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Original article: Case Report

# Metastatic Vs. Malignant Follicular Ameloblastoma: A Case Report

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## Abstract

Metastatic ameloblastoma is a rare odontogenic malignancy, often presenting diagnostic and therapeutic challenges. This case report details a 77–year–old male with a history of recurrent follicular ameloblastoma of the right maxilla, initially treated with multiple surgeries and radiotherapy. After decades of stability, he presented with significant weight loss, respiratory symptoms, and a newly identified left lung mass. Subsequent biopsies confirmed metastatic ameloblastoma, a notably rare progression for this type of tumor. The patient's management involved a multidisciplinary approach, including thoracic surgery, medical oncology, radiotherapy, and palliative care, underscoring the complexities in treating metastatic ameloblastoma. This case highlights the critical need for thorough diagnostic evaluation and the consideration of metastasis in patients with a history of ameloblastoma, despite its rarity.

**Keywords:** Ameloblastoma, Metastatic ameloblastoma, odntogenic tumor, case report

## Introduction

Odontogenic tumors, arising from tissues involved in tooth development, constitute a diverse group of clinical entities, with a predominant representation in the jaw. [1] This category encompasses both benign and malignant neoplasms, with ameloblastoma standing out as a significant clinical entity, comprising 13% to 58% of all odontogenic tumors.[2] Ameloblastoma is a prevalent yet perplexing jaw tumor, accounting for about 10% of mandibular and maxillary tumors, with a higher incidence in males aged 30 to 60.[3] Despite its low metastatic potential (less than 2%), its clinical management is complicated by a high recurrence rate ranging from 50% to 72%.[4] Six histopathological patterns of ameloblastoma are identified, and clinically, it often presents as a slow–growing, painless mandibular mass, emphasizing the importance of early detection for effective management. [5]

Despite common recurrence after resection, distant metastasis is rare, typically occurring late in the disease course, with lung involvement observed in 75% of cases. [6,7] Metastasizing ameloblastoma presents challenges in predicting its clinical behavior histopathologically, as it exhibits no distinguishing characteristics from non–metastatic counterparts.[7] Due to the uncommon nature of metastatic ameloblastoma, management guidance is limited, predominantly relying on case reports.[4] This report aims to present a case of metastatic ameloblastoma involving the lung, detailing its clinical presentation, diagnostic challenges, and therapeutic considerations.

## Case Presentation

A 77 years old male presented in August 2022 to the primary health care clinic with a productive cough for two months and significant weight loss of 10 kg in over 4 months. The patient has a past history of recurrent follicular ameloblastoma in the right maxilla. In 1994, he had an oro–antral fistula closure where multiple sinus polyps were removed, revealing follicular ameloblastoma in the right maxillary and sphenoid sinuses, confirmed by histopathology. Moreover, in March 1997 he presented to the head and neck clinic reporting a jaw swelling, difficulty opening the mouth, and nasal blockage persisting for 3–4 weeks. Additionally, he described a mass on the right nostril's posterior floor of the choana, which manifested after a flu attack and coincided with a reduction in the sense of smell. On June 28, 1997, he underwent an EUA nose biopsy (medial maxillectomy through degloving), and histopathology confirmed a recurrent follicular ameloblastoma in the right maxillary and sphenoid sinuses. Following this procedure, the patient experienced facial deformities, masticatory dysfunction, and abnormal jaw movements, leading to a subsequent total maxillectomy with excisional biopsy in 1999 that confirmed recurrence

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of follicular ameloblastoma. Adjuvant radiotherapy to the right maxilla through medial and lateral oblique fields (60 GYs/30 fractions) was administered between August and October 1999. Subsequent follow–ups from 2000 until August 2022 showed stability with no signs of recurrence.

