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Ameloblastic Carcinoma with Unusual Anterior Mandibular and Pharyngeal Extension in a Patient with Metachronous Renal Cell Carcinoma: A Case Report of a Complex Diagnostic Challenge

Oseyd Khashshan^{1*}, Shahed Khashshan², Tala Khashshan³

1 Department of Oral and Maxillofacial Surgery, Prince Hamzah Hospital, Amman, Jordan.

2 School of Medicine, University of Jordan, Amman, Jordan.

3 School of Medicine, Al-Balqa Applied University, Salt, Jordan.

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Correspondence:

Oseyd Khashshan,
Department of Oral and
Maxillofacial Surgery,
Prince Hamzah Hospital,
Amman, Jordan.
oseyd@yahoo.com

ABSTRACT

Ameloblastic carcinoma (AC) is a rare malignant odontogenic tumor characterized by aggressive local behavior and the potential for regional and distant metastasis. Anterior mandibular involvement with pharyngeal extension is exceptionally rare and poses significant diagnostic challenges. We report a 74-year-old man who presented with dysarthria, restricted tongue mobility, submental swelling, and intermittent intraoral bleeding. Imaging revealed an ill-defined radiolucent lesion in the anterior mandible with cortical destruction and extension into the oropharyngeal region. Incisional biopsy confirmed AC. Metastatic workup demonstrated bilateral cervical lymphadenopathy and multiple pulmonary nodules. A history of renal cell carcinoma (RCC), created diagnostic uncertainty regarding the origin of the distant lesions. The lesion was staged as T4bN2cM1 and deemed surgically unresectable. Palliative management was initiated; however, the patient died shortly thereafter. This case highlights a rare co-occurrence of atypical anatomical presentation and multi-malignancy diagnostic complexity, emphasizing the need for refined diagnostic strategies in similar scenarios.

Keywords: Ameloblastic carcinoma, Pharyngeal invasion, Renal cell carcinoma, Metachronous malignancy, Mandibular tumor, Odontogenic malignancy.

1. Introduction

Odontogenic malignancy comprises a heterogeneous group of lesions arising from the tooth-forming apparatus, ranging from benign entities to aggressive malignancies. Among these, ameloblastoma is one of the most well-recognized benign odontogenics, characterized by local aggressiveness and a high tendency for recurrence. According to the 2022 World Health Organization Classification of Odontogenic and Maxillofacial Bone Tumors (5th edition), ameloblastoma is categorized into four distinct types: conventional ameloblastoma, unicystic ameloblastoma, extraosseous (peripheral) ameloblastoma, and

metastasizing ameloblastoma (1). This classification highlights the principle that behavior does not always correlate with histopathological classification, as malignancy is defined primarily by microscopic features rather than the presence of metastatic behavior alone (1). This distinction is illustrated by the case of metastasizing ameloblastoma, which, despite its metastatic potential, retains benign histological characteristics.

Within this spectrum, AC represents the malignant counterpart of conventional ameloblastoma (1). It is characterized by histopathological features of ameloblastoma in combination with cytologic atypia,

increased mitotic activity, and infiltrative growth (2). Unlike conventional ameloblastoma, which is locally aggressive, but lacks metastatic potential, AC carries a significant risk of distant metastasis, most commonly to the lungs.

This metastatic capability distinguishes AC from both conventional ameloblastoma and the rare

metastasizing ameloblastoma, which, despite its ability to metastasize, remains histologically benign. This hematogenous spread may occur even in the absence of local recurrence and can be present at initial diagnosis or develop years later (Table 1).

Table 1: Comparison of conventional ameloblastoma, ameloblastic carcinoma and metastasizing ameloblastoma

