Medulloblastoma and CNS-PNET Subtypes: Molecular basis to Histopathological features to Clinical Outcome

M Fayez AL HOMSI
College of Medicine, University of Sharjah, Sharjah, United Arab Emirates
Email: malhomsi@yahoo.com

Abstract:

Subtypes of central nervous system (CNS) primitive neuroectodermal tumors (PNET) were recently described. Two of them were found to have clinical significance and carry significant weight on prognosis. Between 1980 and 2014 more than 300 cases of CNS-PNET are identified in the hospital pathology archives. These tumors, like the medulloblastoma (as they are usually called when localized in the cerebellum) are usually composed of undifferentiated small blue cells, with areas showing tendency for glial, neuronal, melanocytic, myoblastic, and other mesenchymal differentiation. One of these CNS-PNET subtype is called lipidized medulloblastoma or medullocytoma. It is characterized by typical features of medulloblastoma with areas of "lipomatous differentiation", low proliferative potential, manifestation in adults, and apparent better prognosis. Another CNS-PNET subtype is called atypical teratoid/rhabdoid tumor (ATT/RT). ATT/RT is characterized by the presence of fields of primitive neuroecdtodermal tumor typical of medulloblastoma and areas of rhabdoid cell differentiation. ATT/RT is usually positive for a triad immunohistochemical analysis of epithelial membrane antigen (EMA), vimentin, and smooth muscle actin (SMA).

Introduction:

Central nervous system primitive neuroectodermal tumors (CNS-PNET) are the most common malignant brain tumors in children, and they are most commonly located in the cerebellum, where they are known as "medulloblastomas". The histogenesis of this tumor had been debated since the original description of the medulloblastoma in 1925 [1]. It is generally regarded as an embroyonal tumor with well-defined clinical and histological features [2,3]. This tumor is usually composed of morphologically undifferentiated small blue cells. It may show a tendency for neuronal [4,5], glial [6], melanocytic [7,8], myoblastic, and other mesenchymal differentiation [9,10].

Recently, two subgroups of CNS-PNET have been identified, namely medullocytoma [11] and atypical tetratoid/rhabdoid tumor [12]. To date, only 12 cases of medullocytoma (lipidized medulloblastoma) [11,13-18], and approximately 133 primary CNS atypical teratoid/rhabdoid tumors (ATT/RT) [12,19-29] had been reported. Medullocytoma is a new clinical pathologic entity characterized by typical features of medulloblastoma with areas of lipomatous differentiation, low proliferative potential, manifestation in adults, and apparent favorable clinical prognosis [11]. In contrast, the ATT/RT are most common in infants less than 2 years of age. They contain rhabdoid cell differentiation and fields of typical primitive neuroectodermal tumor with unique immunohistochemical profile, including epithelial membrane antigen (EMA), vimentin, and smooth-muscle actin (SMA), and they are immunohistochemically negative for germ cell tumor markers [12]. Molecular genetic studies demonstrated that these tumors are also characterized by the cytogenetic finding of monosomy 22, while the classical medulloblastoma has isochromosome 17q [29].

The aim of this study is to identify these two newly recognized subgroups of CNS-PNET, namely medullocytoma and atypical tetratoid/rhabdoid tumor, in the hospital pathology archive.

Materials and Methods:

Cases: Between 1980 and 2014 more than 300 cases of CNS-PNET were identified in the hospital pathology archive.

Immunohistochemical studies: In this project the labeled Streptavidin-Biotin method was used to demonstrate the presence of epithelium membrane antigen, cytokeratine, vimentin, desmin, smooth-muscle Actin, S-100 protein, neurofilament protein, glial fibrillary acidic protein, synaptophysin, alpha fetoprotein, placental alkaline phosphatase, and human chorionic gonadotropin using antibodies on paraffin imbedded tissues. Briefly, after rehydration of the sections, an antigen retrieval method was utilized (microwaving), and followed with antibody incubation overnight. LSAB kit was used to localize the reaction and DAB chromogene to visualize it. Slides were cover-slipped and evaluated by light microscopy.

