CASE REPORT

Paraganglioma of urinary bladder

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aamalik_06@yahoo.com**SUMMARY**

Paraganglioma of the urinary bladder is extremely rare. In this report of a young man, hypertensive crisis and ventricular arrhythmia was provoked during cystoscopic evaluation of a bladder mass. A diagnosis of pheochromocytoma was considered following detection of high serum and urinary catecholamine levels. A preoperative meta-iodobenzylguanidine scan was, however, negative. The bladder mass was surgically removed following initiation of antihypertensive therapy. Pathological confirmation of extraadrenal pheochromocytoma was established. During a serial follow-up, serum and urine catecholamine levels were persistently elevated. This was explained by abnormalities on fluorodeoxyglucose positron emission tomography scan, which were considered to represent a metastatic malignant neuroendocrine tumour. The patient is on palliative chemotherapy for malignant paraganglioma. This case highlights variable presentation of pheochromocytoma, importance of having a high index of clinical suspicion for early recognition and prompt management and serious adverse consequence of a delayed diagnosis.

BACKGROUND

Pheochromocytoma is an uncommon cause of secondary hypertension. Early recognition favourably impacts long-term outcome. Diagnosis is not infrequently delayed due to non-specific clinical presentation, fragmented follow-up care and lack of widespread awareness of the paroxysmal nature of catecholamine release from the tumour. In addition to episodic symptoms, catecholamine excess may also result in paroxysmal or persistent hypertension. Therefore, careful attention to clinical history is important in an early diagnosis. In pheochromocytoma palpitations, diaphoresis, headaches or abdominal pain are often of abrupt onset and usually without provocation or provoked by peculiar circumstances. This should arouse suspicion, particularly in younger patients with paroxysmal or sustained hypertension. Furthermore, pheochromocytoma localised to the bladder wall, and presenting with micturition associated symptoms of catecholamine excess, as in our patient, has been previously reported. Perhaps an earlier diagnosis was possible if physicians involved in this patient's care were aware of this. We also want to emphasise the possibility of a negative metaiodobenzylguanidine (MIBG) scan despite an active tumour and high serum and urinary catecholamine levels. Considering this patient's clinical course, perhaps an MIBG scan was potentially misleading.

CASE PRESENTATION

A 48-year-old Sudanese man was seen in the urology clinic for supra-pubic pain and haematuria over a 2-week duration. Unknown at this time was a 15-year history of episodic palpitation, diaphoresis and headache upon micturition for which no diagnostic testing had been previously performed. As a child, the patient was treated for schistosomiasis. In 1994, he underwent surgery for a perforated duodenal ulcer. Details of this surgery were not available. The patient, however, described an eventful postoperative course. A diagnosis of insulin requiring type 2 diabetes was made 6 months ago. Family history was significant of carcinoma of the stomach and cirrhosis of the liver from which his brother and sister died, respectively.

On examination the patient appeared well built. He was normotensive with a heart rate of 90 bpm. Orthostatic change in blood pressure was not documented. A well healed laparoscopy scar from surgery for a perforated duodenal ulcer was noted. There were no abdominal masses, abdominal tenderness or hepatosplenomegaly. Systemic examination was otherwise unremarkable.

An MRI scan of the abdomen and pelvis was requested which was reported as showing a mass lesion on the posterior aspect of the urinary bladder, extending to the right seminal vesicle which as a consequence was distorted and displaced.

For further assessment cystoscopy under general anaesthesia was performed. A preoperative ECG showed non-specific repolarisation changes in the inferior leads. Cystoscopy revealed a cystic lesion on the right lateral wall of the urinary bladder. This mass extended to occlude the right ureteric orifice. During this procedure frequent premature ventricular contractions and a short run of non-sustained ventricular tachycardia were encountered. In addition, severe hypertension required intravenous labetalol for control. Prompted by concerns for pheochromocytoma, a more detailed history from the patient at this time established long-standing paroxysmal symptoms of catecholamine excess associated with micturition (described above). Diagnosis of pheochromocytoma was further suggested by elevated serum and urinary catecholamine levels.

