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CASE REPORTS

Metastatic Neuroblastoma to the Mandible of Children: Report of Two Cases and Critical Review of the Literature

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Abstract

Neuroblastoma is the most common extracranial solid cancer of infancy, occurring mainly in the adrenal gland, with high metastatic potential. However, involvement of the head and neck region is rare. Here, we present two cases of metastatic neuroblastoma of childhood, in which a mandibular swelling was the first sign of disseminated disease. Case 1 describes a 4-year-old boy with a 2-week history of painful swelling in the left mandibular region, body soreness and weakness. Panoramic radiography and computed tomography showed a destructive lesion in the left mandibular ramus. Case 2 describes a 3-year-old boy with a 1-month history of swelling in the right mandibular area. Panoramic radiograph and cone-beam computed tomography showed a destructive lesion in the right body and ramus of the mandible, displacing tooth germs, with the destruction of vestibular and lingual bone cortices. In both cases, microscopic analyses revealed a diffuse proliferation of small, round, and blue cells with hyperchromatic nuclei and scant cytoplasm. While Case 1 was more undifferentiated, Case 2 presented eosinophilic areas suggestive of neuropil. A large immunohistochemical panel was performed, showing expression of neural markers such as CD56, neuron-specific enolase (in Case 2), chromogranin, and synaptophysin. Both lesions presented a high proliferation index (Ki67 > 70% and 80%, respectively). Positron emission tomography-computed tomography revealed ipsilateral adrenal primary lesions in both cases, with multiple bone metastatic lesions. Besides the mandible, multiple sites of the axial and appendicular skeleton were affected. Treatment consisted of induction chemotherapy, adrenalectomy, consolidation chemoradiotherapy, and post-consolidation therapy.

Keywords Neuroblastoma · Neoplasm metastasis · Mandible · Pediatrics · Oral diagnosis · Case reports

Introduction

Neuroblastoma (NB) is a complex heterogeneous neoplasm arising from the sympathetic nervous system, representing 97% of all neuroblastic tumours, including ganglioneuroblastoma and ganglioneuroma. It is the most common extracranial solid tumour found in children, with an early onset and high metastatic rates. It is estimated that 700 cases of neuroblastoma are diagnosed every year in the United States alone, normally affecting children less than 5 years old with a mean age at diagnosis of 19 months. NB is responsible for approximately 15% of all pediatric cancer fatalities. This neuroblastic tumour originates from neural crest cell derivates in the sympathetic nervous system. Usually, the primary sites comprise the adrenal gland (46% of cases), extra-adrenal abdominal area (18%), posterior mediastinum/thorax (14%), pelvis, and other sites (22% together) [1, 2]. Advanced disease usually shows metastases, and bone marrow, cortical bone, liver, and lymph nodes are the sites most often involved [2]. Hence, we report two cases of metastatic neuroblastoma, in which a mandibular swelling was the primary signal, and a critical review of the literature.

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Case 1

A 4-year-old boy was referred from his treating dentist due to a painful swelling in the mandible, with a 2-week history of body soreness and weakness. On extra-oral examination, the patient presented a significant swelling on the left side of the face. Intra-oral evaluation was impaired because of the trismus, but an expansive lesion covered by normal mucosa could be observed in the left retromolar trigone area (Fig. 1a, b). Medical history was otherwise noncontributory.

Panoramic radiography showed a diffuse radiolucent image in the left mandibular ramus extending to the coronoid process (Fig. 1c). Computed tomography (CT) displayed the destruction of mandibular cortices associated with hyperdense images, similar to the "sun-ray" pattern (Fig. 1d). With these aspects, the main diagnostic hypotheses included osteosarcoma, rhabdomyosarcoma, Ewing's sarcoma, lymphoma, and Langerhans cells histiocytosis.

An incisional biopsy was performed under general anaesthesia in the left retromolar mucosa. The macroscopic aspect presented a gelatinous compound in the deep conjunctive tissue (Fig. 2a). Microscopic analyses revealed a solid proliferation of undifferentiated small round blue cells, with hyperchromatic nuclei and scant cytoplasm, presenting considerable pleomorphism. An alveolar pattern could be seen in some areas. Necrotic areas were absent (Fig. 2b, c). Immunohistochemical analysis showed diffuse expression of synaptophysin and chromogranin and a proliferation index of more than 80% of cells positive for Ki67 (Fig. 2d–f). A large immunohistochemical panel was performed to exclude other malignant lesions, as shown in Table 1. These data strongly suggested the diagnosis of neuroblastoma, and the patient was referred to a pediatric oncology centre.

A positron emission tomography–computed tomography (PET-CT) scan revealed an 18-fluorodeoxyglucose-avid left adrenal mass, the presumable primary tumour site, and multiple metastatic sites in the axial and appendicular skeleton. Additionally, 131-iodine metaiodobenzylguanidine (MIBG) scintigraphy showed MIBG-positive areas in the ilium (Fig. 3a–d), where punch biopsies confirmed neuroblastoma involvement. Then, the patient was diagnosed with Stage M neuroblastoma (High risk) [3].

