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Metastatic Paraganglioma of the Spine With *SDHB* Mutation: Case Report and Review of the Literature

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ABSTRACT

Background: Paragangliomas (PGLs) are rare neuroendocrine tumors that can arise from any autonomic ganglion of the body. Most PGLs do not metastasize. Here, we present a rare case of metastatic PGL of the spine in a patient with a germline pathogenic succinate dehydrogenase subunit B (*SDHB*) mutation.

Methods: In addition to a case report we provide a literature review of metastatic spinal PGL to highlight the importance of genetic testing and long-term surveillance of these patients.

Results: A 45-year-old woman with history of spinal nerve root PGL, 17 years prior, presented with back pain of several months' duration. Imaging revealed multilevel lytic lesions throughout the cervical, thoracic, and lumbar spine as well as involvement of the right mandibular condyle and clavicle. Percutaneous biopsy of the L1 spinal lesion confirmed metastatic PGL and the patient underwent posterior tumor resection and instrumented fusion of T7–T11. Postoperatively the patient was found to have a pathogenic *SDHB* deletion.

Conclusions: Patients with *SDHx* mutation, particularly *SDHB,* have increased risk of developing metastatic PGLs. Consequently, these individuals require long-term surveillance given the risk for developing new tumors or disease recurrence, even years to decades after primary tumor resection. Surgical management of spinal metastatic PGL involves correcting spinal instability, minimizing tumor burden, and alleviating epidural cord compression. In patients with metastatic PGL of the spine, genetic testing should be considered.

Tumors

Keywords: paraganglioma, *SDHB*, spine metastasis

INTRODUCTION

Paragangliomas (PGLs) are rare neuroendocrine tumors that can develop anywhere along the sympathetic and parasympathetic ganglia of the body with an estimated prevalence of 0.2 to 1 per 100,000.[1,2] When PGLs arise from chromaffin cells they frequently overproduce catecholamines. PGLs arising from adrenal chromaffin cells are commonly known as pheochromocytomas and account for 80%–85% of chromaffin cell PGLs.[3] Extra-adrenal PGLs are less frequent, are primarily found along the parasympathetic ganglia of the head and neck, and are more likely to be biochemically silent.[4,5] Extra-adrenal PGLs generally present between ages 40 and 50 with symptoms of mass effect specific to their location of origin.[5–7]

Most PGLs do not metastasize, with only 10%–17% ultimately being metastatic, although extra-adrenal PGLs are thought to have greater metastatic potential.[8,9] Diagnosis of metastatic PGL is difficult as there are no reliable cellular or molecular markers of metastatic disease, and thus progression is necessary for diagnosis.[8,10] Given the rarity of metastatic disease, there is a relative paucity of literature on metastatic extra-adrenal PGL, especially for spinal metastasis.[4,10–14] Here, we present a report of a patient with metastatic extra-adrenal PGL of the spine presenting 27 years after resection of primary spinal nerve root PGL who was found to have a germline succinate dehydrogenase subunit B (*SDHB*) mutation.

CASE PRESENTATION

A 45-year-old woman with history of a large (> 8 cm) spinal nerve root PGL, status postresection 27 years prior at an outside hospital, with a recurrence in the right tibia, status postresection 6 years prior also at an outside hospital, presented for care at our institution with severe thoracic back pain radiating around the rib cage for several months' duration, which was worse with movement. She endorsed feeling

