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First manifestation of oral malignant lymphoma mimicking periodontal pathology: a case report

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ABSTRACT

Background: The oral cavity is not only a site where dental and periodontal diseases develop, but also the site of neoplastic lesions. In such cases, the variety of morphological appearances can make clinical diagnosis challenging. This article aims to highlight how early diagnosis led to the detection of a rare extranodal lymphoma presenting as isolated gingival swelling, enabling timely oncologic treatment, and long-term disease remission.
Case description: A healthy, adult, patient presented with a large swelling of the periodontal tissues of lower right second molar. The lesion showed no clear correlation with the dental status of the area. It was opted for a biopsy of the enlarged tissue, avoiding periodontal treatment or extraction of the molar. Blood tests and medical diagnostic imaging were requested. Histopathological and imaging analysis revealed systemic spread, and a hypermetabolic focus in the right retromolar region corresponding to the oral lesion. This allowed for a diagnosis of extranodal non-Hodgkin lymphoma.
Timely chemotherapy achieved remission and stabilization of the disease. The oral swelling disappeared spontaneously within months. Seven years after therapy, the patient is in good general health with no recurrence of lymphoma. Periodic examinations show an optimal dento-periodontal condition at the site of the molar previously affected by the neoplasm.
Conclusions: Localized pathologic changes of periodontal tissues enabled early detection of a malignant extranodal non-Hodgkin lymphoma, ultimately leading to a timely therapy, successful outcome and patient survival.
Clinical significance: Early identification of atypical periodontal tissue alterations can facilitate the timely diagnosis of systemic disorders and malignancies affecting the periodontium. Accurate diagnosis enables cause-based therapy and improves the patient's prognosis.

1. Introduction

Numerous neoplasms and malformations can manifest in the oral cavity, affecting both soft and hard tissues in the form of benign or malignant tumors. These lesions may originate from oral tissues (primary lesions) or represent secondary manifestations of neoplasms from other organs or anatomical regions. While benign tumors are relatively common in clinical practice, malignant tumors are rare. Due to the significant etiological heterogeneity and the clinical resemblance among many of these lesions, accurate diagnosis is often challenging and requires careful correlation between clinical presentation and histopathological findings [1].

Among the non-primary malignant neoplasms of the oral cavity, lymphomas represent systemic diseases of considerable interest, particularly because of their subtle and complex clinical presentation [2,3]. Traditionally, lymphomas have been classified into two major categories based on histopathological findings such as the presence of binucleated or multinucleated Reed-Sternberg cells, characteristic of Hodgkin lymphoma (HL), and their absence in all other lymphomas, which are grouped under the more heterogeneous category of non-Hodgkin lymphomas (NHL) [4,5].

Hodgkin lymphoma typically affects young adult male patients and presents with painless lymphadenopathy in the lateral cervical, inguinal, or axillary regions, often accompanied by low-grade fever,

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sweating, and pruritus. Histopathological diagnosis is confirmed by the presence of Reed-Sternberg cells, with subtypes including lymphocyte-predominant variants (few Reed-Sternberg cells) or mixed cellularity, which are strongly associated with Epstein-Barr virus (EBV) positivity [6–8].

Non-Hodgkin lymphomas (NHL) represent a diverse group of clinicopathological neoplasms. In the head and neck region, they frequently affect lateral cervical lymph nodes. The lymphadenopathies typically grow more slowly and occur in older patients than in Hodgkin lymphoma. In approximately 30% of cases, NHL can occur in extranodal sites, including the oral mucosa, nasopharynx, maxillary bones, and salivary glands. Histopathologically, the hallmark of NHL is the absence of Reed-Sternberg cells. Most NHLs are derived from B-cell precursors, while a smaller proportion arise from T-cell precursors or, more rarely, peripheral NK cells. In the oral cavity, NHL usually originates from B cells and presents as a diffuse type. T-cell–origin NHL (extranodal NK/T-cell lymphoma) is extremely rare [9–11].

Recognizing the growing relevance of genetic and molecular data, the World Health Organization's 5th Edition of the Classification of Haematolymphoid Tumors (2022) reorganized the classification of lymphomas into three major categories [12–14]: B-cell lymphoid proliferations and lymphomas; T-cell and NK-cell lymphoid proliferations and lymphomas; and Stroma-derived neoplasms of lymphoid tissues.

Regarding the spread and invasiveness of lymphomas, the 11th International Conference on Malignant Lymphomas revised the staging criteria for lymphomas, distinguishing between progressive forms [15–17]: Limited stage (Stage I-E and Stage II-E); Advanced stage (Stage III and Stage IV), the absence or presence of systemic symptoms (fever/night sweats/unexplained weight loss).

