Melanotic Neuroectodermal Tumor of Infancy

Brian S. Soles, MD; Allecia Wilson, MD; David R. Lucas, MD; Amer Heider, MD

• **Context.**—Melanotic neuroectodermal tumor of infancy, albeit rare and generally regarded as benign, is an important tumor to recognize because of its rapid growth, potential for local recurrence, and small round blue cell morphology, which can lead to misdiagnosis of a malignant neoplasm.

• **Objective.**—To review its clinical presentation and immunomorphologic findings, and discuss common entities in the differential diagnosis.

• **Data Sources.**—The study involved PubMed searches, including multiple review articles, case studies, retrospective studies, selected book chapters, and University of Michigan cases.

• **Conclusions.**—Melanotic neuroectodermal tumor of infancy most commonly occurs in the bones of the head and neck region during the first year of life, but it can also present in other locations, including the central nervous system, testes, ovaries, and subcutaneous soft tissues. Histologically, it is composed of a biphasic population of cells, consisting of epithelioid melanin-producing cells and primitive neurogenic cells in a fibrocollagenous stroma. These microscopic findings, especially in small biopsies, can lead to a broad differential diagnosis that includes malignant small round blue cell tumors and malignant melanoma. Melanotic neuroectodermal tumor of infancy commonly has an infiltrative growth pattern, and anatomic constraints often lead to incomplete resection and local recurrence, requiring multiple surgical operations. Because melanotic neuroectodermal tumor of infancy can mimic a more aggressive and aggressively treated malignancy, recognition of this rare tumor is very crucial for pathologists.

(Melanotic Neuroectodermal Tumor of Infancy—Soles et al)

Melanotic neuroectodermal tumor of infancy (MNTI) is a rare, rapidly growing, pigmented neoplasm of neural crest origin first described in 1918, with slightly more than 500 reported cases to date. It typically occurs in infants younger than 1 year and has a slight male predilection.²⁻³ It predominantly involves craniofacial sites in more than 90% of cases, and most commonly arises in the maxilla.³⁻⁴ Rare, non–head and neck sites include epididymis,⁵⁻⁷ testis,⁸⁻⁹ ovaries,¹⁰ and soft tissue and bones of the extremities.¹¹⁻¹⁴ The largest retrospective study² that reviewed 472 reported cases within the literature showed mainly maxillary involvement in 279 cases (62.2%), followed by the skull (70; 15%), mandible (35; 7%), male reproductive system (23; 5%), central nervous system (20; 4%), soft tissue (7; 1%), and female reproductive system (3; <1%). They also determined that the median age of diagnosis was 5 months. A few congenital and prenatal cases have also been identified.¹⁵⁻¹⁶

A variety of names were initially used to describe this entity due to difficulty in determining the cell of origin. These synonyms included melanotic progonoma, melanotic hamartoma, melanoameloblastoma, melanotic adamantinoma, congenital melanocarcinoma, and retinal anlage tumor.¹⁷ It was first proposed to be of neural crest origin in 1966, because of the discovery that many cases are associated with an increase of urinary vanillylmandelic acid excretion.¹⁸ This finding also helped to explain the biphasic population of melanocytic and primitive neuroectodermal cells, both of which are derived from the neural crest.¹⁹

Melanotic neuroectodermal tumor of infancy presents as an enlarging, painless, and firm mass, often underlying an intact epithelial surface, and it may have blue or black discoloration. Melanotic neuroectodermal tumor of infancy can be associated with elevated urinary vanillylmandelic acid in some, but not all, cases.²⁰ The measured levels of vanillylmandelic acid may return to baseline following surgical resection.²¹⁻²² On imaging, the tumor presents as a well-demarcated radiolucent lytic lesion within bone that may have features concerning for local destruction,²⁴ suggestive of a malignant process. Computed tomography scans generally show a hyperdense mass and highlight bone remodeling and expansion. Magnetic resonance imaging usually reveals a circumscribed, enhancing, hypointense mass on T1- and T2-weighted imaging.²⁵ Generally, computed tomography can be used to define the mass for surgical approach, although magnetic resonance imaging better illustrates the extent of the soft tissue component.²⁶

