

Giant cell ependymoma of the spinal cord and fourth ventricle coexisting with syringomyelia

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Abstract

This report presents a case of widespread intramedullary giant cell ependymoma arising from the central canal of the C4 segment of the spinal cord in a 28-year-old man admitted to hospital with tetraplegia and signs of increased intracranial pressure, eight months after surgical spinal cervical decompression without tetraplegia improvement. Magnetic resonance imaging and autopsy revealed a tumour extending from segment C3/C4 of the spinal cord to the lower half of the fourth ventricle with coexisting syringomyelia. This slow-growing ependymoma of low-grade malignancy exhibited unusual morphology as well as degenerative and ischaemic changes. All intramedullary and ventricular tumour segments featured coexistence of two forms of neoplastic cell, classic ependymomal and pleomorphic multinucleated giant cells. The morphological diagnostic criteria of unusual giant-cell variant of ependymoma and tumour-related syringomyelia in adults are discussed, based on the presented case and a review of the literature.

Key words: ependymoma, giant-cell variant, brain tumour, fourth ventricle, intramedullary tumour, syringomyelia, immunohistochemistry, electron microscopy.

Introduction

The World Health Organisation (WHO), apart from four ependymoma patterns (classic or conventional, anaplastic, myxopapillary and subependymoma) and its four histopathological subtypes (cellular, papillary, clear cell and tanycytic) recognized several “other rare patterns with variable differentiation” including an exceptional rare variant termed “giant cell ependymoma” (GCE) [30]. According to the WHO grading system, the pathological spectrum of ependymoma might be very heterogenous. Heterogeneity of the neoplastic cell population within the same tumour is

also a characteristic feature of other exclusive types and variants of ependymoma [7,22].

Participation of giant multinucleated cells in ependymoma cell arrangement is regarded as a GCE hallmark. To distinguish GCE from other tumours which exhibit giant cell participation, perivascular pseudorosettes and coexisting areas of typical ependymoma and giant cells should be identified in light microscopy. In uncertain cases, electron microscopy remains a gold diagnostic standard [4,7,11]. Detailed histological, immunohistochemical and ultrastructural examination were performed to evaluate the still

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rather controversial differentiation and malignancy of GCE [1,14]. Recently reported molecular studies of spinal and intracranial ependymomas might help establish their classification [2].

To date, only a few cases of giant cell ependymoma have been reported [1,3,4,6,9,15,24,27,32]. The case presented in this paper is the first such widespread GCE co-existing with syringomyelia.

Case report

A 28-year-old man was admitted to the Neurological Department, Institute of Psychiatry and Neurology, with tetraplegia and signs of increased intracranial pressure, eight months after surgical spinal cervical decompression without tetraplegia improvement. Twenty-four months before entry, increasing neck pain emerged as the first sign of the disease. Twelve months later it was followed by progressive weakness of upper and lower extremities. On admission magnetic resonance imaging (MRI) revealed widespread fourth ventricle and intraspinal tumour (Fig. 1A) associated with syringomyelia. The patient died suddenly with signs of respiratory insufficiency.

Material and Methods

For histological and immunohistochemical (IHC) examination, samples obtained from the brain autopsy material were fixed in 4% formaldehyde buffered to pH 7.4 and embedded in paraffin. H&E, PTAH, PAS, Klüver-Barrera stainings and IHC reactions according to the labelled streptavidin-biotin complex method with DAB as chromogen were performed in 5 µm sections using antibodies to GFAP, CD68, vimentin, EMA, Ki67, PCNA, NSE, synaptophysin and cytokeratin (all antibodies from Dako).

For electron microscopic examination, fragments of tumour were taken from the paraffin block. After deparaffinizing and washing in water, the material was processed routinely for ultrastructural examination. Ultrathin sections were stained with uranyl acetate and lead citrate, and examined using an Opton 109 DPS electron microscope. For electron microscopic examinations, the samples were retrieved from the material primarily fixed in formaldehyde and embedded in paraffin; therefore, their quality is limited.

Results

The brain autopsy revealed supratentorially moderate hydrocephalus, whereas a pearl-grey tumour loosely filling the lower half of the fourth ventricle and extending intraparenchymally to segments C3-C4 of the spinal cord was found infratentorially. There were uni- and multilocular syrinx cavities along the cervical and thoracic spinal cord (from C4-C5 to Th6) below the lower part of the tumour tissue (Fig. 1B-D).

Histological and immunohistochemical findings

PTAH staining revealed that the upper part of the tumour loosely filling the lower half of the fourth ventricle was separated from both the ventricle lumen and the medulla oblongata by capsule-like glial fibrillar fascicles. Tumour cystic masses compressed the floor of the fourth ventricle, tightening foramen of Luschka regions (Fig. 2A).

Sharply demarcated cervical nodular parts divided by numerous clefts, not infiltrating the medullar parenchyma, extended intraparenchymally into the glial stem (Fig. 2B-C). Strong PTAH and GFAP-positive structure of the glial stem was revealed in segment C4 of the spinal cord below the lower part of the intramedullary tumour and above the syrinxes (Fig. 2C-D). Multifocal ischaemic necrotic fields in resorptive stage with CD68-positive macrophages surrounding thick and hyalinised vascular walls were dispersed within the glial stem (Fig. 2Dd). The widespread syrinxes, extending below the glial stem, were not connected with the central canal in their course along the cervical and thoracic spinal cord (Fig. 2E). Their walls were composed of loose or more dense glial fibres and only a few astroglial cells (Fig. 2E-F). Swelling of myelin sheets and neuron loss were found adjacent to as well as below the tumour masses and syrinx cavities. Their cell infiltration was not found.

In all intraventricular and medullary tumour specimens, perivascular pseudorosettes, mainly composed of elongated medium-size cells of ependymoma, predominated over pseudorosettes made of monster giant cells, representing the heterogeneous cell population.

