Clinical Case Report

Medicine®

OPEN

Surgical treatment of malignant paraganglioma with spinal invasion in a juvenile patient

A case report

Shuzhong Liu, MD[a], Xi Zhou, MD[a], An Song, MD[b], Zhen Huo, MD[c], William A. Li, MD[d], Radhika Rastogi, MD[d], Yipeng Wang, MD[a], Yong Liu, MD[a,*]

Abstract

Rationale: Paragangliomas are rare neuroendocrine tumors that originate in specialized cells derived from the neural crest with metastasis to the thoracic spine being among the rarest forms. Here, we are presenting a detailed analysis of a case of malignant paraganglioma in the thoracic spinal region in a 14-year-old boy. Our focus is to emphasize the importance of considering malignant paraganglioma as a diagnosis and guiding the perioperative management upon surgical treatment. The management of these unique cases has yet to be well-documented.

Patient concerns: A 14-year-old boy presented with a 5-month history of continuous and progressive elevated blood pressure and back pain. The patient, who had been diagnosed of malignant paraganglioma in the left posterior mediastinum for 3 months, received surgical resection of paraganglioma in the left posterior mediastinum, which had involved the left intervertebral foramen of T4. However, the tumor was not completely resected during the first operation.

Diagnoses: Magnetic resonance imaging of spine and positron emission tomography-computed tomography showed spinal cord compression secondary to the epidural component of the T4 mass, with increased marrow infiltration of the left T4 intervertebral foramen, which was difficult to be removed. Postoperative pathology confirmed the diagnosis of spinal involvement of malignant paraganglioma.

Interventions: The patient underwent biopsy and percutaneous vertebroplasty of T4 and paravertebral lesions, and needle-track cement augmentation via a posterior approach.

Outcomes: The patient's neurological deficits improved significantly after the surgery, and the postoperative period was uneventful at the 10-month follow-up visit. There were no other complications associated with the operation during the follow-up period.

Lessons: Combined efforts of specialists from orthopedics, neurosurgery, thoracic surgery, and medical oncology led to the successful diagnosis and management of this patient. Malignant paraganglioma of thoracic spine, although rare, should be part of the differential diagnosis when the patient has a history of paraganglioma and presents with back pain and radiculopathy. We recommend the posterior approach for spinal decompression of the malignant paraganglioma when the tumor has caused neurological deficits. Osteoplasty by cement augmentation is also a good choice for surgical treatment. However, we need to take the potential risk of complications in bone cement applications into full consideration.

Abbreviations: CT = computed tomography, MIBG = metaiodobenzylguanidine, MRI = magnetic resonance imaging, PET-CT = positron emission tomography-computed tomography, RET = RET proto-oncogene, SDHB = succinate dehydrogenase B, SDHC = succinate dehydrogenase C, SDHD = succinate dehydrogenase D, VAS = visual analogue scale, VHL = Von Hippel-Lindau.

Keywords: cement augmentation, complication, malignant paraganglioma, perioperative management, surgical treatment, thoracic spinal invasion

Editor: N/A.

Written informed consent was obtained from the patient and patient's parents for publication of this article, a copy of which is available for review from the editors of Medicine. Because this article does not involve any human or animal trials, it did not require institutional ethical review and approval.

This study was supported by National Natural Science Foundation of China (Project No. 81871746; Grant recipient: Y.W.), and Peking Union Medical College Graduate Student Innovation Fund (2018) (Project No. 2018–1002–02–08; Grant recipient: S.L.). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The authors have no conflicts of interest to disclose.

[a] Department of Orthopaedic Surgery, [b] Department of Endocrinology, Key Laboratory of Endocrinology, National Health and Family Planning Commission, [c] Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [d] Department of Neurosurgery, School of Medicine, Wayne State University, Detroit, MI.

[*] Correspondence: Yong Liu, Department of Orthopaedic Surgery, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, No. 1 Shuaifuyuan Wangfujing, Beijing 100730, China (e-mail: liuyong_pumch@126.com).

How to cite this article: Liu S, Zhou X, Song A, Huo Z, Li WA, Rastogi R, Wang Y, Liu Y. Surgical treatment of malignant paraganglioma with spinal invasion in a juvenile patient. Medicine 2019;98:39(e17145).

Received: 27 January 2019 / Received in final form: 17 July 2019 / Accepted: 20 August 2019

http://dx.doi.org/10.1097/MD.0000000000017145

1. Introduction

Paragangliomas are rare neuroendocrine tumors that may produce catecholamines, where 80% to 90% of paragangliomas are found in the carotid body and jugular tissue.[1–3] They are highly vascularized tumors that can affect any part of the body, including the spine.[4–6] Metastatic spread to the thoracic spine is one of its rare manifestations. In fact, only about 40 cases of malignant paragangliomas of the thoracic spine have been reported in literature to date.[1–25] Clinical presentations can vary based on the region of the spinal lesions. Long-term endogenous overexposure to elevated serum catecholamines can lead to hemodynamic complications, including worsening arrhythmias and cardiomyopathy.[1–25] Diagnosis is established and confirmed via history taking, laboratory values, and pathological studies.[1–3] Due to the diversity and visual similarity of spinal lesions, it is complicated for surgeons to make an accurate diagnosis preoperatively. Here, we report an extremely rare case of malignant paraganglioma in the thoracic spine causing elevated blood pressure and back pain. To our knowledge, this is an extremely rare case of a juvenile patient diagnosed with malignant paraganglioma in the spine. Clinical studies looking at malignant spinal paragangliomas in juvenile patients is lacking due to the extremely low incidence rate, and only 3 cases of juvenile patients have been reported in literature.[9,25] In a review of the literature, we discuss the common perioperative considerations in patients with malignant paragangliomas in the thoracic spine level and how to manage the perioperative hemodynamic complications. The epidemiology, origins, diagnosis, treatment, and prognosis of malignant spinal paraganglioma are also discussed.

