

Delayed Recurrence of Choroid Plexus Carcinoma in the Sacral Spinal Cord 17 Years after Its Initial Presentation

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Abstract

Choroid plexus carcinomas (CPCs) are rare malignant tumors of neuro-ectodermal origin, accounting for less than 1% of all intracranial tumors. The recurrence rates of CPCs are very high and typically occur in the short-term following surgery, even after gross total removal. Here we present a rare case of CPC with spinal metastasis, which occurred long after its initial presentation. A 25-year-old woman with a history of increased intracranial pressure underwent resection for a tumor of the fourth ventricle, with a histopathological diagnosis of CPC. After tumor resection, she received 30 Gy of radiation therapy to the craniospinal axis and 20 Gy to the primary site, followed by nimustine hydrochloride chemotherapy. The residual lesion completely responded to these treatments. She suffered sensory loss in the sacral region 13 years later, followed by refractory skin ulcer in the sacral region 17 years after the initial treatments. Magnetic resonance imaging at 17 years after the initial treatments showed tumor in the sacral region, which was enlarged upon follow-up after 18 months, causing incontinence and loss of urinary intention. She underwent tumor resection, with a histological diagnosis of recurrent CPC. She received salvage re-irradiation. This case shows that CPC can spread via the cerebrospinal fluid pathways and cause spinal metastasis, with relatively slow clinical course. The present case suggests that patients with CPCs may need long-term follow-up imaging of the total neural axis to identify late recurrence at both the primary site and spinal metastasis.

Keywords: choroid plexus carcinoma, spinal dissemination, long-term

Introduction

Choroid plexus tumors (CPTs) are rare tumors arising from the choroid plexus. The histological definition of CPTs includes choroid plexus papilloma (CPP) (World Health Organization [WHO] grade I), atypical choroid plexus papilloma (atypical CPP) (WHO grade II), and choroid plexus carcinoma (CPC) (WHO grade III).¹ Pediatric and adult CPTs show some differences in clinical features, including age at onset, location, histological diagnosis, and prognosis.² Pediatric CPTs occur predominantly in the first

2 years,¹ whereas adult CPTs are distributed evenly throughout all ages.³ Pediatric CPTs were usually located at the lateral ventricle, whereas adult CPTs tended to occur at the fourth ventricle and cerebellopontine angle.² CPC is more common in pediatric CPTs aged <2.9 years, and CPC is less frequent in adult CPTs.³ The two-year overall survival rate is good in patients aged from 10 to 39 years and poor in patients aged more than 40 years or less than 5-10 years.^{2,4}

CPC is the most aggressive type of CPT, and no standard treatment has been established. A review of 89 dif-

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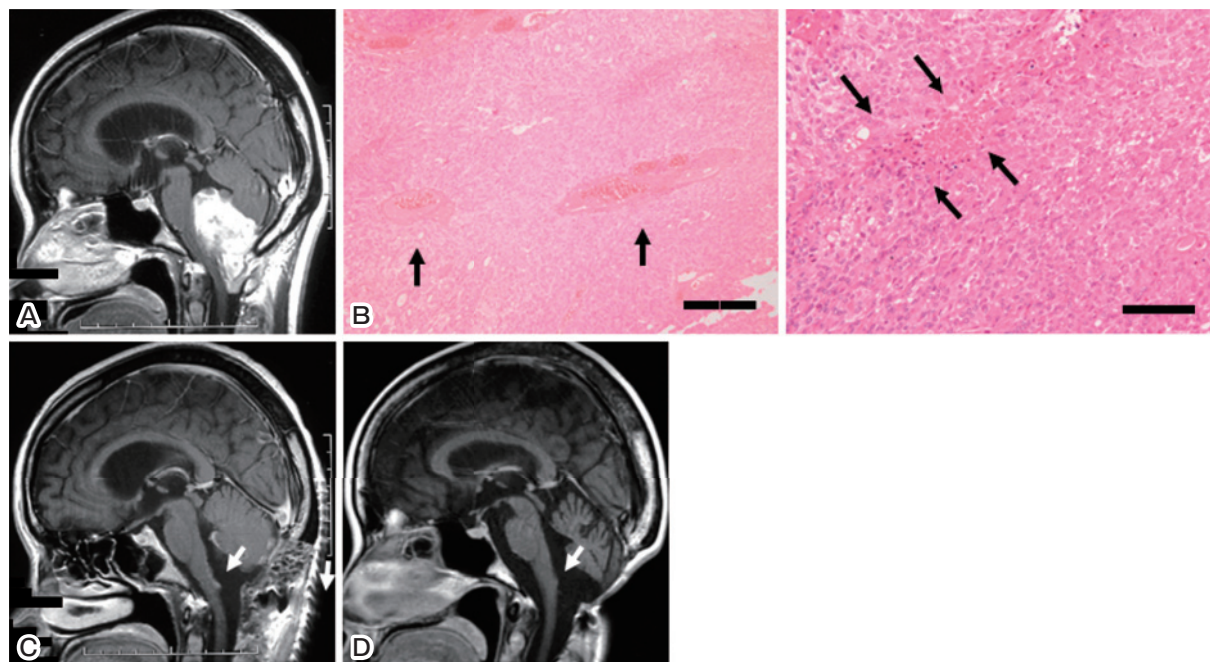


