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A Rare Case of Primary Infra-Temporal Localization Non-Hodgkin Lymphoma

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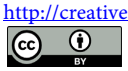


Abstract

Extra-nodal Non-Hodgkin's Lymphomas (NHL) in the head and neck region are most commonly found in the Waldeyer's lymphatic ring. However, Non-Hodgkin's Lymphomas occurring in infra-temporal fossa are exceptionally rare. We report a case of a 38-year-old female patient, who presented with unilateral exophthalmos and facial paresthesia persisting over three months. Imaging and histological investigations revealed a primary Non-Hodgkin's Lymphoma located in the infra-temporal region. The patient underwent chemotherapy with a favorable outcome observed over three years of follow-up. Through this case, we highlight the diagnostic challenges faced when dealing with a non-specific clinical and radiological presentation, as well as a biopsy site that is difficult to access. This case also underlines the need for a multidisciplinary approach involving ENT specialists, radiologists, and oncologists to address the diagnostic and therapeutic challenges associated with such rare presentation.

Subject Areas

Otorhinolaryngology

Keywords

Case Report, Non-Hodgkin's Lymphoma, Infratemporal Fossa, Biopsy, Chemotherapy

1. Introduction

Non-Hodgkin's Lymphoma is a heterogeneous group of malignancies originating from the lymphoid tissue, which can occur in both nodal and extra-nodal sites.

While most head and neck NHL cases are localized to the Waldeyer's lymphatic ring [1], primary NHL arising in the infra-temporal fossa is exceedingly rare with only a handful of cases documented in the medical literature [2]-[5]. The infratemporal fossa, an anatomically complex region housing critical neurovascular structures, presents unique diagnostic and therapeutic challenges due to its hidden location and nonspecific early symptoms, often leading to delayed diagnosis and misdiagnosis as more common conditions such as sinusitis or orbital tumors.

Recent advancements in imaging and diagnostic techniques have significantly improved the management of NHL. Contrast-enhanced MRI and PET-CT are now considered gold standards for staging and assessing treatment response, offering superior sensitivity and specificity compared to traditional CT scans [6]. These imaging modalities are particularly valuable in delineating tumor extent in complex anatomical regions like the infratemporal fossa, guiding biopsy approaches, and monitoring therapeutic outcomes. Histopathological examination remains the cornerstone of NHL diagnosis, with endoscopic biopsy techniques increasingly favored for their minimally invasive nature.

The management of NHL has evolved considerably over the past decade, particularly for limited-stage disease using different protocols of chemotherapy. However, optimal management strategies for rare presentations, such as NHL of the infratemporal fossa, remain poorly defined due to the limited number of reported cases and the heterogeneity of clinical presentations.

This case report highlights the diagnostic complexities associated with infratemporal fossa NHL, emphasizing the importance of a multidisciplinary approach involving ENT specialists, radiologists, and oncologists. It also underscores the role of advanced imaging and endoscopic biopsy techniques in accurately diagnosing and managing such rare presentations. By doing so, we hope to provide valuable insights for clinicians managing similar cases and to underscore the need for further research to establish evidence-based guidelines for this rare presentation.

2. Case Report

A thirty-eight-year-old female patient with no significant medical history, who presented with unilateral left exophthalmia and left facial paresthesia, without any other symptoms (swelling, trismus, odynophagia, otalgia…). These symptoms have been evolving over the past 3 months in the context of apyrexia and preserved general health. The initial ENT examination and nasal endoscopy were entirely normal. Examination of the oral cavity, ear, cranial nerves, and other systems was unremarkable. The MRI analysis identify a clearly malignant, locally advanced tumor involving the left infra-temporal fossa, extending to the maxillary sinus and the lateral and inferior walls of the left orbit, causing grade 1 exophthalmos. This mass was hypo-isointense on T1 and T2 (**Figure 1**, **Figure 2**). The mass had a homogenous and significant enhancement in post-contrast MRI.

The diagnosis was confirmed by a biopsy performed using an endoscopic

endonasal approach to the infratemporal fossa. This method was chosen based on imaging results, which revealed tumor extension into the maxillary sinus. Initially, a large middle antrostomy was performed, but the origin of the lesion within the maxillary sinus wall could not be clearly identified. To improve access and visualization, an endoscopic medial maxillectomy was carried out. During this procedure, the inferior turbinate was sacrificed, while the nasolacrimal duct was preserved. An osteotome was used to remove the medial wall in the area of the inferior meatus, which provided sufficient access to the lesion (Figure 3) and allowed for an effective biopsy.

