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CASE REPORT

Giant cell ependymoma of the thoracic spinal cord

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Abstract We report a new case of giant cell ependymoma (GCE) of the thoracic spinal cord. Ependymomas predominate in children and young adults and are frequently intracranial and infra-tentorial. However, a second age peak at 30–40 years is reported for spinal tumours. Microscopically, ependymomas show a large variety of histological features, among which a rare variant with giant cells. This 59-year-old woman presented with a 6-month history of numbness and burning sensation affecting the left lower limb and hemi-trunk. A cervico-thoracic MRI revealed a solid intra-medullary tumour at the level of T1–T3, slightly T1-hypointense, T2-hyperintense and contrast enhancing. A complete surgical resection was carried out through a C7 to T4 laminectomy. Recovery was complete with no sign of recurrence at 18-month follow-up. The initial histological diagnosis of glioblastoma was challenged on the basis of the imaging and operative findings of a well-circumscribed tumour. The case was sent to us for second opinion and we diagnosed a GCE, WHO grade II, with a biphasic pattern including a predominant giant cell component (>90%), with genetic evidence of polyploidy, and a very limited classic component, showing a characteristic loss of chromosome 22. Our report adds to the clinical, imaging, pathological and genetic characterisation of GCE and brings the first genetic evidence that these rare tumours are at least bi-clonal. It also suggests that GCE have a good prognosis after complete surgical resection.

Keywords Ependymoma · Giant cell · Spinal cord · Glioblastoma · Thoracic spine

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Introduction

Ependymal tumours originate from the ependyma of the walls of the ventricles and the spinal canal and are classified in four major types: subependymoma (WHO grade I), myxopapillary ependymoma (WHO grade I), ependymoma (WHO grade II) and anaplastic ependymoma (WHO grade III) [1].

Ependymomas predominate in children and young adults and are frequently intracranial and infra-tentorial. However, a second age peak at 30–40 years is reported for spinal tumours. In the spine, most tumours are found in the cervical and thoracic segments, in contrast with the myxopapillary variant of ependymoma that predominates in the conus-filum terminale [1, 2].

Microscopically, ependymomas show a large variety of histological and cytological features. Besides the classic monomorphic ependymoma, WHO recognizes several

histopathological variants such as cellular, papillary, clear cells and tanicytic subtypes. Rare variants include ependymoma with lipomatous differentiation, signet ring cell ependymoma, melanocytic ependymoma and giant cell ependymoma (GCE) where the predominant population of giant cells is a potentially misleading feature [1].

Here, we report the case of 59-year-old patient presenting with a thoracic spinal ependymoma showing giant cell predominance and initially misdiagnosed as a malignant glioma.

Case report

A 59-year-old woman presented with a 6-month history of sensory disturbances affecting the left lower limb and left hemi-trunk that she described as numbness and a burning sensation. Her medical history was positive for a recent myocardial infarction treated by coronary stent. The physical examination was unremarkable except for a mild sensory ataxia with no gait disturbance.

Magnetic resonance imaging findings are shown in Fig. 1. Cervico-thoracic MRI revealed an intra-medullary tumour expanding the spinal cord at the level of the T1–T3 vertebral bodies. This enlargement was fusiform, measured 40 mm in its main vertical axis and 12 mm in its largest diameter. The lesion was slightly T1-hypointense, T2-hyperintense and was enhanced after gadolinium injection (Fig. 1).

Surgical resection was performed through a C7 to T4 laminectomy. Intra-operatively, the tumour appeared poorly vascularised, slightly reddish, and was easily cleaved from the surrounding nervous parenchyma.

The post-operative MRI confirmed the complete resection of the tumour mass and the patient recovery was uneventful. At the most recent follow-up, 18 months after surgery, the patient has no recurrence and is free of symptoms.

Pathological examination

The surgical specimen consisted of a dozen of small pinkish fragments that measured 15 × 10 × 10 mm in aggregate. Microscopic examination showed a moderately cellular neoplasm with a predominance of giant cells, non-cohesive, with irregular hyperchromatic and sometimes monstrous nuclei (Fig. 2a). The chromatin of tumour nuclei was often masked by a cytoplasmic pseudo-inclusion. The cytoplasm was abundant, eosinophilic with a ground glass or rhabdoid appearance. Because of the cell polymorphism, the tumour was initially diagnosed as a malignant glioma and sent to our Laboratory of Neuropathology for second opinion.

