Disseminated neuroblastoma with initial presentation as an intraoral mass: case report

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Abstract

Neuroblastoma is an uncommon malignant neoplasm that derives from neural crest progenitor cells that normally give rise to the sympathetic nervous system. It represents 8 to 10% of all extracranial tumors in childhood. The purpose of this paper is to report a case in which a mandibular soft tissue mass was the initial presenting sign of disseminated neuroblastoma in a 2-year-old child, and to discuss the clinicopathologic features and biologic behavior of neuroblastoma. (Pediatr Dent 16:310–13, 1994)

Introduction

Neuroblastoma is the most common extracranial solid cancer of childhood, accounting for 8% of pediatric malignancies.[1–3] It affects relatively young children with a median age of 2 years at diagnosis.[4] This neoplasm is derived from the neural crest progenitor cells that give rise to the sympathetic nervous system, including the adrenal medulla. Because of the distribution of the sympathetic nervous system, neuroblastomas may arise along root ganglia located in the neck, thorax, and abdomen, as well as in adrenal glands.[5] Almost one-third of children with neuroblastoma present with bony metastases. The skull and orbit are common sites of metastases, while the mandible and maxilla are unusual sites.[6,7] Although one study showed that jaw involvement by neuroblastoma occurs in 25% of cases,[8] oral involvement as the presenting feature is rare.[8,9] Since 1987, only two cases[9,10] have been reported in the medical/dental literature as having initial oral involvement.

The young age of the patients and the nondividing state of cells in the mature autonomic nervous system suggest that a mutagenic event may have occurred in prezygotic germ cells, during embryogenesis or during early fetal life, resulting in neuroblastoma development during the neonatal period, in infancy, or childhood.[5] Occasional cases have been reported in both adolescents and adults. Familial aggregations of neuroblastoma raise the issue of inherited susceptibilities.[11] Neuroblastoma also has been associated with other adrenocortical pathologic conditions like Cushing's syndrome.[12] However, there is no consistent linkage of neuroblastoma with a single etiologic agent or genetic disease,[3,5] although both autosomal dominant and autosomal recessive inheritance patterns have been described. Cytogenic manifestations of neuroblastoma include a deletion of the short arm of chromosome 1.[13]

There are several staging systems used for neuroblastoma. The Hospital for Sick Children in Toronto uses the system summarized in the Table.[14] Prognostic variables include age at diagnosis and stage of disease.[5] Several biological markers have prognostic significance, but particular emphasis is placed on the copy number of N-*myc*, since amplification of this oncogene is related to rapid tumor progression.[15,16]

The purpose of this paper is to report a case in which a mandibular soft tissue mass was the initial presenting sign of disseminated Stage IV neuroblastoma in a 2-year-old child and to discuss its clinicopathologic features and biologic behavior.

Case report

A 2-year-old white female with no significant medical history presented to the dental clinic at The Hospital for Sick Children, with a chief complaint of mild to moderate pain of 2 days duration associated with a left mandibular swelling. Extra- and intraoral examination identified a 2.5x2.0-cm soft tissue mass filling the buccal vestibule extending from the mandibular left primary canine to the mandibular left primary second

Table. Staging system for neuroblastoma[14]

Stage I	Tumor confined to the organ or structure of origin.
Stage II	Tumor extending in continuity beyond the organ or structure of origin, but not crossing the midline. Regional lymph nodes on the ipsilateral side may be involved.
Stage III	Tumor extending in continuity beyond the midline. Regional lymph nodes may be involved bilaterally.
Stage IV	Remote disease involving the skeleton, bone marrow, soft tissue, and distant lymph node groups.
Stage IV-S	As defined in Stage I or II, except for the presence of remote disease confined to the liver, skin, or marrow (without bone metastases).