Oral localization of lymphomas generally involves the gingiva, hard and soft palate, buccal mucosa, and tongue, and varies according to the predominant histological subtype [18]. Intraoral appearance is highly heterogeneous, ranging from ulcerated [19] to exophytic [20] lesions, which adds complexity to the diagnostic process.

Taking these considerations into account, a patient presented for dental examination due to a rapidly developing swelling in the periodontal tissues in the retromolar region of the lower right second molar. The differential diagnosis included exophytic lesions of the periodontium and oral soft tissues, such as periodontal abscesses; endo-periodontal lesions; traumatic irritation fibroma; drug-induced hyperplasia; reactive lesions including peripheral giant cell granuloma, pyogenic granuloma, and peripheral ossifying fibroma; pigmented lesions such as melanoma; and neoplastic lesions.

A comprehensive medical history and diagnostic assessment, combined with a biopsy and imaging (CT scan, PET), revealed the presence of a malignant neoplasm. The purpose of this article is to highlight how an early and thorough diagnosis enabled the identification by a dentist of a rare case of extranodal malignant lymphoma with periodontal localization as the first clinical manifestation of an otherwise asymptomatic systemic disease. Timely oncologic treatment led to disease stabilization, full patient recovery, and the complete spontaneous resolution of the periodontal lesion, maintained over a 7-year follow-up period.

2. Case Description

This case report was written in adherence to the CARE guidelines [21].

2.1. June 2018

A 59-year-old healthy, non-smoking woman was treated for acute pulpitis in the maxillary right second molar (tooth: 1.7, #2) at the Endodontics Outpatient Clinic of the AOU Careggi Odontostomatology Operating Unit in Florence.

Two weeks later, the patient returned to the same department reporting a sudden onset of painless gingival swelling in the region of the mandibular right second molar (tooth: 4.7, #31). She had no systemic symptoms and confirmed being in good general health.

2.1.1. Clinical examination

No cutaneous erythema, facial swelling, or asymmetry was observed during the extraoral examination. However, palpation revealed a solid, painless, mobile nodule in the right submandibular angle, not attached to superficial or deep tissues. The nodule was isolated, and no other palpable lymphadenopathy was noted.

Intraorally, a sessile swelling was observed extending distally and lingually from the gingiva and alveolar mucosa of tooth 4.7 (#31). The lesion (approximately 13 mm × 5 mm) appeared erythematous, soft, non-ulcerated, and non-suppurative, with an irregular surface and without tenderness (Fig. 1A). The patient's dental history did not reveal any similar prior occurrences. The molar, covered by a metal crown, was the distal abutment of a fixed dental prosthesis anchored on the second premolar and second molar of the lower right quadrant. The tooth exhibited no mobility and responded positively to vitality testing.

A gentle periodontal probing was performed. Probing depths were shallow (2 to 3mm) on the mesial and buccal surfaces, while a slightly deeper probing up to 5 mm was detected distally and lingually, with moderate bleeding on probing and plaque accumulation. No other pathological sites were identified with probing depth being up to 3mm throughout the mouth.

2.1.2. Radiographic assessment

A periapical radiograph of tooth 4.7 (#31) showed moderate horizontal bone loss distally, and a shallow angular defect mesially.

