Acta Neuropathol (2000) 100:575–579

CASE REPORT

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Spinal cord glioneuronal tumor with "rosetted" neuropil islands and meningeal dissemination: a case report

Received: 28 December 1999 / Revised, accepted: 1 February 2000

Abstract Distinctive glioneuronal tumors arising within the cerebrum and displaying neuropil-like islands and tumor cells immunoreactive for neuronal and glial antigens have recently been described. We report a similar tumor in the cervico-thoracic region of the spinal cord in a 44-year-old woman that recurred 1 year later with dissemination to the lumbar dura and cauda equina. The tumor was composed of "rosetted" neuropil islands displaying immunoreactivity for synaptophysin, whereas the intervening tumor cells were more fibrillar and immunoreactive for GFAP. The tumor cell nuclei immediately surrounding these neuropil islands were immunoreactive to the newly characterized neuronal marker, anti-Hu. While several cases of neurocytomas have been described in the spinal cord, to the best of our knowledge, this is the first example of a glioneuronal tumor with "rosetted" neuropil islands to be reported in the spinal cord.

Key words Glioneuronal tumor · Neurocytoma · Neuropil islands · Spinal cord · Anti-Hu

Introduction

During the past two decades several "neurocytic" or neuronal neoplasms involving the CNS have been reported. Among them, "central neurocytoma" [5] has been well characterized histologically and ultrastructurally. These neoplasms usually follow a benign clinical course. Rarely, these or related neoplasms have shown more aggressive histologic features with tendency for recurrence, and/or craniospinal dissemination [2, 3, 12]. While most neurocytomas are found in the lateral ventricles, often in the vicinity of the foramen of Monro, a few cases have been described in the spinal cord [1, 9, 10, 13, 14]. These spinal neurocytomas, like their cerebral counterparts, followed a benign clinical course after resection.

In recent years, some authors have reported several glioneuronal tumors arising within the cerebrum and displaying mixed histologic, immunohistologic, and ultrastructural features of neurocytoma and glioma [7, 8, 15, 16]. These entities, at present, defy definite nosologic classification. One report [15] described tumors with cells expressing synaptophysin, as well as the newly characterized neuronal nuclear antigens, NeuN [18] and Hu [4, 15]. These cells formed rosette-like structures around neuropil islands that also immunostained for synaptophysin similar to neurocytomas [15]. The intervening cells between these islands, however, immunostained for GFAP. We describe here a very similar glioneuronal neoplasm, somewhat mimicking "central" neurocytoma, which to the best of our knowledge has not been previously described in the spinal cord.

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Case history

The patient was a previously healthy 44-year-old female who presented with numbness and tingling of the right fingers. The symptoms gradually spread with weakness of the right arm, and subsequently paresthesias and weakness of the right leg. Neurologic examination confirmed right-sided sensory-motor deficits and positive Babinski sign. The rest of her clinical examination was otherwise normal.

Magnetic resonance imaging (MRI) was significant for an extensive syrinx of the cervical and thoracic cord associated with an intramedullary tumor that displayed mild gadolinium enhancement (Fig. 1).

She underwent a cervico-thoracic laminectomy and subtotal tumor resection with improvement of some of her symptoms. The tumor was interpreted as a glioblastoma multiforme, and the patient received regional postoperative radiotherapy, 5,000 cGy in 180 Gy fractions to C3 through T9, which was followed by monthly BCNU chemotherapy. Postoperative cervico-thoracic and brain MRI scans showed no recurrent tumor at 6 and 11 months.

Fifteen months after the operation, the patient developed thoraco-lumbar and right chest wall pain with continued paresthesias and weakness of her right leg. Neurologic examination revealed