Feature	Conventional Ameloblastoma	Ameloblastic Carcinoma	Metastasizing Ameloblastoma
WHO Classification (2022)	Benign epithelial Odontogenic Tumor (1)	Malignant epithelial odontogenic Tumor (1)	Benign epithelial Odontogenic Tumor (1)
Histopathology	Benign conventional ameloblastoma Well-differentiated (1)	Malignant cytologic features: atypia, mitoses, pleomorphism Poor to moderate differentiation (2)	Benign conventional ameloblastoma Well-differentiated (1)
Immunohistochemistry	May show BRAF V6006 mutations (1)	May show p53 overexpression, Ki-67, occasional BRAF or other mutations (3)	May show BRAF V6006 mutations (1)
Clinical behaviour	Locally aggressive growth with cortical expansion and resorption (1)	Invasive , destructive and capable of soft tissue infiltration beyond bone (3)	Locally aggressive growth with cortical expansion and resorption, delayed metastasis (1)
Metastatic potential	Non-metastatic (1)	Not required to show metastasis to confirm the diagnosis, but if present, metastasis occurs most commonly to lungs & cervical lymph nodes (3)	Must show metastasis to confirm the diagnosis despite benign histology, most commonly to lungs (1)
Radiographic features	Well-defined borders No focal radiopacities (1)	Ill-defined borders Focal radiopacities (4,5)	Well-defined borders No focal radiopacities (1)
Diagnostic challenge	May mimic odontogenic cysts radiographically and clinically (6)	May resemble benign ameloblastoma on initial biopsies (3)	Histologically difficult due to benign histology despite metastasis (1)
Treatment	Surgical resection with adequate margins (1)	Surgical resection with adequate margins as primary therapy ± radiotherapy/Chemotherapy in advanced cases (1,3)	Surgical resection with adequate margins (1)
Prognosis	Generally favorable with adequate surgical treatment though recurrence is possible (1)	Poor in advanced , metastatic, or inadequately resected cases (3)	Variable (1)

AC may arise de novo or through malignant transformation of a pre-existing conventional ameloblastoma (3,7). Clinically, AC most commonly affects the posterior mandible and presents with rapidly enlarging swelling, pain, cortical bone destruction, and possible regional or distant metastasis, particularly to the lungs (2,4,8). However, despite these aggressive features, accurate diagnosis can be challenging, as early imaging may mimic benign ameloblastoma and histopathological findings may show overlapping

features, requiring careful assessment of clinical, radiological, and histopathological data.

This report describes a rare case of AC arising in the anterior mandible with extensive pharyngeal invasion in a patient with a history of RCC, highlighting a rare combination of atypical anatomical involvement and multi-malignancy diagnostic complexity, which has important implications for diagnostic strategy and clinical decision-making.

2. Case Report

A 74-year-old male was referred with a progressively enlarging submental swelling associated with dysarthria, restricted tongue movement, and intermittent intraoral bleeding. The patient had a medical history of recent weight loss of approximately 5 kg over the preceding 3 months and a left nephrectomy for RCC performed 5 years earlier.

Clinical examination revealed fixation of the tongue to the floor of the mouth and tenderness in the submental region with palpable cervical lymphadenopathy. Panoramic radiography and cone-beam computed tomography (CBCT) obtained using standard maxillofacial imaging parameters demonstrated an ill-defined radiolucent lesion involving the anterior mandible with cortical bone destruction (Figures 1 & 2).

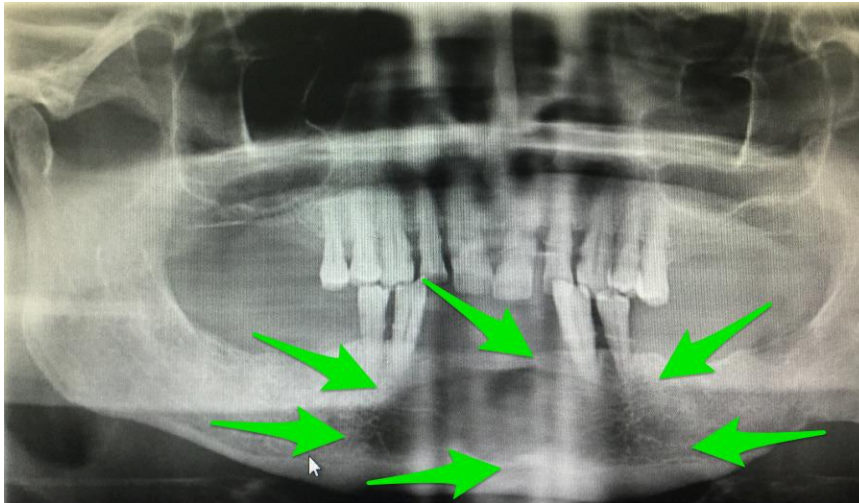


Figure 1: Panoramic radiograph showing an ill-defined non-corticated radiolucent lesion involving the anterior mandible in the interforaminal region (arrows), suggestive of an aggressive process

