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CASE REPORT

Fatal holocord recurrence of a pregnancy-related, low-grade spinal ependymoma: case report and review of an unusual clinical phenomenon

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Abstract

Introduction Pregnancy-related spinal tumors (PRSTs) are unusual tumors that present during pregnancy or within a year after delivery. We describe a fatal holocord recurrence of a spinal ependymoma, which, to the best of our knowledge, is one of the most extensive PRSTs reported thus far.

Case presentation A 21-year-old primigravida presented at 6 months of gestation with urinary incontinence for 2 months and spastic paraparesis for 1 month. MRI showed a conus intramedullary lesion from T10 to 12. Near-total resection of the lesion was performed. The histopathological diagnosis was that of a cellular ependymoma (WHO grade II). The patient presented 6 months later with progressive quadriparesis and breathing difficulty. MRI demonstrated holocord recurrence of the tumor with edema extending to the pontomedullary junction. The patient succumbed to respiratory failure before decompression of the tumor could be performed.

Discussion This case highlights an unusual clinical course of a pregnancy-related, low-grade spinal ependymoma. The possible hormonal and genetic mechanisms underlying the aggressive involvement of the entire spinal cord by the recurrent tumor are discussed in the light of a literature review. Future studies may shed light on the possibility of utilizing these mechanisms as therapeutic targets to alter the clinical course of aggressive spinal ependymomas.

Introduction

Holocord intramedullary tumors form a rare subset of primary spinal cord tumors that extend from the cervicomedullary junction to the conus medullaris, spanning close to 20 contiguous cord segments [1]. A majority of these "panspinal" tumors are pilocytic or diffuse astrocytomas [1, 2]. The occurrence of a holocord ependymoma is anecdotal, with <10 cases reported (Table 1) [3–9] after Cushing's first report of the entity [10]. We describe the first case of a holocord "recurrence" of a low-grade spinal ependymoma. The tumor first presented during pregnancy and had an early recurrence, which, to the best of our knowledge, is the one of the most aggressive pregnancy-related spinal tumors (PRSTs) reported in literature. The tumorogenic mechanisms of pregnancy, their effects on the clinical course of spinal tumors, and possible underlying genetic alterations that contribute to aggressiveness of spinal ependymomas are discussed in the light of a literature review.

Case presentation

A 21-year-old primigravida from a rural background presented at 6 months of gestation with urinary incontinence for 2 months and progressive tightness and weakness of both her lower limbs for 1 month. Neurological examination revealed severe spasticity of both lower limbs that precluded assessment of power. Deep tendon reflexes were brisk and the plantar reflex was bilaterally upgoing. The rest of her neurological examination was normal. MRI of her spine (Fig. 1) showed an intramedullary lesion in the region of the conus extending from T10 to 12 vertebral levels. The lesion was isointense on T1-weighted images (WI) and

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Table 1 Review of reported cases of holocord ependymomas.

Author [Ref. No.]	Age (years)/sex	Radiological findings	Treatment	Follow-up (period and status)
Horrax and Henderson [3]	NA	NA	NA	NA
Fischer et al. [4]	M	C2–L2 lesion with cysts	Laminectomy and excision	NA
Nakamura et al. [5]	NA	NA	NA	NA
Tanaka et al. [6]	15/M	Contrast-enhancing solid lesion in filum terminale; holocord tumorous cyst	Suboccipital craniotomy, C1–T2 laminectomy and decompression of cyst; T12–L4 laminectomy and total excision	NA
Gunes and Ozdemir [7]	19/F	Heterogeneous contrast-enhancing lesion	Total excision in 2 stages: C1–T4 laminoplasty and T5–L2 laminectomy	2 years; Improvement in motor deficits; No recurrence on MRI
Aryan et al. [8]	4 months/M	Heterogeneous peripheral contrast enhancement in cervicodorsal spine, nodular enhancement distally; cervical syrinx, syringobulbia, hydrocephalus	Suboccipital craniotomy and attempted syringotomy; L1–2 laminectomy and biopsy	Died of aspiration pneumonia 6 months after surgery
Bhaisora et al. [9]	15/M	Heterogeneously contrast-enhancing lesion with polar cysts	Near-total excision following C2–T3, T7–L1 laminoplasty and T4–T7 laminectomy	6 months; Improvement in power after initial deterioration
Present case (recurrent tumor)	21/F	Heterogeneous contrast enhancement, edema extending cranially to the pontomedullary junction	Steroids; Planned for decompression	Succumbed to acute respiratory failure 3 months after delivery