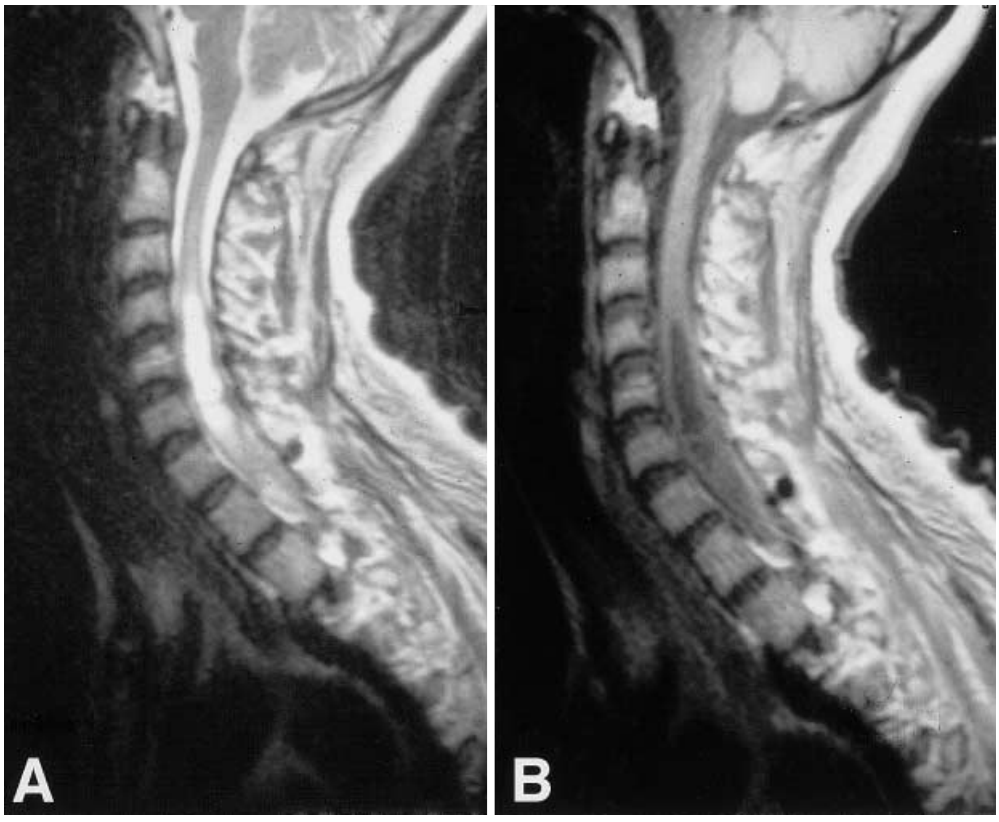


Fig. 1 Sagittal MRI images post-gadolinium contrast displaying a cervico-thoracic syrinx and slightly enhancing tumor at C7-T1: **A** T2 weighted, **B** T1 weighted

right upper and lower extremity weakness and hyperreflexia in the right lower extremity. MRI of the lumbar spine revealed thickening of the cauda equina suggestive of metastatic disease (attempts to obtain and review these films were unsuccessful). Lumbar puncture was negative for malignant cells. L3 laminectomy and nerve root biopsies were performed and displayed cells suspicious for disseminated neoplasm. Postoperative complications led to worsening of her neurologic symptoms and development of hydrocephalus requiring shunt placement. The patient died, but permission for an autopsy was denied.

Materials and methods

The surgical specimens were fixed in 10% buffered formalin and processed for paraffin embedding at outside institutions. Blocks and H&E-stained sections were sent to our laboratory for consultation. Immunohistochemical studies performed in our laboratory included antibodies to synaptophysin (dilution 1:30, Boehringer Mannheim Biochemica, Indianapolis, Ind.), glial fibrillary acidic protein (GFAP; dilution 1:150, DAKO, Carpentiera, Calif.), chromogranin (dilution 1:100, Biogenex, San Ramon, Calif.), leukocyte common antigen (LCA; dilution 1:100, DAKO), NeuN (dilution 1:500, Chemicon, Tamecula, Calif.) and MIB-1 (Ki-67; dilution 1:150, Immunotech, Westbrook, Me.). Anti-Hu immunostaining was performed at Memorial-Sloan Kettering Cancer Center, New York, N.Y. as previously described [4, 15].

Results

The patient's first spinal cord biopsy consisted of small fragments of tissue with relatively uniform tumor cells arranged in clusters and loose sheets. Several, relatively nuclear-free zones of eosinophilic fine fibrillar processes were noted, the larger ones reminiscent of pineocytoma "rosettes" [17] and others similar to the "neuropil islands" often found in central neurocytomas (Fig. 2). The neoplastic cells had indistinct cell borders, minimal amounts of cytoplasm, and small, round to slightly irregular nuclei with fine chromatin and inconspicuous nucleoli. The loose sheets of tumor cells within the intervening areas between the neuropil islands showed mild fibrillar background and small, slightly irregular nuclei with dense chromatin. In some fields, artifactual "halos" were seen around tumor cell nuclei. Rare neuronal-like cells with abundant cytoplasm and large nuclei with prominent nucleoli were also present within the intervening areas and interpreted as neuronal differentiation of tumor cells (Fig. 2B, insert). Rare mitotic figures were identified, but no vascular proliferation, marked nuclear pleomorphism, or areas of necrosis were seen.