2. Case report

In April of 2018, a 14-year-old juvenile patient presented to another hospital with progressive elevated blood pressure and back pain. His computed tomography (CT) and magnetic resonance imaging (MRI) scan revealed features consistent with a malignant solid tumor (Fig. 1A–F and Fig. 2A–F). His MIBG scan done at the time demonstrated extra-adrenal hotspots in the region of the T4 and T5 vertebra level indicating a paraganglioma. After detailed analysis, surgical resection of paraganglioma in the left posterior mediastinum which had involved the left intervertebral foramen of T4 was performed in May of 2018. However, the tumor was not completely resected during the first operation in another hospital due to the high surgical risks. Three months later, the patient who had been diagnosed of malignant paraganglioma for 3 months presented to our institution. In his history of present illness, the patient stated he had been experiencing a paroxysmal and severe back pain for approximately 5 months. The pain in his back could reach 6 points using visual analogue scale and could not be alleviated with rest and hot compresses. The patient denied experiencing any other constitutional symptoms. No pertinent family history was identified, including, hypertension, cancer, and congenital birth difficulties.

On physical examination, the patient showed pressure pain and percussion pain in his thoracic spinal region, decreased sensation to pin-prick and fine-touch of his left lower limb and exhibited a 5-/5 strength in his left lower limb using Medical Research Council grading system. Deep tendon reflexes revealed normal for knee-jerk and Achilles tendon reflexes bilaterally. Ataxia, cranial nerves, mini mental, and the rest of the neurological examination showed no abnormalities. Preoperative hemodynamic and cardiovascular assessments included electrocardiogram, echocardiogram, and chest radiography. Preoperative laboratory assessment was conducted, including routine laboratory tests (electrolytes, liver and kidney function tests, complete blood count), tumor markers, and endocrinological evaluation. The results of the laboratory studies were almost within normal range. Genetic investigation was negative for RET, VHL, SDHB, SDHC, and SDHD mutations. Spinal MRIs were ordered to visualize the metastatic lesions, assess the stability of the vertebral column, and to aid in the formulation of a surgical approach. MRI of the spine showed the density of soft tissue, obvious bony destruction in the left intervertebral foramen region of T4, and mild spinal cord compression secondary to the mass, with increased marrow infiltration of T4 (Fig. 3A–G). Tumor

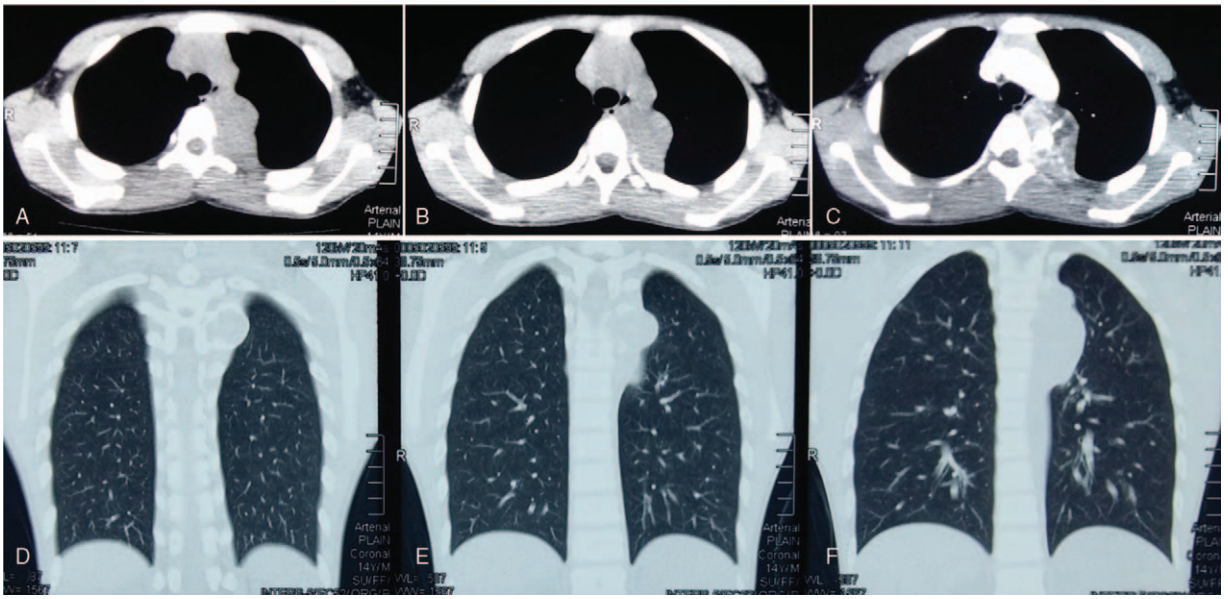

Figure 1. (A–F) Preoperative CT revealing thoracic lesions with high suspicion of spinal soft tissue tumors. CT = computed tomography.

