Melanotic Neuroectodermal Tumor of Infancy: 2 Decades of Clinical Experience With 18 Patients

Amit Chaudhary, MCh, Ashish Wakhlu, MCh,†*
Neetu Mittal, BDS,‡ Sanjeev Misra, MCh,§
Divya Mehrotra, MDS,‖ and A.K. Wakhlu, MCh¶

Purpose: The purpose of this article is to report our experience in the management of 18 patients with melanotic neuroectodermal tumor of infancy involving the maxillary alveolus.

Patients and Methods: All patients presented with hard nontender swelling involving the upper alveolus with facial deformity. Analysis included hematocrit, coagulation profile, serum creatinine, and screening for vanillyl mandelic acid and catecholamines. Imaging studies included x-ray of the maxilla and chest, ultrasound of the abdomen, computed tomography scan (1990 to 1999), and magnetic resonance imaging (after 1999). All surgeries were performed using endotracheal anesthesia, and complete gross excision of the tumor was achieved with coverage of the defect with mucoperiosteal flaps. All specimens were subjected to histopathology and immunohistochemistry.

Results: The expansion of the alveolus produced by the tumor improved in 4 to 6 months. Subsequent dentition was affected by the removal of involved tooth buds during the operation. All the patients are in regular follow-up (maximum 206 months) and there has been no local recurrence or distant metastasis. Mean follow-up time was 130.8 months (95% confidence interval, 168.8-210.6). Overall survival at 17 years was 85.6%. Median survival could not be established due to statistically insignificant sample size, while mean survival time was 189.7 months (95% confidence interval, 103.7-157.8).

Conclusions: In the absence of metastatic disease, melanotic neuroectodermal tumors of infancy can be successfully managed by local excision.

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Melanotic neuroectodermal tumor of infancy (MNTI) is a rare tumor of neural crest origin commonly arising from the maxilla in infants.[1] This tumor is usually evident in the first year of life. The typical clinical presentation is a firm, painless, rapidly growing mass arising from the maxillary alveolus; the tumor elevates the upper lip and can interfere with nursing. Surgery is the treatment of choice with a local recurrence rate of 10% to 15%.[2-5] A 3% incidence of metastasis has also been reported.[3] MNTI was first described in 1918 by Krompecher[6] and 356 patients have been reported in the English language literature to date. There is a paucity of vast experience with this tumor in the literature. This article reports our experience with the management of this tumor in 18 patients. To the best of our knowledge this is the largest number of patients with this tumor from a single institution.

Received from King George Medical University, Lucknow, India.
*Senior Resident, Department of Surgery.
†Professor, Pediatric Surgery.
‡Postgraduate, Oral Surgery.
§Professor, Surgical Oncology.
‖Assistant Professor, Oral Surgery.
¶Professor, Pediatric Surgery.
Address correspondence and reprint requests to Dr Chaudhary: 521/37, Bada Chand Ganj, P.O. – Mahanagar, Lucknow 226 006 UP, India; e-mail: amitwtc@yahoo.co.in

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Patients and Methods

A retrospective analysis based on medical records was performed for patients with MNTI admitted to the Department of Pediatric Surgery, King George Medical University, between October 1984 and January 2004. Cases were identified by computerized search, and all available medical records were reviewed. During the study period, 18 patients (12 males, 6 females) with MNTI were admitted to our department. The mean age was 4.3 (±2.1) months. All the babies presented with a painless slowly grow-