Fig. 1 Preoperative and postoperative magnetic resonance (MR) images and microphotograph of the tumor specimen obtained at initial tumor resection. (A) Preoperative sagittal gadolinium enhanced T1-weighted images showing homogeneously enhanced fourth ventricular mass lesion and obstructive hydrocephalus. (B) Hematoxylin-eosin staining demonstrating that the epithelioid tumor cells proliferated with high cellularity and poorly structured sheet formation. Papillary proliferation of cuboidal epithelial cells, with microvilli around vascular structures, were focally found (arrows in left panel). Necrosis (arrows in right panel) were noted. Bar = 200 μ m (left panel) and 100 μ m (right panel). (C and D) Postoperative MR images (C) and MR images after radiation therapy and 24 cycles of nimustine hydrochloride (D) demonstrating the residual lesion in the floor of the fourth ventricle (arrows) postoperatively and complete remission after radiation therapy and chemotherapy.

ferent studies revealed that the median progression-free survival was 13 months, and the median overall survival was 29 months in pediatric and adult CPCs.⁴⁾ One of the causes of the poor prognosis for CPC is the high probability of intracranial and/or spinal metastasis and metastasis to other organs in pediatric and adult CPCs.^{5,6)} Metastatic recurrence in adult CPCs usually develops within 5 years after initial treatments, and patients with metastasis have suffered aggressive clinical course and died of progressive disease within 18 months.^{5,7-10)}

We present a rare case of adult CPC in the fourth ventricle that slowly developed progressive metastatic disease at 17 years after initial treatment. The consent for publication was obtained from the patient.

Case Report

A 25-year-old woman without past illness or comorbidity presented with new complaints of headaches and vomiting. Neurological examination demonstrated mild truncal ataxia. Brain magnetic resonance (MR) imaging demonstrated a homogeneously enhanced mass lesion at the fourth ventricle, which caused local mass effect and obstructive hydrocephalus (Fig. 1A). Spine MR imaging found no metastatic lesions.

Tumor removal was performed through the trans-cerebellomedullary fissure approach. The tumor was soft, highly vascular, and adherent to the lower half of the floor of the fourth ventricle. The tumor was removed, leaving the lesion adherent to the fourth ventricle floor. Histological examination found that the epithelioid tumor cells had proliferated, with high cellularity and poorly structured sheet formation (Fig. 1B). Although papillary configuration was lost in most areas, papillary proliferation of cuboidal epithelial cells around vascular structures were focally found (left panel in Fig. 1B). More than five mitoses in 10 high-power fields and necrosis were also found (right panel in Fig. 1B). Little pleomorphism was detected. Tumor cells were positive for pan-cytokeratin AE1/AE3, vimentin, S-100, and glial fibrillary acidic protein (GFAP) and negative for CEA. The Ki-67 labeling index was 25%. The tumor was diagnosed as CPC, WHO grade III. Postoperative gadolinium enhanced T1 weighted MR imaging showed residual lesion in the fourth ventricle floor (Fig. 1C). She received adjuvant radiotherapy with 30 Gy of radiation therapy to the craniospinal axis, followed by 24 Gy of additional radiation therapy to the tumor bed. She was scheduled to receive chemotherapy consisting of cisplatin, etoposide, and ifosfamide. However, she developed hives immediately after the administration of etoposide,

