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Case Report

Intraspinal granular cell tumor: a case report and review of literature

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Abstract: Granular cell tumor is a rare neoplasm and is usually benign in nature. GCT can arise anywhere in the body but intraspinal GCT is extremely rare. GCT is difficult to distinguish from intraspinal meningioma, schwannoma or metastatic carcinoma preoperative as its atypical clinical features as well as nonspecific radiological characteristics. A 35-year-old female patient presented with cervical pain and progressive numbness in her left upper and right lower extremities for the past 7 months. She complained of 4 months of slight weakness in her lower extremities and gait disturbances as well. MRI confirmed an intradural extramedullary tumor at the C4 to C5 levels that significantly circumferentially compressed the spinal cord. A C4-C5 laminectomy was performed and the lesion was completely resected. The tumor proved to be a GCT according to pathology. The patient is alive symptom-free and without evidence of tumor recurrence at 44 months of follow-up. GCT should be considered in a differential diagnosis of intraspinal masses despite its rarity. Removal of as much of the lesion remain the first choice whenever possible, they have a tendency for local recurrence if completely excision not achieved. Distinction between malignant and benign intraspinal GCT should be a focus of diagnosis to avoid improper therapeutic management.

Keywords: Granular cell tumor, intraspinal, schwannoma, meningioma, ependymoma

Introduction

Granular cell tumor (GCT) is a rare neoplasm and is usually benign in nature. GCT is thought to be of schwann cell derivation, which is supported by the positive expression of markers such as S-100, neuron specific enolase (NSE) and the histiocytic marker CD68 [1-4]. GCT can exhibit malignant behavior and have high recurrence rates despite its benign histopathological features [2, 5-7]. GCT can arise at any location but tend to appear in the head and neck area, typically the tongue. Less frequent sites are the larynx, gastrointestinal tract, breast, esophagus, and parotid gland [2]. Intraspinal GCT is extremely rare, only 10 cases have been reported in the literature [5, 8-15]. GCT is difficult to distinguish from intraspinal meningioma, schwannoma or metastatic carcinoma preoperative as its atypical clinical features as well as nonspecific radiological characteristics. Here we describe an intraspinal GCT and review the literature for this tumor type.

Case report

A 35-year-old female without remarkable medical history was admitted to our hospital with cervical pain and progressive numbness in her left upper and right lower extremities for the past 7 months. She also complained of 4 months of slight weakness in her lower extremities and gait disturbances. The neurological examination revealed a muscle power grade of 4/5 in the left upper extremity and both lower extremities. She had sensory deficits in her left upper extremity and below the C4 on the right side. A Hoffmann sign on her left side was positive, and deep tendon reflexes were absent in the right lower extremity. Magnetic resonance imaging (MRI) confirmed an intradural extramedullary tumor at the C4 to C5 region, and this caused significant circumferential compression to the spinal cord but produced no cord signal changes. The tumor appeared isointense on T1- and hypointense on T2-weighted images with homogeneous contrast enhancement, which measured 0.5 cm in sagital and 1.8 cm in coro-

