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Emerging Tumor Entities and Variants of CNS Neoplasms

GIOVANNA CENACCHI, MD, AND FELICE GIANGASPERO, MD

Abstract. Since the appearance in 2000 of the World Health Organization (WHO) classification for central nervous system (CNS) neoplasms, numerous descriptions of new entities or variants have appeared in the literature. In the group of neuronal and mixed glioneuronal neoplasms are lesions with distinctive morphological features that are still not included in a precise classification, including extraventricular neurocytoma, papillary glioneuronal tumor, rosette-forming glioneuronal of the fourth ventricle, glioneuronal with neuropil-like rosette, and DNT-like tumor of the septum pellucidum. The glioneuronal tumor with neuropil-like rosette and oligodendroglioma with neurocytic differentiation represent morphological variants of genetically proven diffuse gliomas. The lipoastrocytoma and the pilomixoid astrocytoma enlarge the group of astrocytic lesions. Rare, low-grade gliomas of the spinal cord with extensive leptomeningeal dissemination associated with unusual neuroimaging are described. The chordoid glioma of the third ventricle and the papillary tumor of the pineal region seem to be correlated by a common histogenesis from the specialized ependyma of the subcommissural organ. An embryonal tumor with neuropil and true rosettes combining features of neuroblastoma and ependymoblastoma is discussed. These new, recently described lesions indicate that the complex morphologic spectrum of CNS tumors is far from being completely delineated.

Key Words: Low-grade spinal cord tumor with leptomeningeal dissemination; Neuroglial neoplasm; Papillary neuroglial neoplasm; Papillary tumor of the pineal region; Rosette-forming neuroglial tumor.

INTRODUCTION

Traditionally, the identification of new entities among the neoplasms of central nervous system (CNS) has been based on the presence of relatively homogenous histopathological features associated with similar immunophenotypical and ultrastructural features. The 2000 World Health Organization (WHO) classification has, for the first time, included the most common molecular genetic variables associated with specific clinico-pathological entities (1, 2). Such molecular data has the advantage of overcoming histological variability, and in this way plays a major role in distinguishing between entities and variants. Such distinction is a crucial point for a modern tumor classification, which must represent a common tool for clinicians, scientists, and pathologists. Clinicians and scientists need to have clearly distinct groups of tumor entities for clinical or laboratory purposes. Pathologists, on the other hand, must have the complete spectrum of morphological variants occurring in a given entity for their diagnostic work. Meningiomas are an example of lesions that are lumped together based on molecular genetic findings but have a large spectrum of histological variations: all meningioma variants, with variable frequency, share loss of chromosome 22 or NF2 mutation. Conversely, lesions with similar histological appearance, such as the ''small blue cell'' embryonal tumors, show important different molecular markers that have been fundamental in splitting them into distinct clinico-pathological entities, including loss of chromosome 17p and alterations of SHH or Wnt pathways for the cerebellar medulloblastomas, mutations or loss of INI1 gene for the atypical teratoid/rhabdoid tumor (ATRT), and the more random genetic alterations for the supratentorial PNET. The term ''variant,'' however, does not always imply mere morphological variations within a specific entity; not infrequently, such variations carry with them information on biological behavior in term of less or more aggressiveness. These considerations imply that both entities and variants need to be carefully described and enlisted in a given classification.

New classifications based on gene expression microarrays have appeared on the horizon of the neuro-oncology (3, 4). However, fortunately for the diagnostic neuropathologist, it seems that such new molecular approaches to classification of CNS neoplasms adds crucial information mainly within a histological homogenous group of neoplasms. These considerations can be elicited from a well-quoted recent study on microarray gene expression in pediatric brain tumors (3). This study has shown that microarrays can distinguish between different groups of histologically different pediatric CNS neoplasms such as medulloblastomas, atypical teratoid rhabdoid tumors, and glioblastoma. These data, without minimizing the importance of scientific results, further emphasize that histological analysis is still a quick and relatively inexpensive ''gigantic microarray'' made by the eyes and brains of trained neuropathologists. However, the same study has also clearly demonstrated that within a histologically homogenous group of neoplasms such as medulloblastomas, gene expression analysis can subdivide patients for prognostic categories and stratify them for advanced therapeutic trials. Similarly, a more recent study (4) has shown

From Department of Radiology and Pathology (GC), University of Bologna, Bologna, Italy; Department of Experimental Medicine and Pathology (FG), IRCCS Neuromed, Pozzilli, University of Rome ''La Sapienza,'' Rome, Italy.