NA not available.

hyperintense on T2 WI. It had a ventrally exophytic component. Screening of the rest of the spine was normal. Gadolinium was not administered as a precautionary measure in view of her pregnancy. Ultrasound of the pelvis confirmed a single live intrauterine fetus with an estimated gestational age of 28 weeks.

She underwent T10–T12 laminectomy and resection of the tumor in the left lateral position with somatosensory-evoked potential and motor-evoked potential monitoring under general anesthesia with due precautions for maternal and fetal safety. Intraoperatively, a firm, grayish, and moderately vascular intramedullary tumor was encountered. Near-total resection was achieved, with a thin residue left behind at the conus where the tumor-cord interface was relatively poor.

Histopathological examination revealed a cellular tumor (Fig. 2) with round to oval cells arranged in a fibrillary matrix. The cells had strong and diffuse glial fibrillary acidic protein positivity and focal positivity for epithelial membrane antigen, and demonstrated a MIB-1 labeling index of 10–12%. There was evidence of attempted ependymal rosette formation. No mitosis, necrosis, or microvascular proliferation was seen. These features were consistent with a diagnosis of a cellular ependymoma (WHO Grade II).

Following surgery, the patient underwent physiotherapy with an individualized rehabilitation program tailored toward achieving functional independence. Some of the specific neuromuscular facilitation exercises included sustained stretching of the hamstrings, quadriceps and calf muscles, passive force rocking movements of the lower limbs, and body-weight supported weight-bearing and tilt-table standing activities to reduce spasticity. She was also provided occupational therapy training in newborn care strategies for safe feeding and carrying the child.

At the time of discharge, there was some improvement in spasticity in her lower limbs, and the power had improved to grade 3 at the hip and knee on the left and grade 2 at the hip and knee on the right. She was advised to continue clean intermittent catheterization and was prescribed long knee callipers to aid walking. The caretakers were educated on continuing physiotherapy at home with advice on prevention of decubitus-related complications.

The patient was advised to follow-up after completion of her pregnancy, and the obstetrician was updated about her condition. Following her discharge from hospital, she diligently continued physiotherapy at home, and continued to experience further improvement in her lower limb and bladder function. Three months after an uneventful full-term delivery, she presented in the emergency department with worsening spasticity in the lower limbs for a month, paresthesias and tightness in the upper limbs for 1 week, and difficulty in breathing for a day. On examination, she was noted to have spastic quadriparesis with brisk tendon

