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CASE REPORT

Extranodal T/NK cells lymphoma presenting as persistent facial swelling: case report

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Abstract:

Extranodal NK/T-cell lymphoma (ENKTL) is a histopathological subtype of non-Hodgkin's lymphoma strongly associated with Epstein-Barr virus (EBV) infection. This malignancy is characterized by extensive necrosis, often resulting in severe tissue destruction and midfacial deformities. The present study aims to report a case of ENKTL in which the primary clinical manifestation was persistent, painless facial edema, notably without necrotic features. The patient underwent combined therapy with DeVIC chemotherapy and radiotherapy, demonstrating a favorable tumor response with no evidence of recurrence after a nine-month follow-up period. Accurate and timely diagnosis of ENKTL is critical for optimizing patient outcomes, mitigating tissue destruction, and reducing both morbidity and mortality. Therefore, ENKTL should be considered as a differential diagnosis in cases of unexplained diffuse facial swelling. Additionally, a comprehensive literature review was conducted to examine previously reported cases of ENKTL presenting with facial swelling.

Keywords: Lymphoma, Non-Hodgkin; Extranodal NK-T-Cell.

INTRODUCTION

Extranodal NK/T-cell lymphoma (ENKTL) is a histopathological subtype of non-Hodgkin's lymphoma strongly associated with Epstein-Barr virus (EBV) infection. It predominantly affects the upper respiratory and digestive tracts, particularly the nasal cavity, nasopharynx, and paranasal sinuses, leading to a highly aggressive clinical course[1,2]. ENKTL is considered a rare malignancy, accounting for approximately 10% of all T-cell lymphomas[3]. Its incidence exhibits a distinct geographic distribution, with higher prevalence rates observed in Asian and Latin American populations, a pattern that has been attributed to the endemic nature of EBV infection in these regions[4].

Historically, ENKTL has been referred to by various terminologies, including lethal midline granuloma, polymorphic reticulosis, and midline malignant reticulosis, due to its extensive necrotic presentation and severe midfacial destruction[5,6]. The most recent edition of the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues (5th edition) has proposed a change in nomenclature, removing the "nasal-type" designation, given that this malignancy can arise in multiple extranodal locations beyond the upper aerodigestive tract, including the skin, soft tissues, testes, penis, and gastrointestinal tract[7,8].

Statement of Clinical Significance
ENKTL is a rare and aggressive malignancy. This case presents an atypical manifestation with persistent, painless facial swelling without necrosis, emphasizing the importance of early recognition, differential diagnosis, and advanced evaluation to ensure appropriate management and improved clinical outcomes.

Clinically, ENKTL manifests with a spectrum of symptoms, including nasal obstruction, facial swelling, purulent discharge, epistaxis, and progressive tissue necrosis[1,6,9]. The disease frequently involves the nasal mucosa, nasal septum, paranasal sinuses, and nasopharynx,

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with potential extension to the orbital region, maxillary region, upper lip, palate, and oropharynx. Intraoral manifestations, such as ulceration of the palate and oroantral communication, are commonly observed in advanced stages[4,6]. The hallmark of ENKTL, namely extensive necrosis, is a consequence of tumor cell infiltration and vascular damage induced by cytotoxic lymphocytes, leading to ischemia and tissue destruction[5,10].

The diagnosis of ENKTL remains challenging due to its rarity and the nonspecific nature of its initial presentation. Early symptoms are often misinterpreted as benign inflammatory or infectious conditions, resulting in delayed diagnosis and inappropriate treatment with antibiotics or antifungal agents[1,11]. This diagnostic delay is a significant concern, as disease progression leads to extensive tissue destruction, adversely impacting prognosis, which is closely linked to the stage at initial presentation[12].

Given these diagnostic complexities, this study aims to report a case of ENKTL presenting as a persistent, painless facial edema in the absence of necrotic features. Emphasis is placed on the critical role of advanced imaging modalities and histopathological evaluation in the differential diagnosis of unexplained facial swelling. Furthermore, a literature review was conducted to examine previously reported cases of ENKTL with similar clinical presentations.