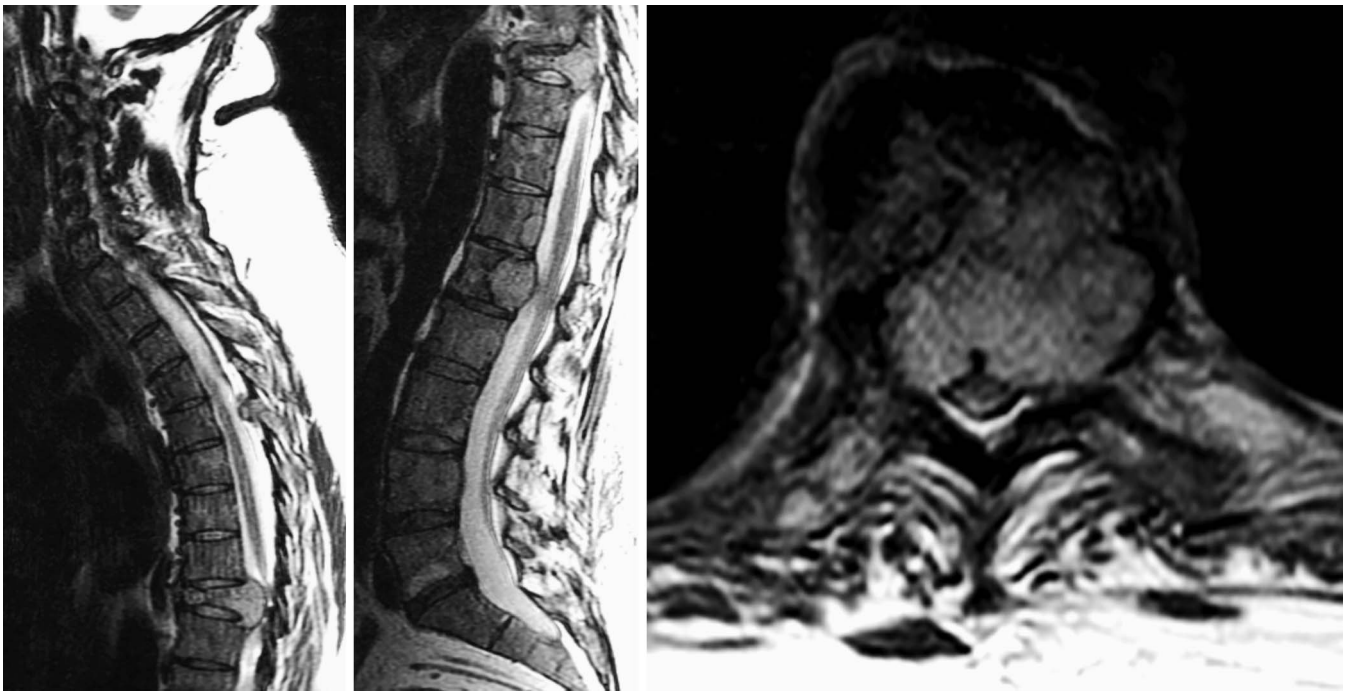

Figure 1. Preoperative T2 magnetic resonance imaging (MRI) complete spine images showing extensive metastatic disease of the spine. (Left) Sagittal T2 MRI of the upper spine showing pathologic compression fracture of the T9 vertebral body with retropulsion of the posterior vertebral body obliterating the cerebrospinal fluid space. (Middle) Sagittal T2 MRI of the lower spine showing extensive metastatic disease throughout the lumbar spine. (Right) Axial T2 MRI at the level of the T9 vertebral body.

weak, although she was able to ambulate normally. She denied lower extremity symptoms, saddle anesthesia, and changes in urination or defecation. Physical exam was normal except for tenderness to palpation along the lower thoracic spine. She reported no overt signs of catecholamine excess such as tremors, headaches, visual symptoms, palpitations, weight loss, and diaphoresis. Preoperatively, both her blood pressure and pulse were within normal limits and she was not on any antihypertensive medications. On imaging with computed tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose positron emission tomography, she was found to have multilevel lytic lesions throughout the cervical, thoracic, and lumbar spine at C1, C4–C7, L1–L3, as well as involvement of the right mandibular condyle and clavicle. She had compression fractures of the C3 and T9 vertebral bodies both with greater than 80% loss of height, and retropulsion causing moderate-to-severe spinal canal stenosis. Spinal canal extension was present at T4, T5, T9, L1, and L4, and most severe at T9, which was considered to be the symptomatic level (Figure 1).

