MELANOTIC NEUROECTODERMAL TUMOUR OF INFANCY: REFINING THE SURGICAL APPROACH

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Running Title: MNTI – Surgical Approach

Abbreviations

GOSH	Great Ormond Street Hospital
MNTI	Melanotic Neuroectodermal Tumour of Infancy
VMA	Vanillylmandellic Acid

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Abstract

Melanotic Neuroectodermal Tumour of Infancy (MNTI) are particularly rare and although predominantly benign, are infiltrative and locally aggressive. Presenting in the first year of life, prompt diagnosis and effective management are critical in minimising morbidity and the risk of recurrence.

A retrospective review of eleven MNTI managed at Great Ormond Street Hospital (GOSH) from 2000 to 2017 was undertaken. Eight tumours presented in the maxilla, two in the skull and one in the mandible. The primary modality of treatment was surgery in ten cases with one patient receiving neoadjuvant chemotherapy. In spite of microscopically incomplete resection in seven cases, only three recurred. Overall, there was a local recurrence rate of 27% with no distant metastases noted.

Disease free survival was 100% with a follow up ranging from 0.75-17 years (median 5). Taking our results in conjunction with the available literature, there is a role for conservative initial surgery of MNTI and this should be coupled with delayed reconstruction and intensive short term follow up. We propose an adapted treatment algorithm that aims to balance the risk of recurrence and malignant change with surgical morbidity in an infant population.

Keywords: Pediatric Oncology; Rare Tumours; Neuroectodermal Tumour, Melanotic/diagnosis, Neuroectodermal Tumour, Melanotic/surgery*

Introduction

MNTI typically present in the first year of life as rapidly expanding, destructive lesions which are dark blue or pigmented in nature. Knowledge of MNTI comes largely from collections of case series and the scarcity of strong evidence-based approaches to their management stems from the rarity of the condition. The best available epidemiological data comes from a systematic review of 472 cases[1]. The majority of reported tumours presented in the maxilla (62%), followed by the skull (16%) and mandible (8%) although there were cases noted in other regions such as the peripheral bones and epididymis. There is a slight male preponderance with a 6:4 male:female ratio presenting at a median age of 4.5 months old[1]. Surgery is the first line of treatment but there is no clear consensus on intra-operative margins and a relatively high rate of recurrence estimated between 10-27% in spite of their predominantly benign nature[2–8].

The aim of this retrospective study is to report a series of eleven patients with MNTI and propose a treatment algorithm focusing on the risks and benefits of both the conservative and radical approaches to the management of MNTI.

Patients and Methods

Institutionally approved as a case note review, a retrospective search of the GOSH histology database yielded twelve cases over the last 17 years. One was a review of slides from the Middle East to confirm the diagnosis and was excluded. Two cases had initial management undertaken elsewhere before onward referral to GOSH and the remainder of the cases were treated in their entirety at GOSH. Each case was reviewed in depth, looking at their clinical, radiological and histopathological features alongside their management and outcomes as summarised in Table 1.

Results

The cohort displayed a male to female ratio of 7:4 and a median age of diagnosis of 5 months old with no ethnical predisposition. Eight tumours were observed in the maxilla, two on the skull and one in the mandible. MRI was available for review in eleven cases with seven patients having CT in addition, an example of which is shown in Fig. 1. Urinary vanillylmandelic acid (VMA) was elevated in two cases.

Surgery was undertaken first in all but one case where chemotherapy was given at another hospital before disease progression prompted onwards referral to GOSH. This represented the one mandibular tumour and was subsequently resected with clear margins and a costochondral graft placed. On review, two years on from surgery, he was disease free with no deleterious effect on speech and normal oral intake for his age.

Two maxillary resections included the floor of the orbit (Brown classification IIIb) and seven out of the eight maxillary resections caused an oro-nasal fistula[9]. With regards to peri-operative feeding; of the eight maxillary tumours, five required a nasogastric tube to be utilised in the post-operative period but the other three adjusted well and were able to maintain adequate oral intake with a pack in situ.

Where the tumour was completely excised, no further treatment was required. However, using the residual tumour classification, there were seven cases with positive (R1) margins[10]. Out of these, three recurred rapidly after surgery and required chemotherapy as part of their primary course of management. Where chemotherapy was given as adjuvant therapy for the aforementioned recurrent tumours, it was started on average eight weeks (range 5-11) following the initial intervention.

