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# Melanotic Neuroectodermal Tumor of Infancy: A Diagnostic Perplexity

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**ABSTRACT**
Melanotic neuroectodermal tumor of infancy (MNTI) is a rare benign tumor of neural crest origin. It is a locally invasive tumor with a high recurrence rate usually occurring in the first year of life. It was first described by Krompecher in 1918. Clinically MNTI are soft, painless, pigmented, non- ulcerative, rapidly growing lesion. We report a case in a seven month old male child presenting with a swelling in the maxillary region. Radiograph of skull revealed a lytic lesion in the maxilla. Mainstay of treatment is complete surgical excision. Histopathological examination with immunohistochemical studies is the key to confirming diagnosis for an early management.

**KEY WORDS:** Neuroectoderm, Melanotic, Infancy, Maxilla.

## I. INTRODUCTION

Melanotic neuroectodermal tumor of infancy (MNTI) is a rare, benign pigmented tumor of neural crest origin.[1,2,3] It is a locally aggressive tumor with a high recurrence rate.[4] According to reports, the suggested rate of recurrence varies between 10%-60% within one year of initial excision[5] and 6.6% is estimated as the rate of malignant transformation.[3]

It usually presents in the first year of life and has a male preponderance.[6.7] It was first described by Krompecher[8] in 1918. It most commonly occurs in the head and neck region involving premaxilla (68-80%) followed by skull (10.8%), mandible (5.8%) and brain (4.3%). Other sites include mediastinum, shoulder, thigh, foot and epididymis.[10]

As per the literature, earlier when the cell of origin was not known, the tumor had been attributed with various names like Congenital melanocarcinoma[8], Retinal anlage tumor[10], Pigmented congenital epulis[11] or Melanotic prognoma.[12]

It is associated with an increased vanillyl mandelic acid excretion in urine, however it is not diagnostic of MNTI.[13,14] Based upon this finding, tumor was proposed of having a neural crest origin.[14,15,16] This finding helped in explaining the bimodal population of primitive neuroectodermal cells and melanocytic cells, both of which are derived from the neural crest.[17]

Clinically MNTI are soft, painless, pigmented, non- ulcerative, rapidly growing lesion. They usually involve the underlying bone, sinuses and may be related with displacement of tooth.
Computed tomography scan show a hyperdense lesion and highlights bone remodelling and expansion. MRI reveals an enhancing, circumscribed hypointense mass.[18] Histopathological examination is necessary for a definite final diagnosis.

Mainstay of treatment is complete surgical excision. The patients should be followed up closely as the tumor is locally invasive and has a high recurrence rate. We present a case of MNTI of maxilla in a seven month old male child.

## II. CASE PRESENTATION

A 7 month old male child presented with feeding difficulty and a swelling in the anterior part of maxilla since 1 month. The swelling progressively increased in size since then. There was no history of intake of any medication during pregnancy. There was no significant past medical history. General and systemic examinations were unremarkable. Growth and developmental milestones were normal for age. On clinical examination, a solitary, well-defined, sessile lesion measuring 3.5x3cm was noted in the pre-maxilla region with presence of facial deformity. The overlying mucosa was smooth and the swelling did not bleed on touch. Radiograph of skull revealed a lytic lesion in the maxilla. On computed tomography scan, a soft tissue swelling in the left maxillary antrum was seen with expansion of the involved bone suggestive of an osteolytic lesion.

Routine laboratory investigations were within normal limits. 24 hour urine sample was tested for the levels of vanillyl mandelic acid (VMA) which were elevated. Wide local excision of the tumor was performed and specimen was sent for histopathological examination. On gross examination, the mass was well circumscribed, lobulated, measuring 3.5x3x2cm. On serial sectioning, cut surface showed a heterogeneous, grayish white tumor measuring 2x1.5x1cm. Microscopically, overlying mucosal epithelium was intact and showed no ulceration. The lesion was unencapsulated, composed of irregular nests, cords and clusters of tumor cells separated by dense fibrovascular stroma. (Fig 1,2) Two populations of cells were seen, large epithelioid melanocytic cells with round nuclei, vesicular chromatin, abundant eosinophilic cytoplasm and small primitive neuroepithelial cells with central, round hyperchromatic nuclei and scant cytoplasm. (Fig 3,4). Bone involvement was also identified in the peripheral part with tumor cells invading the bone (Fig 5). No mitotic figures were identified. No areas of necrosis seen. A diagnosis suggestive of a Small round cell tumor favoring Melanotic neuroectodermal tumor of infancy was given which was further confirmed by immunohistochemical studies. Homatropine methylbromide-45 (HMB-45) marker was positive in the large cells. Synaptophysin showed positivity in the small round cells. S100, CD99 and LCA were negative in large as well as the small cells. The post-operative period was uneventful without any complications. The patient showed no signs of recurrence in the one year follow-up period.

