Rare disease

Melanotic neuroectodermal tumour of infancy

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Summary

Melanotic neuroectodermal tumour of infancy (MNTI) is a rare benign tumour of neural crest origin that was first described by Krompecher in 1918.¹ It is predominantly found in infancy, with about 92% of cases below the age of 12 months and 82% below the age of 6 months. The predominant site of origin is in the premaxilla though it is reported at other sites also including the skull, the mandible, the epididymis and the brain.² The lesions often have areas of bluish discolouration on the surface and are characterised by displacement of the involved tooth bud and local aggressiveness. The present report deals with two cases of MNTI, a 5-month-old baby girl and a 6-month-old baby boy who reported to the Department of Oral and Maxillofacial Pathology, Dr R Ahmed Dental College and Hospital, Kolkata, India. The clinical, radiological, histological and immunohistochemical findings, confirmed the diagnosis of MNTI. Flow cytometry was performed to analyse aneuploidy. The tumours were treated surgically with no history of recurrence to date.

BACKGROUND

MNTI was first described in 1918 in the German literature by Krompecher as congenital melanocarcinoma, following which it was described under many headings such as Mml-anotic prognoma,³ pigmented ameloblastoma,⁴ congenital pigmented epulis,⁵ retinal anlage tumour⁶ and melanotic epithelial odontome,⁷ to name some examples. The plethora of names given to it reflects the conflicting opinions regarding its histogenesis. It was Misugiet *al*⁸ in 1956 who first proposed neural tissue as the source of tumour cells, which was later supported by Borello, who introduced the current terminology of MNTI. Among the different theories proposed, the neural crest cell origin proposed by Borello and Gorlin in 1966⁹ is the most accepted one. Evidence for this derivation stems from tissue culture, immunohistochemical and ultrastructural studies. The classification of this tumour as a tumour of neural crest origin is based on histological analysis of cells that resemble neuroblasts and electron microscopic studies that show neurosecretory granules. The elaboration of higher levels of urinary vanillyl mandelic acid (VMA) in some cases also supports the neural crest origin of MNTI. Similar laboratory finding of high levels of urinary VMA is shared by other tumours of neural origin such as pheochromocytoma, neuroblastoma and retinoblastoma. Kapadia *et al*¹⁰ in their review found 2.5% of cases revealed positive for urinary VMA. These raised levels usually return to normal once the tumour has been excised.¹¹ Electron microscopic studies revealed neural, epithelial and melanotic structures with demonstration of neurosecretory granules; fine, delicate cytoplasmic fibres suggestive of neurofibrils; desmosomal attachments to adjacent cells and melanosomes in many of the cuboidal cells.¹²

Immunohistochemical studies are of assistance in diagnosing difficult cases. The small darkly staining cells exhibit

neuroblast-like differentiation, with strong expression of synaptophysin and neuron-specific enolase (NSE). The pale staining cells exhibited melanocytic differentiation, as indicated by the positive staining with melanocyte specific antibodies HMB-45 and NK1-Beteb.¹³

MNTI has also been analysed by flow cytometry. Although the studies are limited, it is suggested that tumours with aneuploid cells may recur more often.¹⁴

The potential of this tumour for rapid growth, irrespective of its benign nature, requires prompt measures to be taken to minimise adjacent tissue destruction. Treatment modalities include conservative excision, enucleation and curettage with recurrent cases requiring a more radical treatment.

CASE PRESENTATION

Case 1

A 5-month-old baby girl presented to the Department of Oral and Maxillofacial Pathology, Dr R Ahmed Dental College and Hospital with an expansible mass in the anterior maxilla. The mass was first noted 25 days earlier by her mother, who noted rapid enlargement of the tumour to its present size. The infant did not have any symptoms of pain or irritation but developed a habit of constantly feeling the mass with her tongue. Sucking and feeding was also impaired secondary to the swelling. On examination a mass approximately 1.5×1.5 cm in size was seen on the anterior maxilla, as shown in figure 1A. The covering surface mucosa was normal with prominent capillaries without discolouration. On palpation a well circumscribed, firm, non-fluctuant, non-compressible mass was noted that did not yield any cystic fluid on aspiration. Radiographic examination revealed a radiolucent osteolytic lesion with well demarcated borders and displaced unerupted left primary maxillary central incisor floating within it (figure 1B). The

