Published in final edited form as:

Pediatr Blood Cancer. 2012 September ; 59(3): 561–564. doi:10.1002/pbc.24002.

Isochromosome 17q, *MYC* Amplification and Large Cell/ Anaplastic Phenotype in a Case of Medullomyoblastoma with Extracranial Metastases

Karen D. Wright, MD^{1,*}, Kendra von der Embse, BS², Jamie Coleman, MD³, Zoltan Patay, MD, PhD³, David W. Ellison, MD, PhD⁴, and Amar Gajjar, MD¹

¹Department of Oncology, Division of Neuro-Oncology, St. Jude Children's Research Hospital, Memphis, TN

²Ohio University College of Osteopathic Medicine, Northfield, OH

³Department of Diagnostic Imaging, St. Jude Children's Research Hospital, Memphis, TN

⁴Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN

Abstract

Medullomyoblastoma is a rare variant of medulloblastoma, a member of the family of central nervous system (CNS) embryonal tumors. The outcome of standard therapy for CNS embryonal tumors is often unpredictable in the setting of medullomyoblastoma. Here, we present the clinical course and treatment of an almost 4-year-old girl with medullomyoblastoma that was characterized by *MYC* amplification, isochromosome 17q and large cell/anaplastic histopathology.

Keywords

medullomyoblastoma; *MYC* amplification; isochromosome 17q; central nervous system embryonal tumors

INTRODUCTION

Medulloblastoma (MB), a tumor arising in the posterior fossa of the brain, is the most common malignant brain tumor of childhood with a reported 5-year, event-free survival rate exceeding 80% in patients with average-risk disease and 70% in those with high-risk disease [1]. Histopathologically, medullomyoblastoma (MMB) arguably constitutes a variant of medulloblastoma and was originally considered a variant within the World Health Organization's classification system until 2007, after which it was removed on the basis that its phenotype was recognized to exist alongside other variants like classic and anaplastic MB. Rhabdomyoblastic differentiation combined with features of classic MB define its specific histopathology.

Few reported cases have been published since MMB was first described in 1933 by Marinesco and Goldstein [2]. Prognosis has been described as unfavorable with few patients surviving more than 3 years [3–4], implying there may be an argument that these patients would benefit from high risk therapeutic regimens; however, evidence is lacking in this

*Address for correspondence and reprints: Karen D. Wright, MD, Department of Oncology, Division of Neuro-Oncology, St. Jude Children's Research Hospital, 262 Danny Thomas Place – Mailstop 260, Memphis, TN 38105-3678, Tel. 901-595-5898, Fax 901-595-4386, karen.wright@stjude.org.

regard. Current treatment for patients with MMB parallels the standard treatment for those with MB, including tumor resection followed by irradiation and chemotherapy [1, 4].

Outcome indicators reported in MB include the presence of metastatic disease, *MYC* amplification or overexpression, large cell or anaplastic (LC/A) histology, and isochromosome 17q [i(17q)], although the latter remains controversial [5–11]. The role of these factors in the biology of MMB is unknown. We report clinical data and immunohistochemical findings for a case of MMB in the setting of *MYC* amplification, i(17q), and LC/A histopathology.

CASE REPORT

A girl, age 3 years and 10 months, presented to an outside facility with headache and vomiting. Computed tomography (CT) scan of the brain revealed a mass in the fourth ventricle that was confirmed by magnetic resonance imaging (MRI), which also showed leptomeningeal disease (Figures 1A–C). She underwent near-total resection of the primary tumor. Postoperative imaging revealed that there was residual tumor at the margins of the 4th ventricle and interval progression of intracranial metastatic and leptomeningeal disease. Pathology review at St. Jude Children's Research Hospital revealed an embryonal tumor with diverse phenotypes. Some regions appeared consistent with a classic MB phenotype, while others, a large cell phenotype (Figures 2A–B). Foci of cells with rhabdomyoblastic differentiation were also evident with immunoreactivity for desmin and myogenin (Figure 2C and D), consistent with a final diagnosis of MMB. Interphase fluorescence *in situ* hybridization demonstrated i(17q) and scattered cells with *CMYC* amplification (Figures 2E and F); *NMYC* was not amplified (data not shown). The patient was enrolled on the high-risk arm of protocol St. Jude Medulloblastoma 2003 (SJMB03), requiring 39.6 Gy craniospinal irradiation (CSI) with 55.8 Gy boost to the primary site, followed by 4 cycles of cyclophosphamide-based, dose-intensive chemotherapy with autologous stem-cell rescue.