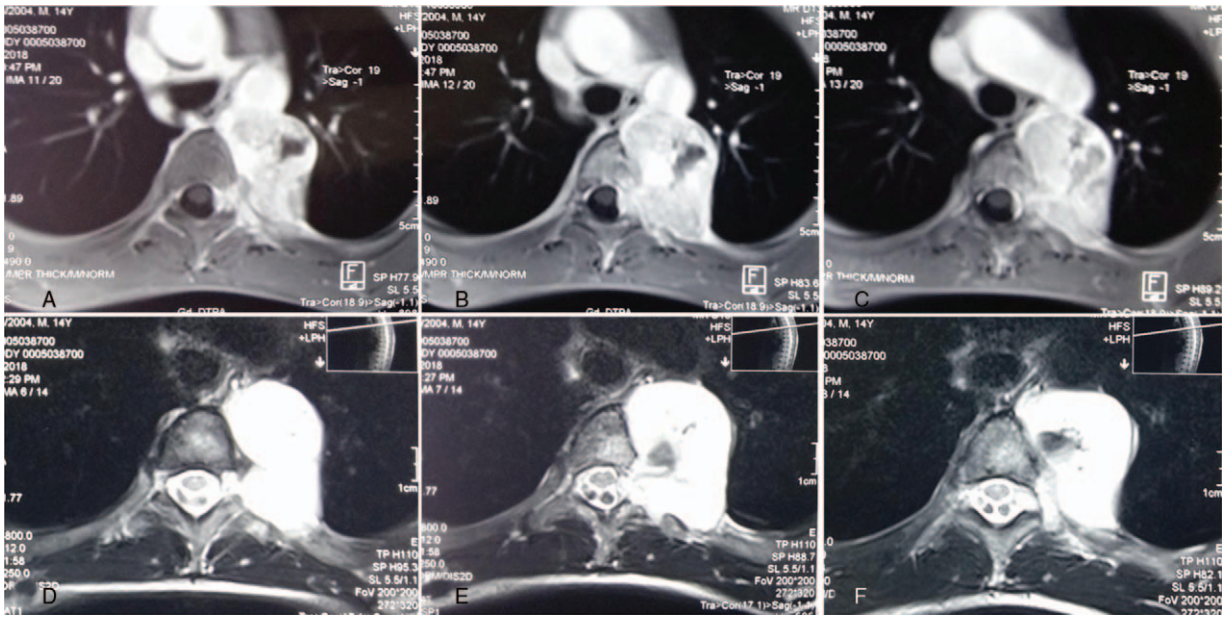

Figure 2. (A–F) Preoperative transverse MRI scan revealing the density of soft tissue measuring 7.0 cm × 5.0 cm × 4.0 cm, obvious bony destruction in the T4, and spinal cord compression caused by malignant paraganglioma, with increased metastatic marrow infiltration of the vertebrae. MRI = magnetic resonance imaging.

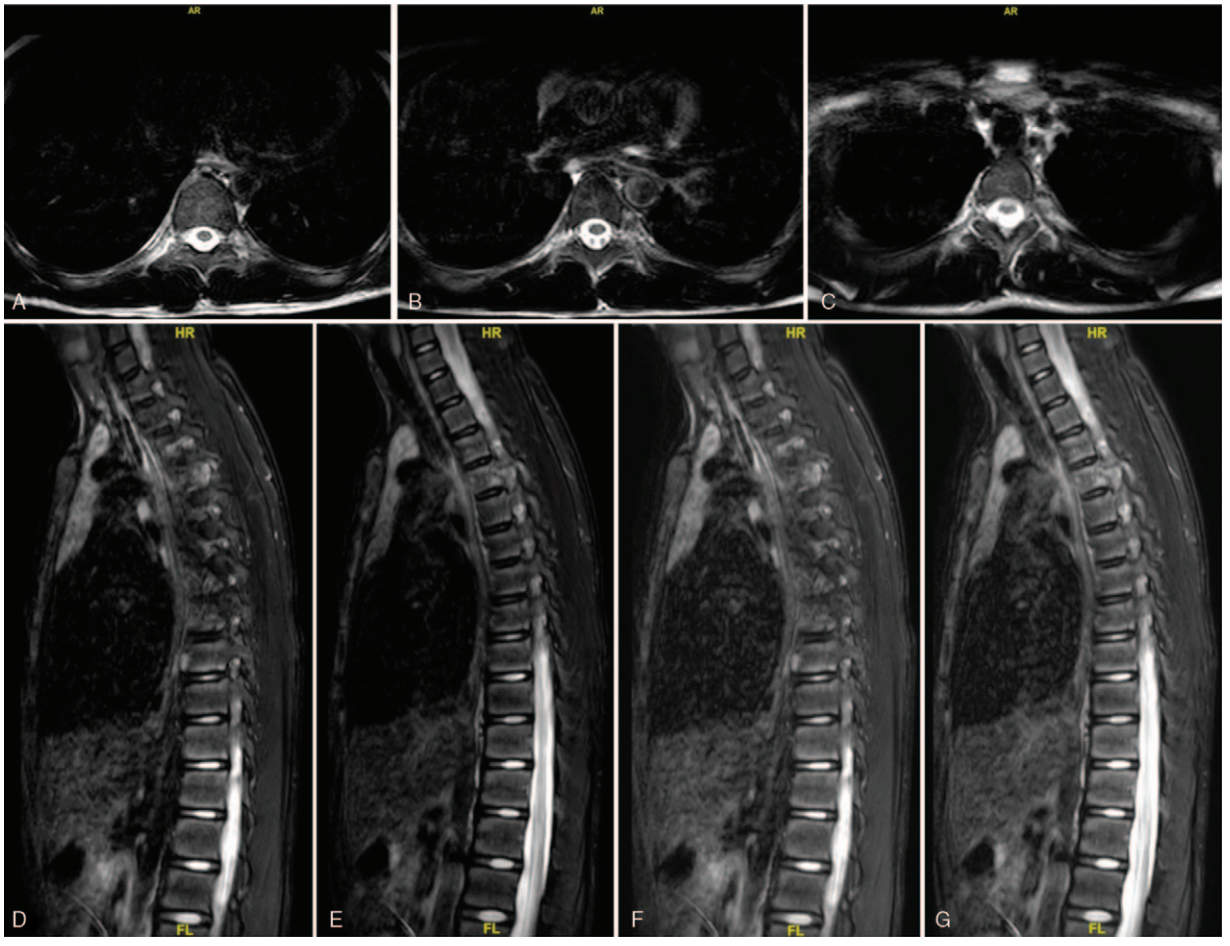

Figure 3. (A–G) Transverse and sagittal MRI scan showing the residual thoracic paraganglioma after the first operation. MRI = magnetic resonance imaging.