On H&E sections, the marked cellular atypia was not associated with mitotic figures, necrosis, vascular proliferation or endothelial hyperplasia. Some capillary vessels within the tumour showed hyalinised walls, suggesting a

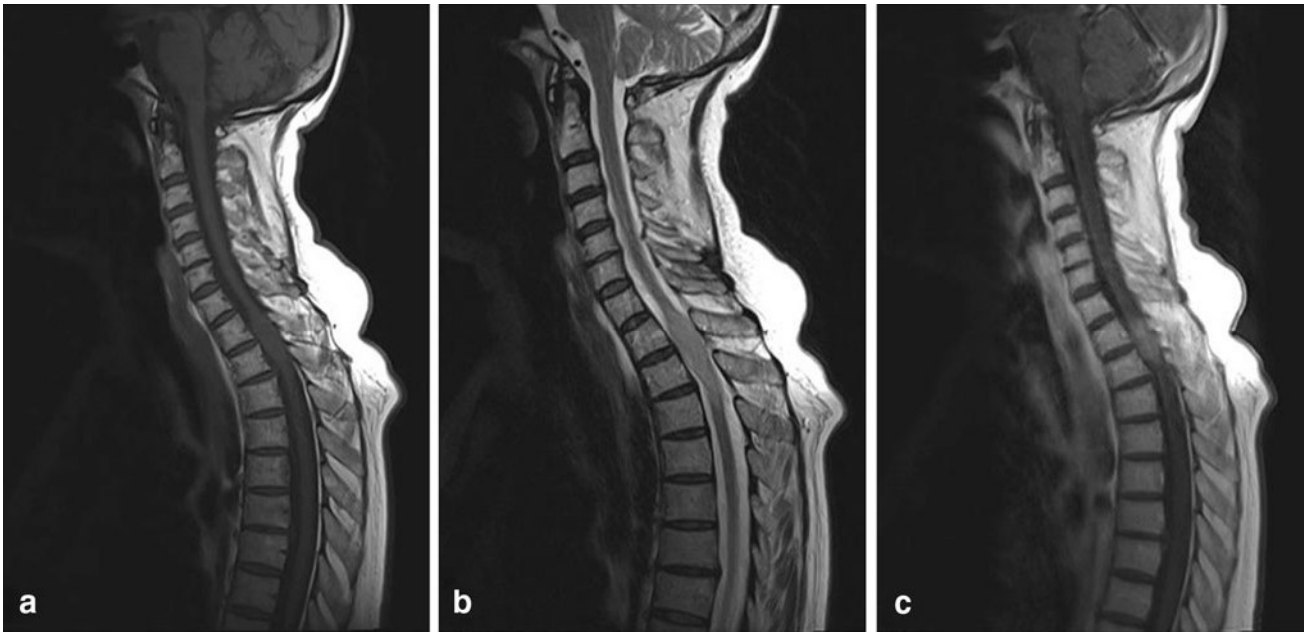

Fig. 1 Pre-operative MRI of the cervico-thoracic spine. The spinal cord is expanded at the level of the T1–T3 vertebral bodies by a fusiform enlargement measuring 40 mm in its main vertical axis and 12 mm in its largest diameter. The lesion is slightly T1-hypointense (**a**), T2-hyperintense (**b**), and is enhanced after gadolinium injection (**c**)

