Case report

Melanotic neuroectodermal tumour of infancy presenting as a lytic lesion in femur: a rare tumour at a rare site with an unusual behaviour

Nishu Bhardwaj,¹ Rajni Yadav ,¹ Venkatesan Sampath Kumar,² Shah Alam Khan²

¹Pathology, All India Institute of Medical Sciences, New Delhi, India

²Orthopaedics, All India Institute of Medical Sciences, New Delhi, India

Correspondence to
Dr Rajni Yadav;
drrajniyadav@gmail.com

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SUMMARY

Melanotic neuroectodermal tumour of infancy (MNTI) is an uncommon tumour, predominantly occurring in head and neck, mostly maxilla, but also in skull and mandible. Although a benign lesion, it is known to recur in 15%–27% of cases, and rarely, may undergo malignant transformation. We present a case of a 5-month-old female patient, who presented with a gradually progressive swelling in the right thigh. On imaging, an osteolytic lesion was seen, involving the metadiaphysis of shaft of right femur. A biopsy was performed, on which diagnosis of MNTI was made. MNTI is rarely seen in extremities. To the best of our knowledge, only six cases have been reported in femur, the present case being the seventh. The tumour showed spontaneous regression on follow-up in our patient, which has rarely been described. A knowledge of characteristic morphology and immunohistochemistry is the key to differentiate it from other tumours.

BACKGROUND

Melanotic neuroectodermal tumour of infancy (MNTI) is an uncommon tumour, considered to be of neural crest origin.¹ Most of the cases occur in the first year of life, however, a few cases have been reported in older children and adults. Various synonyms have been used to describe this entity in the past, including congenital melanocarcinoma, melanotic progonoma, melanotic adamantinoma and neuroectodermal progonoma.² Predominantly affecting the head and neck region (92.8%), the most common site being the maxilla (two-thirds of cases), this tumour has also been diagnosed in skull, mandible, brain and extracranial sites like mediastinum, soft tissue and genital organs.³ However, it is extremely rare in the appendicular skeleton. To the best of our knowledge, eight cases have been reported in long bones of lower extremities, only six in the thigh, the present case being the seventh. We discuss an unusual case of MNTI that presented as a lytic lesion in the femur and showed spontaneous regression, which has rarely been observed with this tumour.

CASE PRESENTATION

A 5-month-old female patient presented with a gradually progressive swelling in the right thigh, without any history of antecedent trauma or other symptoms.

INVESTIGATIONS

X-ray showed broadening of right lower femur with periosteal reaction. MRI showed an osteolytic lesion, measuring 5.8×4×3 cm, involving the distal metadiaphyseal region of femur, with lamellated periosteal reaction and sunburst appearance ([figure 1](#)). Soft tissue signal intensity was also noted, with cortex breach and involvement of muscle planes. The possibilities of osteosarcoma and Ewing sarcoma were suggested.

A biopsy was performed, which showed a biphasic tumour, with a small round cell component arranged in sheets ([figure 2](#)). These cells had scant cytoplasm, hyperchromatic nuclei and were immunopositive for neuron-specific enolase (NSE), synaptophysin and CD56. The second population comprised of larger melanin-containing epithelioid cells arranged in tubules and nests, with abundant cytoplasm, pale nuclei and vesicular chromatin. These demonstrated immunopositivity for HMB-45, melan-A, pancytokeratin and epithelial membrane antigen. The tumour nests were embedded in dense fibrocollagenous stroma and were infiltrating the bony trabeculae. Based on above features, a diagnosis of MNTI was rendered.

TREATMENT

The patient was planned for surgery, but declined any intervention.

OUTCOME AND FOLLOW-UP

The patient was kept on regular follow-up, during which the lesion decreased in size, spontaneously. At the end of 2 years, it had regressed significantly, although not completely resolved.

DISCUSSION

MNTI was first described in 1918 by Krompecher, who called it 'congenital melanocarcinoma'.⁴ The term MNTI was coined by Borello and Gorlin, and is now the universally accepted terminology.¹ There have been several conflicting theories relating to the histogenesis of MNTI, reflected by the varying nomenclature. Initially thought to be of odontogenic or melanocytic origin, the observation that many patients had raised urinary vanillylmandelic acid levels, which returned to normal following excision, as well as ultrastructural studies, confirmed the neuroectodermal origin of this tumour.^{1 5}

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Figure 1 (A) X-ray of right thigh shows broadening of lower femur with periosteal reaction. (B) MRI of right thigh shows an osteolytic lesion involving the distal metadiaphysis of femur with lamellated periosteal reaction and sunburst appearance.

