Medulloblastoma with tri-vergent melanocytic, myogenic and cartiligious elements

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1. Introduction

Medulloblastoma (MB) is the most common paediatric malignant brain tumour. Advancements in genomic technologies has led to the identification of 4 distinct molecular MB subtypes: int/ Wingless (WNT), sonic hedgehog (SHH), Group 3 and Group 4 tumours [1,2]. Each subtype has different genetic signatures that demonstrate good correlation to traditional histological subtypes [1,3], and recently, radiological surrogates [4]. Nonetheless, there remains a rare subset of MB with atypical features that is still poorly understood. Originally termed as 'medullomyoblastomas', it was described to be a histologically biphasic variant of a medulloblastoma with 'medulloblastic and myogenic elements' [5]. Since then, MBs with multi-lineage cell types have been mentioned in a limited number of case reports and small case series [6–12]. It is characterized microscopically by a mixture of primitive neuroectodermal and rhabdomyoblastic cells, the latter of which may either form distinct geographic collections or be admixed among the neuroectodermal cells [13]. However, under the current World Health Organization (WHO) classification, the term 'medullomyoblastoma' is obsolete, and if diagnosed, it will be under 'Medulloblastoma, Not Otherwise Specified (NOS)' [14]. In this paper, the authors describe a MB with tri-vergent features of melanocytic, myogenic and cartilaginous differentiation, in the context of its clinical behaviour, histopathological features and molecular subtyping.

2. Case report

A 3-year-old male with presented with unsteady gait, poor feeding and lethargy. A magnetic resonance imaging (MRI) of his brain reported a 5.8 × 4.0 × 3.4 cm heterogeneously enhancing solid-cystic mass arising from the fourth ventricle, causing obstructive hydrocephalus. The patient underwent a posterior fossa craniotomy and resection of the lesion. Intra-operatively, a vascular tumour of soft consistency was encountered. There were also areas of tumour plastered on the lower aspect of the fourth ventricle. Surgical gross total resection was achieved. Excess cerebrospinal fluid (CSF) under pressure was decanted via an external ventricular drain to relieve the hydrocephalus (Fig. 1).

Final histology confirmed medulloblastoma (WHO Grade IV) with divergent/teratoid differentiation (myogenic, melanotic, cartilaginous differentiation) and large cell component. Immunohistochemistry confirmed the tumour cells were positive for synaptophysin and focally weak for glial fibrillary acidic protein (GFAP). Epithelial membrane antigen (EMA) stain was negative. INI1 expression was retained. The Ki-67 proliferation index was 30%. Melanocytic cells contained a brown pigment bleached by potassium permangante and positive for Fontana Masson stain. Other than HMB4, these cells were S100-positive (Fig. 2).

Cytological studies of the CSF showed no malignant cells. Fluorescence *in situ* hybridization (FISH) was performed to investigate for MYC and MYCN gene amplification respectively. These were negative for both. For molecular subtyping, the patient's tissue was submitted for molecular subtyping using a NanoString nCounter assay [15], as part of a larger cohort (Fig. 3). The patient's MRI images were reviewed in accordance to the subtyping criteria proposed by Perreault et al. [4], and the radiological characteristics correlated to that of a Group 3.

Post-operatively, the patient was commenced on adjuvant chemo-radiation treatment. Fifteen months later, his MRI scan reported tumour relapse and leptomeningeal enhancement. Although rescue chemotherapy was initiated, the tumour continued to progress. In view of the disease's refraction to treatment, a palliative course was pursued for the patient.

3. Discussion

Although MB is the most common embryonal neoplasm of the neuroepithelial tissue, the subgroup 'medullomyoblastoma', is a rare clinical and pathological entity [13]. Current understanding of this tumour, especially its histogenesis in the context of multilineage differentiation, remains exiguous. Various hypotheses about this tumour's origins have been proposed. Some have suggested that this neoplasm arises from pluripotent cells of foetal cerebellar meninges [16], while others claim that the lesion is an alternative subset of teratoid tumours [9,17]. Remaining theories include speculations that the muscular component arises when multipotent endothelial [18,19] or mesenchymal cells [20] near or within the tumour undergo rhabdomyoblastic differentiation. At this stage, it is not known whether multi-lineage differentiation in MB has any distinct genetic features, and any possible congruency with the 4 MB molecular subtypes is still unidentified [9].

Group 3 MB arises exclusively in children, is frequently metastatic, and has the worst prognosis of all subgroups [1]. A key to the aggressiveness of Group 3 tumours is their frequent amplifica-

