

Case Report

Gingival metastasis from thoracic SMARCA4-deficient undifferentiated tumor: a case report

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Abstract – Introduction: Thoracic SMARCA4-deficient Undifferentiated Tumors (SMARCA4-UT) are rare and aggressive malignancies. This case is unique as it describes the first gingival metastasis from thoracic SMARCA4-UT, emphasizing the diagnostic role of dental professionals. **Observation:** A 71-year-old man, heavy smoker (50 pack-years), presented with chest pain, dyspnea, weight loss, and a gingival lesion. Oral examination revealed poor oral health with severe periodontitis, trismus, halitosis, pain on palpation, and a 3 cm friable gingival tumor in sector 2. Premolars showed grade 3 mobility and loss of vitality. 3D imaging confirmed tumor extension. CT, PET-CT, revealed thoracic, adrenal masses and multiple metastases. Histopathology confirmed SMARCA4-UT with gingival metastasis. **Outcome:** The patient's condition deteriorated rapidly, and he died before treatment could be initiated. **Conclusion:** Dental professionals play a key role in suspecting systemic disease from oral manifestations. This case underscores the importance of considering metastasis in atypical oral tumors.

Introduction

Oral metastases are uncommon. They account for approximately 1% of oral neoplasms [1]. One third of these lesions involve soft tissues, and most of the others are intraosseous [1]. Metastatic tumors of the oral soft tissues most commonly affect the attached gingiva (60%) and the tongue (18%) [1]. The most frequent primary sites of oral metastasis are the breast, lung, kidney, bone, and colon [1].

In 2021, Thoracic SMARCA4-Deficient Undifferentiated Tumor (SMARCA4-UT), as a new malignant entity, was added to the fifth edition of the WHO anatomical pathology classification [2]. SMARCA4-UT is rare, with about one hundred cases which have been reported in the literature [3]. This tumor is a high-grade malignant neoplasm, with rhabdoid or undifferentiated phenotype, displaying SMARCA4/BRG1 deficiency, *i.e.*, a gene involved in chromatin remodeling. This mutation was found in more than 20% of human cancers [4], and in about 5% of non-small cell lung carcinomas (NSCLC), mainly adenocarcinomas. Nevertheless, thoracic SMARCA4-UT have genetic differences compared to SMARCA4-deficient non-small cell lung cancer (NSCLC) and display proper morphological characteristics that are similar to Small Cell Carcinoma of

the Hypercalcemic Type (SCCOHT) and Malignant Rhabdoid Tumor (MRT) [2]. Cytopathology, immunohistochemistry, and molecular tests are necessary to diagnose SMARCA4-UT. Histologically, these tumors are characterized with rhabdoid or undifferentiated morphology and strong diffuse expression of cytokeratin, featuring extensive areas of necrosis. Sheets and clusters of large-sized epithelioid cells are observed with variable cell cohesion and well-defined boundaries. These cells exhibit large vesicular nuclei, prominent nucleoli, and large paranuclear intracytoplasmic inclusions. Sometimes, they have eosinophilic cytoplasm with an eccentric nucleus [4]. The deficiency diagnosis is made through immunohistochemistry or molecular biology. Immunohistochemical screening often reveals immunopositivity for CD34, EMA, SALL4, SOX2, INI-1, and immunonegativity for TTF1, P40, SMARCA2 and 4 [4,5]. Loss of TTF1 expression indicates tumor dedifferentiation leading to increased metastatic potential [6].