Figure 1 A. Photograph showing well circumscribed non-ulcerated swelling in the anterior maxilla. B. Intraoral periapical radiograph showing well circumscribed radiolucency with a floating tooth. C. Gross specimen showing brownish-black cut surface. D. H&E-stained section showing characteristic biphasic tumour mass with melanin pigmentation. E–I. Immunohistochemical analysis indicating strong positive expression for synaptophysin, neuron-specific enolase (NSE), HMB-45, glial fibrillary acidic protein (GFAP), respectively and weak expression for S-100. J, K. Flow cytometric analysis of cell cycle showing distribution of total cells. M1, sub-G₀; M2, G₀/G₁ phase; M3, S phase; M4, G₂/M phase. The total distributions of the cells at different phases are M1 3%, M2 92.9%, M3 0.91% and M4 2.9%. A considerable population of cell comprising the sub-G₀ phase indicative of aneuploidy is evident. L. Photograph showing partially erupted deciduous maxillary right central and lateral incisor. M. Photograph showing no erupted deciduous dentition in the mandibular arch. N. Intraoral periapical radiograph showing uneventful bony healing with the absence of permanent left central incisor tooth bud. O, P. Intraoral periapical radiographs showing normal complement of unerupted deciduous teeth in the right and left quadrants, respectively.

patient's medical history, physical examination and admission laboratory values were within normal limits. Examination of urinary VMA revealed normal VMA levels.

Surgical enucleation of the tumour mass was performed. Grossly, the specimen was brownish-black on the inner cut surface surrounded by a fibrous capsule and a partially formed tooth was found within the tumour mass, as shown in figure 1C. Histopathological evaluation revealed the tumour mass comprising a characteristic biphasic tumour cell population in an alveolar pattern. Small round to oval central cells were basophilic, hyperchromatic cells with little cytoplasm resembling primitive neuroblast-like cells and larger, polygonal, epitheloid-like peripheral cells resembled melanocytes with variable deposits of melanin in a fibrous connective tissue stroma (figure 1D). Immunohistochemical analysis of the tumour was strongly positive for synaptophysin, NSE, HMB-45 and glial fibrillary acidic protein (GFAP) as shown in figure 1E–H, respectively, and was weakly positive for S-100 as shown in figure 1I. Flow cytometry suggested a minor population of cells with aneuploidy as represented in figure 1J,K.

Case 2

A 6-month-old first-born baby boy presented with a swelling in the anterior maxilla. The lesion was initially noticed by his parents 2 months previously, and gradually increased in size to attain the present size of approximately 3×2 cm when diagnosed. On examination a smooth, firm, non-tender, non-pulsatile, non-reducible, non-fluctuant swelling causing obliteration of the left nasolabial furrow and the anterior maxilla was seen as shown in figure 2A. The covering surface mucosa was normal with prominent capillaries and blackish pigmentation evident on the surface. Maxillary standard occlusal radiograph revealed well defined hazy radiolucency in anterior region (figure 2B). No fluid was obtained on aspiration. An incisional biopsy was performed and section showed a distinct biphasic pattern with neoplastic cells arranged in an alveolar pattern. Each alveolus were lined by cuboidal cells, many of these containing melanin pigment and central portion containing small round neuroblast-like cells that showed little cytoplasm and round hyperchromatic nucleus (figure 2C). Immunohistochemical studies showed NSE and

Figure 2 A. Intraoral view showing large non-ulcerated anterior maxillary swelling. B. Standard occlusal radiograph of maxilla showing a well defined hazy anterior radiolucency. C. H&E-stained sections showing distinct biphasic tumour mass arranged in an alveolar pattern. D, E. Immunohistochemical analysis indicating positive expression for HMB-45 and neuron-specific enolase (NSE), respectively.

melanoma-associated antigen (HMB-45) to be strongly positive (figure 2D,E).