On August 10, 2022, An X–ray showed a soft tissue mass in the left chest wall, prompting further evaluation. A CT chest scan revealed:

- A large, heterogenous mass in the left lung lower lobe with lobulated borders and multiple areas of necrosis, potentially indicative of lung cancer or sarcoma. Biopsy recommended.
- Suspicious/metastatic subcarinal lymph nodes, warranting bronchoscopic biopsy.
- Bilateral multiple tiny nonspecific pulmonary nodules for follow–up.

A PET scan confirmed intense FDG uptake in the left lower lobe lung mass, subcarinal lymph nodes, and a subcentimetric right upper paratracheal lymph node. A small focus of high FDG uptake was noted in the lower pole of the right thyroid lobe with SUV max of 2.9, raising concerns of synchronous thyroid cancer. Multiple FDG avid right level 2 lymph nodes were observed.

A bronchoscopy with carinal biopsy was conducted, and the surgical pathology report revealed small fragments comprising neoplastic cells with a basaloid–type morphology. The tumor cells exhibited positive staining for p63, high molecular weight cytokeratin (focally), and Ki–67 (less than 5%). Conversely, they tested negative for EMA, CD 117, chromogranin, CD56, S100, CK19, and calretinin. Since the patient has a history of maxillectomy for ameloblastoma in 1997, the differential diagnosis encompassed squamous cell carcinoma basaloid type, basal cell adenoma, basal cell carcinoma, pleomorphic adenoma, adenoid cystic carcinoma, and metastatic ameloblastoma. Clinical and radiological correlation was recommended, and a repeated excisional biopsy was advised for a definitive diagnosis.

The case was subsequently referred to interventional radiology for a CT–guided biopsy of the lung and mediastinum on February 6, 2023. The report stated: “sections show lesional tissue composed of epithelial islands and cords of columnar cells with hyperchromatic nuclei at basal layer, exhibiting peripheral palisading, subnuclear vacuolization and basaloid morphology. The suprabasal cells arranged in a loose, network–like arrangement, recapitulating stellate reticulum (Figure 1A). Large foci of necrosis are also seen (Figure 1B). The tumor cells are positive for CK19 (Figure 1C). They are negative for calretinin (Figure 1D), CD56. P63. Ki67% labeled a mitotic index of about 10–15% (Figure 1E). The features are consistent with metastatic ameloblastoma.” The case was discussed in the thoracic tumor board on 08/06/2023 and it was recommended to be referred to medical oncology for future management as a case of metastatic ameloblastoma.

A comprehensive evaluation was conducted in the oncology clinic. The patient’s performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) scale, which indicated a score of 2. Laboratory assessments, encompassing a complete blood count, revealed a generally normal profile. Additionally, the results of previous radiological studies since August 2022 were reviewed. The current stage and grade, determined through imaging and histopathology, were identified as stage 3. The prognosis was outlined, emphasizing the poor outlook in the presence of metastasis and a lack of response to treatment.

The potential treatment approaches were outlined to the patient. Radical total resection with free margins was discussed. However, conservative surgery could be considered based on the tumor’s size and location. For multinodular ameloblastoma, a combination of curettage and cryotherapy using Carnoy’s solution was also suggested. Systemic chemotherapy, incorporating drugs such as cyclophosphamide, methotrexate, 5–fluorouracil, cisplatin, and bleomycin, was mentioned, with a potential need for adjuvant radiotherapy postoperatively depending on histopathology. Furthermore, the patient was informed about the importance of close postoperative evaluation. Immunotherapy, particularly for variants involving Kras, Nras, and BRAf mutations, was highlighted as a potential treatment option. However, managing patients without mutations posed significant challenges due to limited treatment response.

Later, the patient had recurrent admissions under the medical oncology team with shortness of breath (SOB) and recurrent chest infections, accompanied by hypercalcemia and pleural effusion.

