Melanotic neuroectodermal tumour of infancy

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Melanotic neuroectodermal tumour of infancy is an extremely rare neoplasm arising in newborns and young children, typically involving the face or cranium. A case arising from the maxilla, requiring extensive resection with a near-total maxillectomy, is presented. A thorough review of the literature on this unusual tumour is provided, with emphasis on prognostic factors and appropriate treatment.

Key Words: *Maxillectomy; Melanotic; MNTI; Pediatric; Pigmented*

Tumeur mélanotique neuroectodermique de l'enfance

La tumeur mélanotique neuroectodermique de l'enfance, qui touche surtout la face et le crâne, est extrêmement rare chez les nouveau-nés et les jeunes enfants. Il sera question, dans l'article, d'un cas de tumeur du maxillaire, qui a nécessité une résection étendue, voire une maxillectomie quasi totale. Un examen exhaustif de la documentation sur ce type peu fréquent de tumeur, plus particulièrement sur les facteurs pronostiques et le traitement approprié, complétera l'étude du sujet.

Melanotic neuroectodermal tumour of infancy (MNTI) is a rare, pigmented neoplasm generally arising in infants during the first year of life (1-3). This benign tumour originates from the soft tissue overlying the maxilla in more than 70% of cases, although mandibular, cranial, cerebral and genital involvement have also been described (4,5). The mean age of patients at diagnosis is 4.3 months, with a near-equal male to female ratio of 6:7 (6-8). The present report describes a case of MNTI requiring a near-total maxillectomy, along with an overview of the current pathological knowledge and therapeutic recommendations.

CASE PRESENTATION

A two-month-old male presented with a one-month history of a smooth, firm, rapidly growing mass involving the superior maxillary alveolar ridge. There was no history of airway or feeding difficulties. Maternal, birth and family history were all within normal limits. On physical examination, there was a dark mass involving the premaxilla that was nontender and nonpulsatile (Figure 1).

Both computed tomography and magnetic resonance imaging (MRI) scans revealed an extensive mass filling the maxilla, crossing the midline and involving the orbital floor (Figures 2A and 2B). A fine-needle aspiration biopsy was performed and revealed a dual population of small neuroblastic cells and large melanin-containing epithelial cells. A provisional diagnosis of MNTI was made and confirmed on final histology (Figure 3) following an incisional biopsy.

The child underwent a complete resection of the mass using a modified Weber-Ferguson approach, with the nasal floor, septum and two-thirds of the alveolar ridge resected (Figure 4). The orbital floor was also removed, although the periorbita was preserved. A 5 mm margin was included around the palpable tumour. Nasal stents were placed to prevent stenosis (Figures 5A and 5B). A palatal appliance impression was taken intraoperatively; however, it was not used because of difficulty in retaining the obturator due to early granulation.

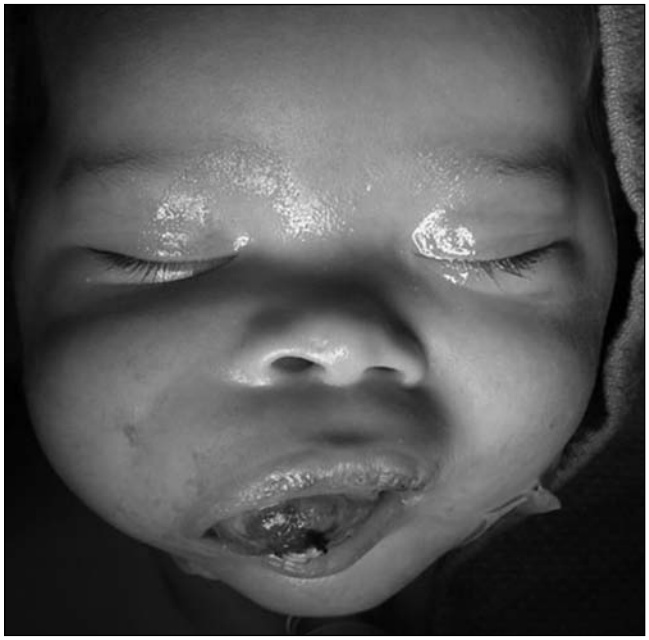

Figure 1) *A two-month-old male with a tumour arising from the maxilla*

The child was followed every three months for the first year, then annually afterwards, with an MRI obtained each year. There is no evidence of recurrence at three years following resection. Visual acuity is normal without strabismus or diplopia.