INVESTIGATIONS

Both patients were subjected to routine haemograms, which were within normal limits.

An intraoral periapical radiograph revealed a radiolucent osteolytic lesion with well demarcated borders and displaced unerupted left primary maxillary central incisor floating within it in case 1.

An upper occlusal radiograph revealed well defined hazy radio opacity in maxillary anterior region in case 2.

Examination of urine for urinary VMA revealed normal VMA levels in case 1.

DIFFERENTIAL DIAGNOSIS

Congenital epulis and gingival cyst of the newborn is the most compatible clinical differential diagnosis with regards to the young age of the patient and maxillary location of the tumour.

The location was also consistent with many odontogenic cysts and tumours, including odontogenic keratocyst, dentigerous cyst, ameloblastoma, adenomatoid odontogenic tumour to name a few, however these occur in an older age group.

Among the many non-odontogenic tumours Ewing sarcoma, langerhans cell histiocytosis, rhabdomyosarcoma, lymphoma, desmoplastic small round cell tumour and peripheral primitive neuroectodermal tumour are common among young children.

Derivation of final diagnosis is from histopathological evaluation aided by immunohistochemical and ultrastructural studies in complicated cases.

TREATMENT

In case 1 total enucleation of the tumour mass was performed in the department of oral and maxillofacial surgery

after proper written consent from the patient's guardians. An alveolar crestal incision was made and the tumour mass with the unerupted tooth was enucleated. A developing tooth bud adjacent to the surgical site was left undisturbed. Haemostasis was achieved comfortably and primary closure was performed with absorbable suture material.

In case 2 after confirmation of the diagnosis, the patient was referred to the paediatric surgery department for total surgical removal of the lesion.

OUTCOME AND FOLLOW-UP

Case 1 was recalled after 2 days post surgery and was kept on regular monthly follow-up with no sign of recurrence in a period of 4 months, whereas no recurrence was observed in a follow-up period of 3 years in case 2. In case 1, the 7 months postoperative follow-up showed that only deciduous maxillary right central and lateral incisors had surfaced in the oral cavity showing an overall delayed pattern of eruption (figure 1L,M). A postoperative intraoral periapical radiograph of the upper arch revealed uneventful bony healing at the surgical site with the absence of the permanent left central incisor tooth bud (figure 1N-P). Case 2 did not report back subsequently for follow-up.

DISCUSSION

Approximately 200 cases of MNTI have been reported in the literature. An exact number is difficult to discern because of the variety of terms that have been applied to the lesion in the past.¹⁶

Krompecher in 1918 first described the tumour as congenital melanocarcinoma.¹ Mummery and Pitts in 1926 named the tumour as melanotic epithelial odontome and suggested it to be of odontogenic origin.⁷ The tumour was then called as melanotic prognoma by Stowens in 1957, who proposed a phylogenetic theory concerned with displaced neuroectodermal tissue from vestigial organ of Jacobson,³ and pigmented congenital epulis by Henry and

Bodian in 1960.⁵ It was Misugi *et al*⁶ in 1956 who first proposed neural tissue to be the source of MNTI, this was later supported by Borello and Gorlin in 1966.⁹

Clinically, MNTI is a fast growing, non-ulcerated swelling in the incisal region of the maxilla. The most common site of occurrence was anterior maxilla as proposed by Dahlback and Thilander in 1964.¹⁶ It has been reported at other sites also including skull, mandible and brain.² However the occurrence of tumour in other anatomical locations such as skin, epididymis, uterus, ovary and mediastinum was independently described by Ashley *et al*¹⁷ in 1964 and Dehner *et al*¹⁸ in 1986. Pontius *et al*¹⁹ in 1965 reported a case with occurrence of multiple lesions although MNTI generally occurs as solitary lesions. Pigmentation on the overlying soft tissue may be observed in only some cases.