Some pseudorosettes of the discohesive pattern formed papillae-like structures containing GFAP-positive and GFAP-negative neoplastic cells (Fig. 3A-B). Elongated medium-size and smaller cells with eosi-

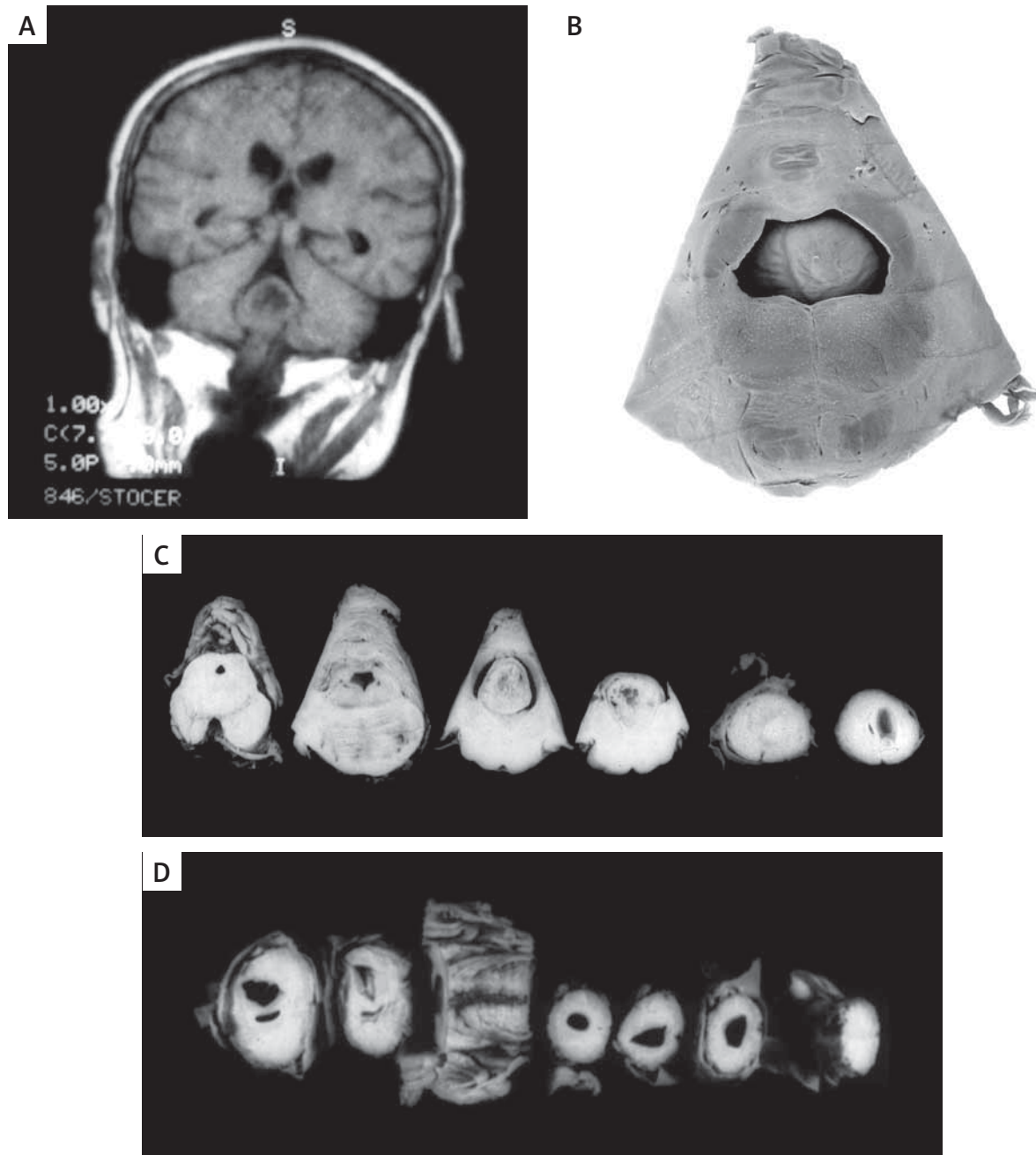


Fig. 1. A. MR image. Moderate hydrocephalus and well demarcated cystic mass enhancing fourth ventricle and cervical segment of spinal cord; B-D. Gross autopsy findings; B. Well circumscribed pearl-grey tumour filling lower half of fourth ventricle (view from the top); C-D. Ventricular and medullary segments of tumour and syrinxes

nophilic cytoplasm and round or oval-shaped nuclei radiating toward the blood vessels formed the majority of pseudorosettes (Fig. 3C).

The same elongated medium-size cells with nuclear hyperchromasia, radiating toward the lumen,

formed a lining of numerous clefts or channels (Fig. 3D) and a few ependymal true rosettes (Fig. 3E). Their formation from cells of the spinal cord central canal was revealed in the specimens of the cervical glial stem (Fig. 3F). The neoplastic cells, including giant