CASE REPORT

A 33-year-old woman was referred to an oral and maxillofacial surgery service for the evaluation of a suspected odontogenic infection in the midface. The patient presented with a 30-day history of progressive swelling in the right maxillary region. During the anamnesis, she reported multiple previous consultations with different specialists, who had prescribed corticosteroids and antibiotics based on initial clinical hypotheses of a nasolabial cyst or an infectious etiology. Additionally, she complained of a mild decrease in nasal airflow in the right nostril, accompanied by intermittent bloody nasal discharge. The patient also reported unmeasured fever episodes and an unintended weight loss of 11 kg over the past month. Her medical history was non-contributory, except for ongoing orthodontic treatment. She reported low alcohol consumption and denied any other significant habits.

On physical examination, the patient appeared to be in good general health, with stable vital signs. However, there was evident facial asymmetry due to diffuse swelling in the right maxillary region, leading to the effacement of the nasolabial fold and elevation of the nasal ala (Figure 1). The swelling was non-tender, firm on palpation, and covered by intact skin without signs of inflammation. A partially obstructive mass was observed in the right nostril. Intraoral examination revealed a diminished right maxillary buccal fold, without fistulation or purulent discharge. Oral hygiene was adequate, and no odontogenic infectious foci were identified. Additionally, no signs of rhinorrhea, epistaxis, necrosis, oronasal fistula, or cervical lymphadenopathy were detected.

A computed tomography (CT) scan of the face was performed, revealing soft tissue thickening with increased contrast enhancement in the right nasolabial fold region. No liquefaction was observed, and the lesion was ill-defined, measuring approximately 3.3 cm in diameter (Figure 1). Cervical CT imaging also demonstrated the presence of enlarged lymph nodes in the right level Ib cervical chain, with the largest measuring 2.5 × 1.2 cm. The adjacent bone structures were intact, showing no signs of cortical erosion. Additionally, maxillary sinus wall thickening was noted, suggestive of chronic sinusopathy.

Based on these imaging findings, the primary differential diagnoses included malignant mesenchymal neoplasm and lymphoma. An intraoral incisional biopsy was performed under local anesthesia through an incision in the anterior region of the maxillary buccal vestibule, providing access to the submucosal tissue corresponding to the area of facial swelling. Histopathological examination revealed fibrous connective tissue exhibiting a atypical dense lymphoid infiltrate composed predominantly of small to medium-sized atypical lymphocytes, arranged in an angiocentric and angioinvasive pattern, with foci of vascular destruction and no evidence of mesenchymal or epithelial differentiation (Figure 2). Perineural distribution of the infiltrate was observed, although no vascular invasion was identified in the examined sections. Subsequent immunohistochemical analysis demonstrated small to medium-sized lymphocytes with slightly irregular nuclei, exhibiting positivity for CD2, CD3, CD56, GATA3, and TIA-1, along with a high proliferative index (Ki-67: 70–80%) (Figure 3). The immunohistochemical panel is summarized in Table 1. Additionally, numerous histiocytes tested positive for CD68/KP1. In situ hybridization confirmed diffuse Epstein-Barr virus (EBV/EBER) positivity within the tumor cells (Figure 3). These findings were consistent with a diagnosis of extranodal NK/T-cell lymphoma (ENKTL), nasal type.