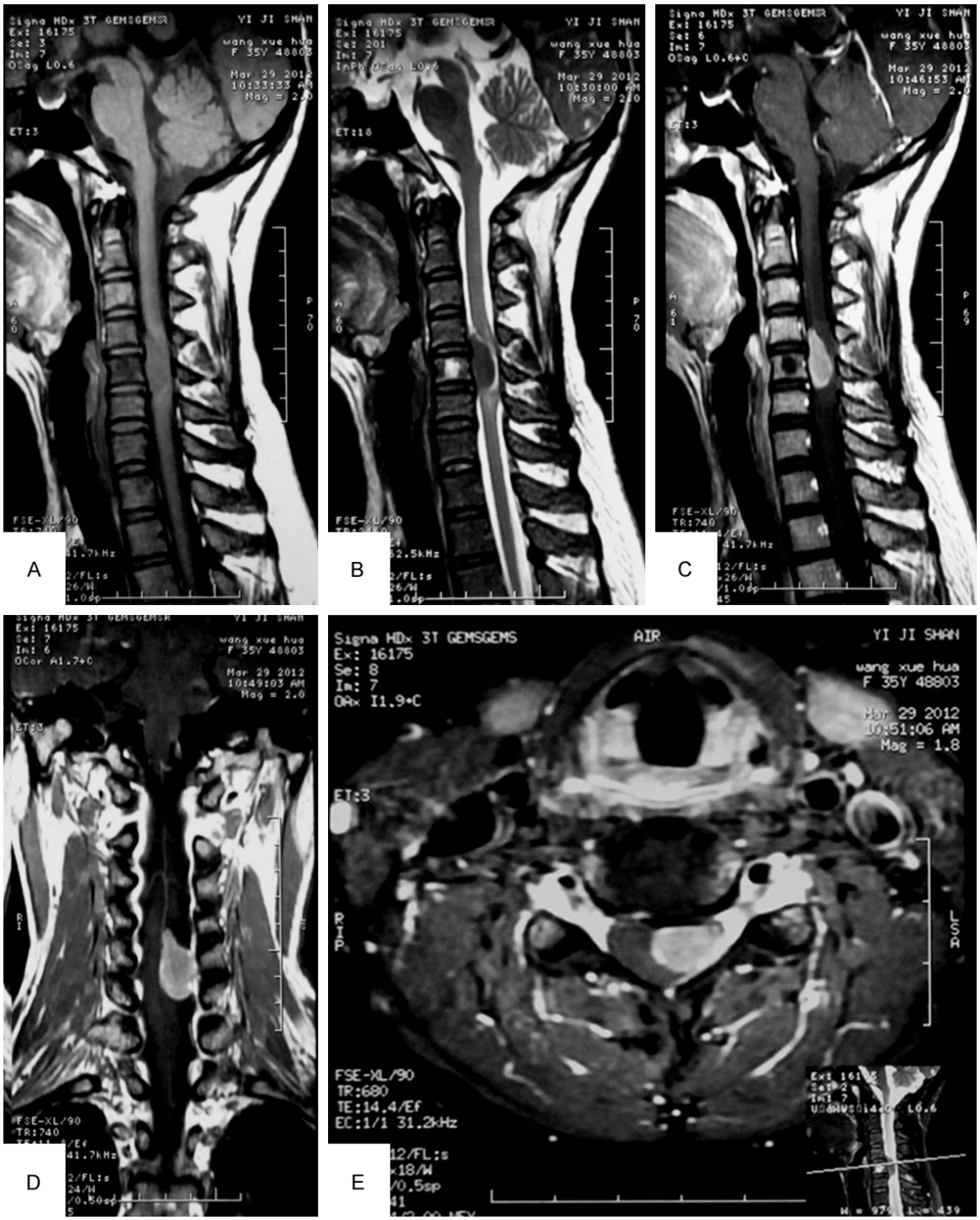

Figure 1. A-E. MRI revealed an intradural extramedullary tumor at the C4 to C5 area that circumferentially compressed the spinal cord. The tumor was isointense on T1- and hypointense on T2-weighted images and with homogeneous contrast enhancement. A second lesion inside the V5 vertebrae appeared hypointense on T1- and hyperintense on T2-weighted images and without gadolinium enhancement.

nal directions and 2.2 cm in vertical dimension. A second lesion was found inside the V5 vertebrae which appeared hypointense on T1- and hyperintense on T2-weighted images without gadolinium enhancement (**Figure 1A-E**). Typical tumor markers were normal according to pro-