Where the tumour did recur, it was noted clinically in all cases within one month of the initial surgery. This pattern has also been mirrored in the literature[2,11]. Following completion of treatment as stated in *Table 1*. there were no local or regional recurrences noted at follow-up with a range of 0.75-17 years.

Discussion

Working-up of cases should comprise routine blood tests, a chest x-ray and screening of urine for VMA and catecholamines, which can be elevated in neuroendocrine tumours[12]. MRI is the preferred modality for imaging with an iso/hypointense expansile lesion being seen on T1 and T2 weightings with marked uptake of gadolinium. T1 shortening due to melanin deposits has been reported but importantly is not always noted[2,13]. CT may also be indicated to assess the bony component, but the radiation dose must be weighed up against how significantly it would change management or aid surgical planning.

Where possible, biopsy should be carried out after the MRI but under the same general anaesthetic and often reveals the dark pigmentation within the lesion (Fig. 2). Early referral of a lesion that is clinically suspicious to a tertiary centre ahead of formal biopsy and a structured approach to treatment is advised even where there may be temptation to curette smaller intra-oral lesions.

On microscopy the characteristic features are of melanin containing epithelium and small, round cells that have a darkly staining nucleus with little cytoplasm (Fig. 3). Staining for synaptophysin and HMB-45 may also further aid in diagnosis[1,14]. Regrettably, histological appearance seems to give little insight into how the tumour will behave. In spite of this, increased cellular proliferation shown by Ki-67 staining and membrane expression of CD99 have been proposed as possible indicators of more aggressive subtypes[15].

Other differential diagnoses include infection, eruptions cysts, infantile haemangioma, neuroblastoma, rhabdomyosarcoma and Ewing sarcoma[1,2]. MNTI are predominantly benign but due consideration to malignant variants should be given. This has been reported to be between 2-6% but debate has been held regarding whether these are misnomers for neuroblastoma[3,4].

Comprehensive review of each case at a paediatric oncology multi-disciplinary team meeting is

mandatory. The management of these tumours is generally accepted as surgical resection but, as we will discuss later, is slightly contentious[1,16–18]. Adjuvant chemotherapy may also be required for persistently recurrent or malignant tumours and is supported by guidelines from the Children's Cancer and Leukaemia Group (CCLG)[3].

For maxillary tumours, resection is undertaken via a vestibular approach. However, utilising a transfacial, combined approach can be justified in certain circumstances. Due to the rapid growth of the tumours in relation to the infant, the resections are significant, and have a lasting impact on their facial development.

To manage the maxillectomy defect, simple measures can be highly effective. Taking an alginate impression post resection enables the fabrication of an acrylic cover plate whilst the patient is on the table. This is then secured using self-tapping screws and a bismuth iodoform paraffin pack can be secured underneath it (Fig. 4). This has been found to be a well-tolerated, functional approach that heeds caution to the risk of recurrence.

In the mandible, surgical management is less straightforward and if the tumour is resected will almost always result in a continuity defect that requires reconstruction with a costo-chondral graft in the first instance. Again, tumours presenting on the skull are more complex and surgical resection with clear margins is desirable but the bony infiltration of MNTI means that this has the potential to carry significant morbidity. Surgery with the aid of navigation and staged resection is often required.[19,20].

Current CCLG guidelines advocate chemotherapy in unresectable tumours or where metastatic disease is present. Additionally, it is indicated where there is progression of disease after two surgical interventions. Two regimes are supported, with the first involving cyclophosphamide and vincristine for benign but recurrent tumours. The second regimen of OPEC/OJEC (vincristine (O), cisplatin (P), etoposide (E), cyclophosphamide (C), and carboplatin (J) as per CCLG guidelines) is reserved for persistently progressing tumours or malignant variants[3,21].

The primary aim in MNTI treatment is to cure with the benefit of minimising the number of surgical interventions and their sequelae an additional consideration. Successful surgery should remove the need for adjuvant therapy.

Recurrence rates have previously been reported varying between 10-15%[3–8]. However, a recent French multi-centre review reported a recurrence rate of 27%[2], which is more in keeping with our series where exactly that percentage of cases recurred. Complete resection gives a low incidence of recurrence. However, out of our cases with positive margins, less than half recurred. This is reflected in the literature and has been attributed to the host response stimulated by surgery removing the residual tumour[3]. This raises the question of the relevance of clear margins in the management of MNTI, especially when considering surgical morbidity in the paediatric population. Some authors have suggested conservative surgery or curettage[2,18], with the majority advocating resection[1].

