CASE REPORT

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

A rare case of diffuse large B-cell lymphoma of the frontal sinus and rapid review of literature

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Abstract

Introduction: Primary lymphoma of the paranasal sinuses, especially involving the frontal sinus, is exceedingly rare. Extranodal non-Hodgkin lymphoma (NHL) located in the head and neck frequently poses diagnostic challenges because its nonspecific symptoms can be mistaken for benign issues such as rhinosinusitis. *Aim*: This case report seeks to emphasize the challenges in diagnosis, the aggressive characteristics, and the effective treatment of an uncommon manifestation of diffuse large B-cell lymphoma (DLBCL) primarily affecting the frontal and ethmoid sinuses. *Case presentation*: We present a case of a 62-year-old male who initially presented with symptoms suggestive of acute rhinosinusitis complicated by periorbital cellulitis. Diagnostic workup included physical examination, laboratory investigations, computed tomography (CT) imaging, magnetic resonance imaging (MRI), histopathological (HP) analysis of biopsy specimens, immunohistochemical staining, and positron emission tomography (PET)–CT. The patient presented with right frontal headache, periorbital edema, palpebral ptosis, and posterior rhinorrhea. Initial CT revealed mucosal thickening, lytic changes, and a mass partially invading the right orbit. Following surgical excision, histopathology confirmed DLBCL with positivity for cluster of differentiation (CD)20, CD79a, B-cell lymphoma (Bcl)-6, and Bcl-2, and a Ki-67 proliferation index of 90%. Subsequent MRI revealed a hypointense mass extending into surrounding structures. Staging CT confirmed stage IVB disease. The patient received six cycles of Rituximab–Cyclophosphamide, Hydroxydaunorubicin (Doxorubicin), Oncovin (Vincristine), Prednisolone (R–CHOP) chemotherapy and radiotherapy for the frontal sinus. At the 6-month and 12-month follow-up CT scans, there was no evidence of metabolically active disease on PET–CT (Deauville score 1). During the 2-year follow-up, the patient remained in complete remission. *Conclusions*: This case underscores the importance of considering malignancy in cases of atypical sinusitis and the crucial role of HP examination of biopsy specimens. This case also highlights the importance of considering malignancy in cases of atypical sinusitis.

Keywords: large B-cell lymphoma, non-Hodgkin lymphoma, extranodal lymphoma, sinus lymphoma.

Introduction

Malignancies of the sinonasal area are rare, accounting for less than 1% of all cancer cases [1, 2]. Primary lymphoma occurring in the paranasal sinuses is quite uncommon, and involvement of the frontal sinus as a primary site is extremely rare. Extranodal occurrences of non-Hodgkin lymphoma (NHL) in the head and neck are often found in areas such as tonsils, nasopharynx, oropharynx, thyroid, salivary glands, or sinuses, making up roughly 15% to 20% of all large cell lymphomas [3, 4].

While diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, its primary presentation within the frontal sinus is sparsely documented [5]. This unusual location can lead to diagnostic challenges, as the presenting symptoms are often nonspecific and mimic benign conditions such as rhinosinusitis [6, 7]. These symptoms may include headache, facial pain or pressure, nasal obstruction, and visual disturbances, which can delay appropriate diagnosis and treatment [6, 7].

Aim

We report a case of a 62-year-old male patient from Romania, who presented with acute rhinosinusitis complicated by periorbital cellulitis and was subsequently diagnosed with stage IVB DLBCL primarily involving the frontal and ethmoid sinuses. This case underscores the challenges in diagnosis presented by this infrequent manifestation, the disease's aggressive characteristics, the critical role of histopathological (HP) analysis of biopsy samples taken during sinus surgery, and the positive results achieved with Rituximab–Cyclophosphamide, Hydroxydaunorubicin (Doxorubicin), Oncovin (Vincristine),

Prednisolone (R–CHOP) chemotherapy and radiation therapy. Additionally, this case emphasizes the necessity of considering cancer when dealing with unusual sinusitis cases.