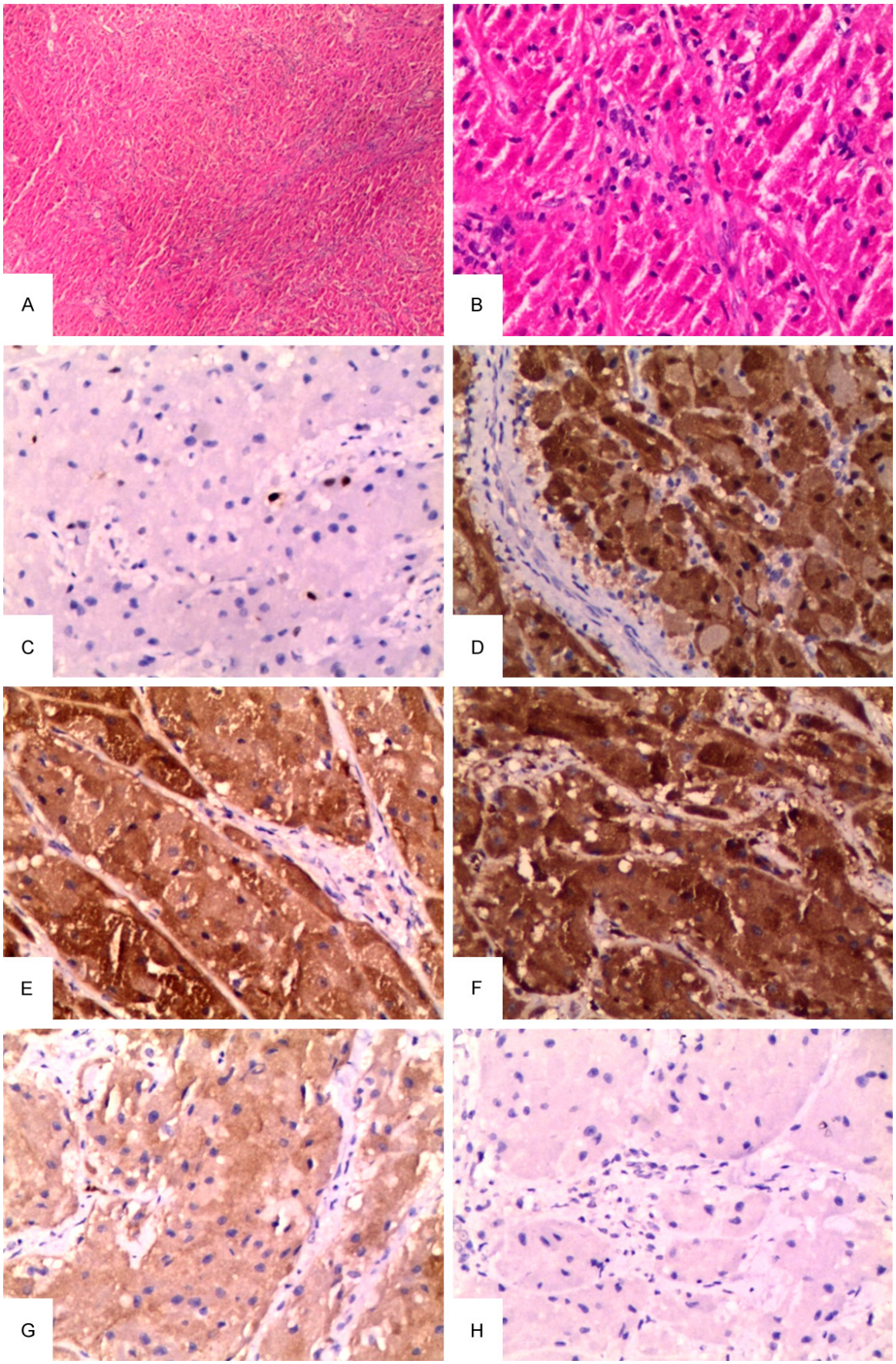
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Figure 2. (A, B) Histopathology confirmed the tumor was composed of clusters and sheets of large rounded, polygonal cells with abundant cytoplasm containing numerous eosinophilic granules. Nuclei were small, oval-to-spherical, and eccentric. (A) (HE × 40), (B) (HE × 200). (C) Ki-67 antigen was below 1% (HE × 200). (D-G) The tumor cells were positive staining for S-100 (D) (HE × 200), NSE (E) (HE × 200), CD68 (F) (HE × 200) and α-inhibin (G) (HE × 200). (H) Immunochemistry confirmed that samples were negative for GFAP (HE × 100).

