Chapter 6

Mediastinal Paragangliomas: Association with Mutations in the Succinate Dehydrogenase Genes and Aggressive Behavior

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Abstract

Introduction: Extra-adrenal pheochromocytomas, otherwise known as paragangliomas (PGLs), account for about 20% of catecholamine-producing tumors. Only 2% are found in the mediastinum. Mediastinal PGLs have been found to be associated with multiple tumors and symptoms and signs associated with catecholamine excess.

Hypotheses: Most mediastinal PGLs are associated with SDHx mutations and may therefore have aggressive behavior presenting with symptoms and signs of norepinephrine and/or dopamine excess.

Objective: Prospectively and retrospectively characterize genetic, clinical, and biochemical data on 10 patients with mediastinal PGLs.

Cases: All 10 primary mediastinal PGL patients had germline SDHx mutations, 6 in SDHB and 4 in SDHD. Chest or back pain were the most common presenting symptoms (5 patients), and catecholamines and/or their metabolites were elevated in 7 patients. In addition, 4 patients had head and neck PGLs, and 2 patients had prior surgery for pheochromocytoma or bladder PGL. Metastatic disease was documented in 6 patients (60%), and a concurrent abdominal mass was found in one patient. Mediastinal surgery was performed in 6 of 10 patients, with postoperative radiotherapy in 2 patients. Two patients received chemotherapy, and one patient was treated with $^{[131I]}$-MIBG. In two patients, a watch-and-wait strategy was instituted, because of stable disease and only minor catecholamine excess.

Conclusion: Mediastinal PGLs are associated with SDHB and SDHD gene mutations and most often have a noradrenergic phenotype and aggressive behavior. The present data strongly suggest that all patients with mediastinal PGLs should be screened for SDHx gene mutations, regardless of age.
Introduction

About twenty percent of the catecholamine-producing tumors are derived from extra-adrenal chromaffin tissues and are termed extra-adrenal paragangliomas (PGLs) (1). PGLs may arise from chromaffin cells associated with either sympathetic or parasympathetic tissues. Although PGLs are found mostly in the abdomen, they are less commonly found in the pelvic sympathetic plexus of the urinary bladder, and only in about 2% of the cases in the mediastinum (2). Approximately 100 cases of mediastinal PGLs have been reported in the literature to date (3-8), of which 30% have been reported to be functional either by catecholamines or metanephrines (9). Malignancy has been estimated in only 5-18% of patients, but data is scarce and divergent (4, 10, 11).

PGLs may occur as part of a hereditary syndrome or sporadically. Multiple endocrine neoplasia type 2, neurofibromatosis type 1 and von Hippel-Lindau syndrome all have been associated with familial syndromes including PGLs. In addition, the genes encoding succinate dehydrogenase (SDH) subunits B (PGL4), C (PGL3), and D (PGL1) have been found to be linked to familial PGL syndromes (12-14). In recent literature, several articles have described clinical characteristics of patients with SDHx mutations and describe distinct genotype-phenotype correlations (15-17). SDHB mutations are mainly associated with abdominal paragangliomas and are associated with very aggressive disease including metastasis (16, 17), whereas SDHD mutation carriers are frequently diagnosed with benign head-and-neck PGLs and pheochromocytomas. Although not impossible, SDHD associated malignant disease is rare (15, 17, 18). In patients with SDHB mutations the biochemical phenotype consists of hypersecretion of both norepinephrine and dopamine in 46% and norepinephrine alone in 41% of cases (17). In SDHD associated disease the noradrenergic phenotype is most prevalent ((19), this thesis).

Therefore, we hypothesized that nearly all mediastinal PGLs are associated with SDHx mutations and may have a predominantly noradrenergic phenotype. In this manuscript, we prospectively and retrospectively identified patients with mediastinal PGLs and report detailed genetic, clinical, and biochemical aspects of these patients and present recommendations to clinicians how to approach these tumors.