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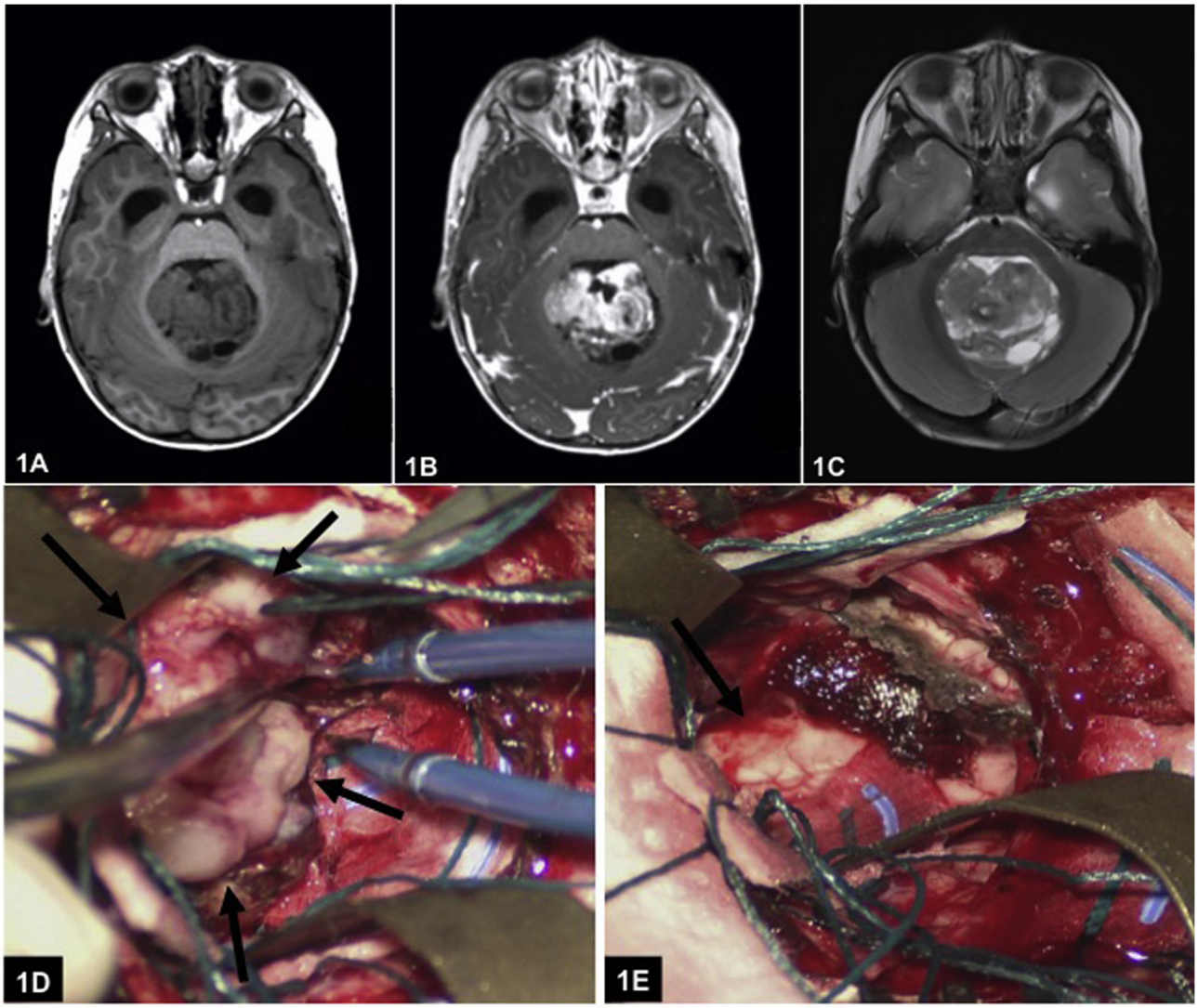

Fig. 1. (A) Axial pre-gadolinium T1-weighted MRI image showing a hypointense midline, spherical mass arising from the 4th ventricle. There is significant mass effect with displacement of bilateral cerebellar hemispheres and obstructive hydrocephalus. (B) Axial post- gadolinium T1-weighted MRI brain image confirmed avid heterogeneous contrast enhancement of the mass. This correlates with a Group 3 MB as per the criteria proposed by Perreault et al. [4]. (C) Axial T2-weighted MRI image depicting varying hyper- and hypointensity signal changes within the mass. (D) Intra-operative photo showing the tumour excision from its cavity. Black arrows point to the tumour. (E) Photo showing the surgical cavity post-excision. Black arrow points to the medullary surface where the tumour was previously adherent to.

tion of MYC [21]. Intriguingly, despite the similarities in the clinical and imaging features of this patient's MB and its molecular subtype, his FISH results do not suggest a MYC-driven involvement. Given its prolific multi-lineage heterogeneity, we postulate that the degree of aberrant cross-talking between multi-typal tumour cells will be exponentially intensified, whereby tumorigenic drivers are likely different in comparison to a conventional MB.

In summary, the authors describe an unusual MB whose trivergent lineage elements combinatorically within the same tumour, that has not been previously reported. Despite multimodality methods, attempts to delineate its biology demonstrates knowledge gaps. Owing to the paucity of knowledge of this infrequent tumour and its poor prognosis, it is critical to continue efforts for integration of large-scale, international MB genomic data. This is especially applicable to rare MB tumours, because ultimately, as illustrated by this case, they are the ones who will need novel therapeutic options.

Acknowledgements

The NanoString molecular subtyping effort was supported by the VIVA-KKH Paediatric Brain and Solid Tumour Programme. The authors would like to thank Professor M.D. Taylor and his team for their kind assistance in helping us to set up the NanoString assay and its working algorithms for our VIVA-KKH Paediatric Brain and Solid Tumour Programme.