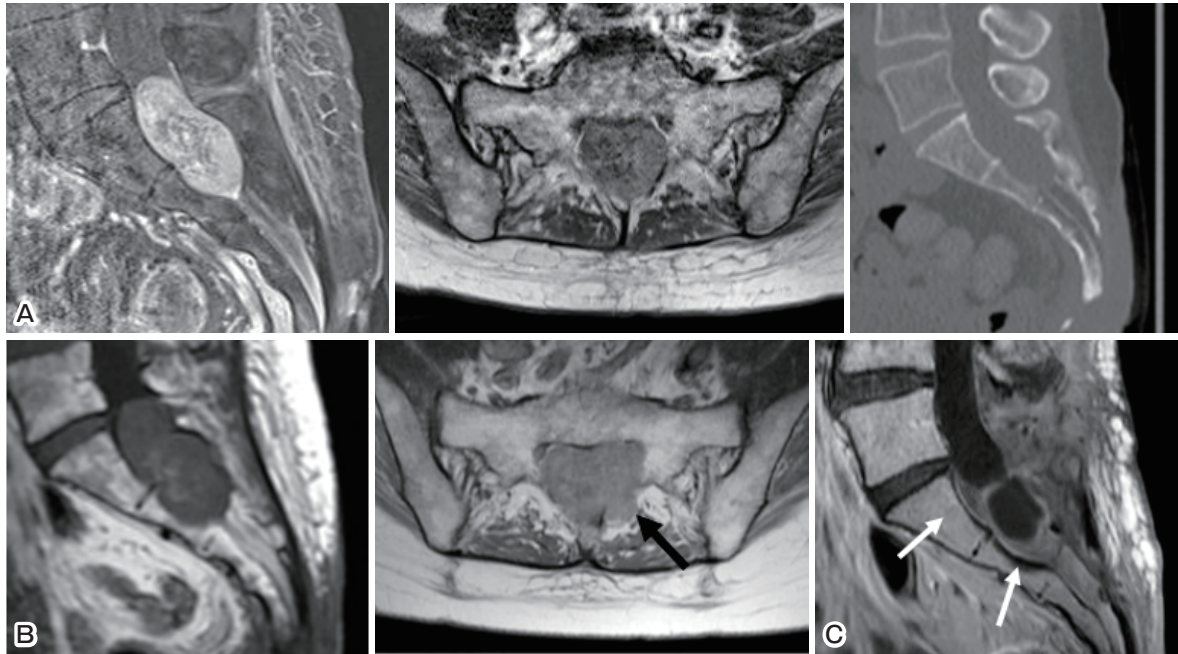


Fig. 2 Preoperative and postoperative sacral magnetic resonance (MR) images of the recurrent tumor in the sacral area. (A) Sacral sagittal (left) and axial (middle) gadolinium enhanced T1-weighted MR images and bone sagittal CT (right) 17 years after initial treatment, demonstrating mass lesion of the sacral canal with osteolytic changes without marginal sclerosis. (B) Sacral sagittal (left) and axial (right) T1-weighted MR images 18 months after the diagnosis of sacral lesion, demonstrating tumor enlargement and extension beyond the dura mater of the sacral canal (arrow). (C) Follow-up sacral gadolinium enhanced T1-weighted images demonstrating that postoperative residual disease (arrows) showed no growth 17 months after salvage radiation therapy.

and the chemotherapy was discontinued. Instead, she received nimustine hydrochloride. She tolerated the procedure well, and, two years after the operation, the residual lesion had completely disappeared (Fig. 1D). She remained in good condition and was followed up with MR imaging of the brain until 16 years after the initial treatment.

She noticed perineal sensory loss 15 years after the initial treatment. She developed refractory skin ulcer in the sacral region. Her wounds gradually worsened, and she was referred to another hospital. Sacral MR imaging demonstrated a mass lesion occupying the sacral spinal canal and osteolytic changes of the sacral canal 17 years after the initial treatment (Fig. 2A). She received conservative treatment at that time. However, she developed loss of urinary intention and incontinence 18 months later. She was then referred to the Department of Orthopedic Surgery at our hospital.

On admission, she had perineal sensory loss and bladder and rectal disturbance. MR imaging indicated growth of the mass lesion and extension beyond the dura mater (Fig. 2B). She was diagnosed with sacral canal tumor and underwent L5-S3 laminectomy and tumor removal. Part of the tumor had strongly adhered to the cauda equina, and this lesion was not removed to prevent neurological deficits. She did not develop additional neurological symptoms, but her preoperative symptoms persisted. Histological examination of the recurrent tumor specimen found

atypical cells showing pleomorphism had proliferated with high cellularity, poorly structured sheets of tumor cells, and blurring of the papillary pattern (Fig. 3). Large necrotic areas were found (left panel in Fig. 3). Immunohistochemical examination revealed that the tumor was positive for GFAP and S-100, focally positive for pan-cytokeratin AE1/AE3 and INI-1, and negative for EMA. The Ki-67 labeling index was 8.0%. Based on these findings, she was diagnosed with recurrent CPC. Postoperative sacral MR imaging showed residual tumor along the cauda equina. She received 50.4 Gy of re-irradiation to the tumor bed. Her perineal sensory loss and bladder and rectal disturbance did not improve. The residual tumor showed no growth at 17 months after re-irradiation (Fig. 2C).