Case presentation

A 62-year-old man presented to the Ear, Nose, and Throat (ENT) Clinic at Municipal Emergency Clinical Hospital, Timişoara, Romania, with a one-month history of right frontal headache, right periorbital edema, palpebral ptosis, and posterior rhinorrhea. He denied any history of local trauma or prior otorhinolaryngological disorders, as well as nocturnal sweating, fever, or weight loss during this period. Prior to presentation, he received treatment including antibiotics, nasal decongestants, analgesics, and anti-inflammatory medications without symptomatic improvement. This lack of response to conventional medical management highlighted the complexity of his condition and prompted further diagnostic evaluation and a tailored therapeutic approach. Physical examination revealed right periorbital edema and mild right eyelid ptosis – cutaneous signs suggestive of Celsus's signs. Nasal endoscopy revealed polypoid formations and purulent discharge within the right middle meatus. The left nasal cavity appeared normal. Laboratory investigations demonstrated leukocytosis (16 000/μL) with neutrophilia (8700/μL), and elevated levels of erythrocyte sedimentation rate (30 mm/h) and C-reactive protein (49 mg/dL).

These findings suggested an underlying infectious process requiring further investigation. The patient was admitted to the ENT Clinic for intravenous antibiotic therapy, computed tomography (CT) imaging, and close clinical monitoring. Based on the clinical presentation, acute rhinosinusitis with suspected periorbital cellulitis prompted the CT imaging request, in accordance with the 2020 *European Position Paper on Rhinosinusitis and Nasal Polyps* (EPOS) guidelines [8].

CT revealed the following: a subcortical hypodensity measuring approximately 10 mm in the left frontal lobe, and several smaller millimetric hypodensities in the right frontal lobe. Mucosal thickening was observed within the right maxillary, right sphenoid, and left frontal sinuses, as well as the ethmoid air cells. Lytic changes were present in the frontal sinus wall (Figure 1, A and B), and a frontal sinus mass with permeative characteristics was noted, partially invading the right orbit (Figure 1, C and D). A deviated nasal septum with rightward convexity and hypertrophic nasal turbinates were also identified.

Based on the clinical and imaging findings (laboratory investigations and CT imaging), a diagnosis of acute rhinosinusitis complicated by periorbital cellulitis was established, prompting functional endoscopic sinus surgery (FESS). A combined endoscopic and external frontal approach was employed. Intraoperative macroscopic examination revealed a solid, pearly white tumor formation without gross evidence of frontal sinus bone destruction. The tumor was discovered to extend from the frontal sinus into the ethmoid sinus and was fully removed from both sites. The excised tissue was submitted for HP analysis. Postoperatively, the patient demonstrated significant improvement, with resolution of periorbital edema and marked improvement in eyelid ptosis.

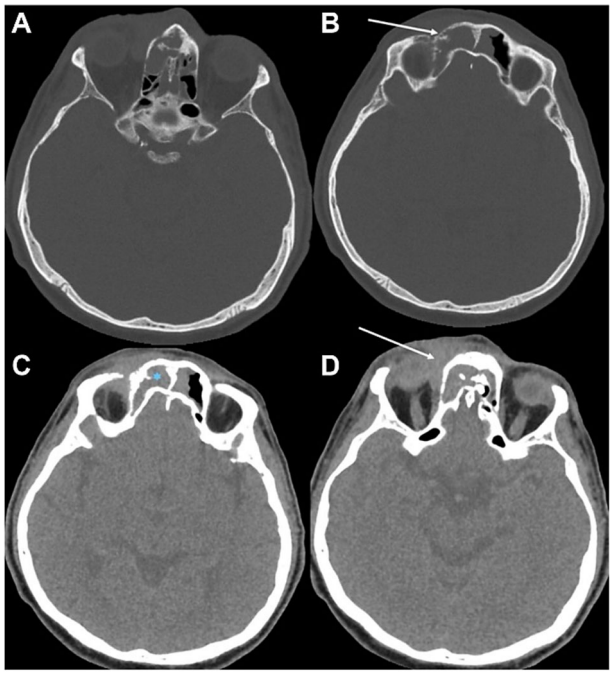

Figure 1 – ***(A and B) Bone window: lytic changes at the level of the frontal sinus walls (arrow); (C and D) Soft tissue window: frontal sinus mass (*) with permeative features that partially invades the right orbit (arrow).***