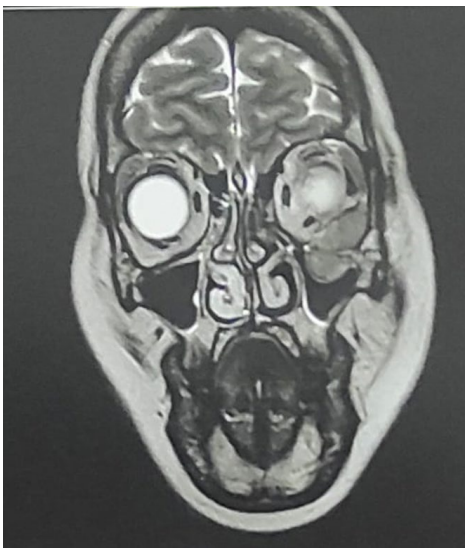


Figure 1. MRI coronal sections showing a hypo-isointense mass in the left infratemporal fossa on T1 and T2 weighted images, extending to the maxillary sinus and the lateral and inferior walls of the left orbit.

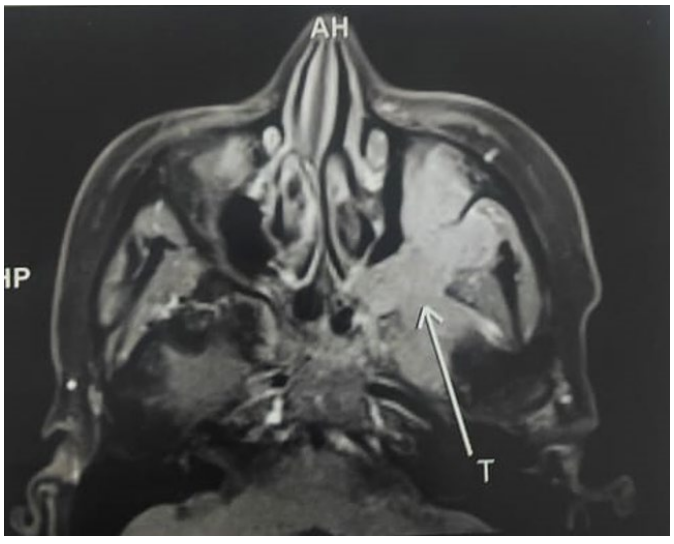


Figure 2. MRI axial sections showing a hypo-isointense mass in the left infratemporal fossa on T1 and T2 weighted images , extending to the maxillary sinus and the lateral and inferior walls of the left orbit.

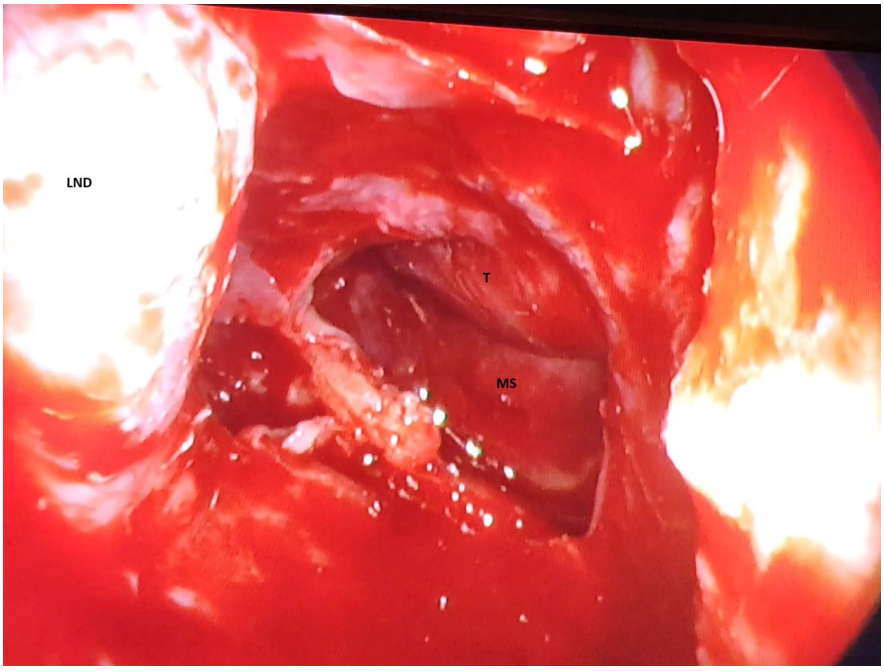
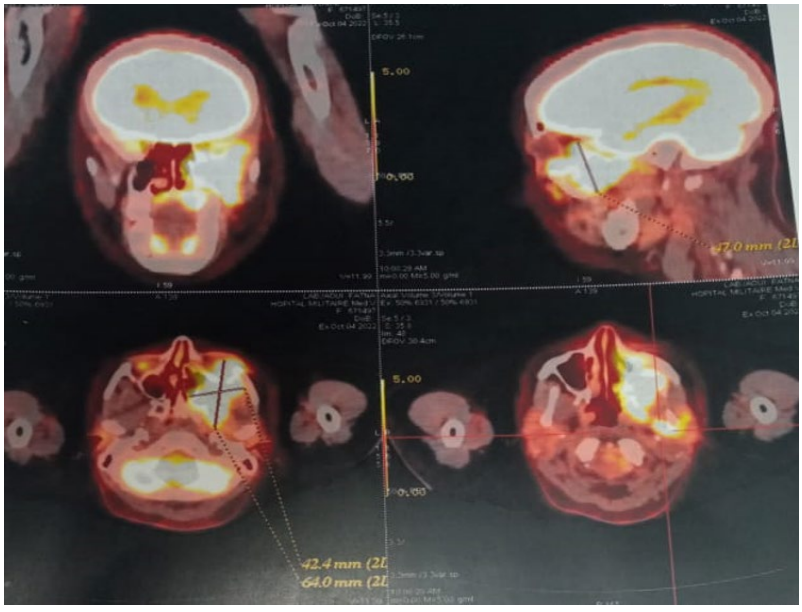