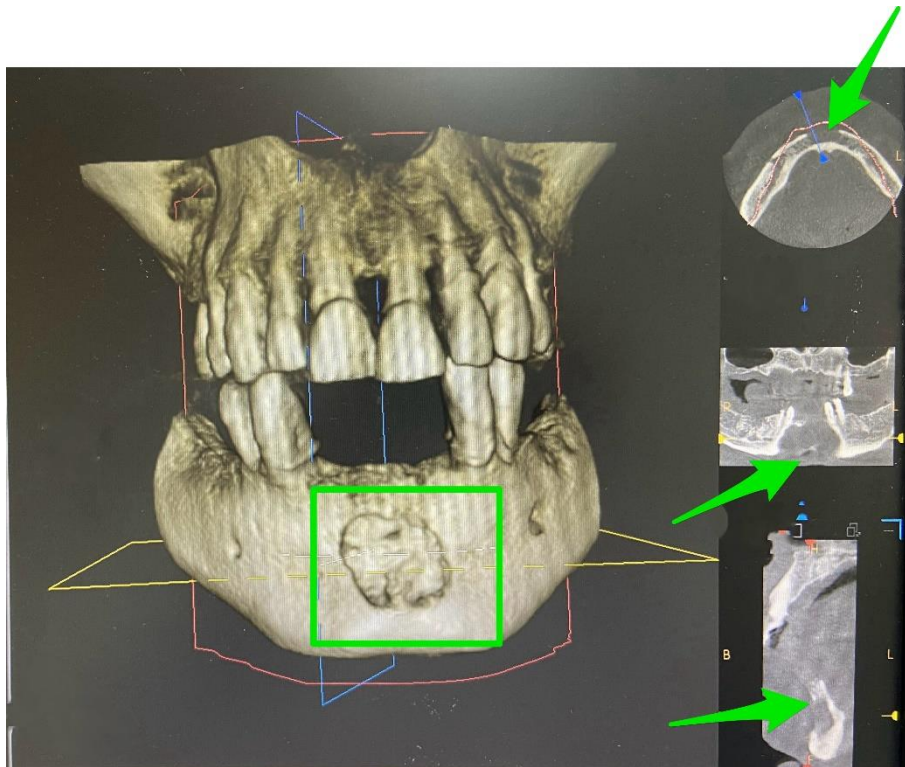


Figure 2: CBCT scan demonstrates extensive labial alveolar bone resorption of the mandible (arrows) with cortical disruption (green rectangle) consistent with an infiltrative destructive process

Contrast-enhanced CT scan using a multi-detector scanner (slice thickness approximately 1–2 mm) and magnetic resonance imaging (MRI) using a 1.5-T system, including T1-weighted, T2-weighted, and STIR sequences, showed a mandibular intraosseous mass measuring approximately 3 × 2 cm with extensive soft-tissue extension involving the submandibular and masticator spaces and extending toward the oropharynx (Figure 3). These imaging modalities were used

complementarily to evaluate both osseous destruction and soft tissue extension. Bilateral enlarged cervical lymph nodes measuring up to 2.5 cm in short-axis diameter were noted, with features suggestive of metastatic involvement, including irregular margins and central necrosis. Fiberoptic nasopharyngoscopy revealed a submucosal mass displacing the pharyngeal wall medially.