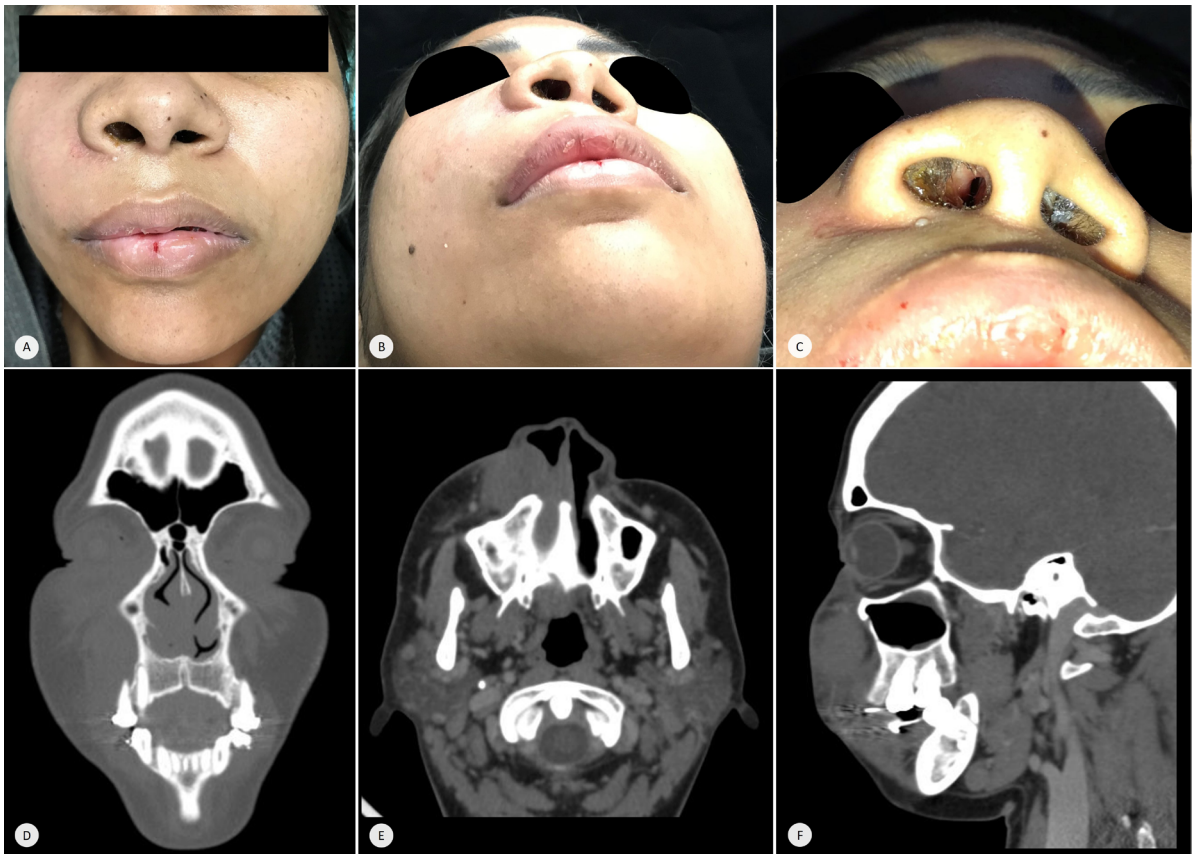

Figure 1. Clinical features and contrast-enhanced computed tomography (CT) of the face. **(A)** Frontal view showing facial swelling predominantly affecting the right middle third of the face. **(B)** Noticeable facial asymmetry due to increased soft tissue volume, leading to elevation of the right nasal wing. **(C)** Intranasal mass partially obstructing the right nostril. **(D)** Coronal CT image demonstrating an area of increased soft tissue density within the right nasal cavity. **(E)** Axial CT section revealing skin and subcutaneous tissue thickening with contrast enhancement near the right nasolabial fold, without evidence of liquefaction. **(F)** Sagittal CT view showing thickening of the sinus membrane. No signs of osteolysis were observed.

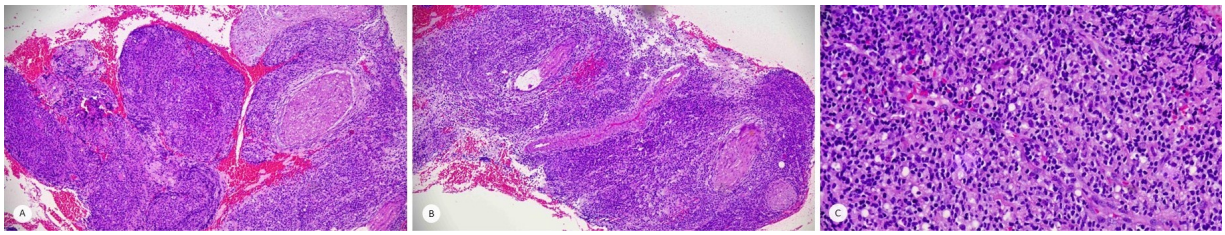

Figure 2. Histopathological features. (**A, B**) Hematoxylin and eosin (HE) staining demonstrating a diffuse lymphoid infiltrate with a characteristic angiocentric growth pattern (A: 200×, B: 200×). **(C)** Higher magnification (HE, 400×) highlighting small to medium-sized neoplastic cells with irregular nuclei and moderately pale cytoplasm.