Patients and Methods

Patients presented in this PGL series, were from Parkland Memorial Hospital in Dallas, Texas, United States, National Institutes of Health (NIH) in Bethesda, Maryland, United States, Leiden University Medical Center in Leiden, the Netherlands, and the Department of Medicine in Košice, Slovak Republic. All patients gave written and informed consent for genetic testing as approved by the institutional review board (IRB) of each respective institution. Records of all patients enrolled in the based pheochromocytoma protocol were considered for inclusion. Only those patients with
radiological and/or histopathological evidence of mediastinal PGL were included in this survey.

Cases 1 and 2 were from Parkland Memorial Hospital. One patient’s chart (Case 1) was retrospectively reviewed; the other patient’s clinical case (Case 2) was prospectively described. From the NIH, a total of six unrelated patients with a history of PGL were identified and included in this study (patients 3 to 8). All of these patients were referred to the NIH for an outline of an optimal plan for (suspected) PGL. Patient 9 was retrospectively identified with a history of mediastinal PGL at the Leiden University Medical Center in Leiden, the Netherlands. One patient (patient 10) was prospectively identified by Lazúrová at the Department of Medicine in Košice, Slovak Republic.

Patient characteristics are summarized in Table 1.

Case reports

Case 1
A 27 year old African-American woman presented in 2001 with a history of severe hypertension and palpitations. At that time, she was diagnosed with a mediastinal PGL (T4 level) which was resected via a right thoracotomy at the age of 18. In early 2006, she developed non-radiating chest pain that prompted several visits to the local emergency department where musculoskeletal pain was diagnosed. A few months later she developed gait abnormalities. She again presented to the emergency department and a CT scan of the abdomen and lumbar spine revealed a 2.5 cm enhancing mass in the retroperitoneum, adjacent to the left psoas at the level of the aortic bifurcation. An Octreoscan was performed to determine if the psoas mass was a recurrence of PGL. The Octreoscan did not identify the psoas lesion, but did indicate that there was a recurrence of the T4 vertebral body lesion. A subsequent chest CT scan showed a heterogeneous mass at the T4 vertebral body with extension into the spinal canal as well as extensive bony destruction of T4. Plasma normetanephrine levels were elevated and metanephrine levels were normal. After adequate α- and β-adrenergic blockade, the patient underwent a preoperative embolization of the tumor. A few days later, she had a lateral extracavitary resection of her recurrent mediastinal and spinal PGL. This was followed by a resection of the psoas lesion. Six months post-surgery, her plasma normetanephrine level was normal. Genetic testing revealed an SDHB mutation (c.725G>A, p.Arg242His). Radiation therapy was started. One year after the diagnosis of recurrent PGL, her plasma normetanephrine level is still normal.

Case 2
A 60 year old Asian-Indian woman with a history of well-controlled hypertension and type 2 diabetes was admitted after presenting with complaints of worsening upper back pain and vague complaints of chest wall pain. Review of systems was significant only for an unintentional 25 kg weight loss over the past 5-6 months. Family history was negative for PGLs and pheochromocytomas. Vital signs at the time of admission were
significant for heart rate of 101 bpm and blood pressure of 136/69 mmHg. Physical exam was unremarkable. A chest radiograph (and later chest MRI) revealed a large mass measuring approximately 7.3 cm likely arising from the posterior mediastinum (Figure 1A). Subsequently, chest CT (Figure 1B) and MRI of the T-spine (Figure 1C, 1D) showed a large left posterior mediastinal mass measuring approximately 5.4 cm transverse x 5.2 cm AP that demonstrated heterogeneous enhancement with a central cystic/necrotic component. The enhancing mass involved the left aspect of T5 vertebral body along the majority of the T6 vertebral body. The patient then underwent FNA of the mass, and pathology was consistent with PGL. Because of elevated plasma normetanephrine levels, she was treated with α-adrenergic blockade. After percutaneous embolization of the tumor was performed twice, patient underwent a two-stage resection of the mass. T6 laminectomy was performed and the spine fused from T3-T9. Tumor was successfully dissected. Genetic testing revealed SDHB missense mutation.