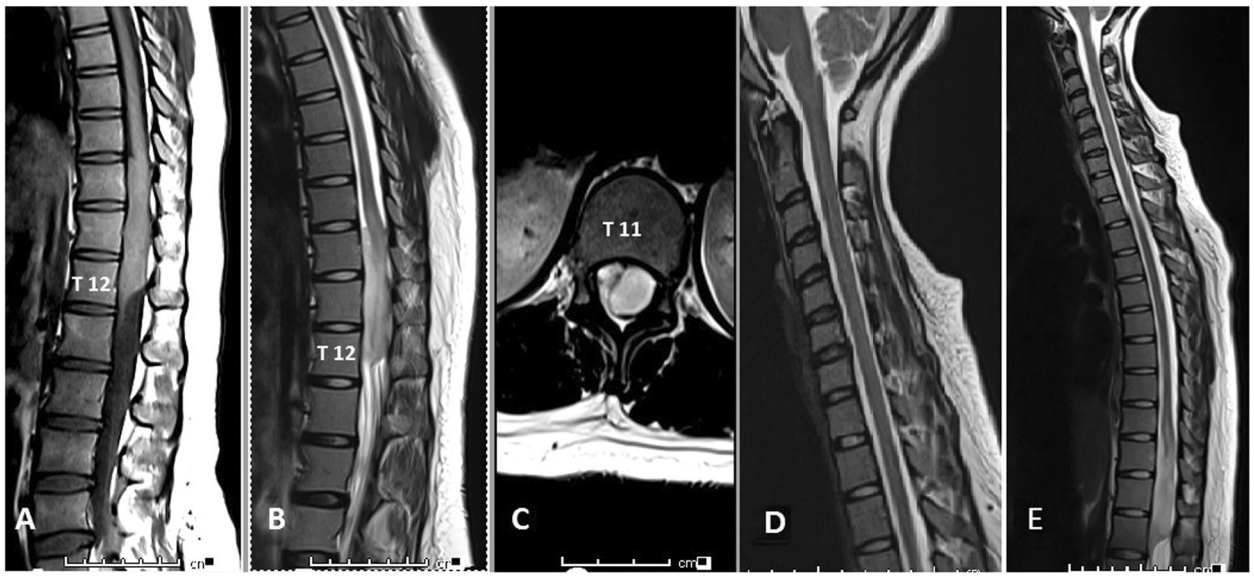

Fig. 1 Plain MRI of the spine showing an intramedullary lesion in the region of the conus. a Sagittal T1-weighted image showing an isointense lesion extending from T10 to T12, **b** Sagittal T2-weighted image demonstrating the lesion to be hyperintense. A ventrally exophytic component is noted. **c** T2-weighted axial sequence at T11 level showing an enlarged cord and the exophytic component. **d** Screening T2-weighted image of the cervical spine and **e** whole-spine screening showing no other lesion.

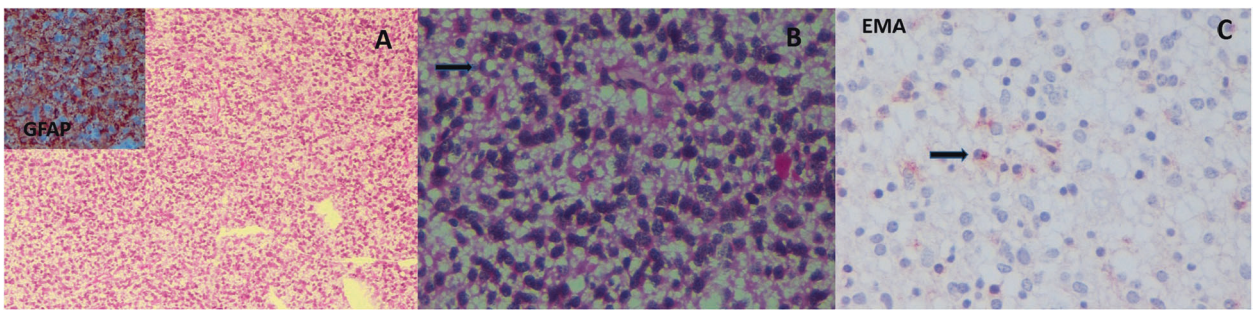

Fig. 2 Histopathological examination demonstrating features of a cellular ependymoma (WHO Grade II). Paraffin section of the lesion showing a cellular tumor with: **a** round to oval cells arranged in fibrillary matrix with strong and diffuse GFAP positivity (Inset), **b** high-power view of the same demonstrating attempted ependymal rosette formation (arrow), and **c** paranuclear dot positivity for EMA (arrow). [Hematoxylin and eosin: **a** ×40; **b** ×400] [Avidin Biotin Complex immunoperoxidase (A-inset) ×400; **c** ×400].

reflexes in the upper and lower limbs. In view of a poor respiratory effort, she required intubation and mechanical ventilation. A whole-spine MRI (Fig. 3) showed a diffusely enlarged spinal cord with a holocord, heterogeneously enhancing intramedullary lesion extending from the conus up to C3 with edema extending cranially to the pontomedullary junction (Fig. 4). There was also evidence of the lesion within the lumbar canal with diffuse thickening of the cauda equina. The recurrent lesion was iso- to hypointense on T1 WI and predominantly hyperintense on T2 -WI with areas of mixed intensity. Brain MRI did not show evidence of intracranial disease. She was started on intravenous steroids and planned for decompression of the tumor. However, her respiratory status deteriorated rapidly, and she suffered a cardiorespiratory arrest soon after admission. She succumbed to her disease the following day.