On the day after admission, percutaneous biopsy was performed of the L1 soft tissue lesion, and this confirmed metastatic PGL. Histologic sections of the biopsy specimen contained abundant groups of nested cells characterized by mild anisonucleosis, stippled nuclear chromatin, and abundant pale eosinophilic and slightly granular cytoplasm. Mitotic figures were seen at 7 in 10 high-power fields (Figure 2A). Immunohistochemical stains for S100, synaptophysin, chromogranin, and succinate dehydrogenase subunit B (SDHB) were performed. Tumor cells stained positive for synaptophysin (Figure 2B) and chromogranin. The S100 stain highlighted a fragmented network of sustenacular cells surrounding the neoplastic cells (Figure 2C). SDHB showed intracytoplasmic granular positivity within vascular endothelium but complete loss of staining in the tumor cells (Figure 2D), indicative of an underlying *SDHx* gene mutation.

Given clinical concern for spinal instability and epidural cord compression, the patient underwent lateral extracavitary approach for partial corpectomy and laminectomy for tumor resection at T9 and posterior instrumented fusion of T7–T11. The patient tolerated the procedure well with 400 mL of blood loss and no hypertensive complications. In consultation with anesthesiology, preoperative alpha blockade was not performed.[15] Grossly, the tumor appeared as fragments of red-brown soft tumor mixed with blood and trabecular bone fragments. Histologic and immunohistochemical analysis was consistent with recent biopsy. A postoperative x-ray was obtained to confirm ade-