Immunohistochemical studies showed the neuropil islands and some tumor cells to be immunoreactive for synaptophysin (Fig. 3A). Anti-Hu staining highlighted tumor cell nuclei to varying degrees, especially those immediately surrounding the neuropil islands (Fig. 3B) and only a few within the intervening areas. NeuN immunostaining was negative (not shown). GFAP immunoreactivity was mostly seen in the intervening tumor cells, especially around blood vessels, but was absent in the neuropil islands (Fig. 3C). Enlarged reactive astrocytes were also highlighted. There was no immunoreactivity to chromogranin or LCA. The proliferative index as assessed by MIB-1 immunostaining of tumor cell nuclei was less than 1%.

Sections from the patient's second biopsy specimen, 15 months later, demonstrated small fragments of dura in-

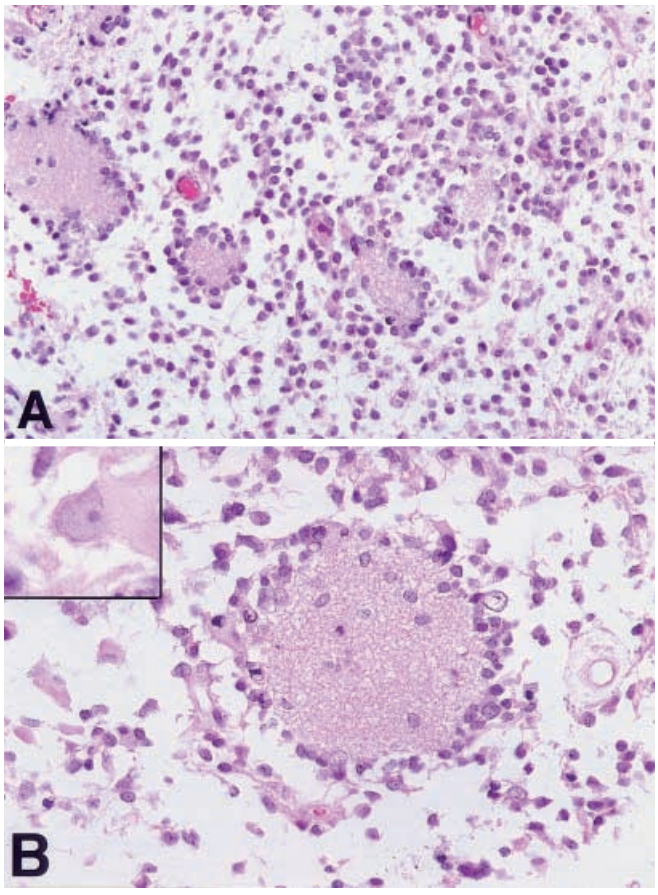
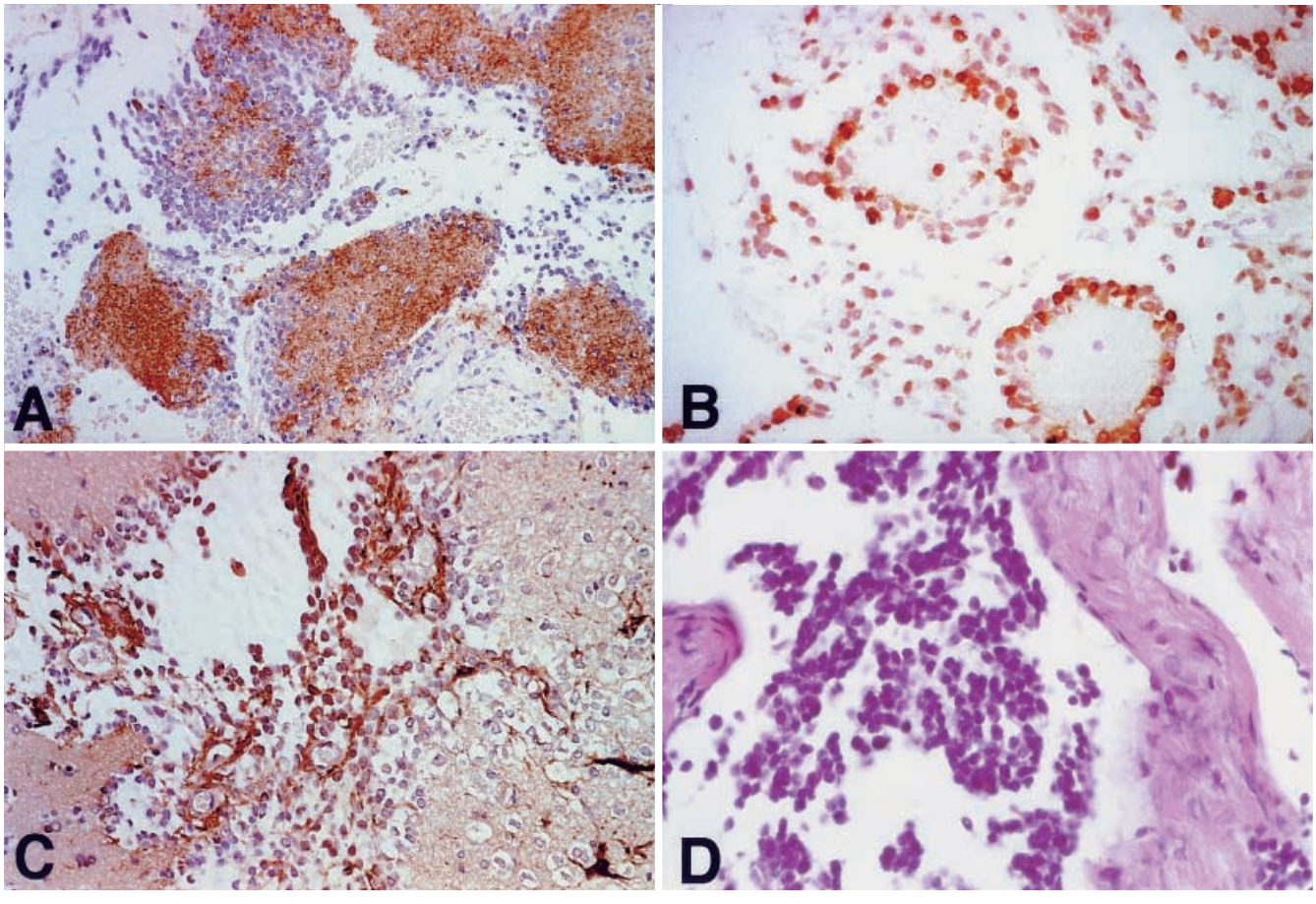