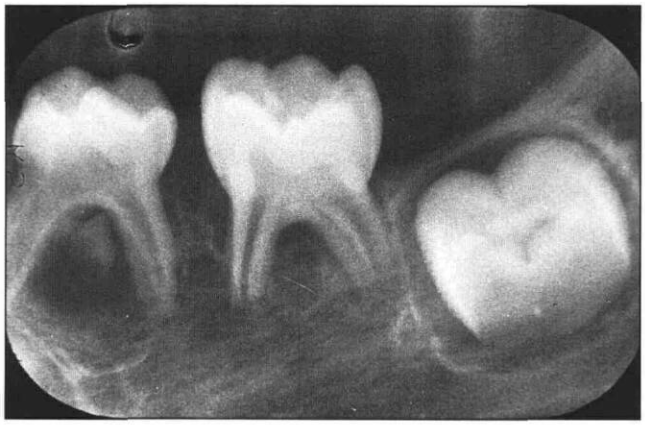

Fig 1. A noncorticated radiolucency with ill-defined borders spans from the primary canine to the primary second molar. The lamina dura of primary first and second molars is destroyed. The follicles of permanent first and second premolars are pushed into the furcation areas of the primary molars, and the crypt cortices appear to have been destroyed.

molar. The overlying intact mucosa was colored red to purple. The mandibular left primary first and second molars had mild to moderate mobility; both teeth were extruded by 1.5 mm and could be depressed back into their sockets. The child was caries free, and there was no history of trauma.

Two periapical radiographs were exposed of the mandibular left primary molars, which revealed bony destruction in the area with irregular margins. Fig 1 shows the lack of lamina dura, expansion of the contact area between the primary molars, and displacement of the permanent tooth follicles into the furcations of the primary molars.

The initial clinical impression was abscess formation, and the patient was treated with an appropriate antibiotic. After three days of antibiotic treatment, the lesion had not decreased in size and the patient was referred to the ear, nose and throat department of The Hospital for Sick Children. A computed tomography (CT) scan of the head and neck region revealed a lesion extending from the buccal vestibule adjacent to the left mandible crossing over to the right orbital region (Fig 2). Some new bone formation in the form of spicules was evident perpendicular to the buccal surface of the left mandible, the masseter and buccinator muscles were displaced laterally, and the pterygoid medially (Fig 3). The sphenoid bone, the ethmoids, the sphenoid sinus and the sella turcica were all invaded.

A biopsy was performed, and histological examination showed soft tissue infiltration by a tumor composed of small, round cells with a fine chromatin pattern, small nucleoli, and high mitotic rate, which were arranged in loosely cohesive sheets and small nests. Immunohistochemistry studies of the sections showed positive staining for neuron-specific enolase. Scanning electron microscopic examination showed tumor cells with interdigitating cell processes containing neurosecretory granules. Molecular genetic studies revealed that the N-*myc* gene was amplified more than 100 times per cell, signifying poor prognosis. The lesion was confirmed to be a Stage IV neuroblastoma. A second CT scan was done on the thorax and abdomen, showing lesions in the right lung apex and suprarenal area, but the site of origin could not be determined.

Due to the extent of the lesion, surgical excision was not possible, and the child was treated with radiotherapy and chemotherapy. The chemotherapy protocol included the use of cyclophosphamide, Adriamycin (Adria Labs, Ontario, Canada), cisplatin, and teniposide (VM26). Currently, the child is in remission, and it has been 18 months since diagnosis.

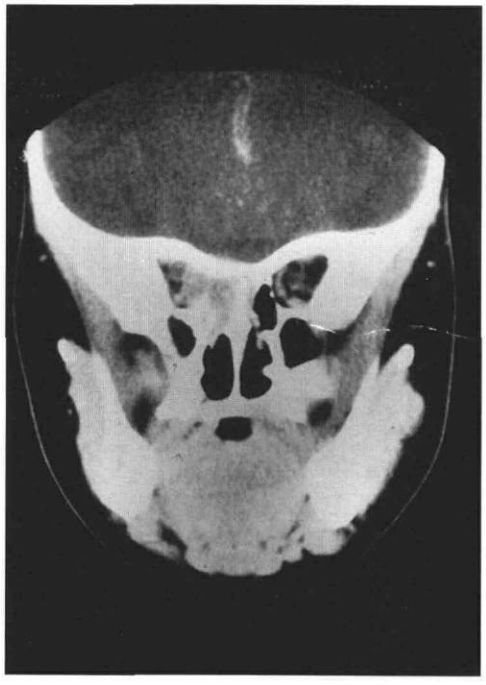

Fig 2. Note the destructive tumor in the sphenoid body, extending into the ethmoids, and beginning to invade the nasal cavity and the right orbital region.