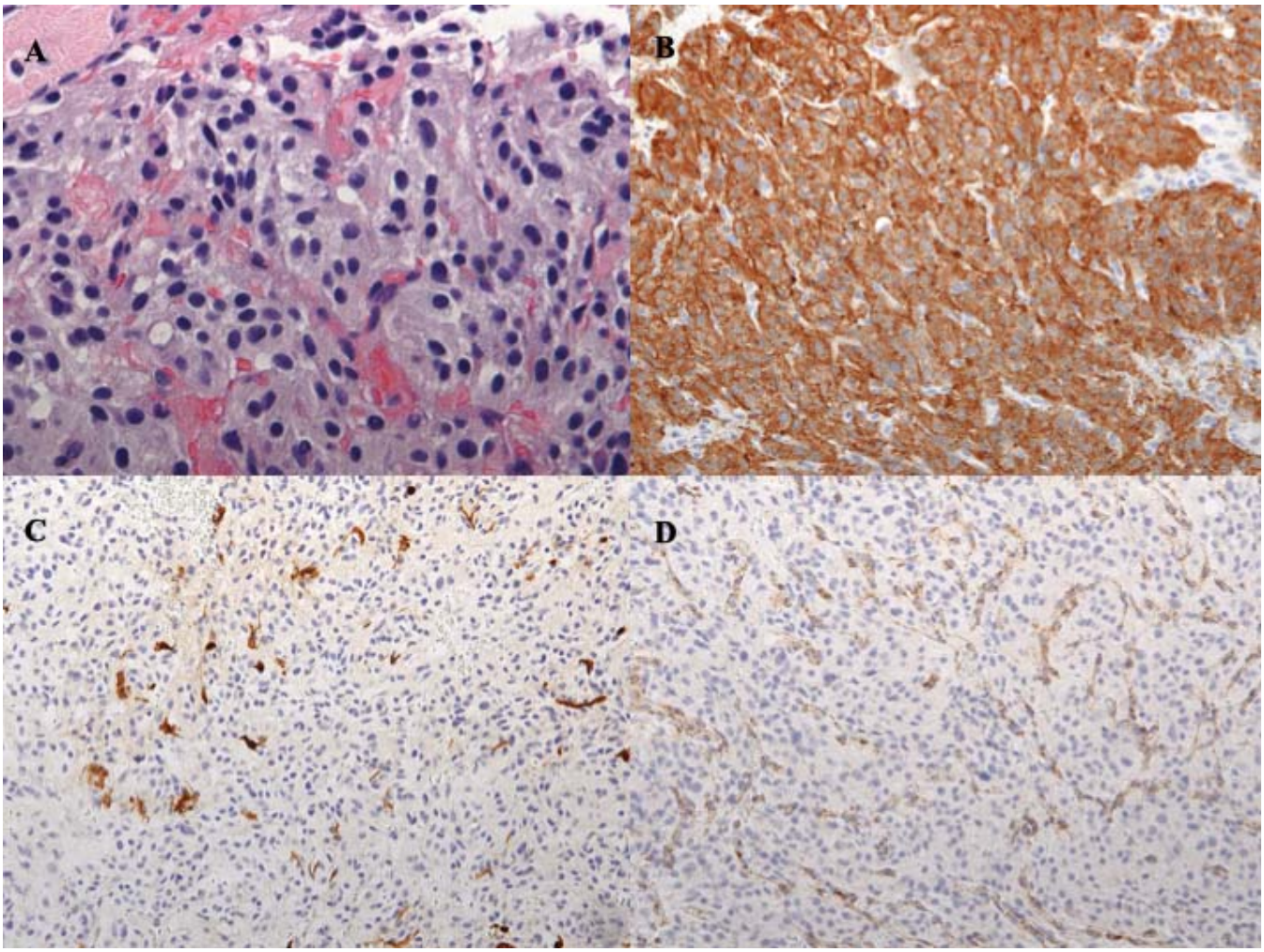

Figure 2. Histologic and immunohistochemical sections of metastatic paraganglioma biopsy specimen. (A) Hematoxylin-eosin stain of metastatic paraganglioma (×60). Histologic sections of the biopsy specimen showing an epithelioid proliferation of cells with nested architecture (''Zellballen'') with a delicate tumor vascular network between nests. The epithelioid cells show round to ovoid nuclei, minimal nuclear pleomorphism, and stippled chromatin with abundant granular amphophilic cytoplasm. Mitotic figures are seen at 7 in 10 high-power fields. (B) Immunohistochemical stain for synaptophysin showing positive granular cytoplasmic staining in tumor cells (×20). (C) Immunohistochemical stain for S-100 highlighting fragmented network of sustenacular cells surrounding tumor cells (×20). (D) Immunohistochemical stain for succinate dehydrogenase subunit B (SDHB) showing absence of SDHB among tumor cells, while maintaining positive internal control within vascular endothelium (×20).

quate positioning of hardware (Figure 3). Patient was discharged on postoperative day 5 with a thoracic lumbosacral orthosis brace and cervical collar. Although no family history of pheochromocytoma or PGL was obtained on review, germline testing was recommended with particular concern for *SDHB* mutation given negative SDHB immunohistochemistry and the aggressive metastatic nature of the PGL. The patient was found to have a pathogenic *SDHB* deletion (c.166_170delCCTCA) which resulted in a frame shift and protein truncation (p.P56Yfs*5). Genetic testing was arranged for at-risk relatives, where several affected individuals were identified.

At 18 months after surgery the patient's metastatic disease is stable (Figure 4). She has received 10 sessions of radiation to the spine and 8 cycles of chemotherapy with cyclophosphamide, dacarbazine, and vincristine. Additionally, she has been receiving monthly octreotide and denosumab injections to promote disease stabilization and prevent further bone loss, respectively. Given the patient's advanced disease, additional screening beyond standard response surveillance was not pursued.

RESULTS AND DISCUSSION

Metastatic extra-adrenal PGL to the spine is a rare phenomenon with limited case reports and 2 small case series described in the English literature (Table 1).[4,10,11] Here, we present what is, to our knowledge, the fourth case report of metastatic

Table 1. Previous reports of metastatic extra-adrenal PGL to the spine.