To counter effects of catecholamine excess, surgical excision of the bladder mass was preceded by pharmacotherapy with atenolol and prazosin. The patient's blood pressure and heart rate were controlled on this regimen. In addition to surgical excision of 5×3 cm bladder mass, bilateral lymphadenectomy and neocystotomy was performed. The intraoperative course was uncomplicated. In recovery, episodes of hypotension required aggressive fluid resuscitation.

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A pathological confirmation of pheochromocytoma was made. Tumour margins were free; however, a lymph node biopsy specimen was suggestive of metastatic disease. The latter was subsequently confirmed by persistently elevated catecholamine levels and abnormal skeletal and hepatic lesions on the fluorodeoxyglucose positron emission tomography (FDG-PET).

The patient at this time is on palliative chemotherapy with cyclophosphamide, vincristin and decarbazine for malignant paraganglioma.

INVESTIGATIONS

Lab investigations showed initial high urine and blood metanephrine with a negative MIBG scan.

31 January 2012

Urine norepinephrine 16 835 nmmol/L (90–500); 2845 μ /L (15–84).

18 January 2012

An MRI scan of the abdomen and pelvis: mass lesion seen on the posterior aspect of the urinary bladder, extending to the right seminal vesicle which appeared distorted and displaced (figure 1).

31 January 2012

MIBG scan: no significant abnormal activity on this scan.

08 February 2012

Blood nor metanephrine 1329 mmol (<0.94) metanephrine 0.39 mmol/L (<0.37)

Urine volume 3200 mL; norepinephrine 16 835 nmmol/L (90–500); 2845 μ /L (15–34)

Epinephrine and dopamine normal values.

Follow-up labs up showed a rising trend of the aforementioned investigation while FDG-PET and bone scan suggested metastatic disease.

25 September 2012

FDG-PET scan: spots of activity of variable intensities and sizes are noted in inferior neck, substernum, mediastinum, liver, left iliac and pelvic region. Findings consistent with metastatic neuroendocrine tumour.

Pathological findings from figure 2.

TREATMENT

Current treatment includes amlodipine and prazosin for hypertension, low-dose insulin for diabetes mellitus and palliative chemotherapy with cyclophosphamide, vincristin and decarbazine.

Figure 1 MRI of the pelvis showing a dense mass occupying more than half of bladder.

OUTCOME AND FOLLOW-UP

Symptoms are well controlled on current management. Follow-up FDG-PET is planned for September 2013.

DISCUSSION

Paraganglioma of the urinary bladder is extremely rare accounting for less than 0.05% of all bladder neoplasm.¹ Zimmerman and coworkers noted the first instance of paraganglioma of the urinary bladder in 1952.² Most patients are young. Age at detection can range from 10 to 70 years. Most common presentation of this tumour is painless haematuria,³ headaches, palpitations and anxiety. Symptoms are paroxysmal and associated with micturition. Episodic hypertension is also encountered. In 2004 the WHO classified pheochromocytoma as endocrine tumours arising from chromaffin cells of adrenal medulla while extra-adrenal tumours are classified as paraganglioma. The distinction between pheochromocytoma and paraganglioma is important due to the risk of malignancy, associated neoplasm and implications on genetic testing. Paraganglioma mainly secrete norepinephrine and adrenal pheochromocytoma epinephrine. This difference in biochemical phenotypes is also expressed in malignant tumours.