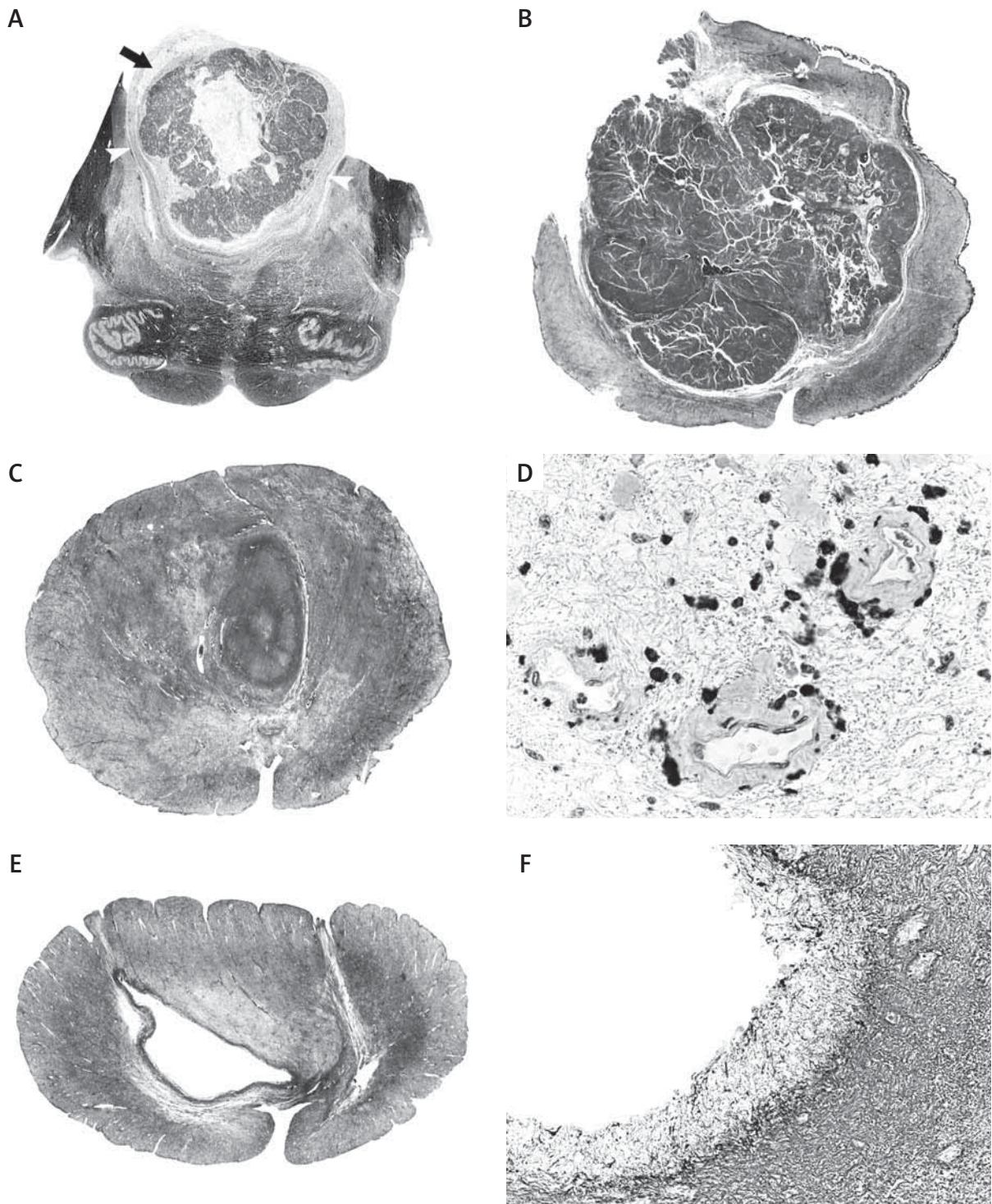


Fig. 2. Tumour specimens in PTAH staining; A. Cystic ependymoma demarcated by glial fascicles (arrow) compressing floor of fourth ventricle and tightening foramina of Luschka regions (arrowheads); B. Intra-medullary cervical tumour segment with numerous clefts; C. Strong PTAH-positive staining of glial stem revealed in cervical (C4) segment of spinal cord; D. Ischaemic necrosis, macrophages and hyalinosis of vessel walls in glial stem. CD-68 $\times 400$; E. Syringomyelia in cervical segment of spinal cord; F. Loose fascicles of glial fibres in syrinx wall. PTAH $\times 100$