Approximately three weeks postoperatively, the patient presented with recurrent symptoms and was readmitted for further evaluation and treatment. During this admission, he received a 7-day course of corticosteroids, antibiotics, and topical nasal decongestants, with subsequent symptomatic improvement. The HP analysis from the initial surgical specimens (obtained three weeks prior) was received, prompting a referral to the Department of Pathology. HP examination revealed a fragment of sinus mucosa exhibiting a tumoral proliferation within the *lamina propria*. This proliferation consisted of large cells with basophilic cytoplasm, vesicular nuclei, and prominent nucleoli, arranged individually (Figure 2, A and B). Immunohistochemical (IHC) analysis demonstrated positivity for leukocyte common antigen (LCA), cluster of differentiation (CD)20, CD79a, B-cell lymphoma (Bcl)-6, and Bcl-2, and negativity for cytokeratin (CK) AE1/AE3 (with positive internal control), Melan A, human melanoma black 45 (HMB45), and CD10 (with positive internal control). These images are presented in Figure 3 (A–F) and Figure 4 (A–D). The Ki-67 cell proliferation index was 90%.

In order to delve deeper into the reason behind the return of symptoms, a contrast-enhanced magnetic resonance imaging (MRI) scan of the brain was conducted. This revealed post-curettage changes in the right paramedian frontal sinus *via* a trans-osseous approach. A hypointense, infiltrative/permeative mass measuring 42×27 mm was visualized within the frontal sinus along the midline, extending into the right paramedian ethmoid air cells. The mass extended beyond and eroded the frontal bone and ethmoid air cells, with extension into the right superior palpebral soft tissues, right paranasal region, and medial aspect of the right orbit. Superiorly, the mass eroded approximately 10 mm of the greater wing of the right sphenoid bone, abutting the meninges but without definitive evidence of invasion. Post-curettage inflammatory changes

were noted in the mucosa of the right frontal sinus. Minimal dependent hemosinus was present in the right maxillary sinus. Multiple midline gliotic-ischemic lesions were observed, with an increase in size compared to prior imaging (if available). A 9 mm lymph node was identified in the right intraparotid region.

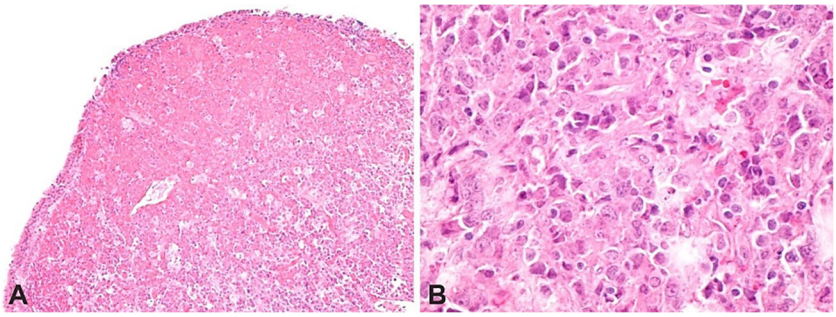

Figure 2 – ***Microscopic aspects on HE staining: (A) Sinus mucosa with tumor proliferation in the lamina propria (×100); (B) Large, polygonal tumor cells with basophilic cytoplasm and vesicular nucleus with 1–2 nucleoli (×400). HE: Hematoxylin–Eosin.***

