Management of Melanotic Neuroectodermal Tumor of Infancy

Márcia Gaiger De Oliveira, DDS, Lester D.R. Thompson, MD, Anna Cecília Moraes Chaves, DDS, Pantelis Varvaki Rados, DDS, Isabel da Silva Lauxen, Biol, and Manoel Sant’Ana Filho, DDS

Melanotic neuroectodermal tumor of infancy is a rare congenital neoplasm involving the head and neck in young patients. The clinical assessment, histologic diagnosis, and management is reviewed, with an emphasis on different treatment alternatives in two new case reports.

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Melanotic neuroectodermal tumor of infancy (MNTI) is a rare, usually benign neoplasm of neural crest origin composed of relatively primitive pigment-producing cells. MNTI usually arises in infants within the first 6 months of life. Because of the uncommon occurrence of this neoplasm, past terms used to describe the tumor include “pigmented epulis,” “retinal anlage tumor,” “congenital melanocarcinoma,” “melanotic epithelial odontoma,” “melanotic ameloblastoma,” and “melanotic progonoma,” to name just a few. It usually arises in the head and neck region and predominantly affects the maxilla, although other sites, such as brain, epididymis, mediastinum, femur, and ovary have also been reported.

The tumor is usually nonulcerated and presents as a soft tissue swelling, frequently affecting bone. Although the tumor cells produce melanin, pigmentation may not be clinically evident. MNTI is a benign tumor, but can be locally aggressive, growing rapidly and resulting in tooth displacement as tumor cells invade bone. With plain radiographs, MNTI appear as intrabony expansile areas of radiolucency, usually with poorly demarcated margins, probably as a result of rapid tumor growth and a tendency to be locally invasive. Extensive tumor calcification may be identified. Teeth are usually displaced and appear within the radiolucent area of the tumor. Computed tomography (CT) scans provide important information regarding the extent of the lesion, thereby assisting in the development of a surgical plan.

We report the clinical and histopathologic features of two cases of MNTI treated surgically, with and without incisional biopsy.

Case Reports

Case 1

A small mass was noted within the maxilla of a male patient at birth, with associated feeding problems developing during the ensuing 2 months. During this time the mass started growing rapidly, resulting in a referral at 2 months to the School of Dentistry, Universidade Federal do Rio Grande do Sul (Porto Alegre, Brazil). No other physical, clinical, or laboratory abnormalities were identified, and there were no congenital anomalies. Clinical examination revealed a fluctuant blue mass covered by an intact mucosa with expansion of the left maxillary alveolar ridge (Fig 1). Radiographic examination revealed a poorly defined osteolytic radiolucency associated with a left upper deciduous central incisor that was displaced anteriorly. CT showed a radiolucent lesion with expansion of the
surrounding bone in the area of the deciduous central incisor (Fig 2).

An incisional biopsy performed under local anesthesia was inconclusive, leading the surgeon to obtain diagnostic material under general anesthesia. Upon receiving a diagnosis of a MNTI, a second

Figure 1. Expansion of the left maxillary alveolar ridge by a slightly “blue-purple” mass with intact overlying mucosa.

Figure 2. Computed tomography scan showing a radiolucent lesion with expansion of the surrounding bone in the area of the deciduous central incisor. The macroscopic mass (inset) is well circumscribed and heavily pigmented.
operation was required to achieve complete surgical extirpation. Postoperatively, a lumbar puncture was negative for malignant cells, and there was no evidence of metastatic or disseminated disease. The patient is alive and well 7.5 years after the original surgery without disease and no recurrent tumor.

Case 2

A 3-month-old girl was referred for investigation of a swelling of the left maxillary alveolus. The lesion was first noted at birth, but started growing rapidly 8 weeks before the visit, causing difficulties with feeding. Clinical examination revealed an expansion of the left maxillary alveolar ridge by a darkly pigmented sessile mass with intact overlying mucosa. There were no other clinical or physical findings of significance. CT scan showed a radiolucent lesion expanding the surrounding bone, and confirmed the displacement of the left and right upper deciduous central incisor and the left upper deciduous lateral incisor.