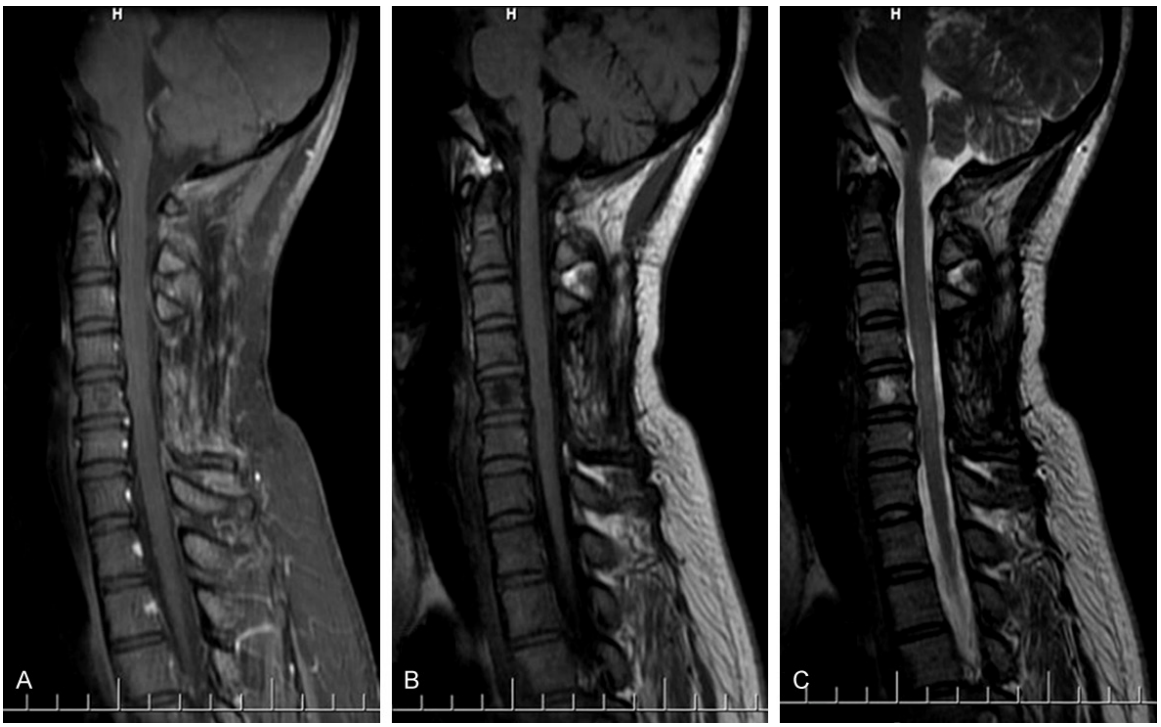

Figure 3. A-C. Postoperative MRI of the spine revealed no evidence of tumor recurrence. The lesion inside the C5 vertebrae was stable.

tein chip assay (CA15-3 14.38 KU/L, CA125 2.48 KU/L, CA19-9 6.30 KU/L, CA242 1.91 KU/L, Fer 13.77 ng/ml, NSE <1.0 ng/ml, free-β-HCG 0.10 ng/ml, PSA <0.04 ng/ml, free-PSA <0.02 ng/ml, AFP <0.24 ng/ml, CEA 0.60 ng/ml, HCG <0.01 ng/ml).

The patient underwent a C4-C5 laminectomy, and after dura mater incision, a gray, hard, well-circumscribed mass was exposed. The lesion arose from the C5 ventral root and elongated to the intervertebral foramina, which was completely removed. Pathological examination of the specimen revealed that the tumor was composed of clusters and sheets of large rounded, polygonal cells with abundant cytoplasm containing numerous eosinophilic granules. Nuclei were small, oval-to-spherical, and eccentric (**Figure 2A**, **2B**). No significant mitotic figures were identified. Immunostaining for Ki-67 antigen was less than 1%, indicating a low proliferative index (**Figure 2C**). The tumor tissue was positive for S-100, NSE, CD68 and α-inhibin (**Figure 2D-G**). Tumor cells were negative for calretinin, GFAP, AE1/AE3 and EMA (**Figure 2H**). Consequently, the tumor proved to be a GCT. At the 3-month follow-up examination, the patient's muscle weakness and sensory deficits were resolved and presently the patient is alive and symptom-free without evidence of tumor recurrence at 44 months of follow-up, and the lesion located inside the C5 vertebrae is stable (**Figure 3A-C**).

Discussion

Granular cell tumor of the central nervous system was divided into two groups: GCT of the infundibulum and GCT originating from the peripheral nerve sheath [16]. Intraspinal GCT belongs to the latter group, which was first described by Markesbery in a 73-year-old de-

Table 1. Clinical dates and MRI features of reported cases with intradural granular cell tumor

