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Case Report

Holocord low grade astrocytoma – Role of radical irradiation and chemotherapy

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KEYWORDS

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Abstract Spinal intradural tumors, especially those extending along the entire length of the spinal cord, termed as 'holocord' tumors are uncommon. Most of these are gliomas, with astrocytomas (low grade) predominating in children and ependymomas in adults. Other histologies, though reported, are even rarer. Management is debatable, with both surgery and radiotherapy of such extensive tumors posing challenges. We describe a case of a 14-year-old girl with holocord astrocytoma extending from cervicomedullary junction till lumbar spine, who recovered full neurological function following radical irradiation of entire spine followed by temozolomide-based chemotherapy. No grade 3/4 bone marrow morbidity was seen. Five years following treatment, she maintained normal neurological function and apparently normal pubertal and skeletal growth despite residual disease visible on imaging. Literature review of existing reports of holocord astrocytomas highlighting management and outcome is presented.

Introduction

Intramedullary spinal cord gliomas are uncommon tumors. Astrocytomas predominate in children while ependymomas are commoner in adults [1]. Sometimes tumors extend along extensive lengths of the spinal cord, making surgery as well as radiotherapy challenging. No large series or guidelines exist to guide appropriate management in such situations.

We describe the case of a child diagnosed to have a low grade astrocytoma of spine, which was successfully managed with radiotherapy and chemotherapy, and regained full neurologic function which was maintained on long term follow up.

Case report

A 14-year-old girl presented to us with progressively worsening weakness of both lower limbs for 5 months. She also had history of focal seizures involving both lower limbs for 2 months and urinary and fecal incontinence for 1 month. There was no history of headache, nausea or vomiting, trauma or tuberculosis. She had normal developmental history and her two older siblings were normal. She had menarche at 13 years of age. She was evaluated by a neurosurgeon.

Magnetic resonance imaging (MRI) of spine showed a cystic intramedullary space occupying lesion extending from C3 to D12–L1 vertebral levels, with multifocal, thick-walled

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enhancement from D4–5 to D12–L1. MRI brain was normal. Biopsy showed grade 2 astrocytoma. The case was diagnosed as a holocord astrocytoma and was referred to us for radical radiotherapy.

On examination, higher mental functions and cranial nerves were normal. Power in bilateral upper limbs was 5/5 and in bilateral lower limbs was 1/5. Sensations were reduced below the xiphoid. There was fecal and urinary incontinence. The child was planned for radiotherapy (RT) to whole spine from C1 to conus medullaris by direct posterior field; with cobalt-60 using a conventional simulator. A dose of 45 gray (Gy) in 25 fractions over five weeks was delivered.

The child tolerated RT well with no grade 3/4 hematologic or neural toxicities. Three months following RT, power in bilateral lower limbs had returned to 4 + /5. Bladder and bowel sensations were restored and sensations were also regained.

Repeat MRI spine with contrast performed at 3 months post-RT showed significant residual disease despite the neurologic improvement. Following this, she received six cycles of chemotherapy with temozolomide 150 mg/m^2 orally D1–5 given every 4 weeks. She has been on follow up since then. Serial MRI examinations have shown a considerable reduction in the spinal tumor and the child continues to be neurologically asymptomatic till last follow up at 5 years. Although no specific tests were performed to establish hormonal function, she attained apparently normal pubertal growth with resumption of menstruation after a brief interruption following treatment.

Discussion

Pediatric intramedullary tumors comprise 35% of all spinal tumors, with a predominance of low grade astrocytomas (LGAs), which constitute 60% of all intramedullary tumors. Intramedullary low grade spinal astrocytomas (IMLGSA) have a slight male predominance. Onset is insidious with symptoms of pain, or sensory, motor or autonomic dysfunction depending upon site and extent of involvement. Gait disturbances, regression of milestones, torticollis, and kyphoscoliosis may be other features. MRI is the imaging modality of choice. Astrocytomas have less well-defined margins and are more likely to be eccentrically located within the spinal cord, unlike ependymomas which are always central in location. Unlike LGAs in the brain, IMLGSA show intense post-contrast enhancement. At least 50% have cysts which are indistinguishable from solid tumors on T2 weighted studies owing to high protein content, but do not enhance with contrast [1–3]. Location is commonly cervicothoracic or thoracic, though most lesions span over multiple levels. Microscopically, IMLGSA show a low degree of cellularity, low mitotic activity, and absence of necrosis and endothelial microvascular proliferation. Pilocytic astrocytomas typically contain Rosenthal fibres.

Rarely, IMLGSA may extend along long segments extending from cervicomedullary junction to conus (< 1% of intramedullary lesions), in which case they are termed holocord astrocytomas. The first report of a holocord tumor was given by Cushing in 1927, histology being ependymoma [4]. Scant literature exists on the appropriate management of holocord tumors. Advancement in MRI technology, neurophysiologic monitoring, and surgical equipment have greatly enhanced the ability for safe and effective treatment [5]. Epstein and Epstein first described 3 cases, which they managed surgically using Cavitron Ultrasonic Aspirator (CUSA) without compromising neurologic function [6]. Benzel et al. described a two-staged microsurgical technique for complete tumor removal in 2 patients with LGA. Somatosensory evoked potential was used as intraoperative monitoring tool. Patients were disease-free and neurologically better at 4 years and 3 years, respectively [7].