Thoracic SMARCA4-UT mostly affects middle-aged men (median = 59 yr) who had a smoking history (90% of cases) [7]. The diagnosis of SMARCA4-UT is made difficult by the variety of clinical manifestations from one case to the other. The nonspecific symptoms include dyspnea, chest pain, pleural effusion, pleural empyema, pleurisy, emphysema, reflux, and asthenia [4]. Moreover, primary tumors are often large and compressive, causing compression and invasion of adjacent

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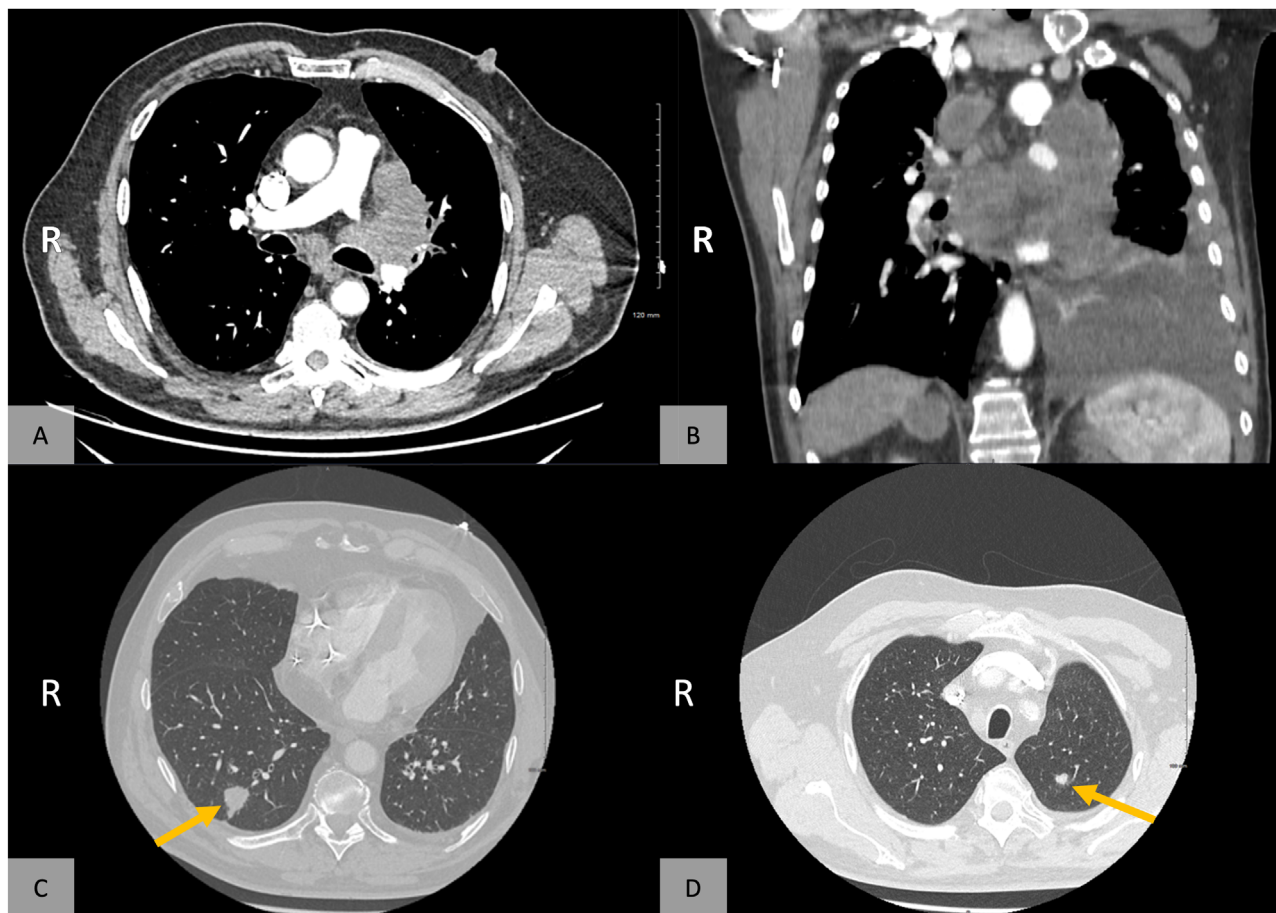


Fig. 1. (A) Axial mediastinal window CT sections show large mediastino-hilar masses, more voluminous at the left and in subcarinal area, left pleural effusion. (B) Coronal mediastinal window CT section. (C-D) Axial lung window CT sections show a postero-basal spiculated nodule of secondary appearance in right lower pulmonary lobe (C), and another one in left apical upper lobe (D) (yellow arrows).