Authors	Country	Year	Age	Sex	Primary PGL size, cm	Primary PGL Location	Interval to Spinal Metastasis, y	Symptoms	Vertebral Level	Treatment	Follow-up, mo	Status	Genetic Testing Performed
Lau et al[4]	USA	2013	47	M	...	Retroperitoneum	0.5	Neck pain	C3	En bloc, CT	52	Dead	*SDHB* (c.380T>G)
Jia et al[10]	China	2018	34	M	6.5	Retroperitoneum	24	Pain, paraparesis	T2	Total, RT	27	AWD	No
			47	M	6.4	Upper mediastinum	37	Pain	T10	Total, RT	48	AWD	No
			47	M	8.5	Upper mediastinum	37	Pain	T3	En bloc	42	NED	No
			58	F	3.5	Retroperitoneum	47	Low back pain, sphincter disturbance	S1	En bloc, RT	54	NED	No
			23	M	7.6	Retroperitoneum	22.5	Pain, hypertension, headache	T2	Total, RT	12	NED	No
			24	M	7	Para-aortic	6	Low back pain, paraparesis	T2, L3, S1	Subtotal, CT	6	Dead	No
			29	M	6.5	Retroperitoneum	9	Pain, weakness, numbness in right arm	C2, L2–4	Subtotal, CT	35	Dead	No
			58	F	6	Retroperitoneum	15	Low back pain, paraparesis	L4	Subtotal, CT	9	AWD	No
			37	M	5.5	Para-aortic	3	Pain, paraparesis	T1	Total, RT	118	Dead	No
			25	M	4.5	Retroperitoneum	0.5	Pain, paraplegia	T7	Total, RT, CT	8	Dead	No
			37	M	6.6	Right mediastinum	3	Pain, paraparesis	T7-8	Total, RT	21	AWD	No
			64	M	8	Retroperitoneum	5	Neck pain, dysarthria	C3-4	Total, RT	30	NED	No
			40	M	6	Retroperitoneum	18	Pain, paraparesis	T3	En bloc	46	NED	No
			56	M	5.5	Retroperitoneum	12	Low back pain	L2, L4, S1	Subtotal, CT	24	Dead	No
			35	M	6.9	Retroperitoneum	10	Low back pain	S1	Total, RT	50	NED	No
Kapetanakis et al[11]	Greece	2017	48	M	...	Retroperitoneum	5	Back pain, palpitations, headache	T4	RT	...	...	No
Lehmen et al[12]	USA	2010	71	M	1.4	Carotid body	10	Neck pain, weakness	C5–6	Subtotal, RT	...	...	No
Kwan et al[14]	Australia	2009	46	M	...	Para-aortic	0	Elevated blood pressure, headaches, palpitations, weakness	T5	Subtotal	3	AWD	*SDHB* mutation
Mediouni et al[18]	France	2014	...	...	...	...	...	Discovered on imaging	Cervical, thoracic, lumbar spine	...	96	AWD	*SDHB*
			...	...	...	...	...	Back pain	Cervical, thoracic, lumbar, sacral spine	...	56	Dead	*SDHB*
			...	...	...	...	...	Weakness	L3	...	303	AWD	No *SDHx* mutation
			...	...	...	...	...	Discovered on imaging	Cervical, thoracic, lumbar spine	...	348	AWD	*SDHD*
			...	...	...	...	...	Low back pain	Lumbar spine	...	1	Dead	*SDHB*
			...	...	...	...	...	Bone pain	Cervical, thoracic, lumbar spine	...	247	AWD	No mutation
			...	...	...	...	...	Discovered on imaging	Thoracic Spine	...	21	AWD	*SDHB*
Narechania et al[21]	USA	2015	21	F	14	Retroperitoneum	0	Fever, tachycardia	T9, S1–S3	RT	...	...	*SDHB* (C.418G>T)
Bickmann et al[22]	Germany	2014	51	F	...	Mediastinum	0	Back pain	L3	...	...	...	*SDHC* (c.7C>T)
Feng et al[23]	China	2013	53	F	4.7	Bladder	19	Back pain, numbness, weakness, fever	T6	Total	18	NED	No

Table 1. Continued.