Irikura et al. have detailed 24 cases of holocord tumors reported till 1990, of which 7 were astrocytomas (mean age 11.3 years, male:female 6:1). Of these, 6 underwent partial resection with or without shunt insertion and improved postoperatively, and the management in the seventh case was not defined [8]. Twelve more cases were added by Schittenhelm et al. [9]. Mean age of these 19 patients collectively was 9.2 years, with a male:female ratio of 2.6. Surgery details available for 14 patients showed gross total removal (GTR) in 6, subtotal resection (STR) in 7 and biopsy in 1 patient. Of these 14 patients, 2 had received preoperative radiotherapy (RT) with no significant benefit, but dose and technique were not described. Ten patients improved neurologically, 2 were stable neurologically despite progression on MRI, 1 had progressed while 1 died. Follow up was available for 9 patients and ranged from 3 months to 4.5 years (Table 1) [5–18].

Radiotherapy has been used in managing IMLGSA in the setting of biopsy or partial removal. Robinson et al. reported on 14 patients with pathologically confirmed IMLGSA (median extent 2 vertebral widths), with surgery (biopsy 7, STR 6, GTR 1) and postoperative RT (10 patients). Overall survival (OS) and progression-free survival (PFS) at 5 years were 100% and 93%, respectively, and bore no correlation with any patient, tumor, or treatment factors. Postoperative worsening of neurological function and Karnofsky's performance status (KPS) was seen in 8 and 9 patients, respectively. At a median follow up of 10.2 years, neurologic function stabilized or improved in 8, and KPS worsened in 5 patients. The authors recommended that patients with limited resection should receive postoperative RT (50.4 Gy in 1.8-Gy fractions) [19]. Another series of 36 spinal tumors, consisted of 7 LGAs, which were managed with surgery (biopsy 2, STR 4, GTR 1) followed by postoperative RT (median dose 45 Gy in 18 fractions); 3 patients received chemotherapy. Three-year actuarial survival was 80%. Overall, motor function was similar between those who received RT and those who did not. No radiation myelopathy was noted at doses up to 50 Gy delivered at 2.5 Gy per fraction [20]. Minehan and colleagues, in a large series of 136 IMLGSAs, showed that postoperative RT, delivered in 75% of these cases, gave no significant survival benefit for those with pilocytic tumors (39.9 vs 18.1 years, $p = 0.33$) but had significant survival benefit for those with infiltrative astrocytomas (24 vs 3 months; $p = 0.006$). Pilocytic histologic type, longer symptom duration, younger age, minimal surgical extent, and postoperative RT predicted better outcome [21]. Pre- and post-operative clinical status and grade have also been termed important prognostic factors [22]. Even for larger tumors with median span of 16 spinal levels (13 patients including 3 IMLGSA), total resection was achieved in 8 and subtotal excision in 5 patients. Six patients received radiotherapy (5 preoperative and 1 postoperative). At a median follow up of 3.4 years, neurologic function improved in 3, stabilized in 7 and worsened in 2 patients. One patient with anaplastic oligodendroglioma died from progression [5].

Table 1 Summary of reports of holocord astrocytomas including demographic and treatment characteristics [5–18].

S.No.	Author	Year	Age (years)	Sex	Sx	Shunt	RT	Result	Follow up
1	Lowenberg*	1939	14	Male	?	?	?	?	?
2	Epstein [6]	1981	15	Male	STR	No	No	Improved	nr
3			5	Male	STR	No	Yes, preop	Improved	nr
4			4	Female	STR	No	Yes, preop	Improved	nr
5	Tedeschi [10]	1982	12	Female	STR	?	?	Improved	nr
6	Nikaido [11]	1984	2	Male	GTR	?	?	Died	nr
7	Benzel [7]	1987	23	Male	GTR	?	?	Improved	4 years
8			2.5	Male	GTR	?	?	Improved	3 years
9	Irikura [8]	1990	27	Male	STR	?	?	Improved	9 months
11	Vles [12]	1990	11	Female	?	?	?	?	?
10	Shafrir [13]	1992	4/12	Male	?	?	?	?	?
12	Minehan [14]	1995	nr	nr	?	?	?	?	?
13	Lau [15]	1998	4/12	Male	?	?	?	?	?
14	Chacko [16]	2000	14	Male	GTR	No	No	Improved	3 months
15	Sandalcioglu [17]	2002	4/12	Male	STR	Yes	No	Neurologically stable, progression on MRI	4.5 years
16	Komotar [18]	2005	1/12	Male	Biopsy	Yes	No	Neurologically stable, progression on MRI	3.5 years
17	Tobias [5]	2008	13	Male	GTR	No	No	Improved	31 months
18			11	Female	GTR	No	No	Improved	20 months
19	Schittenhelm [9]	2009	13	Female	STR	Yes	No	Progression	8 months
20	Goyal (present case)		14	Female	Biopsy	No	No	Neurological improvement, residual disease on MRI	5 years

GTR: gross total resection; MRI: magnetic resonance imaging; nr: not reported; preop: preoperative; RT: Radiotherapy; STR: subtotal resection; ?: unknown.

* Cited by Tanaka H, Shimizu H, Ishijima B, Nakamura Y (1986) Myxopapillary ependymoma of the filum terminale with a holocord cyst: A case report. No Shinkei Geka 14:997–1003 (in Japanese).

To our knowledge, radiotherapy alone or following biopsy has never been reported in holocord astrocytomas prior to this report. Also, the role of temozolomide-based chemotherapy is evolving in very young children in an effort to delay radiation, but their role in residual IMLGSA has been largely unexplored [23]. Our experience shows that whole spine radiotherapy to doses to 45 Gy along with chemotherapy is safe and effective, as evidenced by the complete neurological recovery despite residual disease visible on imaging studies in our patient, and warrants further evaluation.

Conflict of interest

None declared.

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