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CASE REPORT

The Association of Circulating M-MDSCs and the Tumor Progress in Embryonal Brain Tumor following Therapy: Case Report

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ABSTRACT

Embryonal tumors are primitive neuroectodermal tumors of the central nervous system (CNS). It possesses the capability to resist chemotherapy and radiation, and it can spread through cerebrospinal fluid (CSF) routes, making it challenging to cure and prone to relapse. Myeloid-derived suppressor cells (MDSCs) are a heterogeneous cell population that plays a vital role in suppressing the immune response. In this case report, we described a 9-years-old child who was diagnosed with an embryonal brain tumor. The patient initially attained a complete response but subsequently experienced a relapse. The progression of recurrent tumors is associated with circulating monocytic MDSCs (M-MDSCs). This finding indicates the potential utility of circulating M-MDSCs as a clinical indicator for embryonal brain tumors following therapy. It may have the chance to become a new tool for tracking and modulating the growth of brain tumors.

KEYWORDS

Embryonal tumors; MDSCs; Tumor progression

INTRODUCTION

Embryonal tumors are a group of biologically heterogeneous neuroepithelial tumors. They represent 15.7% and 4.3% of brain tumors diagnosed between 0 year to 14 years and 15 years to 19 years, respectively [1,2]. The World Health Organization (WHO) 2007 classifies embryonal tumors by their cellular lineage and location:

Medulloblastoma, supratentorial primitive neuroectodermal tumors (sPNETs), and atypical teratoid/rhabdoid tumors (AT/RTs). These malignant neoplasms are often diagnosed in children, in whom curative treatments include surgery, radiotherapy, and chemotherapy. Despite it being a significant advance in therapeutic strategies, the patients with poor outcomes and a median survival of 12 months after diagnosis [3,4]. Thus, monitoring the treatment response and adjusting treatment to prolong the patient's survival is essential. An expensive MRI image is currently the only way to track treatment response.

Myeloid-derived suppressor cells (MDSCs) constitute a heterogeneous group of cells that play a pivotal role in suppressing the immune response, contributing to the promotion of tumor advancement. MDSCs consist of three main components of cells: Granulocytic or polymorphonuclear MDSCs (PMN-MDSCs), monocytic MDSCs (M-MDSCs), and early MDSCs (e-MDSCs) [5]. The vital role of MDSCs in cancer is now widely recognized, and their presence relates to adverse clinical outcomes in patients [6-9].

In this investigation, the primary objective of this case report is to provide an overview of the disease progression in a patient diagnosed with embryonal tumors while uncovering the correlation between tumor response and the presence of circulating M-MDSCs following the treatment.

CASE REPORT

The case is a 9-year-old boy without a specific past medical history and with a normal perinatal history and developmental milestones. He suffered from intermittent back pain and headache for more than two months, followed by poor appetite and nausea/vomiting for one month. The progressive blurred vision was told as well. In mid-Jan 2020, some seizure episodes were observed, with bilateral eye upward gaze, right upper limb flexion with colonic movement, and lower limbs tonic extension posture once every 5 days - 6 days. The condition progressed, and the frequency increased to twice daily in mid-Feb 2020. Poor verbal response and unsteady gait were noted in late Jan 2020. Due to stupor consciousness, he was brought to a local hospital on 2020/02/24. Brain MRI showed marked hydrocephalus, and the left lateral ventricle temporal horn tumor was impressed (Figure 1A). He was then transferred to Taipei Veterans General Hospital and underwent a craniotomy in 2020/3/2.

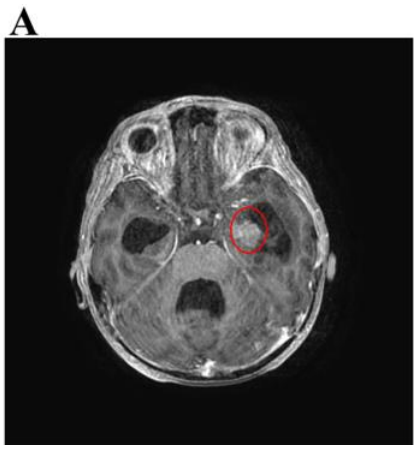

Figure 1: The MRI images at various stages throughout the tumor progression. **A)** The MRI scans taken prior to the surgery in February 2020.