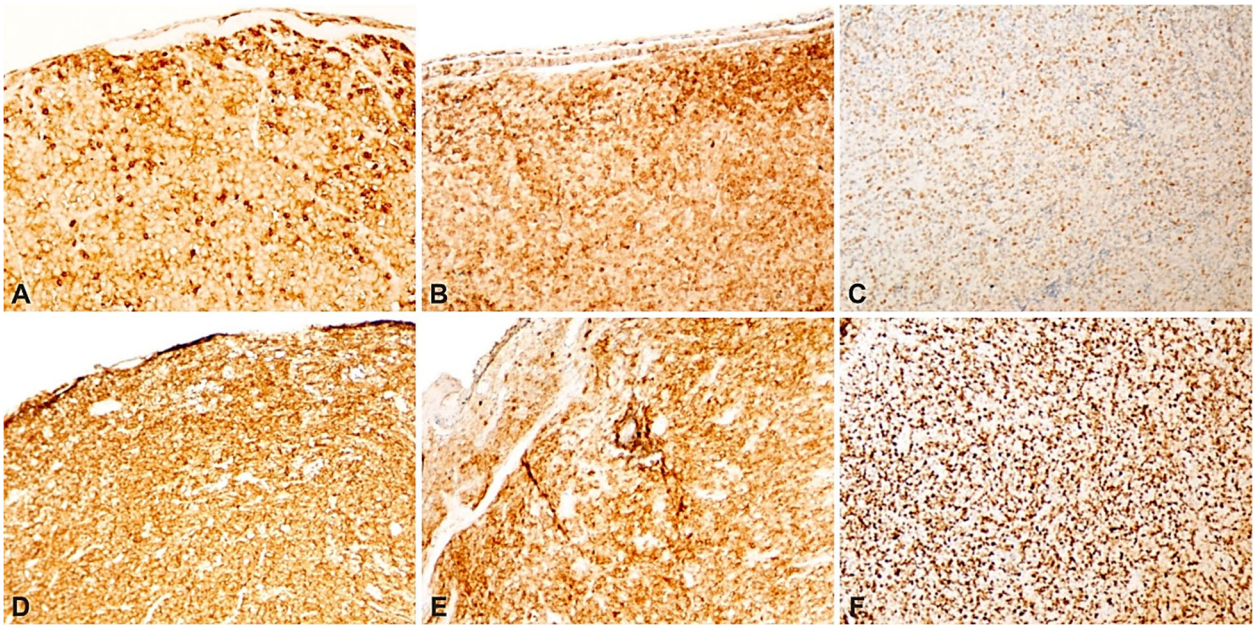

Figure 3 – ***Immunohistochemical profile of tumor cell-positive reaction for: (A) LCA (×200); (B) Bcl-2 (×100); (C) Bcl-6 (×100); (D) CD20 (×100); (E) CD79a (×100); (F) Ki-67 (×100). Bcl-2/-6: B-cell lymphoma-2/-6; CD20/79a: Cluster of differentiation 20/79a; LCA: Leukocyte common antigen.***