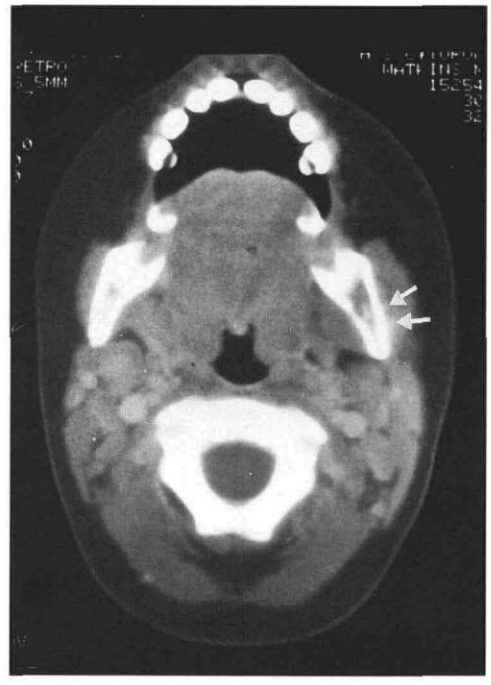

Fig 3. The soft tissue tumor has displaced the left masseter muscle laterally and caused internal spiculations of the mandible.

Discussion

Most signs and symptoms of neuroblastoma are

attributable to local problems from the primary tumor or are the result of hormone produced by the tumor. Most tumors are hormonally active and produce catecholamines that result in hypertension, diarrhea, dehydration, hypokalemia, skin rashes, and flushing.[17] Unsuspected tumors may be detected on routine physical examination by screening for urinary catecholamines[18] or when investigative procedures such as radiographs are performed for other reasons.

Most neuroblastomas arise in the adrenal medulla, but a significant number are found in the cervical, thoracic, and lower abdominal sympathetic chains.[19] Up to 10% of cases have no identifiable site of origin, and most — because of location deep within the body or because of rapid growth rate — are very large at diagnosis.[5]

Metastases to the skull are frequent. Sphenoid bone involvement or tumor invasion of the retrobulbar soft tissue produces the distinctive orbital proptosis and ecchymoses.[3] Moreover, extensive hepatic involvement and skin metastases are characteristic of neonatal neuroblastoma.[5] Skeletal metastases occur more frequently in older patients (> 2 years), and incidence of skeletal metastases at initial diagnosis is as high as 35–74%.[2] Regarding jaw involvement, one study reviewed 36 cases and found that the mandible is much more frequently involved (33 of 36 cases) than the maxilla, and that the body of the mandible is the most commonly involved site, followed by the angle and the ascending ramus.[17] Moreover, no area of the skeleton is spared — even the dental pulp has been reported to be involved.[20]

The radiographic appearances of osseous metastases are quite variable, with no characteristic features. The appearance can range from a mottled area of decalcification to large areas of bone destruction with irregular margins that may have some new bone formation. Others present spicules of bone within the soft tissue mass associated with the bone destruction. The spicules are roughly perpendicular to the bone surface and may resemble the "sunburst appearance" observed in other tumors.[6]

In differentiating it from other lesions, the patient's age provides one clue to the condition. Hand-Schüller-Christian disease produces osteolytic lesions that have a more well-defined margin than do malignant tumors, with no soft tissue swelling. Osteomyelitis, leukemia, Ewing's sarcoma, Wilms' tumor, and lymphosarcoma may be suggested by the appearance of the mottled type of bone lesion from neuroblastoma.[3,6,7] However, neuroblastoma is a unique tumor biochemically, possessing metabolic pathways for catecholamine synthesis and catabolism.[15] Therefore, the clinical diagnosis is based on multiple bone metastases, elevated blood levels of catecholamines, or elevated urinary levels of homovanillic acid (HVA) and vanilmandelic acid (VMA).[7,15,17,19]

Histologically, the tumor cells are small, dark, and either round or slightly elongated. They tend to grow in haphazard masses. The nuclei are hyperchromatic and regular, and the scant cytoplasm has granules of stored catecholamines. Careful searching near the periphery of the tumor usually reveals the cells arranged in characteristic rosettes, with young nerve fibrils growing into the center of each rosette.[19]