Figure 3. Endoscopic view of the tumor using endoscope 30 (LND: lacrymonasal duct, T: Tumor, MS: Maxillary sinus).

Histopathological examination revealed Diffuse large B-cell lymphoma subtype of non-Hodgkin lymphoma.

Tumor was staged based on complete diagnostic work-up, including history and physical examination, blood count, renal and liver function, albumin, β_2-microglobulin and quantitative immunoglobulin, viral serology, and radiological examination (Positron-emission tomography and cerebral MRI does not show any lymph node or other organ to be involved), confirming the infra-temporal fossa as the sole location with a low risk using the IPI score (**Figure 4**).



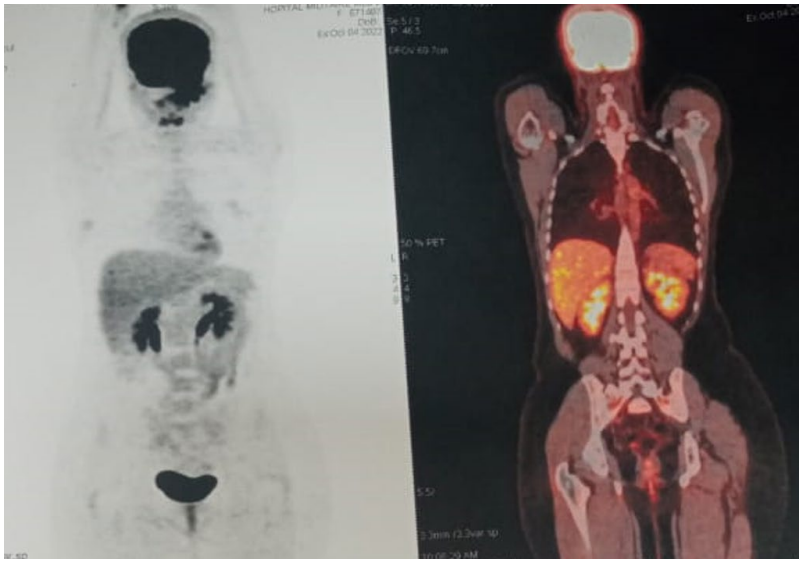


Figure 4. Positron-emission tomography showing an isolated pathologic hypermetabolic tumor of the left infratemporal fossa.

The patient was scheduled for chemotherapy and given six cycles of the R-CHOP regime (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) with an interim PET scan after each two cycles. The patient remained asymptomatic, and CT SCAN after two years did not reveal any recurrence (**Figure 5**). The patient is disease-free after three years of follow-up.

