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*Case Report*

# Rare tongue base metastasis from SMARCA4-deficient undifferentiated non-small cell lung carcinoma: a case report

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**Abstract:** SMARCA4-deficient non-small cell lung cancer (SMARCA4-dNSCLC) is a rare, aggressive subtype with a high propensity for early metastasis and poor prognosis. Common metastatic sites include the bone, brain, adrenal glands, liver, and spleen; metastasis to the base of the tongue, however, is exceptionally rare. We present a unique case of SMARCA4-dNSCLC with concurrent metastases to both the adrenal gland and the base of the tongue. A 44-year-old male presented with cough and shortness of breath. Imaging revealed a right hilar mass, a left adrenal gland mass, and a nodule at the right tongue base. Histopathological examination of biopsies from the tongue base and mediastinal lymph nodes confirmed the diagnosis of SMARCA4-deficient undifferentiated NSCLC with metastases (T3N2M1c, stage IVB). Following a multidisciplinary discussion, the patient received combination therapy with paclitaxel, cisplatin, and tislelizumab. After three cycles, a partial response (PR) was achieved. The treatment was well-tolerated without significant adverse events, and the patient's condition remained stable with no signs of recurrence. This case highlights the unusual co-occurrence of a common (adrenal) and a rare (tongue base) metastatic site in SMARCA4-dNSCLC, which posed considerable diagnostic challenges. It expands the known clinical spectrum of this malignancy and underscores the importance of recognizing its rare metastatic patterns to guide accurate diagnosis and treatment.

**Keywords:** SMARCA4-deficient non-small cell lung cancer, immunohistochemistry, base of the tongue metastasis

## Introduction

Globally, lung cancer remains the leading cause of cancer mortality and ranks second in incidence [1]. The two main classifications of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC accounting for approximately 85% of cases. With the emergence of targeted therapy and immunotherapy the classification of lung cancer is no longer limited to traditional histology but increasingly focuses on molecular subtyping. Currently, the treatment strategies of NSCLC have fully shifted towards precision classification based on driver gene mutations. Some patients with NSCLC have mutations in genes such as KRAS, EGFR, ALK, ROS1, BRAF, HER-2, MET, NTRK, and RET [2], which have become important therapeutic targets. However, not all lung cancer patients have these common mutations. Approximately 15% of NSCLC patients have SMARCA4 gene deficiency [3]. SMARCA4 is a tumor suppressor gene encoding the BRG1 protein. BRG1 is the core subunit of the SWI/SNF genome remodeling complex [4]. This complex plays a central role in coordinating several key cellular processes, including transcription, DNA repair, cell cycle control, and differentiation [5].

SMARCA4-dNSCLC often exhibits poorly differentiated or undifferentiated histological features, poor response to conventional therapy, high aggressiveness, poor outcomes, and a tendency for early distant spread [3]. The high mortality and poor prognosis of lung cancer are closely related to its tendency to metastasize to distant sites. Studies have shown that nearly

50% of lung cancer patients develop distant metastases during diagnosis and treatment, with common sites including bone, liver, brain, and adrenal glands [6], while metastases to the gastrointestinal tract, oral cavity, and tongue are relatively rare. Previously, Rong Xiao and Kim MK reported cases of SMARCA4-dNSCLC metastasizing to the rectal sigmoid colon and the oral cavity, respectively [7, 8]. As far as we know, no cases of SMARCA4-dNSCLC with synchronous metastases to the base of the tongue have been reported. However, the diagnosis and treatment of SMARCA4-dNSCLC are inherently challenging: conventional treatments have limited effects, and the genetic deficiency further complicates management. Although some studies suggest that immune checkpoint inhibitors (ICIs) show good efficacy in such patients [9], their long-term effects remain unclear [10], and currently there is a lack of standardized diagnostic and treatment guidelines for such patients.

This article presents the first reported case of SMARCA4-dNSCLC with synchronous metastases to both the adrenal gland and the base of the tongue. By detailing the clinical characteristics, diagnosis, treatment, and response of this patient, we aim to fill a knowledge gap on the metastatic patterns of this aggressive cancer and provide a valuable reference for its clinical management.