## III. DISCUSSION

In 1918 the tumor was first designated by the name congenital melanocarcinoma.[8] A tumor that was composed of pigmented epithelium and small cells resembling neuroblasts derived from the retinal neuroepithelium, was reported by Halpert and Patzer which they called Ciliary body of the eye.[4]

It was advocated that the tumor originated from the entrapment of retinal anlage in the embryologic fusion lines of developing maxilla.[4] In 1965, Misugs et al reported that the tumor had a neural crest origin.[19] Stowens suggested that the tumor had a resemblance to Vomeronasal organ of Jacobson.[20]

MNTI has a predilection for males occurring in the first year of life with a peak incidence before 6 months of age. Most common site of occurrence is maxilla.[6,7] In our case lesion was present in the left maxillary antrum. Other locations include mandible, skull, mediastinum, soft tissues of extremities, epididymis.

The local recurrence rate after the initial surgical excision varies from 10-60% and 6.5% with distant metastasis. Incomplete resection of the tumor or invasion of the tumor edge into the bone may cause recurrence.[21,22,23]

Clinically MNTI is a locally invasive, expansile, painless swelling mainly involving the craniofacial region. Tumor may show pigmentation but it is present in every case despite the fact that the tumor cells produce melanin.[24] In our case there was no definitive evidence of melanin pigment. Conventional radiograph reveals radiolucency. On computed tomography scan, the tumor appears as hyperdense masses. Magnetic resonance imaging shows hypodense lesion with few areas of hyperdensity.[22] Extensive tumor calcification can also be seen.[24]

Vanillyl mandelic acid (VMA) is a major catabolite of catecholamines. Elevated levels of its excretion in urine is commonly associated with tumors of neural crest origin.[14] Therefore post-excision of the tumor, a decrease in urinary levels of VMA confirms the neurocristopathic hypothesis.[10] However it is not a specific finding and many cases have been reported with normal levels of VMA. In this case, patient had elevated levels of VMA.

On ultrastructural examination, tight juctions, melanosomes in various stages of development and single cilium are found in the larger epithelioid cells and dense core membrane bound neurosecretory granules, neurofilaments and cytoplasmic processes are found in the small cell population.[25,26,27]

On histopathological examination, the tumor shows dual population of cells arranged in alveolar pattern in a background of fibrovascular stroma. Larger polygonal cells resemble melanocytes and other cell component comprises of small round cells having round, hyperchromatic nuclei and scant cytoplasm resembling neuroblast- like cells.[9]

Immunohistochemistry plays an important role in confirming the diagnosis.

Most of the swellings of jaw occurring during infancy are benign odontogenic cysts or tumors.[28] There are few lesions that have a propensity to grow rapidly in an expansile manner due to which they can be misdiagnosed clinically as a malignant tumor.[28]

Differential diagnosis of maxillary swellings in an infant includes Congenital Epulis, Teratoma, Neuroblastoma, Ewings sarcoma, Rhabdomyosarcoma, Melanoma, Congenital eruption cyst, Burkitt's lymphoma, Hemangioma and Lymphangioma.[7]

Congenital epulis occurs at the time of birth and is usually pedunculated in contrast to MNTI which are sessile lesions. It is associated with feeding difficulty as was seen in our case.[24]

Teratomas are diagnosed and differentiated upon histopathological examination which includes elements derived from ectoderm, mesoderm and endoderm.

Neuroblastoma is a malignant tumor, most common site of involvement is abdomen. Metastatic neuroblasts occurs usually in the mandible with the patient presenting as periorbital ecchymosis, Horner's syndrome, changes in occlusion and jaw deviation on opening of mouth.[29] It is HMB-45 negative on immunohistochemical analysis.