The treatment course consisted of three phases: induction, consolidation and post-consolidation. The induction phase was initiated using six cycles of high-dose chemotherapy (cisplatin, cyclophosphamide, doxorubicin, dexrazoxane, etoposide, ondansetron, and vincristine). After the

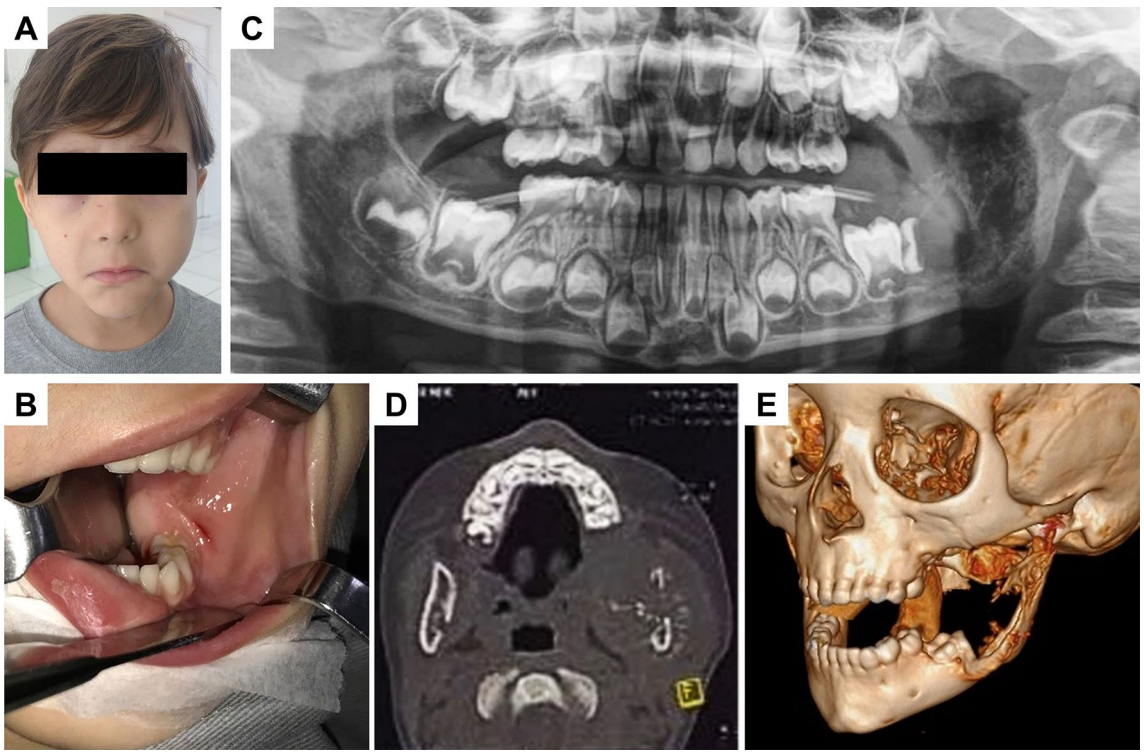

Fig. 1 Clinical features of metastatic neuroblastoma (Case 1). **a** Extra-oral presentation with facial asymmetry due to a left mandibular enlargement. **b** Intra-oral presentation displaying slight mucosal discolouration near the left retromolar trigone. **c** Panoramic radiographic presenting radiolucent image in the left mandibular ramus. **d** Computed tomography evidencing a "sun-ray" pattern in left mandibular ramus. **e** 3D tomography reconstruction illustrating the bone destruction in the left mandibular ramus