In the first admission on 06/08/2023, a chest X–ray revealed a massive left–sided pleural effusion. Thoracentesis was performed, and a bronchodilator and incentive spirometer were administered. An ultrasound–guided thoracentesis took place on 07/08/2023 without immediate complications. A follow–up CT scan of the head and chest on 08/08/2023 indicated disease progression. The chest CT showed enlarged mediastinal lymph nodes, subcarinal lymph nodes extending into the lower trachea and left main bronchus, causing occlusion and atelectasis. There was an increase in the size of the left lower lobe mass, suggesting a combination of atelectasis and metastasis. The left pleural effusion increased, and a small to moderate

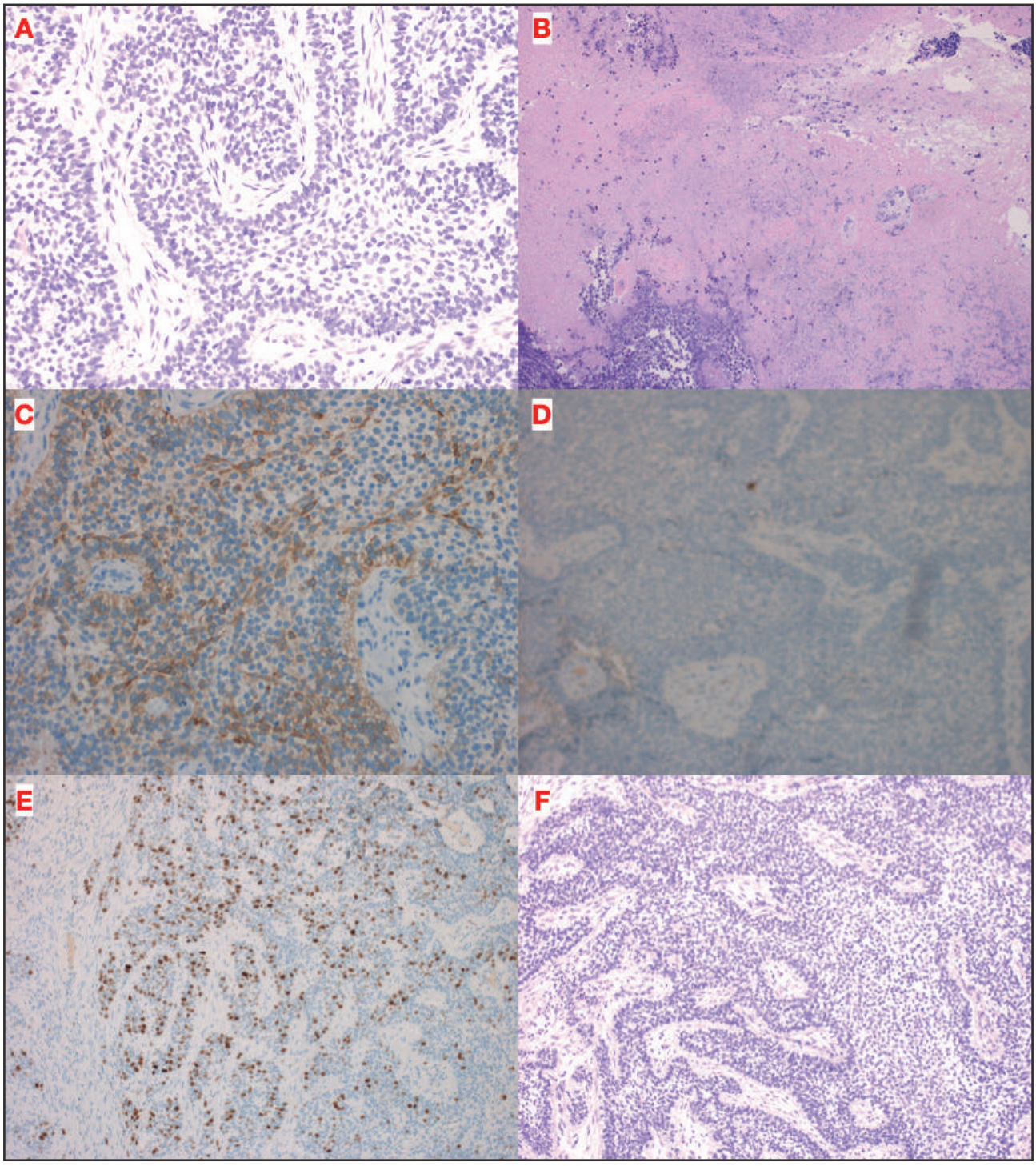


**Figure 1.** Histopathological slides of the lung and mediastinum biopsy

(A) Tumor cells at 20x magnification – The suprabasal cells are arranged in a loose, network–like structure, resembling stellate reticulum. (B) Large foci of necrosis – Areas of significant tissue necrosis within the tumor mass. (C) CK19 positive tumor cells – Tumor cells showing positive staining for CK19, indicating epithelial origin. (D) Tumor cells negative for calretinin – Tumor cells demonstrate no staining for calretinin, ruling out certain differential diagnoses. (E) Ki67 mitotic index 10–15% – Tumor cells exhibiting a moderate level of proliferative activity, with a Ki67 labeling index of 10–15%. (F) Tumor cells at 10x magnification – Tumor cells arranged in typical patterns of ameloblastoma at a lower magnification.

left–sided pneumothorax appeared. Stable emphysema and pulmonary nodules were noted in the right lung. The head and neck CT showed no evidence of metastasis or acute abnormality. A thoracic surgery assessment indicated disease progression, with no recommended surgical intervention or stenting for the totally occluded left main bronchus. Observation was advised for the pneumothorax.