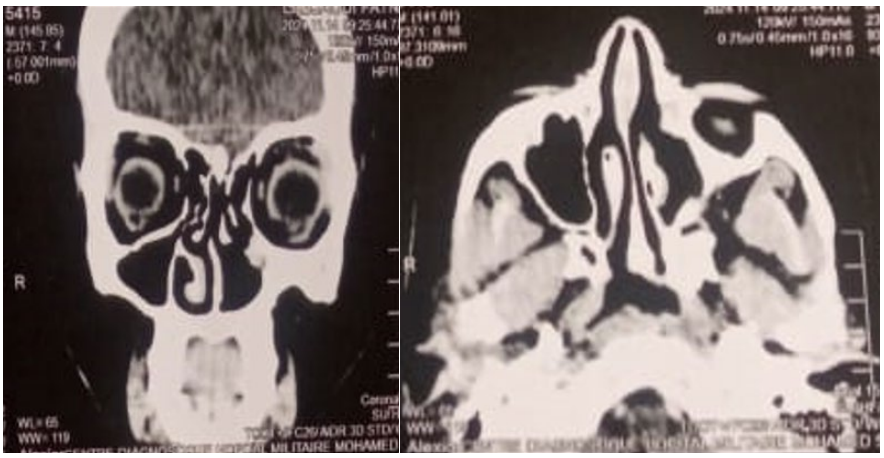


Figure 5. Coronal and axial CT scan showing no recurrence after two years of follow up.

3. Discussion

Lymphoma is a malignant tumor of hematopoietic system, which often occurs in lymph nodes and lymphoid tissue outside lymph nodes and mononuclear macrophage system. Head and neck lymphoma accounts for 3% of all malignant tumors, and it is the third most common tumor in head and neck (12%) after squamous cell carcinoma (46%) and thyroid cancer (33%) [1]. They are generally divided into Hodgkin lymphoma and non-Hodgkin lymphoma, according to its progress,

NHL can be divided into indolent non-Hodgkin's lymphoma such as MALTL and FL, aggressive non-Hodgkin's lymphoma such as Diffuse large B-cell lymphoma and highly aggressive non-Hodgkin's lymphoma like Burkitt lymphoma [7].

Primary tumors of the infratemporal fossa are infrequent, and NHL in this region is extremely rare. To the best of our knowledge, there are only five cases of primary NHL of the infratemporal fossa to be reported in the literature [2]-[5].

NHL is predominantly found in males of Caucasian descent [8]. Other risk factors for the development of NHL include inherited and acquired immunodeficiency diseases, EBV, H. pylori and HTLV-I infections, chromosomal abnormalities, drug induced immunocompromised states, autoimmune diseases (e.g., rheumatoid arthritis and Sjogren's disease), exposure to pesticides and radiation, phenytoin therapy, previous history of Hodgkin's disease or chemotherapy, and excessive intake of meat and fat [9].

Due to the complex anatomy and the proximity of infratemporal fossa tumors to different cranial nerves and neurovascular structures, infratemporal fossa tumors pose a surgical challenge and have highly variable clinical symptoms at presentation, which poses a great challenge to the early diagnosis and treatment. According to A Systematic Review of Clinical Characteristics and Treatment Outcomes of Tumors Involving the Infratemporal Fossa. The most common presenting symptoms included facial hypoesthesia (18.5%), auricular/preauricular pain (16.8%), headaches (9.2%), jaw deviation (9.2%), hearing loss (7.6%), and facial pain (6.7%). The trigeminal nerve was the most impacted cranial nerve (46.7%), followed by the abducent (20.0%) and oculomotor (13.3%) cranial nerves [10]. The literature search revealed 4 cases of primary non-hodgking lymphoma of the infratemporal fossa between 1978 and 2015 (**Table 1**). Our case seems to be the fifth, three of 5 cases were female and 1 of them were male. Symptoms were divers from swelling, pain and exophthalmia (**Table 1**). In our case, the symptoms were atypical, with mild exophthalmos and facial paresthesia.

Table 1. Reported cases of primary infra-temporal localization non-hodgkin lymphoma.

Authors	Published year	Number of cases	Sex	Age	Symptoms	
Peerless AG *et al.* [2]	1978	1	F	25	Pain of the mandible	2 weeks
Boulaich M *et al.* [3]	2003	1	NA	NA	NA	NA
Thakur JS *et al.* [4]	2009	1	F	41	swelling in preauricular region	2 years
Giri AK *et al.* [5]	2015	1	M	44	painless bulge of the left cheek	1 year
Current case		1	F	38	Exophthalmos and facial paresthesia	3 months

NA = non available, F = female, M = male.