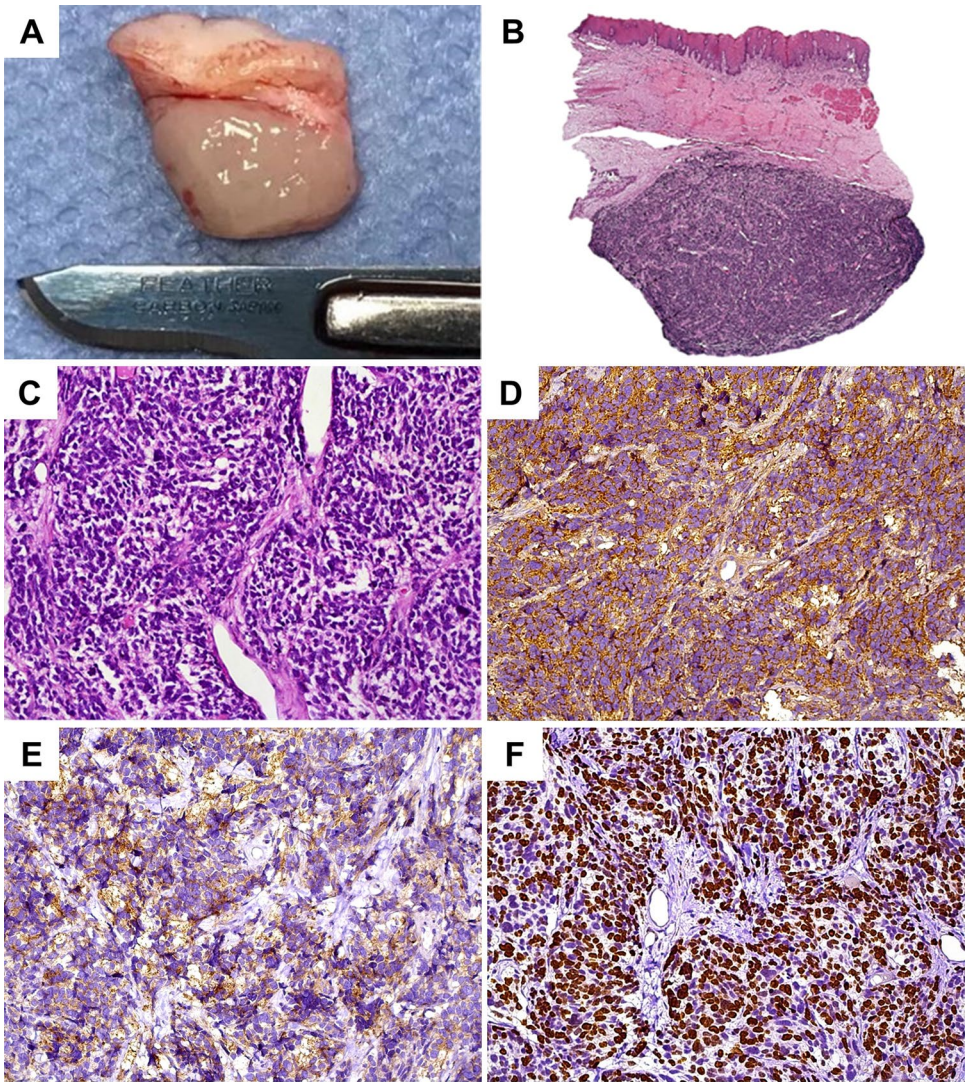

Fig. 2 Macroscopic and microscopic features of metastatic neuroblastoma (Case 1). **a** Macroscopic view after the incisional biopsy, showing a submucous lesion presenting a pale gelatinous aspect. **b** Mucosal fragment lined by squamous epithelium, presenting a solid proliferation of hyperchromatic cells in the deep connective tissue (HE, *orig. mag.:* 4×). **c** Diffuse proliferation of pleomorphic small round blue cells (HE, *orig. mag.:* 200×). **d** Strong and diffuse immunohistochemical positivity for chromogranin (DAB, *orig. mag.:* 200×). **e** Focal immunohistochemical positivity for synaptophysin (DAB, *orig. mag.:* 200×). **f** Ki67 positivity in more than 80% of the neoplastic cells (DAB, *orig. mag.:* 200×)

second chemotherapy cycle, the patient showed a partial response and was submitted to a left adrenalectomy with regional lymphadenectomy. Adrenal tissue showed about 20% of residual poorly differentiated neuroblastoma, with dystrophic calcifications and fibrotic areas. The consolidation phase was started with a higher-dose chemotherapy cycle (cyclophosphamide 1407 mg), a myeloablative regimen using BuMel (busulfan plus melphalan), an autogenous bone marrow transplantation, and 3D radiotherapy in the primary tumour site (20 Gy in 10 cycles of 200 cGy each) and for the residual lesion in the left mandible (30 Gy in 15 cycles of 200 cGy each). At the end of consolidation therapy, no signs of active disease were seen on MIBG or PET-CT. Then, the post-consolidation phase was initiated using 13-cis-retinoic acid therapy (160 mg/m^2/day, 14 days/month, for 6 months). During the treatment phases, acyclovir, fluconazole, and Bactrim® were used prophylactically.

Almost 2 years after treatment, the patient is in continuous follow-up by oncology and oral medicine services, with no evidence of recurrence.

Case 2

A 3-year-old boy was referred to our oral diagnosis clinic, with a recent history of rapid swelling in the right mandible area, present for about 1 month. Medical history was otherwise unremarkable. Extraoral examination revealed facial asymmetry due to extensive swelling in the right mandibular body region, extending below the inferior border of the mandible (Fig. 4a). Intraoral examination showed a prominent vestibular swelling in the right mandibular region, firm to palpation, with a slightly reddish colouration around the cuspid of an unerupted permanent molar (Fig. 4b). Panoramic radiograph showed a poorly defined radiolucency affecting the right body and ramus of the mandible, displacing the tooth germs of the first and second permanent lower right

Table 1 Immunohistochemical reactions performed in the current two cases of metastatic neuroblastoma

Antibody	Clone	Manufacturer	Dilution	Result	
				Case 1	Case 2
Ki67	Mouse monoclonal MIB-1	DAKO	1:100	> 80%	> 70%
CD56 (NCAM)	Mouse monoclonal 1B6	Novocastra	1:50	Positive	Positive
NSE	Mouse monoclonal BBS/NC/VI-H14	DAKO	1:800	Positive	Positive
Chromogranin	Mouse monoclonal DAK-A3	DAKO	1:800	Positive	Positive
Synaptophysin	Mouse monoclonal SY38	DAKO	1:100	Positive	Positive
S100	Mouse polyclonal	DAKO	1:10,000	Negative	Negative
AE1AE3	Mouse monoclonal AE1/AE3	DAKO	1:300	Negative	Negative
Desmin	Mouse monoclonal D33	DAKO	1:500	Negative	Negative
Myogenin	Mouse monoclonal F5D	DAKO	1:800	NP	Negative
Myo-D1	Mouse monoclonal 5.8 A	DAKO	1:300	Negative	NP
CD45 (LCA)	Mouse monoclonal 2B11+PD7/26	DAKO	1:200	Negative	Negative
CD20	Mouse monoclonal L 26(1,2)	DAKO	1:300	Negative	Negative
CD3	Mouse polyclonal	DAKO	1:300	Negative	Negative
CD10	Mouse monoclonal 56C6	DAKO	1:100	NP	Negative
TdT	Rabbit polyclonal	DAKO	1:50	NP	Negative
CD99	Mouse monoclonal 12E7	DAKO	1:100	Negative	Negative
Fli1	Rabbit polyclonal	Santa Cruz	1:100	Negative	Negative