organs, including superior vena cava syndrome, esophagus stenosis, and spinal cord compression [4]. The prognosis for these cancers is very poor, with a median survival of about 4 to 7 months. Most patients die from complications due to local invasion [4]. Metastases are very common (77% of cases) [5] and can invade mediastinum, hilum, pulmonary parenchyma, and pleura. Metastases have been reported in lymph nodes (59–91%), adrenal glands (27–48%), bones (24–55%), lungs (29%), liver, digestive system, central nervous system, kidneys [5,8], and one case of intraocular metastasis has been described [9]. We present here a case of oral metastasis.

Observation

A 71-year-old man was hospitalized in pneumology department for chest pain, deterioration of health, a weight-loss of 10 kg in less than 6 months, and dyspnea with pleural effusion. His main medical history was obstructive sleep apnea syndrome, Parkinson's disease, arterial hypertension, cardiac pacemaker implantation, recurrent renal colic, and gout. The patient declared a smoking history of 50 pack-years.

Thoracic CT-scan revealed a large bilateral mediastino-hilar mass and multiple spiculated nodules of secondary appearance, without noticeable bone lesion (Fig. 1).

Abdomino-pelvic CT-scan revealed bilateral adrenal nodules of secondary sites appearance (Fig. 2).

Cranial CT-scan didn't detect brain lesion.

The bronchial fibroscopy revealed an infiltration of the left upper and lower lobar bronchi, but the multiple biopsies performed were non-contributive. Pleural fluid cytology revealed the presence of suspicious cells. CT-scan-guided transparietal biopsies of left lung parietal nodule and left adrenal secondary site was performed. Histopathological examination revealed an extensive infiltration by a poorly differentiated atypical epithelioid or even rhabdoid proliferation. Tumors were composed of large undifferentiated polygonal cells poorly cohesive arranged in small clusters. Frequent foci of necrosis were noted. Tumor cells featured abundant eosinophilic cytoplasm with unclear boundaries. Nuclei were large, hyperchromatic, round or angular, sometimes vesicular, with a high mitotic activity.

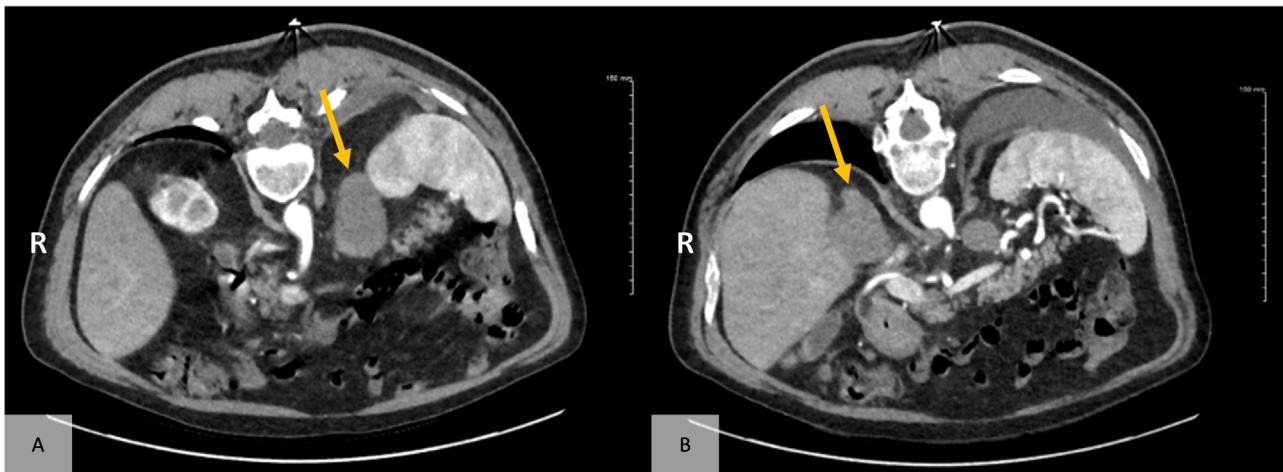


Fig. 2. Axial abdominopelvic arterial Phase CT sections revealed bilateral adrenal masses of secondary sites appearance (A: left mass; B: right mass). Note the left basal pleural effusion.