Imaging evaluation, chiefly computed tomography and magnetic resonance imaging, in conjunction with surgical and endoscopic procedures, are important in determining the exact location of the tumor, its size, spread to local and distant lymph nodes, and spread to extra lymphatic sites, including the bone marrow.

Contrast computed tomography is the principal imaging modality for lymph node staging in the neck, chest, including mediastinum, abdomen, and pelvic cavity. With the introduction of fast scanners (multi slice scanners), the examination through the body (neck, chest, abdomen, pelvic cavity) can be accomplished within seconds. Contrast magnetic resonance imaging is useful for the assessment of the brain, intraspinal canal, including spinal cord, and bone marrow. On computed tomography, extranodal lymphomas are characterized by an iso dense (to muscle), homogeneous, submucosal mass frequently associated with enlarged lymph nodes in the neck. Unlike carcinomas, ulceration and irregular margins are not encountered. On MR imaging, most lymphomas are low in signal intensity on T1-weighted images and intermediate in signal intensity on T2-weighted images. The signal intensity on the T2-weighted images, however, may range from low to high depending on the cellular composition of the lymphoma, admixture of fibrotic changes, and extracellular water accumulation [11].

The diagnosis of lymphoma is based on the histopathologic examination, the biopsy of tumor in such anatomically complex territory is difficult to approach surgically. It can be done by different technique: open approach, endoscopic endonasal technique, or lateral endoscopic approach. Each approach has strengths and limitations, especially regarding surgical exposure of the targeted area. In our case, the diagnosis was confirmed via an endoscopic endonasal biopsy of the infratemporal fossa, chosen due to tumor extension into the maxillary sinus. After an initial middle antrostomy failed to identify the lesion's origin, an endoscopic medial maxillectomy was performed, allowing adequate access for biopsy.

The accurate staging of extranodal NHL is important for effective planning of the treatment approach [12]. Staging is determined by detailed history, clinical examination, and radiological investigations. Conley *et al.* [12] found nodal disease in 50% of all cases at the time of presentation or during management, and they advised detailed work up of all patients. It is further recommended that all cases of NHL should undergo a complete evaluation, including a complete hemogram, liver and renal functions, serum 2-microglobulions, chest X-ray, bone marrow biopsy, gallium scan, and cerebrospinal fluid analysis, as well as CT scans of the abdomen, pelvis, and bones [13]. CT scan can identify the nodal and extranodal sites of involvement and provides an important approach to monitoring the response to therapy. Magnetic resonance imaging is useful in identifying bone marrow and central nervous system involvement. However, in recent years, because of its higher sensitivity, ^{18}F-fluorodeoxyglucose positron-emission tomography with computed tomography (PET-CT) has replaced CT in monitoring response to therapy [6].

Staging and response assessment should be performed in accordance with Ann Arbor staging and the Lugano classification criteria [6] [14] [15]. The Ann Arbor system provides the basis for staging of lymphomas. In the Ann Arbor system, the stage depends on the number of lymph node regions involved, the presence of extranodal disease, the presence of disease above and below the diaphragm, and

the existence of systemic symptoms. In addition, each stage is subdivided into categories: category A for those patients without systemic symptoms and category B for those with defined systemic symptoms of weight loss, unexplained fever, or drenching night sweats. These types of systemic symptoms are not as commonly associated with NHL as with HL but are prognostically significant, if present.

Treatment of NHL consists of chemotherapy, radiotherapy, or surgery. Patients with localized disease are treated primarily by radiotherapy (30 - 55 Gy). Sometimes, in the case of limited extra-nodal NHL, surgery with or without radiotherapy is used [16]. Patients with stage II-IV are treated primarily with chemotherapy. CHOP chemotherapy is used in most cases using the monoclonal antibody rituximab added to CD20-positive cases. High-dose chemotherapy and autologous bone marrow transplantation can be curative in some patients after relapsing from standard therapy.