LCA leukocyte common antigen, *NCAM* neural cell adhesion molecule, *NP* not performed, *NSE* neuron-specific enolase, *TdT* terminal deoxynucleotidyl transferase

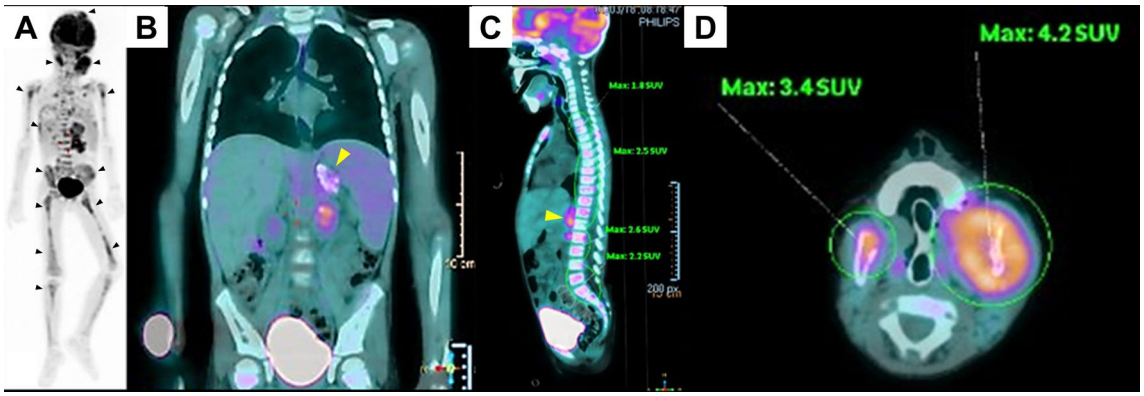

Fig. 3 Positron emission tomography-computed tomography (PET-CT) aspects of metastatic neuroblastoma (Case 1). **a** PET-CT using 18-fluorodeoxyglucose shows multiple bone metastases in multiple sites (black arrowheads). **b, c** Neuroblastoma primary lesion is located in the left adrenal gland (yellow arrowheads), along with several metastatic lesions in the vertebral column (C). **d** Bilateral mandibular metastatic lesions

molars (Fig. 4c). Cone-beam computed tomography (CBCT) revealed a hypodense image in the same mandibular area, with the destruction of vestibular and lingual bone cortices (Fig. 4d, e).

An intraoral incisional biopsy was performed under general anaesthesia, which revealed a diffuse proliferation of small round blue hyperchromatic cells, separated by fibrous septa. Groups of pleomorphic neoplastic cells in a loosely eosinophilic material (neuropil) were characteristic. Mitotic figures and necrotic areas were frequent (Fig. 5a–c). Immunohistochemical analysis showed diffuse expression of CD56 (NCAM), NSE, and with less intensity, chromogranin and synaptophysin, and a proliferation index of more than 70% of cells positive for Ki67 (Fig. 5d, f and Table 1). A diagnosis of neuroblastoma (probably metastatic) was rendered, and the patient was referred to a pediatric oncology service.

PET-CT showed an anomalous concentration of [18F]-fluorodeoxyglucose (FDG) in the following areas: right cervical region (multiple lymphadenopathies, some coalescent), abdominal region (primary lesion in the right adrenal gland), and osseous system (expansive lesion in the right mandible, and multiple medullar lesions in the axial and appendicular