## Case presentation

A 44-year-old male, active smoker with a 20-pack-year history, presented with a one-month history of cough and shortness of breath. A PET/CT scan performed at an outside institution revealed a right upper lobe lung malignancy with a left adrenal metastasis, involvement of right hilar, mediastinal, and right cervical lymph nodes, and focal radiotracer uptake in the right tongue base of undetermined nature (possibly inflammatory). He was subsequently transferred to this institution for further evaluation. Physical examination identified a hard, non-tender, poorly mobile, and well-defined mass (approximately 3 × 4 cm) in the right anterior cervical region, with diminished breath sounds on the right side. Initial laboratory studies were unremarkable. Contrast-enhanced chest CT showed an irregular soft-tissue mass in the right upper hilar region with multiple enlarged lymph nodes (**Figure 1A-C**). Abdominal CT confirmed a round-like left adrenal mass (**Figure 1D**). Nasopharyngolaryngoscopy and oropharyngeal MRI identified a mass at the right tongue base (**Figures 1E**, **2A-C**). Pathological examination of specimens obtained via EBUS-TBNA from the 4R lymph node station and right hilar lymph nodes, as well as a subsequent tongue base biopsy, confirmed SMARCA4-deficient undifferentiated non-small cell lung carcinoma, with the tongue lesion consistent with metastatic spread. Immunohistochemical analysis of the tongue base biopsy revealed the following CKpan (+), SMARCA4 (BRG1) (-, expression deficiency), CK5/6 (-), P40 (-), TTF1 (8G7G3/1) (-), INSM1 (-), Syn (-), CD20 (-), CD3 (-), Ki-67 (+, 80%); In situ hybridization: EBERs (Epstein-Barr encoded RNAs) (-). Immunohistochemical analysis of the 4R (right lower paratracheal) lymph nodes yielded the following: CKpan (+), SMARCA4 (BRG1) (-, expression loss), CK5/6 (-), P40 (-), TTF1 (8G7G3/1) (-), CK7 (-), Syn (focal+), Ki-67 (+, 40%). Immunohistochemical profiling was notable for ALK (D5F3) negativity and strong positive EGFR (EP38Y) expression in 90% of tumor cells (**Figures 3B**, **3C**, **4B**, **4C**). A definitive diagnosis of SMARCA4-deficient undifferentiated NSCLC with adrenal and tongue metastases (T3N2-M1c, Stage IVB) was established (**Figures 3A**, **3D**, **4A**, **4D**). Following multidisciplinary team discussion, palliative chemoimmunotherapy was initiated with the regimen: Paclitaxel (300 mg d1) + Cisplatin (70 mg d1-2) + Tislelizumab (200 mg d1), administered every 3 weeks. After three cycles, follow-up imaging on July 22, 2025, demonstrated significant regression of the primary lung lesion, adrenal metastasis, and cervical lymph nodes (**Figure 5A-E**), corresponding to a partial response (PR). The tumor response to treatment is detailed in **Table 1**. The treatment was well-tolerated, with a favorable safety profile documented in **Table 2**. As of the last clinical follow-up on October 2, 2025, the patient remains clinically stable on ongoing chemoimmunotherapy, which confirms a sustained treatment benefit exceeding six months. Patient was highly satisfied with the treatment and reported a positive experience (**Figure 6**). Written informed consent was obtained from the patient. This case study was approved by the Science and Technology Ethics Committee of Guangxi Medical University Cancer Hospital (approval number: KY2026619).

