Metastatic Mandibular Neuroblastoma: A Rare Cause of Tooth Mobility

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Neuroblastoma (NBL), a malignant embryonic tumor derived from neural crest cells, is the most common tumor worldwide among children less than 1 year of age. Metastasis to the mandible is uncommon. This article reports the case of a 15-month-old male diagnosed with NBL with bone metastasis including the mandible which resulted in severe tooth mobility. Dentists or pediatricians should consider the primary or metastatic tumors of the maxillofacial region in the differential diagnosis in children presenting with premature loss of teeth related to tooth mobility.

Keywords: *neuroblastoma, metastasis, mandible, tooth mobility*
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INTRODUCTION

Neuroblastoma (NBL), a malignant embryonic tumor derived from neural crest cells, is the most common extracranial solid tumor in childhood and the most frequently diagnosed neoplasm in infants.[1] Neuroblastoma detection in early life or *in utero* suggests that early disruption of normal developmental processes plays a role in tumor initiation.[2]

Because NBL is a disease of a sympathico-adrenal lineage of the neural crest, tumors may develop anywhere in the sympathetic nervous system. They predominantly occur in the adrenal glands, abdomen, chest, or pelvis.[1] Clinical manifestations are highly variable and dependent on the site of primary tumor and the presence or absence of metastatic diseases or paraneoplastic syndromes. At the time of diagnosis, metastases, which are usually found in the lymph nodes, liver, bone, and bone marrow, may occur in as many as half of all cases.[3] Among the extreme heterogeneous characteristics of NBL, metastatic involvement of the mandible with severe tooth mobility appears as an uncommon sign of morbidity and disease extensity. Herein, we report our experience with a 15-month-old male diagnosed with NBL with mandibular metastasis that caused severe tooth mobility.

CASE REPORT

A 15-month-old male infant under treatment for neuroblastoma was referred to Istanbul University, Faculty of Dentistry for consultation regarding a severely mobile tooth with a major risk of aspiration.

At 8 months of age, the infant was brought to Istanbul University, Oncology Institute, Division of Pediatric Hematology-Oncology with complaints of reluctance to breastfeed, excessive crying, irritability, and abdominal swelling. No significant event was defined in his past medical history or in the family history. On physical examination, he had growth retardation, was pale, and had a large mass in the right quadrant of the abdomen. Vital signs and cardiac, pulmonary, neurological, and genitourinary examinations were all normal. Analysis of a complete blood count showed mild

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to moderate anemia. Laboratory tests indicated an increase in serum lactate dehydrogenase (LDH) and serum neuron-specific enolase (NSE) and urine vanylmandelic acid (VMA). Other biochemistry results were in normal limits.

An abdominal ultrasound and abdominal magnetic resonance imaging (MRI) revealed a mass originating from the right adrenal gland. A bone marrow aspiration and biopsy were performed and typical rosette formation was observed. The mass originating from the right adrenal gland, typical rosette formation in the bone marrow and elevated urine VMA level led to the diagnosis of Stage 4 neuroblastoma.[1,2] A detailed metastatic work-up including a chest computed tomography, bone scintigraphy imaging of the whole body, and MRI of particular bony sites was performed. Bone (right temporal bone, sphenoid bone, bilateral femur) and liver metastases in addition to the bone marrow metastases were detected.

The child was treated with chemotherapy according to the Turkish Pediatric Oncology Group Neuroblastoma Protocol[4] (TPOG–NBL 2003). Chemotherapy regimens consisting of combinations of vincristine, cisplatin, etoposide, alternating with combinations of cyclophosphamide, ifosfamide, carboplatin, and etoposide were used. Due to progression despite 6 chemotherapy courses, salvage chemotherapy with vincristine, topotecan, and cyclophosphamide were administered.

At 15 months of age, while receiving salvage chemotherapy an extraoral left-sided facial swelling extending from the zygomatic bone to the angle of the mandible was observed. The overlying skin was intact. No sign of extension of the extraoral swelling into the oral cavity was detected. Intraoral examination revealed incomplete primary dentition. The primary maxillary and mandibular central incisors and the mandibular right first molar were present with severe mobility. The mandibular alveolar arch demonstrated a marked and irregular thickening in the buccolingual direction (Figure 1).

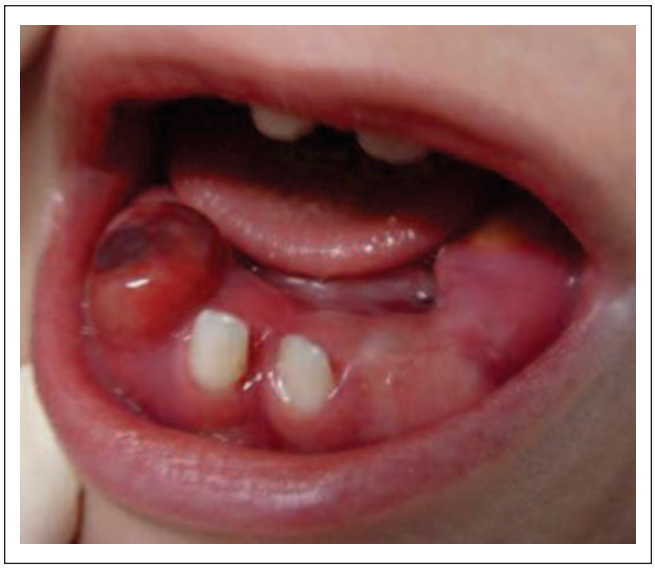

Figure 1. Note the metastatic lesion over the extraction socket and irregularity of mandibular arch in buccolingual direction.