Figure 1: Patient 2; A: Chest MRI showing mediastinal mass; B: CT of chest showing paraganglioma; C: MRI showing posterior mediastinal tumor
Case 3
In 2001 a 25-yr-old male patient was evaluated for a sharp pain on the left side of the chest. A posterior mediastinal mass on a chest X-ray was found. Additional imaging using chest CT and MRI scan revealed a left paraspinal (T2-3) mass. The patient underwent surgery in January 2002 without further pre-operative histological diagnosis or α-adrenergic blockade. During surgery the left paraspinal mass was removed together with a partial resection of the T2 and T3 vertebrae. Histopathological investigation revealed PGL cells with microvascular invasion. After surgery, he was treated with local radiotherapy. Four years later, a nodule with a diameter of 1.0 x 1.2 cm in the right middle lobe was detected, that had increased in size in comparison to previous CT scans. [18F]-fluoro-deoxyglucose positron emission tomography ([18F]-FDG PET) tumor imaging showed uptake in the left sternum, scapula, right lower lung zone, left lung apex, posterior mediastinum superior mediastinum and thoracic spine. Hence a lobectomy with lymph node extirpation was performed and pathological examination revealed PGL cells. A year after lobectomy and 6 years after his initial presentation, a new pulmonary, thoracic spine, and paraspinal mass of approximately 2.2 cm in the area of vertebrae T3 and T4 were detected. Chest CT scan revealed lytic lesions of the T4 vertebral body and multiple bilateral lung nodules (<1cm) that appeared to have grown. He underwent a partial thoracic corpectomy, a posterior thoracic decompression and fixation of T1-T5 with an iliac crest bone graft. Histopathological examination revealed a PGL with areas of necrosis. Because of widespread metastatic PGL, the patient was referred to the NIH for further diagnostic investigations and therapy. Family history was negative for both PGLs and pheochromocytomas. Plasma metanephrine levels were normal. Genetic analysis revealed an SDHB mutation (c.136C>T, p.Arg46x).

Case 4
In 1999 a 45-yr-old male patient was diagnosed with bilateral carotid body tumors. Family history was positive for head and neck PGLs. Without further pre-operative investigations or treatment, he underwent surgery with no hemodynamic problems. However, after the operation irregular heartbeats and a blood pressure of 160/95 mmHg were noticed. At that time the patient was being treated with several anti-hypertensive medications with suboptimal results. Complaints of weakness, palpitations and panic attacks resulted in performing a cardiac stress test that revealed dysrhythmias. A mediastinal tumor was found on chest X-ray, which was further localized by CT and a biopsy that revealed PGL cells. An embolization and partial tumor resection were performed, but because the localization adjacent to major vessels, esophagus and trachea, resection was incomplete. A year later, repeated chest CT scan revealed a mediastinal mass of approximately 6 x 5 cm with compression of the right main pulmonary artery. He was referred to the NIH for further evaluation and therapy.
<table>
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<th>Gender, age&lt;sup&gt;a&lt;/sup&gt;</th>
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<th>Biochem.</th>
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<th>Outcome</th>
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<td>1 F, 18</td>
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<td>T4 vertebral body, Recurrent disease</td>
<td></td>
<td>Thoracotomy</td>
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<td>6 M, 19</td>
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<td>Lesion liver, lesion anterior of vena cava (celiac access). Meta left ilium</td>
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<td>-</td>
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<td>10 M, 18</td>
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<td>Surgery (incomplete)</td>
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Legend: Biochem. = Biochemical phenotype, NM = Normetanephrine, DA= Dopamine, VMA = Vanillylmandelic acid, T = Thoracic, L= Lumbar, XRT = Radiotherapy, Meta= Metastasis, CVD = Cyclophosphamide, Vincristine, Dacarbazine, HNP = Head and neck paraganglioma, PGL = Paraganglioma, Pheo = Pheochromocytoma;<sup>a</sup>Age at diagnosis;<sup>b</sup>Urine measurement
His plasma normetanephrine levels were elevated. Imaging revealed multifocal PGL disease with recurrence of the carotid body tumor, a large mediastinal mass adjacent to the left atrium and a mass in the left suprarenal area. Genetic analysis for germ line mutations revealed a SDHD mutation (c.170-1G>T, splice site mutation).