Following diagnosis, the patient was referred to a hemato-oncology service for further management. Disease staging revealed no evidence of additional lymphadenopathy, and no neoplastic cells were identified in the bone marrow biopsy specimen. Nasofibroscopy findings were unremarkable. According to the Lugano Staging System, the disease was classified as stage IE, and the patient was categorized as low risk based on the Prognostic Index of Natural Killer Cell Lymphoma with EBV.

The patient underwent five cycles of combined chemotherapy using the DeVIC regimen (dexamethasone, etoposide, ifosfamide, and carboplatin) in conjunction with radiotherapy, administered at a total dose of 50 Gy in 25 fractions. Upon completion of treatment, clinical examination revealed complete resolution of facial swelling, with no residual abnormalities in the paranasal region or right nostril. A post-treatment positron emission tomography-computed tomography (PET/CT) scan demonstrated only laminar

thickening of the maxillary sinus mucosa. Additionally, subcentimetric cervical lymph nodes were observed without abnormal metabolic activity, and no signs of metabolically active metastatic lesions were detected (Figure 4).

At the nine-month follow-up, no evidence of recurrence was noted. The patient continues to undergo regular clinical and imaging surveillance under the care of the hemato-oncology team.

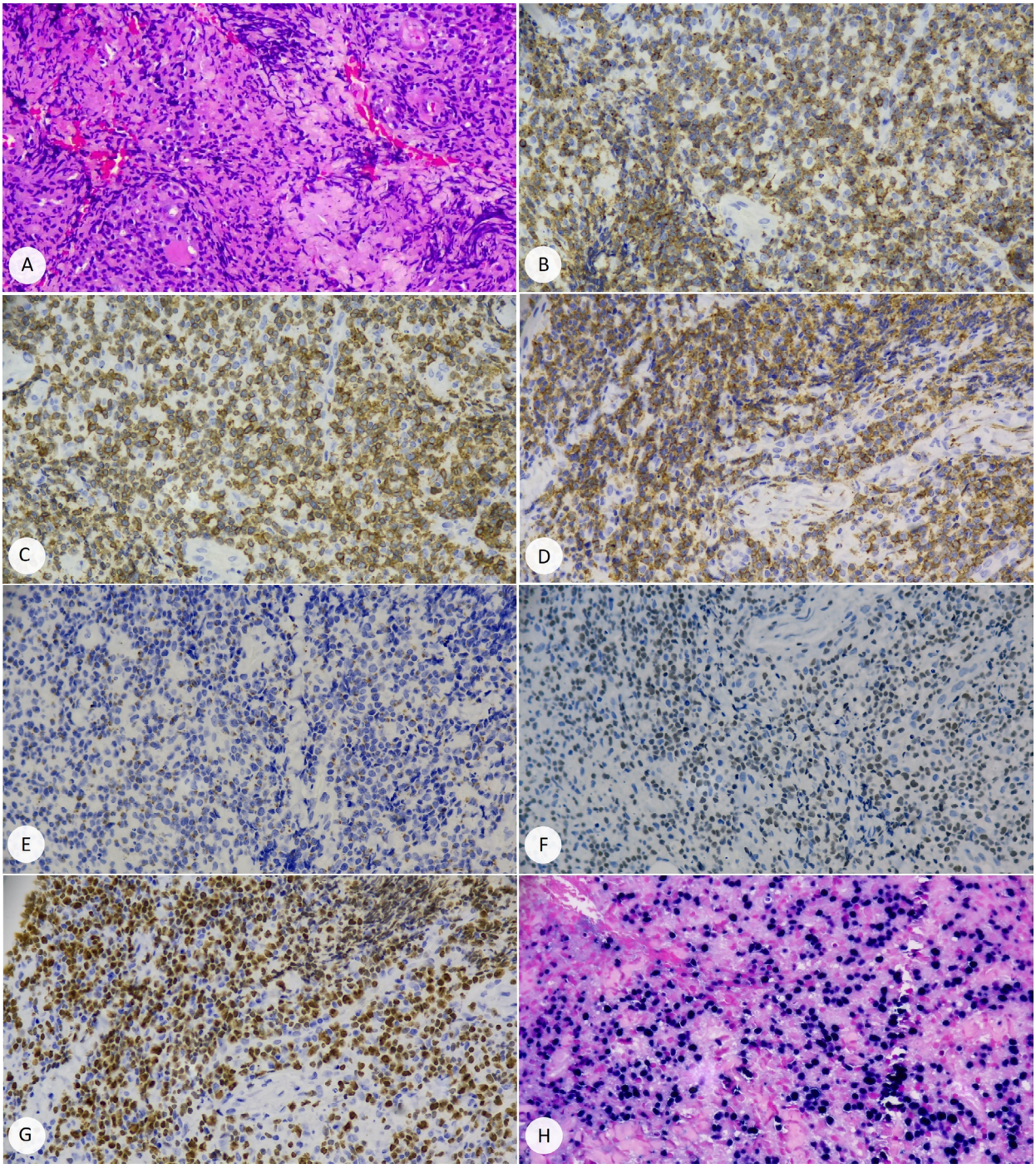

Figure 3. Immunohistochemical and in situ hybridization analyses. **(A)** Hematoxylin and eosin staining (400×). **(B–F)** Immunohistochemical staining showing strong positivity of the neoplastic cells for CD2 (B, 400×), CD3 (C, 400×), CD56 (D, 400×), TIA-1 (E, 400×), and GATA3 (F, 400×). **(G)** High proliferative activity demonstrated by the Ki-67 index, estimated at approximately 70–80% (Ki-67, 400×). **(H)** In situ hybridization for Epstein-Barr virus (EBV) showing strong nuclear positivity for EBER (400×).

DISCUSSION