Results:

More than 300 cases of CNS-PNET were identified in the hospital pathology archive. These malignant cerebellar tumor are more common in children (82%, peak age 3-7 years). They made 19% of CNS tumors in children. They also can be seen in adults (18%, median 28 years). They made 1% of CNS tumors in adults. Despite these differences they had same 5 year actuarial survival of 50%. Long-term survival in adults was observed in two situations. One when surgical resection followed by radiotherapy to the posterior fossa and spinal cord are carried out, and the other when histological diagnosis of lipidized medulloblastoma (medullocytoma) is recognized. The lipidized medulloblastoma (medullocytoma) is seen in adults with cerebellar neoplasm exhibiting mature-type adipocytes in PNET background with low mitotic activity. These features are found to be associated with favorable prognosis. Immunohistochemistry of these neoplasms shwed positivity for GFAP (also in adipocytes), synaptophysin, neurone specific enulase, S-100, and vimentin. The *p*53 is negative and MIB-1 labling index is usually < 5%. Teratoid/rhabdoid tumors (ATT/RT) was usually misdiagnosed as PNET-MB, because it has PNET-like histology. It was seen in infants and children (1 - 14.9 years), and it carried grim prognosis. This type was seen in the cerebellum and cerebellopontine angles in 75%, in the cerebrum in 20%, in the pineal gland region in 6%, and in multiple sites in 10%. The histology of these ATT/RT showed rhabdoid cells in 100% of the cases (11% were purely composed of rhabdoid cells), PNET histology in 67%, mesenchymal features in 31%, and epithelial elements in 25%. Immunohistochemistry of these ATT/RT neoplasms shwed positivity for EMA and vimentin in all cases (100%), SMA in 97%, GFAP in 73%, keratin in 66%, NFP in 38%, and desmin in 9%. Cytogenetics of ATT/RhT ahowed monosomy 22 in a third of cases and partial deletion of 22q11 in another third, while "typical" PNET showed i(17q) in half of the cases.

Discussion:

Identification of important parameters to use prospectively for the routine evaluation of primitive neuroectodermal tumors. This study will be valuable in identifying those

laboratory evaluations which are of most benefit in providing accurate diagnoses. This will allow more effective and individualized treatment modalities to be applied in certain cases. Immunohistochemical analysis of a subset of primitive neuroectodermal tumors called "medullocytoma". The objective of this study is to identify this newly recognized subset of primitive neuroectodermal tumors, which is thought to carry a better prognosis than the classical primitive neuroectodermal tumor. This will be useful in providing more informed knowledge about this group of tumors to patients affected by this type of brain tumors. Evaluation of these cases and identification of this subset of primitive neuroectodermal tumors will enable us to perform correletion between the histological features and immunohistochemical analysis on one hand, and the clinical outcome and follow-up on the other hand.

Immunohistochemical catheterization of the atypical teratoid/rhabdoid tumors, which (by some investigators is considered a separate tumor misdiagnosed as PNET) form another subset of the primitive neuroectodermal tumors occurring in children of two years of age or younger. These tumors carry a grim prognosis and analysis of these cases will again enable us to estimate a more informed clinical outcome in terms of prognosis.

The study contributes to the following developmental issues: 1) To better understand the disease process in patients developing this type of brain tumor, namely primitive neuroectodermal tumors. 2) To delineate further the specific features of the subtypes of these neuroectodermal tumors, namely the "medullocytoma" and the atypical teratoid/rhabdoid tumors, in patients in terms of their morphological presentations. 3)To classify the "subtypes" of these neuroectodermal tumors of the brain in our patient population. 4) To identify those "subsets" of tumors in our patients for appropriate treatment modalities.

In conclusion, it is obvious that primitive neuroectodermal tumors have been well known, though their histogenesis raised tremendous debate. Fairly recently two "subtypes" of these tumors have been characterized. One carry a grim prognosis and occurs in children of two years of age or younger, and the other has a better prognosis than the usual primitive neutroectodermal tumor and usually occurs in adults. This retrospective study made use of more than 300 cases archived since 1981, and enabled us to identify these two main "subsets" of the primitive neutroectodermal tumors of the brain to help predict more accurately their histologic behaviour and their clinical outcome. In turn this will be used prospectively to better evaluate primitive neuroectodermal tumors and make us better informed about the prognosis of these tumors, based on their morphological and immunohistochemical profiles.