Ewings sarcoma is a rare malignant tumor of neuroectodermal origin most commonly affecting the long bones and pelvis. It infrequently occurs before the age of 5. Rarely it occurs in the head and neck region involving mandible and occasionally maxilla.[30] It demonstrates characteristic membranous immunostaining for CD99.

Embryonal rhabdomyosarcoma occurs in children less than 15 years of age with a peak incidence between 2-6 years. These tumors in the oral cavity usually involve palate or tongue.[31] Immunohistochemically it shows desmin and myogenin positivity.

Oral mucosal melanoma occurs in $4^{th}$-$7^{th}$ decade usually in the palate region. On immunohistochemical analysis, HMB-45 and S100 shows positivity. S100 was negative in our case. HMB-45 and NSE positivity in this case pointed out melanocytic and neuroblastic differentiation of tumor cells respectively.[32,33,34]
Congenital eruption cyst occurs within the mucosa of underlying tooth that are about to erupt.[35]

Endemic type of Burkitt's lymphoma involves jaws and facial bone. Mean age of presentation is 7-14 years. Immunohistochemically, it is positive for Leukocyte common antigen.[36]

Central hemangiomas and lymphangiomas show bluish discoloration and are usually pulsatile and may bleed on touch because of the pumping action of the affected teeth.[37,38]
Mainstay of treatment is complete surgical excision with 2-5 mm margins.[27] Chemotherapy may be given as adjuvant treatment in cases of extended MNTIs.[22,39]

Although malignant cases are unusual but according to a study, 31 out of 472 cases (6.5%) showed malignant transformation.[16,22] Histopathologic criteria associated with an aggressive behavior includes mitotic rate greater than or equal to 2 per high power field, Ki-67 proliferation of >25% and CD-99 positivity. Metastasis is reported in about 3% cases.[21,40,41]

## IV. CONCLUSION

MNTI is an expansile, rapidly progressing tumor, therefore early diagnosis and appropriate management at a relevant time is the goal for preventing any chances of recurrence. Histopathological examination along with immunohistochemical confirmation is the key to confirming diagnosis and differentiating it from other vast variety of small round cell tumors occurring in infancy.

**Conflicts of Interest**
There are no conflicts of interest.

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## FIGURES

**Figure 1: Microphotograph showing nests, cords and clusters of tumor cells interspersed within a dense fibrotic stroma. (H & E stain, 4X).**

