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## Histopathologic Modification in CNS Neuroectodermal Tumor: A Long Term Follow Up of a Clinical Case

Franceschi E<sup>1\*</sup>, Bartolotti M<sup>1</sup>, Brandes AA<sup>1</sup>, Antonelli M<sup>2</sup>, Giangaspero F<sup>2,3</sup>, Tallini G<sup>3</sup>, Capper D<sup>4</sup>, Pession A<sup>5</sup>, Scarpelli M<sup>6</sup>, Vecchioni S<sup>7</sup>, Balestrini D<sup>8</sup>, De Diase D<sup>9</sup> and Foschini MP<sup>10</sup>

<sup>1</sup>Department of Medical Oncology, Bellaria-Maggiore Hospitals, Azienda USL – IRCCS, Institute of Neurological Sciences, Bologna, Italy

<sup>2</sup>Department of Radiological, Oncological and Anatomic-Pathological Sciences, Sapienza University, Rome, Italy

<sup>3</sup>IRCCS Neuromed, Pozzilli (Is), Italy

<sup>4</sup>Department of Neuropathology, University of Heidelberg, Clinical Cooperation Unit Neuropathology, German Cancer Research Center (DKFZ), Heidelberg, Germany

<sup>5</sup>Department of Medicine (DIMES) Anatomic Pathology-Molecular Diagnostic Unit AUSL of Bologna, University of Bologna School of Medicine, Bologna, Italy.

<sup>6</sup>Section of Pathological Anatomy, Polytechnic University of the Marche Region, School of Medicine, United Hospitals, Ancona, Italy

<sup>7</sup>Department of Neurological Sciences, Section of neurosurgery, United Hospitals, Ancona, Italy

<sup>8</sup>Department of Radiotherapy, Bellaria-Maggiore Hospitals, Azienda USL – IRCCS Institute of Neurological Sciences, Bologna, Italy

<sup>9</sup>Department of Pharmacy and Biotechnology (FaBiT), Molecular Pathology Unit AUSL di Bologna, Bellaria Hospital, University of Bologna, Bologna, Italy

<sup>10</sup>Department of Biomedical and Neuromotor Sciences, Section of Anatomic Pathology, University of Bologna, Bellaria Hospital, Bologna, Italy

\*Corresponding author: Enrico Franceschi, Department of Medical Oncology, Bellaria-Maggiore Hospitals, Azienda USL – IRCCS, Institute of Neurological Sciences, Via Altura 3, 40139 Bologna, Italy, Tel: +39 (0)51 6225697; Fax: +39 (0)51 6225057; E-mail: enricofra@yahoo.it

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### Abstract

**Background:** Post-therapy differentiation in medulloblastoma (MB) is a rare event that has been described only in pediatric age.

**Methods:** We describe the long term follow up of a case of medulloblastoma maturation after chemotherapy and radiotherapy in an adult MB patient.

**Results and Discussion:** A 20-year-old patient was partially resected of a MB with ki-67 of 60%. DNA methylation-derived subgroup showed a molecular SHH profile. The patient received cranio-spinal tomotherapy (32.4 Gy in 18 fractions) with a boost on posterior fossa (23.4 Gy in 17 fractions, total dose: 55.8 Gy in 32 fractions). The MRI performed 2 months after revealed a minimal volumetric increase. The patient underwent 2 cycles of Cisplatin - Etoposide chemotherapy. The MRI showed stable disease. The patient underwent second surgery. The specimen showed neuronal cells showing various degrees of maturation from neurocytic to ganglion cells. No embryonal cells were present. Mitoses were absent. The residual lesion showed the post-therapy neuronal maturation of a medulloblastoma. DNA methylation-derived subgrouping confirmed the SHH profile. No other treatments were delivered after the

second resection. To date the patient is still alive and free from progression 54 months after primary surgery.

**Conclusion:** After a long term follow up, we showed that tumor maturation in an adult patient with medulloblastoma is characterized by a favorable outcome. Physicians should take into account that tumor maturation may occur and that its recognition is essential to define the prognosis and to manage adult patients.

