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## Bilateral and symmetric C1-C2 dumbbell ganglioneuromas associated with neurofibromatosis type 1: A case report

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**Author contributions:** Tan CY and Liu JW contributed equally to this work; Tan CY and Liu JW designed the report; Lin Y, Tie XX, Cheng P, Qi X, Gao Y, and Guo ZZ collected the clinical data of the patient; Tan CY and Liu JW analyzed the data and wrote the paper.

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### Abstract

#### BACKGROUND

Ganglioneuroma (GN) is a rare and benign tumor that originates from autonomic nervous system ganglion cells. The most frequently involved sites are the posterior mediastinum, the abdominal cavity, and the retroperitoneal space. It rarely occurs in the cervical area, compressing the spinal cord. Neurofibromatosis type 1 (NF-1) is an autosomal dominant inheritance disorder, whose prevalence rate approximates one per 3000.

#### CASE SUMMARY

We report an extremely rare case of bilateral and symmetric dumbbell GNs of the cervical spine with NF-1. A 27-year-old man with NF-1 presented with a one-year history of gradually progressive right upper extremity weakness and numbness in both hands. Magnetic resonance imaging showed bilateral and symmetric dumbbell lesions at the C1-C2 levels compressing the spinal cord. We performed total resection of bilateral tumors, and the postoperative histopathological diagnosis of the resected mass was GN. After operation, the preoperative symptoms were gradually relieved without complications. To our knowledge, this is the sixth report of cervical bilateral dumbbell GNs.

#### CONCLUSION

In some cases, cervical bilateral dumbbell GNs could be associated with NF-1. The exact diagnosis cannot be obtained before operation, and pathological outcome is the current gold standard. Surgical resection is the most effective option, and disease outcome is generally good after treatment.

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**Core tip:** Ganglioneuroma is the final mature form of neuroblastic tumors which mainly involves the posterior mediastinum and the retroperitoneal space. We report a rare case of cervical bilateral dumbbell ganglioneuromas associated with neurofibromatosis type 1. Only five cases have been reported. Due to non-specific symptoms, signs, and radiological images, it is difficult to make a definite diagnosis before postoperative pathology. The prognosis of this tumor is good. Complete resection is the exhaustive treatment. Furthermore, incomplete resection does not increase the risk of progression if tumor residuals are smaller than 2 cm.

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## INTRODUCTION

Ganglioneuroma (GN) is a rare, slow-growing, fully-differentiated tumor originating from neural crest cells of sympathetic ganglia or the adrenal medulla, with 60% occurring in children and young adults<sup>[1-3]</sup>. This benign tumor can arise *de novo* or results from neuroblastoma maturation (spontaneous remission phenomenon), spontaneously or following chemotherapy/radiotherapy<sup>[4]</sup>. Histologically, it comprises mature Schwann cells, ganglion cells, the fibrous tissue, and nerve fibers<sup>[5]</sup>. The most common anatomical sites include the posterior mediastinum (41.5%), the abdominal cavity including adrenal glands (21%), and the retroperitoneal space (37.5%)<sup>[6]</sup>. However, the tumor may occur in any location containing sympathetic nervous system cells, such as trigeminal GN reported by Deng *et al*<sup>[7]</sup> and GN of the external auditory canal and middle ear published by Almofada *et al*<sup>[8]</sup>. Occasionally, it grows into the spinal canal and causes heavy compression. Generally, GN is unilateral and solitary. Here, we report an extremely rare case with bilateral and symmetric dumbbell GNs of the cervical spine associated with neurofibromatosis type 1 (NF-1). NF-1, also known as von Recklinghausen disease, is usually present during the first decade of life. The diagnostic criteria for NF-1 were established by the National Institutes of Health<sup>[9]</sup>. The most common benign tumor in NF-1 is neurofibroma<sup>[10,11]</sup>. To the best of our knowledge, only five cases with bilateral and dumbbell GNs of the cervical spine have been previously reported in the English literature, including two associated with NF-1<sup>[1-3,12,13]</sup>. The purpose of this report is to present an additional case and discuss the related clinical features, diagnosis methods, surgical choice, and prognosis.