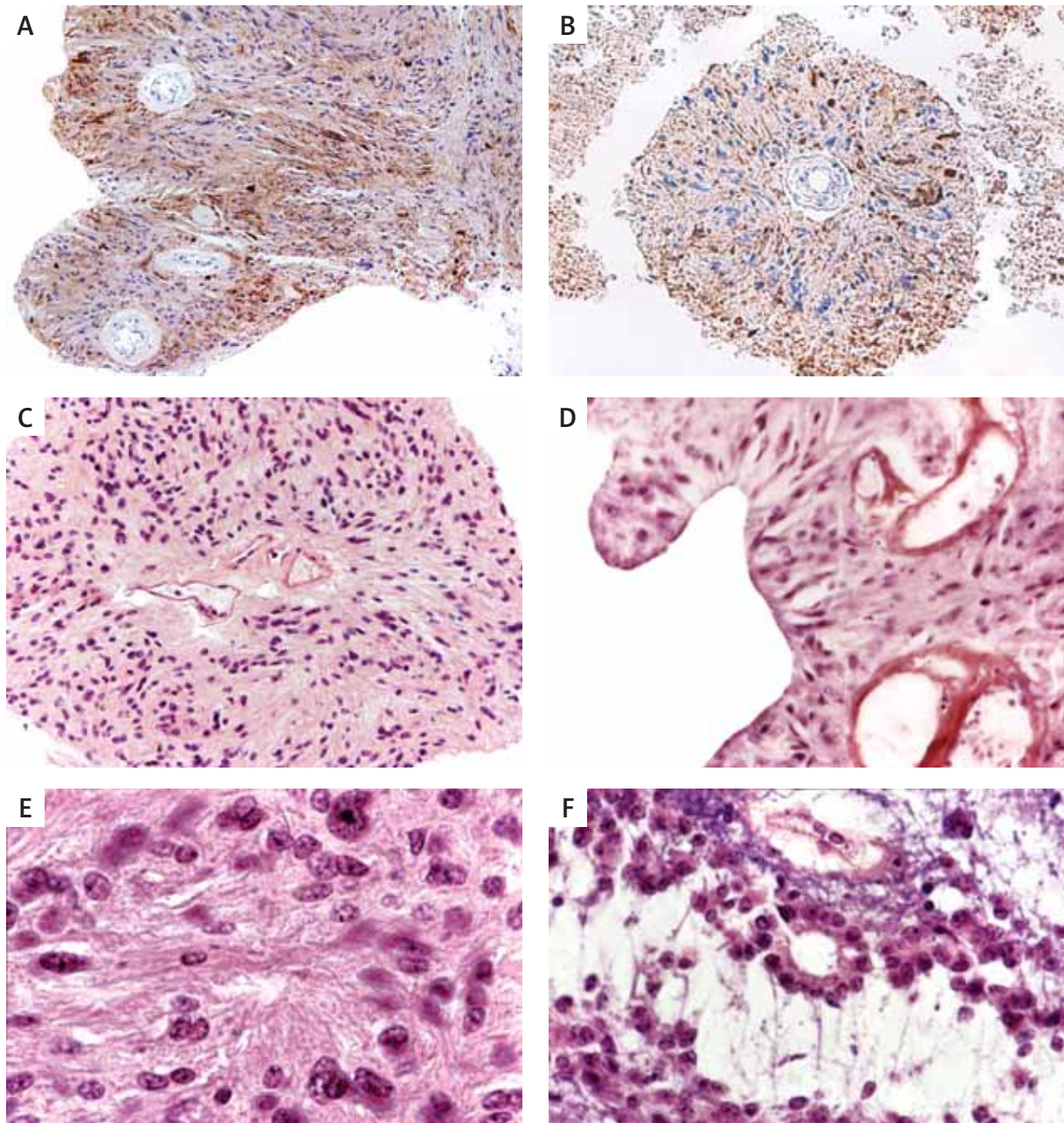


Fig. 3. Giant cell ependymoma with areas of medium-size cells of classic type ependymoma; a-c. Pseudorosettes and papillae-like structures; A. GFAP $\times 50$; B. GFAP $\times 100$; C. HE. $\times 200$; D. Elongated cells radiating toward lumen lining clefts and channels. PTAH $\times 400$; E. Ependymal “true” rosette formed by elongated cells (with few mitoses) radiating toward a lumen. PTAH $\times 1000$; F. Ependymal rosettes arising from central canal of spinal cord. PTAH $\times 1000$

cells, were cytokeratin, EMA, synaptophysin and NSE-negative.

In some pseudorosettes and cell clusters on the periphery of all nodular segments, pleomorphic round or multiform, frequently multinuclear, giant cells

with bizarre and hyperchromatic nuclei were seen (Fig. 4A-C). Their intranuclear inclusion-like bodies or “pseudoinclusions”, probably result in intranuclear cytoplasm invaginations were eosinophilic and GFAP-positive or negative similar cytoplasm-like re-