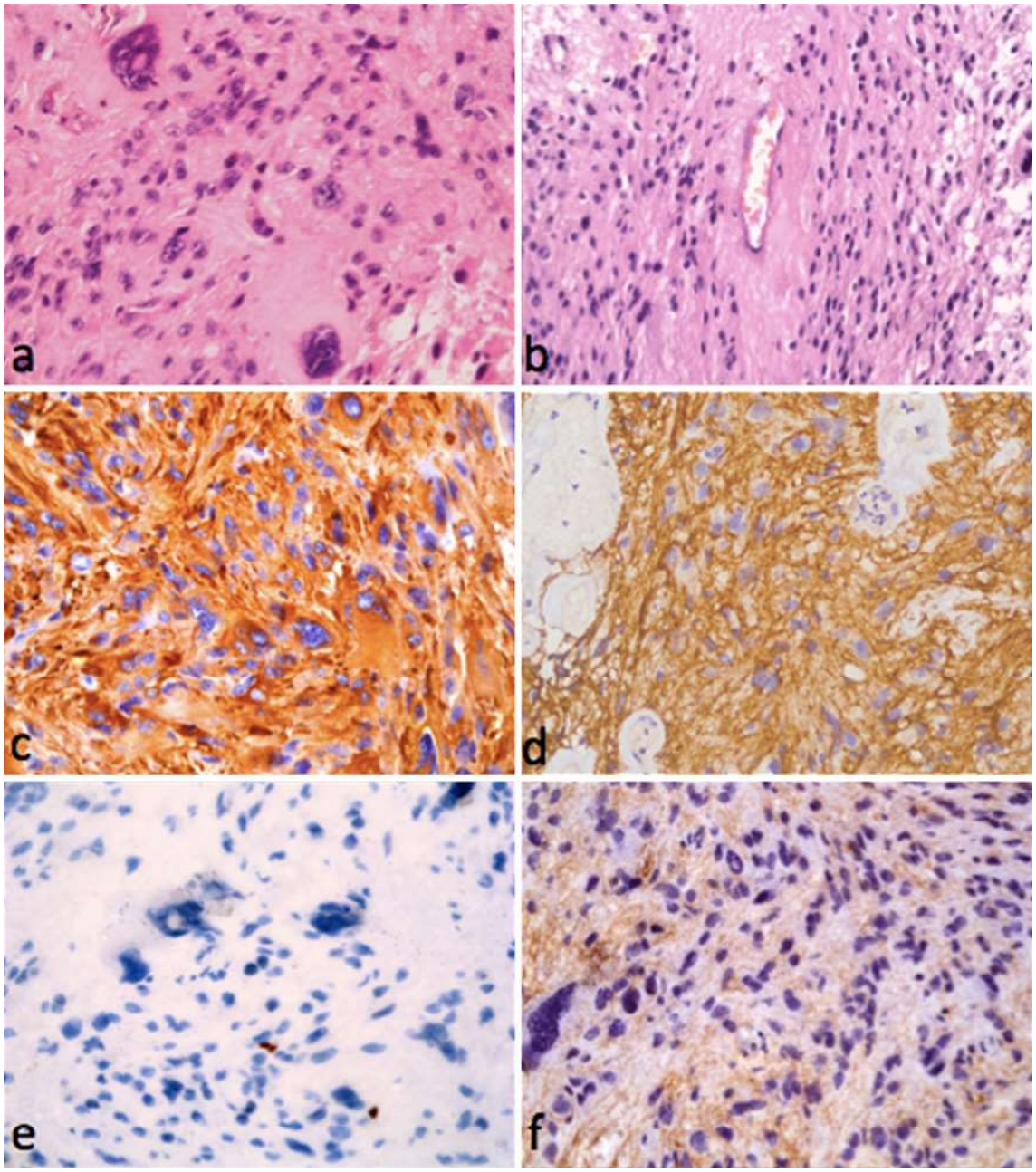

Fig. 2 Surgical specimen. Original magnification 400×. H&E stains showing the giant cell component featuring pleomorphic cells with large nuclei showing irregular chromatin and cytoplasmic pseudo-inclusion (**a**) and the classic component with characteristic perivascular pseudorosette (**b**). Immunostains showing cytoplasmic positivity (in *brown*) for GFAP (1:1,000, Dako) (**c**), membranous staining for CD99 (1:25, Dako) (**d**), nuclear staining for Ki-67 (1:500, Dako) (**e**), and absence of staining for Merlin-A (1:200, Abcam) (**f**)

slowly growing process. There were no Rosenthal fibres. In only one small fragment, accounting for <10% of the surgical specimen, the tumour showed the characteristic features of a classic ependymoma with minimal cell polymorphism and pseudo-rosette formation. In this area, nuclei were round or ovoid, with salt and pepper chromatin, and showed no atypia or mitosis (Fig. 2b). There was a sharp limit between this classic component and the giant cell component.