Authors	Country	Year	Age	Sex	Primary PGL size, cm	Primary PGL Location	Interval to Spinal Metastasis, y	Symptoms	Vertebral Level	Treatment	Follow-up, mo	Status	Genetic Testing Performed
Sasaki et al[24]	Japan	2013	72	M	...	Neck	5	Neck pain, weakness, shoulder pain	C4	Subtotal, RT	3	AWD	No
He et al[25]	China	2013	42	F	10	Retroperitoneum	0	Back pain	T10, L1, L2	Total	48	NED	No
Richter et al[26]	Germany	2011	16	F	15	Retroperitoneum	0.75	None	L1	CT, subtotal, RT	120	NED	No
Persu et al[27]	Belgium	2009	27	F	...	Carotid body	13	. . .	Multiple levels, unspecified	...	...	...	No *SDH*, *VHL*, *RET* mutations
Prabhu et al[28]	India	2008	29	F	...	Retroperitoneum	12	Back pain	L5	RT	...	...	No
Yamaguchi et al[29]	Japan	2003	27	M	...	Cardiac	0	Neck pain	C2, C4, T10	RT, subtotal	20	Dead	No
U-King-Im et al[30]	UK	2002	32	F	...	Carotid body	14	Back pain, paraplegia	T1–2, T9	RT	54	AWD	No
Mori et al[31]	Japan	2001	65	M	9	Retroperitoneum	12	Abdominal pain	T11	RT	...	...	No
Absher et al[32]	USA	2000	52	M	7	Retroperitoneum	0	Chest pain, back pain	T10, L1	CT, RT	...	...	No
Blasius et al[33]	Germany	1998	16	F	14	Retroperitoneum	0	Cramp-like pain	L3	Total, CT	10	NED	CGH: Isochromosome 1, loss of chromosome 3, low-level gains of chromosomes. 4, 5, 6q, 9p, llq, 13q
Brodkey et al[34]	USA	1995	54	M	...	Retroperitoneum	14	Neck pain, paresthesia, weakness	C2	Total	30	NED	No
			32	M	...	Carotid body	4	Back pain, paresthesia	T7, T10–T12	Subtotal, RT	24	AWD	No
Gabriel et al[35]	USA	1995	68	F	4	Glomus jugulare	21	Leg pain	Sacrum	RT	...	...	No
North et al[36]	USA	1990	28	F	4	Carotid body	9	Neck pain	C6, T9, L3	Subtotal, RT	12	AWD	No
Siddiqui et al[37]	UAE	1988	29	M	7	Para-aortic	6	Bone pain	Lumbar spine	RT, CT	24	Dead	No
Osborn et al[38]	USA	1986	47	F	...	Glomus jugulare	4	Neck pain, numbness, diplopia	C7	. . .	...	...	No
Kapetanakis et al[39]	Greece	2018	52	M	...	Carotid body	3	Neck pain, weakness	C2–3	Subtotal, RT	...	...	No
Lv et al[40]	China	2016	38	F	10	Retroperitoneum	0	Lumbago, numbness, weakness	L1	Subtotal, RT	96	AWD	No
Jang Khan et al[41]	Pakistan	2016	50	M	...	...	0	Back pain, weakness	T3–4	...	...	...	No
Kitagawa et al[42]	Japan	2015	61	M	...	Retroperitoneum	12	Back pain	T6	En bloc	36	AWD	No

Abbreviations: AWD, alive with disease; CGH, comparative genomic hybridization; CT, chemotherapy; NED, no evidence of disease; PGL, paraganglioma; RT, radiation therapy.