References:

1. Bailey P, Cusing H. Medulloblastoma cerebelli: a common type of midcerebellar glioma of childhood. Arch Neurol Psychiatry 14:192-244, 1925.

2. Rorke LB. The cerebellar medulloblastoma and its relationship to primitive neuroectodermal tumors. J. Neuropathol Exp Neurol 42:1-15, 1983.

3. Russell DS, Rubinstein LJ. Pathology of tumours of the nervous system. London: Edward Arnold, 251-79, 1989.

4.   Burger PC, Grahmann FC, Bliestle A, Kleihues P. Differentiation in the medulloblastoma. A histological and immunohistochemical study. Acta Neuropathol 73:115-23, 1987.

5.   Gould VE, Jansson DS, Molenaar WM, et al. Primitive neuroectodermal tumors of the central nervous system. Patterns of expression of neuroendocrine markers, and all classes of intermediate filament proteins. Lab Invest 62:498-509, 1990.

6.   Mannoji H, Takeshita I, Fukui M, Ohta M, Kitamura K. Glial fibrillary acidic protein in medulloblastoma. Acta Neuropathol 55:63-9, 1981.

7.   Dolman CL. Melanotic medulloblastoma. A case report with immunohistochemical and ultrastructural examination. Acta Neuropathol 76:528-31, 1988.

8.   Kalimo H, Paljarvi L, Ekfors T, Pelliniemi LJ. Pigmented primitive neuroectodermal tumor with multipotential differentiation in cerebellum (pigmented medullomyoblastoma). A case with light and electron-microscopic, and immunohistochemical analysis. Pediatr Neurosci 13:188-95, 1987.

9.   Anwer UE, Smith TW, DeGirolami U, Wilkinson HA. Medulloblastoma with cartilaginous differentiation. Arch Pathol Lab Med 113:84-8, 1989.

10.   Smith TW, Davidson RI. Medullomyoblastoma. A histologic, immunohistochemical, and ultrastructural study. Cancer 54:323-32, 1984.

11.   Soylemezoglu F, Soffer D, Onol B, Schwechheimer K, Kleihues P. Lipomatous medulloblastoma in adults. Am J Surg Pathol 20(4):413-418, 1996.

12.   Rorke LB, Packer RJ, Biegel JA. Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood:definition of an entity. J Neurosurg 85:56-65, 1996.

13.   Budka H, Chimelli L. Lipomatous medulloblastoma in adults: a new tumor type with possible favorable prognosis (Letter). Hum Pathol 25:730-1, 1994.

14.   Chimelli L, Hahn MD, Budka H. lipomatous differentiation in a medulloblastomas. Coffin CM,Mukai Kiyoshi, Dehner LP. Glial differentiation in a medulloblastoma. Acta Neuropathol 81:471-3, 1991.

15.   Davis DG, Wilson D, Schmitz M, Markesbery WR. Lipidized medulloblastoma in adults.Hum Pathol 24:990-5, 1993.

16.   Ellison DW, Zygmunt SC, Weller RO. Neurocytoma/lipoma (neurolipocytoma) of the cerebellum. Neuropathol Appl Neurobiol 19:95-8, 1983.

17.   Giangaspero F, Cenacchi G, Roncaroli F, Rigobello L, Manetto V, Gambacorta M, Allegranza A. Medullocytoma (Lipidized Medullobastoma). A cerebellar neoplasm of adults with favorable prognosis. Am J Surg Pathol 20(6):656-664, 1996.

18.   Walter A, Dingemans KP, Weinstein HC. Cerebellar astrocytoma with extensive lipidization mimiking adipose tissue. Acta Neuropathol 88:485-9, 1994.

19. Agranovich Al, Ang LC, Griebel RW, et al. Malignant rhabdoid tumor of the central nervous system with subarachnoid dissemination. Surg Neurol 37:410-414, 1991.

20. Biggs PJ, Garen PD, Powers JM, et al. Malignant rhaboid tumor of the central nervous system. Hum Pathol 18:332-337, 1987.