Fig. 2 **A** Spinal cord glioneuronal tumor displays loose sheets of uniform, small tumor cells intervening between "rosetted" neuropil islands. **B** Higher magnification of "rosetted" neuropil island with rare ganglion-like tumor cell (*insert*). H&E staining. **A** × 200, **B** × 400, **insert** × 800

filtrated by collections of atypical cells (Fig. 3D), but the histology was vitiated by fixation/processing artifacts. Nevertheless, the tumor cells had minimal cytoplasm and round to slightly irregular nuclei similar to the first biopsy sample. Rare mitotic figures were identified. Immunohistochemical studies performed at an outside institution demonstrated no tumor cell immunoreactivity for keratin or LCA. No tissue remained in the block, precluding further sectioning for additional immunohistochemistry. However, a destained H&E slide showed equivocal immunostaining for synaptophysin.

Attempts to perform ultrastructural studies on the small amount of paraffin-embedded material remaining from the first biopsy specimen were unsuccessful.

Fig. 3 **A** Positive immunostaining of neuropil for synaptophysin. **B** Anti-Hu immunostained tumor cell nuclei rosetted around the neuropil islands. **C** Antibody for glial fibrillary acidic protein immunostained intervening tumor cells. **D** Small cell tumor infiltrate within lumbar dura with second biopsy; H&E staining. **A** × 100, **B** × 400, **C** × 400, **D** × 600



Discussion

We describe a primary spinal cord neoplasm occurring in the cervico-thoracic region of a 44-year-old woman. The tumor recurred 1 year after initial biopsy/resection and showed meningeal dissemination involving the lumbar dura and possibly the cauda equina. The tumor had features highly reminiscent of a neurocytoma with uniform, round nuclei surrounding nuclear-free neuropil islands and formed rosettes. The nuclei expressed anti-Hu immunoreactivity and the neuropil islands strongly reacted for synaptophysin. However, the tumor cells intervening between these rosettes had nuclei with coarse chromatin, and irregular nuclear contours, and many of these cells expressed GFAP immunoreactivity.

Ependymoma and oligodendroglioma were easily excluded based on immunophenotyping. Primitive neuroectodermal tumor (PNET) was unlikely because of the relative benign histology and low proliferation rate. The possibility of craniospinal dissemination from a central neurocytoma, which has been reported [2], was improbable given the negative imaging studies of the brain.