MNTI typically occurs in the first year of life with a slight male predilection.² However, in the lower extremities, the tumour has been reported more commonly in females (7/9). Seen at cranio-facial sites in more than 90% of cases, this tumour is extremely uncommon in the long bones of extremities, with only 10 cases

Figure 2 (A) Microscopy shows a biphasic tumour composed of a small round cell component (black arrow) and larger epithelioid cells (blue arrow) embedded in a fibrocollagenous stroma; H&E ×200. (B) The small round cell component is composed of cells with scant cytoplasm, hyperchromatic nuclei arranged in sheet-like pattern; H&E ×400. (C) Second population consists of larger melanin-containing epithelioid cells arranged in tubules and nests; H&E ×400. (D–F) The small round cells are immunopositive for synaptophysin (D), NSE (E) and CD56 (F); IHC ×200. (G–I) The epithelioid cells are immunopositive for CK (G), EMA (H) and HMB-45 (I); IHC ×200. CK, cytokeratin; EMA, epithelial membrane antigen; IHC, immunohistochemistry; NSE, neuron-specific enolase.

Table 1 Presentation, treatment and behaviour of MNTI cases involving long bones of lower extremities

No	Author	Age (months)/sex	Site	Treatment/outcome
1	Johnson <i>et al</i> ⁶	18/female	Femur	Chemotherapy, radiotherapy/death
2	Elli <i>et al</i> ⁷	3/female	Femur	Declined/NA
3	Choi <i>et al</i> ⁸	5/male	Femur	Surgery, chemotherapy/death
4	Lei <i>et al</i> ⁹	7/female	Tibia	Follow-up/resolved
5	Rekhi <i>et al</i> ¹⁰	12/male	Femur	Surgery, chemotherapy, radiotherapy/NA
6	Barnes <i>et al</i> ³	2/female	Fibula	Surgery/disease free since 3 years
7	Scheck <i>et al</i> ¹¹	6/female	Femur	Not known
8	Lacy and Kuhar ¹²	5/female	Femur	Surgery/NA
9	Present case	5/female	Femur	Follow-up/resolved

MNTI, melanotic neuroectodermal tumour of infancy; NA, not applicable.

out of nearly 500 cases that have been reported until now. To the best of our knowledge, only eight cases have been reported in the lower extremities, the present case being the ninth. Of these, involvement of femur was present in six cases, ours being the seventh, whereas one case each was reported in tibia and fibula (table 1).^{6–12}

Johnson *et al* reported the first case in femur of an 18-month-old female patient.⁶ In long bones, the tumour has a variable presentation and behaviour, ranging from a rapidly growing mass lesion, with a malignant course, as reported by Johnson *et al*, to an asymptomatic, indolent periosteal thickening, as described by Lei *et al*.^{6,9} In our case, the patient came with a gradually progressive swelling in the thigh.

Typically, CT scan reveals a well-demarcated, radiolucent, lytic lesion within the bone. CT and MRI are useful in determining the extent of the lesion accurately, thus providing a good basis for surgical planning, but are of limited value in differentiating MNTI from other malignant or benign lesions.¹⁰ On microscopy, the tumour has a characteristic dual population, larger melanogenic epithelioid cells and smaller primitive neurogenic cells (neuroblast-like). Mitoses and necrosis are typically uncommon. Although usually well defined, the margins of the tumour may be infiltrative, with nests of cells present between bony trabeculae simulating a more malignant entity.¹³

In extremities, the differentials are limited, mainly Ewing sarcoma, neuroblastoma, rhabdomyosarcoma, non-Hodgkin's lymphoma and malignant melanoma.⁸ Immunohistochemistry is helpful in establishing the diagnosis of MNTI and differentiating it from other small round cell tumours of infancy. Both cell types are positive for vimentin and NSE. The epithelioid cells express cytokeratins, and markers of the melanocyte differentiation, like HMB-45 and dopamine b-hydroxylase. However, S100 is usually negative, which helps exclude the diagnosis of malignant melanoma. The small cell component, on the other hand, is positive for neuroendocrine markers like synaptophysin, chromogranin, CD56, and negative for cytokeratin.¹⁴

Although generally considered benign, the biological behaviour of MNTI is not fully understood. It is a locally aggressive tumour with a recurrence rate of 15%–27% following conservative resection. Moreover, distant metastasis has been reported in 6.5% of cases. Due to the rarity of the tumour, there are no clearly defined criteria to differentiate benign from malignant lesions. However, histopathological findings, including mitoses $\geq 2/10$

high-power fields, Ki-67 proliferation index >25% and predominance of neuroblast-like component, have been associated with more aggressive behaviour. Furthermore, it has been suggested that the age of diagnosis may indicate the risk of recurrence.¹³ Out of the six cases reported in the lower extremity, only one had a malignant course. Curiously, in our case, the tumour showed spontaneous regression, over a short follow-up period of 2 years, without any therapeutic intervention. Interestingly, Lei *et al* also reported a case in the tibia of an infant, with an atypical presentation, that is, diffuse periosteal involvement, and progressive spontaneous resolution without any evidence of residual/recurrent disease after a 13-year follow-up period.⁹ They suggested that a possible mechanism of spontaneous regression might be an improved efficacy of the immune system with age, which may also explain the decreased risk of recurrence with increasing age.