The histopathological examination showed that the resected embryonal tumor is composed of tumor cells with round to oval nuclei and a scant amount of faint eosinophilic cytoplasm resembling those small blue round cell

tumors and embedded in fibrillar and myxoid backgrounds (Figure 2A). Rosette's formation is noted. Most round tumor cells are immuno-reactive for synaptophysin and focally positive for EMA (Figure 2B). The tumor cells preserve the nuclear expression of INI-1 and BRG1 immunostaining. The histopathologic features are compatible with a malignant embryonal tumor and are most likely embryonal tumors with multilayered rosettes. Then he had radiotherapy for left ventricular tumor bed 5600cGy/30Fx, and craniospinal axis 3600cGy/20Fx during 2020/04/15-05/26, followed by ten cycles of chemotherapy with a combination of carboplatin, etoposide, and vinblastine, which was completed on 2021/4/27 (Figure 1B). Unfortunately, the tumor recurrent presenting with spinal seeding was found in March 2022 (Figure 1C), and salvage treatment (radiotherapy, systemic and intrathecal chemotherapy) was provided since April 2022. During the therapeutic procedure, the patient underwent an MRI scan to monitor tumor advancement, and the variability of circulating M-MDSCs was assessed using flow cytometry (Figure 3). It was below 1% performance among Lin-, HLA-DR-, CD11b+ cell population, and the tumor in the olfactory groove was a stable disease. Upon discovery, the expression of circulating M-MDSCs exhibited a sharp increase, rising from 0.7% on 2022/11/29 to 1.6% on 2022/12/29 and subsequently jumping to 2.3% on 2023/03/11. Concurrently, MRI images revealed the ongoing deterioration and growth of the tumor. Then, his parents decided to stop the treatment after June 2023. The last MRI with tumor progression is shown in Figure 4.

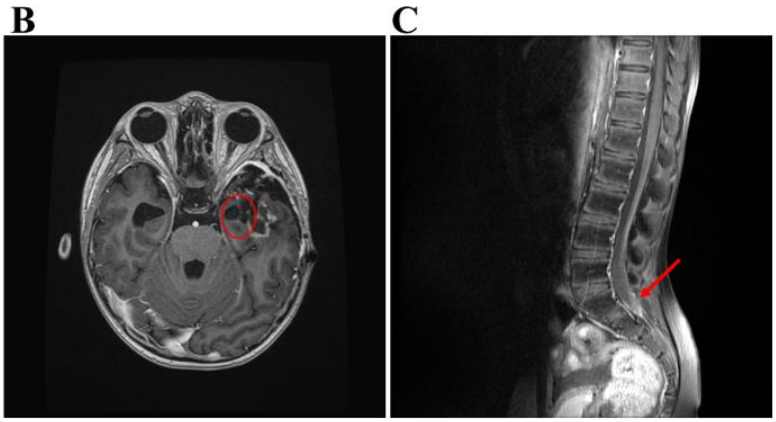

Figure 1: The MRI images at various stages throughout the tumor progression. **B)** The MRI scans conducted post-treatment in April 2021, showed a satisfactory level of tumor control. **C)** The tumor presented with spinal seeding in March 2022. The tumor regions are highlighted with a red circle or arrow.

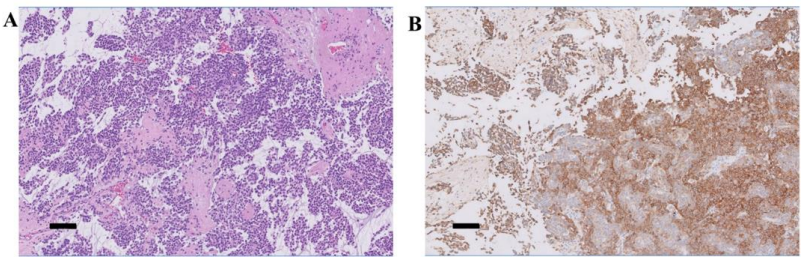

Figure 2: Histological Features of Tumor Section. **A)** The tumor cells exhibit a small, round, blue cell morphology (Hematoxylin & Eosin, x200). **B)** The tumor cells are positive for synaptophysin (Synaptophysin, x200). Scale bar represents 100 μm.

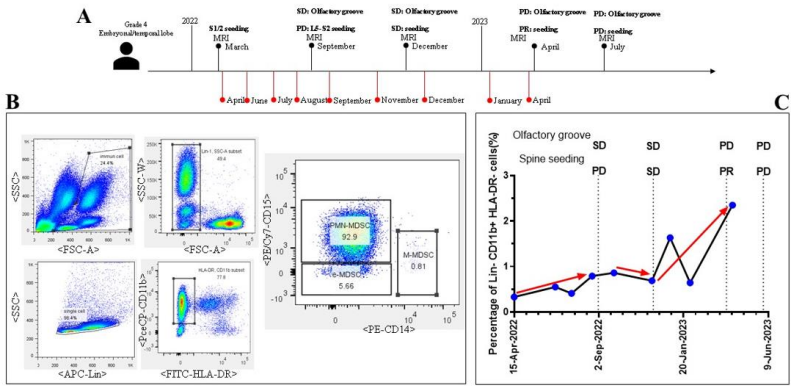

Figure 3: The correlation between circulating M-MDSCs and tumor advancement. **A)** The timeline for MRI scans (black solid circle above the timeline) and liquid biopsy (red solid circle below the timeline). **B)** The circulating M-MDSCs were identified as Lin-, HLA-DR-, and CD11b+ cells. **C)** The fluctuations in circulating M-MDSCs were linked to tumor progression.