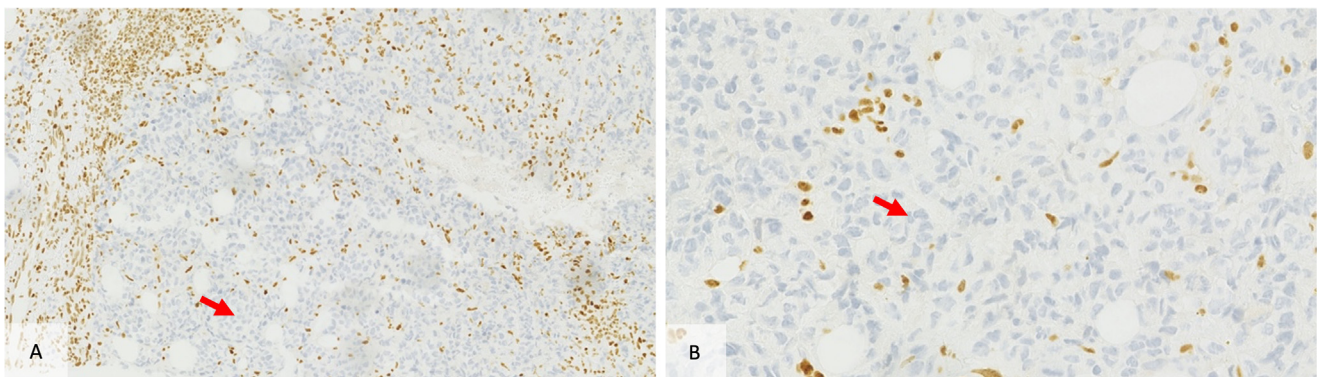


Fig. 3. Immunohistochemistry SMARCA4 of Thoracic SMARCA4-UT in left lung parietal nodule using chromogenic detection with diaminobenzidine (DAB) chromogen (brown) and counterstain with hematoxylin (blue), showing SMARCA4 loss expression (red arrows) (magnifications x20 [A] and x40 [B]).

Immunohistochemically, the tumor cells were negative for TTF1, P40, CK AE1/AE3, CK5/6, CK7, CD20, CD30, KL1, MDM2, Calretinin, Desmin, Melan A, HMB45, LCA, CD56, S100 protein, SOX10, OCT4, PLAP, SALL4, ALK1, ROS1 and positive for CD34, INI-1, EMA. Also, tumor cells lost SMARCA4 nuclear expression (Fig. 3), confirming the diagnosis of SMARCA4-UT. Thus, the patient was diagnosed with stage IV disease.

18-FDG-PET-CT-scan showed large hypermetabolic left para-hilar ganglio-tumor complex, associated with pulmonary, lymph nodal, peritoneal, bone, muscular, adrenal, and subcutaneous hypermetabolic lesions, with suspicion of right tonsillar and gastric hypermetabolic involvements (Fig. 4A), and discrete left maxillary hypermetabolism (Figs. 4B and 4C).

Otorhinolaryngological examination revealed posterior right tonsillar hypertrophy with a small ulcer area, featuring a high right-sided lateral cervical adenopathy.

The patient was referred to our stomatology department for a left maxillary premolar gingival lesion that evolved for more than one month. His attending physician initially suspected a dental abscess, for which he prescribed two courses of antibiotic therapy.

At the clinical examination, the patient presented with mild trismus, poor oral health, with chronic periodontitis Stage III according to the Chicago 2017 classification, xerostomia, halitosis, and pain at palpation [10]. The stage of periodontitis could be evaluated, but the grade could not be determined due to the absence of dental follow-up in our department. The tumor size was of 3 centimeters in its major axis. It was proliferative, friable, and invaded the vestibular and the palatal gingiva in the premolar sector (Fig. 5). The left maxillary premolars presented grade 3 mobility according to the Miller classification [11]. The first premolar was endodontically treated and restored with a crown. The second premolar tested non-vital.