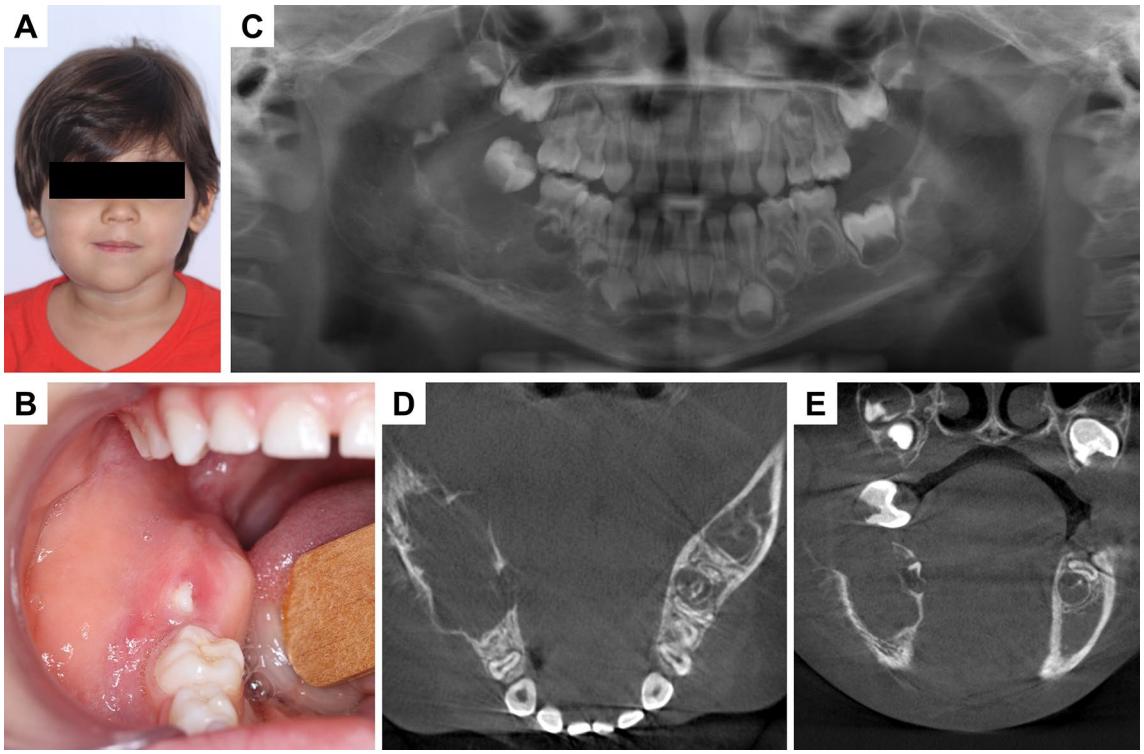

Fig. 4 Clinical features of metastatic neuroblastoma (Case 2). **a** Extra-oral presentation showing facial asymmetry with a right mandibular swelling. **b** Intra-oral presentation showing prominent vestibular swelling in the right mandibular region. **c** Panoramic radiographic showing a poorly-defined radiolucency affecting the right body and ramus of the mandible, displacing the tooth germs of the first and second permanent lower right molars. **d, e** Cone beam computed tomography revealed a hypodense image in the right mandibular body, with the destruction of vestibular and lingual bone cortices

skeleton), as shown in Fig. 6a–h. A punch biopsy in the left iliac crest confirmed neuroblastoma involvement. Then, the patient was diagnosed with Stage M neuroblastoma (High risk) [3]. In this case, the patient did not submit to any surgical procedure but received a similar chemotherapy protocol as was used with the Case 1 patient. After 6 months of treatment, the mandibular lesion presented significant improvement, with bone formation and maintenance of teeth germs (Fig. 7).

Discussion

About 65% of the neuroblastomas occur in the abdomen, typically showing an abdominal mass that may be palpable and painful. However, the symptoms depend on the primary tumour size and metastatic sites, which can cause compression and invasion of vital structures. Weight loss, fever, and fatigue usually indicate advanced disease and bone marrow involvement [1, 2]. Metastases to the head and neck are rare, showing in less than 1% of all cancers that affect this site in pediatric patients [4], and the mandible-maxilla ratio corresponds to 6.25:1. When the mandible is affected, the tumour presents as a rapidly enlarging mass with bone destruction, tooth mobility or displacement, and colour alteration of the oral mucosa [5]. Additionally, radiographic images present a poorly defined and destructive radiolucent lesion, sometimes demonstrating the "sun-ray" pattern that mimics osteosarcoma features [6]. Only 17 cases of metastatic neuroblastoma to the mandible were described in the English language in the PubMed database in the last 39 years (Table 2). Of these cases, 12 were male (mean age 37.5 months, ranging from 8 to 84 months) and five females (mean age 83.2 months, ranging from 20 to 180 months) [5–21]. Usually, the adrenal glands represented the primary tumour site [5, 8–10, 12, 14–16, 21]. Moreover, two cases of abdominal neuroblastoma with metastatic component differentiated in ganglioneuroblastoma to the mandible were reported [22, 23] (not included in the Table 2).

The neuroblastoma diagnosis confirmation is made under the histological analysis of the incisional biopsy, the vanillylmandelic and homovanillic acids levels in the serum and urine (not specific to the diagnosis, although 75% of neuroblastoma cases show high levels; these tests were not performed in these cases), bone marrow aspirate biopsies (to