Correspondence to: Felice Giangaspero, MD, Neuropatologia c/o Neurochirurgia, Policlinico Umberto I, Viale del Policlinico 155, 00161 Rome, Italy. E-mail: f.giangaspero@libero.it

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New Entities and Variants

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Papillary tumor of the pineal region*
Embryonal Tumors
Embryonal tumor with abundant neuropil and rosettes

* This tumor together with the chordoid glioma of the third ventricle may be histogenetically related to the specialized ependyma of subcommissural organ.

that microarray analysis can overcome the well-known subjectivity of the histological diagnosis of nonclassical high-grade glial tumors (i.e. glioblastoma vs anaplastic oligodendroglioma), providing a more accurate predictor of prognosis in these nonclassical lesions than does pathological classification.

This review, far from being exhaustive, presents an account of what might be taken into consideration for inclusion in the next edition of WHO classification (Table) based on the recent literature and authors' personal experience with new entities or variants. Moreover, emerging issues underlying some tumor categories or single tumor variants will be discussed.

NEURONAL AND MIXED NEURONAL-GLIAL TUMORS

The WHO classification recognizes the potential for differentiating along both glial and neuronal lines only for embryonal neoplasms (medulloblastoma, supratentorial PNET, ATRT, etc.), while it reserves exclusively for select entities the designation of mixed glioneuronal tumors—which constitute a group characterized by low frequency, favorable prognosis, a variable extent of neuronal differentiation, and less consistently, glial differentiation. However, the issue is complicated by the fact that such neuronal differentiating capacity has also been demonstrated for neoplasms currently classified as purely glial, i.e. subependymal giant cell astrocytoma (5) and pleomorphic xanthoastrocytoma (PXA) (6). Moreover, malignant gliomas with features of neuronal differentiation detected by electron microscopy or immunohistochemistry have been also occasionally reported (7, 8).

In the last few years there have been reports of neuronal and mixed glioneuronal neoplasms of distinctive morphological appearance that are still not included in a precise classification niche. Most of these lesions are low grade, and their recognition and taxonomic placement are imperative in order to avoid misidentification as ''ordinary'' gliomas and prevent useless aggressive treatment.

Extraventricular Neurocytomas

Extraventricular neurocytomas (EVNs) are mentioned but not formally listed in the 2000 WHO classification of tumors of the nervous system. Nonetheless, reports of such lesions are increasing and recent studies have better delineated the clinico-pathological features of such lesions (9, 10).

Extraventricular neurocytic neoplasms that arise within central nervous system parenchyma share histological features with the more common central neurocytoma, but exhibit a wider morphological spectrum. Neurocytes most often demonstrate finely granular, slightly eosinophilic cytoplasm. Less often than in the intraventricular counterpart they exhibit cytoplasmic clearing, which in combination with round nuclei suggests a diagnosis of oligodendroglioma. They more often display astrocytic, typically pilocytic features and/or ganglionic differentiation. Focal glial fibrillary acidic protein (GFAP) reactivity is present in tumor cells with neurocytic features in almost half of the cases (10). More than 50% of EVNs exhibit ganglion cell differentiation either focally or diffusely. Moreover, they represent a spectrum with regard to cellularity and proliferation rates. Some are clearly well differentiated, whereas others show one or more of the ''atypical'' histological features associated with aggressive behavior, such as vascular proliferation, necrosis, and increased mitotic activity. With regard to biological behavior, like central neurocytoma, most EVNs are well differentiated and do not recur, especially after complete resection. However, one third of EVNs recur within a relatively short period of follow-up. Subtotal resection, high proliferation rates, atypical histological features, and older patient age appear to be associated with an increased likelihood of recurrence (10).