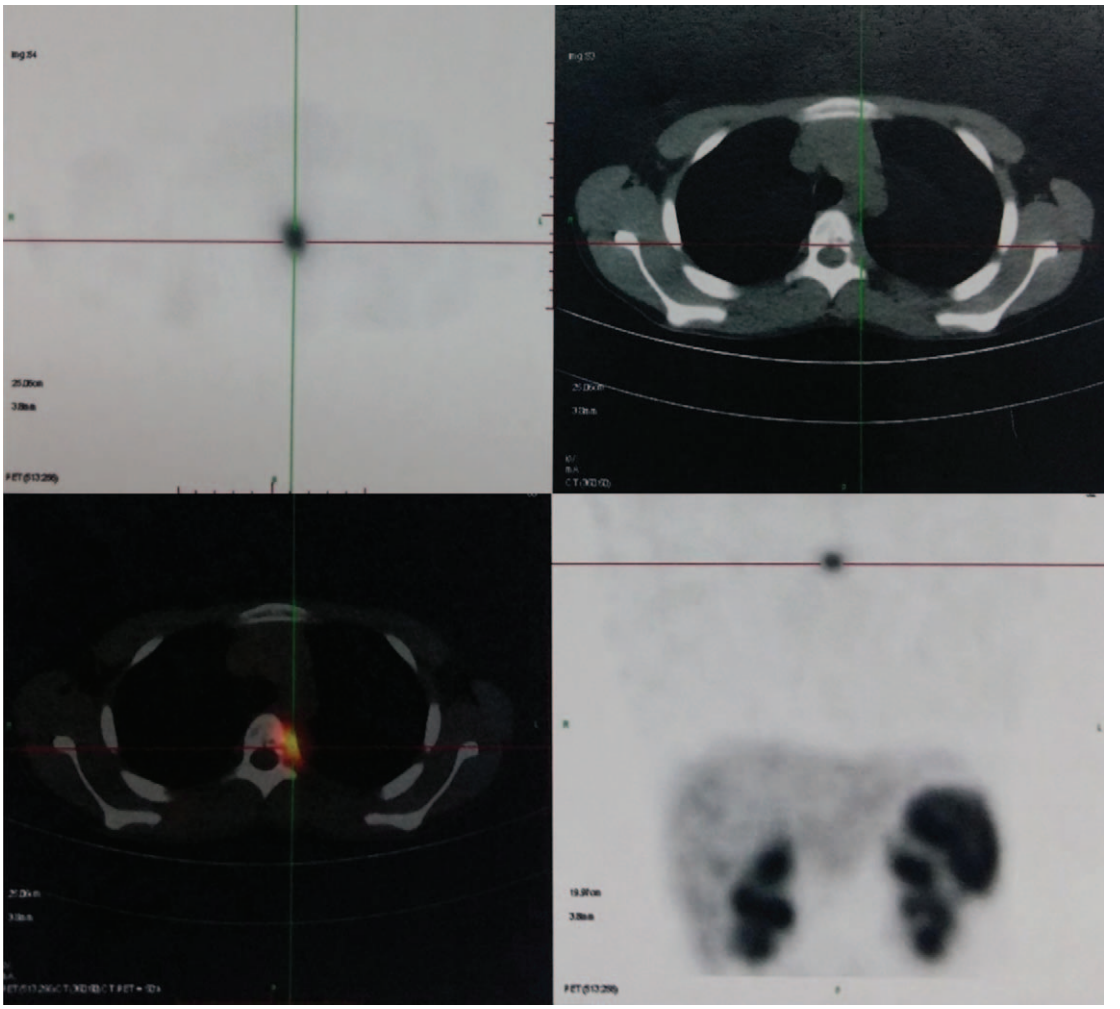

Figure 4. Positron emission tomography-computed tomography revealed the residual thoracic paraganglioma after the first operation.

infiltrated through T4 body into the posterior elements, thus extraosseously spread into the left lateral aspect of the epidural space extending posteriorly, resulting in spinal cord compression with the nerve root (Fig. 3A–G). The positron emission tomography-computed tomography (PET-CT) revealed high intake in T4, with high suspicion of malignant paraganglioma (Fig. 4).

Subsequently, cement augmentation was performed to destroy the functional tumor and stabilize the spine. We performed a cement augmentation procedure of the spinal tumor to alleviate the symptoms caused by the spinal cord compression and subsequently stabilize the vertebral spine to prevent multiple vertebral bodies from collapse. Because of the size and location of the lesion and the extent of the involvement, the risk of surgical intervention is exceedingly high. The blood pressure and heart rate markedly increased to 211/109 mm Hg and 70 beats/minute, respectively, when the needle penetrated the tumor, and gradually decreased to normal within 5 minutes. Postoperatively, X-ray and three-dimensional reconstruction CT scan of the thoracic spine revealed part of bone cement leaked into the spinal canal (Fig. 5A and B and Fig. 6A–I). However, the patient experienced pain relief but no other symptoms. Pathological examination confirmed the diagnosis of malignant paraganglioma (Fig. 7A–G). Pathological result was positive for chromogranin A, S-100 indicating paraganglioma, and biopsy samples were negative for Melan-A, AE1/AE3, calretinin, and α-inhibin, with 2% Ki-67 positive nuclei.

One week after the operation, the patient's left lower extremity muscle strength improved to grade V compared to the preoperative status, grade V-, and the symptoms was relieved significantly. Moreover, VAS score of his back pain improved to 0 to 1 points compared to the preoperative status, 8 points. The patient and his parents were unwilling to undertake any further treatments and was discharged and monitored on an outpatient basis. The dosage of phenoxybenzamine was gradually reduced, and was stopped 2 months later. The postoperative 10-month follow-up visit showed no tumor progression and no new symptoms.