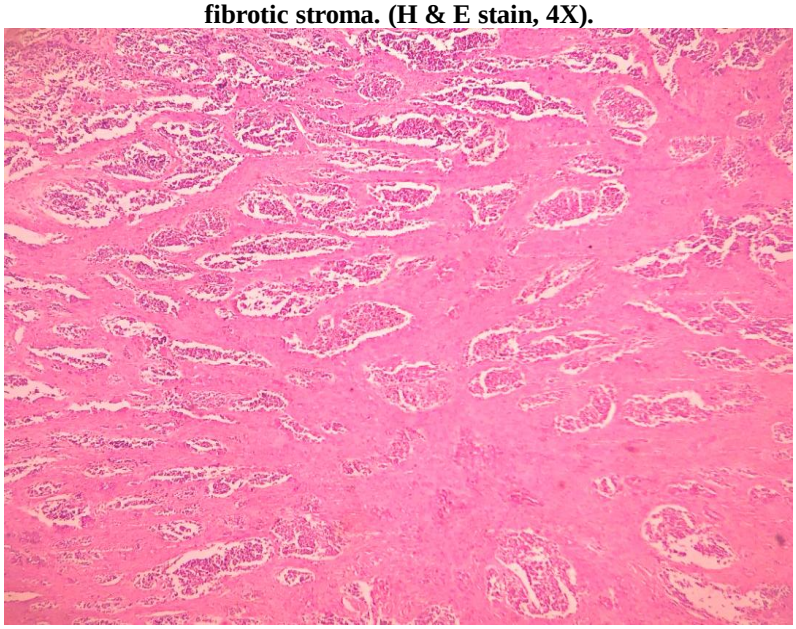


**Figure 2: Microphotograph showing tumor cells arranged in alveolar pattern (H & E stain, 10X).**

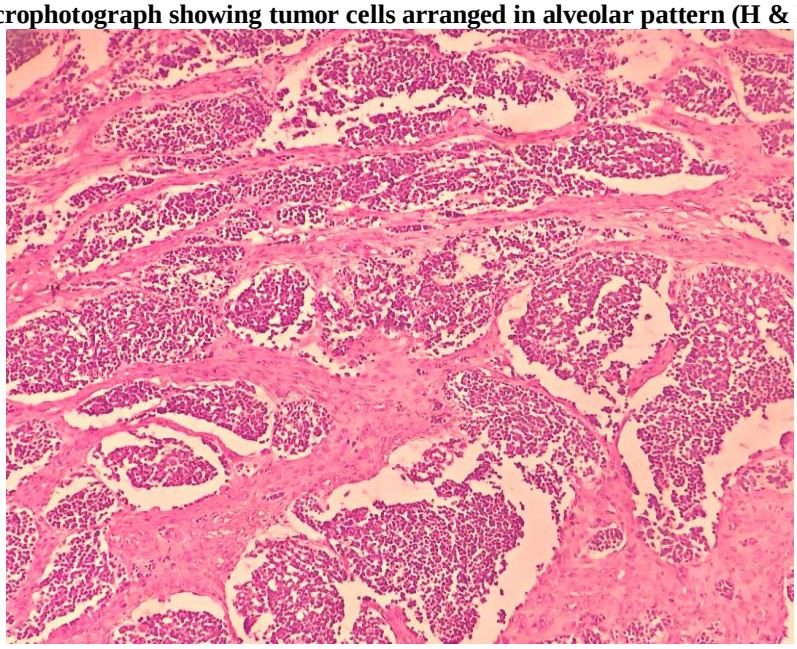


**Figure 3: Photomicrograph shows biphasic population of epithelioid melanocytic cells along with smaller primitive neurogenic cells. (H & E stain, 40X).**