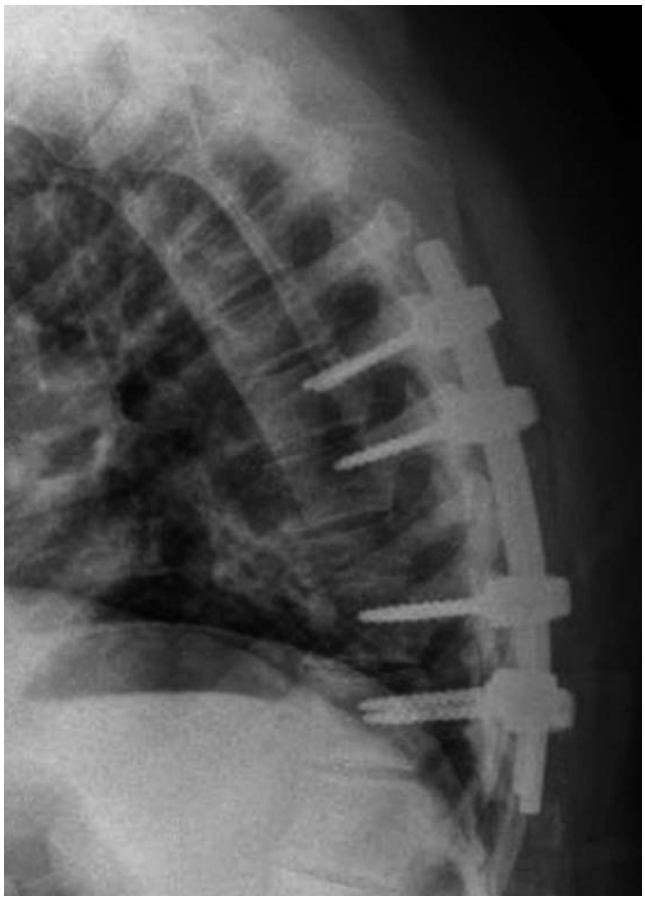

Figure 3. Postoperative sagittal x-ray of the spine showing instrumentation.

PGL to the spine found to have a mutation of an *SDH* subunit, (*SDHA, SDHB, SDHC, SDHD*) or assembly factor (*SDH-AF2*).[4] While there are limited data available on the metastatic tendencies of extra-adrenal PGL, studies looking at both metastatic pheochromocytomas and extra-adrenal PGLs have found bone to be the most common site of metastasis followed by liver and lung.[16–19] The spine is the most common site of bone metastasis.[16] In this case our patient had an interval of 27 years between total resection of her primary tumor and spinal metastasis. This extended interval is consistent with previous case reports as shown in Table 1.[10,12,20]

Genetic testing is recommended for all patients with PGLs and their first-degree relatives.[3,43] Over the past several years it has been shown that 20%–40% of patients with pheochromocytoma and extra-adrenal PGL have a germline mutation in *SDHx*, *NF1*, *VHL*, or *RET*.[44–46] While mutations in *NF1*, *VHL*, and *RET* genes cause well-characterized hereditary syndromes, the association between *SDHx* mutations and PGLs was more recently

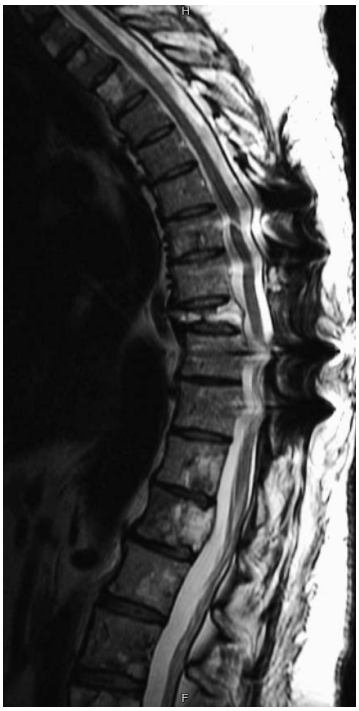

Figure 4. Post-operative T2 magnetic resonance imaging of thoracic spine at 1.5 years showing stable disease.