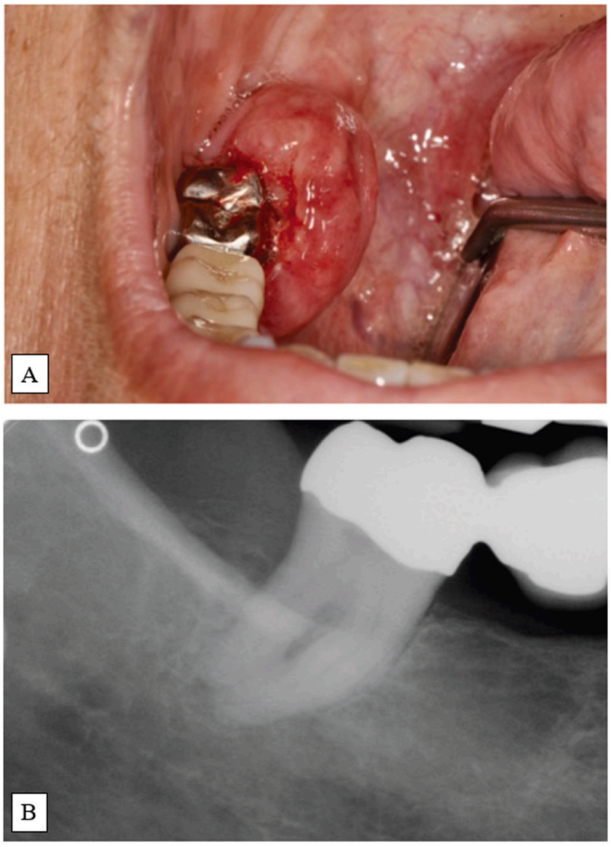


Fig. 1. Initial clinical and radiographic examination (June 2018). A) Intraoral clinical examination revealed a sessile newly formed tissue extending from the distal mucosa of the mandibular right second molar to its lingual side. The lesion was soft in consistency, non-tender, and measured ≥10 mm in length. B) Intraoral periapical radiograph of the affected area.

Furcation involvement was noted without root resorption or secondary caries (Fig. 1B).

2.1.3. Periodontal diagnosis and biopsy

Based on clinical findings and radiographic evaluation, the operator (RP) ruled out plaque-induced periodontitis or odontogenic origin of the lesion. Periodontal suspicion was of Systemic Disorders of Periodontal Tissues Independent of Periodontitis [22,23]. The key discriminating features were the rapid onset of the swelling, absence of pain, and lack of correlation with periodontal findings. Therefore, no surgical corrective periodontal treatment was performed and only an incisional biopsy was planned.

Following administration of 1.8 mL of 2% articaine with epinephrine 1:100,000, the biopsy was performed by an experienced surgeon (FC) using a Bard-Parker #15 scalpel. Two converging full-thickness oblique incisions were made in the upper area of the lesion to obtain an adequate tissue sample, while minimizing disruption to surrounding structures. The biopsy included both superficial and deeper tissue components. The site was closed with chromic gut 4-0 sutures. The specimen was immediately placed in a formalin-based fixative solution (KLESSIDRA 30 – Bio-Optica Milano S.p.A., Italy) and submitted to the Hematopathology, Histopathology, and Molecular Diagnostics Unit, Diagnostic Services Department, AOU Careggi, Florence. Hemostasis was achieved before dismissing the patient, who was immediately referred to her primary care physician for further systemic investigation, without waiting for the formal histopathological report.

2.2. July 2018

Blood tests revealed abnormalities in platelet count, alkaline phosphatase, alpha-globulin, ESR, fibrinogen, and LDH, suggesting an active pathological process with possible systemic involvement.

Whole-body CT scan showed multiple nodules in the lungs (all lobes), liver (right lobe) (Fig. 2A), bones (ribs, sternum, vertebrae, sacrum, ilium, and pubic bone), and lymphadenopathy in the lateral cervical region (more pronounced on the right), paratracheal (bilaterally), and below the tracheal bifurcation.

Whole-body PET-CT (FDG-18) detected hypermetabolic lymphomatous activity in the head and neck region, specifically the posterior nasopharyngeal wall, bilateral posterior neck, right parapharyngeal and right lateral cervical areas. A prominent hypermetabolic focus was observed in the right retromolar area, corresponding to the site of the oral lesion biopsied (Fig. 2B). Additional hypermetabolic foci were noted in the hilar-mediastinal region, pulmonary and hepatic parenchyma, and throughout the skeleton (cranial vault, sternum, scapulae, ribs, spine, pelvis, femurs).

Liver Biopsy: Due to a nodular lesion in the right liver lobe seen on CT, an ultrasound-guided fine-needle biopsy was performed, confirming the histopathological diagnosis of ALK-positive Anaplastic Large Cell Lymphoma (ALK + ALCL), as per the Radiodiagnostics Department, AOU Careggi.

The oral lesion histopathology (Fig. 3) allowed the diagnosis of a rare extranodal Anaplastic Large Cell Lymphoma (ALK-positive, T-cell type) in accordance with WHO classification criteria [5,12–14].

Based on CT, PET, and liver biopsy results, the disease was staged as Stage IV-A advanced lymphoma without systemic symptoms [16]. Detailed histopathological findings are described in Fig. 3.

2.2.1. Chemotherapy and oral management

The patient began systemic chemotherapy in July 2018 with CHOEP regimen (cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone), completing six cycles by December 2018 at the Hematology Unit, Oncology Department, AOU Careggi. Concurrently, a rigorous professional oral hygiene protocol was implemented to maintain optimal plaque control.