Tumor sample from the first surgery was not available for retrospective hormonal and genetic analysis, and the recurrent tumor could not be obtained for analysis as the relatives did not consent for an autopsy. Based on the radiological and clinical findings, a final diagnosis of an aggressive holocord recurrence of the conus ependymoma was made.

Discussion

The hormonal milieu of pregnancy is known to predispose to the occurrence of tumors across various organ systems with an incidence of around 1 in 1000–2000 pregnancies [11]. The commoner pregnancy-related tumors include breast, hematological, and dermatological malignancies

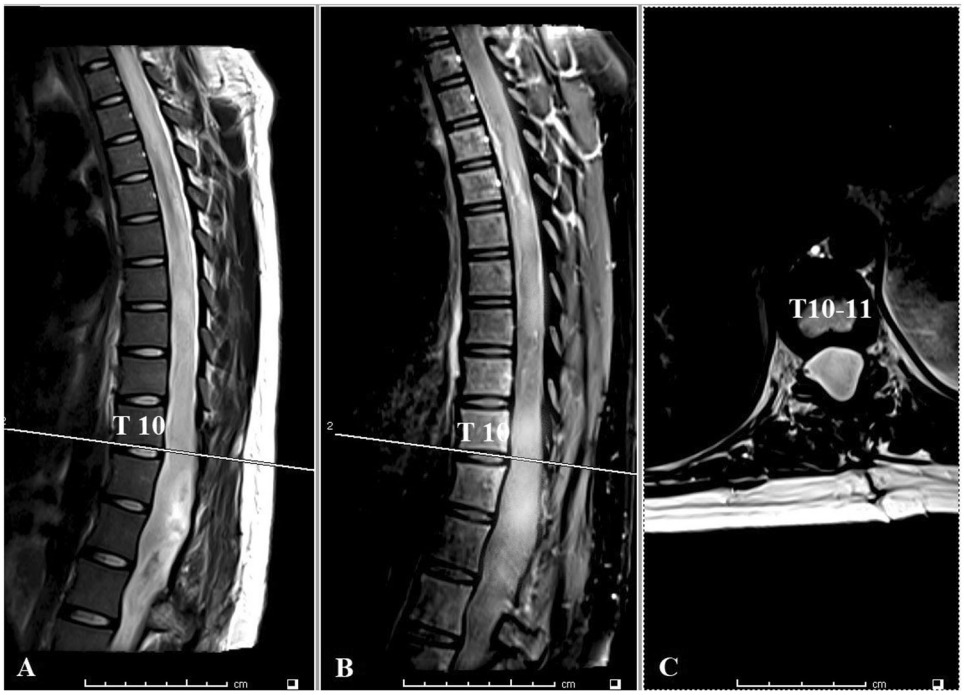

Fig. 3 Thoracic spine MRI showing a diffusely enlarged spinal cord with a holocord intramedullary lesion. a T2-weighted sequence demonstrating the lesion to be predominantly hyperintense with areas of mixed intensity in the conus. **b** Gadolinium enhanced T1-weighted sagittal image showing heterogeneous enhancement in the dorsal spine. **c** T2-weighted axial sequence at T10–11 level showing an enlarged cord.