## CASE PRESENTATION

A 27-year-old man was referred to the Department of Neurosurgery of The First Hospital of China Medical University, presenting with a one-year history of gradually progressive right upper extremity weakness and numbness in both hands. One month previously, his parents found him walking unsteadily and turning aside. Physical examination revealed multiple coffee spots, cutaneous and subcutaneous neurofibromas. He had no family history of neurofibromatosis. Upon neurologic examination, muscular strengths of right and left limbs were graded as 4- and 4, respectively. Muscular tensions at both lower extremities were increased slightly, and deep reflexes were also hyperactive. Additionally, incomplete sensory loss below C3 was observed.

On cervical magnetic resonance imaging (MRI), we found multiple nodules around the periphery of bilateral carotid and vertebral arteries, which demonstrated low signal intensity on T1-weighted images, slightly high signal intensity on T2-weighted images, and intense contrast enhancement. The spinal cord signal intensity increased

at the C2 level due to compression. The bilateral intervertebral foramina at the C2-4 levels were expanded, with unusual soft tissue signal extending outside (Figure 1).

The patient underwent surgical decompression of the spinal cord in the prone position through posterior midline incision. After biting off the spinous process at the C2 level and the vertebral plate at the C1-2 levels, bilateral nerve root cuffs at the intervertebral foramen at the C1-2 levels were distended, crimping the dorsal dural sac. Then, the bilateral nerve root cuffs were incised, revealing a hard and tough reddish tumor. After total resection of the tumor piece by piece, dural sac compression was relieved. The dural sac was curved. Finally, we explored the subdural cavity, and no residual tumor was found.

Under a light microscope, tumor cells were spindle-shaped, with nearly the same size. The nucleus was fusiform, mitosis was rare, and ganglion cells were scattered in the tumor tissue. Immunohistochemistry showed S-100 (+), vimentin (+), NF (Scattered+), NeuN (Scattered+) and the Ki67 labeling index of 3% (Figure 2). Based on the above observations, the mass was diagnosed as GN.

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## FINAL DIAGNOSIS

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Bilateral and symmetric dumbbell GNs of the cervical spine with NF-1.

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## TREATMENT

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The patient underwent surgical decompression of the spinal cord in the prone position through posterior midline incision.

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## OUTCOME AND FOLLOW-UP

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The postoperative period was uneventful, with no neurological deficits. The preoperative symptoms of the patient were gradually relieved within a week. After a month, the patient returned to our hospital with a postoperative MRI scan showing total resection of bilateral tumors, with no recurrence (Figure 3).