Surgical excision was performed under general anesthesia, with curettage of the bone. The tumor was well demarcated. The crown of a deciduous tooth was attached to the enucleated specimen. The patient had an uneventful postoperative course and is alive and well without evidence of disease or recurrence 4 years after the initial presentation.

Pathologic Findings

Macroscopically, both intact lesions had a dark blue tinctorial surface, with sectioning through the hard mass revealing a mottled white-grey and dark blue cut surface (Fig 2, inset). The tumors were 4 cm in greatest dimension.

Microscopically, both tumors were remarkably similar, displaying a densely sclerotic fibrous connective tissue stroma separating a biphasic neoplastic proliferation. A fibrous capsule was seen in both cases, but the tumors were considered circumscribed rather than encapsulated. One population was composed of centrally located small, darkly stained cells with hyperchromatic nuclei and scant cytoplasm. There were no other clinical or physical findings of significance. CT scan showed a radiolucent lesion expanding the surrounding bone, and confirmed the displacement of the left and right upper deciduous central incisor and the left upper deciduous lateral incisor.

Surgical excision was performed under general anesthesia, with curettage of the bone. The tumor was well demarcated. The crown of a deciduous tooth was attached to the enucleated specimen. The patient had an uneventful postoperative course and is alive and well without evidence of disease or recurrence 4 years after the initial presentation.

Discussion

Several theories have been proposed to explain the pathogenesis of this neoplasm which recapitu-
lates the early stages of retinal development (retinal anlage tumor). A congenital dysembryogenetic neoplasm arising from neural crest cells is the posited theory best supported by embryologic, ultrastructural, biochemical, immunohistochemical, electron microscopic, and molecular genetic studies. Support for this proposed neuroectodermal origin is given with secretion of vanilmandelic acid or other catecholamines by the neoplastic cells, a finding characteristic of other tumors of neural crest origin, such as pheochromocytoma, neuroblastoma, and ganglioneuroblastoma. After tumor excision, vanilmandelic acid levels will usually return to normal. Further support for the neuroectodermal derivation is the expression of melanotransferrin (a melanoma-specific peptide that may play a role in iron metabolism) in MNTI.

Tumors are circumscribed but not encapsulated. There is a biphasic tumor cell population arranged in a background fibrous connective tissue stroma. The small, darkly staining cells comprise the majority of the cells and have a “neural” quality with scant, fibrillar cytoplasm surrounding round nuclei with coarse and heavy nuclear chromatin deposition. Usually identified in a central location, these “neuroblastic-like” cells are surrounded by a second population of larger epithelioid cells. These cells have significantly greater amounts of opaque cytoplasm filled with melanin pigment granules surrounding nuclei that contain a more vesicular nuclear chromatin. The melanin pigment can be so dense as to obscure the nucleus. By definition, mitotic figures are inconspicuous and these tumors lack necrosis and hemorrhage.

Immunohistochemical studies have shown that the large epithelioid cells are variably positive for vimentin, cytokeratin, epithelial membrane antigen, neuron-specific enolase, glial fibrillary acidic protein, synaptophysin, Leu 7, and HMB-45. The smaller, hyperchromatic cells are positive for neuron-specific enolase, glial fibrillary acidic protein, and synaptophysin. S-100 protein is usually nonreactive, although rare cases may be focally immunoreactive. Whereas the neoplastic cells show polyphenotypic expression with neural, melanocytic, and epithelial markers, no photoreceptor (retinol-binding protein) or myogenic differentiation is noted. Furthermore, alpha-fetoprotein and neurofilament are also nonreactive, helping to separate other primitive neuroectodermal tumors from MNTI.