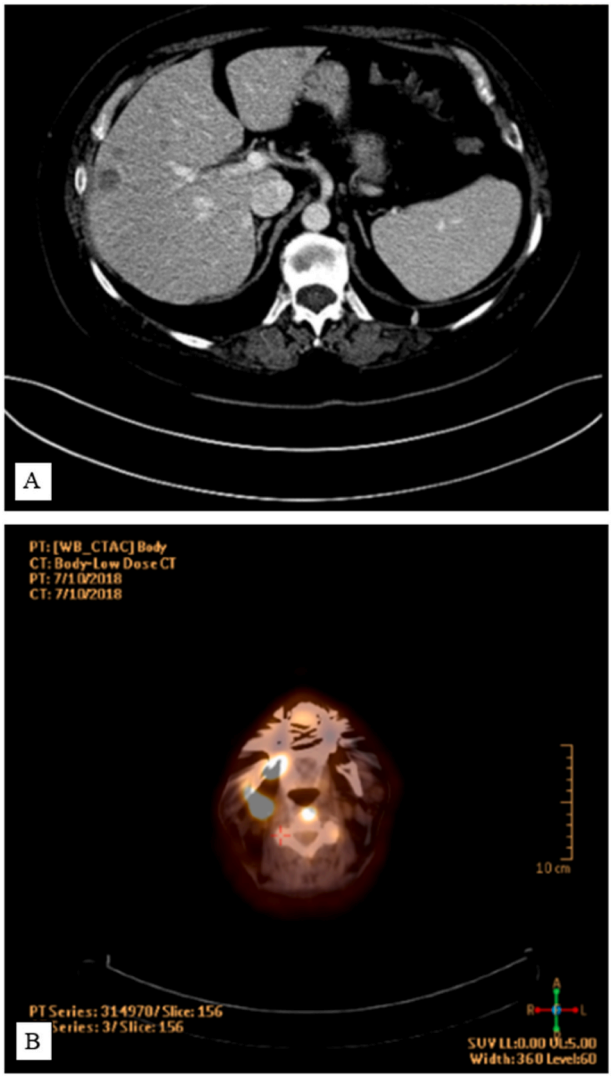


Fig. 2. Medical imaging (July 2018). A) CT scan of the liver shows multiple metastatic lesions, predominantly in the right lobe. The largest lesion, located just beneath the ninth rib, is superficial and slightly over 2 cm in diameter. B) FDG-PET scan reveals a focus of intense hypermetabolic activity in the head and neck region, corresponding to the soft tissues of the right retromolar area, likely matching the intraoral swelling.

2.3. December 2018

After six months, follow-up CT imaging showed resolution of lymphadenopathy and disappearance of hepatic hypodense lesions (Fig. 4A). A follow-up PET scan showed complete resolution of the hypermetabolic focus in the right retromolar region corresponding to the original oral lesion (Fig. 4B).

2.4. March 2019

Three months post-chemotherapy, an oral examination revealed complete spontaneous resolution of the periodontal lesion. A gingival recession was observed on the lingual aspect of tooth 4.7 (#31), associated with submarginal caries beneath the crown margin (Fig. 5A). Periodontal charting confirmed a healthy periodontium, with shallow probing depths (PD < 3 mm), as well as full mouth plaque and bleeding scores of 22% and 17%, respectively. A new prosthetic rehabilitation was planned and executed.

A periapical radiograph confirmed mesial and distal carious lesions.