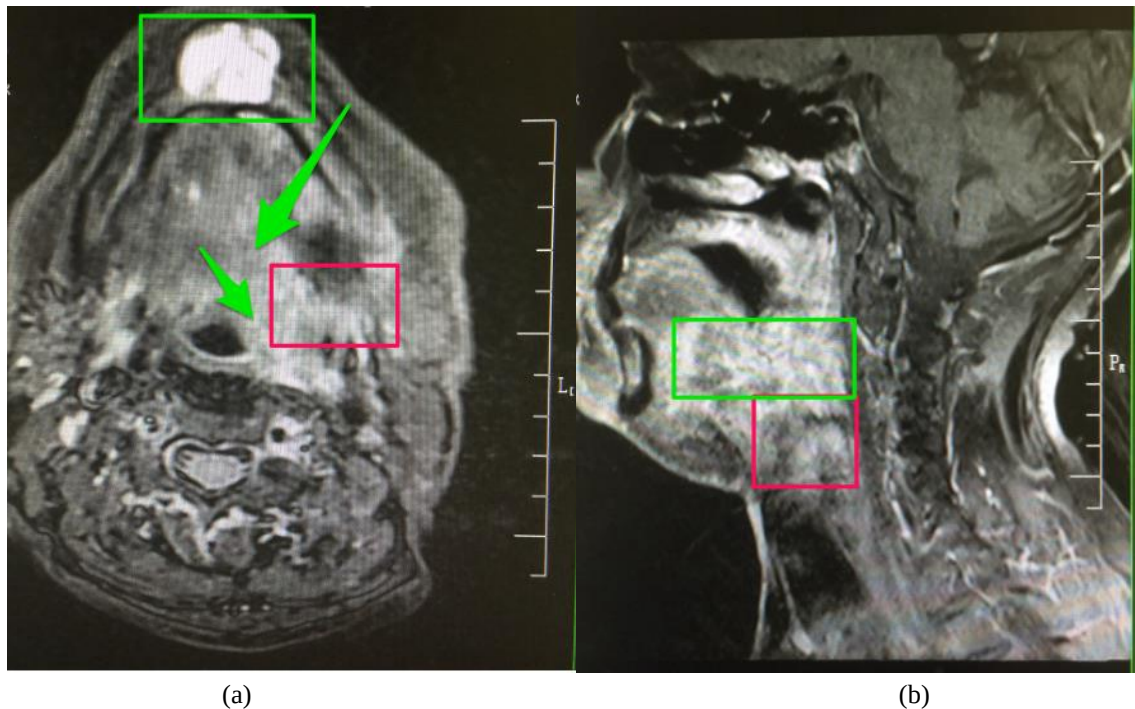


Figure 3: MRI demonstrating mandibular tumor extension with pharyngeal invasion.

(a) Axial T2 STIR image showing an irregular intraosseous lytic lesion crossing the mandibular midline with associated soft tissue mass extending into the left submandibular space (long arrow), resulting in compression of the oropharyngeal lumen (short arrow). The lesion shows evidence of extension into the left masticator space, including the medial pterygoid muscle (rectangle). (b) Sagittal post-contrast T1 image showing a large heterogeneously enhancing mass involving the base of tongue and pharyngeal region (the tonsillar area, uvula, and epiglottis) (green rectangle), extending inferiorly toward the hyoid bone (red rectangle)

Incisional biopsy established the diagnosis of AC arising in a background of a residual ameloblastoma component. Histopathological examination demonstrated malignant epithelial islands exhibiting marked cytologic atypia, in association with areas consistent with a pre-existing ameloblastoma. High-resolution chest CT demonstrated multiple bilateral pulmonary nodules, the largest measuring approximately 1.5 cm, involving both lung fields with a predominance in the lower lobes, findings considered suspicious for metastatic disease.

Definitive histopathological confirmation was not feasible due to the patient's rapidly deteriorating condition. However, given the aggressive nature of the primary tumor and its known propensity for pulmonary metastasis, these findings were clinically and radiologically interpreted as consistent with distant metastatic disease (M1), representing a key diagnostic limitation. Accordingly, the tumor was staged as T4bN2cM1 according to the American Joint Committee on Cancer (AJCC) 8th edition staging system (9).

Following multidisciplinary discussion, the lesion was considered surgically unresectable and palliative management was recommended. The patient's condition deteriorated rapidly despite initiation of palliative management, including supportive care and analgesia, and he died within 4 weeks, likely due to progressive metastatic disease.

This report describes a rare case of AC in the anterior mandible with extensive pharyngeal invasion in a patient with a history of RCC. The coexistence of two malignancies at different times created significant diagnostic uncertainty regarding the origin of metastatic lesions. Early recognition, comprehensive imaging, and multidisciplinary evaluation are essential for appropriate management. However, prognosis remains poor in advanced unresectable disease. This case highlights the potential impact of early recognition of atypical presentations on improving diagnostic pathways, potentially reducing delays and supporting more efficient clinical decision-making in advanced cases.

3. Discussion

AC is a rare odontogenic malignancy, occurring in less than 1% of all ameloblastoma cases, and most frequently arises in the posterior mandible (8). Typically, it presents with rapid growth, pain, cortical bone destruction, and soft tissue invasion (3,10,11). Although several reports have described its clinical and metastatic characteristics, involvement of the anterior mandible with extensive pharyngeal extension remains uncommon (3). Furthermore, the presence of a metachronous RCC introduced additional diagnostic complexity in interpreting distant lesions. This unique clinical profile of findings highlights the variability in tumor presentation and contributes additional insight into the spectrum of clinical behavior associated with AC.