By ultrastructural examination, the biphasic nature of the tumor cells is also confirmed, with dense-core, membrane-bound neurosecretory granules, neurofilaments, and cytoplasmic processes identified in the small cell population and modified tight junctions, melanosomes at various stages.
of development, and a single cilium identified in the epithelioid population.6,17,18

The differential diagnosis of MNTI is quite broad, but must be separated from other pediatric “small round cell” neoplasms such as neuroblastoma, Ewing’s sarcoma, peripheral neuroepithelioma, rhabdomyosarcoma, peripheral primitive neuroectodermal tumor, desmoplastic small round cell tumor, malignant melanoma, and lymphoma. Histopathologically, the biphasic neoplastic population and polyphenotypic immunohistochemical expression is quite distinctive and unique from most of the other pediatric “small blue round cell” neoplasms.2,19 MNTI may share a common histologic and immunophenotypic expression with cellular blue nevus, melanoma, neuroblastoma, and rhabdomyosarcoma, but MNTI does not express diffuse reactivity with S-100 protein, lacks other markers of neuroendocrine differentiation, and lacks myo-D1, myoglobin, myogenin, and muscle-specific actin reactivity. Melanoma is distinctly rare in pediatric patients and even more so if the “mucosal” sites of development of MNTI are considered. Cellular blue nevus characteristically has a spindle cell population, the cytoplasm of which is filled with pigment, while MNTI does not contain spindle cells. Teratoma, especially immature types, may show isolated foci of MNTI, but these foci are of no prognostic significance. Curiously, even though there is a histologic similarity with neuroblastoma and other pediatric neoplasms, there is no genetic basis at present to link them.7,20

A limited review of the English literature (1990 to 2003) confirms that most MNTI occur in the maxilla and oral cavity in pediatric patients, with >90% occurring in infants <1 year of age.2,20-23 There is no gender predilection with patients usually presenting with a unilateral, nonulcerated mass, present since birth, frequently associated with recent rapid enlargement. Symptoms are usually present for an average duration of about 2 months. A radiolucent expansion of the bone with tooth displacement is noted on plain radiographs, while vascular enhancement will be appreciated on postcontrast images. The extent of the lesion is best delineated with a CT.

Given the typical clinical features of these tumors in the oral cavity, we believe that complete surgical excision with negative margins can be performed without a prior biopsy. This approach avoids unnecessary anesthetic risk and reduces manipulation of the lesion, because it has been reported that the tumor seems to grow faster at previous biopsy sites.8,12 Although a conservative approach, consisting of local excision and curettage, has been adopted for the management of MNTI, the extent of the surgical excision has been debated.2,3,9,17 Different authors have reported large blunt dissection, en bloc excision of the tumor with reconstruction of the defect with autogenous costochondral graft, the use of chemotherapy alone, or in association with radiation therapy, or radiation therapy alone.8,18,22 However, the successful management of the two patients reported herein suggests that aggressive or radical surgery may not be necessary. Given the pigmentation of the lesion, it is usually possible to visualize the tumor limits and enucleate it as a whole (see Fig 2, inset). This would avoid tumor fragmentation that may lead to recurrence.

Unfortunately, the biological behavior of this neoplasm cannot be predicted by gross or histologic characteristics, requiring close and careful clinical follow-up.2,10,17,25 Rates of local recurrence up to 45% after conservative excision have been reported.2,12,13,17 Recurrent tumors seem to grow more aggressively, tend to have indistinct borders, and may show osteoid formation, suggesting that the surgical procedures may trigger reactive bone formation.11,24 Some authors have demonstrated a significant presurgical reduction of the “neuroblastic-like” component with chemotherapy.22 When metastasis develops (up to 7% of cases),2,6,10,17,18,21 it is the “neuroblastic-like” component that is regarded as the aggressive part of the neoplasm. These malignant MNTI develop widespread metastasis and cause death within a few months. Consequently, these tumors are histologic mimics of neuroblastoma rather than MNTI.7,9 In this setting, surgery with adjuvant radiation and/or chemotherapy is the usual treatment. The usefulness of DNA ploidy by flow cytometry in predicting tumor behavior is controversial, although aneuploidy is associated with tumor recurrence.17

**Conclusion**

Melanotic neuroectodermal tumor of infancy is a well-characterized biphasic neoplastic lesion that occurs in infancy and may be treated conservatively by surgical excision without an incisional biopsy, thus avoiding further manipulation of the lesion.
The distinguishing features of a biphasic tumor cell population with melan pigment allow for separation from other pediatric neoplasms, thereby avoiding unnecessary therapy. Close clinical follow-up is suggested for the first few years after presentation to identify recurrence or the rare development of metastatic disease.

References