Complete excision of the lesion with adequate margins is the accepted treatment. Other options include chemotherapy, radiotherapy, with/without surgery, depending on whether the tumour is amenable to resection.¹⁰ Our case and that reported by Lei *et al* both highlight that all MNTIs may not need aggressive treatment, and there is a need for providing therapeutic options on case-by-case basis. The biological behaviour of the tumour is poorly understood, and needs to be elucidated further to develop effective management guidelines.

Learning points

- ▶ Melanotic neuroectodermal tumour of infancy is an uncommon tumour, mostly occurring in maxilla and rarely seen in long bones of extremities.
- ▶ Recognition of the hallmark biphasic population and immunohistochemistry is the key to diagnosis.
- ▶ Though surgical resection is the recommended treatment, rare tumours can regress spontaneously.

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ORCID iD

Rajni Yadav <http://orcid.org/0000-0001-7597-4895>

REFERENCES

- 1 Borello ED, Gorlin RJ. Melanotic neuroectodermal tumor of infancy--a neoplasm of neural crest origin. Report of a case associated with high urinary excretion of vanilmandelic acid. *Cancer* 1966;19:196–206.
- 2 Kruse-Lösler B, Gaertner C, Bürger H, *et al*. Melanotic neuroectodermal tumor of infancy: systematic review of the literature and presentation of a case. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;102:204–16.
- 3 Barnes DJ, Hookway E, Athanasou N, *et al*. A germline mutation of CDKN2A and a novel RPLP1-C19MC fusion detected in a rare melanotic neuroectodermal tumor of infancy: a case report. *BMC Cancer* 2016;16:629.
- 4 Krompecher E. Zur Histogenese und morphologie Der adamantinoma und sowstiger Kiefergeschwulste. *Beitr Pathol Anat* 1918;64:165–97.
- 5 Cutler LS, Chaudhry AP, Topazian R. Melanotic neuroectodermal tumor of infancy: an ultrastructural study, literature review, and reevaluation. *Cancer* 1981;48:257–70.
- 6 Johnson RE, Scheithauer BW, Dahlin DC. Melanotic neuroectodermal tumor of infancy. A review of seven cases. *Cancer* 1983;52:661–6.
- 7 Elli M, Aydin O, Pinarli FG, *et al*. Melanotic neuroectodermal tumor of infancy of the femur. *Pediatr Hematol Oncol* 2006;23:579–86.
- 8 Choi IS, Kook H, Han DK, Baek HJ, *et al*. Melanotic neuroectodermal tumor of infancy in the femur: a case report and review of the literature. *J Pediatr Hematol Oncol* 2007;29:854–7.
- 9 Lei L, Ellsworth BD, Young LW, *et al*. Spontaneous regression of diffuse periosteal melanotic neuroectodermal tumor of infancy in the tibia, with 13-year follow-up. *J Pediatr Hematol Oncol* 2019;41:148–51.
- 10 Rekhi B, Suryavanshi P, Desai S, *et al*. Melanotic neuroectodermal tumor of infancy in thigh of an infant--a rare case report with diagnostic implications. *Skeletal Radiol* 2011;40:1079–84.
- 11 Scheck O, Ruck P, Harms D, *et al*. Melanotic neuroectodermal tumor of infancy occurring in the left thigh of a 6-Month-Old female infant. *Ultrastruct Pathol* 1989;13:23–33.
- 12 Lacy SR, Kuhar M. Melanotic neuroectodermal tumor of infancy presenting in the subcutaneous soft tissue of the thigh. *Am J Dermatopathol* 2010;32:282–6.
- 13 Soles BS, Wilson A, Lucas DR, *et al*. Melanotic neuroectodermal tumor of infancy. *Arch Pathol Lab Med* 2018;142:1358–63.
- 14 Barrett AW, Morgan M, Ramsay AD, *et al*. A clinicopathologic and immunohistochemical analysis of melanotic neuroectodermal tumor of infancy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002;93:688–98.

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