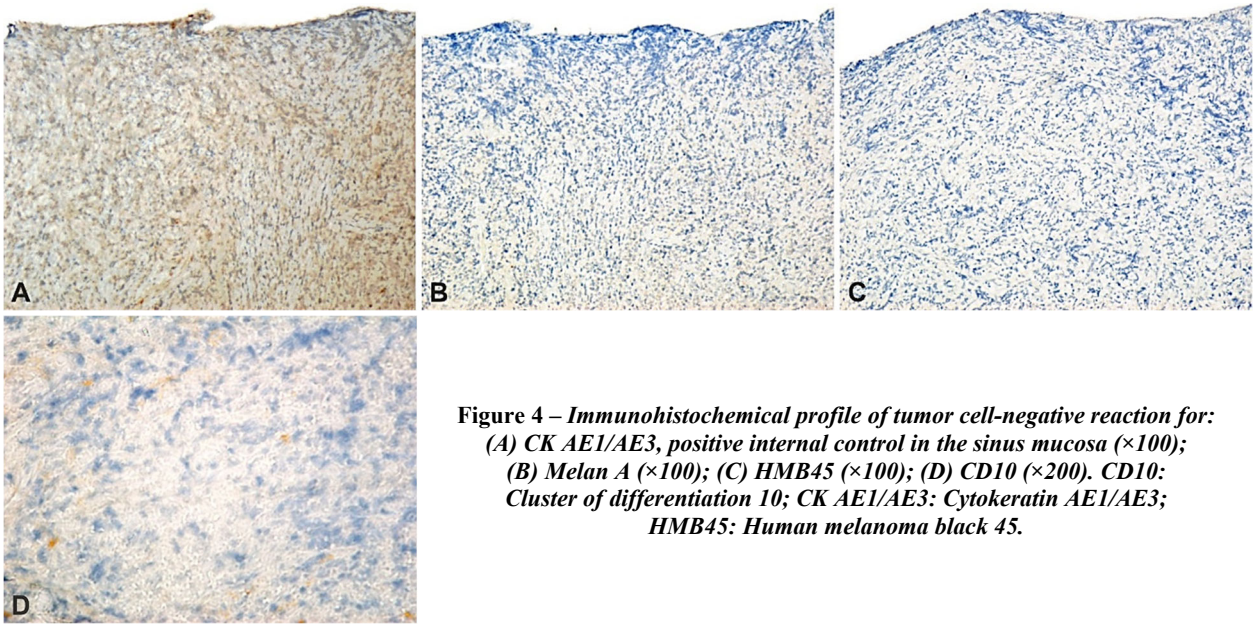

Figure 4 – ***Immunohistochemical profile of tumor cell-negative reaction for: (A) CK AE1/AE3, positive internal control in the sinus mucosa (×100); (B) Melan A (×100); (C) HMB45 (×100); (D) CD10 (×200). CD10: Cluster of differentiation 10; CK AE1/AE3: Cytokeratin AE1/AE3; HMB45: Human melanoma black 45.***

Initial laboratory tests revealed normal blood cell counts. The patient had an *Eastern Cooperative Oncology Group* (ECOG) performance status of 2 and an *International Prognostic Index* (IPI) score of 4, categorizing him in the high-risk group according to the *Revised International Prognostic Index* (R-IPI). A diagnosis of stage IVB DLBCL

was confirmed, with IHC analysis indicating positivity for CD20, CD79a, Bcl-6, and CD10, along with a Ki-67 proliferation index of 90%. The patient completed six cycles of R–CHOP chemotherapy, which he tolerated well. Following this, he received external beam radiation therapy (EBRT) targeting the right frontal sinus, administered using a linear accelerator at 6 MV, totaling 40 Gy in 20 fractions spanning 30 days. Routine blood tests remained within normal ranges during his time in both the ENT and Hematology Departments. The patient was discharged with a follow-up appointment scheduled for six months later, which includes a CT scan of four regions.

At the 6-month follow-up, the patient was readmitted to the Hematology Department for the scheduled four-region CT scan. The results show:

▪ Cervical region: findings were consistent with chronic fronto-ethmoidal sinusitis. The parotid, submandibular, and thyroid glands demonstrated normal topography, size, and structure. Prevertebral soft tissues appeared normal on CT examination. No lateral cervical lymphadenopathy was present.

The patient remained clinically stable, and a 12-month hematological follow-up was scheduled. This included a series of CT scans with and without contrast enhancement, followed by a PET–CT.

After the 12-months period, the patient presents for the 12-month check-up, where he underwent a series of CT scans, which revealed the following:

▪ Brain (native and contrast-enhanced): post-surgical alterations were observed in the right fronto-ethmoidal sinus following a right anterior-posterior ethmoidectomy and a combination of endoscopic and external right frontal sinus surgery. A remaining pseudotumor, approximately 42×21 mm in axial dimensions and 26 mm in craniocaudal length, was present on the right side of the frontal sinus and partially within the right ethmoid sinus, with anterior extension into the soft tissue of the right frontal area and right naso-orbital angle, along with slight extraconal intra-orbital involvement. The mass resulted in thinning and localized osteolysis of the anterior and inferior walls of the frontal sinus, the right nasal bones, and the medial aspect of the right orbital roof. Several native hypodense lesions bilaterally, measuring up to 16 mm, were seen in the frontal and parietal lobes as well as the semioval centers; these lesions did not enhance following contrast, indicating prior ischemic changes.