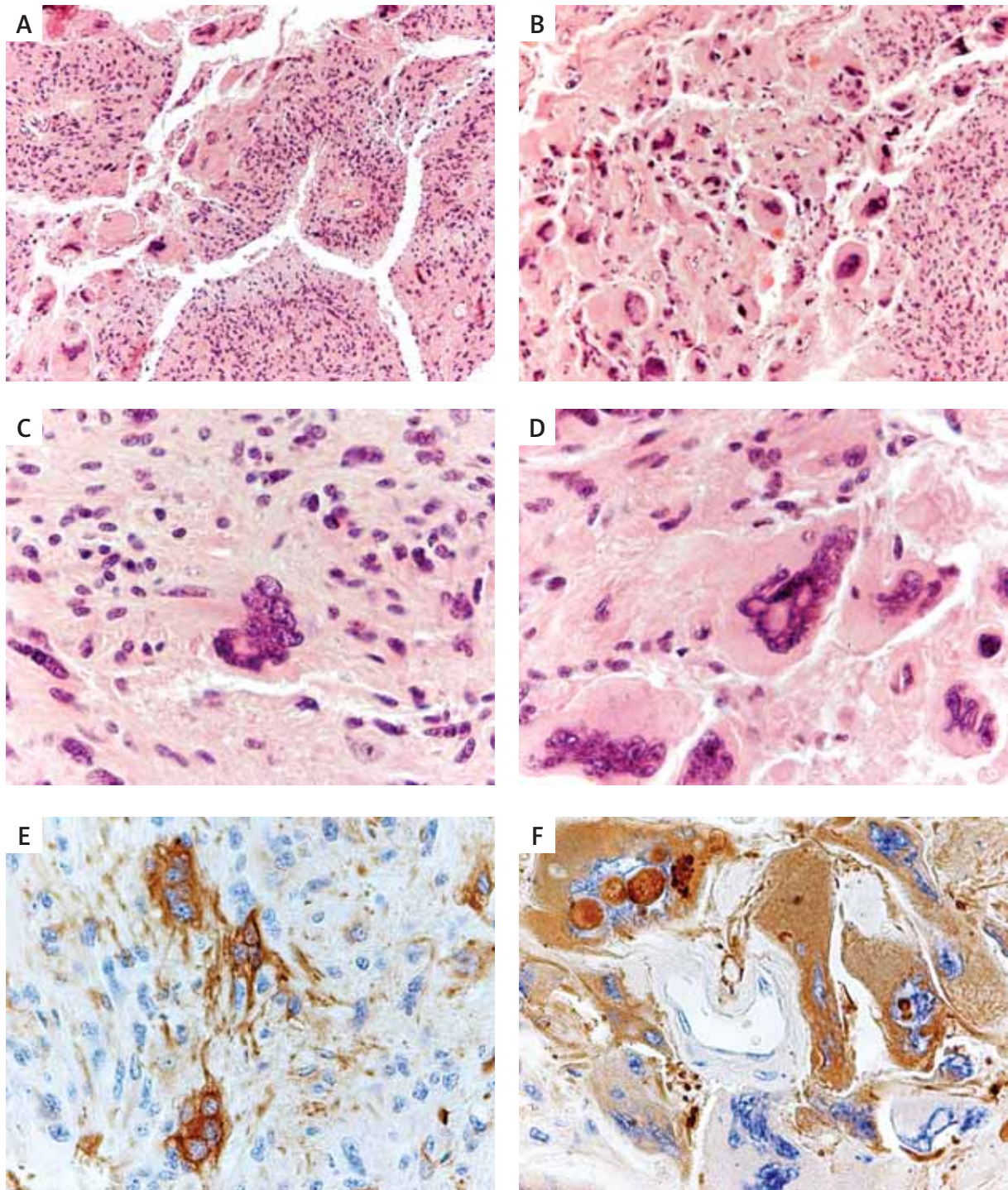


Fig. 4. Giant cell ependymoma – nuclear pleomorphism of giant cells. a-b. Clusters of round giant cells with eosinophilic cytoplasm between pseudorosettes composed of medium-size cells; A. HE. $\times 100$; B. HE. $\times 200$; C. Multinucleated giant cell in area of elongated classic ependymoma cells. HE. $\times 400$; D-F. Numerous intranuclear pseudoinclusions in bizarre giant cells; D. Giant cells with eosinophilic cytoplasm and intranuclear invaginations. HE. $\times 400$; E. GFAP-negative intranuclear pseudoinclusions in giant cells dispersed between cells of classic-type ependymoma. GFAP $\times 400$; F. Perivascular pseudorosette composed of GFAP-positive monster cells with GFAP-positive intranuclear pseudoinclusions. GFAP $\times 400$

action respectively (Fig. 4D-F). Mitotic activity and Ki67 index of all tumour segments was low in both small and giant cells. A few mitoses mainly in medium-size cells were found (Fig. 3C).

The moderate tumour vascularity contained thin-walled central vessels of pseudorosettes and of fibrillar fascicles between lobulated nodular structures. Focal necroses did not reveal pseudopalisade features. There were multifocal ischaemic necroses either in coagulative or in resorptive stages around vessels with at different times vascular thrombi or hyalinized walls in ependymoma and in the glial stem (Fig. 5A-B). Microvascular glomerular proliferation was identified only beside ependymoma tissue on the tumour periphery and in the glial stem (Fig. 5C). Fibrillar structures of the glial stem composed of elongated neoplastic cells, resembling pilocytic astrocytoma,

with Rosenthal fibres, were revealed in segment C4 of the spinal cord (Fig. 5C). Syrxinx cavities were observed along the cervical and thoracic segments of the spinal cord below ischaemic focal necroses of the glial spinal stem tissue (Fig. 2E-F).

Ultrastructural findings

Electron microscopy revealed numerous blepharoplasts (ciliary basal bodies) in ependymoma cells. These blepharoplasts showed morphological alterations. The structure of their 9 typical peripherally-placed microtubule doublets was often unrecognizable (Fig. 6A-B). Peripheral microtubules were visible only in some blepharoplasts (Fig. 6C-D). Junctional complexes between adjacent cells were long and tortuous (Fig. 7). Giant cells frequently showed bizar-