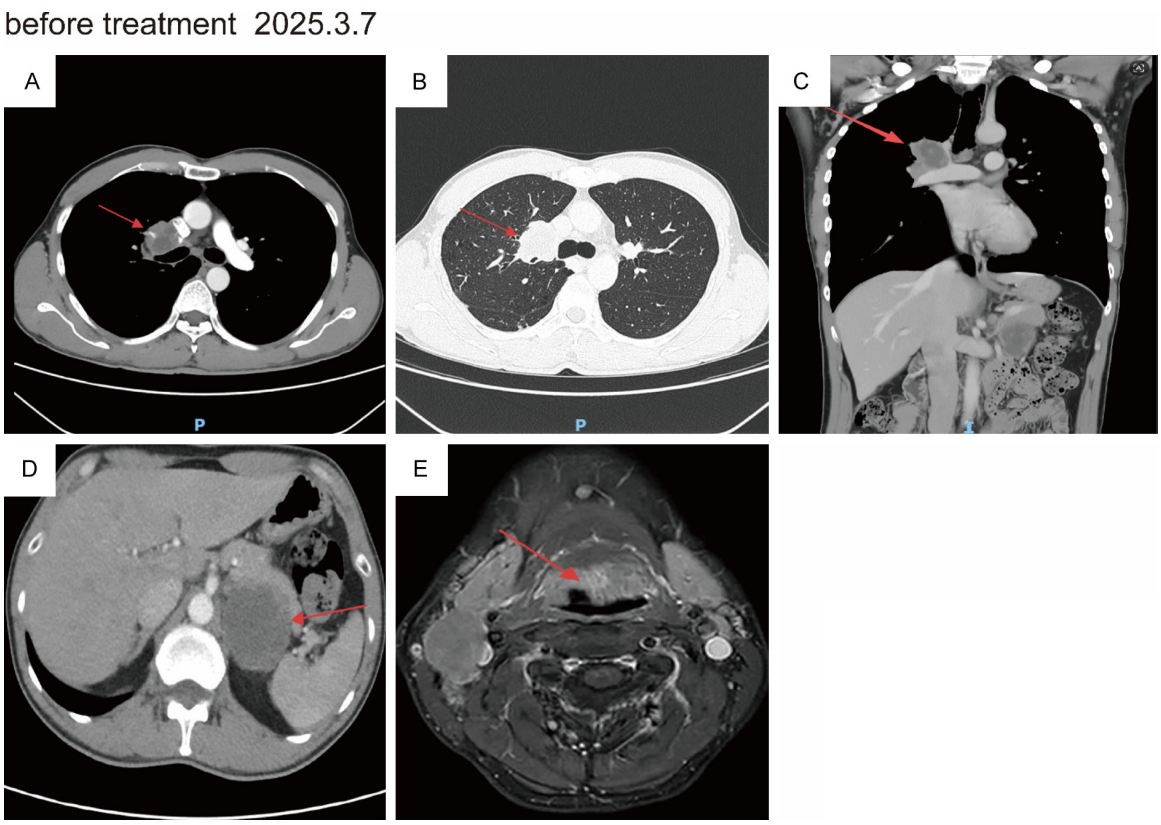


**Figure 1.** Response evaluation during the clinical course. A-C. The pretreatment chest CT revealed an irregular soft tissue mass in the right upper hilum, measuring approximately 3.2 × 3.4 × 3.7 cm. The mass exhibited ill-defined margins, lobulation, spiculation, and heterogeneous enhancement, with encasement of the right upper lobar pulmonary artery. D. A pretreatment abdominal CT image demonstrates a round-like mass in the left adrenal gland, measuring approximately 5.3 cm × 5.3 cm × 6.4 cm. The mass exhibits a relatively well-defined margin and shows heterogeneous mild enhancement at the periphery on contrast-enhanced scans (arrow). E. Pretreatment oropharyngeal and neck MRI demonstrated a focal depression on the right tongue base (estimated 3.5 × 1.9 × 1.9 cm; arrow) along with multiple bilateral cervical lymph nodes, some of which were necrotic and the largest measuring 3.4 × 2.0 × 3.2 cm.

## Discussion

Patients with SMARCA4-dNSCLC harbor mutations in the SMARCA4 gene, which encodes the BRG1 protein. BRG1 serves as the catalytic ATPase subunit of the SWI/SNF chromatin remodeling complex and is one of its most frequently mutated components. These mutations drive tumorigenesis through multiple mechanisms, including the perturbation of key signaling pathways such as PI3K/AKT [11]. The SWI/SNF complex is also involved in immune regulation [12]. Functionally, knockdown of BRG1 accelerates tumor growth, while overexpression inhibits glycolysis - evidenced by reduced glucose uptake, lactate production, and lower ATP levels - and inhibits the proliferation of NSCLC cells and in vivo tumor growth. Mechanistically, BRG1 mediates the physical interaction between SHP1 and PKM2. This interaction reduces PKM2 phosphorylation at tyrosine 105, promotes tetramer formation, and consequently modulates PKM2 subcellular localization and pyruvate kinase activity, ultimately inhibiting tumor growth [13]. Thus, SMARCA4 mutations are clear drivers of tumor progression. Furthermore, studies by Wang suggest that SMARCA2/4 mutations promote tumor progression through mechanisms such as inducing EMT, OXPHOS reprogramming, DNA repair defects, and genomic instability [14]. SMARCA4 mutations also lead to enhancer remodeling, resulting in the silencing of immune signaling pathways (such as STING1 and IL1β). This reduces T-cell infiltration, lowers the efficacy of immunotherapy, and leads to treatment resistance [14]. Collectively, SMARCA4 deficiency is linked to poor prognosis and suboptimal responses to conventional therapy.

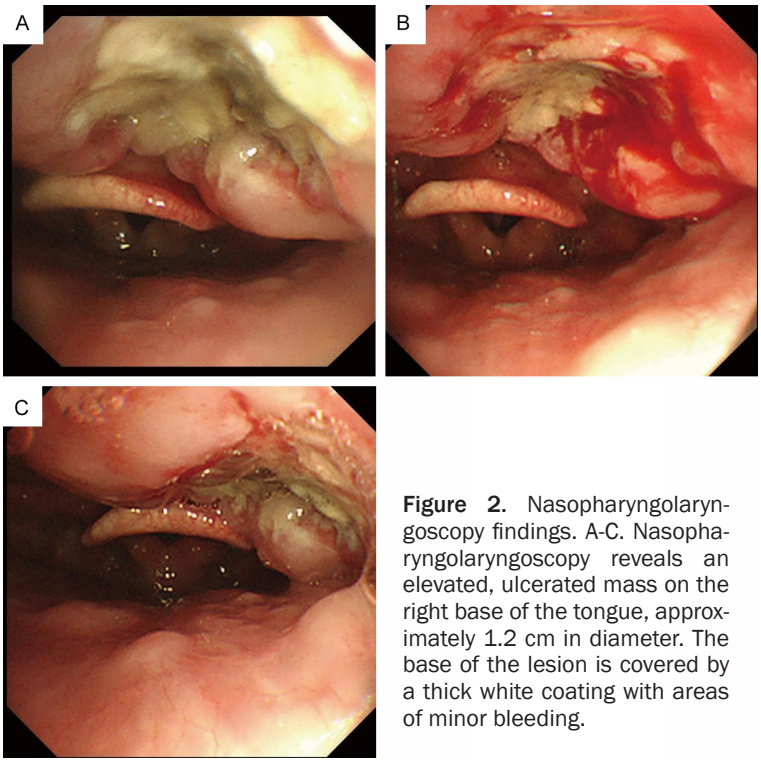


**Figure 2.** Nasopharyngolaryngoscopy findings. A-C. Nasopharyngolaryngoscopy reveals an elevated, ulcerated mass on the right base of the tongue, approximately 1.2 cm in diameter. The base of the lesion is covered by a thick white coating with areas of minor bleeding.