Subsequent admissions followed, with the patient readmitted on 15/08/2023 with left lung collapse,

confirmed by chest CT (Figure 2). The patient was referred to the radiotherapy team, and an evaluative PET/CT scan was done (Figure 3). Then, palliative mediastinal irradiation was done, starting on 17/08/2023 and completed on 23/08/2023 with acceptable tolerance. Kras, Nras, and BRAf mutation testing revealed no detectable mutations. The patient was discharged on 27/08/2023.

In a reevaluation on 14/09/2023, the high–resolution chest CT showed a decrease in the size of mediastinal lymph nodes, a better aeration of the left lung, and stable left lower lobe mass. However, there was a mild worsening of the loculated left upper and lower small pleural effusion.

On 02/12/2023, subsequent CT scans revealed interval progression of the condition, with an increase in the size of cystic mediastinal lymph nodes and the left lower lobe mass, indicating disease progression. Despite asymptomatic progression, the patient continued regular follow–up in the outpatient department with radiological imaging. PDL1 testing and a referral to pulmonology for possible palliative stent were recommended for further evaluation.

Admitted again on 18/12/2023 with SOB and a productive cough, the patient's condition rapidly declined, with worsening SOB that is aggravated by physical activity. The Pulmonology team recommended the consultation of the thoracic surgery team or a referral to another center with appropriate capabilities. However, a family meeting was conducted by the oncology medical team and discussed the patient's poor prognosis and declined performance with no promising interventions or treatments to be offered, leading to a signed "do not resuscitate (DNR)" and referral to the palliative care team for maximum supportive care.

## Discussion and Conclusion

The patient's case highlights the difficulty and intricacy involved in ameloblastoma diagnosis and