Due to the possible risk of aspiration during breast-feeding, the mobile primary molar tooth was extracted using sterile gauze. The extracted tooth was rootless, which clearly defined the severe mobility. Since the patient was already under wide spectrum antibiotic therapy for neutropenic fever, no additional medication was administered following the tooth extraction. Forty-eight hours after the extraction, approximately 0.5 cm diameter in size, a reddish-purple soft tissue mass unexpectedly arose from the extraction socket. The patient's parents were instructed to wash the extraction area with a 0.1% chlorhexidine rinse. Ninety-six hours following the extraction, the tumor enlarged to approximately 1 cm in diameter, with superficial foci of hematomas (Figure 1). Assessment of the previous cranial MRI revealed a 2.6x2 cm lesion involving the left mandibular ramus. A current MRI was obtained and revealed a lesion in the right mandibular ramus (4x4x3.2 cm) and advanced progression of the lesion in the left ramus extending to anterior mandible with the invasion of tooth roots leading to a "floating tooth" appearance. In addition, marked soft tissue involvement was present in the subperiosteal region of the left mandibular ramus with minimal extraosseous extension (Figure 2A and B). Given these results, and the fact that bone metastases are common in neuroblastoma the mass growing from the extraction socket was considered to be a metastatic lesion.

The patient's course thereafter was stormy and complex, and he died of progressive disease 3 months later at the age of 18 months.

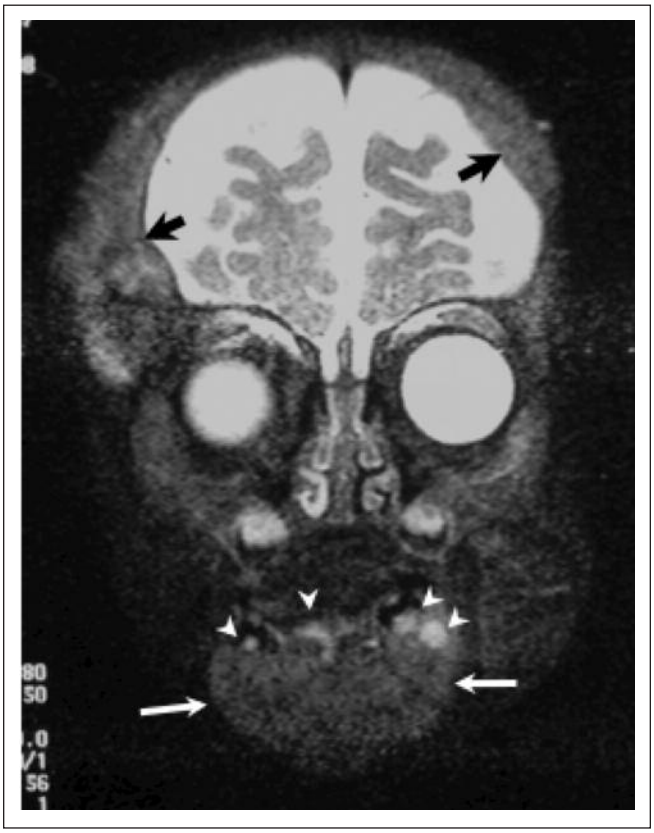

Figure 2A. Coronal T2-weighted MR images show (a) A soft tissue mass replacing mandibular corpus (white arrows) with invasion of tooth roots (arrowheads).