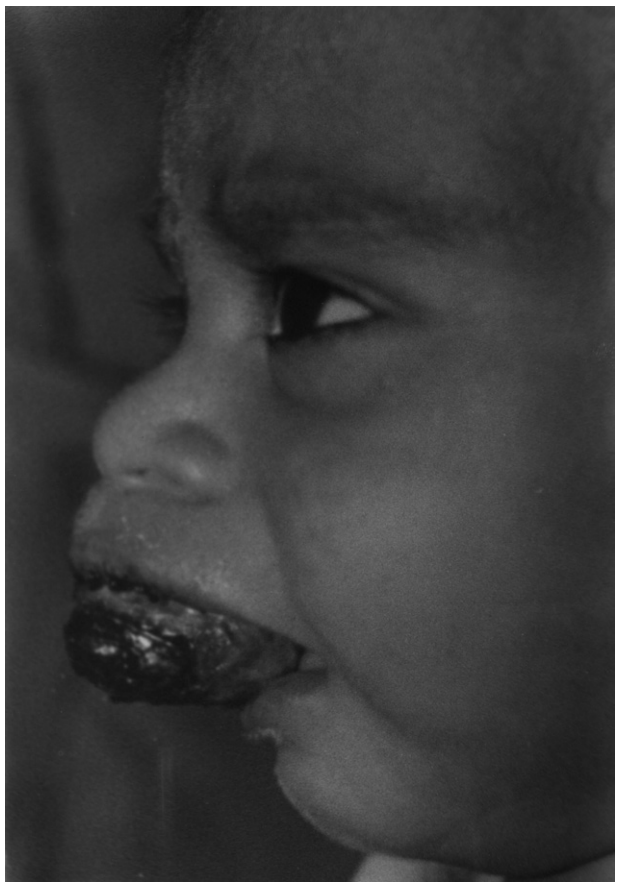

FIGURE 1. Photograph showing clinical appearance of melanotic neuroectodermal tumor of infancy.

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ing swelling in the maxillary alveolus (Fig 1). The swelling was present on the lateral maxillary alveolus in 13 patients (left side in 8 and right side in 5), protruding externally and giving rise to facial asymmetry. In 2 children the midline maxillary alveolus was involved, raising the upper lip. Three patients had involvement of the alveolus and hard palate with the tumor protruding in the oral cavity leading to feeding difficulty. There was no family history of similar tumors in any of our patients. On examination, in all patients the swelling was smooth, hard, bluish black in color, and fixed to the bone. The overlying mucosa was thin and slightly mobile; none of the patients showed ulceration of the mucosa. Details of the patients are shown in Table 1.

Investigations included hematocrit, coagulation profile, and serum creatinine. Urinary vanillyl mandelic acid expression was positive in 6 of the patients. Hematological screening for catecholamines was within normal limits in all, and x-ray of the maxilla in all patients showed expansion of the bone by a radiolucent lesion. Computed tomography scans were performed for 14 patients admitted after 1990 and uniformly revealed a central area of radiolucency with sharp margins displacing the surrounding bone and tooth buds (Fig 2). Magnetic resonance imaging of 8 patients admitted after 1999 revealed a hypointense mass with focal areas of hyperintensity in T1-weighted images and an isointense mass on T2-weighted images. Ultrasound of the abdomen and whole body skeletal screening was within normal limits in all children. Fine needle aspiration cytol-

Table 1. EIGHTEEN PATIENTS WITH FOLLOW-UP AND OUTCOME

Case	Age (mo)	Gender	Site	Follow-Up (mo)	Outcome
1	8	Male	Rt max alveolus	198	Alive and well
2	2	Male	Lt max alveolus	152	Alive and well
3	3	Female	Lt max alveolus	202	Alive and well
4	6	Female	Ant max alveolus	206	Alive and well
5	5	Female	Lt max alveolus	102	Alive and well
6	2	Male	Lt max alveolus and palate	98	Expired
7	4	Male	Lt max alveolus	156	Alive and well
8	2	Male	Rt max alveolus	172	Alive and well
9	6	Male	Rt max alveolus and palate	164	Alive and well
10	8	Male	Rt max alveolus	152	Alive and well
11	2	Male	Lt max alveolus	134	Alive and well
12	3	Female	Ant max alveolus	94	Alive and well
13	6	Female	Rt max alveolus	74	Alive and well
14	5	Female	Lt max alveolus	188	Alive and well
15	2	Male	Rt max alveolus and palate	90	Alive and well
16	4	Male	Lt max alveolus	88	Lost to follow-up
17	2	Male	Rt max alveolus	72	Alive and well
18	6	Male	Lt max alveolus	12	Alive and well

Abbreviations: Ant, anterior; Lt, left; Rt, right; Max, maxillary.

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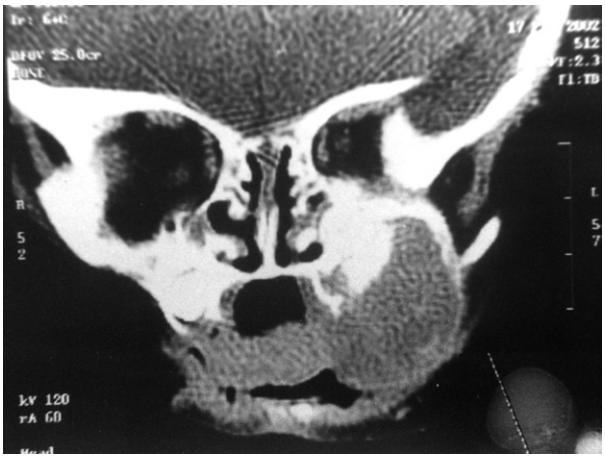

FIGURE 2. Computed tomography scan of the patient in Figure 1, showing radiolucent lesion expanding the maxillary alveolus.