Shafer *et al* in 1983 commented that MNTI occurs predominantly in children, with about 92% of patients presenting with the tumour in the first year of life, and about 82% usually in the age range of 1–6 months. The mean age of presentation was 4.3 months.² Hupp *et al* in 1981, in a review of 139 positively confirmed cases of MNTI showed 43% of them occurring within the first 3 months of age.²⁰ Isolated cases of occurrence of MNTI in older adults are also reported.²¹ An equal gender predilection was proposed by Mosby *et al*²² in 1992.

High levels of urinary VMA elaborated by the tumour was first reported by Borello and Gorlin in 1966 suggesting a neural crest origin of the tumour as this finding is shared with other neural crest tumours such as pheochromocytoma and neuroblastoma.^{9 15}

Batsakis²³ in 1987 described the radiological findings of MNTI proposing that the teeth involved in the lesion appear to be floating within the radiolucent area of the tumour.

Microscopically, MNTI always has a distinctive histological character.¹⁰ A dense fibrous stroma supports a dual population of small neuroblast-like cells with hyperchromatic nuclei and sparse cytoplasm and large melanin-containing cuboidal epithelial cells, the latter arranged in alveolar or tubular structures. Ultrastructurally, two cell forms seen by light microscopy were recognised, with possible intermediate forms. The large polygonal pigmented cells showed desmosomal thickenings in the cell membrane and presence of melanin granules at different stages of maturation in the cytoplasm whereas the non-pigmented cells were small neuroblast-like cells with hyperchromatic nucleus, scanty cytoplasm and neurite-like cytoplasmic processes.¹² Immunohistochemical studies to identify various tissue markers in MNTI were first reported in 1985. Melissari *et al*²⁴ confirmed the neural crest origin of MNTI by using NSE, a marker for neuronal and peripheral neuroendocrine cells and neuroendocrine tumours and S100 protein stain found in glial tissue and in Schwann cells. The small neuroblast-like cells show positivity to CD56, NSE, synaptophysin and chromogranin and the large melanocytic cells react positively to a variety of cytokeratins, NSE, HMB45 and chromogranin. A few scattered cells are positive to S100 protein stain. This pattern shows evidence for neural, melanocytic and epithelial differentiation.¹³

Though MNTI is a benign lesion, a few cases have been reported where death occurred due to disseminated MNTI. A local recurrence rate of 15% after conservative excision was reported by Block *et al*²⁵ in 1980 and malignant trans-

formation rate of approximately 2% was suggested by Cutler *et al*²⁶ in 1981. In a few cases reported as malignant, the histological features have taken on a neuroblastoma-like appearance. In spite of the potential for local recurrence, many authors believe conservative surgical treatment to be the treatment of choice as the debulking effect of surgery and initiation of the bodily defences suffice to curb the growth of the tumour. A more aggressive form of treatment comprises total resection and even radiotherapy and chemotherapy, or a combination of both.²⁷

Learning points

- ▶ The rapid clinical growth rate of the tumour could lead to the possibility of misdiagnosing melanotic neuroectodermal tumour of infancy (MNTI) as a malignant lesion with subsequent over treatment.
- ▶ A complete investigation of the patient should be performed before the treatment modality is finalised.
- ▶ A long-term follow-up with physical and radiographic examination at monthly intervals for the first postoperative year is essential to rule out recurrences.
- ▶ Permanent reconstruction of the maxillary alveolus and missing dentition should be considered in the long-term treatment protocol and may have to be delayed until after growth is completed. In the interim, transitional removable partial dentures may be necessary.
- ▶ The skills of an orthodontist, prosthodontist, oral surgeon, oral pathologist and/or dentist are required, for the correct diagnosis, treatment and rehabilitation of the patient and to correct any functional and cosmetic deformity.

Acknowledgements Kaushik Bhattacharya, Infectious Diseases & Immunology Division, Indian Institute of Chemical Biology, Kolkata, India.

Competing interests None.

Patient consent Obtained.

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Pattanayak (Mohanty) S, Ray JG, Richa, Mukherjee S, Mandal C, Chaudhuri K. Melanotic neuroectodermal tumour of infancy. *BMJ Case Reports* 2010; 10.1136/bcr.01.2010.2645, date of publication

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