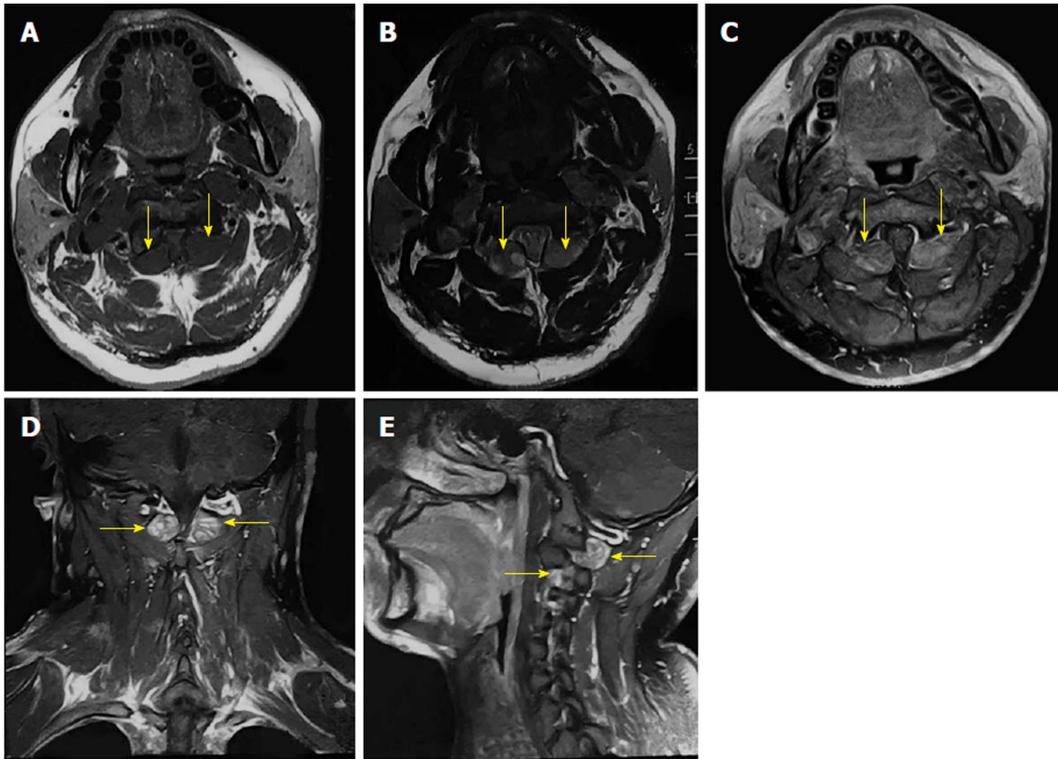
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## DISCUSSION

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GN was first described in 1870<sup>[14]</sup>. Since then, an increasing number of related case reports have been published, providing comprehensive data and knowledge. GN incidence is not well documented, although reports suggested that it may account for 0.1 to 0.5% of central nervous system tumors<sup>[15]</sup>. GN rarely involves the cervical region, compressing the spinal cord. Meanwhile, bilateral dumbbell GNs with NF-1 in the cervical region are even rarer. Only five cases have been reported in the current English literature (Table 1). Of these cases, three showed intradural extension and two displayed extradural growth; the current case also involved the extradural space. However, in the majority of cases whether multiple or single, given that these tumors originate from sensory root ganglions, extradural extension from the intervertebral foramen is more common. Stout *et al*<sup>[16]</sup> reported a male/female ratio of GN of approximately 2/3, but the cases summarized here were all male and NF-1 is irrespective of gender or ethnicity<sup>[17]</sup>. Whether gender difference exists in GN remains unknown. Weiss reported that GN is most frequently diagnosed in patients aged between 10 and 29 years<sup>[18]</sup>. The mean age at diagnosis of our six cases was 37 years, ranging from 15 to 72 years. This difference may be associated with symptom severity and patient enthusiasm for the hospital. Besides, NF-1 is usually present during the first decade of life and malignancies occur up to four to six times more common in patients with NF-1 than in the general population<sup>[9]</sup>. Therefore, GN associated with NF-1 seems to be more likely to diagnose earlier.

The tumor is hardly symptomatic or completely asymptomatic depending on its location. According to previous reports, only 10% of GNs may involve the spinal canal<sup>[19]</sup>. With tumor growth in the spinal canal, a series of compression symptoms may occur. In the six cases, tetraparesis caused by compression to the spinal cord from bilateral masses was the most frequent symptom, and commonly appeared earlier. Sensory dysfunction may also be involved. With time, some patients may develop respiratory problems. Intriguingly, few patients feel pain in the neck or develop palpable masses. In addition, a few tumors exhibit hormone secretion activity, presenting a broad range of symptoms depending on the hormones