Extranodal NK/T-cell lymphoma (ENKTL) is a rare and aggressive malignancy associated with a poor prognosis, particularly when diagnosed at an advanced stage[13,14]. This neoplasm predominantly affects male patients in their fourth and fifth decades of life[1,15]. However, cases in younger individuals and females have been reported, as observed in the present case of a 33-year-old woman. Although uncommon in this demographic, ENKTL should not be excluded from the differential diagnosis of unexplained facial swellings, particularly in regions with a high prevalence of Epstein-Barr virus (EBV) infection.

Table 1. Immunohistochemical panel.

Antibody	Clone	Result
CD2	AB75	Positive (diffuse)
Pan-T - CD3	Rabbit Policlonal	Positive (difuse)
CD4	4B12	Negative
CD5	4C7	Negative
CD7	CBC.37	Negative
CD8	C8/144B	Negative
CD10	56C6	Negative
Pan-B – CD20	L26	Negative
CD25	4C9	Negative
Anti-Ki 1 – CD30	Ber-H2	Negative
CD56	123C3	Positive (diffuse)
CD68	KP1	Positive (histiocytes)
CD138	MI15	Negative
FOXP3	EP340	Negative
GATA-3	L50-823	Positive (diffuse)
Granzima B	11F1	Negative
Ki67	MIB-1	Positive (70-80%)
PD-1	NAT105	Negative
S100	Rabbit Policlonal	Negative
TIA-1	TIA-1	Positive (diffuse)

ENKTL typically manifests as an erythematous facial swelling in the midline, frequently involving the nasal cavity, lips, and cheeks[4,6]. Common early symptoms include nasal obstruction and epistaxis, which may be mistaken for benign inflammatory conditions. As the disease progresses, lesions evolve into ulcerated, necrotic masses, leading to significant midfacial destruction. Advanced cases often present with intraoral manifestations, including palatal ulceration and oronasal fistulas[5,16].

The present case was notable for its atypical presentation, as the patient exhibited facial swelling covered by intact, non-ulcerated skin, with no evident necrosis or bone destruction. These findings underscore the importance of thorough clinical evaluation, as even subtle or indolent presentations may indicate early-stage ENKTL. Early detection is crucial, as delayed diagnosis often results in disease progression, increasing morbidity and reducing survival rates. According to Susarla et al.[17], ENKTL should always be considered among the differential diagnoses in cases of unexplained facial swelling, particularly when there is no response to conventional treatment.