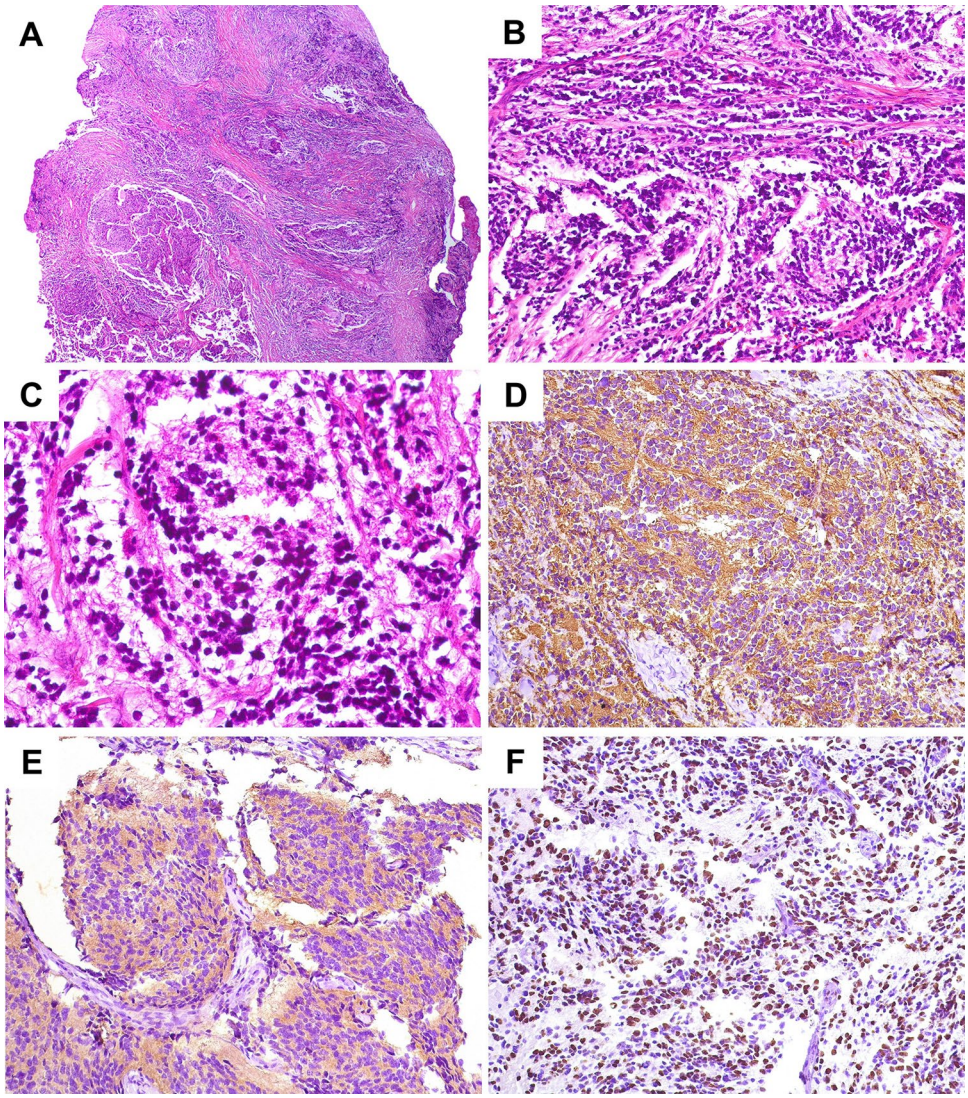

Fig. 5 Microscopic features of metastatic neuroblastoma (Case 2). **a** Lobular proliferation of hyperchromatic cells, separated by hyalinized fibrous stroma (HE, *orig. mag.:* 25×). **b** Uniform small round blue cells with scant cytoplasm presenting in some areas as single-line cords (HE, *orig. mag.:* 200×). **c** Clusters of neuroblasts in a background of eosinophilic neuropil (HE, *orig. mag.:* 400×). **d** Strong and diffuse immunohistochemical positivity for CD56 (DAB, *orig. mag.:* 200×) and **(e)** neuron-specific enolase (DAB, *orig. mag.:* 200×). **f** Ki67 positivity in more than 70% of the neoplastic cells (DAB, *orig. mag.:* 200×)

assess the marrow involvement) [1], and image exams like 18-fluorodeoxyglucose PET/CT and MIBG scintigraphy (the exam with high specificity) [24].

The International Neuroblastoma Risk Group staging system (INRGSS, 2005) is the newest risk classification system that uses pretreatment criteria and is superior to the International Neuroblastoma staging system (INSS, 1986) [25]. In the INRGSS, neuroblastoma is classified into four stages (L1, L2, M, or MS) combined with four pretreatment risk groups (Very Low, Low, Intermediate, or High), totalling 16 classification subsets. The INRGSS classification takes into account the metastatic disease occurrence, patient age, image-defined risk factors (IDRF, Table 3), histologic category, tumour differentiation grade, MYCN amplification, presence/absence of 11q aberrations, and tumour cell ploidy. Because both patients described above presented distant metastatic disease and were older than 18 months, they were automatically diagnosed as Stage M neuroblastoma (High risk), according to INRGSS (Table 4) [3, 26]. At least 13 of the 17 cases (76.5%) reported in Table 2 could also be classified similarly to our cases, while 4 of the 17 cases (23.5%) represent Stage MS neuroblastoma (Very Low or High risk, depending on the existence of an MYCN amplification or an 11q aberration), according to the INRGSS classification.

The neuroblastoma treatment and prognosis are variable, depending on the risk classification and tumour features. Some specific cases can show spontaneous disease regression, permitting expectant observation during a 90-week