▪ PET–CT conclusion: normal PET–CT examination from an oncological perspective, with no pathological ^{18}F-Fluorodeoxyglucose (FDG) uptake (Deauville score 1).

At the two-year hematological follow-up, the patient remained in complete remission, with no evidence of recurrence. The patient demonstrated a favorable response to treatment and remains in complete remission. The patient, diagnosed with stage IVB DLBCL (CD20+, CD79a+, Bcl-6+, CD10+, Ki-67 90%) involving the frontal and ethmoid sinuses, has achieved and maintained complete remission.

Discussions

Malignancies originating in the frontal sinus are uncommon. Sinonasal cancers often do not present symptoms in their initial stages, and due to their unusual location, tumors in the frontal sinus are commonly misidentified as sinusitis at first. The reported incidence of frontal sinus malignancies is about 0.011 per 100 000 people over a span of 12 years, with squamous cell carcinoma being the most prevalent histological type, followed by NHL [9, 10].

In populations in the West, malignant lymphomas arising in the paranasal sinuses and nasal cavities account for about 2% of all NHL cases. This incidence is notably higher in Asian countries, reaching up to 6.7% [11, 12]. Within the sinonasal tract in Western populations, the maxillary antrum, nasal cavity, and ethmoid sinus are the most frequent sites of NHL involvement, with B-cell origin predominating. In contrast, the nasal cavity is the most commonly affected site in Asian populations, where T-cell lymphomas are more prevalent [13].

Early-stage symptoms of frontal sinus malignancies are poorly defined, with symptoms typically arising only as a consequence of mass effect [9]. The differential diagnosis for sinonasal DLBCL must also consider other malignancies of the sinonasal region, including neuroendocrine carcinoma, olfactory neuroblastoma, Ewing sarcoma, and paraganglioma. These entities exhibit comparable nonspecific symptoms, such as nasal blockage, nasal discharge, chemosis or proptosis, postnasal drip, and repeated paranasal infections. These symptoms are also commonly seen in benign disorders like chronic rhinosinusitis, with or without the presence of nasal polyps [14, 15]. CT is a standard imaging modality for evaluating paranasal sinus disease and morphological changes. However, differentiating malignant from benign lesions based solely on morphological features can be challenging. Increased awareness of these diagnostic challenges and prompt evaluation are crucial for successful management of this rare and heterogeneous group of diseases [9, 16].

In order to provide context for this case, a literature review was performed to find analogous instances of primary frontal sinus lymphoma. Reported cases have involved patients ranging from 11 to 69 years of age, with male predominance. Common presenting symptoms included headache, periorbital pain or swelling, nasal congestion or discharge, and visual disturbances, as seen in cases reported by Knudson *et al.* (2019) [17], who described an 11-year-old male with conjunctivitis and proptosis; Khan *et al.* (2015) [18], who reported a 69-year-old male with headaches, dizziness, and nasal congestion; Nagafuji *et al.* (2018) [9], who presented a 67-year-old male with diplopia and eyelid swelling; and Yang *et al.* (2022) [19], who described a 65-year-old male with a progressively enlarging orbital mass affecting vision.

Imaging often demonstrated involvement of adjacent structures, such as the orbit, ethmoid sinuses, or anterior cranial fossa, sometimes with bone destruction, as noted by Knudson *et al.* [17] and Haksever *et al.* [20], who described destruction of the anterior and posterior walls of the frontal sinus. Other findings included opacification of the sinuses, reported by Khan *et al.* [18] and Nagafuji *et al.* [9], or soft tissue shadows, as reported by Yang *et al.* [19]. Histopathologically, most cases were B-cell lymphomas, typically positive for CD20 and CD79a. Additional markers such as CD10, Bcl-6, Bcl-2, or multiple myeloma oncogene-1 (MUM-1) were expressed.