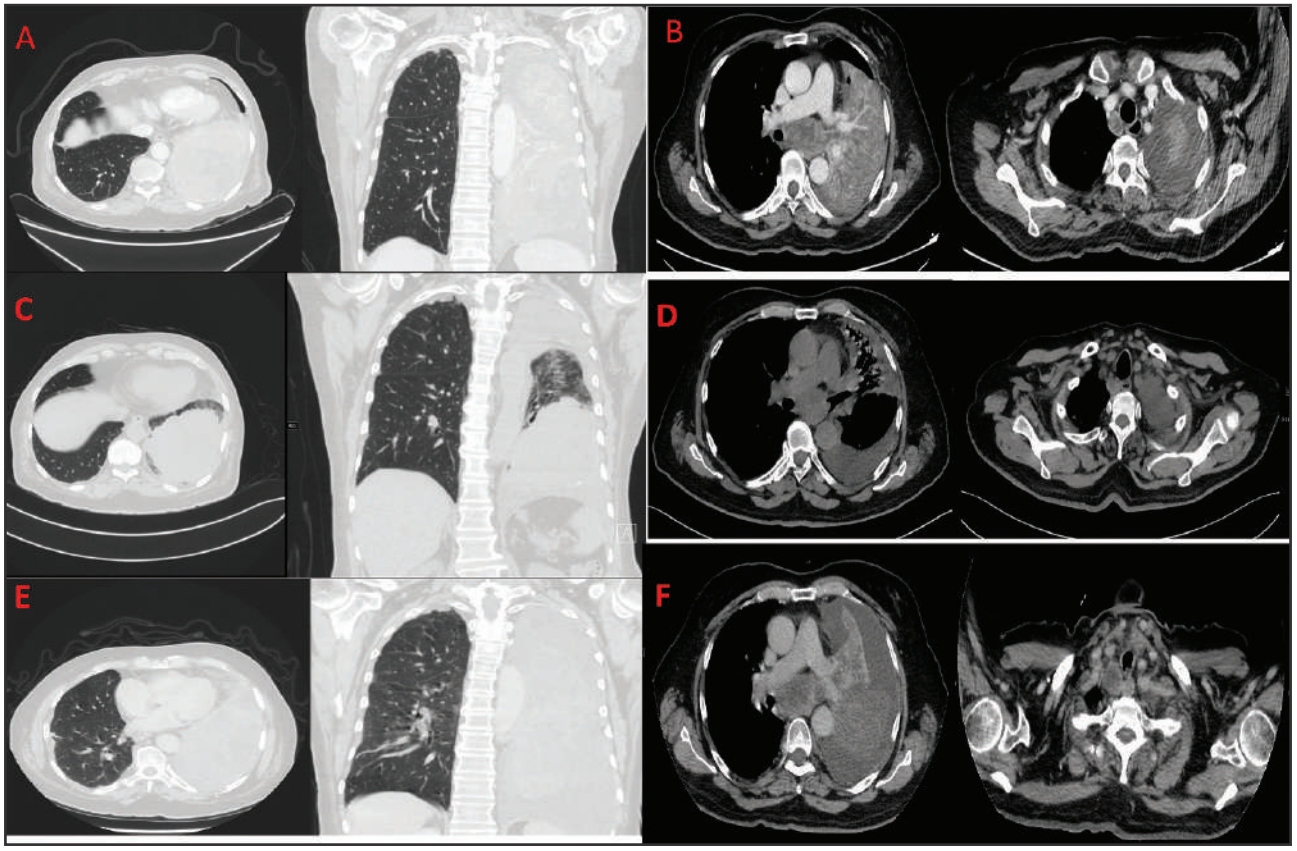


**Figure 2.** Pre–radiotherapy chest CT scan

(A&B) CT chest before radiotherapy, (A) CT in lung window showed left lung lower lobe large mass (red arrow) measuring 10.2 x 9.1 cm. The mass extended into the lower trachea with complete occlusion of the left main bronchus and its branches resulting in compled collapse of the left lung. There is large left pleural effusion and small left–sided pneumothorax. (B) CT chest in soft tissue window showed enlarged subcarinal lymph nodes (white arrow), the largest measures 3.6 cm short axis with hypodense/necrotic center. (C&D) CT chest one month after 20 Gy/5 fractions of palliative mediastinal irradiation, (C) CT chest in lung window showed insignificant interval change in size of left lower lobe mass (red arrow) measuring 9 x 11 cm, interval better aeration of left lower lobe, and (D) CT chest in soft tissue window showed innterval decrease in size of subcarinal lymph node measuring 2.7 cm. (E&F) CT chest 4 months post radiotherapy, (E) CT chest in lung window showed interval increased in size of the left lower lobe large mass measures 12 x 9 cm, interval increassed in left pleural effusion and complete left lung collapse (F) CT chest in soft tisse windwow showed interval increase in size of the necrotic subcarinal lymph node