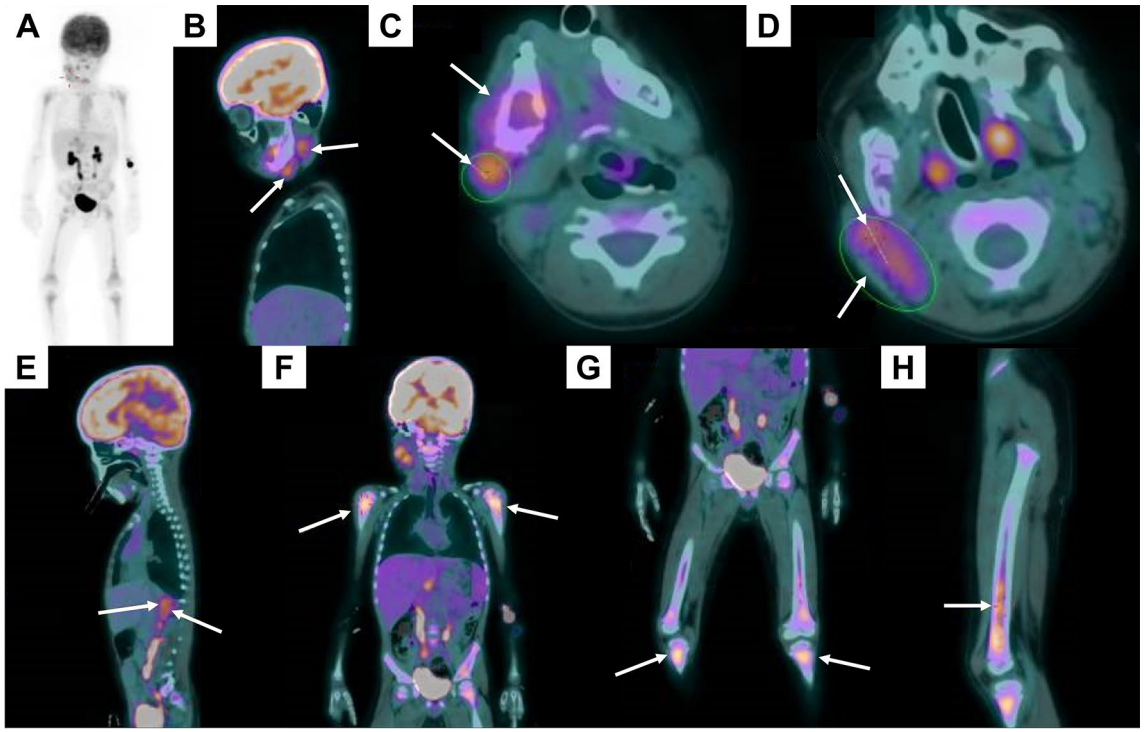

Fig. 6 Positron emission tomography-computed tomography (PET-CT) aspects of metastatic neuroblastoma (Case 1). **a** PET-CT using 18-fluorodeoxyglucose shows multiple areas affected by neuroblastoma (white arrows). **b–d** Multiple coalescent lymphadenopathies in the right cervical region, with an expansive lesion in the right mandible (C). **e** Neuroblastoma primary lesion is located in the right adrenal gland. **f–h** Multiple bone metastases were found in the upper and lower limbs

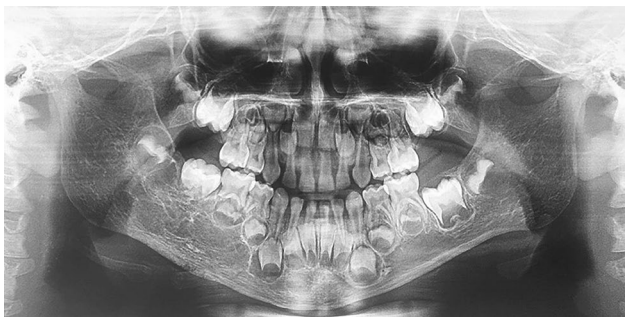

Fig. 7 Panoramic radiographic (Case 2) after 6 months of treatment, showing bone formation and maintenance of tooth germs in the right mandibular area

interval. On the other hand, patients with non-High-risk tumours, Stage L1, or Stage MS show a favourable prognosis, needing minimal therapy (surgery with or without chemotherapy). The remaining High-risk tumour patients (Stage L2 and M), as the two current patients, have a poor prognosis, with 5-year overall survival below 50%. For these cases, current treatment regimens include induction chemotherapy, surgery, radiotherapy, consolidation therapy with myeloablative chemotherapy, and autologous stem cell rescue [2, 27].

Conclusion

In summary, we have reported two additional challenging cases of metastatic neuroblastoma, in which the mandibular lesion led to the diagnosis of advanced disease. In both cases, a rapid and effective interaction between oral medicine, oral pathology, and oncology services was paramount to managing these patients and boosting their chance of survival.

Table 2 Cases of neuroblastoma presenting with metastasis to the mandible

Case	Case report	Sex	Age	Signs and symptoms	Primary tumour site	Treatment	Follow-Up
1	Reich et al., [12]	Female	13 years	Recurrence of neuroblastoma with right mandibular paraesthesia	Left adrenal gland	Chemotherapy and radiotherapy	Died after 1 month
2	Borler et al., [13]	Male	02 years	Left mandibular swelling	–	Chemotherapy and radiotherapy	Died after 3 weeks
3	Chan et al., [11]	Female	02 years	Pain associated with a left mandibular swelling	–	Chemotherapy and radiotherapy	18 months in remission
4	Ogunsalu and Smith [10]	Male	02 years	Left mandibular swelling	Left adrenal gland	Chemotherapy and radiotherapy	Died after 43 weeks
5	Pellegrino and Berardi [9]	Male	06 years	Left mandibular swelling	Left adrenal gland	Adrenalectomy, chemotherapy and local radiotherapy	2 years in remission
6	Otmani and Khattab [8]	Male	03 years	Generalized bone pain and swelling of the left mandible	Left adrenal gland	Palliative chemotherapy	Died after 4 weeks
7	Baber et al., [7]	Female	15 years	Left preauricular swelling and pain	–	Chemotherapy	–
8	Parker et al., [21]	Male	08 months	Mandible mass, intraoral bruising, tooth loosening, and progressive weight loss	Right adrenal gland	Chemotherapy and adrenalectomy	2 years in remission
9	Kürklü et al., [20]	Male	01 years	Irritability and abdominal mass	Right adrenal gland	Chemotherapy	Died after 43 weeks
10	Udall and Cho, 2011 [19]	Male	10 months	Mass in the right mandibular ramus	–	Chemotherapy	–
11	Manor et al., [5]	Male	07 years	Mass in the left mandible and tooth loosening and displacement	Left adrenal gland	Chemotherapy and adrenalectomy	–
12	Dwojak et al., [18]	Male	03 years	Facial swelling and ear and jaw pain	–	–	–
13	Eley et al., [6]	Male	02 years	Swelling in the right mandible and right retromolar region	–	Chemotherapy, autologous hematopoietic stem cell transplantation and surgical resection of the right hemimandible	9 months in remission
14	Piccardo et al., [17]	Male	06 years	Recurrence of neuroblastoma in the right mandibular branch	–	Radioiodine therapy	–
15	Mittal et al., [16]	Female	03 years	Swelling in the right mandible and loosening of teeth, fever, anorexia and weight loss	Right adrenal gland	Chemotherapy	Died after 6 weeks
16	Wade et al., [15]	Male	11 months	Mass in the ramus of the right mandible	Left adrenal gland	Chemotherapy	6 months in remission
17	Waldron et al., [14]	Female	20 months	Swelling in the right mandible, discomfort and changes in gait and a palpable mass in the abdomen	Left adrenal gland	Chemotherapy, radiotherapy and immunotherapy with monoclonal antibodies	6 months in remission