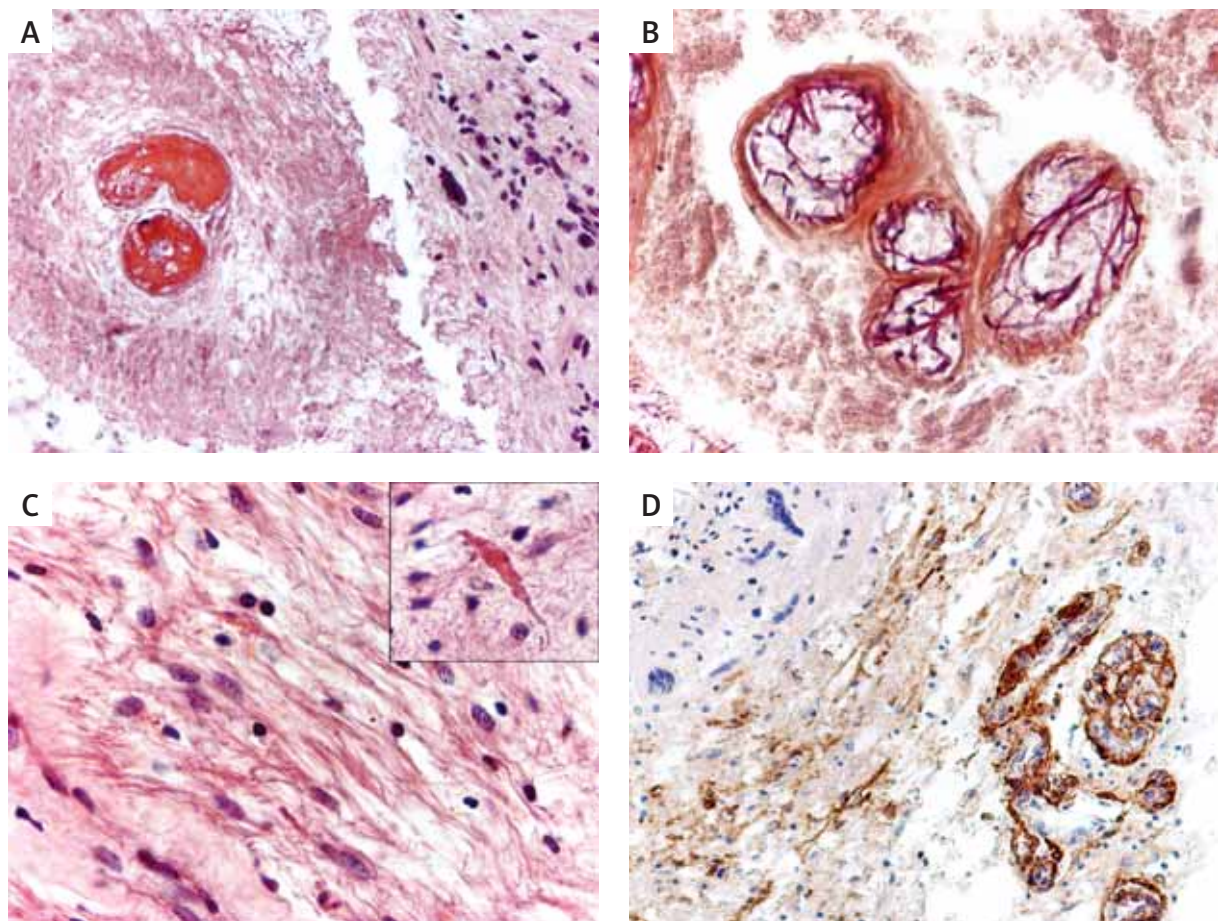


Fig. 5. A-B. Thin-walled vessels with occlusive thromboses surrounded by ischaemic necroses; A. PTAH $\times 200$, B. $\times 400$; C. Peripheral tumour tissue; glomerular blood vessels. Ki67 $\times 200$; D. Glial stem. Fibrillar structures resembling astrocytoma pilocyticum with Rosenthal fibres (insert), HE. $\times 400$

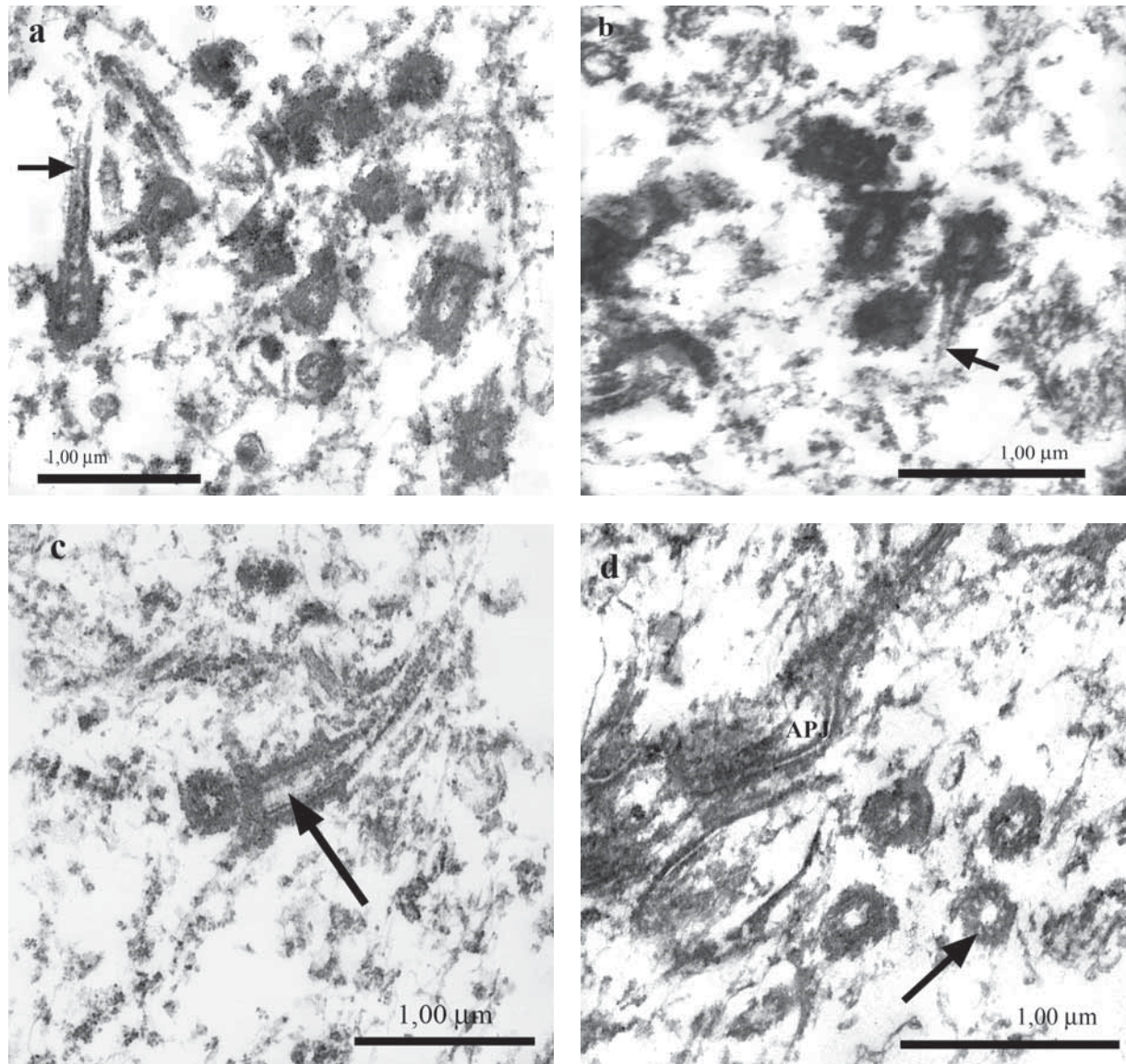


Fig. 6. A-D. Cluster of changes of blepharoplasts with distorted structure in cross and longitudinal sections into cytoplasmic tumour cell. Blepharoplasts with visible peripheral microtubules (arrows), APJ – adhesive plaque junctions

re nuclei with characteristic invaginations of the cytoplasm, which were separated from the chromatin by nuclear membrane (Fig. 8A-C). Some of the giant cells were multinucleated (Fig. 9).

Discussion

This paper presents a case of widespread intramedullary ependymoma arising from the central canal spinal cord that extended along the cervical

segments from C3/C4 to the lower half of the fourth ventricle, with coexisting syringomyelia of cervical and thoracic segments from C5 to Th6. This slow-growing, low-grade malignant tumour with degenerative cystic, vascular and ischaemic changes exhibited unusual polymorphic morphology.