The most important clinical prognostic variables in patients with neuroblastomas are age at diagnosis, stage of the disease, and the site of the primary tumor.[3,5] Several biologic variables appear to have predictive value as independent markers. For example, amplification of the N-*myc* gene in tumor cells, deletion of chromosome 1p, and increased serum ferritin levels are found predominantly in patients with advanced stages of disease.[3,13,18,21]

Surgery alone is the treatment of choice for Stage I and II patients at any age, while chemotherapy, radiotherapy, and surgery together are recommended for young children (< 1 year) with Stage III and IV neuroblastoma. Patients with Stage IV-S disease have an excellent prognosis (> 90%) without the use of adjuvant chemotherapy and radiotherapy. Young patients with Stage III and IV neuroblastoma (> 1 year) have a poor prognosis despite treatment. These patients may benefit from bone marrow transplantation.[15] When the tumor is localized in infancy, the 5-year survival rate is about 75 to 80%. With disseminated tumors, it drops to 5 to 20%.[5] In view of the poor prognosis, screening infants by urinary testing for VMA and HVA to detect earlier and potentially less malignant tumors has begun in Japan and North America in the hope that preclinical detection will reduce mortality.[15]

It has been 18 months since the diagnosis. The patient is now 3 1/2 years old and doing reasonably well after chemotherapy and radiotherapy. However, long-term followup is necessary to watch for possible recurrence and the effects of the treatment. The prognosis for Stage IV disease is poor with a median survival time of around 27 months.[9] This case illustrates the importance of early recognition and proper diagnosis of an unexplained intraoral swelling.

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Physicians urge parents to protect their children from dangerous ultraviolet sun rays

Physicians have issued their strongest warning for parents that children are in great danger from exposure to the sun's ultraviolet rays. This warning follows the creation of an Ultraviolet (UV) Index to forecast the local UV radiation exposure daily by the Environmental Protection Agency (EPA) and the National Weather Service.

"Children spend about three times as much time in the sun as adults," said Marge Hogan, MD, fellow of the American Academy of Pediatrics. "The object is to teach children and their parents to avoid excessive sun exposure and start protecting them during infancy."

"At least one out of every six children will develop skin cancer during their lifetime," said William E. Jacott, MD, a family physician and vice chair of the AMA's board of trustees. "Before the age of 20, people are exposed to 80% of their dangerous lifetime ultraviolet radiation. If we begin early to educate and protect our children, we can reduce the incidence of skin cancer by 78%."

According to the American Academy of Dermatology, sunscreen should be applied generously and reapplied several times a day for maximum benefit, especially if a child goes swimming or is in the water. Sunscreen works by shielding the skin from the ultraviolet rays of the sun.

"Most parents don't realize that regular use of a sunscreen with an SPF of 15 or higher can greatly reduce the incidence of skin cancer," said Peyton E. Weary, MD, president of the American Academy of Dermatology. "There are over 700,000 new cases of skin cancer each year and most of these are preventable."

"Don't 'forget to cover a child's sensitive areas, such as ears, scalp, neck and nose. A product made especially for lips should also be used," adds William B. Riley Jr., MD, president-elect of the American Society of Plastic and Reconstructive Surgeons. "This should be done at least 30 minutes before going outside, so that skin has time to absorb it. A bad sunburn is serious because it doubles the risk of melanoma."

"Some people are more susceptible to skin cancer than others," said Dr. Jacott. "People with fair skin, people with freckles, people with light eyes — all of these genetic characteristics are considered risk factors for skin cancer. Latinos, African-Americans and darker-skinned Caucasians should also protect themselves from the sun."

If a child gets a sunburn, a mild lubricating cream or cortisone cream should be applied to relieve the discomfort, according to Dr. Hogan. "You can ease the pain of less-severe bums and redness with a towel soaked in cool water. However, if a child gets a severe sunburn accompanied by pain, nausea and chills, you should call your physician immediately," she said.

In 1993, an estimated 9,100 people died from skin cancer. The most serious skin cancer is melanoma, which was diagnosed in about 32,000 people in 1993.