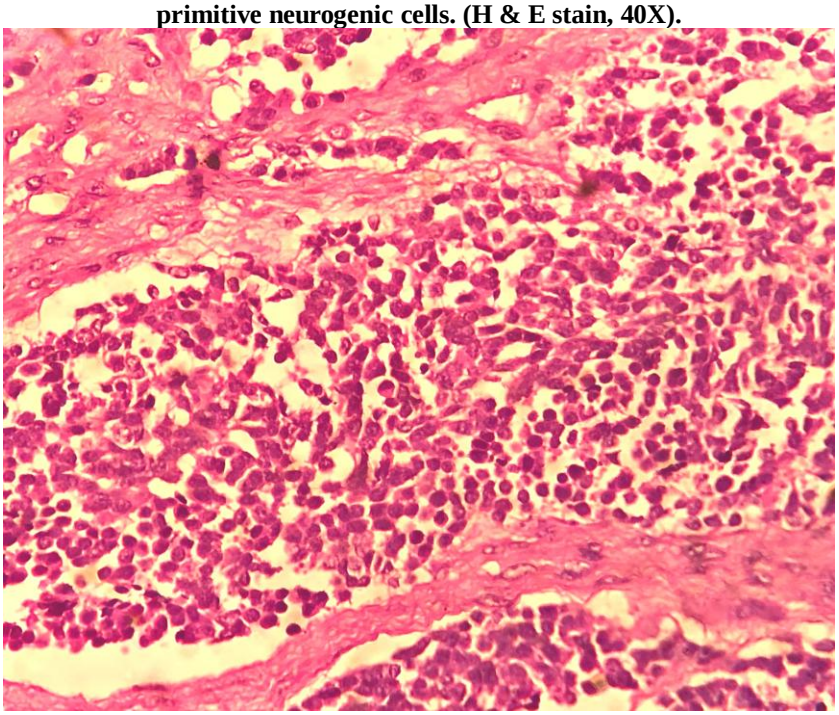


**Figure 4: High power view shows neuroblast-like cells in the central part. (H & E stain, 40x).**

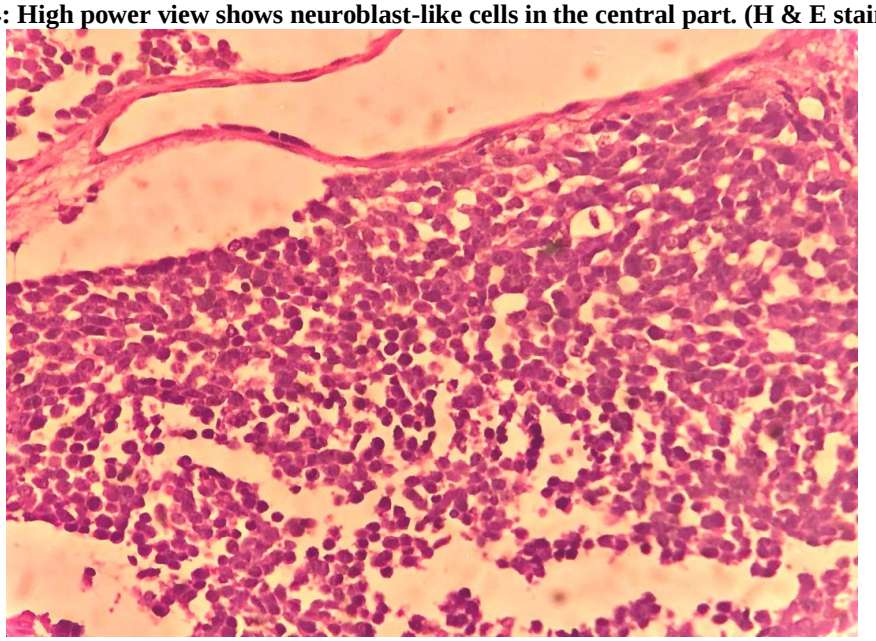
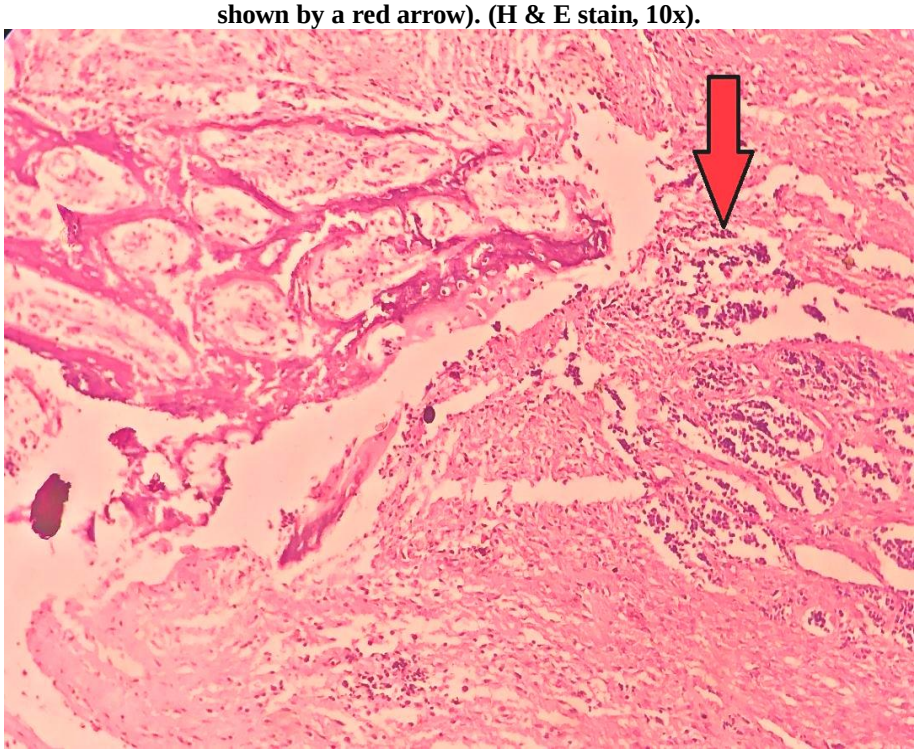


**Figure 5: Microphotograph showing infiltrative growth of the tumor invading into the bone (tumor cells shown by a red arrow). (H & E stain, 10x).**



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