Papillary Glioneuronal Tumor

This uncommon lesion is uniquely characterized by pseudo-papillary structures of hyalinized blood vessels surrounded by astrocytic cells (Fig. 1b, c). In the intervening regions between the pseudo-papillae are sheets of synaptophysin-positive neuronal cells that range in differentiation from cells that resemble neurocytes to mature ganglionic cells (11–15). These tumors occur in patients of various ages and there is no gender predilection. Occurrence in young children as well as in elderly persons

has been observed (13, 14). The tumors present radiographically as contrast-enhancing cystic masses of variable size, affecting the cerebral hemispheres without any specific location (11, 15) (Fig. 1a). Mitoses are absent or rare and the Ki-67 proliferative index is usually very low (12). Follow-up data indicate no evidence of recurrence in tumors totally resected grossly during intervals ranging from 6 months to 7 years (11, 13, 15).

Rosette-Forming Glioneuronal Tumor of the Fourth Ventricle

This lesion occurs in the fourth ventricle and is characterized by biphasic architecture (16, 17). One component consists of uniform neurocytes engaged in the formation of neurocytic rosettes as well as perivascular pseudorosettes in a fibrillary, partly microcystic matrix (Fig. 1d–f). The second astrocytic component resembles pilocytic astrocytoma and consists of fibrillary spindle cells with oval nuclei associated with occasional Rosenthal fibers, granular bodies, glomeruloid capillaries, and microcalcification. Ganglion cells are occasionally present. Radiologically, they are midline and occupy the ventricular system. Multicentric lesions characterized by multiple lesions in the cerebellar vermis, pons, midbrain, and thalamus can be observed (16, 17). The mean age at diagnosis in the original report was 31.5 years with a range of 12 to 59 years (16). The lack of atypia and the low Ki67 labeling indices reflect the indolent postoperative course of these unique tumors. Nonetheless, their location and frequent extension within the adjacent structures does not always permit a total resection without neurological dysfunction. Such lesions, which have been originally reported under the designation of dysembryoplastic neuroepithelial tumor (DNT) of the cerebellum (18), are not to be confused with the more aggressive ''rosetted glioneuronal tumor'' (see below).

DNT-Like Tumor of the Septum Pellucidum and Caudate Nucleus Area

The DNT is now a well-known, seizure-producing entity that occurs characteristically in the cerebral cortex of children and young adults. The histological features include multinodular architecture, heterogeneous cellular composition, and frequent association with cortical dysplasia. DNT are stable or very slow growing and require no postoperative adjuvant therapy (19). The attempt to include ''a nonspecific form'' of DNT as pathological entity (i.e. a heterogeneous group of histologically benign and even malignant lesions defined more on their clinical and radiological features than on histopathological ones) has found strong opposition (20).