Discussion

Here, we present a rare case of adult CPC with slowly progressive metastatic recurrence 17 years after initial treatment. In this case, the differential diagnosis was difficult due to the poorly differentiated features of tumor cells. The presence of papillary proliferation around vascular cone and the finding of immunohistochemical analyses, including positivity for pan-cytokeratin, GFAP, and INI-1 and negativity for EMA, support the diagnosis of CPT, rather than clear cell or papillary ependymoma papillary meningioma, or atypical teratoid rhabdoid tumor.¹⁰⁾

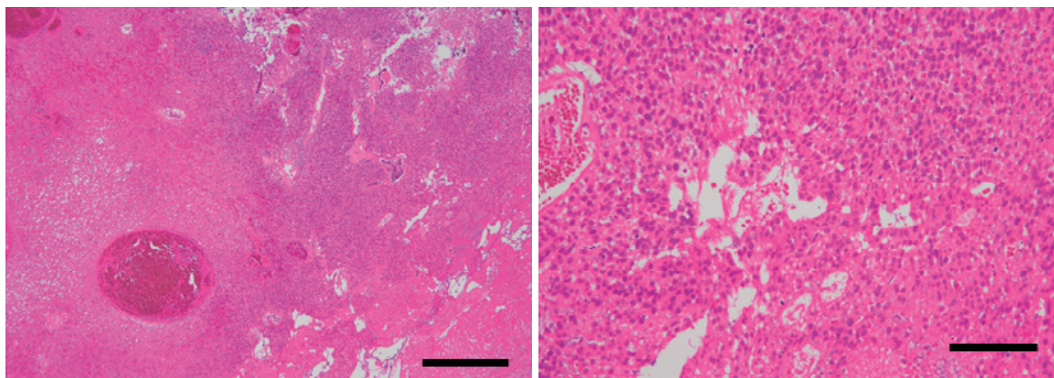


Fig. 3 Microphotograph of the specimen of the recurrent tumor. Hematoxylin-eosin staining demonstrating that atypical cells showing pleomorphism proliferated with high cellularity, poorly structured sheets of tumor cells, and blurring of the papillary pattern. Large necrotic areas were noted (left panel). Bar = 500 μ m (left panel) and 100 μ m (right panel).

Only seven patients with adult CPC with metastatic disease have been reported (Table 1). One of the seven patients had spinal metastasis at the onset and progressive disease after combination therapy with craniospinal irradiation and administration of nivolumab.⁸⁾ The five males and two females were aged 16-60 years at onset. The primary lesion was located at supratentorial locations in four cases and in infratentorial locations in two cases. The initial treatment was gross total resection in five patients, with adjuvant radiation therapy in five patients and adjuvant chemotherapy or immune checkpoint inhibitor in four patients. Metastatic disease developed from 3 months to 8 years after these initial treatments, within one year in three patients (43%) and five years in six patients (86%) after initial treatment.^{5,7-9,12)} Leptomeningeal spread around the spinal cord was most common in these patients.^{7-9,11,13)} Four of five patients died of progressive disease within 18 months after the salvage treatment.

Our case had the characteristics of longest latency to the development of recurrent disease and slow progression after presentation of metastatic disease. Various mechanisms may cause the relatively slow clinical course from the histological and radiological findings. Such a long latency to spinal metastasis is frequently reported in patients with CPPs and atypical CPPs,¹⁴⁾ with the intervals before spinal metastasis ranging from 5 years to 19 years (median: 6 years) in six patients with CPP and two patients with atypical CPP.¹⁵⁾ The present histological findings were reviewed to explore the mechanism for long latency and relatively slow growth. The histological findings of both the primary and recurrent lesions fulfilled the criteria for CPC.¹⁾ Nuclear atypia, pleomorphism, high cellularity, and necrosis became more evident in the recurrent specimen, but the Ki-67 labeling index dropped from 25% to 8% at recurrence. These findings suggested that decreased proliferating activity could be the one of the reasons for the long latency and slow growth. The neuroimaging findings suggested that the spinal lesion could grow at a local

site relatively rapidly from the findings of osteolytic changes without marginal sclerosis. Considering the rate of increase in the 20 months after the diagnosis of the sacral lesion, some time may have elapsed before the development of the lesion, and the lesion had then grown rapidly. This case was also characterized by the absence of diffuse leptomeningeal spread, which was a common feature in the previous cases of spinal metastasis of CPC.^{7-9,11,13)} CPPs and atypical CPPs show various patterns of spinal metastasis, such as diffuse leptomeningeal spread,^{15,16)} multiple nodular pattern,¹⁷⁻¹⁹⁾ and localized pattern.^{20,21)} Tumor control was good for the localized spinal metastasis but poor for the diffuse leptomeningeal spread.^{20,21)} These macroscopic and microscopic findings in our case could explain the relatively slow clinical course after initial treatment.