SMARCA4-dNSCLC was first described in the early 21st century [4]. Subsequent research, including work by Agaimy, has confirmed that it as an NSCLC subtype with unique morphological, immunophenotypic, and molecular features [15], leading to its recognition as a distinct thoracic tumor entity in the 2021 WHO Classification of Thoracic Tumors (5th edition) [16]. Epidemiological studies frequently associate SMARCA4-dNSCLC with smoking, which is consistent with the patient's long-term smoking history in this case. Furthermore, age ≥65 years, smoking, tumor diameter >5 cm, and distant metastasis have been identified as independent predictors of poor prognosis in this subtype [10]. Although the present patient had a smoking history and dual distant metastases (adrenal gland and tongue base), the tumor exhibited significant regression after three cycles of platinum-based chemotherapy combined with immunotherapy. This favorable response may be partially attributed to the relative sensitivity of SMARCA4-dNSCLC to platinum-based drugs [17]. As the SWI/SNF complex participates in DNA damage repair, its absence makes tumor cells more sensitive to DNA-damaging drugs such as platinum-based chemotherapy [18]. Additionally, the combination of platinum with PD-L1 inhibitors has shown efficacy in some SMARCA4-deficient NSCLC patients, particularly those with low BRG1 expression [17]. This is consistent with the treatment outcome of this patient. However, there is evidence suggesting that a subset of patients with SMARCA4-dNSCLC exhibit suboptimal responses to platinum-based doublets or chemo-immunotherapy combinations [19]. This heterogeneity in treatment response may be related to the specific category of SMARCA4 mutation (type I or II) and overall tumor heterogeneity, with type I mutations reportedly linked to superior outcomes with immune checkpoint inhibitors [5, 9]. The efficacy of platinum-based chemotherapy in SMARCA4-dNSCLC remains controversial. While the mechanistic rationale - that the absence of the SWI/SNF complex may make tumor cells more susceptible to DNA-damaging agents like platinum is compelling - robust clinical evidence from Dagogo-Jack [19] has not demonstrated that platinum-based dual-drug therapy is superior to other regimens. This difference between the previous theory and the clinical outcomes may be attributed to profound tumor heterogeneity, the influence of specific co-mutations, or the context of prior therapies. The significant therapeutic response observed in our patient is clinically consistent with a profile suggestive of a type I SMARCA4 mutation. However, this remains a hypothesis rather than a confirmed association due to the lack of genetic testing for mutation classification. Consequently, identifying predictive biomarkers for treatment response emerges as a critical objective for future research.

This patient had a high Ki-67 index and features of multiple lymph node metastases to the tongue base and adrenal gland. Diagnosis at stage IV aligns with the characteristic of SMARCA4-dNSCLC being prone to early metastasis [20], consistent with most study results. Over 88% of such patients have a Ki-67 index ≥30%, indicating strong tumor aggressiveness. That study also confirmed that patients receiving