Four weeks after completion of CSI, she presented with hepatomegaly. Disease evaluation revealed no local recurrence, decreased leptomeningeal burden in her brain, and stable disease in the spine. Unexpectedly, numerous liver lesions were found in the absence of a ventriculoperitoneal shunt (Figures 1D–E). Ultrasound-guided liver biopsy revealed a neoplastic process with cytological features of the primary tumor, but no rhabdomyoblastic differentiation. CT scan of the chest, abdomen and pelvis showed extensive extracranial metastatic disease present in the liver, soft tissues and lymph nodes (Figure 1E). Whole body maximum intensity projection images from PET-CT revealed osseous lesions throughout the axial and appendicular skeleton (Figure 1G). Because of her disease progression, the patient was placed on a modified neuroblastoma-like chemotherapy regimen consisting of cyclophosphamide, doxorubicin, etoposide and cisplatin. Carboplatin replaced cisplatin for the remaining 2 courses after she developed bilateral Grade IV hearing loss. After 6 months of therapy, CT of the chest, abdomen and pelvis revealed a partial response with decrease in the size and number of liver lesions (Fig. 1F); brain and spine MRIs were stable. She died of progressive leptomeningeal disease 11 months after diagnosis.

DISCUSSION

Although the overall survival rate of patients with MB has improved during the last 10 years, successful treatment of those with high-risk disease remains a challenge [1, 12]. Multimodal risk factors for aggressive disease have been identified using diagnostic imaging, histopathology and cytogenetics; however, the role of such factors remains vague in MB and the topic of ongoing studies. Because of this knowledge gap, MMB, often

considered a rare variant of MB, remains controversial in the literature in regard to its classification, prognosis and treatment.

Although there have been reported cases of survival of individuals with MMB for more than 10 years after presentation, the previous average survival for such patients has been documented at less than 3 years in the absence of available long-term follow-up data [3–4]. The persistent leptomeningeal involvement and occurrence of intra-abdominal metastases in the absence of a ventriculoperitoneal shunt in this case highlight the aggressive nature of the disease when in the presence of negative prognostic markers, specifically LC/A phenotype and *MYC* amplification [5–10, 13–16]. Amplification of *MYC* has been shown to be associated with poor outcome and tends to occur with greater frequency in conjunction with LC/A subtypes [7–10, 14, 17–18]. Moreover, LC/A phenotype with *MYC* amplification often presents with metastatic disease at diagnosis [15].

Unfortunately, fresh frozen tumor tissue was not available for expression profiling. Interestingly, immunohistochemistry on the tumor revealed a sonic hedgehog (SHH) subtype (data not shown). *CMYC* amplification as evident in our patient's tumor, however, has not been reported in the SHH subtype of MB [14]. Lastly, i(17q) is not common among the SHH group of MB [14]. These discrepancies in conjunction with the lower survival rate among patients with MMB treated on MB protocols raise the issue of whether MMB represents a distinct entity from MB or a variant based on similar clinical features and genetic profiling to that of MB.

An integrative genomic approach using gene expression profiles and DNA copy-number alterations has identified 4 disparate subgroups of MB with distinct genetic abnormalities and clinical outcomes [19]. Further analyses of the signaling pathways dysregulated in these various MB subtypes have caused speculation about the role of key gene amplifications, such as those of *WNT*, *SHH*, and *MYC* [14]. With this in mind, does the gene expression pattern of tumors classified as MMB, in fact, fall within one of the four typical MB subgroups or would these tumors cluster closer to other small round blue cell tumors of myogenic origin instead?

Applying genetic approaches will help us to better classify MMB, an entity with its own unique clinical behavior, histological features and evolving molecular characteristics. The rarity of MMB and corresponding paucity of tumor samples, however, preclude the application of large-scale genomic analyses to any direct development of novel therapeutics for this disease at this time. MMB cases warrant further investigation to determine whether they represent a subtype of MB or a distinct entity and to establish better treatment regimens for patients diagnosed with MMB.

Acknowledgments

This research was supported in part by grant P30 CA21765 from the National Institutes of Health, the Noyes Brain Tumor Foundation, Musicians Against Childhood Cancer (MACC) and the American Lebanese Syrian Associated Charities (ALSAC). We also thank St. Jude Children's Research Hospital's Biomedical Communications Department (Klo Spelshouse) for preparing the figures and Scientific Editing Department (Cherise Guess, PhD) for reviewing the manuscript.