Patients with Non-Hodgkin's Lymphoma (NHL) present with limited-stage disease, typically defined as non-bulky stage I or II disease without systemic symptoms, generally have low-risk features and favorable outcomes, though delayed relapses have been observed. Historically, treatment involved three cycles of CHOP chemotherapy combined with involved-field radiation therapy, which initially improved overall survival compared to eight cycles of CHOP alone [17]. However, long-term follow-up revealed that the survival advantage diminished due to late relapses and secondary cancers linked to radiation, suggesting chemotherapy alone may suffice [18]. With 5-year overall survival rates of 85% - 95% for limited-stage disease, recent strategies aim to reduce chemotherapy cycles or omit radiation therapy. Patients with low-risk disease defined by an IPI below 2 treated with rituximab-based chemoimmunotherapy have a favorable prognosis. In patients with limited disease, several randomized clinical trials have shown the equivalence of four cycles compared to six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy [19] [20]. PET-CT-guided therapy has also been explored, showing that patients achieving a complete metabolic response after four cycles of R-CHOP do not benefit from additional radiation. Similarly, phase 2 trials and population-based studies suggest that four cycles of R-CHOP are sufficient for patients with a complete metabolic response after three cycles [13] [21]. However, optimal management remains unclear for patients with positive interim PET-CT results, high stage-modified IPI scores, or high-risk biologic features, as these groups have been underrepresented in recent trials [22].

The response during therapy can be assessed with the use of CT to detect non-responding or progressive diseases. Studies evaluating the merit of interim PET-CT have yielded conflicting results, although PET-CT after two to four cycles of treatment appears to be prognostic, particularly when the response is assessed with the use of quantitative methods [23]. In our case, the patient received six cycle of chemotherapy the interim pet-scan was done after every two cycles of R-CHOP.

Prognosis is calculated according to the International Prognostic Index, and it declines with an increase in the patient's age, LDH levels, histological grade, or stage of the NHL. According to the International Prognostic Index, the 5-year survival for all ages is about 73% - 83% for low grade, 51% - 69% for low-intermediate, 43% - 46% for high-intermediate, and 26% - 32% for high-grade NHL [16]. Shima *et al.* [1] found decreased (28%) 5-years survival rates in young patients (≤20-years-old) irrespective of the stage of extranodal NHL. In our case, the patient underwent chemotherapy, and she is in complete remission for over two years of evolution.

Patients should be clinically monitored every 3 months for 2 years, then every 6 to 12 months [24]. Patients who remain event-free for 2 years from the time of diagnosis have an expected overall survival that is almost similar to survival in the general, age-matched population [25]. However, physicians should monitor patients for long-term risks, including late infectious complications, autoimmune disorders, secondary cancers, and cardiovascular events.

4. Conclusion

Primary Non-Hodgkin's Lymphoma of the infra-temporal fossa is a rare entity, and we found only five cases one previous report of isolated NHL of the temporal region. The diagnostic and therapeutic management of primary Non-Hodgkin's Lymphoma (NHL) in the infratemporal fossa presents significant challenges due to its rare occurrence, nonspecific clinical presentation, and complex anatomical location. In this case, the patient's initial symptoms of unilateral exophthalmia and facial paresthesia were subtle and could easily be attributed to more common conditions, delaying the diagnosis. The anatomical complexity of the infratemporal fossa further complicated imaging interpretation and biopsy procedures. Advanced imaging, including MRI and PET scans, played a critical role in delineating the tumor's extent and guiding the biopsy approach. The decision to use an endoscopic endonasal approach for biopsy was driven by the tumor's extension into the maxillary sinus and the need to minimize morbidity. However, the initial middle antrostomy failed to provide adequate access, necessitating an endoscopic medial maxillectomy. This adjustment, which involved sacrificing the inferior turbinate while preserving the nasolacrimal duct, underscores the intricate balance between achieving diagnostic accuracy and maintaining functional outcomes. The choice of the R-CHOP chemotherapy regimen was based on the tumor's histopathology (Diffuse large B-cell lymphoma) and staging, which indicated a low-risk profile according to the International Prognostic Index. The multidisciplinary collaboration among ENT specialists, radiologists, oncologists, and pathologists was instrumental in ensuring a comprehensive evaluation and tailored treatment plan. The patient's favorable response to chemotherapy, evidenced by complete remission on follow-up PET scans, highlights the effectiveness of this approach. This case underscores the importance of a high index of suspicion, advanced imaging, and a multidisciplinary strategy in managing rare NHL presentations. It

also contributes to the limited literature on infratemporal fossa NHL, offering valuable insights for clinicians facing similar diagnostic and therapeutic challenges.

Ethical Approval

Informed consent was obtained from the patient for the publication of this case report, ensuring ethical compliance and respect for the patient's autonomy and privacy.

Conflicts of Interest

The authors declare no conflicts of interest.

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