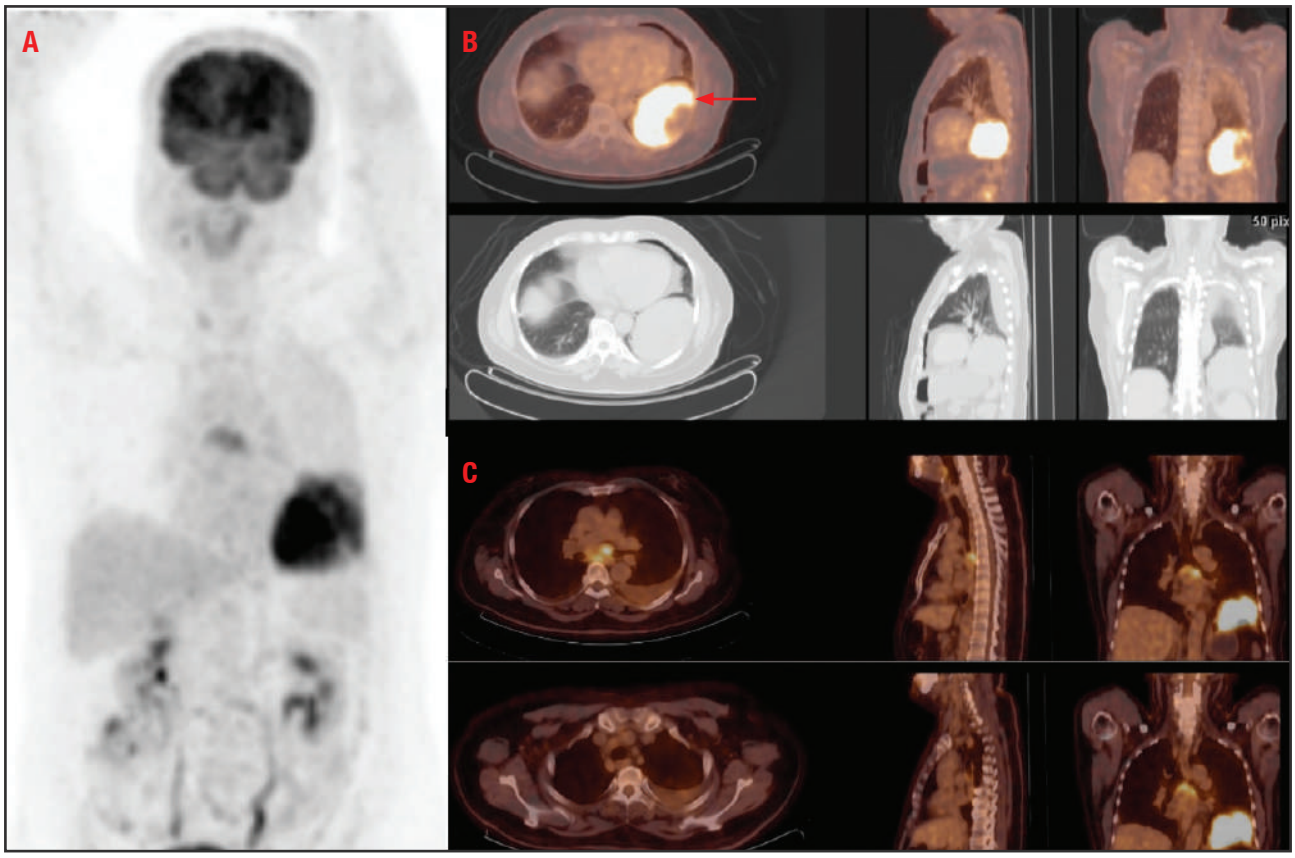


**Figure 3.** Pre–radiotherapy 18F–FDG PET/CT scan.

(A) maximum intensity projection (MIP), (B) CT and fused PET/CT in lung window and (C) fused PET/CT showed left lower lobe highly FDG avid large lung mass with areas of hypometabolism due to necrosis and SUVmax of 9.7 (red arrow) and enlarged metabolically active subcarinal lymph node with areas of hypometabolism due to necrosis and highest SUV max of 5.5 (white arrow).

treatment, especially in the disease's malignant and metastatic forms. Ameloblastoma is a benign neoplasm that originates from the odontogenic epithelium and can be locally aggressive. This tumor grows slowly and may not cause any symptoms, but it can present as painless swelling in the jaw or nose.[8–10]

Recurrence of ameloblastoma is well–known to have a high probability of occurring[10,11], which presents a serious concern[12], as our case illustrates. Research corroborating our findings demonstrates that recurrent ameloblastoma tumors may display unusual microscopic alterations or even manifest as malignancy.[12,13] Given the primary tumor's crucial location and the considerable surgical challenges it presents, it is reasonable to assume that the recurrence in our patient's case resulted from incomplete surgical resection. Metastasizing ameloblastomas (MA) are tumors that have spread beyond their original site of benign histologic appearance and are rare cases of ameloblastic neoplasms.[14]

Differentiating the diagnosis in our case was difficult because the patient initially had characteristics that were consistent with a benign ameloblastoma, but the metastatic lung tumor had malignant features, most notably necrosis. Currently, AC is a completely different organism that exhibits cellular atypia. Despite the lack of metastases, ameloblastoma with cellular atypia is classified as carcinoma. It is necessary to distinguish between these two terms because their differences are unclear.[15] Research has focused on the molecular characteristics of METAM's malignant behavior in order to distinguish it from non–metastasizing ameloblastomas and to inform the development of timely and effective therapeutic interventions.