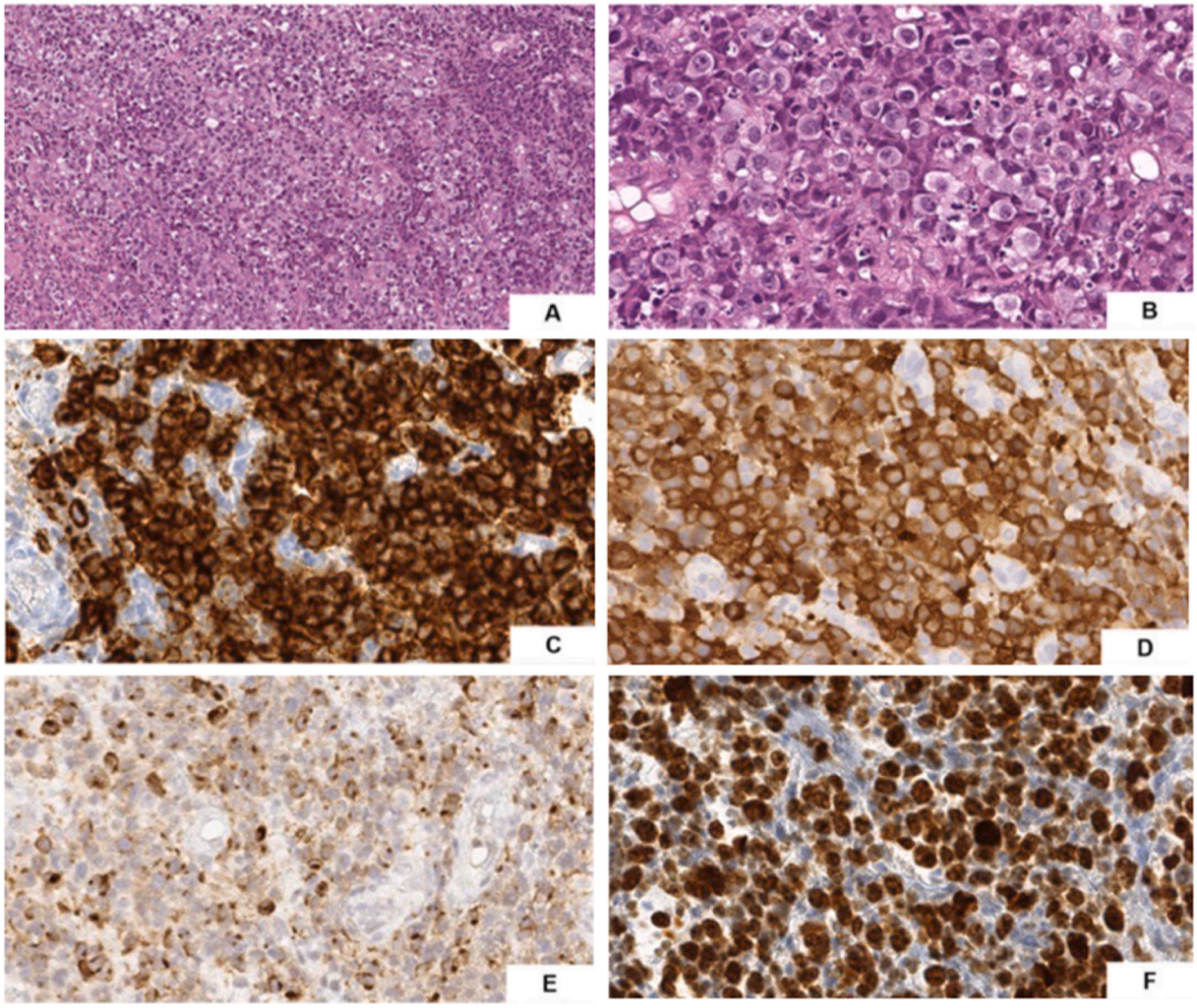


Fig. 3. Histopathology. The predominant tumor population consisted of large cells with abundant clear cytoplasm and rounded nuclei, admixed with more pleomorphic elements, occasionally exhibiting the characteristic "hallmark cell" morphology. A) Hematoxylin and eosin (H&E), original magnification × 10. B) H&E, original magnification × 40. The neoplastic cells showed strong immunoreactivity for CD30 (C, × 40), ALK (D, × 40), and Granzyme B (E, × 40). The Ki-67 proliferation index was estimated at 90% (F, × 40).

No bone loss had occurred during chemotherapy. Tooth 4.7 (#31) was subsequently treated endodontically (Fig. 5B).

2.5. March 2025

Seven years later, a comprehensive oral evaluation was performed at the Endodontics Outpatient Clinic, AOU Careggi. The previous lesion around tooth 4.7 (#31) had completely resolved. The gingival margin and alveolar mucosa appeared clinically healthy (Fig. 6A and B), and periodontal probing showed physiological sulcus depths within 3mm. A periapical radiograph revealed stable endodontic and periodontal conditions, and the prosthetic restoration remained intact (Fig. 6C). The patient expressed heartfelt gratitude for the attentive dental care, and provided consent for the use of the collected data in scientific publication.

3. Discussion

The occurrence of neoplastic lesions in the oral cavity places significant medical, ethical, and legal responsibility on oral professionals.

Oral professionals commonly encounter diseases of odontostomatological origin in their routine practice, and diagnostic or therapeutic errors typically result in localized, often reparable, oro-dental damages. In contrast, the failure to recognize or appropriately assess a neoplastic lesion in the oral cavity can lead to serious life-threatening consequences for the patient.

Among malignant neoplasms presenting in the oral cavity, lymphomas are systemic pathologies that pose a diagnostic challenge; particularly non-Hodgkin's lymphomas (NHL) in their extranodal forms. Oral involvement is rare, although lymphomas represent the second most common oral malignancy after oral squamous cell carcinoma. They account for 2.2% of all malignant tumors of the head and neck, 3.5% of intraoral malignant tumors, 5% of salivary gland malignancies, and 2.5% of all NHL cases [24]. They also represent approximately 3% of all lymphomas in the general population. The most commonly affected sites include the gingiva, palate, maxilla, mandible, tongue, buccal mucosa, vestibule, lips, and floor of the mouth [25–27].