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ogy was performed in the first 6 patients whereas the diagnosis in the rest was clinical.

Disease-free and overall survival was calculated from the time of diagnosis. Statistical analysis for overall survival was performed using the Kaplan-Meier method with SPSS statistical software (release 10.0; SPSS Inc, Chicago, IL). All deaths were counted as an event for the analysis of overall survival. Patients lost to follow-up were also counted as an event (worst case scenario). Mean follow-up time was 130.8 months (95% confidence interval, 168.8-210.6).

SURGERY AND PATHOLOGIC DETAILS

The average age at surgery was 9 months. Surgery was performed under endotracheal anesthesia by an intraoral approach. A mucoperiosteal incision was made and the mucosal flap elevated to remove the tumor by enucleation; the tumor was well-circumscribed and could be easily enucleated out of the alveolar crest; however, the related primary teeth and tooth buds had to be sacrificed. The cavity was then curetted to remove all traces of blue black tissue, after which primary closure could be achieved in only 6 patients. In the remaining patients a local mucoperiosteal flap and costocondral graft was used to cover the defect. The costocondral graft was harvested by removing the costal cartilage of the right sixth rib subperiostially. The cartilage was then trimmed to bridge the defect in the maxilla and sutured in place with absorbable suture to the mucoperiosteum. A mucosal flap taken from the cheek or inside of the upper lip was then used to cover the cartilage graft putting the epithelial surface outward.

On gross examination the excised specimens were bluish black or brown in color and well encapsulated. The histological features of the specimen were typical of MNTI in all patients. The tumors showed cells arranged in clusters or lines with cleft-like spaces within a fibrous stroma. A biphasic cell population consisting of large epitheloid cells with cytoplasm containing melanin pigment and small ovoid, undifferentiated cells closely resembling neuroblasts were seen (Fig 3). Immunohistochemistry became available at our institution in 1995 and was performed in the last 12 patients. The tumor was positive for neuron-specific enolase, synaptophysin, S-100.

TECHNIQUE OF IMMUNOHISTOCHEMISTRY

The tissue section was fixed and immunostaining of the paraffin-embedded tissue was performed by avidin-biotin-peroxidase method with 30 minutes of incubation at room temperature.

Results

Postoperatively the patients were allowed oral intake after recovery from anesthesia. The average time to discharge was 5 days after surgery. The majority of the patients had no feeding difficulty. Before dis-

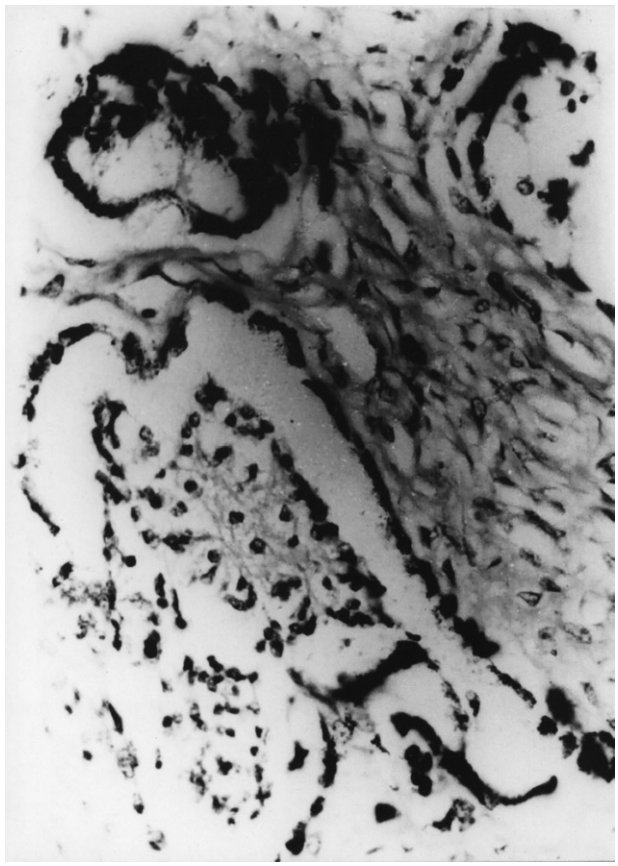

FIGURE 3. Histology of the excised tumor showing biphasic cell population.