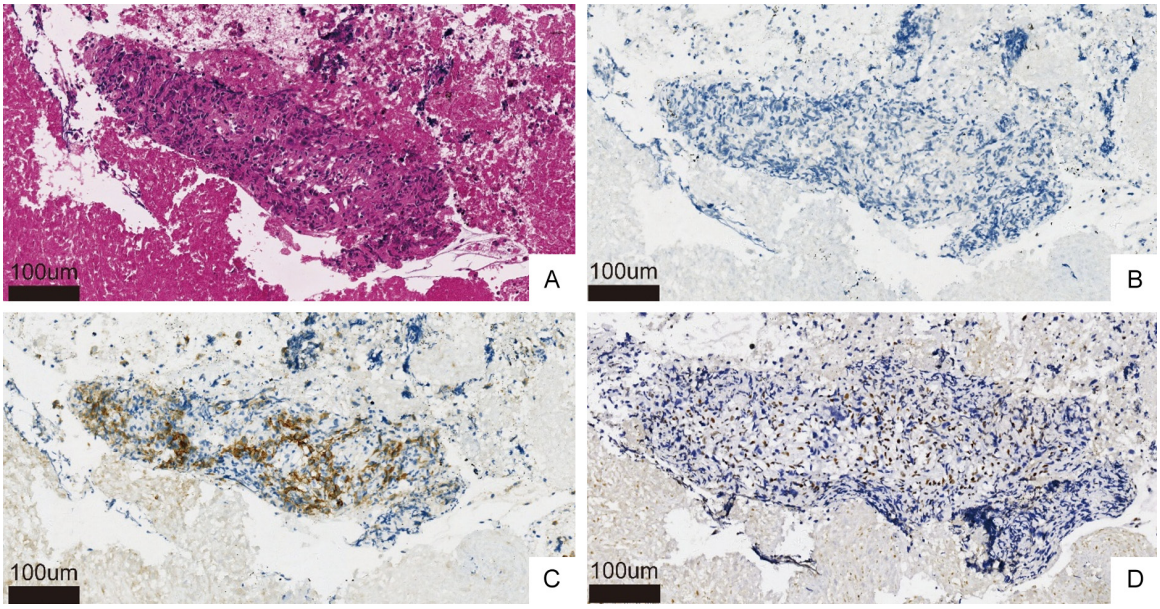


**Figure 3.** Histopathological and immunohistochemical (IHC) analysis of the station 4R lymph node biopsy. Magnification 200 times. A. Hematoxylin and eosin (H&E) staining reveals a proliferation of tumor cells with significant atypia. B. IHC staining for ALK (D5F3) is negative, demonstrating a lack of ALK protein expression. C. IHC staining for EGFR shows strong and diffuse positivity in a high percentage of tumor cells, indicating abundant EGFR protein expression. D. IHC staining for SMARCA4 (BRG1) shows retained nuclear expression (brown) in a minority of cells (internal control), while the majority of tumor cells show loss of nuclear expression (blue), confirming SMARCA4 deficiency.

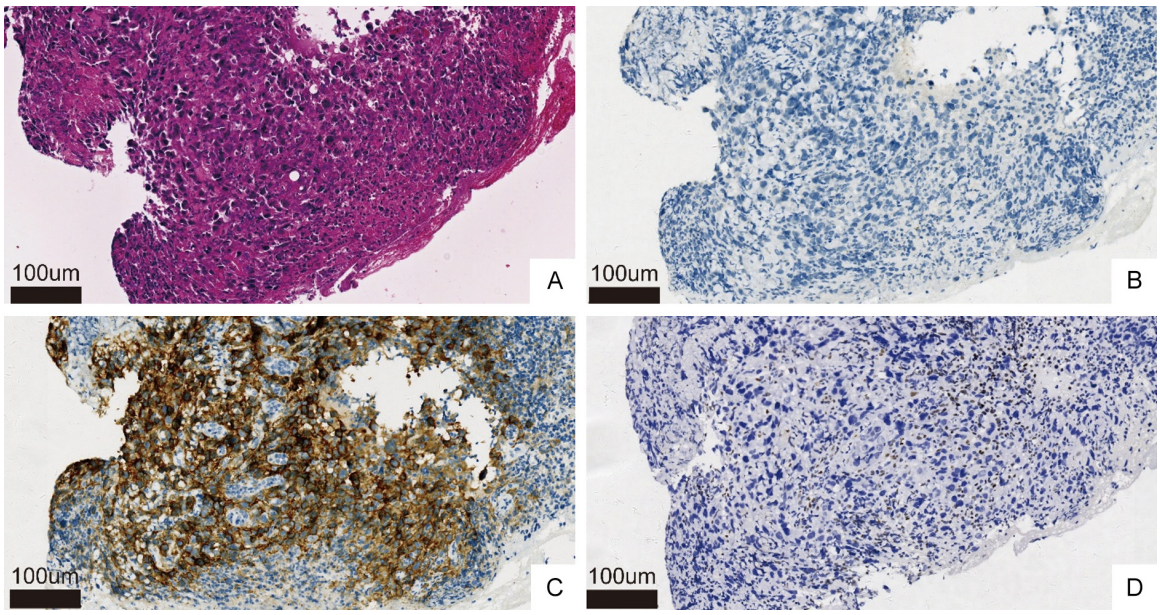


**Figure 4.** Histopathological and immunohistochemical (IHC) analysis of tongue base biopsy tissue. Magnification 200 times. A. Hematoxylin and eosin (H&E) staining reveals a proliferation of tumor cells with significant atypia. B. IHC staining for ALK (D5F3) is negative, demonstrating a lack of ALK protein expression. C. IHC staining for EGFR shows strong and diffuse positivity in a high percentage of tumor cells, indicating abundant EGFR protein expression. D. IHC staining for SMARCA4 (BRG1) shows retained nuclear expression (brown) in a minority of cells (internal control), while the majority of tumor cells show loss of nuclear expression (blue), confirming SMARCA4 deficiency.