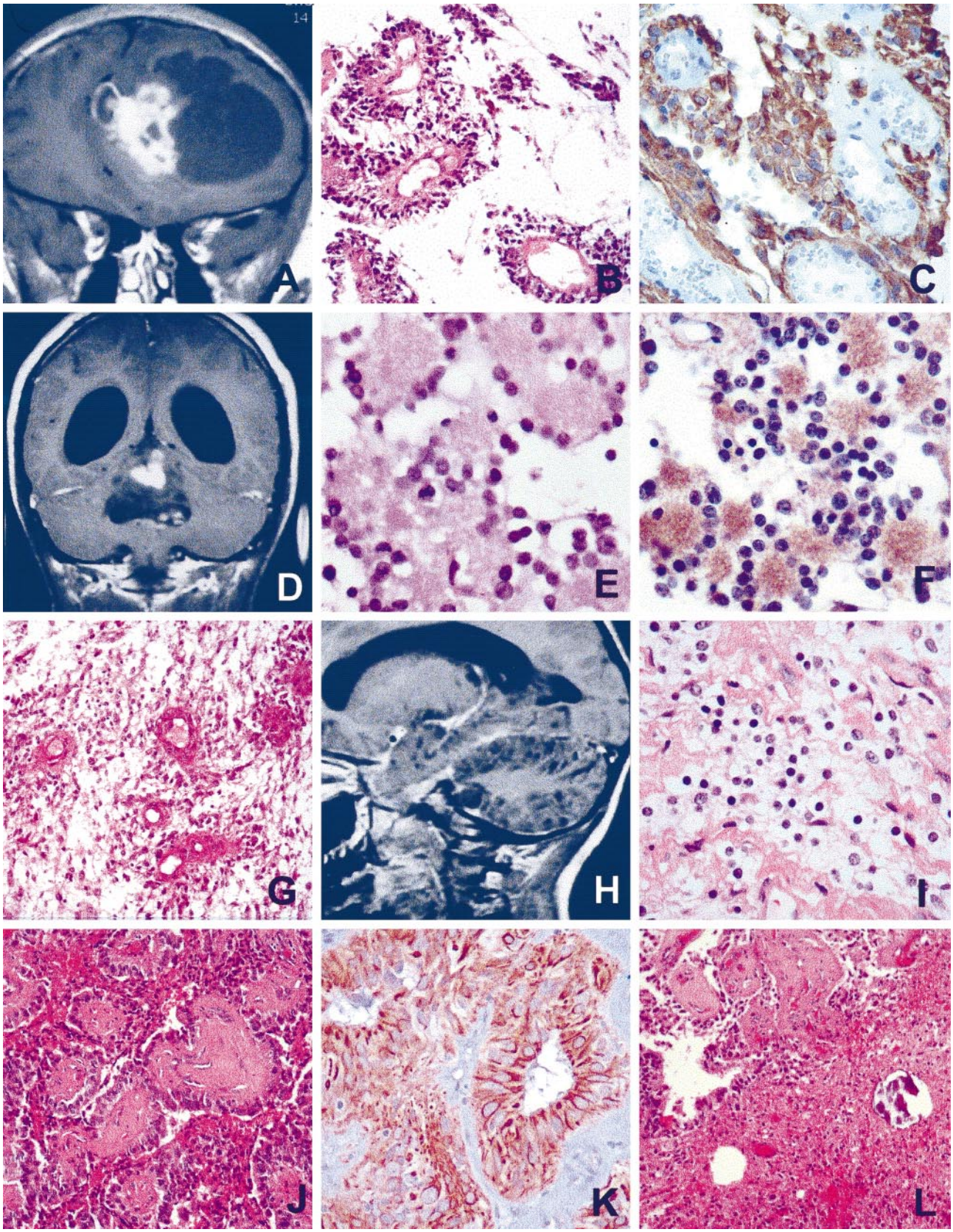
More recently, DNT-like lesions have been reported to occur in extracortical locations (21). The better-characterized location of such DNT-like lesions is the caudate nucleus/septum pellucidum area (22, 23). As a consequence of this location, the presenting symptoms are those of increased intracranial pressure, in contrast to the seizures observed in the classic intra-cortical counterpart. Radiographically, the tumors extend into the lateral ventricle from the septal region and obstructed the foramen of Monro causing varying degrees of hydrocephalus. The lesions are lobular, well-delineated, hypointense on T1-weighted MRI and hyperintense on T2 images and nonenhancing. The histological features include a mucin-rich background, oligodendrocyte-like cells, ''floating neurons,'' and specific glioneuronal elements. Distinction from more aggressive neoplasms such as oligodendrogliomas or well-differentiated, diffuse astrocytomas is mandatory because these tumors appear to behave in the benign fashion similar to that of cortical DNTs (23).

Glioneuronal Tumor with Neuropil-Like Islands and Oligodendroglioma with Neurocytic Differentiation

Glioneuronal tumor with neuropil-like islands (GTNI) represent a distinctive glioneuronal neoplasm affecting the cerebral hemispheres of adult patients composed mainly of fibrillary, gemistocytic, or protoplasmatic astroglial elements of WHO grade II to III. These tumors display sharply delimited, neuropil-like islands of intense synaptophysin reactivity populated and rimmed in rosette fashion by cells demonstrating strong immunolabeling for the neuronal antigens (24). These cells include small neurocytic elements as well as larger, more pleomorphic forms. In addition, well-differentiated neurons of medium size to large ganglion cells can be present. Both the astrocytic component and the diagnostic neuronal islands may exhibit marked proliferative activity, suggesting capability of malignant progression of both components (25, 26).