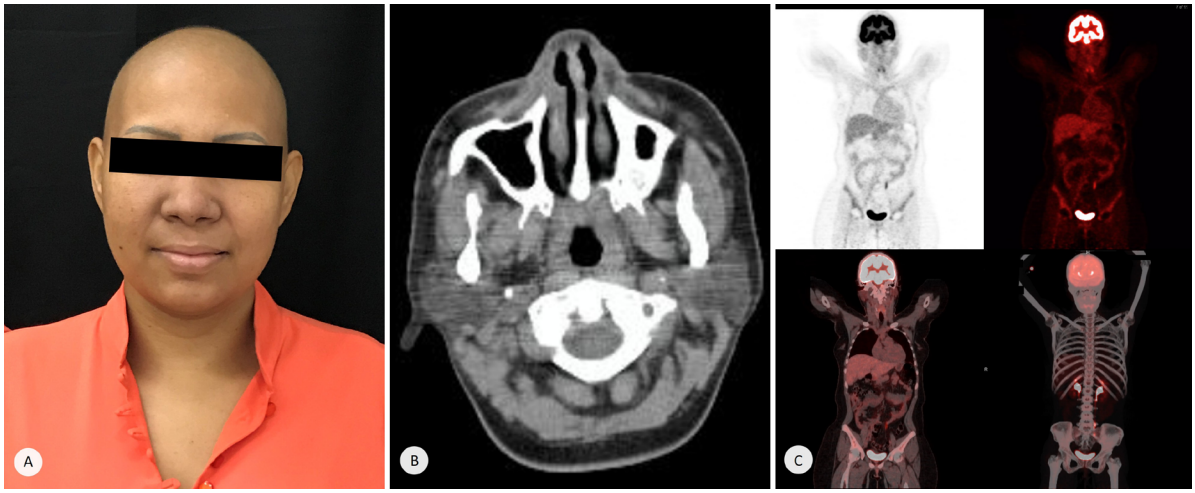

Figure 4. Post-treatment clinical, CT, and PET-CT findings. **(A)** Frontal view showing a reduction in facial asymmetry following treatment. **(B)** Axial CT image demonstrating regression of the previously observed hypodense lesion in the right nasolabial fold and nasal cavity. **(C)** Positron emission tomography-computed tomography (PET-CT) scan showing no evidence of increased metabolic activity, indicating the absence of residual or recurrent disease.

A review of previously reported cases of ENKTL presenting as nondestructive facial swellings was conducted. The present case was not included among the previously published reports summarized in Table 2. Based on clinical features, 15 comparable cases were identified[12,17-30]. The mean age at diagnosis was 40.06 years (range: 4–69 years), with a male-to-female ratio of 1.14:1. Symptom duration varied widely, from 3 to 96 weeks (mean: 17.4 weeks), though two studies[24,26] did not provide this information.

In the present case, diagnosis was established within 30 days of symptom onset, significantly earlier than the average reported in the literature. Similar to our patient, three individuals (20%)[22,24,27] experienced unexplained weight loss, and five (33.3%)[12,21,22,24,27] reported fever. Notably, pain was absent in our case, aligning with literature findings, where only four patients (26.6%)[18,19,22,23] reported pain as a symptom. Nasal obstruction was a frequent complaint, observed in six cases (40%)[12,18,24,26,27,30], while nasal discharge or epistaxis was reported in five cases (33.3%)[12,18,26-28]. Lymphadenopathy was identified in two cases (13.33%)[21,22], and additional symptoms included headache, visual disturbances, splenomegaly, odynophagia, dysphagia, dysphonia, and facial nerve involvement.

Despite the initial clinical suspicion of a benign condition, no complementary imaging studies had been performed prior to referral in this case. Computed tomography (CT) and magnetic resonance imaging (MRI) play a crucial role in the early evaluation of ENKTL, providing valuable insights into tumor extent, soft tissue involvement, and lymph node status[6,15]. In our case, CT imaging not only ruled out alternative diagnoses but also identified subtle bone involvement, a finding that contrasts with the majority of cases in the literature.