**Keywords:** Adult medulloblastoma; Differentiation; Radiotherapy; Chemotherapy

### Introduction

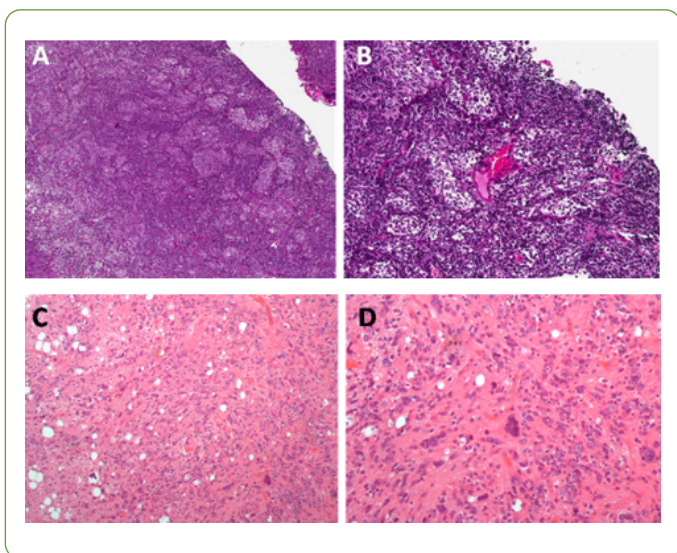
Medulloblastoma (MB) is an embryonal tumor of the cerebellum and represents the most common malignant neoplasm of the central nervous system (CNS) in children. MB is rare in adults, (less than 1% of primitive CNS tumors) with an incidence of 0.6–1 case per million per year [1]. MB is potentially a curable disease and current treatments allow 5-year overall survival (OS) rate of up to 75%. MB comprises a collection of different tumor subgroups: WNT, SHH, Group 3, and Group 4. [2-8]. In adults, the SHH subgroup represents the largest subgroup, accounting for about 60% of all tumors. The treatment for MB in adults is represented by surgical resection followed by radiotherapy (36 Gy in 20 fractions, followed by a

boost of 18 Gy in 10 fractions to the posterior fossa, up to a total of 54 Gy), adding chemotherapy for high-risk patients. Post therapeutic neuronal maturation is a rare event that can occur in some pediatric neoplasms, such as neuroblastoma and MB [9-14]. Here we report the long term follow up of an adult MB that experienced post-therapy neuronal maturation and a favorable outcome.

## Case Presentation

A 20-year-old patient started to experience symptoms with headache and vomiting. The MRI of the brain showed a 4 × 4 cm lesion on the left cerebellar hemisphere. The patient underwent a partial resection of the lesion.

The histopathologic diagnosis was of a nodular/desmoplastic medulloblastoma (**Figures 1A and 1B**). Focal anaplastic changes characterized by enlarged end pleomorphic nuclei with atypical mitoses were also found. Ki-67 reached 60% in internodular areas and 3% in other areas.



**Figure 1** (A and B) Histopathology in the initial medulloblastoma sample, (C and D) Histopathology in medulloblastoma sample and at time of second surgery.

DNA methylation-derived subgroup was performed with Illumina Human Methylation 450 k BeadChip arrays [3]. The lesion showed a molecular SHH profile.

Spinal metastases were excluded by cranio-spinal MRI. Cerebrospinal fluid (CSF) was negative for neoplastic cells. After ovarian tissue preservation the patient received cranio-spinal tomotherapy (32.4 Gy in 18 fractions) with a boost on posterior fossa (23.4 Gy in 17 fractions, for a total dose of 55.8 Gy in 32 fractions).

The MRI performed 2 months after tomotherapy completion showed a minimal increase of the residual lesion. Thereafter, the patient received 2 cycles of Cisplatin 25 mg/m<sup>2</sup> on days 1 to 4 and Etoposide 40 mg/m<sup>2</sup> on days 1 to 4 every 28 days [4-8]. Disease assessment with brain MRI showed stability of the lesion. Given the refractoriness of the lesion, the patient underwent second surgery. Histopathology showed a neoplasm composed of neuronal cells with various degrees

of maturation from neurocytic to ganglion cells, in absence of embryonal cells. No mitoses were found and the Ki-67 was only 2% (**Figures 1C and 1D**).

A strong and diffuse positive staining for synaptophysin was observed. The residual lesion was suggestive of a post-treatment neuronal maturation of a medulloblastoma. DNA methylation-derived subgrouping confirmed the molecular SHH profile. Moreover, chromosomal alterations were similar to the initial lesion. No other treatments were delivered after the second resection. To date the patient is still alive 54 months after primary surgery, without disease relapse.

## Discussion

In this case report we showed that neuronal maturation may occur also in adult MB patients. Tumor maturation is associated with better prognosis in neuroblastoma [9,10] and in pediatric MB [12-14]. Similarly, after a long follow up, our adult patient was alive and free from disease progression. Treatment-induced maturation is a phenomenon that has also been observed in other tumors of embryonal origin, such as embryonal testicular germinal cells tumor (GCT). Indeed, it has been observed that in some cases, following treatment with platin, residual masses have differentiated teratomatous histology [15-20].

However, the mechanism of the maturation is unclear. It is possible that chemotherapy determines the activation/deactivation of molecular pathways that drives immature cells toward maturation and differentiation [12].

In this case, the diagnosis of tumor maturation, with the absence of mitoses and the reduction of ki67, discouraged the administration of further chemotherapy, given the fact that differentiated cells are more resistant to cytotoxic agents (as has already been seen in testicular cancer maturation) [20].

## Conclusion

In conclusion, we suggest remembering that tumor maturation may happen also in adult patients with neuroectodermic pediatric tumors (i.e. PNET, medulloblastoma) and the recognition of this phenomenon is of importance in managing the patients.

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