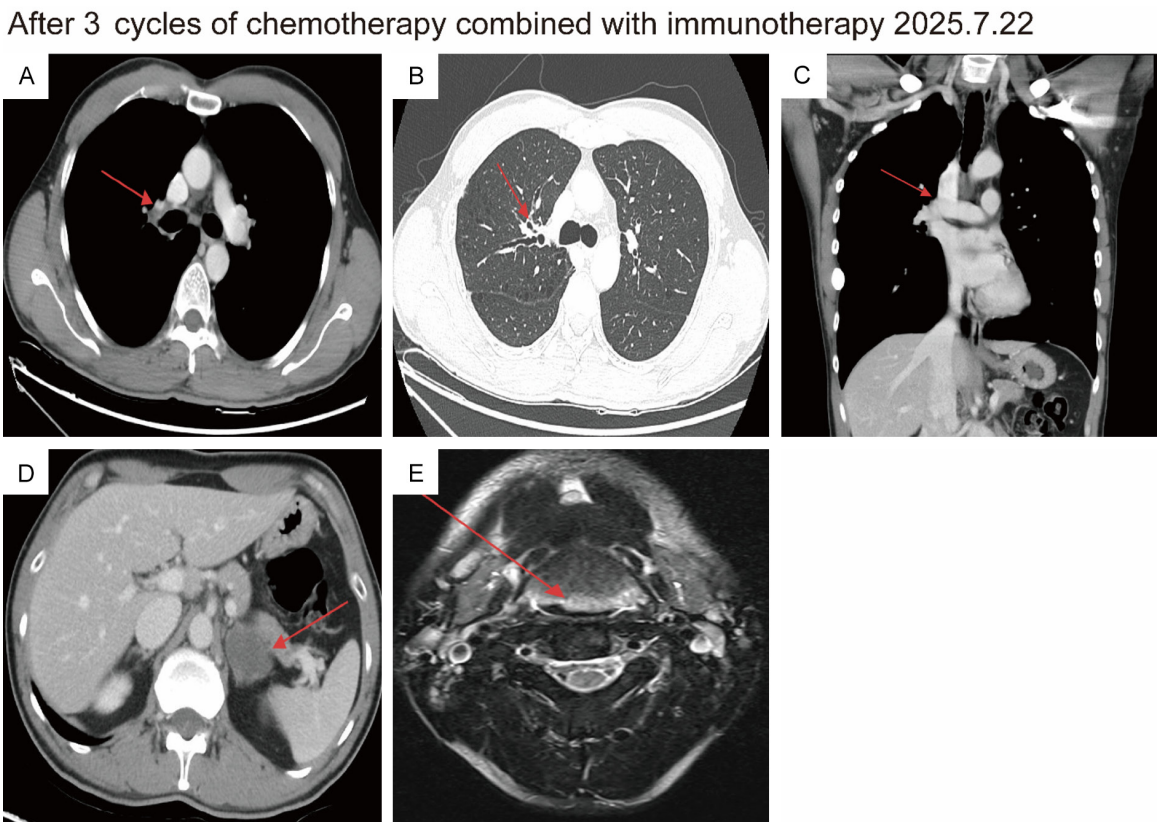


**Figure 5.** Response evaluation during the clinical course. A-C. After 3 cycles of treatment, follow-up CT demonstrated a significant reduction in the tumor, which measured approximately 1.3 cm × 1.0 cm × 0.6 cm (arrow). D. Follow-up abdominal CT after 3 treatment cycles revealed a markedly reduced mass, measuring 3.0 cm × 3.8 cm × 3.3 cm (arrow). E. The post-treatment MRI after 3 cycles revealed a modest decrease in the size of both the tongue base mass (approximately 3.5 × 1.5 × 1.5 cm; arrow) and the multiple bilateral cervical lymph nodes, the largest of which demonstrated a short-axis diameter of 0.7 cm.

**Table 1.** Tumor response assessment according to RECIST 1.1

| Target Lesion | Baseline | Post-Cycle 3 |
|---|---|---|
| Primary lung lesion | 44.43 mm | 13.50 mm |
| Base of tongue | 35.64 mm | 25.10 mm |
| Cervical metastatic lymph node | 42.93 mm | 14.80 mm |
| Left adrenal gland | 51.79 mm | 38.37 mm |
| Sum | 174.79 mm | 91.77 |
| Change | -- | -47.5% |
| Overall Response | -- | Partial Response (PR) |

Note: RECIST 1.1, Response Evaluation Criteria in Solid Tumors; PR, Partial Response; SD, Stable Disease. The overall response is based on the comprehensive assessment of target lesions, non-target lesions, and the emergence of new lesions. The best overall response in this case was Partial Response.

immunotherapy combined with chemotherapy had longer survival [5]. Like ordinary non-deficient lung cancer, SMARCA4-dNSCLC patients often present with main clinical symptoms such as cough. However, Kim JH. found that only a minority of patients exhibited symptoms like cough, hoarseness, or sputum production [21]; this patient presented with cough only, and the tongue base and adrenal metastases did not cause corresponding symptoms. One study showed about 56.52% of SMARCA4-dNSCLC patients were asymptomatic at initial diagnosis, discovered incidentally during physical examination [22], making them highly susceptible to missed diagnosis. Unlike previously reported SMARCA4-dNSCLC metastases to the oral cavity [8] or sigmoid colon/rectum [7] (which presented with symptoms related to the metastatic site, such as jaw swelling/pain or bloody stools), lung cancer metastasis to the tongue base has a low incidence and lacks specific symptoms, making