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From the Divisions of Anatomic and Clinical Pathology (Dr Soles) and Anatomic Pathology (Drs Wilson and Lucas), Department of Pathology, Michigan Medicine, University of Michigan, Ann Arbor.
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Corresponding author: Amer Heider, MD, Department of Pathology, Michigan Medicine, University of Michigan, 1540 East Medical Center Drive, 11-105-D, Ann Arbor, MI 48109-4272 (email: aheider@med.umich.edu).
PATHOLOGY

Grossly, MNTI is a firm, lobulated, and well-circumscribed mass (Figure 1, A). Typically, the mass superficially infiltrates and compresses rather than deeply invades adjacent structures. The tumor frequently presents with a blue-black hue due to its pigmented nature. On cut surface the tumor can be gray to black (Figure 1, B) depending on the amount of melanin pigment. Microscopically, MNTI is made up of islands of small, round neoplastic cells embedded in a background of fibrocollagenous stroma (Figure 2). A biphasic population of cells consisting of larger epithelioid melanogenic cells and smaller primitive small neurogenic cells (neuroblast-like) is the histologic hallmark for this tumor (Figure 3). The cells can form sheets, nests, cords, pseudoglandular structures, or sometimes pseudoalveolar spaces. These structures are usually composed of both the larger melanogenic cells and the smaller neurogenic cells, but both populations can also be present in isolation from the other. Generally, the melagenic cells are located at the periphery, whereas the neurogenic cells are located centrally within the nests or spaces. The melanogenic cells are epithelioid, polygonal, or cuboidal, and moderate to large in size. The nuclei have smooth to vesicular chromatin and occasional prominent nucleoli. These cells have abundant eosinophilic cytoplasm and usually contain melanin granules (Figure 4). Ultrastructurally, they are surrounded by a basal lamina and form desmosomes with adjacent cells. The neurogenic population is made up of small primitive cells with a high nuclear to cytoplasmic ratio. They have round, hyperchromatic nuclei with occasional “salt and pepper” chromatin (Figure 4). They have scant cytoplasm with dense vesicles on electron microscopy. Some cases show neurofibrillary stroma surrounding the neurogenic cells. The background is made up of dense fibrocollagenous stroma that is well vascularized. Mitoses are typically rare and necrosis is very unusual, unless tumor behavior is overtly malignant (see below). The edge of the tumor at bone can be infiltrative, with nests of cells located between bony trabeculae. This infiltrative growth pattern along with the small neurogenic cells can give the false impression of a more malignant entity (Figure 5).

Immunohistochemistry is useful in the diagnosis of MNTI. Both cell types are positive for vimentin and neuron-specific enolase (Figure 6, A). The larger epithelioid melanogenic cells are commonly positive for cytokeratins (Figure 6, B) and some markers of the melanocyte differentiation, including HMB-45 (Figure 7, A) and dopamine β-hydroxylase. Synaptophysin positivity in the larger, epithelioid cells is variable. In some instances, these melanogenic cells may be positive for epithelial membrane antigen. The smaller neurogenic cells are positive for synaptophysin and negative for cytokeratin (Figure 6, B). These neuroblast-like cells may occasionally be positive for glial fibrillary acidic protein (GFAP) but are only rarely positive for neurofilament and CD99. Both populations are typically negative for S100 (Figure 7, B), with only focal expression reported in a few cases. Poci of glial and divergent skeletal muscle differentiation can be seen within some cases of MNTI and may stain accordingly with myogenic markers such as desmin, muscle-specific actin, and myogenin, findings that can contribute to misdiagnosis as rhabdomyosarcoma.