Dental panoramic X-ray and bone window CT images revealed resorption of the vestibular cortical bone on left maxillary premolar teeth (Fig. 6).

The biopsy revealed undifferentiated atypical malignant cells, similar to those found in lung and adrenal tumors, confirming the diagnosis of metastasis (Fig. 7). The patient died a few days after admission and before a treatment plan could be set up.

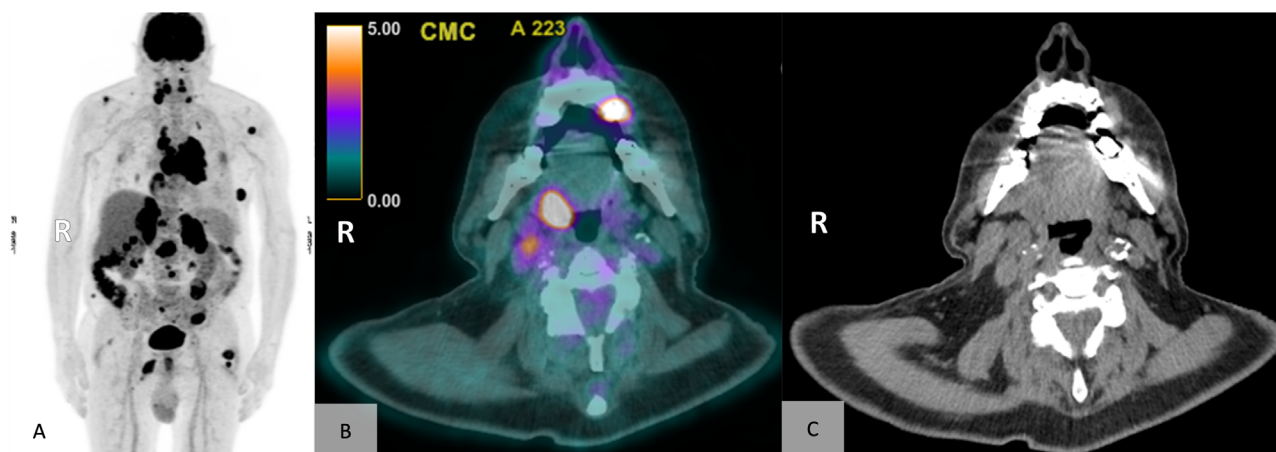


Fig. 4. (A) Whole body positron emission tomography PET revealed hypermetabolic left para-hilar ganglio-tumor complex, associated with pulmonary, lymph nodal, peritoneal, bone, muscular, adrenal, and subcutaneous hypermetabolic lesions. PET (B) merged with axial CT sections (C) revealed hypermetabolic right tonsillar lesion featuring lateral cervical adenopathy, and hypermetabolic lesion in left maxillary premolar sector.



Fig. 5. Clinical gross photograph of the left maxillary premolar gingival lesion.

Differential diagnoses

Epidermoid carcinoma: This was the principal differential diagnosis, as epidermoid carcinoma is the most common malignant tumor in the oral cavity, accounting for approximately 90% of all oral cancers. Also, the patient's severe smoking history (50 pack-years) is a known major risk factor for squamous cell carcinoma. However, the lack of squamous differentiation in the biopsy, along with the undifferentiated histopathological features and loss of SMARCA4 expression, ruled out this diagnosis.

Dental abscess: This was considered due to the patient's poor oral hygiene. However, the rapid progression, lack of associated dental infection, and histopathological findings (undifferentiated atypical cells) did not support this diagnosis.

Epulis: A benign lesion commonly found in the oral cavity. This was ruled out due to the presence of malignant features in the biopsy (poorly differentiated tumor cells with necrosis).