The biological behavior is similar to that of standard diffuse astrocytoma with tumor progression or recurrence, occurring in most of patients with a follow-up of more than 2 years (24, 25). This tumor appears not to be confined to the cerebrum. A rosetted glioneuronal tumor has been described in the spinal cord of a 44-year-old woman. The tumor recurred 1 year after surgery and showed meningeal dissemination involving the lumbar dura and the cauda equina (27). These tumors are largely astroglial in appearance and their resemblance to diffuse astrocytomas is emphasized by the discovery, by comparative genomic hybridization in one case, of chromosomal imbalances commonly observed in diffuse astrocytomas such as gains on 7q and losses on 9p (24).

This entity shares similarities with recently reported cases of oligodendrogliomas with neurocytic differentiation showing perivascular rosettes or large Homer Wright rosettes with strong immunoreactivity for synaptophysin (28). Three of the 4 reported cases had the molecular markers of oligodendroglioma, i.e. loss of chromosome



1p and 19q, and the patients experience the typical clinical course with multiple recurrences. Interestingly, one of the original cases of GTNI had an oligodendroglial component (24). Such divergent neurocytic differentiation does not seem to alter the biological behavior of the astrocytic and/or oligodendrocytic neoplasms.

The presence of neurocytic/neuronal differentiation in the midst of typical and also genetically proven diffuse gliomas implies that such neoplasms take origin from a glioneuronal rather than a purely glial progenitor cell capable of generating neuronal, oligodendroglial, and astrocytic components. Moreover, they share the molecular hallmarks as well as the biological behavior of diffuse astrocytoma and oligodendroglioma, respectively; therefore their appropriate placement in a future classification should be that of morphological variants rather than distinct clinico-pathological entities.

ASTROCYTIC TUMORS

Lipoastrocytoma

Lipidization is a well known, albeit infrequent feature in primary neuroepithelial neoplasms of the CNS. Lipids may accumulate within the cytoplasm as multiple droplets giving rise to a xanthomatous appearance, as exemplified by pleomorphic xanthoastrocytoma (29) and lipidized glioblastoma (30). In addition, lipidization may result in an adipocyte-like appearance of neuroepithelial tumor cells. Examples of the latter phenomenon include cerebellar neurolipocytoma (31), as well as rare instances of cerebral primitive neuroectodermal tumor (32), central neurocytoma (33), and ependymoma (34).

A recent report illustrates 2 cases of low-grade astrocytic neoplasms with diffuse lipoma-like changes (35). The neoplasms occurred in 2 young patients aged 2 and 12 years and were composed of a population of pleomorphic astrocytic cells showing cytoplasmic vacuolization due to lipidization. The patients' follow-up indicated a very favorable prognosis. Although 2 subsequent small recurrences developed in one patient, these seemed more likely related to a subtotal resection of the large tumor at the first operation than to a rapid tumor re-growth. The recurrent lesions were histologically similar to the original tumor and showed no increase in mitotic activity and Ki-67 labeling index. Molecular genetic analyses performed on one tumor did not reveal any of the molecular genetic alterations typically associated with the initiation or progression of diffusely infiltrating astrocytomas. Moreover, on electron microscopy, the neoplastic cells with adipocyte features exhibited a peri-cellular basal lamina. These neoplasms appear to represent a rare variant of low-grade astrocytoma in children, distinct from diffuse astrocytoma, pilocytic astrocytoma, and pleomorphic xanthoastrocytoma.