No.	Main Author	Year	Age/Sex	Onset of Symptoms	Location	MRI Results		
						T1	T2	Enhancement
1	Markesbery WR [8]	1973	73/F	Upper gastrointestinal bleeding	C1 level (extramedullary)	None	None	None
2	Strömblad LG [9]	1987	10/F	Back pain	T12-L1 level (extramedullary)	None	None	None
3	Critchley GR [10]	1997	17/F	Thoracic back pain	T10 level (intramedullary)	S Hyperintense	Isointense	Homogeneous
4	Burton BJ [11]	1997	22/F	Back pain, muscle weakness	C2-C4 level (extramedullary)	NS	NS	NS
5	Takayama Y [12]	2004	49/M	Buttock and thigh pain	L1-L2 level (extramedullary)	Hypointense	S Hyperintense	Homogeneous
6	Qu J [13]	2009	16/F	Back, thoraco-lumbar pain	T11-T12 level (extramedullary)	Isointense	Hypointense	Homogeneous
7	Weinstein BJ [5]	2010	20/F	Abdominal pain, back pain	L1-L2 level (extramedullary)	Isointense	Isointense	Homogeneous
8	Lee CH [14]	2013	22/F	Muscle weakness, hypoesthesia	T1-T2 level (extramedullary)	Isointense	Isointense	Homogeneous
9	Lee CH [14]	2013	12/F	Arm pain and tingling	C5-C6 level (extramedullary)	Isointense	Isointense	Homogeneous
10	Vaghasiya VL [15]	2014	13/F	Left lower limb pain	L1-L3 level (extramedullary)	Isointense	Hypointense	Homogeneous
11	This report	-	35/F	Cervical pain	C4-C5 level (extramedullary)	Isointense	Hypointense	Homogeneous

F = female; M = male; C = Cervical; T = Thoracic; L = Lumbar; S = slightly; NS = not stated.

Table 2. Treatment, immunochemistry and follow up of reported cases with intradural granular cell tumor

No.	Main Author	Year	Tumor size (mm)	Tumor origin	Extent of resection	Immunochemistry				Follow up	Recurrence	Adjuvant therapy
						S-100	CD68	NSE	Ki-67			
1	Markesbery WR [8]	1973	10 × 21 × 7	NS	Autopsy	NS	NS	NS	NS	Autopsy	Autopsy	Autopsy
2	Strömblad LG [9]	1987	NS	Spinal nerve	Completely	+	NS	NS	NS	NS	NOR	None
3	Critchley GR [10]	1997	NS	Nerve root	NS	+	NS	NS	NS	22M	12M	Radiation
4	Burton BJ [11]	1997	NS	Nerve root	Near total excision	+	NS	NS	NS	28M	7M	Radiation
5	Takayama Y [12]	2004	20 × 11 × 11	L2 nerve	Completely	+	NS	+	NS	6M	NOR	None
6	Qu J [13]	2009	10 × 21 × 7	Coccygeal nerve	NS	+	+	NS	NS	NS	NS	None
7	Weinstein BJ [5]	2010	12 × 17	Nerve root	Completely	+	+	+	<1%	6M	NOR	None
8	Lee CH [14]	2013	22 × 13	Nerve root	Completely	+	+	NS	NS	12M	NOR	None
9	Lee CH [14]	2013	35 × 23	NS	Completely	+	NS	NS	NS	NS	NOR	None
10	Vaghasiya VL [15]	2014	25 × 32 × 60	NS	Partial residual	+	NS	+	<1%	NS	NOR	None
11	This report	-	5 × 18 × 22	Nerve root	Completely	+	+	+	<1%	44M	NOR	None

NS = not stated; L = Lumbar; "+" = positive; M = month; NOR = no evidence of recurrence.

ceased patient during autopsy [8]. To date, 10 cases of intraspinal GCT have been reported in the literature [5, 8-15]. Including this case, the mean age of patients with intraspinal GCT was 26.3 years, ranging from 10 to 73 years; only two patients have been older than 35 years of age, younger than those with diagnosed GCT at another position [2]. Intraspinal GCT revealed a notably female predominance, thus far, only one patient was male (**Table 1**).

The clinical presentation for intraspinal GCT is dependent on the location of the tumor and its effects on surrounding neural tissues and the spinal cord. Nerve root irritation symptoms such as pain, sensory paresthesia, sensory dysesthesias and motor weakness may occur in patients with intraspinal GCT. Pain is the most common and earliest presenting symptom and was documented in 9 of the 11 cases, most of them manifesting as local back pain or radicular pain (**Table 1**). On examination, most patients had mild to moderate motor deficits and sensory paresthesia. Tumor growth caused spinal cord compression that produced symptoms of myelopathy, including gait ataxia, sensory loss, weakness and hyperreflexia [5, 8-15]. Clinical manifestation of intraspinal GCT is similar to other extramedullary intraspinal tumors, such as schwannoma, meningioma and ependymoma [17-19].