Discussion

The previously named "SMARCA4-deficient thoracic sarcoma", sometimes confused with SMARCA4-deficient occur in non-small cell lung carcinoma (SD-NSCLC), was recently redefined in the 2021 World Health Organization Classification of Thoracic Tumors [2]. These tumors have unique clinicopathologic phenotype and poorer overall survival than SD-NSCLC [5]. The tumors from SMARCA4-UT spectrum can develop in the head region, particularly in the sinonasal area, predominantly originating from the nasal cavity [12]. This includes SMARCA4-deficient Sinonasal Carcinoma, and within the expanded spectrum, SMARCA4-deficient Sinonasal Teratocarcinosarcoma, whose histological features recapitulate the pattern seen in other SMARCA4-deficient undifferentiated malignancies of the thorax, ovary, and other visceral organs [12]. In a recent review, Agaimy *et al.* pointed out that these tumors can be easily confused with metastatic SMARCA4-deficient undifferentiated thoracopulmonary malignancies that may occur in the head and neck, and less frequently in sinonasal areas [12].

As for most cases of SMARCA4-UT described in the literature, the present patient had a smoking history [4,5,7] and was diagnosed with stage IV disease [4]. The combination of cytopathology, immunohistochemistry and molecular tests is necessary to diagnose SMARCA4-UT. According to Perret *et al.*, the diagnosis of SMARCA4-UT usually requires the following three criteria: 1) rhabdoid or poorly differentiated phenotype; 2) complete or major loss of SMARCA4 and