There is no established surgical margin but a 5mm macroscopic margin has been proposed[22,23]. Complete resection seems to provide the most reliable cure, but a successful outcome can also be achieved with preservation of key anatomical landmarks and microscopically incomplete resection. Any significant surgical intervention to the facial skeleton in a child is likely to cause altered growth and development. This could burden the patient with long-term rehabilitative care and reconstructive needs. In certain anatomical sub-sites, if an extensive resection can deliver a macroscopically clear margin then this may be appropriate. However, in more anatomically sensitive sites, then the balance in favour of a more conservative approach may be more acceptable. This alternative may be coupled with a delayed approach to reconstruction and intensive short-term follow-up to aid clinical surveillance and allow early detection of potential recurrence. If unsuccessful, repeated surgery with or without chemotherapy would then be indicated.

Indications for conservative initial surgery are where resection would involve the orbital floor,

extensive intracranial dissection or interrupt mandibular continuity. These areas carry significant risks and pose problems with reconstruction that will likely affect the child's future development. Bearing in mind the nature of MNTI, it is difficult to justify radical surgery to obtain microscopically clear margins. The emphasis on conservative surgery in these areas is not absolute and consideration should be given to ease of surveillance and the anticipated difficulty in managing recurrent disease. However, on balance, the possibility of successful management with a minimum or morbidity is favoured.

Discussion at the paediatric oncology MDT is essential for all cases, especially taking into account the differential diagnoses and possibility of malignant variants[3–5]. Our proposed treatment algorithm has been amended from the CCLG guidelines and is shown in Fig. 5.

It is important to highlight the limitations of this paper, which is a common theme amongst rare diseases, that our conclusions are drawn from small numbers. We would support a multicentre international database collaboration to further delineate disease patterns and outcomes.

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Declarations

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Patient Consent: Consent has been obtained

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Legends

Figure 1. CT and MRI demonstrating a MNTI presenting in the left occipital, temporal and parietal bone with marked spiculated periosteal reaction and extradural involvement of the left middle and posterior cranial fossae. Also noted is extensive temporoparietal lobe oedema adjacent to the lesion.

Figure 2. Maxillary MNTI presenting in a three-month-old girl causing incompetent lips and difficulty feeding. Biopsy revealed the pathognomic darkly pigmented appearance of the tumour owing to the presence of melanin deposits.

Figure 3A. Melanotic neuroectodermal tumor of infancy(MNTI). The neoplastic proliferation consists of a biphasic cell population comprised of nests and cords of eosinophilic epithelioid cells

accompanied by darker-staining cells within a fibrous stroma. (Hematoxylin and eosin; magnification x 40).

Figure 3B. Tumor nests composed of two cell types: larger epithelioid cells in intimate association with smaller, hyperchromatic round cells. Light melanin pigmentation is seen in a few epithelioid cells.(Hematoxylin and eosin; magnification x200).

Figure 4. Surgical Management of a Maxillary MNTI. A: En-bloc surgical resection preserving the orbital rim and floor. B: Placement of a cover plate over a bismuth iodoform paraffin paste pack, secured with self-tapping screws visible in the right posterolateral maxilla. C: Assessment of the specimen returned with positive margins but here good granulation was noted upon pack change two weeks after the initial intervention with no signs of local recurrence. D: Photograph taken one year after initial surgery demonstrating good healing and no signs of recurrence. The oro-nasal fistula will be closed with local flaps in two-layers.

Figure 5. Revised treatment algorithm adapted from CCLG guidelines[3]

*As defined by a resection involving the orbital rim or floor, interrupting mandibular continuity or requiring extensive intracranial dissection.

Table 1. Melanotic Neuroectodermal Tumours of Infancy Treated at GOSH from 2000 to 2017

*Success was defined as disease free survival at the given follow-up

†Margins of surgery as per the residual tumour classification[10]

‡Maxillary resections as per Brown's classification[9]

§OPEC/OJEC—vincristine 1.5 mg/m^2 (O), cisplatin 80 mg/m^2 (P), etoposide 200 mg/m^2 (E), cyclophosphamide 600 mg/m^2 (C), and carboplatin 500 mg/m^2 (J) as per CCLG guidelines[3]