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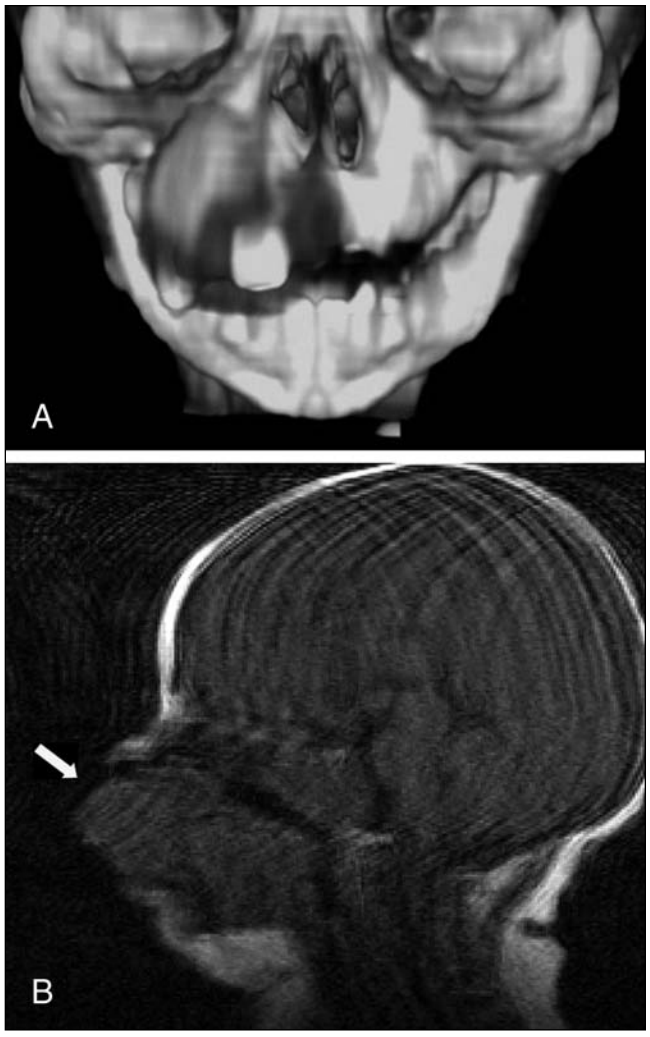

Figure 2) A *Preoperative three-dimensional computed tomography scan showing an extensive tumour involving the maxilla and orbital floor.* **B** *Sagittal magnetic resonance imaging demonstrating depth of tumour invasion. Arrow shows anterior extent of tumour*

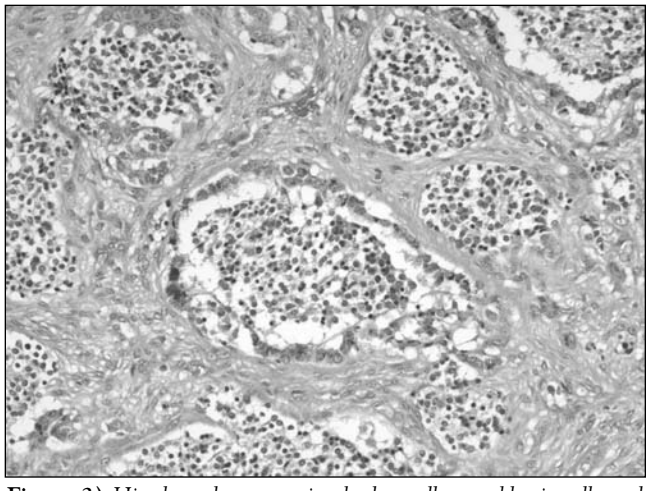

Figure 3) *Histology demonstrating both small neuroblastic cells and large melanin-containing epithelial cells*