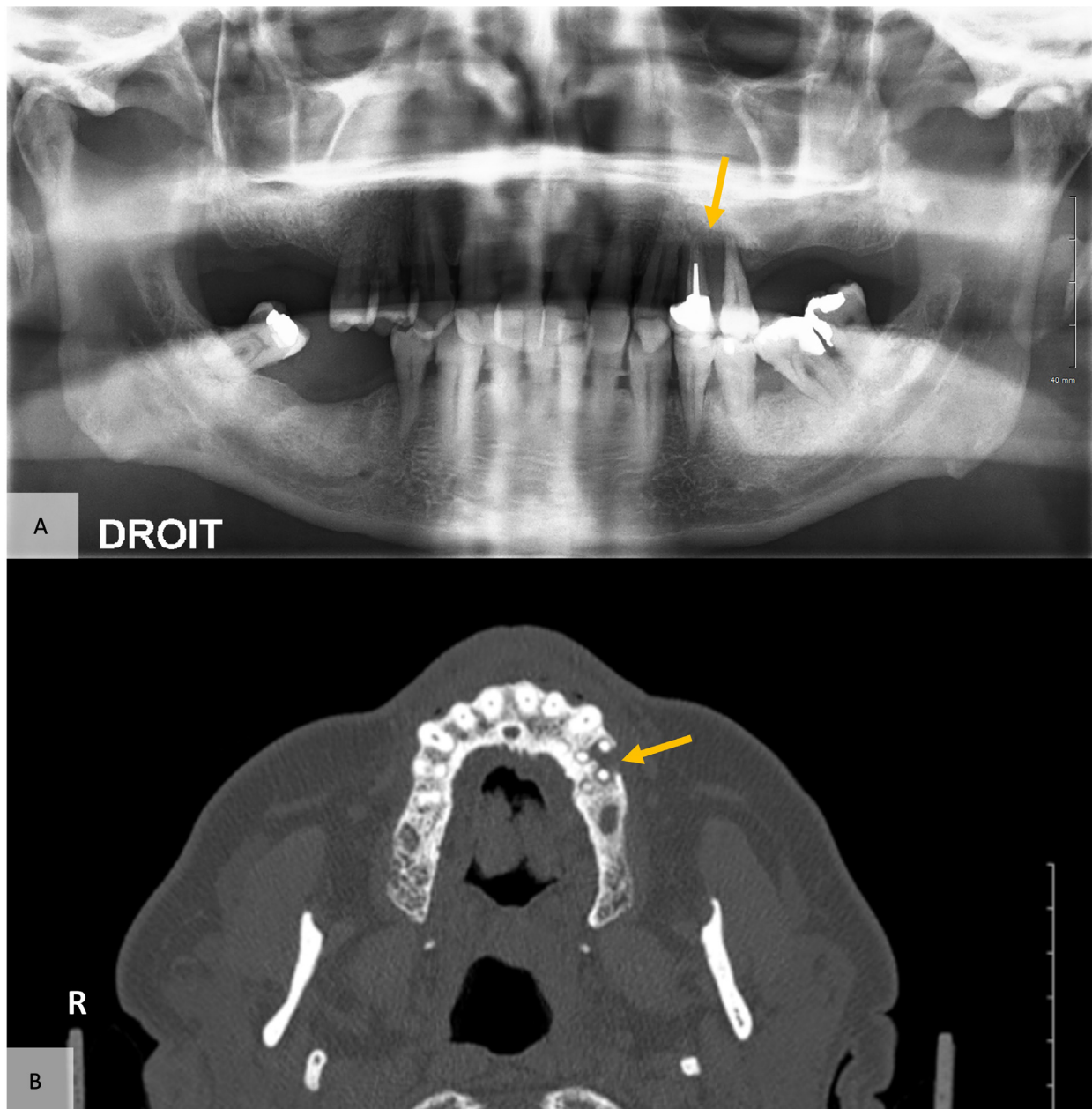


Fig. 6. (A) Dental panoramic X-ray shown periapical bone resorption bone on left maxillary premolar teeth. (B) Axial bone window CT section revealed resorption of the vestibular cortical bone on left maxillary premolar teeth.

SMARCA2 expression; 3) focal or diffuse expression of at least two species of the following markers: SOX2, CD34, and SALL4 [5]. In the present case, a poorly differentiated atypical epithelioid or even rhabdoid phenotype was observed. Although the second criterion was met, immunohistochemical screening revealed negativity for SALL4 (67% of cases [4]) and positivity for CD34 (65%–76.2% of cases [4]). SOX2 was not tested in present case. Also, in the present case, tumoral tissue was negative for TTF1 (100% cases), AE1/3 (62% cases), P40 (100% cases), ALK1 (93.3% cases), ROS1 (100% cases), and positive for EMA (discreet and heterogenous, like 67% cases), INI1 (100% cases). These data are in agreement with earlier studies [4,5].

Endobuccal metastasis of SMARCA4-UT had never been described before.

About five months have passed between the initial diagnosis and the patient's death, it is in line with the dreadful prognosis of this cancer as mentioned in literature [4], with a median survival of 4 to 7 months.

Given that this case report is addressed to dental professionals, it is essential to underline the role of dentists as the first-line practitioners in evaluating oral lesions. Often, such lesions are investigated initially as odontogenic conditions, especially in patients with poor oral health or risk factors for common dental pathology. While the exclusion of a local dental etiology is a critical first step,