References

1. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St. Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *Lancet Oncol.* 2006; 7:813–820. [PubMed: 17012043]

2. Marinesco G, Goldstein M. Sur une forme anatomique, non encore decrite, de medulloblastome, Medullo-myoblastome. *Annl Anat & Path.* 1933; 10:513–515.
3. Jaiswal AK, Jaiswal S, Mahapatra AK, et al. Unusually long survival in a case of medullomyoblastoma. *J Clin Neurosci.* 2005; 12:961–963. [PubMed: 16326277]
4. Helton K, Fouladi M, Boop F, et al. Medullomyoblastoma: a radiographic and clinicopathologic analysis of six cases and review of the literature. *Cancer.* 2004; 101:1445–1454. [PubMed: 15368333]
5. Rutkowski S, von Bueren A, von Hoff K, et al. Prognostic relevance of clinical and biological risk factors in childhood medulloblastoma: results of patients treated in the prospective multicenter trial HIT'91. *Clin Cancer Res.* 2007; 13:2651–2657. [PubMed: 17473196]
6. Brown HG, Kepner JL, Perlman EJ, et al. "Large cell/anaplastic" medulloblastomas: a Pediatric Oncology Group Study. *J Neuropathol Exp Neurol.* 2000; 59:857–865. [PubMed: 11079775]
7. Stearns D, Chaudhry A, Abel TW, et al. c-myc overexpression causes anaplasia in medulloblastoma. *Cancer Res.* 2006; 66:673–681. [PubMed: 16423996]
8. Aldosari N, Bigner SH, Burger PC, et al. MYCC and MYCN oncogene amplification in medulloblastoma. A fluorescence in situ hybridization study on paraffin sections from Children's Oncology Group. *Arch Pathol Lab med.* 2002; 126:540–544. [PubMed: 11958658]
9. Badiali M, Pession A, Basso G, et al. N-myc and c-myc oncogenes amplification in medulloblastomas. Evidence of particularly aggressive behavior of a tumor with c-myc amplification. *Tumori.* 1991; 77:118–121. [PubMed: 2048223]
10. Pfister S, Remke M, Benner A, et al. Outcome prediction in pediatric medulloblastoma based on DNA copy-number aberrations of chromosome 6q and 17q and the MYC and MYCN loci. *J Clin Oncol.* 2009; 27:1627–1636. [PubMed: 19255330]
11. Biegel JA, Janss AJ, Raffel C, et al. Prognostic significance of chromosome 17p deletions in childhood primitive neuroectodermal tumors (medulloblastomas) of the central nervous system. *Clin Cancer Res.* 1997; 3:473–478. [PubMed: 9815707]
12. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *J Clin Onc.* 2006; 24:4202–4208.
13. Ellison D. Classifying the medulloblastoma: insights from morphology and molecular genetics. *Neuropathol Appl Neurobiol.* 2002; 28:257–282. [PubMed: 12175339]
14. Ellison DW, Dalton J, Kocak M, et al. Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. *Acta Neuropathol.* 2011; 121:381–396. [PubMed: 21267586]
15. Leonard JR, Cai DX, Rivet DJ, et al. Large cell/anaplastic medulloblastomas and medullomyoblastomas: clinicopathological and genetic features. *J Neurosurg.* 2001; 95:82–88. [PubMed: 11453402]
16. Eberhart CG, Kepner JL, Goldthwaite PT, et al. Histopathologic grading of medulloblastoma: a Pediatric Oncology Group study. *Cancer.* 2002; 94:552–560. [PubMed: 11900240]
17. von Hoff K, Hartmann W, von Bueren AO, et al. Large cell/anaplastic medulloblastoma: outcome according to Myc status, histopathological, and clinical risk factors. *Pediatr Blood Cancer.* 2010; 54:369–376. [PubMed: 19908297]
18. Lamont JM, McManamy CS, Pearson AD, et al. Combined histopathological and molecular cytogenetic stratification of medulloblastoma patients. *Clin Cancer Res.* 2004; 10:5482–5493. [PubMed: 15328187]
19. Northcott PA, Korshunov A, Witt H, et al. Medulloblastoma comprises four distinct molecular variants. *J Clin Onc.* 2010; 29:1408–1414.

Figure 1.

Figure 2.