MRI of 8 patients revealed that with T1-weighted imaging, isointense lesions were identified in 6 cases, hypointense lesion was noted in 1 case, and slightly hyperintense lesion occurred in 1 case. T2-weighted images revealed isointense lesions in 4 cases, hypointense lesions in 3 cases, and a slightly hyperintense lesion in 1 case. All lesions were enhanced homogeneously (**Table 1**). Imaging characteristics of intraspinal GCT are nonspecific and frequently cannot be differentiated from schwannoma and meningioma. Lee suggested that low signal intensity speckled dots in the tumor may be a differential diagnostic point for MRI results [14]. However, we did not observe this feature in our case or in prior reported cases of intraspinal GCT.

The diagnosis of intraspinal GCT is difficult prior to surgical intervention because of the nonspecific clinical and radiological characteristics. GCT mimic schwannomma even intraoperatively, as it tightly adhere to the nerve root and can be found in all described cases, hence we assumed this originated from the nerve root (**Table 2**). However, the median patient age at diagnosis of intraspinal nerve sheath tumor was 47 years of age and with a male predominance [17]. Thus, an intraspinal lesion in young female with the radiological features of a nerve sheath tumor, the differential diagnosis of GCT should be taken in our consideration despite its rarity.

Optimal treatment for intraspinal GCT is microsurgical *en-bloc* resection of the entire mass. Although there are no reports of metastasis or malignant change, intraspinal GCT has been reported to recur when total resection is not achieved [11]. Complete excision of some cases is difficult due to tumor infiltration into the spinal cord and nerve root involvement. Thus, tumor should be separated from the adherent nerve root if possible and sometimes, dissection of the nerve root which is assumed to be the mass origin is unavoidable. Hence, nerve root function should be confirmed with electrophysiological monitoring prior to surgery.

The extent of surgical resections has not been described for two patients with intraspinal GCT and a third patient was diagnosed during autopsy. In the other 8 cases, 6 were completely excised, one was nearly completely excised, and partial or residual tumor tissue was left behind in 1 case. Tumor recurred in a patient 12 months and a near total excision case 7 months respectively after the initial operation, and recurrent tumors were stabilized with adjuvant radiotherapy (**Table 2**). One recurrent GCT was atypical according to histopathology [11].

Our patient had a typical GCT according to histopathology, and featured clusters and sheets of large rounded, polygonal cells with abundant cytoplasm containing numerous eosinophilic granules, with small, oval-to-spherical, eccentric nuclei and tissue was positive for S-100, NSE, and CD68 [2-4, 6]. Malignant and benign GCT is histologically similar so 6 distinguishing histologic features are used for diagnosis: vesicular nuclei with large nucleoli, increased mitotic activity (>2 mitoses/10 high-power fields at 200 × magnification), necrosis, spindling, high nuclear to cytoplasmic ratios, and pleomorphism. Benign GCT lack these features, and GCT that fulfill one or two criteria are

classified as atypical, GCT meeting three or more criteria are classified as malignant [7]. Our patient had a benign GCT based on these criteria, and no malignant intraspinal GCT have been reported except one atypical intraspinal GCT [11].

Adjuvant radiotherapy have been thought to have no influence on the outcome of cerebral GCT, and no specific chemotherapy suggested for treating these patients [20, 21]. However, the recurred lesions of intraspinal GCT were stable by radiotherapy and Burton suggest that it could be of value in some cases [11], but another partial residual of intraspinal GCT have been shown not to increase in the absence of radiotherapy [15], the long term effectiveness of radiotherapy is uncertain. Pazopanib, a potent receptor tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 was used to treat a malignant GCT with metastatic lesions and, the tumors decreased in size according to contrast enhancement imaging in both soft tissues and lungs after four months of observation [22].

Conclusions

Despite its rarity, GCT should be considered in a differential diagnosis of intraspinal masses. Removal of as much of the lesion remain the first choice whenever possible, they have a tendency for local recurrence if completely excision not achieved. Distinction between malignant and benign intraspinal GCT is important to avoid inappropriate therapeutic management. Pazopanib is a novel approach for GCT management and radiotherapy has value for some cases, but longitudinal efficacy is unclear.

Disclosure of conflict of interest

None.

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