3. Discussion

Malignant paragangliomas found in the spine are rare forms of cancer at the level of the thoracic region.[1–3,22–28] Thoracic tumors are particularly unique because preganglionic tissue is not normally found in this region, thus these paragangliomas are presumed to arise from the thoracic lateral horn sympathetic

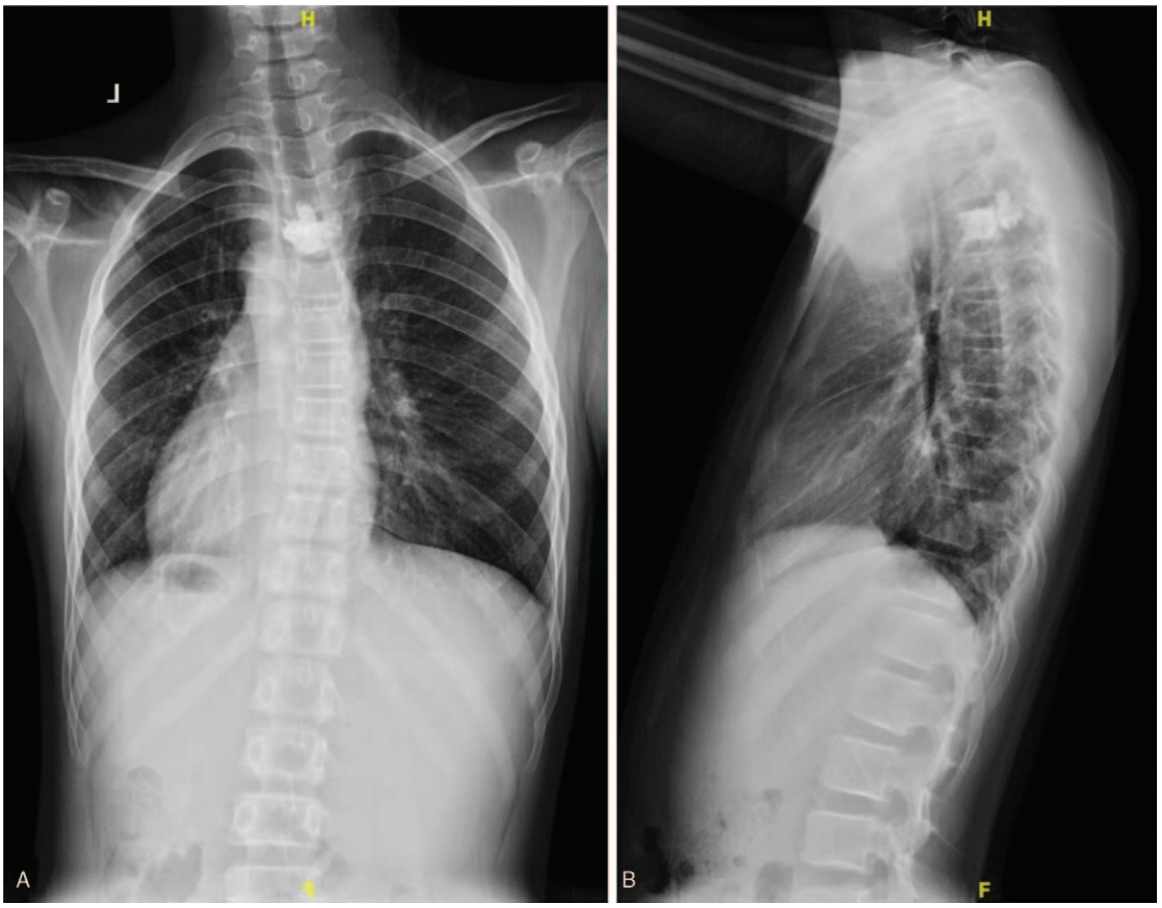

Figure 5. (A and B) Posteroanterior and lateral X-ray image of the thoracic spine obtained postoperatively.

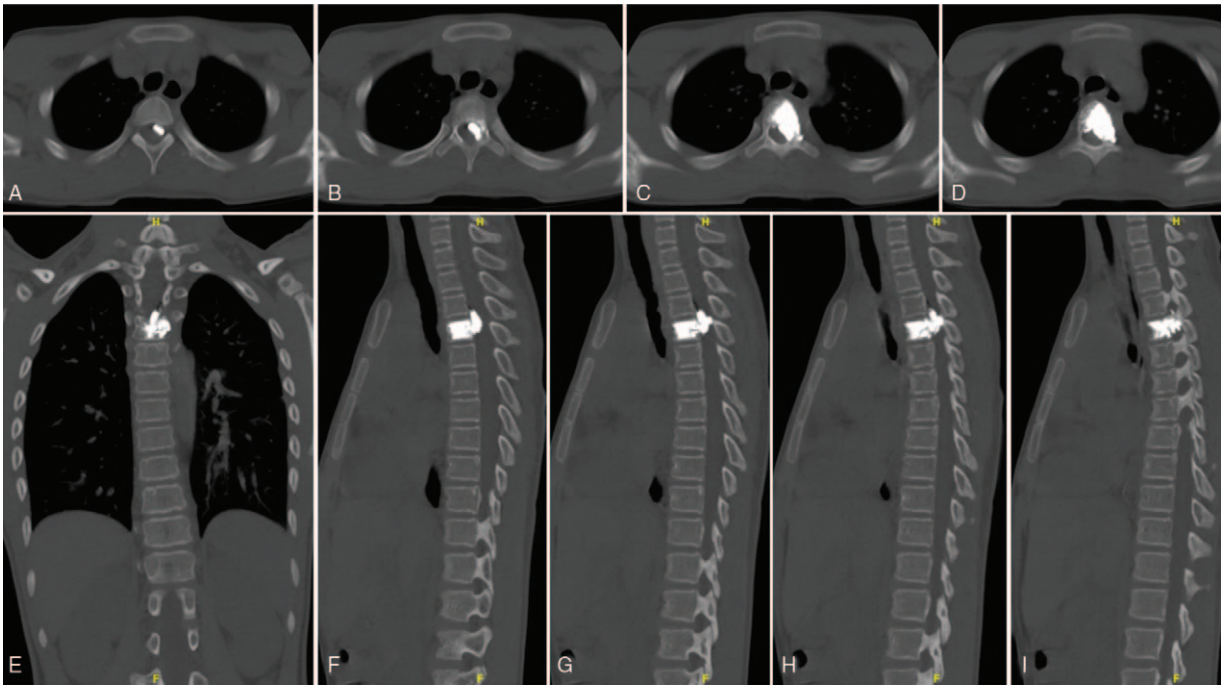

Figure 6. (A–I) A three-dimensional reconstruction CT scan showed that part of bone cement leaked into the spinal canal. CT = computed tomography.