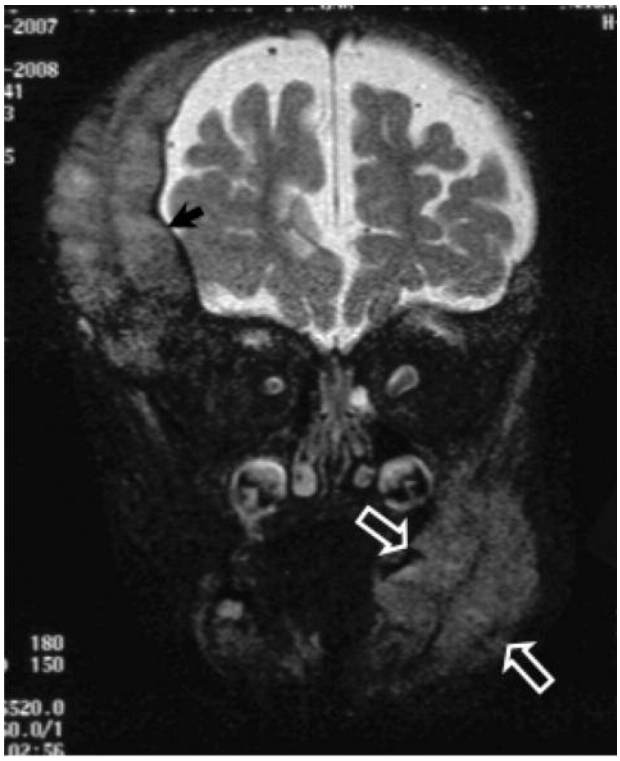

Figure 2B. Coronal T2-weighted MR images show left mandibular ramus was markedly involved by the metastatic lesion with asssociated soft tissue mass (hollow white arrows). Calvarial metastates due to neuroblastoma are also seen (black arrows).

DISCUSSION

NBL is the most common extracranial pediatric solid tumor in childhood under the age of 15 years and is the most common neoplasm in infancy.[1]

The treatment methods used in the management of high-risk NBL include chemotherapy, surgery of the primary site, radiotherapy for residual and unresectable sites, stem cell transplantation, and biotherapy.[2] Although an initial partial response to chemotherapy was observed in this case, the disease progressed and the patient died at the age of 18 months.

The most frequent metastatic sites for NBL at diagnosis were reported to be bone marrow (70.5%), bone (55.7%), lymph nodes (30.9%), liver (29.6%), and intracranial and orbital sites (18.2%).[3] Mandibular metastasis of NBL is uncommon. The most frequent locations for mandibular metastasis of malignant disease are the premolar and molar regions due to a predominance of red bone marrow in these areas.[5,6] In our case, the location of the metastatic lesion was consistent with this predominance. Metastasis to the mandible may present with various clinical manifestations such as slight discomfort or pain, swelling, and numb chin syndrome. Unfortunately for infants, who are the leading sufferers of NBL, the awareness and verbalization of such complaints may not be possible.

Because of the early age at which children are treated for NBL, both the primary and permanent dentitions are at risk for treatment-associated abnormal development. The primary dentition begins to develop at about 6 weeks of gestation and continues until about the age of 3 years, at which time tooth root formation is complete. Crowns are halfway mineralized at birth and become fully formed during the first year of life; the mandibular teeth develop earlier than do the maxillary teeth.[7] Chemotherapy interferes with the cell cycle and intracellular metabolism and may thereby cause retarded dental development, microdontia, localized enamel defects, enlarged pulp chambers, and root stunting, particularly in children less than 5 years of age.[8,9] The nature and extent of the sequelae vary with the type and doses of medication, the frequency of treatment cycles, and the patient's age at diagnosis.[9]

Furthermore a vast number of either benign or malignant neoplasms as well as several tumor like conditions developing in the soft or hard tissues in the vicinity of teeth can be responsible for tooth mobility, root stunting, premature loss of teeth, pain and intraoral swelling of jaws. Such symptoms may also suggest a metastatic mass in children with a history of tumor. Root stunting as an adverse effect of antineoplastic agents together with bone resorption around the teeth caused by aggressive and infiltrative growth of a metastatic mass result in remarkable tooth mobility. A "floating tooth" impression, as present in this case demonstrates radiographic features of alveolar bone resorption with poorly defined borders, loss of dental lamina and dental crypt, enlargement of tooth follicles, irregular external root resorption, displacement of tooth and tooth germs.[10,11] In the differential diagnosis of "floating teeth" appearance Burkitt's lymphoma, Langerhans cell histiocytosis, metastatic neuroblastoma should be considered.[11] In this case root stunting may have been due to either the adverse effects of antineoplastic treatment or metastatic involvement of the mandible. Irregular thickening of the alveolar bone and anterior dislocation of teeth were also evidence for metastatic tumor involvement. Incomplete primary dentition was strongly suggestive of agenesis that may have been associated with chemotherapeutic agents.

In childhood malignancies alterations in the normal structures of the oral cavity and developmental pattern of tooth eruption may appear as the first indicators of significant systemic conditions. Routine dental consultation may draw physicians' attention to considering the general health status of the patient or the degree of progression of an existing morbidity. Even in this case of advanced NBL, a mobile and rootless primary molar and unusual recovering of the extraction socket should alert dental professionals to warn physicians about obtaining a current MRI to check for metastatic lesions to the mandible and subsequently monitor the disease progression. Therefore, a teamwork approach that includes dental care providers alleviates the possibility of oro-dental problems, provides the ability to monitor the maxillomandibular and dental development more effectively, and allows for timely intervention.

CONCLUSION

NBL with metastasis to an unusual location, such as the mandible, presents a diagnostic problem in the dental

practice. However, symptoms such as unexplained tooth mobility and premature loss of primary teeth in a child with NBL should be considered as significant signs of possible metastases to the jaw. Hence, a metastatic work-up including an MRI with a particular focus on the mandible is important in demonstrating the metastatic site, thus avoiding unnecessary intervention.

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