Sections were immunostained for NeuN, class 3 β tubulin, synaptophysin, neurofilament, microtubule associated protein type 2 (MAP-2), CD99, CD56, INI-1, epithelial membrane antigen (EMA), GFAP, S-100 protein, vimentin, Sox-2, INH-1, Merlin-A, Ki-67, p53 and EGFR. Both components of the tumour (i.e., giant cell and classic ependymoma) were strongly positive for vimentin, S-100 protein, GFAP, CD99, INI-1 and Sox2 (Fig. 2c, d). EMA positivity was seen in most cells as a cytoplasmic

paranuclear inclusion. Some giant cells also expressed MAP-2 in their cytoplasm. There was no expression of neuronal markers and the antibody anti-neurofilament only enhanced some residual axons at the periphery of the tumour. The proliferative index measured with antibody anti-Ki67 was <2%, even among the most atypical cells (Fig. 2e). EGFR expression was moderate, mainly cytoplasmic and there was no p-53 expression. Merlin-A was expressed in less than 10% of tumour cells (Fig. 2f).

Interphase Fluorescent In Situ Hybridisation (FISH) was carried out on chromosomes 7, 9 and 22 using the following probes: DNA LSI 22q11.2 and 22q13, DNA LSI ABL 9q34, LSI EGFR 7p12 and control probe CEP7 7p11.1-q11-1 (D7Z1). The shortage of tissue precluded testing of other chromosomes. Interestingly, the genetic findings in the classic and the giant cell components were in sharp contrast. The classic component showed a monosomy of chromosome 22 and a disomy of chromosomes 7 and 9. There was no amplification of EGFR. The giant cell component showed large gains of chromosomes 7, 9 and 22, probably in the context of overall polyploidy.

Discussion

Giant cell ependymomas are rare tumours, with 15 cases described so far in the literature [3–14]. They were initially described in the filum terminale [14] but have later been reported in the brain, both in supratentorial [3, 5, 11] and infra-tentorial [6, 9, 10] locations, and in the spinal cord [4, 7, 8, 13, 15]. In addition, a couple of tanicytic ependymomas with giant cells have been reported in the filum terminale [16, 17]. The clinical and histological features of GCE have been reviewed recently [8].

Only five cases of GCE previous to this one have been reported in the spinal cord at cervical [4, 7, 13] and thoracic [15] levels, with only one case described in the lumbar spine [8]. This is in keeping with the known predominance of spinal cord ependymomas at cervical levels [1, 2]. The age of patients with spinal GCE ranges from 22 to 67 years with 4/6 cases occurring in patients less than 35 years. There is no gender predilection (F/M = 1).

Symptoms at presentation are related to tumour location. The disease course is subacute or chronic with patients complaining of muscle weakness, sensory loss or pain, and/or clumsiness of gait lasting for 3 months up to 2 years.

When reported, MRI findings are those of an intramedullary tumour iso- or hypo-intense on T1-weighted imaging, hyperintense on T2-weighted imaging and contrast enhancing. In three cases, the tumour was cystic and in 2/3 it was associated with a syringohydromyelic cavity [4, 7, 15].

Intra-operatively, the tumour always appears well demarcated from the surrounding spinal cord with a clear cleavage plane. This is a particularly important finding that should prompt caution in the pathologist facing worrisome giant cells at time of frozen sections. Indeed, the differential diagnosis of gliomas with giant cells classically encompasses high-grade diffuse gliomas and glioblastoma, pleomorphic xanthoastrocytoma (PXA) and subependymal giant cell ependymoma (SEGA). In the spinal cord, however, PXA are extremely rare with only one case on record [18] and SEGA is unheard of [19]. Therefore, the differential diagnosis of a tumour with giant cells must include benign tumours with degenerative changes such as GCE, pilocytic astrocytoma or "ancient" schwannoma, as well as malignant gliomas such as glioblastoma multiforme or metastasis. Indeed, in our case as in previously reported cases [4, 7, 8, 13], the initial histological diagnosis was a malignant glioma. Such mistake may have dramatic therapeutic consequences, both per- and post-operatively [15]. Per-operatively, a diagnosis of glioblastoma can orientate the surgeon towards a debulking surgery rather than a complete resection of the tumour, which is the major prognostic factor for spinal ependymoma [1]. Post-operatively, a diagnosis of malignant glioma will determine the need for adjuvant therapy, i.e. radiotherapy and chemotherapy, which are unnecessary for completely resected grade II ependymomas.