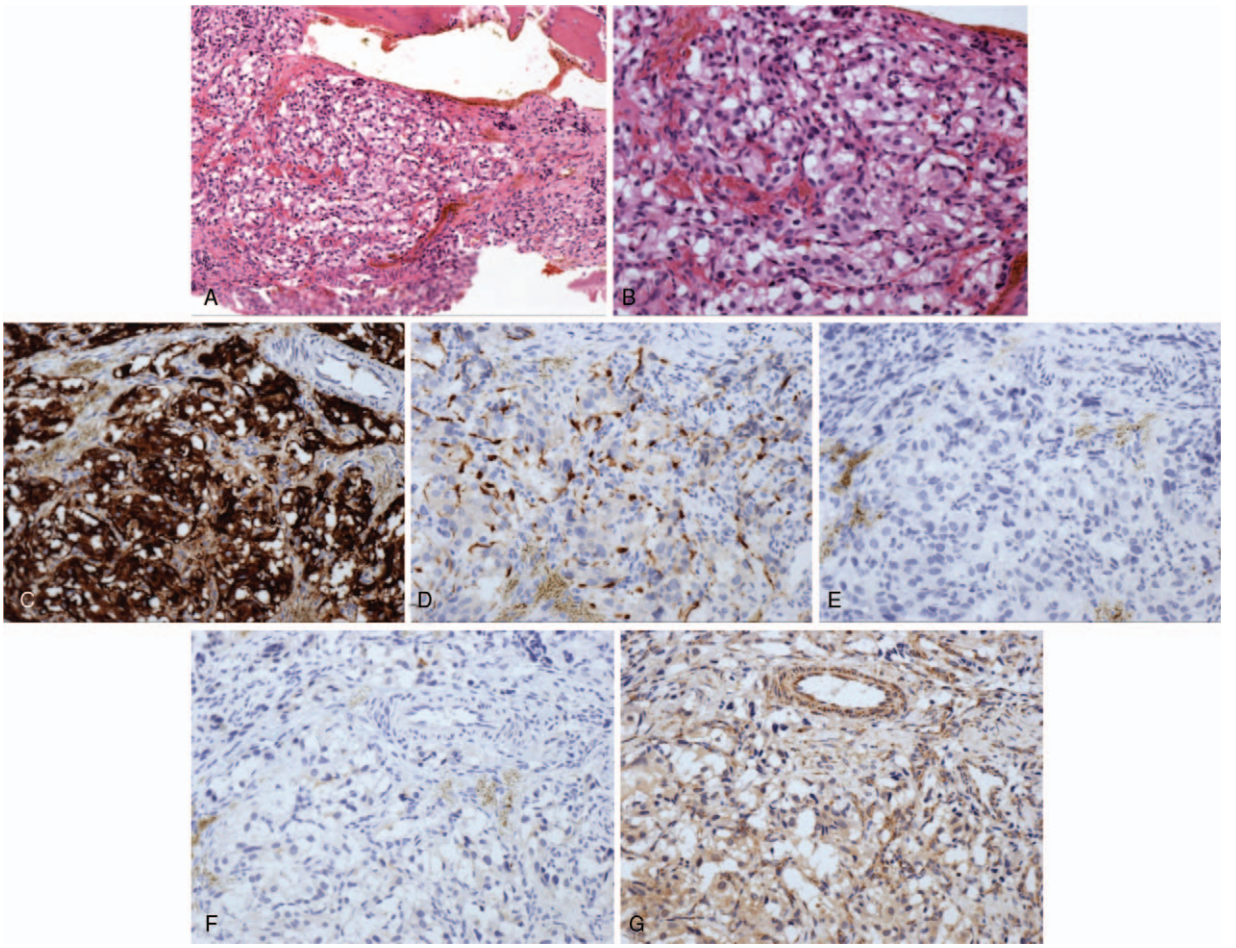

Figure 7. Pathologic histology of spinal tumors. (A and B) Microphotography showing characteristic nests of tumor cells separated by vascular septa (zellballen) with cells showing significant nuclear pleomorphism with prominent nucleoli (H&E, original magnification 100×, and 200×). (C) Chromogranin A immunostaining is strongly positive in the chromaffin cells. Chromogranin A is present in the secretory granules. (D) The sustentacular cells of the spinal metastases of pheochromocytoma showing characteristic staining of S100. (E and F) The sustentacular cells of the spinal metastases of paraganglioma showing AE1/AE3, Melan-A immunostaining is negative. (G) Ki-67 immunostaining shows 2% Ki-67 positive cells. Ki-67 staining is localized in the tumor nuclei.

neurons that communicate with the sympathetic trunk.[22,24,25] There are nearly 40 reported cases of thoracic spinal paragangliomas in the literature with the majority compressing the spinal cord and being found in the extradural space.[1–25] Based on our review of the case reports on PubMed, malignant spinal paraganglioma is slightly more common in the thoracic region and is more commonly diagnosed during the fourth and the fifth decades of life for the sporadic form.[1–25] Familial forms develop at a younger age and are usually bilateral, whereas sporadic tumors are unilateral.[26,27] Despite all technical, diagnostic, and therapeutic progress over the last decades, more systematic research should be done for further awareness. By increasing attentiveness for thoracic spinal paragangliomas, physicians may accurately diagnosis and manage this rare disorder.[22,25]