Currently characteristic genetic or molecular abnormalities have not been identified in MNTI. One report indicated that 1 of the 3 cases tested had BRAF-V600E mutation. A genomic and transcriptomic analysis of a rare case involving the fibula was performed. It showed a germ line heterozygous mutation of CDKN2A and RPLP1-C19MC gene fusion. Another report of a mandibular case with multiple recurrences and dominant neuroblastic component showed loss of heterozygosity with deletion of chromosome 1p and gain of chromosome 7q.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of MNTI includes other small round blue cell tumors of childhood, especially neuroblastoma, Ewing sarcoma, alveolar rhabdomyosarcoma, and lymphoma, in addition to melanogenic tumors, including malignant melanoma and clear cell sarcoma of soft tissue. The key morphologic features of MNTI used to distinguish it from these other entities are the clinical presentation, the biphasic population of epithelioid melanogenic cells and
primitive neurogenic cells, and its characteristic immuno- 
histochemical findings. Small biopsies can invoke a 
diagnostic challenge, particularly misdiagnosis as neuro- 
blastoma. Melanotic neuroectodermal tumor of infancy 
typically lacks pronounced rosette formation and diffuse 
expression of neuroendocrine markers as seen in neuro- 
blastoma. Moreover, neuroblastoma would not have a 
population of melanogenic cells with melanin pigment and 
would be negative for cytokeratin and HMB-45. Ewing 
sarcoma is composed of nests of small monomorphic 
sheets of round cells and does not contain a concomitant 
population of large pigmented epithelioid melanogenic 
cells. Ewing sarcoma demonstrates characteristic diffuse 
strong membranous immunostaining for CD99 and typi-
cally harbors EWSR1 gene rearrangement. Most cases of 
Ewing sarcoma have t(11;22)(q24;q12) with EWSR1-FLI 
chimeric fusion. Although rare cases of MNTI were 
reported to react with CD99, lack of molecular signature 
of ES is extremely helpful for distinction, particularly when 
dealing with a limited sample. Alveolar rhabdomyosarco-
a, although more common in the extremities, frequently 
presents in the head and neck region. It is composed of 
nests of poorly differentiated small hyperchromatic cells 
separated by fibrous septa. Despite some morphologic 
overlap, at least focally, alveolar rhabdomyosarcoma cells 
are positive for desmin, with diffuse strong reaction for 
myogenin. Moreover, it has characteristic translocations 
t(2;13) or t(1;13) with PAX-FOX01 gene fusions. Molecular 
and FISH analyses may be necessary to avoid a diagnostic 
pitfall with MNTI because divergent muscular differentia-
tion is well described in MNTI. Both ES and alveolar 
rhabdomyosarcoma have extensive necrosis, which is not a 
typical histologic feature of MNTI. Hematolymphoid 
cells, both benign and malignant, can resemble the 
neurogenic cells morphologically, with crushing artifact 
in smaller biopsies. Nonetheless, the immunoprofile of

Figure 2. On low power, melanotic neuroectodermal tumor of infancy resembles a small round blue cell tumor, in this case consisting of sheets of 
cells in a fibrocollagenous stroma (hematoxylin-eosin, original magnification ×100).

Figure 3. Higher-power image depicts a biphasic population of cords and nests made up of larger epithelioid melanogenic cells admixed with 
smaller primitive neurogenic cells (hematoxylin-eosin, original magnification ×200).

Figure 4. Large, polygonal melanogenic cells with cytoplasmic melanin granules intermixed with small primitive neurogenic cells are depicted 
(hematoxylin-eosin, original magnification ×400).

Figure 5. Infiltrative growth of melanotic neuroectodermal tumor of infancy into the bone is often present (hematoxylin-eosin, original magnification 
×100).
MNTI differs completely from that observed in lymphomas, where hematolymphocytic markers are expressed but epithelial or melanotic markers are not. Again, because MNTI has no known recurrent molecular alterations, molecular and cytogenetic studies are very helpful to differentiate it from the other entities that have known characteristic translocations, such as are found in many hematolymphoid neoplasms.