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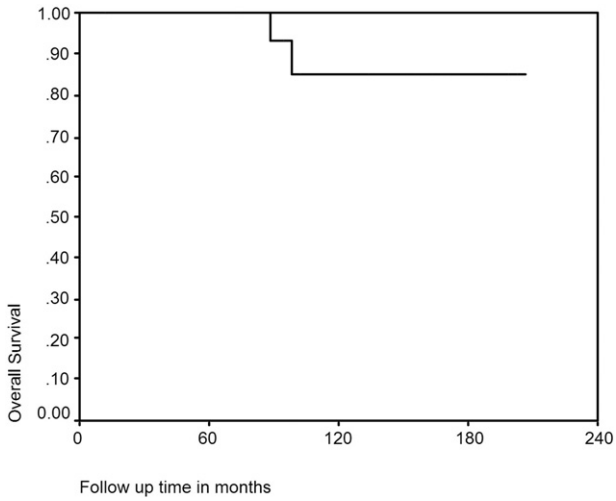

FIGURE 4. Kaplan-Meier survival curve showing actuarial overall survival.

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charge all patients were referred for pedodontic consultation. None required any dental prosthesis. We found clear-cut male predilection of the disease (12 males: 6 females) and all the patients who expressed vanillyl mandelic acid (VMA) in their urine were males. All the patients are in regular follow-up except 2 and are free from any local recurrence or distant metastasis. One patient was lost to follow-up at 88 months without disease while 1 patient expired outside the hospital (cause, not known). Overall survival at 17 years was 86.7% (Fig 4). Median survival could not be established due to statistically insignificant sample size, while mean survival time was 189.7 months (95% confidence interval, 103.7-157.8).

Discussion

Krompecher was the first to describe melanotic neuroectodermal tumor of infancy in 1918.[6] The tumor is now accepted as being of neuroectodermal origin on the basis of ultrastructural, immunocytochemical, and electron microscopic studies.[1] As of 2005, 356 patients had been reported[7-8] and to the best of our knowledge, ours is the largest single center experience with MNTI to date. Ninety percent of the tumors are seen in the head and neck region,[1] maxilla being the most common site (68.8%), followed by skull (10.8%), mandible (5.8%), and brain (4.3%).[8] All of our patients had involvement of the maxillary alveolus. No definite gender predilection exists in the literature,[5] though 12 out of our 18 patients were male. The tumor is unique in its ability to synthesize melanin[4] and may also elaborate VMA in urine.[1,9] Six of our patients, all male, tested positive for VMA in urine. This exclusive production of VMA by male patients has not been mentioned in previous literature.

The etiology of MNTI is unknown. None of our patients had a positive family history. The expression of VMA is characteristic of tumors arising from neural crest cells but we do not know why VMA expression was limited to male patients in this study. This finding has not been reported previously in literature.

Fine needle aspiration cytology was done in the first 6 of our patients because we were unsure of the diagnosis while in the rest of the patients preoperative diagnosis was made clinically. Radiographic findings were typical showing a central area of radiolucency with sharp margins displacing the surrounding bone and tooth buds. Computed tomography scans were very helpful in planning surgical excision.

All 18 patients except 2 were otherwise healthy and well except for the symptoms due to physical effect of the swelling and cosmetic disfigurement. There was no recurrence in any case but 1 of our patients was lost to follow-up without disease after 6 years, and another patient expired due to unrelated causes. There are reports of wide excision, subtotal maxillectomy, and use of titanium miniplates for reconstruction[5,10,11] in the literature but these were not required in our patients. A thorough local excision and curettage of the cavity to remove all traces of bluish black tissue sufficed for cure in all 18 patients. Although the majority of tumors are benign, a local recurrence rate of 10% to 15% and a malignancy rate of 3.2% are reported[8] in the literature. Histopathology and immunohistochemistry was diagnostic of MNTI. All 16 patients who were alive without disease are under follow-up (oldest patient 17 years of age now) and are free of any local recurrence or distant metastasis.

Based on our experience we feel that the diagnosis of MNTI is mainly clinical. The physical findings are classical and the radiological features are characteristic. Further to this the detection of VMA expression in urine does not fulfill any diagnostic or therapeutic goal at present. Immunohistochemistry clarifies the neural crest as the cell of origin of MNTI and characterizes the tumor but no prognostic benefit is available from this investigation at present. In neuroblastomas the expression of neuron-specific enolase is a poor prognostic feature but this was not seen to apply to MNTI in our study. We conclude that early conservative surgical excision provides an excellent result with good prognosis for patients with melanotic neuroectodermal tumor of infancy.

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