We seriously considered the possibility of primary neurocytoma of the spinal cord. Several cases of primary "central" neurocytoma have been described in the spinal cord [1, 9, 10, 13, 14]. The age in these cases varied from 12 to 67 years with no predilection to specific segments of the spinal cord. All cases demonstrated neurocytic differentiation by either immunohistochemical or ultrastructural methods, though none of the cases were reported to display GFAP immunoreactivity of the tumor cells. Nevertheless, the presence of GFAP immunoreactive tumor cells in the current case was not inconsistent with the diagnosis of neurocytoma since GFAP immunostaining has been reported in cerebral neurocytomas [12, 16]. Rare ganglion-like cells, as identified in our case, have been described in central neurocytomas [6, 11, 15, 19], spinal cord neurocytomas [1, 13, 14], and in the recently described central glioneuronal tumors [7, 15, 16]. We considered the remote possibility of ganglioneurocytoma [11], a term put forward to describe neuronal tumors with small neuronal cells (neurocytes) admixed with ganglion cells. However, given the paucity of ganglion cells in our case, this diagnosis seems unlikely.

Our case had some features inconsistent with "central" neurocytomas; namely, the relatively rapid fatal course (although it is unclear as to whether this was due to tumor progression or complications surrounding shunt placement) and the significant component of tumor cells expressing GFAP. These cells were arranged in sheets, as if they were "stromal" cells, in which the neurocytic element was segregated in large neurocytic rosettes.

This tumor bore a striking similarity to the recently described [15] glioneuronal neoplasms found in the cerebrum of four adults (20–40 years of age). The authors designated these neoplasms as "glioneuronal tumors with "rosetted" neuropil islands". The neurocytic component expressed no obvious mitotic activity by the MIB-1 marker, whereas the glial component did. The glial component varied from case to case and comprised fibrillary, gemistocytic, or protoplasmic astroglial elements (WHO grade II–III) but no pilocytic cells. One patient died 36 months after diagnosis with bi-hemispheric progression of the tumor and three were alive, one with tumor at 54 months and two free of tumor at 83 and 14 months after surgery and radiation therapy. The nine cases of cerebral glioneuronal neoplasms described by Komori et al. [7] also displayed somewhat similar histologic and immunohistologic features with regard to the neuronal component, but the glial component was limited to pseudopapillae composed of hyalinized vessels covered by a single layer of GFAP-positive astrocytes. These cases did not demonstrate aggressive histologic features and followed the typical benign course of "central" neurocytomas after resection. Komori et al. [8] also reported in abstract form two cases of mixed neuronal-glial tumors arising in the fourth ventricle that showed low-grade astrocytoma or pilocytic astrocytoma component and primitive neuroepithelial cells with possible differentiation to small neurons as evidenced by weak synaptophysin immunostaining of rosette-like structures.

In our case, due to the small size of the biopsy, the relative proportion of glial to neurocytic component could not be accurately assessed, although they appeared to be equally distributed. Also, our case differed from the cases described by Teo et al. [15] in that the neurocytic tumor cells, while expressing Hu immunoreactivity, did not show NeuN immunoreactivity. NeuN is expressed in tumor cells in association with terminal neuronal differentiation. It is possible that in our case the tumor cells had different maturational stages.

Of the six fully reported cases of spinal neurocytomas, three had postoperative radiation therapy [9, 14]. One of the cases described by Tatter et al [14] demonstrated a recurrence, similar to our case, with more aggressive features, i.e., dissemination and mitotic figures; however, that patient was free of disease 5 years later. Two of the three patients with cerebral glioneuronal tumors who received radiotherapy in the series of Teo et al. [15] also continued to have tumor progression. With so few spinal neurocytomas reported and only a single spinal glioneuronal tumor with neurocytoma features described here, it is difficult to speculate about the biologic behavior of these tumors following radiotherapy, chemotherapy, or both.

In summary, glioneuronal tumor with "rosetted" neuropil islands is an appropriate designation for this variant of glioneuronal neoplasms [15]. This tumor appears not to be confined to the cerebrum but can occur in the spinal cord as illustrated in this case. Like its cerebral counterpart, the spinal tumor may have an unfavorable biologic behavior.

Acknowledgements The authors are greatly indebted to Dr. Marc Rosenblum and Dr. S. Humayun Gultekin for performing the anti-Hu immunostaining on this case and their expert interpretations. We are also appreciative of Dr. Robert Morgan and Dr. Philip Dreisbach for providing the clinical history. Lastly, we thank

Pauline Chu for her technical excellence in histology/immunohistochemistry.

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