Pilomyxoid Astrocytoma

Pilocytic astrocytoma (PA) is a well-recognized entity usually associated with a favorable outcome even after subtotal resection. Subarachnoid extension occurs rarely with a classical PA, but does not necessarily indicate a fatal outcome. However, there are rare examples of PAs that pursue an aggressive behavior with rapid dissemination. While some of the disseminating lesions may be histologically classical PA, there could also be distinct subtypes among tumors diagnosed under this category. Tihian et al described a variant of astrocytoma in children with a monomorphous pilomyxoid pattern and suggested that it might exhibit a more aggressive behavior than a classical PA (36). These tumors exhibited some features of PA but are monomorphous and more myxoid and are associated with less favorable outcome than classical PA in the same site and age group. In contrast to the classical PA, these tumors lacked the alternating solid and loose areas interspersed with microcysts.

Typically the cells radiate from vessels producing an angiocentric pattern, vaguely resembling perivascular rosettes (Fig. 1g). This pattern was more irregular and fibrillar than the perivascular rosettes encountered in ependymomas. Rosenthal fibers are absent and granular bodies are exceptionally rare. Mitoses and even necrosis may be present. Most patients with this lesion present in the first 2 years of life. The frequent sites are those of conventional pilocytic astrocytoma, particularly the hypothalamic/chiasmatic region. Recent reports indicate the occurrence of lesions with similar histology in adult patients (37, 38). The presence, however, in some cases of pilomyxoid astrocytoma of areas resembling *bona fide*

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Fig. 1. Papillary glioneuronal neoplasm: Contrast enhancing cystic lesion (**A**); pseudo-papillae covered by cuboidal cell (**B**); strongly positive for GFAP (**C**). Rosette-forming glioneuronal tumor of the fourth ventricle: Large contrast enhancing lesion occupying the fourth ventricle (**D**); the lesion is partially composed of neurocytic rosettes (**E**) with a central core positive for synaptophysin (**F**). Pilomyxoid astrocytoma: this lesion is characterized by an angiocentric pattern with a myxoid background (**G**). Low-grade spinal tumor with extensive leptomeningeal dissemination: meningeal dissemination in such lesion is associated with microcystic changes of the brain parenchyma (in this case cerebellum and brainstem) (**H**); a meningeal biopsy shows intense infiltration by a low-grade lesion composed of small cells with oligo-like features (**I**). Papillary tumor of the pineal region: the neoplasm shows pseudo-papillae covered by epitheliomorphic cell (**J**) with intense positivity for keratin (**K**); interface between the papillary tumor and the adjacent pineal parenchyma with calcium concretions (**L**).

PA suggest a spectrum of histological components (38) and raises the difficulty of establishing minimal diagnostic criteria for pilomyxoid tumors as well as for PAs.

GLIAL TUMORS OF UNCERTAIN ORIGIN

Spinal Low-Grade Tumors with Extensive Leptomeningeal Dissemination

The leptomeningeal dissemination of low-grade gliomas is an event reported in clinical neuro-oncology practice more and more frequently. This is probably related to the more extensive use of MRI. Among low-grade neoplasms of astrocytic origin, it is well known that *bona fide* PA and fibrillary astrocytomas can disseminate. Moreover, PXA and low-grade mixed glio-neuronal tumors can occasionally disseminate (39). Recently, 3 unusual cases of spinal low-grade gliomas with diffuse leptomeningeal dissemination have been reported (40). The histological appearance of such low-grade neuroectodermal neoplasms could not be comfortably included in a specific category within the current WHO classification of CNS neoplasms.