Case 5
In 2004 a 26 yr-old male patient had complaints of progressive lower back pain after exercise. A CT scan showed a large enhancing necrotic retroperitoneal mass measuring 13.4 x 8.5 x 15.6 cm, metastatic lesions in L3 and L4, a 3.1 x 2.5 cm in diameter lesion in the superior right paratracheal region, a 3.4 x 2.5 cm in diameter lesion within the left superior mediastinum, and multiple enlarged lymph nodes. All of his plasma metanephrine levels were negative. A biopsy revealed no conclusive diagnosis. A year later, he was referred to the NIH for further evaluation and treatment. Family history was negative for PGLs and pheochromocytomas. No complaints suggesting excess of catecholamine production were mentioned. On physical examination no abnormalities were found. His plasma catecholamine levels and their O-methylated compounds were all normal. He underwent an uncomplicated surgical removal of the abdominal mass in another hospital, which proved to be PGL on pathological investigation. He was treated with 6 cycles of etoposide and cisplatin chemotherapy with limited effect on residual tumors. Treatment with octreotide was added. Follow-up revealed persistent masses in the left and right superior mediastinal area, lower abdomen, retroperitoneal region, L3-L4 vertebrae and the right humerus. However, his plasma catecholamine levels were normal except for an elevated chromogranin A. Follow-up studies one year later revealed stable disease. Genetic analysis revealed a SDHB mutation (c.137G>A, p.Arg46Gln).

Case 6
A 19 yr-old male initially presented in 1976 with hematemesis and was found to have a gastric leiomyosarcoma (gastro-intestinal stromal cell tumor (GIST), which was resected. Two years later, a right carotid body was diagnosed and removed. On initial surgery, he developed bradycardia and a brief episode of asystole upon which surgery was postponed. Elevated catecholamines and hypertension led to analysis for and the diagnosis of a pheochromocytoma in the right adrenal gland, which was surgically removed as well. On additional imaging studies, a paratracheal mass was found. A left glomus jugulare tumor was identified and treated with radiation therapy (4000cGy). Thirteen years after his initial episode of hematemesis, he presented himself to the NIH for further evaluation of PGL. A chest and abdominal CT scan showed a mass in the left superior mediastinum and abdominal metastases including lesions in the liver, with equivalent [123I]-MIBG uptake. Urinary biochemistry revealed increased levels of norepinephrine, vanillylmandelic acid (VMA) and normetanephrine. He was treated
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with 12 cycles of cyclophosphamide, vincristine and dacarbazine under continuing α-adrenergic blockade with prazosin. [18F]-FDG PET showed uptake in the paratracheal mass with intense activity, a focus in vertebra T8, two abdominal masses and six liver lesions. The patient was treated with [131I]-MIBG. Currently, there is stable metastatic disease with a suspect 2 cm lesion in the left ilium. Plasma normetanephrine levels remain elevated. Genetic analysis revealed a SDHD mutation (c.57delG, p.Leu20CysfsX66).