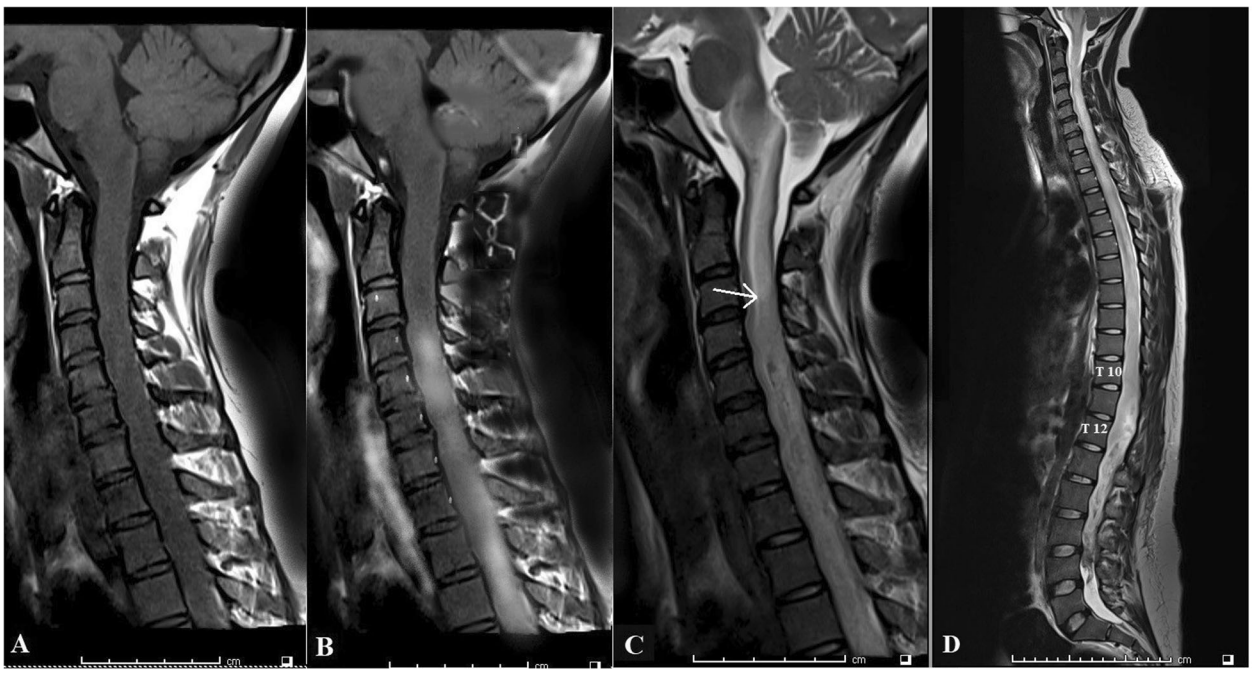

Fig. 4 Holocord recurrence of the lesion. a Sagittal T1-weighted image of the cervical spine demonstrating an isointense lesion expanding the cord; **b** Sagittal gadolinium enhanced T1-weighted image showing heterogeneous contrast enhancement in the cervical region; **c** Sagittal T2-weighted image showing the hyperintense intramedullary lesion extending up to C3 (arrow) with edema extending cranially to the pontomedullary junction. **d** Sagittal T2-weighted image of the whole spine showing a diffuse holocord involvement by the lesion. Diffuse thickening of the cauda equina is noted as well.

[12], while spinal lesions like hemangiomas, giant cell tumors, nerve sheath tumors, and metastases [13] form a rarer subset. The term "pregnancy-related spine tumor" (PRST) refers to a spinal intra- or extramedullary tumor presenting either during pregnancy or within a year after delivery [13]. Among all the PRSTs reported in literature, intramedullary ependymomas have been reported only eight times (Table 2) [4, 14–19].

Various mechanisms have been postulated to explain the growth of PRSTs and also the exacerbation of symptoms in

Table 2 Review of pregnancy-related spinal ependymomas published till date.

Author [Ref. No.]	Age	Location	Presentation	Treatment	Follow-up (period and status)
Fischer et al. [4]	27	Holocord	NA	Laminectomy and excision	NA
Schweitzer and Batzdorf [14]	NA NA	NA NA	Initial symptoms occurred during pregnancy (details not available)	Decompression in both cases (details not available)	NA NA
Jaeger et al. [15]	28	T12–L2	Acute paraplegia 12 h after attempted spinal anesthesia at delivery	Laminotomy and excision	8 months; motor improvement, no change in bladder dysfunction
Uzun et al. [16]	21	C2–C4	Progressive quadriparesis starting from the first trimester	Laminectomy and excision	NA
van der Hoeven et al. [17]	31	C5–T1	Back pain second trimester onwards	"Debulking"	NA
Fujii et al. [18]	26	C3–T5	Numbness in both lower limbs starting from the first trimester, acute paraparesis just before delivery	Laminectomy and excision	1 year; no change in motor or bladder dysfunction
Bitterman et al. [19]	28	T7–T9	Back pain in the first trimester; progressive paraparesis second trimester onwards	Laminectomy and excision	9 weeks; motor improvement, normal bladder function
Present case	21	T10–T12 Holocord recurrence	Urinary incontinence and progressive paraparesis in the second trimester Worsening of paraparesis 2 months after delivery; quadriparesis and acute respiratory compromise in the 3rd month after delivery	Laminectomy and excision Steroids; planned for decompression	6 months; mild initial improvement in motor status Succumbed to respiratory failure