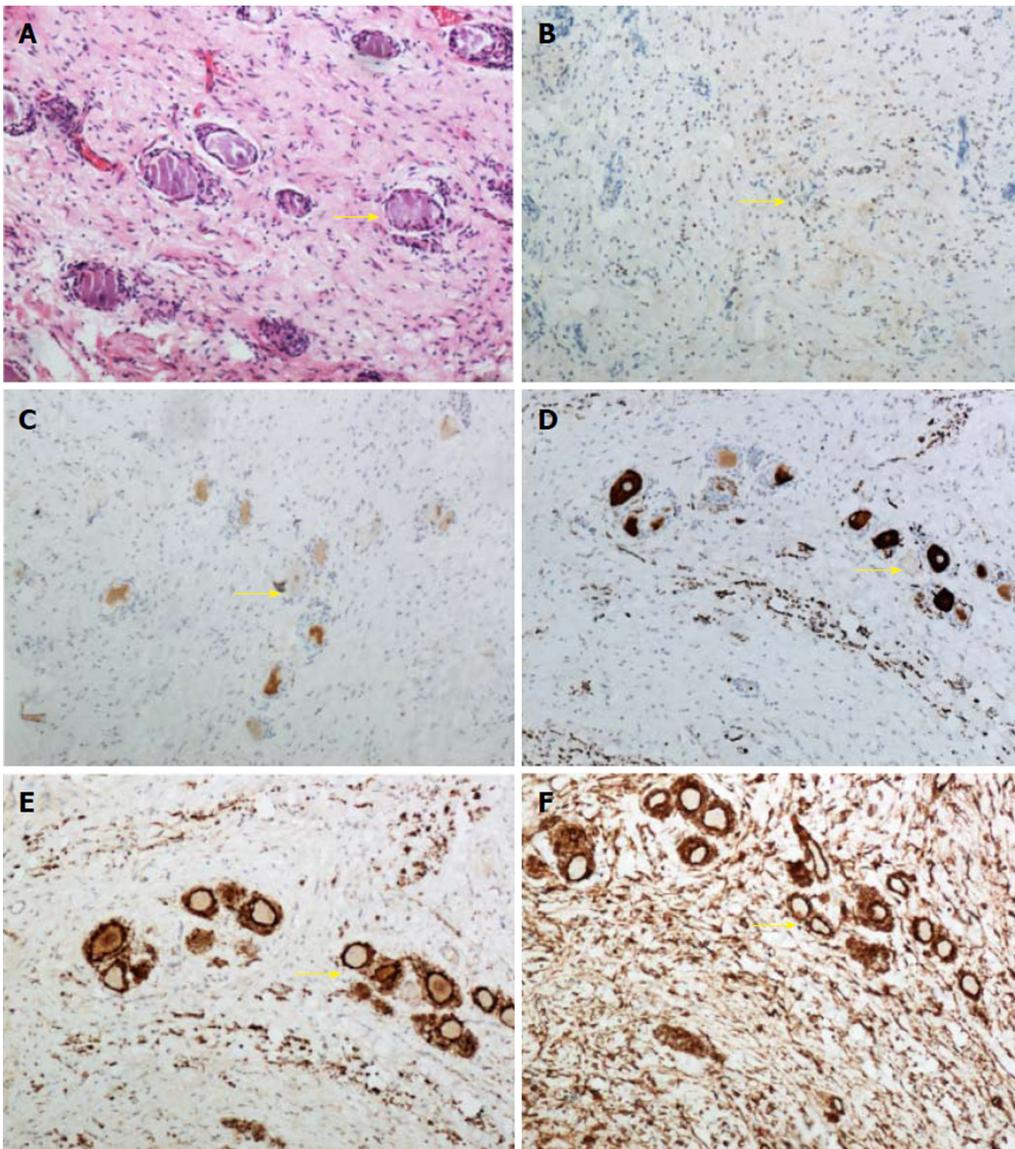


**Figure 1** Preoperative magnetic resonance images of the patient. A: Axial T1-weighted image shows bilateral dumbbell masses displaying low signal (arrows); B and D: Axial and coronal T2-weighted images show bilateral dumbbell masses displaying high signal (arrows); C and E: Axial and sagittal T1-weighted images after administration of gadolinium-diethylenetriaminepentaacetic acid depict prominent heterogeneous enhancement of the lesions (contrast dose: 15 mL: 7.04 g) (arrows).

produced, *e.g.*, catecholamine production causes hypertension, vasoactive intestinal peptide secretion results in diarrhea, and estrogen production causes female secondary sex characteristic and rophany<sup>[3]</sup>. Recently, we have demonstrated metaiodobenzylguanidine uptake and elevated catecholamine metabolite amounts in urine<sup>[20]</sup>. These characteristics may be used as tools for differential diagnosis.