At the time of histological review, we based our diagnosis of GCE on the finding of a small tumour component with classical ependymoma features, accounting for less than 10% of the tumour. The immunohistochemical profile was similar in both classic and giant cell components with widespread positivity for GFAP, CD99 and Vimentin and cytoplasmic EMA. We assigned a grade II as, besides cell polymorphism, we found no other feature suggestive of anaplasia such as high mitotic activity, area of necrosis or microvascular proliferation. Moreover, several features were indicative of slow growth, such as the presence of hyalinised vessels and a low proliferative index (Ki-67 <2%) even in the most atypical areas. Therefore, like others [2, 4, 8, 13] we suggest that the giant cells in GCE result from degenerative alterations in a slowly growing tumour. At 18-month follow-up, the patient is free of recurrence, which reinforces this hypothesis.

The genetics of GCE have been reported in only two cases [14, 15]. Zec et al. [14] carried out a karyotypic analysis on eighteen metaphasic nuclei in a GCE of the filum terminale and found a stemline characterized by 40, XY, -1, -10, -14, -16, -20 and -22. Using FISH on a GCE of the thoracic spine, Shamji et al. [15] found non-specific gains of chromosomes 7 and 10, most likely reflecting an overall state of polyploidy. They found no amplification of EGFR and no loss of chromosome 10q, which are classical

glioblastoma-associated genetic alterations. Previous reports have not found convincing evidence of p53 involvement on the basis of immunohistochemistry. Accordingly, in the current case, we found no positivity for p53. EGFR expression was moderate and cytoplasmic, in keeping with the gain of chromosome 7 in the giant cell component. Importantly, by FISH, we showed that the classic component of the tumour had a characteristic genetic profile of ependymoma with monosomy of chromosome 22, and disomy of chromosomes 7 and 9. These results are in keeping with the markedly reduced immunostaining for Merlin-A, the protein product of the *NF2* gene located on 22q12. However, the giant cell component showed a completely different profile with gains of all chromosomes tested (chromosomes 22, 7 and 9) probably in the context of an overall polyploidy. This is of particular interest for two reasons. First, this is the first strong genetic evidence that GCE are at least bi-clonal, as suggested by histology. Second, the loss of 22q, seen in the classic component of our tumour, has been reported in up to 30% of ependymomas [1] and ependymomas seen in the context of neurofibromatosis type 2 show a deletion of the *NF2* gene at locus 22q12. In the current case, we did not have the opportunity to conduct a genetic analysis on peripheral blood leukocytes. However, the patient had no sign of neurofibromatosis type 1 or 2 and had a negative family history for these diseases.

In conclusion, we report a new case of GCE of the thoracic spinal cord. This is the 16th case of GCE described so far and the 6th GCE located in the spinal cord. Our report adds to the clinical, imaging, pathological and genetic characterisation of these rare tumours. It suggests that GCE are bi-clonal tumours and that they have a good prognosis after complete surgical resection. This case also emphasizes the potential histological pitfalls in diagnosing spinal tumours with worrisome giant cells. It should be remembered that ependymomas account for 50–60% of primary spinal cord tumours in the adult and are therefore much more frequent than malignant gliomas in this location [1]. Because ependymomas show many histological variants, among which GCE, they may be confused with other primary or metastatic tumours. It is therefore recommended to be extremely careful before issuing a diagnostic of high-grade glioma when both imaging and operative findings are those of a located, well circumscribed intra-medullary tumour. Ependymoma and its numerous variants should be excluded first.

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Conflict of interest None.

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