All evaluated tumour segments featured the coexistence of different types of tumour cells forming arrangements characteristic of ependymoma. Clefts or channels, true ependymal rosettes and numerous

perivascular pseudorosettes composed of medium-size elongated cells evidenced the ependymal origin, forming areas of classic low-grade ependymoma (WHO grade II). Pseudorosettes of the classic type of ependymomal cells predominated over clusters of pseudorosettes composed of monster and multi-nuclear pleomorphic cells, which were located particularly on the tumour periphery. In addition, in the region between the intramedullary tumour and syrinxes, the picture mimicked pilocytic astrocytoma.

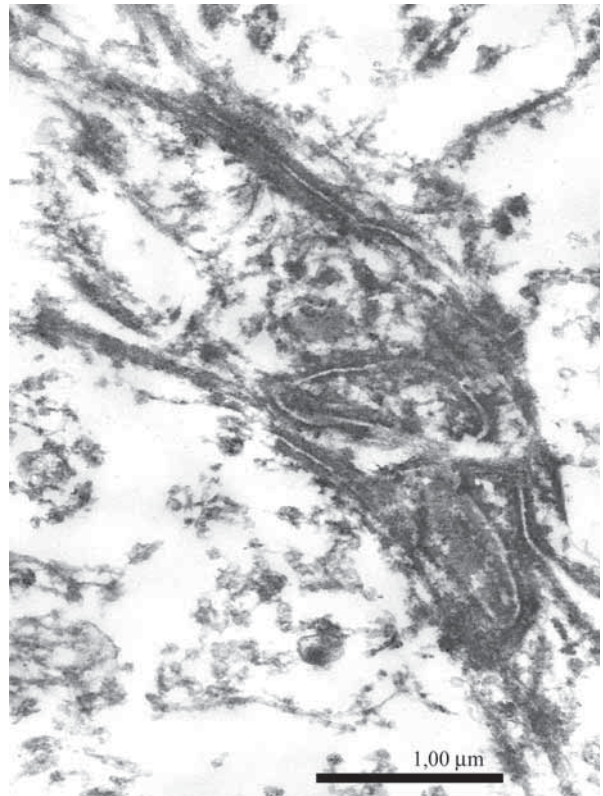
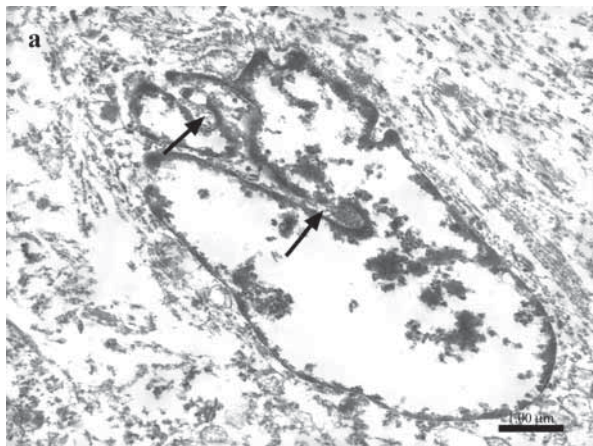


Fig. 7. Intercellular junctions (APJ) between ependymoma cells

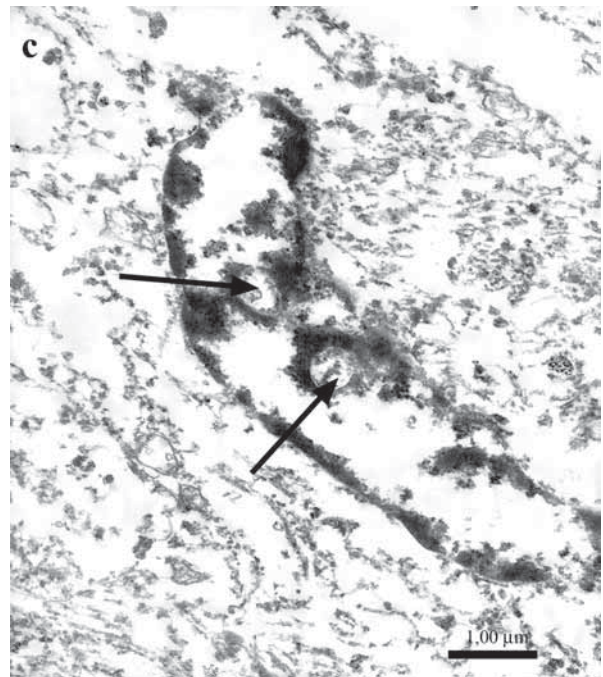
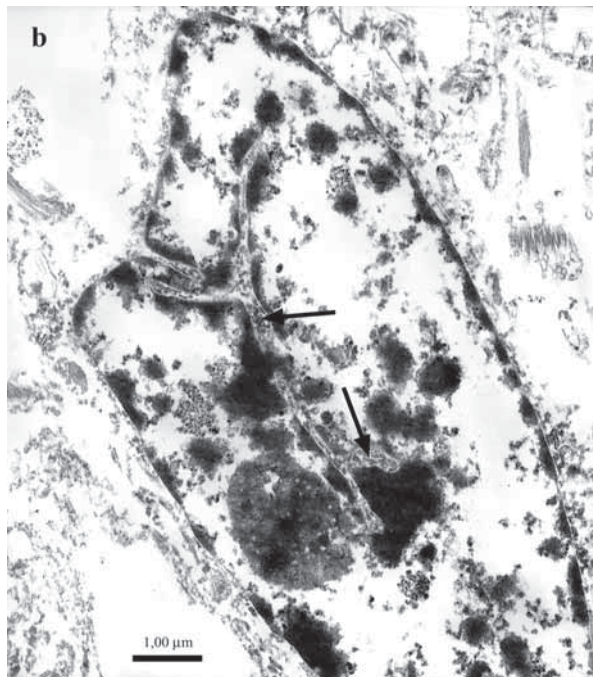


Fig. 8. A-C. Nuclei into giant cells with invaginations of cytoplasm. Note nuclear envelope (arrows) separating chromatin from invaginated cytoplasm