21. Bonnin JM, Rubinstein LJ, Palmer NF, et al. The association of embroyonal tumors originating in the kidney and in the brain. A report of seven cases. Cancer 54:2137-2146, 1984.

22. Briner J, Bannawart F, Kleihues P, et al. Malignant small cell tumor of the brain with intermediate filaments- a case of primary cerebral rhabdoid tumor. Pediatr Pathol 3:117-118, 1985 (Abstract).

23. Chou SM, Anderson JS. Primary CNS malignant rhabdoid tumor (MRT): report of two cases and review of literature. Clin Neuropathol 10:1-10, 1993.

24. Cossu A, Massarelli G, Manctto V, et al. Rhabdoid tumours of the central nervous system. Report of three cases with immunocytochemical and ultrastructural findings. Virchows Arch A Pathol Anat Histopathol 422:81-85, 1993.

25. Ho PSP, Lee WH, Chen CY, et al. Primary malignant rhabdoid tumor of the brain: CT characteristics. J Comput Assist Tomogr 14:461-463, 1990.

26. Jakate SM, Marsden HB, Ingram L. Primary rhabdoid tumour of the brain. Virchows Arch Pathol Anat Histopathol 412:393-397, 1988.

27. Kapur S, Patterson K, Chandra R. Primary rhabdoid tumor of the cerebellum. Pediatr Pathol 5:101, 1986 (Abstract).

28. Kepes JJ, Moral LA. Malignant rhabdoid tumors (MRT-S) of the central nervous system (CNS) and their morphological features seen in other CNS neoplasms. J Neuropathol Exp Neurol 50:362, 1991 (Abstract).

29. Oka H, Scheithauer BW. Clinicopathological characteristics of atypical teratoid/rhabdoid tumor. Neurol Med Chir (Tokyo) 39(7):510-7, 1999.

30. Goh CH, Lu YY, Lau BL, Oy J, Lee HK, Liew D, Wong A. Brain and spinal tumour. Med J Malaysia 69(6):261-7, 2014.

31. Nowak J, Seidel C, Pietsch T, Alkonyi B, Fuss TL, Friedrich C, von Hoff K, Rutkowski S, Warmuth-Metz M. Systematic comparison of MRI findings in pediatric ependymoblastoma with ependymoma and CNS primitive neuroectodermal tumor not otherwise specified. Neuro Oncol pii: nov063, 2015.
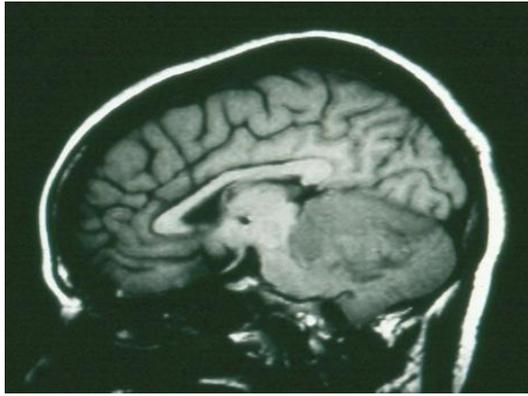
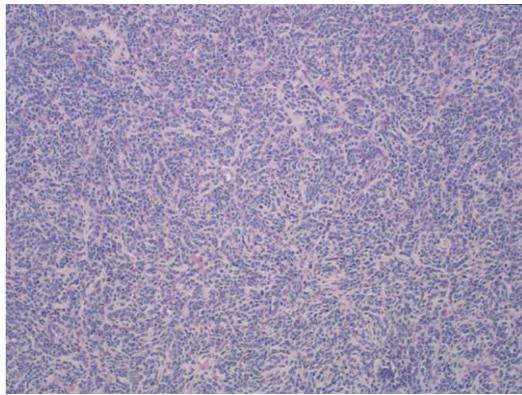Figure 1. "Typical" medulloblastoma MRI.