Case 7
In 2002 a 36-yr-old female patient complained of episodic hypertension, palpitations, chest discomfort, pre-syncope and shortness of breath for a few years. Complaints were particularly associated with urination. Biochemical and imaging studies revealed a pheochromocytoma located in the urinary bladder. A 0.4 x 4.0 cm PGL of the anterior urinary bladder wall was removed. However, after surgery catecholamine levels remained elevated and patient was re-operated because recurrent disease was considered. During surgery there were no hemodynamic complications, but recurrent disease was not found. She was referred to the NIH for further evaluation. A chest MRI revealed a mediastinal mass with a diameter of 2.3 cm next to the esophagus. Although [123I]-MIBG scintigraphy revealed no definite abnormalities, [18F]-FDG PET showed uptake in the posterior mediastinum. This lesion was also identified with correlated uptake of octreotide in the posterior mediastinum. An echocardiogram was performed and revealed a mass on the posterior wall of the left atrium adjacent to the right lower pulmonary vein with a diameter of 2.9 x 2.2 x 2.4 cm. Plasma normetanephrine and dopamine levels were elevated. Mediastinal PGL was surgically removed. Follow-up imaging revealed no indication of recurrent disease Biochemical analysis remains normal up to date. Genetic testing revealed a SDHB mutation (c.136C>T, p.Arg46x).

Case 8
In 2001 a 50-yr-old female patient was referred to the NIH with suspected metastatic PGL. Her medical history revealed surgery on both right and left carotid body tumors at the age of 19 and 30, respectively. She did well until she experienced one episode of palpitations, anxiety and headache one year prior to presentation. Because of upper respiratory symptoms, her primary care physician ordered a chest X-ray, which showed a primary lesion in the mediastinum. CT and MRI imaging revealed a lesion in the left neck, the AP window (2.8 cm), the left hilus (3.3 cm), the right hilus (3 cm) and multiple parenchymal nodules. Her plasma catecholamine and metanephrine levels were within normal limits. The mediastinal lesion was found to be positive on [18F]-fluorodopamine PET and octreotide imaging, together with the neck lesion. Because of stable asymptomatic disease a watch-and-wait policy was decided. In 2007 progressive multilevel metastatic disease was found on [18F]-FDG PET and [18F]-fluorodopamine imaging with the known mediastinal lesion, 4 additional lesions in the mediastinum, 4
lung lesions, and a suspected lesion in the sacrum. Currently, a treatment plan is pending. Genetic analysis revealed a SDHD mutation (c.242C>T, p.Pro81Leu).

**Figure 2:** [18F]-fluorodopamine images of patient 8 revealing a mass in the posterior mediastinum suspect for a paraganglioma

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**Case 9**
In 2002 a 41-yr-old male was diagnosed with bilateral head and neck PGLs after an analysis for hearing loss and tinnitus. Besides excess sweating, no paroxysmal or other complaints were mentioned. Family history was negative for pheochromocytoma or PGL. Physical examination revealed no further abnormalities. Twenty-four hour urine collection revealed elevated levels of VMA, without elevation of other catecholamines. Metanephrines were not measured at that time. [123I]-MIBG scintigraphy showed no pathological uptake. Abdominal MRI identified a 1 cm nodule in the left adrenal consistent with an adenoma. Chest CT revealed two hypervascular lesions in the aortic-pulmonary window of approximately 1 cm in diameter, suspect for PGL. Octreoscan and [18F]-fluorodopamine PET scan revealed increased uptake in these lesions. No biopsy was performed. Subsequent genetic analysis revealed a SDHD gene mutation (c.274G>T, p.Asp92Tyr). Because of only minor elevations of only VMA, no clinical complaints and the estimated low risk for malignant disease, a watch-and-wait strategy was decided.

**Case 10**
In 2006 an 18-yr-old man was admitted to the hospital with a blood pressure of 220/120 mmHg. Investigations for secondary cause of hypertension were initiated. Plasma normetanephrine levels were found to be 10 times elevated, thus pheochromocytoma was strongly suspected. Furthermore, family history revealed that his father died suddenly and had head and neck PGL. On CT and [123I]-MIBG imaging a 9 x 7 x 5 cm large tumor in the posterior mediastinum with growth into T5 was found. The operation was performed with incomplete tumor removal. Histopathological investigation showed PGL. Genetic analysis revealed a SDHB mutation (c.286+2T>A, splice site mutation).
Discussion

In this report we found all 10 patients with mediastinal PGLs to be associated with either SDHB or SDHD mutations. From these 10 patients 60% developed metastatic disease, suggesting that these tumors are often aggressive and should be carefully followed. Furthermore, we found that chest pain and a noradrenergic phenotype are typical for patients with mediastinal PGLs. We conclude that all patients with mediastinal PGLs should be screened for SDHx mutations, regardless of age.