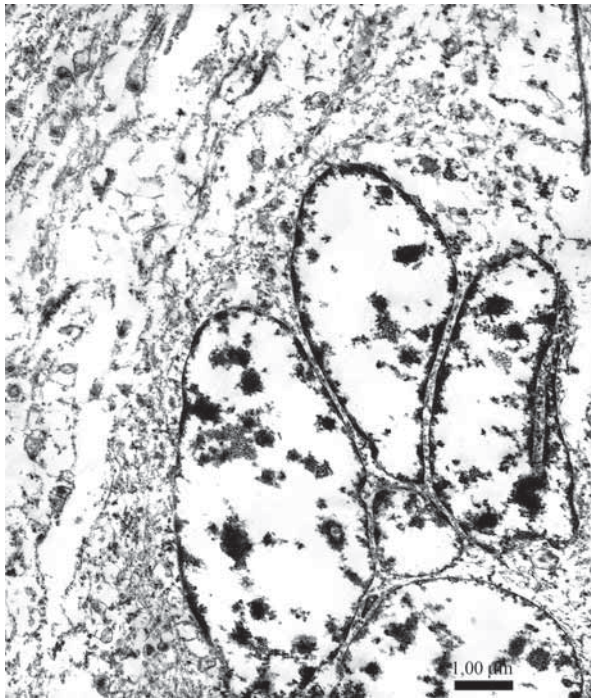


Fig. 9. Multinucleated giant cell

It has been shown that the localization and histological classification of ependymoma are a significant predictor of clinical outcome [12,18,29]. In adults, ependymomas develop most frequently in the spinal cord. In our study, widespread tumour was both intramedullary and intracranial, with secondary multi-segmental syringomyelia. There are several pathomechanisms of syringomyelia. Comparable examination of the most upper and lower part of tumour in our case suggest that intramedullary ependymoma spreading up along the cervical spinal cord to the fourth ventricle pressed on Luschka's foramina of the medulla oblongata. Secondary hydrocephalus was due to the impairment of free flow of the cerebrospinal fluid (CSF) [8]. Progressive growth of the spinal cord tumour and changes of vascular density are accompanied by intramedullary pressure and degenerative changes with hyalinosis of vessel walls [5,25]. Secondary compression of long spinal tracts, neurons and vessel walls leads to blood flow changes, degenerative and ischaemic necrotic changes in the tumour and glial stem below the tumour, which was also revealed in our case.

Microcirculation impairment supports the hypothesis that highly extended syrinxes might result

from disruption of the blood-brain barrier followed by the development of degenerative cysts and tumour-ischaemic-related syringomyelia secondary to ependymoma [19,20,25,28]. The intramedullary part of the ependymoma in our case was not capsulated, but sharply demarcated from adjacent parenchyma by fibrillar glial fascicles, similarly to other reported cases [11]. A possibility of varied cell differentiation in the same tumour is now well known [7,22,23]. According to the WHO grading system, the pathological spectrum of ependymomas might be very wide, including in rare cases a giant cell component [30]. In the first description of giant cell variant of ependymoma, entire participation of bizarre multinuclear cells was reported in two cases located in the region of the filum terminale. The first one was uniformly composed of pleomorphic giant cells, whereas in the second case foci of giant cells were revealed in a myxopapillary ependymoma [32]. In the majority of subsequently reported GCEs, focal clusters of giant cells participated with classic ependymoma cells arrangement [1].

Additionally, some authors have described a few cases of unusual variant ependymoma (not GCE?) in which giant cells participated with ependymoma cells of varied type [11,21,23]. Giant pleomorphic tumour cells are a characteristic feature of other glial tumours, including giant cell astrocytoma, pleomorphic xanthoastrocytoma and glioblastoma [30,31]. Specialized ependymal differentiation was also reported in different types of gliomas [14,29,31]. Our ultrastructural examination revealed numerous junctional complexes between adjoining cells and blepharoplasts with changed morphology, confirming ependymal character of the tumour despite the limits of formalin-fixed and paraffin-embedded material [14,16,17].

To date, GCE cases which exhibited focal or entire participation of giant cells coexisting with conventional ependymoma were reported along with lower or higher grade malignancy and anaplasia findings. In our case of GCE, wide monomorphic areas of conventional ependymoma predominated over clusters of pleomorphic giant cells, which were characterized by an unusually low Ki67 index. GFAP immunopositivity of intranuclear inclusions was shown in those cells, which suggests they could arise in connection with cytoplasmic intranuclear invagination. It was evident also ultrastructurally [16,17]. The cytoplasmic intranuclear "pseudoinclusions" reported mainly in ma-

lignant gliomas with giant cells were revealed sporadically in material of intramedullary or ventricular ependymoma (2 of 21 biopsy cases), and recently in one case of GCE and one case of intramedullary clear cell variant of ependymoma [1,10,13,26].

Spinal cord ependymomas of classic type are usually classified among slow-growing WHO-II grade tumours characterized by long-term survival [29,30]. The issue of grading of giant-cell variant ependymoma and the origin of specialized ependymal differentiation of multinucleated giant cells is still rather controversial. It is emphasized that these tumours are unusual variants of ependymoma whose architectural pattern is sufficiently distinctive to be recognized in H&E stains [7,11].

In the presented case, a low index, lack of vascular glomerular endothelial proliferation and pseudopalisading necroses of the tumour were revealed. Despite nuclear hyperchromasia, the pleomorphic giant cells and intranuclear pseudoinclusions in their bizarre nuclei, there was a lack of other features of anaplasia. Therefore, the WHO criteria for anaplastic (grade III) ependymoma were not fulfilled [5,6,29,30].

To summarize, our histological, immunohistochemical and ultrastructural findings were consistent with the diagnosis of a low-grade (WHO grade II) giant cell ependymoma exhibiting ischaemic and degenerative changes coexistent with syringomyelia. To date, similar lower grade malignancy of this unusual variant of ependymoma has been reported in only a few cases [6,32].

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