Histopathological diagnosis of ENKTL presents significant challenges, particularly due to the extensive coagulative necrosis that characterizes advanced lesions. This often necessitates multiple biopsies to establish a definitive diagnosis[1]. A hallmark feature of ENKTL is its angiodestructive growth pattern, wherein tumor cells induce fibrinoid necrosis of vascular walls[5,6,14].

Microscopically, ENKTL exhibits a heterogeneous population of atypical lymphoid cells with irregular nuclei, interspersed with inflammatory cells and frequent mitotic figures[6,23]. Agrawal et al.[5] analyzed 11 cases of ENKTL and reported necrosis in 100% of cases, with angiocentric and angioinvasive features observed in 63.3% of cases. These findings highlight the diagnostic significance of these histomorphological characteristics. In our case, the initial histological examination was inconclusive, necessitating additional immunohistochemical and molecular studies for diagnostic confirmation.

The immunophenotypic profile of ENKTL is characterized by CD45(+bright), CD2(+), surface CD3(-), cytoplasmic CD3ε(+), CD56(+bright), and T-cell receptor (TCR)(-) expression[5,14,23]. Additionally, cytotoxic markers, such as granzyme B, intracellular T-cell antigen 1 (TIA-1), and perforin, are typically positive[23]. CD30 expression is variable, predominantly observed in larger malignant cells[14]. Rare cases exhibit a T-cell phenotype with CD4, CD8, and/or CD7 positivity[5].

In our case, the tumor cells demonstrated positivity for CD2, CD3, CD56, GATA3, and TIA-1, with a high proliferative index (Ki-67: 70–80%). Furthermore, in situ hybridization for Epstein-Barr virus (EBV/EBER) showed diffuse positivity within the neoplastic cells. The presence of EBV in tumor cells is considered a key diagnostic criterion and has prognostic significance[5,14,31].

Standard anthracycline-based chemotherapy regimens, commonly used for other lymphomas, are ineffective in ENKTL due to high P-glycoprotein expression, which confers resistance to anthracyclines. Recent advancements in radiotherapy techniques and L-asparaginase-based chemotherapy have significantly improved treatment outcomes[9,32]. Among chemotherapeutic agents, L-asparaginase is considered the cornerstone of ENKTL treatment, particularly in advanced disease[14].

The current standard treatment for limited-stage ENKTL, primarily involving the nasal and paranasal regions, consists of radiotherapy combined with chemotherapy regimens incorporating platinum or L-asparaginase[14,32]. High-dose radiotherapy (>50 Gy) has been associated with improved local disease control and survival outcomes[14,16]. A regimen combining radiotherapy (50 Gy) with reduced-dose DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) chemotherapy has demonstrated a complete response (CR) rate of 77% and an overall response rate of 81%[32].

Our patient was treated with a carboplatin-based DeVIC regimen in combination with radiotherapy (50 Gy in 25 fractions), achieving complete clinical remission. This outcome aligns with literature findings, supporting the efficacy of combined chemoradiotherapy in treating localized ENKTL. The estimated five-year overall survival rate for ENKTL ranges between 40%

Table 2. Review of cases of ENKTL presenting as swellings on the face.