It remains challenging to diagnose GN before operation because of non-specific features. MRI is a relatively accurate diagnostic tool for preoperative identification. Commonly, this tumor has the following manifestations: clearly defined boundary, encapsulation, homogeneous low or intermediate signal intensity in T1-weighted images and heterogeneous intermediate or high signal intensity in T2-weighted images. Besides, it exhibits slight, heterogeneous contrast enhancement. However, in many GN reports, MRI signals are not consistent. Reports analyzed and explained the relationship between the histological structure of this tumor and MRI manifestations. Interestingly, different Schwann's cell, ganglion cell, collagen fiber, fat tissue, or myxomatous stroma proportions within the tumor cause imaging differences<sup>[21]</sup>. Recently, diffusion-weighted MRI has been reported to be useful in differentiating benign and malignant paraspinal peripheral nerve sheath tumors. In their work, the apparent diffusion coefficient value of schwannomas is higher than that of neurofibromas because neurofibromas are more cellular tumors than schwannomas<sup>[22]</sup>.

As a subgroup of neuroblastic tumors, which range from immature, undifferentiated to mature, differentiated tumors, GN is the final mature form according to the International Neuroblastoma Pathology Classification<sup>[23]</sup>. Although it is a benign lesion, progression, late relapse, and even malignant transformation have also been reported<sup>[24,25]</sup>. Thus, long-term radiological follow-up is essential. Resection is currently the most direct and effective treatment option for such lesions. The six cases reported all underwent operation; of these, two reached complete excision, including the present one. None of the six patients developed complications. Postoperative quality of life was better than preoperative one in all the cases. Considering the purpose of the surgical treatment was to decompress the spinal cord, in some cases it is not necessary to achieve total resection, *e.g.*, when the paraspinal portion of the tumor causes no symptoms. Instead, performing total resection blindly may affect spine cord stability and even injure it, causing severe complications. A more cautious surgical approach in such situations should be suggested<sup>[26]</sup>. Furthermore, incomplete resection does not increase the risk of progression when the residual tumor is smaller than 2 cm<sup>[20]</sup>. Large residual tumors with local progression



**Figure 2 Histopathology of the resected lesion.** A: Hematoxylin and eosin staining showing spindle-shaped tumor cells, fusiform nuclei, and ganglion cells scattered in the tumor tissue (arrow). B-F: Immunohistochemistry showing Ki-67 (1%+) (B), NeuN (Scattered+) (C), NF (Scattered+) (D), S-100 (+) (E), and Vimentin (+) (F) (arrows).

may contain immature components. Therefore, how to ensure that immature components are removed during the initial surgery appears to be particularly important. Recently, biopsy has been used in GN diagnosis, but it is not always reliable and even misleading preoperatively. Whether it could help define prognosis after operation is worth investigating. Postoperative chemotherapy seems not to be sufficient in previously reported patients<sup>[20]</sup>.