Biochemical confirmation of pheochromocytoma is usually by urinary and plasma fractionated metanephrine and catecholamine. Urinary metanephrine and normetanephrine have a sensitivity of 96% and a specificity of 98%.^{4–5} Plasma fractionated metanephrine is used if there is high index of suspicion, but has lower specificity of around 86%. CT and MRI scans are used for localisation of primary tumours and metastatic disease. Functional imaging with ¹²³I an MIBG scan is performed if the abdominal CT is negative, the tumour is more than 10 cm (increase risk of malignancy) and for paraganglioma.⁶ However, MIBG imaging is negative in 15% of cases of benign pheochromocytoma and 50% of cases of malignant pheochromocytoma. FDG PET is more sensitive than CT/MRI for the detection of metastases.^{7–8}

Most of the pheochromocytoma tumours are benign, and are potentially curable. Approximately 10% of pheochromocytoma are malignant, while 25% of paraganglioma are malignant, especially those associated with succinate B dehydrogenase deficiency.^{9–10} Clinical, radiological and biochemical features cannot distinguish a benign from a malignant lesion. Malignant pheochromocytoma is clinically diagnosed by presence of distal metastases mainly to the liver, lymph nodes, lungs or bones. The malignant tumours are diagnosed when metastases are found at non-chromaffin sites. In some cases malignant metastases are present at the time of diagnosis and others are recognised following surgical resection.^{11–12}

The most common metastatic sites are local lymph nodes, bone (50%), liver (50%) and lungs (30%).¹³ CT and MRI scans can detect primary tumours and metastatic/extra-adrenal lesions above 1 cm with sensitivity 78–98% and specificity of 29–92%. A radiodensity of 40–50 hounsfield units on a CT scan is suggestive of malignant chromaffin tumours.¹⁴ Thompson¹⁵ proposed that pheochromocytoma of adrenal gland scoring (PASS) system which score multiple microscopic findings. A PASS of <4 accurately identifies clinical and histological benign and PASS of >4 identifies all tumours that are histologically malignant.

Most of cases of pheochromocytoma are sporadic. However some are associated with hereditary or familial syndrome. At least 10 different genes have been implicated in pathogenesis of these tumours. Mutational analyses of ret-proto oncogene (RET),

Figure 2 (A) The tumour is involving the submucosa and muscular tissue. (B) The tumour is composed of nests of polygonal cells. (C) The tumour is extending close (1 mm) to painted deep margin. (D) Tumour is positive for chromogranin.

succinate dehydrogenase B (SHDB), succinate dehydrogenase D (SHDD) and VHL revealed mutation in 25% of sporadic cases suggesting that one-third of patients with pheochromocytoma have inherited the disease.¹⁶ The patients with malignant pheochromocytoma should be offered testing for SDHB, VHL and SHDD mutations as about 40–50% of such patients will have a detectable mutation. Malignant and/or extra-adrenal pheochromocytoma, particularly in the abdomen, is strongly associated with SHDB mutation. It has been suggested that SDHB mutation analysis should always be performed in cases of familial chromaffin tumours.

The medical management is directed towards control of hypertension with α -blockage and β -blockage. The surgical treatment is debulking of the tumour mass. In some cases where surgical treatment is not possible, radiotherapy can be used. Malignant pheochromocytoma remains incurable. Palliative chemotherapy regimen commonly used is a combination of cyclophosphamide, vincristin and decarbazine^{17 18} with improvement of symptoms and a remission rate of 50% observed in some of the patients'. This remission lasts 1–2 years. I¹³² MIBG has been used in few case series for pheochromocytoma which takes up MIBG to achieve symptoms palliation and tumour regression. The 5-year mortality rate in patients with malignant pheochromocytoma and paraganglioma is greater than 50%.

In our patient despite the characteristic symptoms of catecholamine excess associated with micturition, diagnosis of pheochromocytoma was delayed. A possible explanation for this includes failure to extract vital historical information from the patient over the years or failure to link his symptoms with a

catecholamine secreting tumour. The latter emphasises the need for greater awareness among physicians of variable clinical presentation associated with pheochromocytoma. Furthermore, in patients with unexplained paroxysms of palpitations, diaphoresis, headaches and abdominal pain, detailed clinical assessment and a high index of suspicion are necessary for early diagnosis of pheochromocytoma which is potentially curative following early surgical excision.