The case presented in this study illustrates the critical importance of considering a neoplastic origin when confronted with an unusual lesion. During a routine oral examination, the operator noted a rapidly developing gingival swelling adjacent to a mandibular molar, despite the absence of periodontal pathology, endodontic pathology and systemic symptoms. This prompted the clinical suspicion of Systemic Disorders of Periodontal Tissues Independent to Periodontitis [22,23]. The clinician performed a biopsy on suspicion of malignancy and referred the patient for further diagnostic evaluation, rather than initiating the workflow for

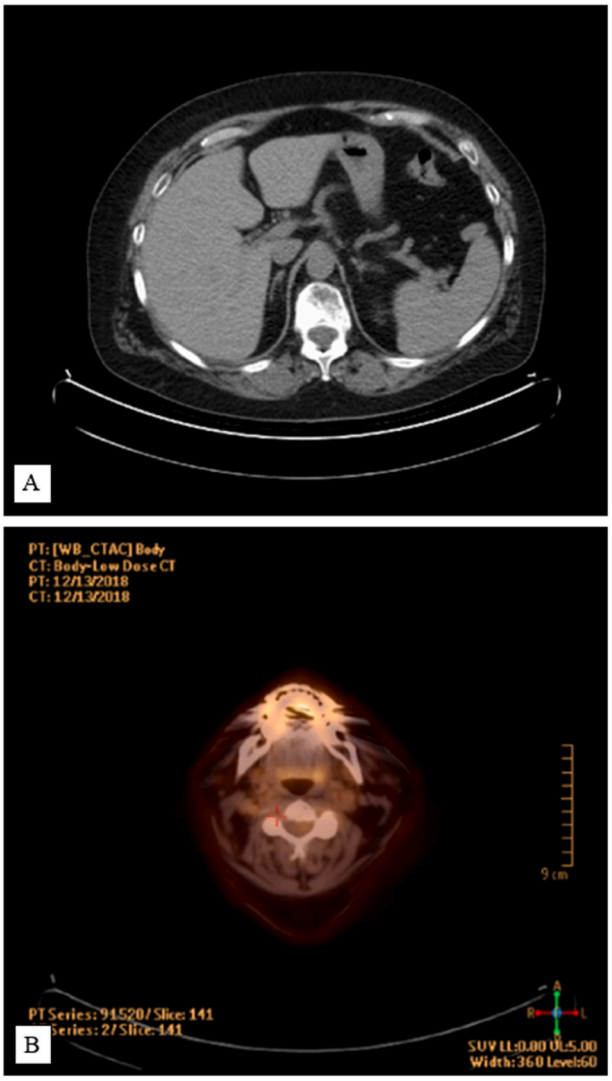


Fig. 4. Medical imaging six months after chemotherapy (December 2018). A) Follow-up CT scan of the liver shows no detectable hypodense lesions previously observed in the initial scan. B) FDG-PET scan demonstrates resolution of the previously noted hypermetabolic focus in the head and neck region, corresponding to the right retromolar soft tissues.

the treatment of plaque-induced periodontal disease. The patient's favorable outcome reflects the benefits of a multidisciplinary approach [28]. Close coordination between dental and medical specialists enabled timely histopathological assessment and prompt systemic therapy. Early interventions without adequate planning or interdisciplinary coordination may inadvertently compromise the diagnostic process, delay accurate identification of malignancy, or increase the risk of local tissue complications. The gingival swelling was the first clinical sign of a rare and aggressive extranodal T-cell non-Hodgkin lymphoma. Although the disease was already at an advanced stage, it remained systemically asymptomatic until oral manifestation. Oral involvement of the ALCL is extremely rare, and to the best of our knowledge, only a few cases have been reported in literature to date [29–31]. For the case described, early detection of the oral lesion was therefore a fortunate event that ultimately enabled life-saving intervention.