Treatment strategies varied across the reviewed cases. Knudson *et al.* [17] employed a multi-agent chemotherapy regimen [Rituximab–Cyclophosphamide, Oncovin (Vincristine), Prednisolone, Adriamycin (Doxorubicin), Methotrexate (R–COPADM)] followed by maintenance Rituximab. Similarly, Nagafuji *et al.* [9] and Yang *et al.* [19] utilized the R–CHOP regimen, which includes Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone. In contrast, Khan *et al.* [18] utilized a regimen of Adriamycin, Cytoxan, Rituxan, and Vincristine for five months. Yang *et al.* [19] also incorporated radiotherapy in their treatment plan. These variations in treatment regimens highlight the need for individualized treatment approaches based on the specific characteristics of each case, including disease stage, patient factors, and available resources.

In this case, a diagnosis of stage IVB malignant non-Hodgkin DLBCL affecting the frontal and ethmoid sinuses was confirmed through biopsy, HP and IHC evaluations, and CT scans of four regions. The patient underwent and tolerated six cycles of R–CHOP chemotherapy, followed by EBRT to the right frontal sinus, administered using a linear accelerator at 6 MV, with a cumulative dosage of 40 Gy in 20 fractions over a span of 30 days. The patient showed a positive response to the treatment, with no signs of recurrence noted at the 2-year follow-up evaluation.

Over the past two decades, significant advancements in lymphoma treatment have included the introduction of Rituximab, a chimeric monoclonal antibody targeting CD20, a molecule expressed on over 90% of B-cell lymphomas. The management of sinonasal lymphoma primarily involves non-surgical approaches, with chemotherapy serving as the central component of treatment for the majority of patients. In instances of aggressive or localized disease, radiotherapy might be considered as an additional therapeutic option [16, 21, 22]. Although the R–CHOP regimen is widely recognized as the standard treatment for DLBCL, around 30–40% of patients either do not attain a complete response or face a relapse following initial therapy. In the context of sinonasal lymphomas specifically, radiotherapy has been used as an alternative or supplementary strategy. However, while radiotherapy can lead to immediate clinical benefits, it frequently carries a greater risk of local or distant recurrence [14].

Conclusions

The diagnosis of NHL with atypical or uncommon localization, such as within the sinonasal region or other extranodal sites, presents a significant diagnostic challenge. This is primarily due to the nonspecific nature of early clinical presentations and the ability of NHL to mimic various benign conditions, often leading to diagnostic delays. A timely and accurate diagnosis is crucial, as prognosis and treatment strategies are highly dependent on the location, stage, and biological characteristics of the lymphoma. As a result, healthcare providers should keep a strong awareness of the possibility of NHL in patients who present with unclear or ongoing symptoms related to the sinonasal region and head and neck. Prompt and accurate diagnosis facilitates timely initiation of targeted therapy, ultimately improving survival outcomes and quality of life for these patients. Further research focusing on biological behavior and optimal treatment protocols for NHL in rare locations is essential to further enhance patient outcomes and advance the field of lymphoma management.

Conflict of interests

The authors declare no conflict of interests.

Institutional Review Board Statement

This study followed the Helsinki Declaration on Medical Protocol and Ethics. The study was approved by the Ethics Committee of Victor Babeș University of Medicine and Pharmacy, and the Municipal Emergency Clinical Hospital, Timișoara, Romania (Reference No. E-4677/30.08.2023).

Informed Consent Statement

Informed consent was obtained from the patient for data collection and study publication.

Data Availability Statement

Data are contained within this article.

Acknowledgments

We would like to acknowledge Victor Babeș University of Medicine and Pharmacy, Timișoara for their support in covering the costs of publication for this research paper.

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Received: February 18, 2025

Accepted: March 27, 2025