A class I skeletal relationship exists. The palate has completely mucosalized except for a 5 mm × 10 mm anterior fistula (Figure 6). Mild signs of velopharyngeal insufficiency are present and were thought to be secondary to the fistula, until further evaluation revealed a submucous cleft. Dental rehabilitation and closure of the fistula is planned near the time of permanent dental eruption, with possible surgical correction of the cleft should symptoms persist.

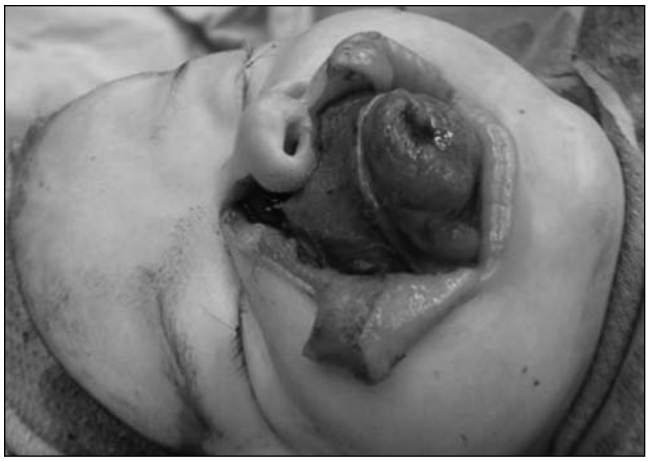

Figure 4) *Intraoperative photograph demonstrating the Weber-Ferguson approach*

DISCUSSION AND LITERATURE REVIEW

This is the first reported case in which a patient was diagnosed both with an MNTI involving the maxilla and a submucous cleft. The concomitant presence of the submucous cleft together with a postoperative palatal fistula complicated the diagnosis and treatment of his velopharyngeal insufficiency. This will require further evaluation before definitive management.

Since first described in 1918, there have been approximately 250 cases of MNTI reported in the world literature (9). The variety of other names assigned to the tumour, including melanocarcinoma, melanotic epithelial odontoma and melanotic prognoma, reflects its confusing histogenesis (10). Patients typically present with a rapidly growing, nonulcerated mass, affecting the craniofacial region in 90% of cases (11,12). Although melanin is produced by the tumour, pigmentation may not be clinically evident (13,14). Local invasion may be accompanied by bony destruction, tooth displacement and feeding difficulties (6,15,16).

Despite this locally aggressive behaviour, MNTI is generally classified as a benign tumour (11,17). A review by Cutler et al (18) demonstrated malignant features in only 1.9% of MNTI cases, with estimates from more recent publications as high as 6% (17,19). Unfortunately, it is difficult to determine the potential for malignancy or recurrence based on clinical assessment, imaging or histopathology (20).

Computed tomography imaging typically reveals a well-demarcated, hyperdense lesion with contrast enhancement and hyperostosis of adjacent bone (21-24). On MRI scans, these lesions tend to be hyperintense on T1 and hypointense on T2 (21,22,24). Despite these characteristic findings, imaging will seldom be diagnostic and tissue biopsy is therefore required.