SDHx mutations are mutations in the genes encoding subunits of mitochondrial complex II succinate dehydrogenase and are associated with familial paragangliomas. Succinate dehydrogenase is an enzyme complex in the mitochondrial respiratory chain and consists of 4 subunits, of which SDHD and SDHB will be discussed here. Carriers of the SDHD mutation often present with multifocal head and neck PGL (15). The SDHB mutation predisposes patients to have extra-adrenal localizations and metastatic disease (up to 30-50%) (16, 17). The predominant biochemical phenotype is hypersecretion of norepinephrine and/or dopamine (17). From our long expertise we occasionally examined and treated patients with mediastinal tumors that were all found to have SDHx mutations and some of them were aggressive. Therefore, we hypothesized that patients presenting with these tumors have SDHx mutations. In our series, we identified 10 patients with mediastinal PGL of which 6 had SDHB mutations (patients 1, 2, 3, 5, 7 and 10) and 4 were found to have an SDHD mutation (patients 4, 6, 8 and 9). This combined retrospective and prospective study shows for the first time that indeed mediastinal PGLs are associated with either SDHB or SDHD gene mutations.

Mediastinal PGLs typically occur in either the aortico-pulmonary window (in the region of the aortic arch) or they are located in the posterior mediastinum (20). The majority of patients in our series had tumor involvement in the posterior mediastinum (Figure 1C). Chest or back pain were the most common presenting symptoms and were found in 5 out of 9 patients (patients 1, 2, 3, 5, and 7). Several patients reported complaints related to catecholamine excess as well (patients 1, 4, 7, 9 and 10). Pain as a presenting symptom has been reported more often, especially in SDHB related malignant paragangliomas (17). Clinicians may initially conclude that the patient has musculoskeletal pain, thus leading to delayed diagnosis, as was exemplified by our case 1. The high prevalence of malignant disease in our mediastinal PGLs, could well have contributed to the prevalence of pain as a presenting symptom in our cohort.

In 7 of the 10 patients (4 with SDHB and 3 with SDHD mutations) catecholamine excess was found, of which patient 9 had only borderline elevations. Norepinephrine and its metabolite normetanephrine were the predominant biochemical phenotype and two patients revealed additional excess of dopamine at presentation or follow-up. This is in line with other reports of SDHB paragangliomas predominantly secreting norepinephrine (17). Although dopamine has been reported to be associated with malignant disease (21), this was not the case in our series with patients 7 and 9.
presenting with non-metastatic disease. We conclude that mediastinal PGLs tend to display a noradrenergic or dopaminergic biochemical phenotype.

Definitive therapy for PGLs remains surgical removal, with the mediastinal localization often as a complicating factor. Since most mediastinal PGL secrete catecholamines, we strongly recommend all these patients to be treated with appropriate α-adrenergic blockade prior to surgical removal of the tumor to block catecholamine action, as was recently reviewed (22). No randomized trials have evaluated the efficacy of post-operative radiation for thoracic PGLs, thus it is currently unknown if patients should receive post-operative radiation in the aim of preventing recurrence, irresectable tumors or metastatic disease (23). [¹³¹I]-MIBG treatment and chemotherapy could be considered in patients with malignant mediastinal paragangliomas (24). On an individual basis a watch and wait strategy can be employed, considering the extent of the disease, operability, comorbidities and underlying genetic mutation.

In conclusion, mediastinal PGLs are frequently functional, metabolically active, and associated with SDHx mutations. Chest and back pain are common presenting symptoms. Mediastinal PGLs frequently produce catecholamines with a predominantly noradrenergic and/or dopaminergic phenotype. Prior to any invasive procedures adequate α-adrenergic blockade is mandatory. All mediastinal PGLs should be screened for SDHx mutations, regardless of age.
References