Malignant melanoma is another main consideration in the differential diagnosis. Melanoma in this population would typically present with overtly malignant morphology and would be negative for cytokeratins but positive for melanoma markers and S100. Clear cell sarcoma classically occurs on the extremities in young adults rather than in infants and is composed of uniform spindled to ovoid cells with clear to pale eosinophilic cytoplasm. Lack of the primitive-appearing neurogenic cells is a very important morphologic key to distinguish it from MNTI. Clear cell sarcoma is associated with recurrent characteristic translocations, mainly t(12;22)(q13;q12), resulting in EWS-ATF1 chimeric gene, and less commonly t(2;22)(q34;q12). The age of presentation of MNTI may overlap with congenital granular cell tumor of the newborn (congenital epulis), but the characteristic histology would help rule this entity out. Odontogenic tumors of childhood may be considered clinically due to the location and presentation, but they rarely occur before 6 years of age.

**PROGNOSIS AND CURRENT TREATMENT**

Although generally considered benign, the biologic behavior of MNTI is not fully understood. It can be clinically concerning to parents and clinicians because of its rapid growth rate, and the significant risk of local recurrence. Recurrence rate was variably reported as ranging from 15% to 27%. It is purported to be due to multicentric growth and incomplete surgical resection, leading to multiple surgical operations in some cases. Recurrence can be fatal, especially when involving the central nervous system or other vital structures. Reported malignant cases are unusual and have been noted in 31 of 472 cases (6.5%), and there are no clearly defined criteria or markers to easily differentiate benign and malignant lesions. Histopathologic findings, including mitotic rates greater than or equal to 2 per 10 high-power fields, a Ki-67 proliferation index greater than 25%, and positivity for CD99, have been associated with more aggressive behavior. Some reports suggested that predominance of a neuroblast-like component and an inconspicuous large cell component were also associated with an aggressive course and high risk of local recurrence. Interestingly, age of diagnosis appears to be a prognostic indicator of disease recurrence, according to the largest retrospective review data. They found that infants receiving a diagnosis within the first 2 months of life were more likely to have recurrence within 6 months and had a shorter disease-free survival.

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**Figure 6.** Immunohistochemical staining shows (A) diffuse positivity for neuron-specific enolase and (B) positivity for pan-cytokeratin limited to the melanogenic cells (immunohistochemical stain, original magnification ×100).

**Figure 7.** The melanogenic cells are (A) positive for HMB-45 and (B) negative for S100 (immunohistochemical stain, original magnification ×100).
free survival. Infants who received a diagnosis at age 4.5 months or older had minimal risk of recurrence, and infants who received a diagnosis within 2 to 4.5 months of age had an intermediate chance of recurrence. However, a recent, relatively large series of 11 patients from a French cohort questioned that observation. Metastasis was reported to occur in 3% of cases. Metastatic spread has been documented to lymph nodes and the central nervous system. Complete local surgical excision is considered the treatment modality of choice. Chemotherapy and/or radiation have only been used in a limited number of cases. It was reported in 24 patients of 249 (9.6%) and mostly prior to surgical resection in attempts to increase the chance of a complete resection. Neoadjuvant therapy is usually reserved for inoperable tumors, involvement of the central nervous system and other vital structures, or when clear surgical margins are not achievable. Little is known about chemotherapy effects on the tumor and morphology. Nonetheless, it appears to induce maturation of the primitive tumor cells, reduction of the neuroblast-like component, and predominance of epithelial melanogenic component.

**CONCLUSIONS**

Melanotic neuroectodermal tumor of infancy, although rare, is an important neoplasm to be aware of within the pediatric population because of its close resemblance to more aggressive malignancies, especially other small round blue cell tumors and melanoma. The characteristic biphasic histologic features of larger epithelioid melanogenic cells and smaller primitive-appearing neurogenic cells are distinctive in most cases. Immunohistochemistry and molecular studies can be helpful in resolving the diagnostic challenge in difficult cases, especially in small biopsies. Because of its rapid and infiltrative growth, and its high local recurrence rate, as well as the existence of rare malignant examples, early diagnosis with complete excision is necessary for the best clinical outcome. Given the rarity of the disease, large prospective studies are difficult to conduct. Molecular profiling of a large cohort of MNTI cases may aid in shedding light on this rare tumor biology.

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