**Table 2.** Record of adverse events and toxicities during treatment

| Adverse Event | Baseline | | Post-Cycle 1 | | Post-Cycle 2 | | Post-Cycle 3 | | Post-Cycle 4 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Hematological Toxicity (Reference) | Value | Grade | Value | Grade | Value | Grade | Value | Grade | Value | Grade |
| Hemoglobin (135-170 g/L) | 105 | 0 | 105 | 0 | 100 | 0 | 107 | 0 | 110 | 0 |
| Neutrophils (1.8-6.3 × $10^9$/L) | 3.94 | 0 | 3.27 | 0 | 3.25 | 0 | 3.49 | 0 | 4.99 | 0 |
| ALT (8-40 U/L) | 15 | 0 | 21 | 0 | 26 | 0 | 22 | 0 | 23 | 0 |
| AST (5-40 U/L) | 28 | 0 | 21 | 0 | 27 | 0 | 26 | 0 | 22 | 0 |
| Platelets (125-350 × $10^9$/L) | 359 | 0 | 223 | 0 | 100 | 1 | 274 | 0 | 241 | 0 |
| Creatinine Clearance (74.45-156.38 mL/min) | 97.4 | 0 | 91.3 | 0 | 83.0 | 0 | 74.5 | 0 | 71.5 | 1 |
| Non-Hematological Toxicity | Grade | | Grade | | Grade | | Grade | | Grade | |
| Nausea | 0 | | 1 | | 1 | | 1 | | 1 | |
| Vomiting | 0 | | 0 | | 0 | | 0 | | 0 | |
| Peripheral Neuropathy | 0 | | 0 | | 0 | | 0 | | 1 | |
| Fatigue | 0 | | 0 | | 1 | | 1 | | 0 | |

Note: Toxicity was graded per CTCAE v5.0.

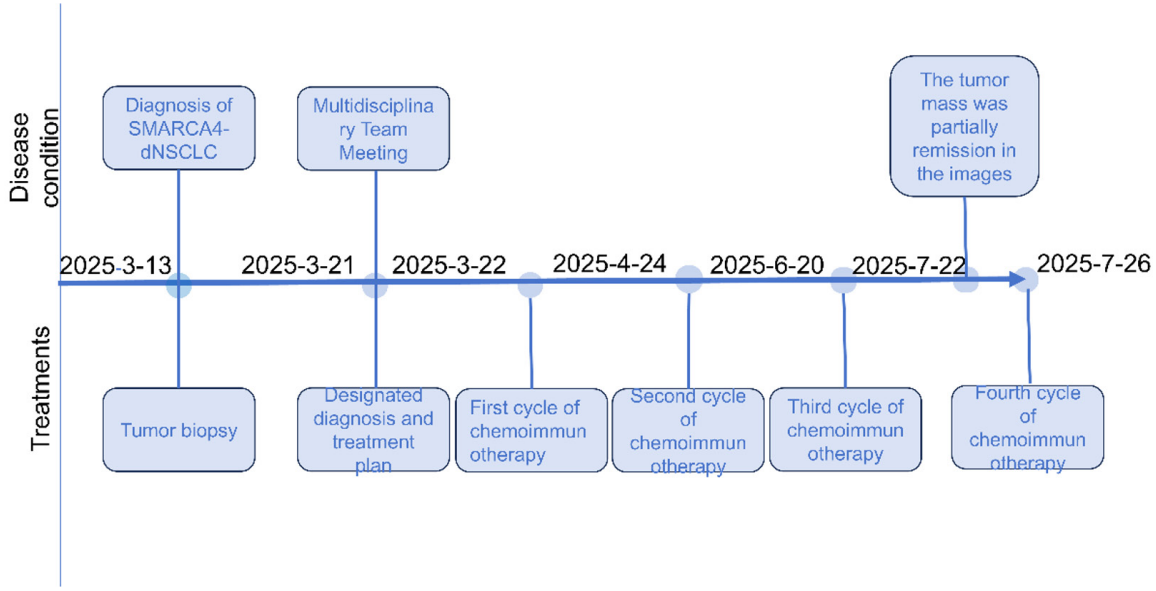


**Figure 6.** The whole clinical timeline of the patient, with major treatment and disease condition.

initial diagnosis particularly difficult. This suggests that first-contact physicians should perform careful and comprehensive examinations to avoid missed or misdiagnosis. Our reported patient's chief complaint did not mention symptoms related to the tongue base or adrenal metastases. When lung cancer patients present with atypical symptoms (e.g., intraoral mass, hoarseness, dysphagia), the possibility of rare metastases should be highly suspected, and detailed examinations including nasopharyngolaryngoscopy should be performed. These patients are prone to adrenal metastasis, consistent with numerous reports [5, 23], a mechanism potentially related to the adrenal gland's rich blood supply and abundant lymphatic pathways, among other factors [24]. The occurrence of tongue base metastasis in this patient might be mediated via lymphatic spread (the tongue base is a region rich in lymphoid tissue [25]) or expression of specific cell adhesion molecules (e.g., the CXCR4/CXCL12 axis), although the exact mechanism remains unclear and warrants further study.