The original spinal lesion in each of the 3 cases was a generic, low-grade neuroectodermal neoplasm. Characterization was strongly limited by the very small amount of material available for histological examination. In the postmortem examination of one case and in the cerebellar biopsy of a second case, the tumor was made up of small round nuclei with clear cytoplasm of relatively monomorphous appearance, which could be interpreted as ''oligodendroglioma.'' Two reports of similar diffuse childhood spinal ''oligodendroglioma'' appeared recently in the literature (41, 42). In one report (41), the primary spinal tumor was clinically evident in the spine, in the other, an intramedullary cervical tumor was a late MRI finding confirmed at the postmortem examination (41). The MRI findings of these cases, reported to be histologically similar, showed 2 distinct patterns. One pattern was that of diffuse thickening and abnormally enhancing subarachnoid space as reported in published cases of diffuse fibrillary astrocytomas of the spinal cord and other sites. The second pattern of leptomeningeal dissemination has the appearance of ''small cysts'' scattered all over the brain and spinal cord surface, giving the impression of a diffuse ''microcystic meningoencephalopathy'' (Fig. 1h, i). In a series of 5 disseminated low-grade gliomas with such unusual cystic appearance all cases were primary in the spinal cord or medulla (43). It is still a matter of further investigation whether this cystic appearance represents the possible degeneration of the leptomeningeal structure involved in the spread of any slow growing tumor or the specific macroscopic appearance of a still not characterized, distinct variety of low-grade glioma. So far, no cases of nonspinal or brainstem-disseminated low-grade gliomas having such an unusual MRI pattern of leptomeningeal dissemination have been reported. The issue of pediatric spinal cord low-grade tumor associated with diffuse leptomeningeal dissemination has been also addressed in an abstract by Burger et al, in which they documented the presence of scattered synaptophysin-positive cells among a large population of round small cells infiltrating fibrotic meninges in 3 of 4 cases studied (44).

Specialized Ependyma of the Subcommissural Organ-Related Tumors: Chordoid Glioma of the Third Ventricle and Papillary Tumor of the Pineal Region

The chordoid glioma of the third ventricle is a rare, morphologically distinctive and clinically benign tumor allocated in the 2000 WHO classification under the category of neuroepithelial tumors of uncertain histogenesis together with astroblastoma and gliomatosis cerebri. On the basis of ultrastructural similarities combined with the stereotyped and striking location of the lesion, it has been proposed that such neoplasms may originate from the specialized ependymal cells of the subcommissural organ (45–47). The subcommissural organ is a small structure found in the dorsocaudal region of the third ventricle throughout the vertebrate phylum and composed of 2 cell types: modified ependymal cells with a secretory function and releasing glycoproteins, and hypendymal cells, also neuroepithelial in nature. A similar histogenesis has also been proposed by Juovet et al for the papillary tumors of the pineal region (48). These authors have recently reported a series of 6 neoplasms all located in the pineal gland region, characterized by an epithelial-like growth pattern in which the vessels were covered by a layer of tumor cells. Immunolabeling for cytokeratin and vimentin was seen in all cases (Fig. 1j–l). True rosettes were present but lacked the features of rosettes observed in pineal gland tumors such as pinealocytoma and pineoblastoma. The immunohistochemical profile resembled that seen in choroid plexus tumors. Ultrastructurally there were features of ependymal differentiation such as microvilli and zipper-like junction. These features plus evidence of cytoplasmic zonation were reminiscent of the specialized ependyma of the subcommissural organ. All lesions occurred in adult patients ranging in age from 19 to 56. The clinical behavior was characterized by local recurrence and even spinal dissemination.

EMBRYONAL TUMORS

Embryonal Tumor with Abundant Neuropil and True Rosettes

This is a lesion that combines feature of ependymoblastoma and neuroblastoma. The lesion is characterized by heavily cellular regions and fibrillar neuropil-like areas containing mitotically active and multilayered ependymoblastoma-like rosettes (49). Other rosettes of the Flexener-Wintersteiner type can be present. The fibrillar

areas show strong synaptophysin immunoreactivity. The rosettes are GFAP-negative, but small foci of GFAP-positive glial cells may be found in the more solid areas. Eberhart et al reported 7 cases in very young children (49), and similar cases have been described as ependymoblastoma (50) and neuroblastoma (51). However, the biological behavior does not differ from other embryonal neoplasms.

Conclusions

The numerous new entities or variants appeared in the literature in the last few years suggest that the complex morphologic spectrum of CNS neoplasms is far from being completely delineated. Most of the above reported lesions, given their rarity, have been defined only on the basis of their histological, ultrastructural, and immunohistochemical phenotype. A molecular characterization of them will be an important step towards the understanding of the basic mechanisms of neuro-oncogenesis.

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