Comparison with previously published reports further emphasizes the unusual nature of the present case. Most reported ACs arise in the posterior mandible, particularly the molar-ramus region, and typically present as painful swelling associated with cortical destruction and rapid enlargement (3,4,8,10,11). In contrast, the present lesion originated predominantly within the anterior mandible and crossed the midline, a location that is considerably less common.

Although local soft tissue invasion is a recognized feature of AC, extension into the pharyngeal region has rarely been documented. Khan et al. reported a maxillary

AC with sinonasal extension that clinically mimicked inflammatory disease, highlighting the potential for unusual adjacent anatomic spread and delayed diagnosis (5). Similarly, the present case produced dysarthria, tongue fixation, and pharyngeal compression due to extensive posterior extension beyond the cortical surface of the mandible. These findings expand the recognized spectrum of locally advanced disease and demonstrate that AC may present with symptoms more suggestive of upper aerodigestive tract pathology than the classical locoregional cervical extension of a mandibular odontogenic malignancy.

Pulmonary metastases have been reported as the most common site of distant metastasis in AC (2,3,4,8,11,12). However, unlike previously published cases in which the primary tumor represented the sole malignant process, the current patient had a history of RCC, creating substantial uncertainty regarding the origin of the pulmonary lesions. To our best knowledge, reports describing AC occurring in the setting of a metachronous RCC are exceptionally rare. This coexistence introduces a diagnostic challenge that is largely absent from previous case reports and emphasizes the importance of histopathological confirmation whenever feasible.

While previous reports have described aggressive local invasion or diagnostic challenges associated with AC, these features are typically reported in isolation. The present case is distinguished by the coexistence of multiple atypical characteristics, including anterior mandibular involvement, extensive pharyngeal extension, and the presence of a metachronous RCC. This unique combination represents a rare and complex clinical scenario that extends beyond previously reported patterns and contributes to a broader understanding of the variability and diagnostic complexity of AC.

Radiographically, AC may resemble conventional ameloblastoma; however, features, such as ill-defined margins, cortical perforation, and extension into surrounding soft tissues, suggest malignancy (3,4,8,10). Definitive diagnosis relies on histopathological examination demonstrating cytologic atypia, mitotic activity, and architectural features consistent with malignant transformation (3,7).

Differential diagnosis in the present case with such findings raises consideration of several odontogenic and non-odontogenic malignant processes.

Squamous cell carcinoma of the overlying oral mucosa was an important clinical consideration (1,13). However, this diagnosis was considered less likely in the present case, because the overlying edentulous gingiva appeared clinically intact and no relevant primary mucosal lesion was identified.

Metastatic disease to the mandible represented another significant differential diagnosis, particularly in view of the patient's previous history of RCC. The presence of a known primary malignancy elsewhere in the body therefore complicated interpretation of the mandibular lesion and pulmonary nodules. The presence of pulmonary lesions could represent either the primary tumor (lung cancer metastasizing to mandible) or metastases from another primary site. In approximately one-quarter of cases, jaw metastases represent as the initial indication of an undiscovered malignancy at a distant site (13). The mandible is the most common site for jaw metastases (more than maxilla), particularly in elderly patients. The most common primary sites in men are lung, prostate, and kidney (13).

Primary intraosseous carcinomas of the jaws also formed an important component of the differential diagnosis (1). These include primary intraosseous squamous cell carcinoma, intraosseous mucoepidermoid carcinoma, AC, and other odontogenic carcinomas, all of which may present as aggressive radiolucent lesions (1,2,3,11).

Osteosarcoma of the mandible was also considered, because it commonly presents as an aggressive destructive jaw lesion (1). Radiographically, osteosarcoma often demonstrates a mixed radiolucent-radiopaque appearance, variable bone formation, and occasionally a characteristic "sunburst" periosteal reaction (1). In contrast, the present lesion was predominantly radiolucent. Furthermore, cervical lymph node metastasis is less commonly encountered in osteosarcoma than in epithelial malignancies, making this diagnosis less favored (1).