The histological profile of MNTI demonstrates a biphasic cell population within a stroma of moderately vascularized fibrous tissue (1). Large, epithelioid, melanin-containing cells are arranged in alveolar or tubular formations around clusters

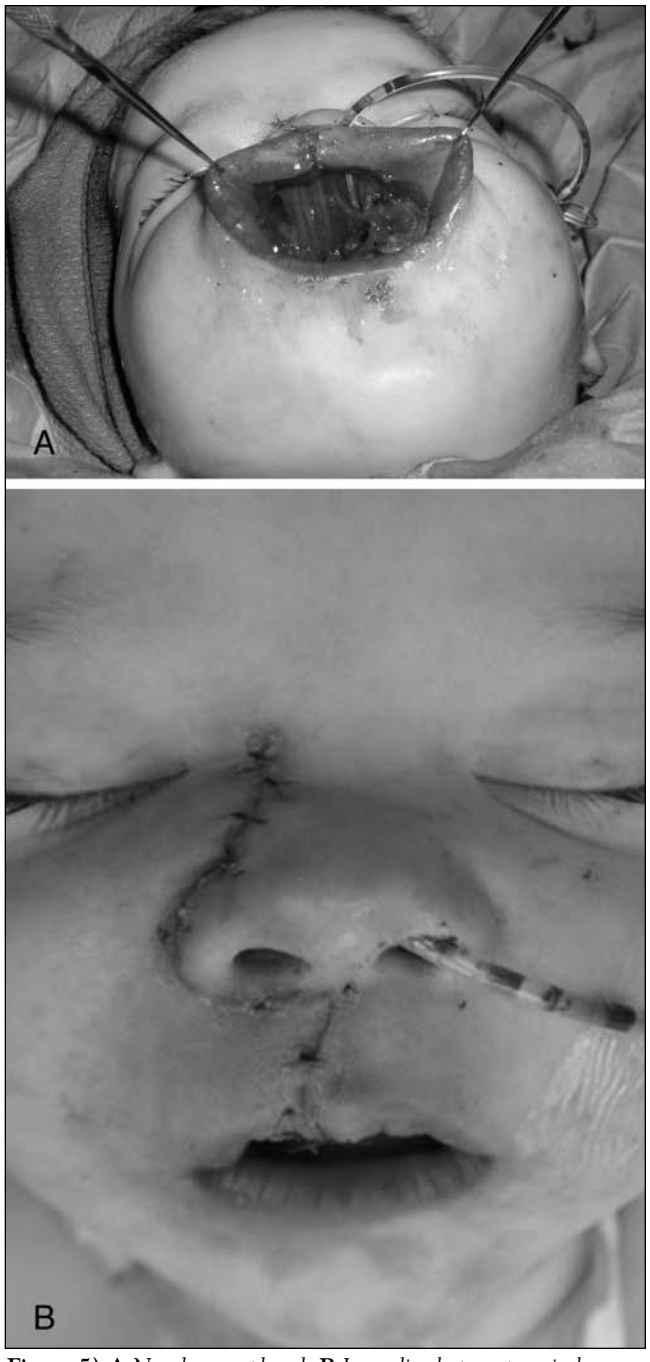

Figure 5) A *Nasal stents placed.* **B** *Immediately postoperatively*

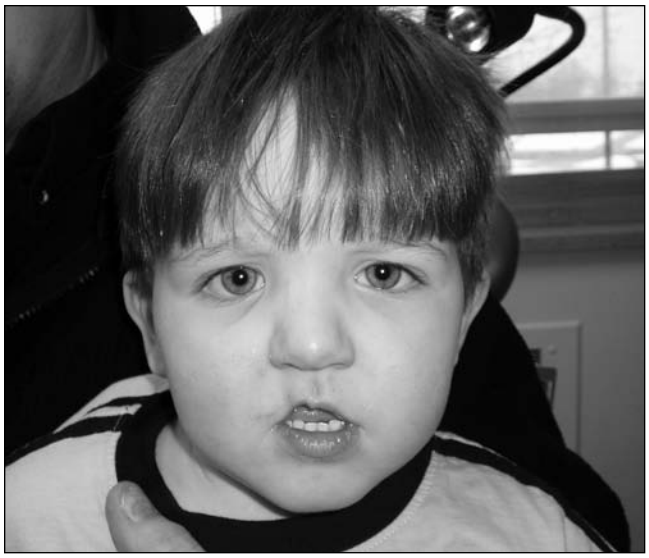

Figure 6) *Patient three years postoperatively with no evidence of tumour recurrence*

of small neuroblastic cells (15,25,26). A differential diagnosis would include other small round cell tumours occurring in infancy, such as rhabdomyosarcoma, neuroblastoma, melanoma and lymphoma. The diagnosis can be especially difficult, given the rarity of MNTI.