This case provides an opportunity to make the important consideration that any unusual lesion that is not clearly related to dental or periodontal disease must be approached with diagnostic vigilance as oral manifestations of neoplasia, either primary or secondary, might be possible. Clinical features and differential diagnosis of exophytic oral

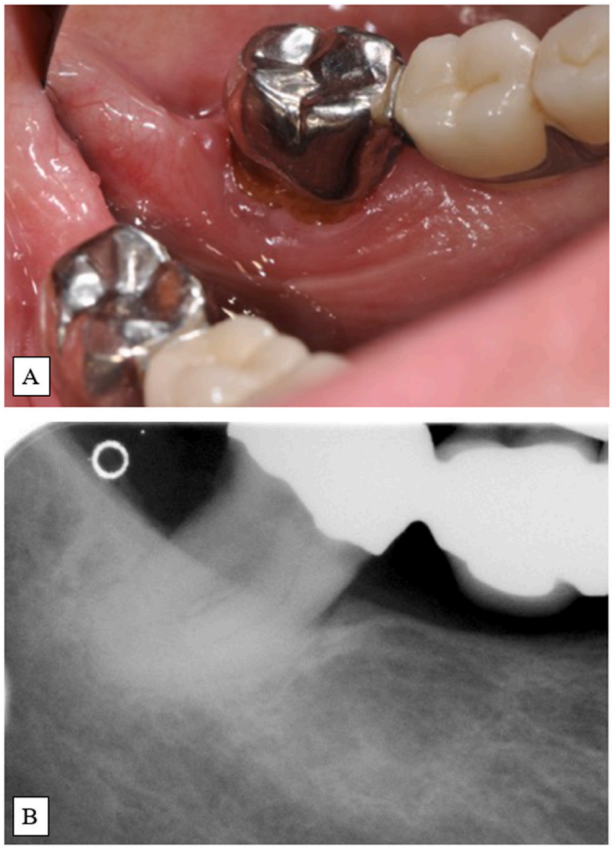


Fig. 5. Clinical and radiographic examination after chemotherapy (March 2019). A) Lingual view of the mandibular right second molar. Gingival recession is noted, along with signs of demineralization on the exposed lingual root surface leading to poor integrity of the crown margin. B) Intraoral periapical radiograph showing distal and mesial carious lesions on the mandibular right second molar.

lesions have been reported in Table 1. Dental and periodontal examination excluded odontogenic pathologies from the differential diagnosis, such as periodontal abscesses and endo-periodontal lesions, due to the vitality of the involved tooth and a periodontal presentation inconsistent with plaque-induced periodontitis. No traumatic source was identified to suggest a traumatic irritation fibroma. Medical history was negative for medications linked to drug-induced hyperplasia. Biopsy was ultimately used to distinguish other reactive lesions, such as peripheral giant cell granuloma, pyogenic granuloma, peripheral ossifying fibroma, and pigmented lesions such as melanoma from the definitive diagnosis of a neoplastic lesion.

Premature surgical interventions without precise diagnosis may constitute erroneous treatment and need to be avoided. Potential risks, such as post-operative hemorrhage or systemic dissemination, are not well documented due to the rarity of such cases. In this patient, the gingival swelling resolved spontaneously during chemotherapy, with full morphological and functional recovery of the affected tissue. No periodontal treatment was performed beyond professional hygiene maintenance.

The localization of the extranodal lymphoma in the gingiva may be explained by the concept of lymphocytic homing. Lymphocytic homing is a regulated, multistep process by which lymphocytes exit the bloodstream and migrate into specific sites of inflammation and immune activation. In this patient, although no carious lesions or evident local irritants were present, a mildly inflamed periodontal pocket was found distal to the molar. Bacterial pathogens and their byproducts, along with the pathogenetic mechanisms of periodontal disease, stimulate chemokine gradients that attract lymphocytes [32], potentially promoting the