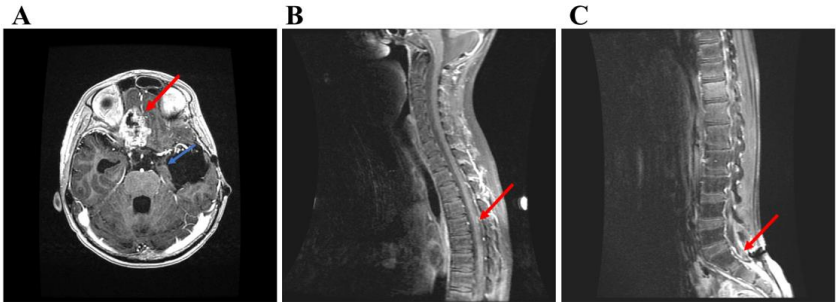

Figure 4: The lasted MRI images scans. **A)** The brain MRI images displayed the initial site marked by a blue arrow and the new lesion site indicated by a red arrow. **B)** The MRI images of the spine depicted the presence of T-spine seeding, highlighted by a red arrow. **C)** The MRI images of the spine showed the presence of L-spine seeding, marked with a red arrow.

DISCUSSION

In this report, we present a rare case involving a 9-years-old child who was diagnosed with an embryonal brain tumor through pathological analysis. At the outset, the integrated approach of fractionated radiotherapy combined with chemotherapy demonstrated remarkable treatment effectiveness. Despite the impressive initial tumor response, embryonal tumors possess the ability to spread through cerebrospinal fluid routes [2], leading to spinal seeding. The recurrence and metastasis of the tumor add complexity to the treatment process. Many patients who develop metastatic disease in the spinal or cerebral regions [10,11] often require intrathecal chemotherapy and may subsequently develop hydrocephalus, which is typically associated with a poor prognosis. Disease-free survival is only extended for one year before metastasis occurs, highlighting the clinical complexity associated with the metastasis [12] of embryonal tumors.

Treatment strategies for embryonal tumors commonly involve surgery, chemotherapy, and radiotherapy. Nevertheless, the presence of treatment resistance and the risk of neurocognitive impairment [13] pose significant challenges in clinical. For this reason, monitoring the tumor progress and modifying medication according to the observed changes is essential, which can lead to improved treatment outcomes. We noted that circulating M-

MDSCs were associated with primary embryonal tumor progression. This pattern is similar to individuals with head and neck cell carcinoma, with a notable increase in CD11b+HLA-DR-CD14+CD33+ cells among patients with a high tumor burden compared to those in the low tumor group [14]. This finding hints at the potential of circulating M-MDSCs as a valuable indicator for tracking the progression of embryonal tumor patients.

As medical technology advances, immunotherapy represents a rapidly evolving field that focuses on enhancing the innate immune mechanisms to eradicate cancerous cells, including immune checkpoint inhibitors, oncolytic viruses, cancer vaccines, and adoptive cell therapies. To further improve the effectiveness of immunotherapy, identifying a suitable target to stimulate an immune response can significantly enhance tumor response rates. Remarkably, the patient's recurrent tumor progression was correlated with the levels of M-MDSCs in peripheral blood. Furthermore, this indicator displayed an early increasing trend, indicating tumor growth even before it was evident on MRI scans. This discovery aligns with prior research that demonstrated a correlation between the population of circulating MDSCs and tumor size in patients with head and neck cancer [14]. Our previous study in a 4-NQO-induced HNSCC murine model has demonstrated that the circulating M-MDSCs are a therapeutic target and an index for monitoring the progression of oral cancers [15]. These studies underscore potential future treatment directions and targetable markers for embryonal brain tumors.

CONCLUSION

This case represents an initial correlation report between the progression of embryonal brain tumors and circulating M-MDSCs following therapy, suggesting their potential utility as clinical indicators. The circulating M-MDSC levels can provide insights into the progression of the tumor. A significant increase in these levels can act as an indicator of tumor growth and deterioration, facilitating the detection of changes in the tumor and assisting in the selection of treatment strategies for patients with embryonal brain tumors.

AUTHOR CONTRIBUTIONS

C-HC: Data curation, Formal Analysis, Investigation, Methodology, Writing - Original draft. L-YY: Data curation, Methodology, Validation, Funding acquisition, Writing - Review & editing. L-SC: Pathology, Data curation. C-FH: Visualization, Formal Analysis, Investigation, Funding acquisition, Writing - review & editing. C-SC: Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Visualization, Writing - Review & editing.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author/s.

CONFLICT OF INTEREST

The author declares that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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INSTITUTIONAL REVIEW BOARD STATEMENT

This study was approved by the institutional review board of Taipei Veterans General Hospital (IRB: 2020-11-006A and 2021-08-010B).

INFORMED CONSENT STATEMENT

The patient gave their informed consent for inclusion before they participated in this study.

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