Lymphoma (particularly Burkitt lymphoma or other aggressive B-cell lymphomas) may likewise involve the jaws and can present with aggressive bone destruction, and regional lymphadenopathy (1). However, lymphomas more frequently manifest as diffuse marrow infiltration, multifocal disease, or widespread nodal involvement and are often associated with systemic manifestations, such as fever, night sweats, and unexplained weight loss (1). While more common in

younger patients, sporadic cases still occur in adults (1).

Metastasizing ameloblastoma should also be considered, because pulmonary lesions may occur in both entities (1). However, metastasizing ameloblastoma retains the benign histological appearance of conventional ameloblastoma despite distant metastasis, whereas AC demonstrates definitive cytologic atypia, increased mitotic activity, and other malignant histopathological features within the primary tumor (1,3).

The coexistence of a previous RCC and a newly diagnosed AC created substantial diagnostic uncertainty regarding the origin of the suspected metastatic lesions. Consequently, this case highlights the importance of integrating clinical history, radiologic findings, histopathological examination, and, when feasible, immunohistochemical or molecular studies to achieve accurate diagnosis in patients with multiple primary malignancies (14-16).

RCC is characterized by unpredictable metastatic behavior and the potential for delayed dissemination to atypical sites, including the oral and maxillofacial region, which may overlap with the metastatic patterns of other malignancies (14). Conversely, AC typically metastasizes to the lungs and regional lymph nodes (2,3,4,8,11,12).

This case highlights a significant discriminative limitation in the diagnostic evaluation of metastatic disease in patients with multiple metachronous primary malignancies. The absence of histopathological confirmation of pulmonary nodules, due to the patient's deteriorating condition, precluded definitive determination of their origin, thereby affecting the validity of M-staging component of TNM-staging. In similar clinical scenarios, a more definitive diagnostic approach would typically involve tissue biopsy of suspicious lesions, followed by immunohistochemical analysis to differentiate between potential primary sources. Markers, such as cytokeratins (e.g., CK19, p63), may support an odontogenic epithelial origin, whereas markers, such as PAX8, CD10, and vimentin, are more characteristic of RCC (15,16). Furthermore, advanced molecular profiling techniques could provide additional diagnostic accuracy by comparing the genetic signatures of the primary tumor and metastatic lesions. Although such approaches were not feasible in the present case, their application represents an important strategy for improving diagnostic precision in complex

cases involving multiple malignancies. This limitation necessitates the need for standardized diagnostic protocols in such complex oncologic scenarios. Collectively, these findings highlight the need for a more structured diagnostic approach in patients with multiple primary malignancies, integrating clinical history, imaging characteristics, histopathological and, when feasible, molecular confirmation to improve diagnostic precision.

Management of AC primarily involves wide surgical resection with tumor-free margins whenever feasible (8,10,11,17). From a surgical perspective, early detection could allow complete resectability, whereas advanced cases, like this, highlight the limitations of surgical intervention. Adjuvant radiotherapy may be considered in cases with positive margins, unresectable disease, or extensive soft tissue invasion.

Chemotherapy has shown limited benefit in the management of AC, particularly in advanced and unresectable cases (3,4,10,11,16). This limitation highlights an important therapeutic gap and emphasizes the need for alternative treatment strategies. In recent years, molecular profiling has gained attention as a potential tool for identifying targetable alterations, such as BRAF mutations or p53 expression, which may offer new treatment modalities for individualized therapy (18). Although such approaches were not applicable in the present case, their exploration represents a promising direction for future research, particularly in patients with advanced disease where conventional treatment options are limited. These therapeutic challenges further emphasize the need for continued research into targeted and molecular-based therapies to improve outcomes in aggressive forms of AC. Prognosis

is generally poor in advanced cases with extensive local invasion or distant metastasis (3,4,8,10,17). This case further emphasizes that advanced presentations of AC remain therapeutically challenging, reinforcing the importance of early detection and the potential future role of molecularly guided therapies.

4. Conclusions

This case illustrates the diagnostic challenge of metastatic rare odontogenic malignancies, particularly when coexisting with another metachronous primary malignancy, particularly when encountering unusual anatomical extension. It emphasizes the need for a structured and multidisciplinary diagnostic approach to enhance clinical interpretation and reduce the risk of delayed or inaccurate diagnosis. Increased awareness of such presentations may support more efficient diagnostic pathways and improved clinical outcomes in comparable scenarios.

Ethics Approval

This study was conducted in accordance with institutional ethical standards and the Declaration of Helsinki.

Conflict of Interests

The authors declare no conflicts of interest.

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