Immunohistochemical stains can greatly assist in establishing the diagnosis. The larger, epithelioid cells stain positive most frequently with cytokeratin, epithelial membrane antigen, vimentin and HMB-45, reflecting epithelial and melanocytic differentiation (3,27). These larger cells are usually nonreactive with S-100 protein, aiding in differentiation from tumours such as melanoma. (14,28). The nests of smaller cells in MNTI are often positive for neurogenic markers such as synaptophysin, neuron-specific enolase and glial fibrillar acidic protein (15,25,27). The variability seen in staining results likely represents the multiphenotypical character of this tumour (1).

Ultrastructural studies with electron microscopy have been used alongside histochemical staining to support the theory that MNTIs belong to a group of neuroectodermal tumours arising from neural crest origin (17). Tumours in this group also include neuroblastoma, Wilm's tumour, Ewing sarcoma and primitive neuroectodermal tumour. Elevated urinary vanillymandelic acid and the ability to differentiate primitive neural crest cells to neuroblastic and melanocytic lineages provide additional evidence (29-32). Increased alpha-fetoprotein levels and positive staining for the c-myc antigen, characteristic of other neural crest tumours, has also been described (5,27,29,33,34). Despite these microscopic and immunohistochemical similarities, there are no shared genetic changes linking MNTI with the other neuroectodermal tumours (14,35).

Surgical excision remains the mainstay of treatment for patients with MNTI, as the only modality with proven efficacy (2,15). Given the benign nature of most tumours, there has been some controversy over the optimal surgical management and necessity of adequate margins. Views range from conservative enucleation, to curettage of adjacent tissue, to recommended margins of up to 5 mm (2,18,20,36,37). Efforts should be directed toward the preservation of vital structures and organs (38). Lesion pigmentation and preoperative imaging often assist in delineating tumour margins (14). Adjuvant chemotherapy and radiation are ineffective in controlling recurrences where total excision has not been achieved, and their role is therefore extremely limited (39,40). Authors have advocated their role in metastatic disease and in cases of recurrence after a second resection, although there remains little evidence of added benefit (38,39).

The local recurrence rate following excision ranges from 10% to 15%, although it has been reported as high as 45% (11,12,25,41,42). Shaia et al (38) examined the risk of recurrence over the past 20 years and found that it did not differ from historical data since the tumour was first diagnosed 90 years previously. More than 80% of recurrences occur in the

first four months, (25) with the majority of recurrent tumours occurring in patients initially diagnosed before 12 weeks of age (38). Most patients can achieve cure with repeated surgery (16).

Metastastic spread is rare, occurring in only 3% of patients (5). When metastases develop, the smaller neuroblastic cells predominate in the secondary deposits (14,41,43,44). Histology therefore resembles neuroblastoma more than MNTI (14).

In recent years, a great deal of scientific effort has been put into identifying prognostic markers for MNTI, with little success. Histology has been proven to be an unreliable guide to clinical outcome (15). Flow cytometry has been attempted, again with little success (25,42). Promise may lie with staining for CD99 and Ki-67, both of which have been shown to be associated with aggressive tumours in single studies (15,45). The best indicator of prognosis continues to be close postoperative follow-up with frequent imaging.

CONCLUSIONS

MNTI is a rare pediatric tumour of neural crest origin. The vast majority of tumours occur in the head and neck, predominantly with maxillary involvement. As in our case, imaging, histology and immunohistochemical staining contribute to making a challenging diagnosis. The tumours are treated surgically, with little benefit from adjuvant treatments. Careful follow-up is required given high recurrence rates.

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