Pathological examination is the gold standard for diagnosing SMARCA4-dNSCLC, and immunohistochemistry (IHC) is the primary method to distinguish this tumor from other types. A diagnosis of SMARCA4-deficient tumor can be

made if IHC shows negative BRG1 staining, regardless of whether a SMARCA4 gene mutation is detected [26, 27]. SMARCA4-deficient undifferentiated tumor (SMARCA4-dUT) highly overlaps pathologically with SMARCA4-dNSCLC, but SMARCA4-dUT should exhibit corresponding histological morphology besides BRG1 loss; however, it is more malignant, has a worse prognosis, and shows better efficacy only with immune checkpoint inhibitors [26]. In the pathological diagnosis of SMARCA4-UT and SMARCA4-dNSCLC, SMARCA4-dNSCLC typically presents as conventional adenocarcinoma or less commonly squamous cell carcinoma, while SMARCA4-UT more often exhibits rhabdoid morphology and frequently shows high expression of markers like SOX2, CD34, SALL4 [28], whereas SMARCA4-dNSCLC rarely expresses SALL4 and CD34. Kim [21] found from an imaging perspective that SMARCA4-dNSCLC often presents as lobulated, located in the lung periphery, frequently invading the pleura or chest wall; while Crombé [29] found SMARCA4-UT primary tumors were mainly located in the mediastinum and pleura with ill-defined margins. Unlike this case report, our patient had central SMARCA4-dNSCLC with ill-defined margins, indicating that imaging findings are insufficient to accurately distinguish between them, further emphasizing the importance of IHC and molecular subtyping in differential diagnosis. Besides differentiation from SMARCA4-UT, it also needs to be distinguished from neuroendocrine carcinoma, large cell lymphoma, germ cell tumors, thymic carcinoma, and NUT carcinoma; positive SMARCA4 can help exclude these tumors [27].

Consistent with previous reports, the immunophenotype of SMARCA4-dNSCLC is characterized by frequent negativity for TTF-1 (~80% of cases) and P40 (81.4%) [10, 30]. This profile, which also typically includes negative staining for ALK (Ventana D5F3) and p-TRK, was recapitulated in the present case [23]. Furthermore, molecular phenotypic studies have confirmed CK-pan positivity and P40 negativity across different tumor locations [31]. In our patient, the diagnosis of SMARCA4-dNSCLC was supported by negative BRG1, TTF-1, and P40 staining, alongside positive CK-pan. According to Sauter, the loss of epithelial structure with diffuse strong cytokeratin positivity generally rules out SMARCA4-dNSCLC [32]. In this case, the preserved epithelial structure in pathological images and the positive CK-pan staining (likely originating from the tongue base metastasis and confirming epithelial origin [33]) align with the diagnosis. However, focal synaptophysin (Syn) positivity introduced diagnostic complexity, as Syn is a key marker of neuroendocrine differentiation [34]. In the context of a SMARCA4-deficient tumor, such focal positivity necessitates a comprehensive assessment incorporating additional neuroendocrine markers (e.g., CD56, CgA) and morphological features to definitively exclude a true neuroendocrine carcinoma [35].

In addition to the defining SMARCA4 mutation, SMARCA4-dNSCLC frequently harbors co-mutations in genes such as KRAS, KEAP1, and STK11 [9]. However, these are predominantly nonsense mutations for which no targeted therapies are currently available. A small subset of patients may present with concurrent driver gene alterations like ALK or EGFR; such patients often demonstrate a favorable response to first-line targeted therapy [36, 37]. In the present case, immunohistochemistry (IHC) for ALK and EGFR was performed on biopsy specimens from both the tongue base and the station 4R lesions, yielding an ALK-negative result and strong EGFR positivity (90%). While IHC detection of EGFR protein expression serves as a preliminary, rapid, and cost-effective method to screen for patients who may benefit from EGFR-TKI therapy [38], several researchers emphasize that it cannot entirely replace standard genetic testing methods like PCR for routine EGFR mutation analysis. Even with negative IHC results, further genetic analysis remains necessary [39, 40]. Although the high EGFR protein expression observed in this patient was a notable finding [41], the absence of confirmatory genetic testing for an activating EGFR mutation precluded the consideration of EGFR-TKIs as a therapeutic option [42]. Consequently, this line of treatment was not pursued.

## Conclusion

This study reports a case of SMARCA4-dNSCLC with dual metastases to the adrenal gland (common) and base of the tongue (rare), expanding the understanding of rare metastatic patterns in this disease and filling a gap regarding tongue base metastasis in SMARCA4-dNSCLC. Case analysis indicates that platinum-based chemotherapy combined with immunotherapy (dur-

valumab) can achieve partial response in patients, suggesting that this regimen may provide clinical benefit for patients with high tumor burden and multiple metastases in SMARCA4-dNSCLC. However, the molecular heterogeneity and diverse treatment responses of SMARCA4-dNSCLC require further study. Although high EGFR protein expression was found in this case, targeted therapy was not attempted due to lack of molecular confirmation, highlighting the importance of integrating morphology, immunohistochemistry, and molecular testing in multimodal diagnosis. Future efforts should explore the mechanisms of interaction between SMARCA4 deficiency and the immune microenvironment, as well as the clinical significance of its co-mutation with common driver genes, to develop more effective personalized treatment strategies for these patients.

## Disclosure of conflict of interest

None.

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