No standard treatment has been established for metastatic disease of CPCs. Previous patients who were treated by only salvage chemotherapy died within two years after diagnosis.^{7,8,11)} Although a meta-analysis on newly diagnosed CPCs demonstrated that chemotherapy prolonged the overall survival rate in both completely and incompletely resected CPCs,³⁾ only chemotherapy could not control the recurrent disease. In our case, the residual lesion was stable after salvage irradiation. Previously, hypo-fractionated salvage radiation therapy to the spinal cord controlled the disseminated lesion for 12 months,¹³⁾ but progression occurred thereafter. Clearly, further studies are necessary to establish standardized radiation and chemotherapy strategies for the dissemination of CPC in adult patients.

There were some limitations in this report. First, spinal disease was not evaluated after initial treatment until the development of symptoms. We presumed that the sacral lesion took a long time to develop, and rapid growth occurred after development from the findings of the sacral bone. However, the timing of development of the spinal disease and the growth rate of recurrent disease remains unclear. Second, the effect and complication of re-irradiation to the cauda equina was not sufficiently evalu-

Table 1 Summary of cases of adult choroid plexus carcinoma with recurrent metastatic disease

Authors	Age at initial treatments and sex	Location	Sites of metastasis	Duration to metastasis after initial treatment	Initial treatment	Salvage therapy	Follow up periods after dissemination	Outcome
Vaquero et al (1979) [12]	26F	Lateral ventricle	Cerebellum and spinal subarachnoid space at L3	4 years	GTR+LBI	GTR/LSI	unknown	unknown
Misaki et al (2011) [9]	38M	Septum pellucidum	Diffuse leptomeningeal spread around the spinal cord and brainstem	3 months	GTR/RT/TMZ	WVI 30 Gy+ WSI 30 Gy + LBI 60 Gy/TMZ	11 months	dead
Samuel et al (2013) [11]	16F	Temporal-occipital lobe	Cerebellopontine angle and diffuse leptomeningeal spread	5 years	GTR/LBI 54 Gy/ICE	HDC with autologous stem cell rescue	18 months	dead
Pellerino et al (2015) [13]	50M	IVth ventricle	Diffuse leptomeningeal spread around the spinal cord	8 years	GTR/LBI 42 Gy	Biopsy/LBI 20 Gy/ARA-C/TMZ	42 months	alive
Bohara et al (2015) [7]	60M	Trigone	Diffuse leptomeningeal spread around the spinal cord and brainstem	3 months	GTR/WBI 30 Gy+ LBI 10 Gy + Cyber knife/TMZ	CDDP+ETP/Intrathecal MTX and VCR	13 months	dead
Bahar et al (2017) [5]	51M	Not described	Subarachnoid space at L5 to S1	3 years	STR	GTR/CSI 30 Gy/GKS	6 years	unknown
Kim et al (2019) [8]	40M	IVth ventricle	Diffuse leptomeningeal spread around the spinal cord	7 months*	STR/CSI 36 Gy/Nivolumab	ETP/CBDCA/MTX	11 months	dead
Our case	25F	IVth ventricle	Localized lesion in the sacral canal	17 years	STR/CSI 30 Gy+ LBI 24 Gy/ACNU	PR/LSI 50.4 Gy	37 months	alive

Abbreviations: RT, radiotherapy; GTR, gross total removal; STR, subtotal removal; PR, partial removal; CSI, craniospinal irradiation; LBI, local-brain irradiation; LSI, local-spine irradiation; WBI, whole-brain irradiation; ICE, ifosfamide + cisplatin+ etoposide; ETP, etoposide; MTX, methotrexate; VCR, vincristine; TMZ, temozolomide; ACNU, nimustine hydrochloride; CBDCA, carboplatin; GKS, Gamma knife surgery; ARA-C, cytarabine; HDC, high-dose chemotherapy; VCR, vincristine; CDDP, cisplatin; WVI, whole-ventricle irradiation; WSI, whole-spine irradiation; *This case had metastatic lesion at onset, and this lesion progressed after initial treatment.

ated due to the short follow-up period after retreatment.

Conclusion

We recommend continued follow-up of adult patients with CPC using both brain and spine MR imaging.

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Conflicts of Interest Disclosure

All the authors have no conflicts of interest.

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