NA not available.

previously asymptomatic lesions [13, 20–24]. These include hormonal and hemodynamic changes, presence of estrogen receptors (ERs) and progesterone receptors (PRs) [25, 26] and increased levels of angiogenic and growth factors [27]. For example, neuro-epithelial tumors including ependymomas have been proven to express the receptors ER-β [13] and PRs [28] either of which can modify tumor progression. In the case of vertebral hemangiomas, the mechanism of growth is thought to be multifactorial. Implicated factors include hormonal changes that increase venous distensibility, and hemodynamic changes that result in redistribution of blood volume through the vertebral venous plexus [22]. The latter hemodynamic mechanism also explains the nocturnal exacerbation of symptoms, with the supine position heightening uterine pressure on the vena cava and causing subsequent venous congestion and cord compromise [17].

Review of the previously reported pregnancy-related spinal ependymomas (Table 2) reveals that the clinical presentation and outcomes in all these cases were similar to those of regular spinal ependymomas. One patient presented with a holocord tumor after delivery [4] similar to our case. The tumor in the other patients was limited to three or four spinal segments. While five of these patients developed neurological deficits and underwent tumor resection during pregnancy, one of them was diagnosed to have a spinal lesion after a failed attempt at spinal anesthesia during delivery [15]. One patient was found to be harboring a spinal ependymoma on postpartum evaluation of long-standing nocturnal back pain [17]. There was no tumor recurrence in any of the patients with documented follow-up. Our case is unique in that the tumor presented with an aggressive and fatal holocord recurrence within 6 months of near-total resection. Although a definite pathological diagnosis of the recurrent tumor was not possible in our case, the radiological characteristics were consistent with those of a holocord recurrence.

Clinical outcomes of low-grade spinal ependymomas are generally favorable, and biological aggression and poor outcomes are generally limited to WHO Grade III ependymomas [29, 30]. A hypothesis to explain the aggressiveness of the low-grade tumor in our case would be that the tumor had strong steroid-receptor positivity, and hence was highly sensitive to the pregnancy-induced hormonal changes. A study of various primary spinal cord tumors [31] demonstrated cytoplasmic-ER and -PR positivity in a majority of the ependymomas. Findings from other studies as well [13, 28] indicate a strong possibility that steroids can promote the onset, differentiation, and growth of spinal ependymomas.

While the above hypothesis sounds tenable, it can only explain tumor aggressiveness till the early postpartum period, beyond which hormonal levels normalize to their pregravid status [13]. This then draws forth a possibility of an

underlying molecular alteration that could have contributed to the aggressive recurrence of the tumor. A likely candidate would be a focal *MYCN* amplification [32] reported to occur in a subgroup of spinal ependymomas including the lower grade ones. *MYCN*-amplified tumors typically demonstrate increased aggressiveness, early metastases with craniospinal dissemination, rapid progression after relapse, resistance to treatment, and poor overall survival [32]. We could not establish a *MYCN* alteration or histological evidence of malignant progression in our case. However, the clinical features like spinal cord invasion at presentation, holocord progression, and a dismal survival despite a near-total resection of the primary tumor were pointers to the above-mentioned genetic alteration.

This case highlights an unusually aggressive clinical course of a low-grade spinal tumor during pregnancy. Further research is warranted on exploring characteristics like steroid-receptor positivity and genetic alterations like the *MYNC* amplification in spinal ependymomas. This could be utilized in formulating targeted genetic [33–36] or hormonal therapies to alter the biological behavior of such tumors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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