Table 2 (continued)

Case	Case report	Sex	Age	Signs and symptoms	Primary tumour site	Treatment	Follow-Up
18 and 19	Current cases reports	Male	4 years (Case 1) 3 years (Case 2)	Painful swelling in the left mandibular region, soreness, and weakness (Case 1) Swelling in the right mandibular region with tooth germ displacement (Case 2)	Left adrenal gland (Case 1). Right adrenal gland (Case 2)	Chemotherapy, autologous hematopoietic stem cell transplantation, adrenalectomy (except Case 2), and radiotherapy	18 months in remission (Case 1) Under treatment (Case 2)

Table 3 Image-defined risk factors (IDRF) in neuroblastic tumours [3]

Ipsilateral tumour extension within two body compartments
Neck-chest
Chest-abdomen
Abdomen-pelvis
Neck
Tumour encasing carotid and/or vertebral artery and/or internal jugular vein
Tumour extending to the base of the skull
Tumour compressing the trachea
Cervico-thoracic junction
Tumour encasing brachial plexus roots
Tumour encasing subclavian vessels and/or vertebral and/or carotid artery
Tumour compressing the trachea
Thorax
Tumour encasing the aorta and/or major branches
Tumour compressing the trachea and/or principal bronchi
Lower mediastinal tumour, infiltrating the costovertebral junction between T9 and T12
Thoraco-abdominal
Tumour encasing the aorta and/or vena cava
Abdomen/pelvis
Tumour infiltrating the porta hepatis and/or the hepatoduodenal ligament
Tumour encasing branches of the superior mesenteric artery at the mesenteric root
Tumour encasing the origin of the coeliac axis and/or of the superior mesenteric artery
Tumour invading one or both renal pedicles
Tumour encasing the aorta and/or vena cava
Tumour encasing the iliac vessels
Pelvic tumour crossing the sciatic notch
Intraspinal tumour extension whatever the location provided
More than one-third of the spinal canal in the axial plane is invaded, and/or the perimedullary leptomeningeal spaces are not visible, and/or the spinal cord signal is abnormal
Infiltration of adjacent organs/structures
Pericardium, diaphragm, kidney, liver, duodenum-pancreatic block, and mesentery
Conditions to be recorded, but not considered IDRFs
Multifocal primary tumours
Pleural effusion, with or without malignant cells
Ascites, with or without malignant cells

Table 4 International neuroblastoma risk group staging system (INRGSS) classification for neuroblastic diseases stage and risk group [3, 26]

Stage	Description
L1	Localized tumour not involving vital structures as defined by the list of IDRFs and confined to one body compartment
L2	Locoregional tumour with the presence of one or more IDRFs
M	Distant metastatic disease (except Stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

Stage	Age (months)	Histologic category	Grade of tumour differentiation	*MYCN* amplification	11q aberration	Ploidy	Pretreatment risk group
L1/L2	Any	GNm and GNBint	Any	Any	Any	Any	Very low
L1	Any	Any, except GNm or GNBint	Any	No	Any	Any	Very low
				Yes	Any	Any	High
L2	< 18	Any, except GNm or GNBint	Any	No	No	Any	Low
					Yes	Any	Intermediate
	≥ 18	GNBnod and NB	Differentiating	No	No	Any	Low
					Yes	Any	Intermediate
			Poorly diff. or Undiff.	No	Any	Any	
			Any	Yes	Any	Any	High
M	< 18	Any	Any	No	Any	Hyperdiploid	Low
	< 12	Any	Any	No	Any	Diploid	Intermediate
	12 to < 18	Any	Any	No	Any	Diploid	Intermediate
	<18	Any	Any	Yes	Any	Any	High
	≥ 18	Any	Any	Any	Any	Any	High
MS	< 18	Any	Any	No	No	Any	Very low
					Yes	Any	High
				Yes	Any	Any	High

GNm ganglioneuroma maturing, *GNBint* ganglioneuroblastoma intermixed, *GNBnod* ganglioneuroblastoma nodular, *NB* neuroblastoma, *diff.* differentiated, *Undiff.* undifferentiated

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Compliance with ethical standards

Conflict of interest The author declares that hey have no conflict of interest to disclose.

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