Typical manifestations include headaches, palpitations, paresthesia, fatigue, flushing, perspiration, or paroxysmal hypertension.[1–3] Among the above symptoms, paroxysmal hypertension can often mimic the most common cause of elevated blood pressure, making timely diagnosis of paraganglioma difficult without a high level of suspicion.[1–25] Few reports of malignant paragangliomas metastatic spread to the spine causing clinical symptoms have been documented so far. The location of the spinal lesion determines the neurological deficits, and there is a great deal of variability.[26,27] The location of the spinal lesion determines the neurological deficits, and there is a great deal of variability. Compression of the cervical vertebra often exhibit symptoms of paresthesia and weakness in the upper extremities, while those located in the thoracic and lumbar regions usually show symptoms of back pain, lower extremity paresthesia and weakness, and dysuria.[27] In our case, the patient sought medical attention after experiencing a 5-month history of back pain. Moreover, back pain is also a common symptom and it may make the differential diagnosis more difficult. Paraganglioma may become malignant via their metastatic tendency, and the metastases can help us diagnose a malignant paraganglioma.[1–3,26,27] Clinical studies looking at malignant paraganglioma in the spine is lacking due to the extremely low incidence rate. Imaging studies including CT, MRI, bone scan, and PET-CT are nonspecific, making it difficult to differentiate malignant spinal paraganglioma from other common spinal lesions.[28] However, imaging studies may play a crucial role in the decision making of surgical intervention. Genetic testing should be part of the diagnostic process. Von Hippel–Lindau syndrome, multiple endocrine neoplasia 2, and neurofibromatosis type 1 are

associated with pheochromocytoma and paraganglioma. Clinically, screening for such diseases should be carried out by clinical symptoms and mutation analyses.[27] Moreover, the discovery of gene mutations is closely related to the choice of treatment options. The "gold-standard" diagnosis of paraganglioma relies on pathological findings.[1–3,26,27] Due to its exceptional rarity, malignant paraganglioma of thoracic spine have not been well recognized and commonly appear as an ill-circumscribed lesion that occupies the spinal region.[26–29]

Surgery is the best treatment for malignant spinal paragangliomas causing back pain, radiculopathy, and paralysis.[1–25] This protocol enables accomplishment of 2 objectives: it alleviates the neurological deficits by decompressing the stenosis while provides histopathological specimens for diagnosis at the same time.[26,27] Nevertheless, there are several considerations to be kept in mind when deliberating on surgical intervention to malignant paraganglioma with spinal involvement, including preoperative hemodynamic instability and cardiac arrhythmia control, possible incomplete tumor resection, intraoperative blood loss, as well as postoperative adjuvant therapy.[26,27]

As the tumor is highly vascular, there may be significant intraoperative blood loss which may influence the hemodynamic instability and necessitate blood transfusion. Intraoperative blood loss can be significantly minimized by applications of preoperative alpha blockade and preoperative transarterial embolization of the main feeders.[26,27] During the preoperative period, patients should receive alpha blockade with phenoxybenzamine for at least 4 weeks with a blood pressure goal of 140/90 mm Hg, and their cardiovascular functions should also be monitored. Moreover, unnecessary manipulation of the tumor should be avoided, as it can encourage the tumor to spread to adjacent tissues and may promote catecholamine release, causing hemodynamic complications.

To date, surgical management of malignant paraganglioma of spine has remained under evaluation, with no standard criteria. Osteoplasty by cement augmentation may be a treatment option for patients with malignant paraganglioma in the spine, who cannot undergo appropriate surgery or decline open surgery.[26,27] However, we need to fully recognize the potential risk of complications in bone cement applications. The safety of this approach still needs to be confirmed in further studies with larger sample sizes and longer follow-up periods. One postoperative complication was cement leakage into the spinal canal and subsequent spinal cord compression.[26,27] The other aspect is for the oncological implications. With the injection of bone cement, the pressure in the vertebral body increases rapidly, and the tumor cells are more likely to release into blood and cause systemic metastases.[26,27] Under this circumstance, surgical extent, cement volume, and postoperative complications are critical factors that need further investigation.[26]

The survival benefit of resection of spinal metastases is still unproven. However, such a procedure does have the benefit aiming at controlling residual tumor.[1–25] The improved survival benefited from reducing the tumor burden, decompressing the spinal stenosis to alleviate radiculopathy, and facilitating subsequent chemotherapy and radiation therapy. Moreover, recurrence and metastasis are common postoperative complications, which we are anticipating may occur in our patient. Due to the rarity of this disorder, the rates of recurrence and the survival rates are still unproven to date. In terms of our single-center experience, the recurrence and metastasis of the disease are closely related to malignancy degree, tumor size, incomplete surgical resection, the local progression, and the decline of the body's immunity. They account for a significant percentage of morbidity following resection of malignant paraganglioma in the spine.[1–25]

In conclusion, we expect that this report can draw the attention from the research community to how we diagnosed and managed a patient with paraganglioma and secondary spinal involvement. Although uncommon, malignant paraganglioma of the spine should be part of the differential diagnosis when the patient presents with back pain and neurological deficits together with hypertension, and pathological examination remain the "gold standard" for diagnosing malignant paraganglioma. Moreover, osteoplasty by cement augmentation is also a good choice for surgical treatment. However, we need to take the potential risk of complications in bone cement applications into full consideration.

Acknowledgments

We would like to thank our colleagues at the Department of Orthopaedic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Author contributions

Conceptualization: Shuzhong Liu, An Song, Yipeng Wang, Yong Liu.
Funding acquisition: Shuzhong Liu, Yipeng Wang, Yong Liu.
Investigation: Shuzhong Liu, Xi Zhou, An Song, Zhen Huo, Yipeng Wang, Yong Liu.
Methodology: Shuzhong Liu.
Resources: Shuzhong Liu, Xi Zhou, Zhen Huo, Yong Liu.
Supervision: Yipeng Wang, Yong Liu.
Writing – original draft: Shuzhong Liu, An Song, William A. Li, Radhika Rastogi.
Writing – review & editing: Shuzhong Liu, William A. Li, Radhika Rastogi, Yipeng Wang, Yong Liu.

