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COMMENTARY

Genetic profiling of CNS tumors extends histological classification

Werner Paulus · Paul Kleihues

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This issue of *Acta Neuropathologica* includes two papers, both from Heidelberg, which provide insight into the genetics and classification of two enigmatic brain tumors.

Embryonal tumor with multilayered rosettes

Embryonal tumor with abundant neuropil and true rosettes (ETANTR) was first described by Eberhart et al. [2], but is not listed as distinct tumor entity in the 2007 WHO classification [6]. ETANTR is a malignant embryonal tumor typically manifesting in supratentorial location within the first 3 years of life. Histologically, it represents a primitive neuroectodermal tumor (PNET) with "ependymoblastic" rosettes, i.e. multilayered arrangements of mitotically active tumor cells around a central lumen. Additional features are neuropil-like areas and occasional neurocytes and ganglion cells [3].

Ependymoblastoma has a long and varied history since its initial description by Bailey and Cushing in 1926 and is categorized under CNS PNET in the current WHO classification [6]. Like other rare and poorly defined entities, ependymoblastoma has been in danger of being eliminated from classifications, the most common argument being that ependymoblastic rosettes are not specific and may occur in several other embryonal CNS tumors, including atypical teratoid/rhabdoid tumor, medulloblastoma and supratentorial PNET, rather than defining a tumor entity. Recently, Judkins and Ellison [4] have proposed that the diagnosis of ependymoblastoma be retired, "once and for all", from the lexicon of neuropathology. However, the plea to abolish this tumor type is not supported by findings of Korshunov et al. [5] in this issue of Acta Neuropathologica. In a large series of 21 ependymoblastomas and 20 ETANTRs obtained from eight centers, the authors identified by FISH analysis in 95% of ETANTRs and 90% of ependymoblastomas a unique focal amplification at 19q13.42. This presumably leads to an upregulation of the miRNA clusters MIR-371-373 and C19MC [8]. This genetic aberration was not detected in a large series of other pediatric brain tumors, including medulloblastoma, supratentorial PNET, ependymoma and atypical teratoid/rhabdoid tumor. The findings of Korshunov et al. [5] carry important implications since they clearly demonstrate that ependymoblastoma and ETANTR have a common genetic signature which in turn suggests an origin from a common precursor cell population. These embryonal neoplasms may constitute polar ends of a single tumor entity. This is also supported by several cases of ETANTR recurring as ependymoblastoma, i.e. without mature neuropil. Since multilayered rosettes are the most prominent histological feature in both subtypes, we suggest the term "Embryonal tumor with multilayered rosettes (ETMR)", a new entity for which amplification at 19q13.42 represents a specific and sensitive marker.

Gliomatosis cerebri

This lesion is defined as malignant glial tumor which diffusely infiltrates the brain, involving three or more lobes, leading to enlargement of anatomic structures without discernible point of origin. It is frequently bilateral

W. Paulus (✉)
Institute of Neuropathology, University Hospital Münster,
Domagkstr. 19, 48129 Münster, Germany
e-mail: werner.paulus@uni-muenster.de

P. Kleihues
Department of Pathology, University Hospital,
Zurich, Switzerland

and often extends to infratentorial structures, even to the spinal cord. Gliomatosis cerebri (GC) is considered of astrocytic origin, although GFAP expression may be scant or absent. Previously categorized as tumor of uncertain origin, the 2007 WHO classification [6] has assigned GC to the group of astrocytic neoplasms. Similar to ependymoblastoma, GC has been an endangered species, as it can be argued that GC simply reflects diffuse astrocytoma with extensive invasion. In another paper published in this issue, Seiz et al. [9] have genetically analyzed 35 cases of GC. Their most important finding is the absence of *IDH1* and *TP53* mutations in GC as defined above, suggesting that prototypical GC is biologically different from diffuse astrocytomas, thus providing a genetic basis for the classification of GC as separate tumor entity. The report also underscores the remarkable lineage specificity of *IDH1*/*IDH2* mutations. While present at high frequency in diffuse astrocytomas, anaplastic astrocytomas and secondary glioblastomas derived thereof, they are absent in primary glioblastomas. The few reported cases of primary GBM with *IDH1* mutation are probably misclassified [7]. Similarly, *IDH1* mutations are uncommon in pediatric malignant gliomas [1], supporting the view that these develop through molecular pathways and from precursor cells different from those in adult cases. Seiz et al. [1] found *IDH1* (42%) and *TP53* mutations (10%) in cases histologically diagnosed as GC, but with a discernible, solid tumor mass, suggesting that these tumors, also referred to as type 2 GC, constitute a mixed collection of neoplasms, probably including cases that developed through progression from classical GC.

While the genetic findings of Korshunov et al. and Seiz et al. are highly relevant for the classification of brain tumors, they may also be useful for the diagnosis of individual cases. In addition, they may become important as predictive factors and novel targets for cancer therapy.

References

1. Antonelli M, Buttarelli FR, Arcella A et al (2010) Prognostic significance of histological grading, p53 status, YKL-40 expression, and IDH1 mutations in pediatric high-grade gliomas. J Neuro Oncol (in press). doi:10.1007/s11060-010-0129-5
2. Eberhart CG, Brat DJ, Cohen KJ, Burger PC (2000) Pediatric neuroblastic brain tumors containing abundant neuropil and true rosettes. Pediatr Dev Pathol 3:346–352
3. Gessi M, Giangaspero F, Lauriola L et al (2009) Embryonal tumors with abundant neuropil and true rosettes: a distinctive CNS primitive neuroectodermal tumor. Am J Surg Pathol 33:211–217
4. Judkins AR, Ellison DW (2010) Ependymoblastoma: dear, damned, distracting diagnosis, farewell!. Brain Pathol 20:133–139
5. Korshunov A, Remke M, Gessi M et al (2010) Focal genomic amplification at 19q13.42 comprises a powerful diagnostic marker for embryonal tumors with ependymoblastic rosettes. Acta Neuropathol (this issue). doi:10.1007/s00401-010-0688-8
6. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (2007) WHO classification of tumours of the central nervous system, 4th edn. International Agency for Research on Cancer, Lyon
7. Nobusawa S, Watanabe T, Kleihues P, Ohgaki H (2009) IDH1 mutations as molecular signature and predictive factor of secondary glioblastomas. Clin Cancer Res 15:6002–6007
8. Pfister S, Remke M, Castoldi M et al (2009) Novel genomic amplification targeting the microRNA cluster at 19q13.42 in a pediatric embryonal tumor with abundant neuropil and true rosettes. Acta Neuropathol 117:457–464
9. Seiz M, Tuettenberg J, Meyer J et al (2010) Detection of IDH1 mutations in gliomatosis cerebri, but only in tumors with additional solid component: evidence for molecular subtypes. Acta Neuropathol (this issue). doi:10.1007/s00401-010-0701-2