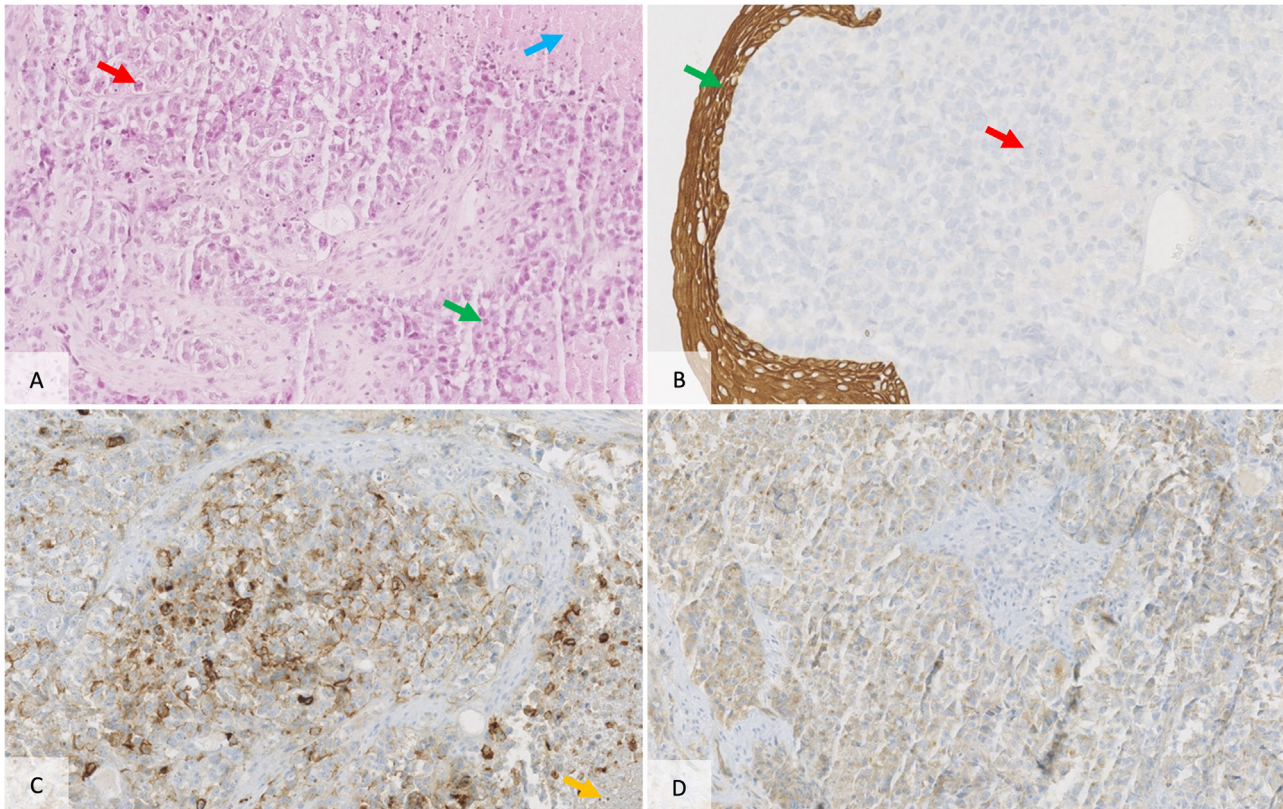


Fig. 7. Histology of Thoracic SMARCA4-UT gingival metastasis (magnifications x20). (A) Haematoxylin-eosin saffron (HES): trabeculae and solid nests of large rhabdoid cells (green arrow). Nuclei are large, clear, and nucleolated (red arrow). Large areas of necrosis (blue arrow). (B) No keratinization shown by immunohistochemistry AE1/AE3 using chromogenic detection with DAB (brown) and counterstain with hematoxylin (blue): immunonegativity for AE1/AE3 was observed in tumors cells (red arrow), normal epithelium cells (green arrow). (C) Mild heterogeneous immunopositivity for EMA (brown), and occasionally dot-like in pattern (yellow arrow). (D) Mild heterogeneous immunopositivity for Synaptophysin (brown).

clinicians must remain mindful of the possibility of an underlying systemic or metastatic disease, particularly when the lesion shows atypical features or fails to respond to conventional treatment. This case therefore reinforces the importance of maintaining a high level of vigilance in distinguishing between odontogenic and metastatic processes, as the clinical, prognostic, and therapeutic implications differ profoundly.

Conclusion

Thoracic SMARCA4-UT are uncommon cancer with high-grade malignancy with strong capability to invade adjacent and distant organs.

Most of patients are at stage IV of the disease when there are diagnosed. It contributes to a very poor prognosis, with a median survival about 4 to 7 months.

To our knowledge, the present report of a patient with a gingival metastasis from thoracic SMARCA4-UT is the first one.

This case highlights the need for dental professionals to remain vigilant in distinguishing odontogenic from metastatic oral lesions.

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This study did not receive any funding.

Conflicts of Interest

There is no conflict of interest in regards to this article.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon request.

Author contribution statement

The main author is Dr Alexis Lagrost, who worked as co-author with Dr Eugénie Bertin and Dr Elise Weber, with the help of Dr Isabelle Bedgedjian.

Informed consent

Consent was obtained from the patient.

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