elucidated.[6,47–49] SDH is a mitochondrial enzyme complex that plays a role in both the tricarboxylic acid cycle and in the electron transport chain. *SDH* genes function as classical tumor suppressor genes where somatic loss of heterozygosity of the wild-type allele is observed in tumors.[6,50] While the precise pathogenic mechanism of *SDH*-mutation-dependent tumor formation is incompletely understood, the leading theory revolves around the role of succinate as an oncometabolite.[51] Specifically, it is thought that disruption of SDH complex function, which leads to an accumulation of succinate, increases the risk of cancer because succinate accumulation competitively inhibits α-ketoglutarate dependent enzymes such as prolyl hydroxylases and histone demethylases. Inhibition of hypoxia-inducible factor prolyl hydroxylases leads to the stabilization of hypoxia-inducible factors, which normally promote angiogenesis and cell survival in hypoxic conditions. Inhibition of histone demethylases causes a cell to adopt a hypermethylator phenotype that is thought to silence genes associated with neuroendocrine differentiation.[52–54] *SDHx* mutations are the most frequent hereditary cause of extra-adrenal PGLs with autosomal-dominant mutations in *SDHD* and *SDHB* being the most common.[6,49] Immunohistochemical and genetic testing all PGLs for *SDHx* mutation, and in

particular for *SDHB* mutation, is critically important as 30%–70% of metastatic PGLs have been found to have an *SDHB* germline mutation.[48,55,56] Thus, while there are no definite histological markers of metastatic PGL, *SDHB* mutation is a strong independent predictor in addition to primary tumor size > 5 cm and extra-adrenal location.[8] Interestingly, although our patient's primary tumor was reportedly > 8 cm in size and extra-adrenal in location she was not screened for *SDHB* mutation prior to receiving care at our institution for her spinal metastasis.

Whole-body scanning for detection of metastatic PGL is recommended at the time of primary tumor detection.[3] Metastatic disease can be detected through a combination of anatomical (CT, MRI) and scintigraphic imaging techniques (fluorodeoxyglucose positron emission tomography, metaiodobenzylguanidine scintigraphy, and more recently somatostatin receptor scintigraphy with 68Ga-DOTATATE).[57,58] Fluorodeoxyglucose positron emission tomography is currently the preferred imaging technique for detecting metastatic disease although several recent studies suggest that 68Ga-DOTATATE may have greater sensitivity particularly in the context of SDH-related disease.[3,59,60] Long-term imaging follow-up in addition to annual clinical evaluation and laboratory testing is required for all patients with PGLs as approximately 50% of metastatic PGLs present metachronously and in particular for patients with *SDHx* mutations, who have an increased risk for metastatic disease.[19] At this time no clear guidelines exist regarding the optimal frequency of imaging for PGL patients.[3] In terms of laboratory testing, the Endocrine Society recommends lifelong annual testing of plasma or urine metanephrine levels to assess for recurrent or persistent disease.[3]

Treatment of metastatic PGL of the spine involves a combination of surgery, radiation therapy, and chemotherapy. As with other metastatic tumors of the spine the primary goals of surgery are management of spinal instability caused by lytic lesions, and decompression of the spinal cord secondary to any epidural tumor.[61] Surgical resection of the primary tumor has been shown to improve overall survival in cases of synchronous metastatic PGL.[62] Radiation therapy is the primary of method of local control for metastatic disease that is unresectable. Chemotherapy is reserved for widely metastatic disease with cyclophosphamide, dacarbazine, and vincristine being the preferred regimen.[63] Overall, metastatic PGL is difficult to treat with 5-year overall survival at approximately 60%.[61]

In conclusion, metastasis to the spine is a rare but important complication in patients with PGL that can lead to significant pain and disability. Genetic testing is recommended for all patients with PGLs. Patients with *SDHx* mutations are more likely to develop metastatic disease and *SDHx* mutation status is the current best predictor of metastatic PGL. *SDHx* mutation carriers must have frequent long-term imaging surveillance performed given the potential for metastasis several years to decades after primary resection. Neurosurgical management of metastatic PGL of the spine involves correcting spinal instability and alleviating epidural cord compression. When caring for patient with metastatic PGL of the spine, genetic testing for patients and their families should be considered.

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