## CONCLUSION

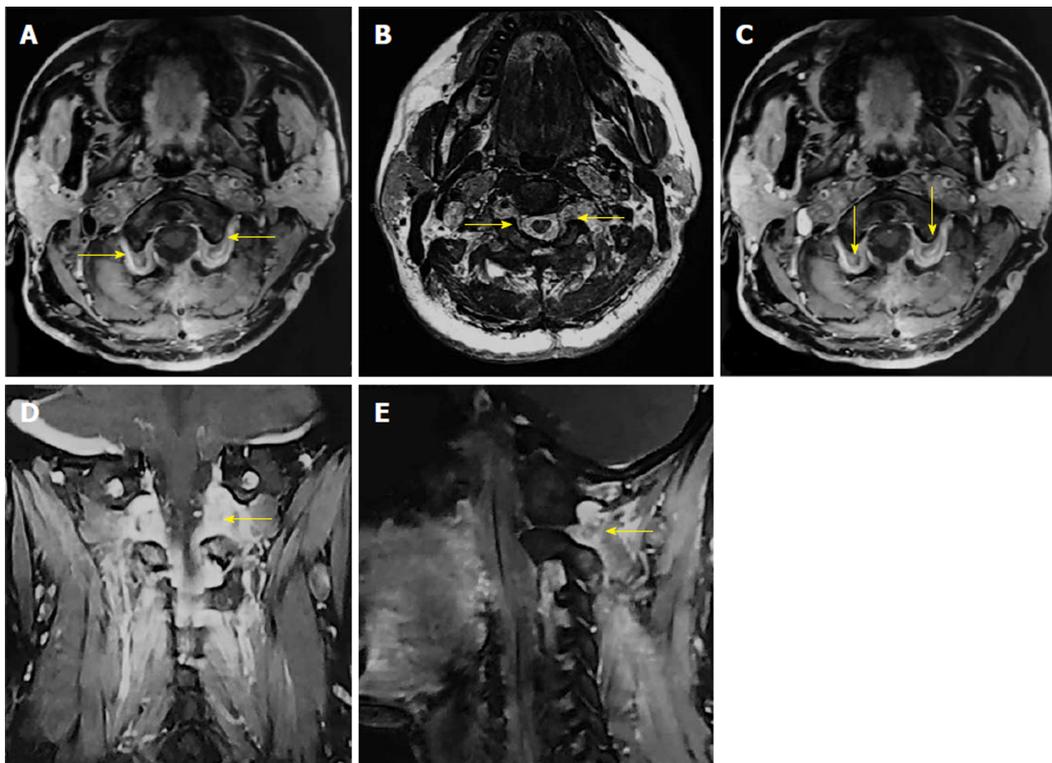
In conclusion, cervical bilateral dumbbell GNs causing spinal cord compression with associated symptoms are extremely rare. In some cases, such tumors could be associated with NF-1. The exact diagnosis cannot be obtained before operation, and pathological outcome is the current gold standard. Surgical resection is the most effective option, and disease outcome is generally good after treatment.

The patient in our case underwent total resection, but we suggest it is not necessary to reach complete resection by literature review. Our study demonstrates that this tumor has a good prognosis after operation and total resection is not necessary.

**Table 1** Summary of previously reported cases with cervical bilateral dumbbell ganglioneuromas

Ref.	Age/Sex	Extension	Site	Treatment	NF-1	Presentation	Prognosis	Follow-up imaging
Hioki <i>et al</i> <sup>[12]</sup>	72/male	Intradural/extradural	C1-2	PR	-	Tetraparesis; sensory dysfunction	Symptom remission	No recurrence or increase after 2 yr
Kyoshima <i>et al</i> <sup>[3]</sup>	35/male	Intradural/extradural	C2-3	PR	+	Tetraparesis; respiratory dysfunction	Hypesthesia	None
Miyakoshi <i>et al</i> <sup>[2]</sup>	15/male	Extradural	C1-2; C3-4	PR	+	Tetraparesis; sensory dysfunction	Symptom remission	No recurrence or increase after 2 yr
Ugarriza <i>et al</i> <sup>[1]</sup>	53/male	Extradural	C2	TR	-	Tetraparesis; respiratory dysfunction; sensory dysfunction	Tetraparesis	None
Ando Hioki <i>et al</i> <sup>[13]</sup>	20/male	Intradural/extradural	C1-2; C2-3; C3-4	PR	-	Tetraparesis; sensory dysfunction	Symptom remission	No recurrence or increase after 2 yr

PR: Partial resection; TR: Total resection.



**Figure 3** Postoperative magnetic resonance images of the patient. Axial T1-weighted image (A), axial and coronal T2-weighted images (B and D), and axial and sagittal contrast-enhanced T1-weighted images (C and E) showing no evidence of recurrence (arrows).

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