References

[1] Jia Q, Yin H, Yang J, et al. Treatment and outcome of metastatic paraganglioma of the spine. Eur Spine J 2018;27:859–67.
[2] Yin M, Huan Q, Sun Z, et al. Clinical characteristics and surgical treatment of spinal paraganglioma: a case series of 18patients. Clin Neurol Neurosurg 2017;158:20–6.
[3] Wang ZH, Wang YT, Cheng F, et al. Pathological features of paraganglioma in the lumbar spinal canal: a case report. Medicine (Baltimore) 2018;97:e12586.
[4] Dillard-Cannon E, Atsina KB, Ghobrial G, et al. Lumbar paraganglioma. J Clin Neurosci 2016;30:149–51.
[5] Turk O, Yaldiz C, Antar V, et al. Spinal paragangliomas: surgical treatment and follow-up outcomes in eight cases. Medicine (Baltimore) 2018;97:e12468.
[6] Jimenez P, Tatsui C, Jessop A, et al. Treatment for malignant pheochromocytomas and paragangliomas: 5 years of progress. Curr Oncol Rep 2017;19:83.
[7] Gusmão MS, Gomes EG, Fernandes RB, et al. Paraganglioma in the spine: case report. Rev Bras Ortop 2012;47:263–6.
[8] Asad S, Peters-Willke J, Nott L. Malignant paraganglioma, a rare presentation with foot drop: a case report. J Spine Surg 2015;1: 99–102.
[9] Lv G, Lu L, Dai Z. Paragangliomas of the spine. Turk Neurosurg 2017;27:401–7.
[10] Yokomoto-Umakoshi M, Umakoshi H, Tsuiki M, et al. Paraganglioma as a risk factor for bone metastasis. Endocr J 2018;65:253–60.

[11] Kim BJ, Kwak MK, Ahn SH, et al. Lower bone mass and higher bone resorption in pheochromocytoma: importance of sympathetic activity on human bone. J Clin Endocrinol Metab 2017;102: 2711–8.
[12] Akhtar S, Sattar S, Bari E, et al. Secretory paraspinal paraganglioma of thoracolumar spine: case report and review of literature. Surg Neurol Int 2016;7(Suppl 37):S889–92.
[13] Jeffs GJ, Lee GY, Wong GT. Functioning paraganglioma of the thoracic spine: case report. Neurosurgery 2003;53:992–5.
[14] Conti P, Mouchaty H, Spacca B, et al. Thoracic extradural paragangliomas: a case report and review of the literature. Spinal Cord 2006;44:120–5.
[15] Zileli M, Kalayci M, Basdemir G. Paraganglioma of the thoracic spine. J Clin Neurosci 2008;15:823–7.
[16] Kwan RB, Erasmus AM, Hunn AW, et al. Pre-operative embolisation of metastatic paraganglioma of the thoracic spine. J Clin Neurosci 2010;17:394–6.
[17] Nawaz MA, Samarage M, O'Neill K, Punjabi P. Management of a giant thoracic hypervascular paraspinal ganglioma. Ann Thorac Surg 2012;93:e7–8.
[18] Simpson LN, Hughes BD, Karikari IO, et al. Catecholamine-secreting paraganglioma of the thoracic spinal column: report of an unusual case and review of the literature. Neurosurgery 2012;70:E1049–52.
[19] Feng N, Li X, Gao HD, et al. Urinary bladder malignant paraganglioma with vertebral metastasis: a case report with literature review. Chin J Cancer 2013;32:624–8.
[20] Chacón-Quesada T, Rodriguez GJ, Maud A, et al. Trans-arterial onyx embolization of a functional thoracic paraganglioma. Neurointervention 2015;10:34–8.
[21] Jang Khan NA, Ullah S, Siddiqui HU, Karim A. Spinal cord compression by metastatic thoracic spine paraganglioma. J Ayub Med Coll Abbottabad 2016;28:617–9.
[22] Reddy A, Morón F. Primary extradural paraganglioma of the thoracic spine: a case report. J Radiol Case Rep 2017;11:1–7.
[23] Kapetanakis S, Chourmouzi D, Gkasdaris G, et al. Functional extra-adrenal paraganglioma of the retroperitoneum giving thoracolumbar spine metastases after a five-year disease-free follow-up: a rare malignant condition with challenging management. Pan Afr Med J 2017;28:94.
[24] Noorda RJ, Wuisman PI, Kummer AJ, et al. Nonfunctioning malignant paraganglioma of the posterior mediastinum with spinal cord compression. A case report. Spine (Phila Pa 1976) 1996;21:1703–9.
[25] Hutchins KD, Dickson D, Hameed M, Natarajan GA. Sudden death in a child due to an intrathoracic paraganglioma. Am J Forensic Med Pathol 1999;20:338–42.
[26] Liu S, Zhou X, Song A, et al. Successful treatment of malignant pheochromocytoma with sacrum metastases: a case report. Medicine (Baltimore) 2018;97:e12184.
[27] Liu S, Song A, Zhou X, et al. Malignant pheochromocytoma with multiple vertebral metastases causing acute incomplete paralysis during pregnancy: literature review with one case report. Medicine (Baltimore) 2017;96:e8535.
[28] Yi X, Zhang Y, Zhou C, et al. Lumbosacral intraspinal paraganglioma: clinicopathologic and computed tomography/magnetic resonance imaging features of 13 cases. World Neurosurg 2018;113:e586–97.
[29] Kapetanakis S, Chourmouzi D, Gkasdaris G, et al. A rare case of spinal cord compression due to cervical spine metastases from paraganglioma of the jugular foramen-how should it be treated? J Surg Case Rep 2018;2018:rjy005.