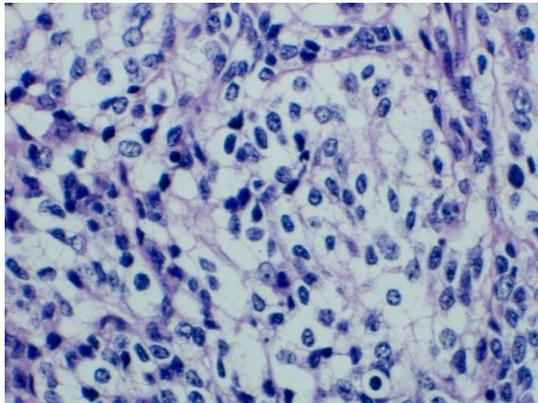Figure 2. "Typical" medulloblastoma. Histology.

Figure 3. Medullocytoma (lipidized medulloblastoma). Histology.

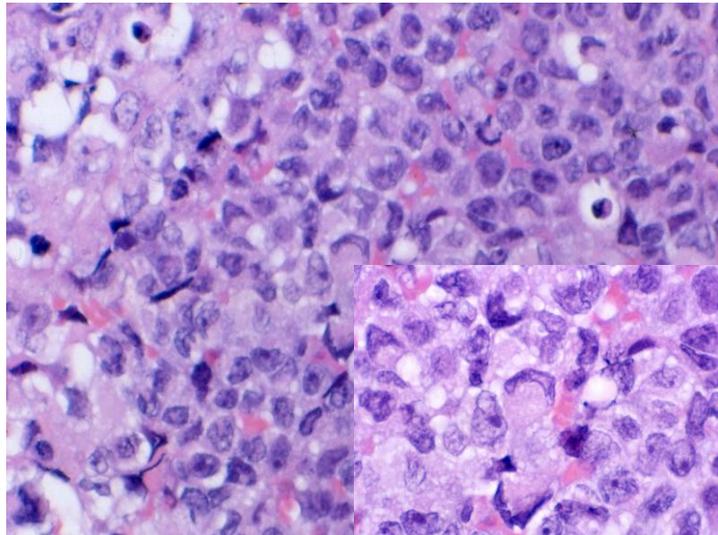Figure 4. Atypical teratoid/rhabdoid tumors (ATT/RT). MRI.

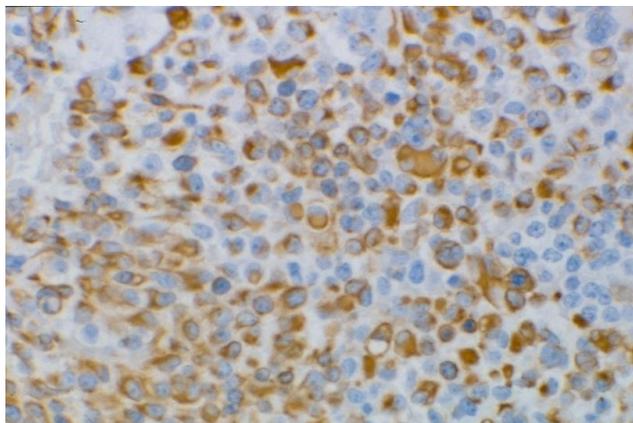Figure 5. Atypical teratoid/rhabdoid tumors (ATT/RT). Histology.

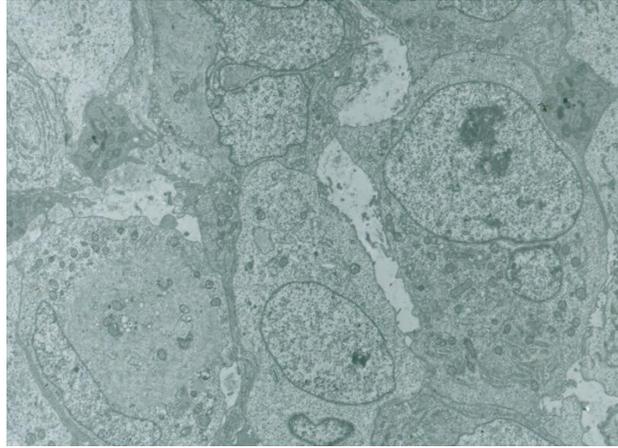Figure 6. Atypical teratoid/rhabdoid tumors (ATT/RT). EMA Immunohistochemistry.

Figure 7. Atypical teratoid/rhabdoid tumors (ATT/RT). Electron microscopy.