Learning points

- ▶ Pheochromocytoma is a rare disease. Its recognition is important as it is potentially lethal if missed.
- ▶ The physicians must be aware of its much varied presentation.
- ▶ Pheochromocytoma should be considered in differential of secondary hypertension.
- ▶ Genetic screening is advised in all cases of paraganglioma, malignant pheochromocytoma and in selected cases of pheochromocytoma.

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REFERENCES

- 1 Dahaam P, Gschwend JE. Malignant non urothelial neoplasm of urinary bladder. *Rev Eur Urol* 2003;44:672–81.
- 2 Zimmerman IJ, Biron RE, Mac Maham HE. Pheochromocytoma of the 2 urinary bladder. *N Engl J Med* 1953;249:25–6.
- 3 Fydenberg M, Ferguson R, Langdon P, *et al.* Malignant pheochromocytoma of the bladder active or inactive. *Br J Urolo* 1991;67:54.
- 4 Kudva YC, Sawka AM, Young WF Jr. Clinical review 164: the laboratory diagnosis of adrenal pheochromocytoma: the mayo clinic experience. *J Clin Endocrinol Metab* 2003;88:4533.
- 5 Perry CG, Sawka AM, Singh R, *et al.* The diagnostic efficacy of urinary fractionated metanephrine measured by tandem mass spectrometry in detection of pheochromocytoma. *Clin Endocrinol (Oxf)* 2007;66:703.
- 6 Whalen RK, Althausen AF, Daniels GH. Extra-adrenal pheochromocytoma. *J Urol* 1992;147:1.
- 7 Pacak K, Eisenhofer G, Carrasquillo JA, *et al.* 6-[18F]fluorodopamine positron emission tomographic (PET) scanning for diagnostic localization of Pheochromocytoma. *Hypertension* 2001;38:6.
- 8 Ilias I, Yu J, Carrasquillo JA, *et al.* Superiority of 6-[18F]-fluorodopamine positron emission tomography versus [131I]-metaiodobenzylguanidine scintigraphy in the localization of metastatic pheochromocytoma. *J Clin Endocrinol Metab* 2003;88:4083.
- 9 O'Riordain DS, Young WF Jr, Grant CS, *et al.* Clinical spectrum and outcome of functional extraadrenal paraganglioma. *World J Surg* 1996;20:916–22.
- 10 Amar L, Peyrard S, Rossignol P, *et al.* Changes in urinary total metanephrine excretion in recurrent and malignant phaeochromocytomas and secreting paragangliomas. *Ann N Y Acad Sci* 2006;1073 383–39188.4083.
- 11 Goldstein RE, O'Neill JA Jr, Holcomb GW III, *et al.* Clinical experience over 48 years with pheochromocytoma. *Ann Surg* 1999;229:755.
- 12 Pattarino F, Bouloux PM. The diagnosis of malignancy in phaeochromocytoma. *Clin Endocrinol (Oxf)* 1996;44:239.
- 13 Bravo EL, Tagle R. Phaeochromocytoma: state of the art and future prospects. *Endocr Rev* 2003;24:539–5534.
- 14 Sahdev A, Reznek RH. Imaging evaluation of the nonfunctioning indeterminate adrenal mass. *Trends Endo Metab* 2004;15:271–6.
- 15 Thompson LD. Pheochromocytoma of the adrenal gland scaled score (PASS) to separate benign from malignant neoplasms: a clinicopathologic and immunophenotypic study of 100 cases. *Am J Surg Pathol* 2002;26:551–66.
- 16 Neumann HP, Neumann HP, Bausch B, *et al.* Germ-line in nonsyndromic pheochromocytoma. *N Engl J Med* 2002;346:1459–66.
- 17 Patel SR, Winchester DJ, Benjamin RS. A 15-year experience with chemotherapy of patients with paraganglioma. *Cancer* 1995;76:1476.
- 18 Huang H, Abraham J, Hung E, *et al.* Treatment of malignant pheochromocytoma/paraganglioma with cyclophosphamide, vincristine, and dacarbazine: recommendation from a 22-year follow-up of 18 patients. *Cancer* 2008;113:2020.

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