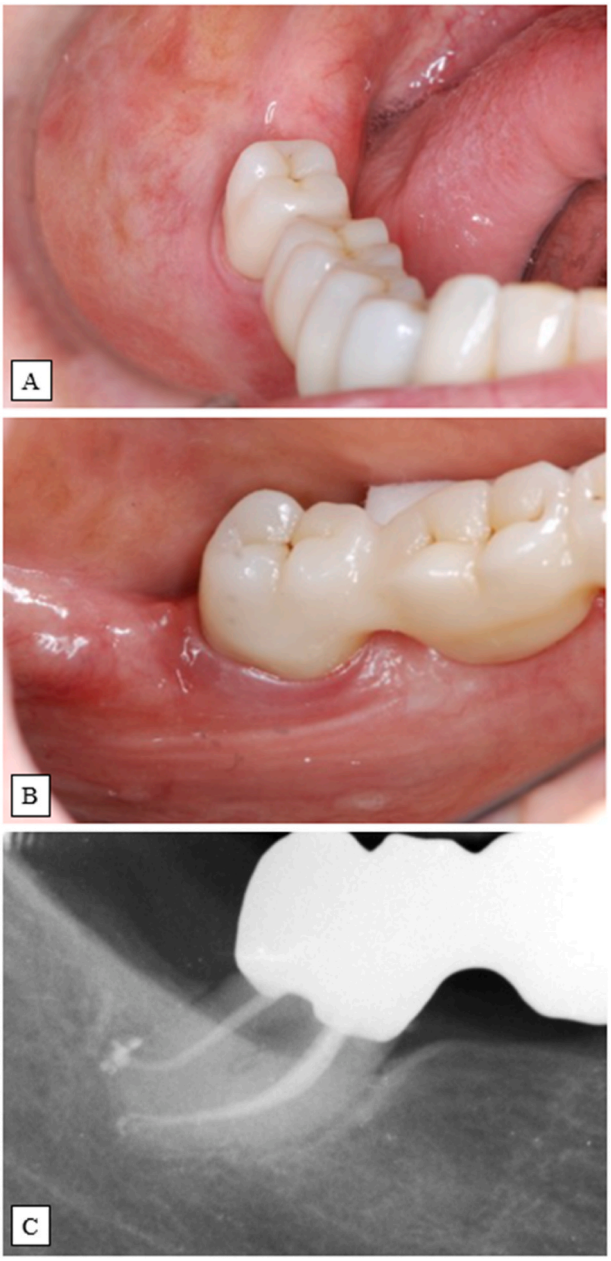


Fig. 6. Clinical and radiographic follow-up seven years after initial diagnosis (March 2025). The patient remains in stable medical condition and maintains good oral health. A) Buccal clinical view. B) Lingual clinical view. C) Intraoral periapical radiograph.

local infiltration and proliferation of malignant cells [33,34]. Therefore, the inflamed periodontal pocket may have acted as a nidus for lymphoma manifestation. Of particular interest, the presence of teeth has been associated with a higher frequency of malignancy localization in periodontal tissues and gingiva, whereas in edentulous patients the tongue represents the most common site [35]. This finding further strengthens the hypothesis that local factors within the periodontal pocket may favor the attraction of circulating oncogenic cells.

4. Conclusions

Localized pathological changes in the periodontal tissues enabled the early detection of a Stage IV extranodal anaplastic large cell lymphoma. Prompt intervention led to a successful treatment outcome and patient survival. Atypical periodontal lesions not clearly attributable to dental or periodontal disease may represent the first clinical manifestation of systemic malignancy and should therefore be approached with careful diagnostic vigilance.

Table 1
Clinical features and differential diagnosis for exophytic gingival lesions.

Lesion	Clinical Features
Periodontal Abscess	**Appearance:** Painful swelling; possible suppuration. **Associated with:** Deep periodontal pockets; subgingival foreign body. **Local site:** Tooth may be tender and mobile.
Endo-Periodontal Lesion	**Appearance:** Painful swelling; possible suppuration. **Associated with:** Deep localized periodontal pockets. **Local site:** Necrotic tooth or tooth with existing endodontic therapy. **Radiographic appearance:** Consistent with endodontic pathology.
Traumatic Irritation Fibroma	**Appearance:** Asymptomatic swelling. **Associated with:** Chronic irritation or trauma. **Local site:** May present with fractured restorations or cusps. Does not recur once the irritant is removed.
Drug-Induced Gingival Hyperplasia	**Appearance:** Asymptomatic swelling. **Associated with:** Systemic intake of phenytoin, cyclosporine, calcium channel blockers, or other medications triggering hyperplasia. **Local site:** Often generalized.
Reactive Lesions peripheral giant cell granuloma, pyogenic granuloma, peripheral ossifying fibroma	**Appearance:** Sessile or pedunculated swelling, ranging from red with a tendency to bleed to pink with firm consistency. **Associated with:** Chronic irritation or trauma. **Local site:** May recur if the local irritant persists.
Pigmented Lesions	**Appearance:** Asymptomatic, generally pigmented (dark, brown, or blue); irregular borders; rapid enlargement. **Local site:** Rare in gingiva. Biopsy is mandatory due to high risk of malignancy.
Neoplastic Lesions	**Appearance:** Heterogeneous, possibly ulcerated and bleeding. **Local site:** Often inconsistent with local anatomy. May involve adjacent bone on radiographs.

CRediT authorship contribution statement

Riccardo Pace: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Riccardo Di Gianfilippo:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Francesco Cairo:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **GiovanPaolo Pini Prato:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

Patient consent - statement

We have obtained a complete written informed consent from the patient for the publication of this study and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of generative AI statement

During the preparation of this work, the authors used a generative AI language model to improve the grammar of paragraphs written by the authors. After using this service, the authors reviewed and edited the

content as needed and take full responsibility for the content of the published article.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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