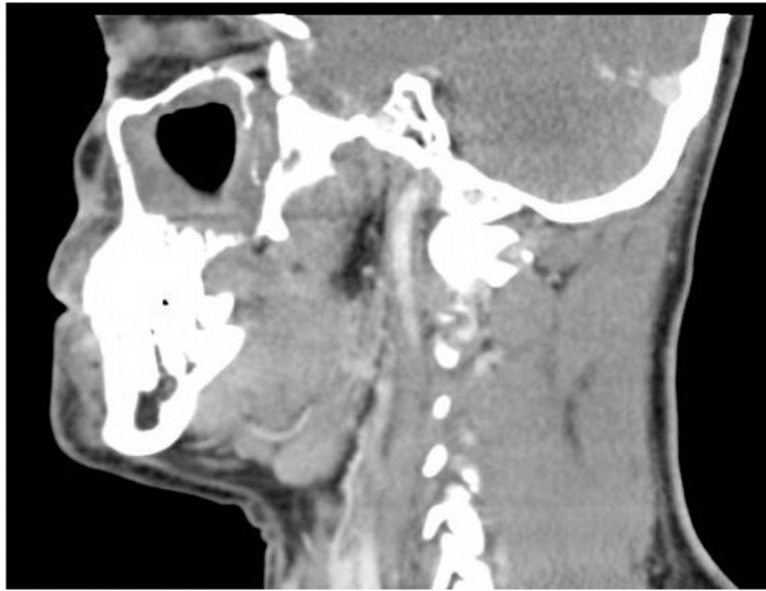


**Fig. 10.** Histology of excisional biopsy. Epstein-Barr encoded RNA in situ hybridization (original magnification 300x).

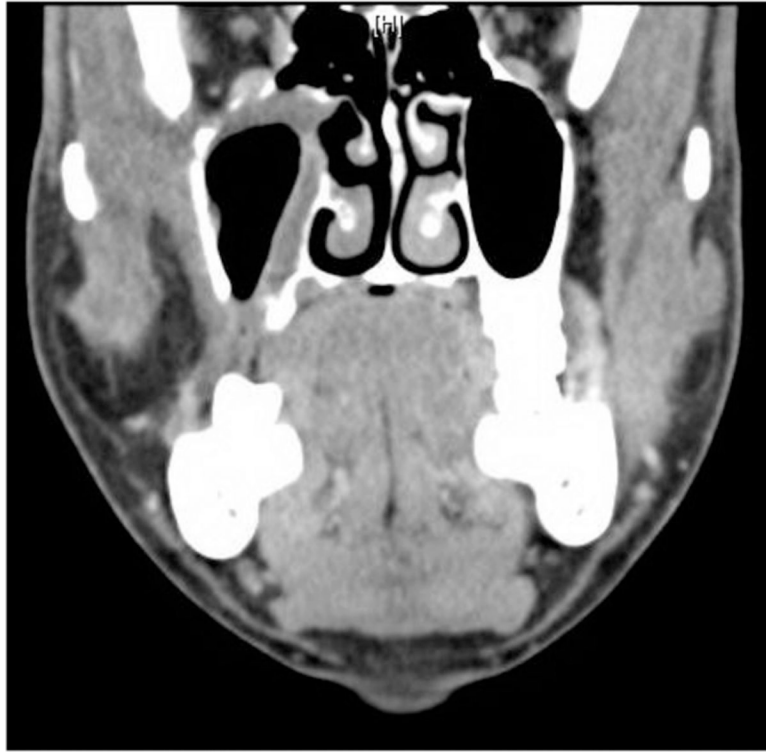




**Fig. 11.**  
A 1-week post-treatment CT neck with contrast soft tissue window, axial cut, showed interval decrease in size of soft tissue mass in left maxillary sinus and masticator space.



**Fig. 12.**  
A 1-week post-treatment CT neck with contrast soft tissue window, sagittal cut, showed interval decrease in size of soft tissue mass in left maxillary sinus and masticator space.



**Fig. 13.** A 1-week post-treatment CT neck with contrast soft tissue window, coronal cut, showed interval decrease in size of soft tissue mass in left maxillary sinus and masticator space.



**Fig. 14.**  
Interval resolution of previously noted right level IIb necrotic lymph node (Fig. 6).