Study	Sex	Age	Evolution time	Clinical features	Treatment	Outcomes
Huang et al.[18]	M	22	12 weeks	Facial swelling; periorbital cellulitis; swelling of the nasal mucosa with obstruction and bleeding; foul-smelling mushroom-shaped mass on the hard palate; pain; sore throat	CT	Death 7 months later, after receiving five courses of CT
Paik et al.[19]	M	46	12 weeks	Periorbital edema; severe refractory sinusitis; facial tingling; pain and facial numbness; visual field loss; decreased hearing; necrotic appearing turbinates; purulence and fibrinous debris in the naris	CT	Death
Seishima et al.[20]	F	60	96 weeks	Recurrent swelling of the upper lip, skin, and cheeks; induration and erythematous tumors on the chin, bilateral cheeks, right upper arm, and bilateral axillae	CT	Death 8 months after the CT
Susarla et al.[17]	F	64	8 weeks	Midface swelling, with erythema; nerve damage; focal necrosis in the maxillary vestibule without exudate or bleeding; no saliva drainage from the Stensen's duct, induration of the mucosa.	CT + RT	No recurrence for 3 years
Miles et al.[21]	M	4	36 weeks	Swelling, cervical lymphadenopathy and fever.	CT	Death
Wood et al.[22]	M	30	8 weeks	Hemifacial edema, decreased vision; fever; weight loss; painful swallowing and headaches; preauricular lymphadenopathy, superficial ulceration in the palate	CT + RT + Allo-SCT	Complete vision loss; Positive response to therapy
Sokołowska-Wojdyło et al.[23]	F	49	3 weeks	Painful swelling of the cheek and lower eyelid; indurated elevation of the oral vestibule; gross swelling of the maxillary alveolar processes involving the hard palate; inflamed oral mucosa; paresthesia of the nerve V2; annular inflammatory erythematous plaques on the trunk and extremities.	NI	Death OD 6 weeks after the initial office presentation
Pontes et al.[24]	F	41	NI	Erythematous facial asymmetry with elevation of the nasal wing and inferior eyelid; nasal obstruction; mild fever; weight loss; ulceration affecting the gingiva and buccal mucosa; alveolar bone loss exposing the roots teeth	CT	Death 3 months after start of chemotherapy
Coha et al.[12]	M	41	24 weeks	Swelling of the nose, paranasal region, and cheek; nasal obstruction; postnasal secretion; dysphonia; intermittent fever;	CT	Death 2 months after the initial diagnosis
Devi et al.[25]	F	25	8 weeks	Edema in right side of the nose and cheek, involving the infraorbital region and lower lid.	CT	Positive response to therapy
Harisankar[26]	F	26	NI	Swelling of the nasal skin and right lower eyelid; nasal obstruction; bloody discharge	CT	NI
Tan et al.[27]	M	55	4 weeks	Facial swelling; purulent discharge and epistaxis from the nostril; weight loss; fever; exophytic ulcerated mass on the nostril causing obliteration of the nasal cavity.	CT	Complete remission after 8 months
Schwarz et al.[28]	F	23	6 weeks	Edema, erythema, tenderness, warmth of the nares, periorbital area, and purulent nasal drainage.	CT	Positive response to therapy
Tan et al.[29]	M	69	36 weeks	Midfacial erythema and edema involving the periorbital and maxillary regions; necrotic eschar.	CT + RT	Positive response to therapy
Guedes et al.[30]	M	46	8 weeks	Nasal obstruction; dysphagia; dysphonia; facial edema; enlarged cervical lymph nodes; erosive lesion on the nasal region; perinasal crusts and perforation of the nasal septum	NI	Death 30 days after admission

NI: not informed, CT: Chemotherapy, RT: Radiotherapy, Allo-SCT: Allogeneic haematopoietic stem cell transplantation.

and 50%, with prognosis being heavily dependent on the stage at diagnosis[33]. Delayed diagnosis increases the risk of locoregional spread, extensive facial destruction, and severe aesthetic impairment, significantly impacting patients' quality of life[5,11,33].

CONCLUSION

ENKTL should be considered in the differential diagnosis of unexplained facial swelling, particularly in cases refractory to initial treatment. Complementary imaging, histopathological, and immunohistochemical evaluations are essential for accurate diagnosis, facilitating early intervention and improved prognosis. This case underscores the importance of early detection, as timely diagnosis enables effective treatment, limits disease progression, and enhances patient outcomes and quality of life.

AUTHORS' CONTRIBUTIONS

LTMQC: conceptualization, data curation, formal analysis, investigation, writing – original draft, writing – review & editing. AB: conceptualization, investigation. HKFB: data curation, formal analysis. LLS: data curation, writing – review & editing. IJCN: data curation, formal analysis. PAV: writing – review & editing. MAL: conceptualization, writing – review & editing. HMP: investigation. YSR: investigation. EZ: conceptualization, investigation, project administration, writing – review & editing.

CONFLICT OF INTEREST STATEMENT

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Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: The study was conducted in accordance with the ethical principles established by the Institutional Research Ethics Committee, ensuring compliance with current ethical and scientific guidelines. Written informed consent was obtained from the patient.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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