Compared to AC (35%)(16,17), benign ameloblastomas (64% in conventional, 81% in unicystic, and 63% in peripheral) have a higher frequency of the BRAF p.V600E mutation, which has been associated with the tumor's aggressive behavior.[17] Additionally, mutations in CDKN2A, which encodes p16, and TP53, which encodes p53, have been linked to AC. Genes including BRAF, MYCN, ARIDIA, MLL2, RUNX1, or ASXL1 have been shown to have mutations in MA. Consequently, distinct mutation profiles have been discovered in AC and MA in addition to BRAF mutations, which may aid in the differential diagnosis of these two lesions.[16] In our case, the absence of BRAF mutation in the patient further complicated the diagnostic

dilemma, presenting challenges in distinguishing between AC and MA and thereby determining an optimal treatment strategy. Neoadjuvant BRAF inhibitor therapy is a great option for tumors containing BRAF mutations. In cases where the tumor has a single BRAF mutation, limited surgical treatment is administered, and in cases where there are multiple concurrent BRAF mutations, the tumor undergoes extensive resection. On the other hand, because SMO mutant tumors have a high chance of recurrence, they need to be surgically removed with wider margins and with certainty beforehand.[14]

In conclusion, our patient's case demonstrates the complexity of ameloblastoma diagnosis and treatment, especially in its malignant and metastatic forms. Diagnostic and treatment decisions are aided by molecular profiling, which includes BRAF mutations; however, the negative BRAF status of our patient makes treatment selections more challenging. Ameloblastoma is still primarily treated with surgical excision, however in some circumstances, targeted therapies and chemotherapy may be taken into consideration. Since MA frequently has a poor prognosis, more research is desperately needed to create efficient treatment plans for this difficult condition.

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## Funding and Conflict of Interest

No funding was received for this study, and the authors declare no conflict of interest.

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