Clinical Medicine Insights: Case Reports

CASE REPORT

Paraganglioma of Prostatic Origin

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Abstract

Introduction: Paragangliomas are usually benign tumors arising from chromaffin cells located outside the adrenal gland. Prostatic paraganglioma is an unusual entity in adult patients, with only 10 cases reported in the medical literature.

Case report: A 34-year-old male with a history of chronic prostatitis consulted for perineal pain. On digital rectal examination the prostate was enlarged and firm, without nodules. The PSA level was 0.8 ng/mL and the catecholamines in the urine were elevated. On ultrasound a retrovesical 9 cm mass of undetermined origin measuring was present. A PET-CT scan showed a pelvic lesion measuring 9 cm with moderate increase in glucidic metabolism localized in the area of the prostate. A biopsy of the prostate revealed a neuroendocrine tumor, possibly a prostatic paraganglioma. A body scintigraphy with MIBG I-123 ruled out the presence of metastases or multifocal tumor. A radical prostatectomy with excision of the pelvic mass was performed under adrenergic blockade. One year after surgery the patient is asymptomatic and disease free.

Discussion/conclusions: Prostatic paraganglioma is a rare, usually benign tumor, which should be considered in the differential diagnosis of prostate tumors in young males. Its diagnosis is based on the determination of catecholamine in blood and 24-hour urine and in imaging studies principally scintigraphy with MIBG I-123. Diagnostic confirmation is by histopathological study. The treatment consists of radical resection under adrenergic blockade and volume expansion. Given the limited number of cases reported, it is difficult to establish prognostic factors. Malignancy is defined by clinical criteria, and requires life long follow-up.

Keywords: prostate, prostate tumor, paraganglioma

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Introduction

Paragangliomas are tumors arising from chromaffin cells located outside the adrenal gland. They develop in the paraganglion system, which originates in the neuroendocrine cells migrated from the neural crest, along with the autonomic nervous system. Generally they are benign, slow growing neoplasms, although malignant behavior and distant metastases has been described. Prostatic paraganglioma is an unusual entity with 10 reported cases in adult males. We present the case of a 34-year-old patient diagnosed with chronic prostatitis in which this type of neoplasm was identified.

Case Report

A 34-year-old male consulted for intermittent non-radiating perineal pain of 2 months duration. The past history was significant for symptoms of chronic prostatitis that responded well to non-steroidal anti-inflammatory drugs for the past 4 years. On physical examination the abdomen was soft without masses or organomegaly. A digital rectal examination revealed a large and rubbery mass in the area of the prostate. The serum PSA was 0.8 ng/mL. An abdominal ultrasound revealed a retrovesical mass measuring 9 cm in diameter of undetermined origin. On CT scanning an heterogeneous mass measuring 90 × 88 × 75 mm with well-defined borders located below and behind the bladder, which was anteriorly displaced was seen. The origin of the mass appeared to be the prostate. Neither abdominal nor pelvic pathological lymph nodes, nor bone lesions were observed (Fig. 1).

A prostate biopsy was performed, which showed bilateral infiltration by a neuroendocrine tumor with a low proliferation index (Ki67 index below 1%) suggestive of paraganglioma of possible prostatic origin.

Determination of catecholamine and its metabolites in 24-hour urine yielded the following results: Vanillylmandelic acid 22.2 mg/24 h (reference value: 2.0–9.0), adrenaline 47 µg/24 h (<18), noradrenaline 158 µg/24 h (<76) and dopamine 285 µg/24 h (<390).

PET-CT with injection of 150 µCi/kg of ^{18}F-FDG showed a pelvic lesion of 9 cm with a moderate increase in glucidic metabolism located in the prostate site and ascending to the vesico-rectal region (SUV max 3.6), not demonstrating other evident pathological deposits of the radio-medicine FDG, discarding a multifocal or disseminated disease (Fig. 2).

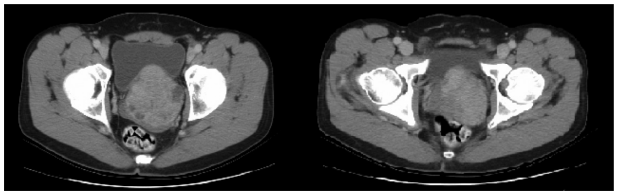

Figure 1. CT scan.

The body scintigraphy with 4 mCi of 123 I meta-iodobenzylguanidine (MIBG), with images 4 hours after administration in the adrenal area and after twenty-four hours in the rest of the body found no significant alterations.

Six weeks after performing the study, the patient suffered intermitent episodes of cold sweats and elevated blood pressure (200/120 mmHg), lowered heart rate (50 beats/minute), dyspnea with minimal activity, and asthenia, which began five minutes after micturition or defecation and were self-limited. Treatment with Doxazosin mesylate was initiated. The symptoms worsened with constipation or if the patient forgot to take the alpha-blockers. Phenoxyibenzamine at progressively higher doses and Propanolol, were added to control the symptoms.

Eight weeks after the initial consultation, a radical prostatectomy with excision of the pelvic mass and preservation of the neurovascular bundles was performed under adrenergic blockade. The postoperative recovery was uneventful and the patient was discharged on post-operative day 8 with normal blood pressure on no medications.

Macroscopically, a multinodular ovoid mass weighting 181 grams and measuring 9 × 7 × 5.5 cm was described. The external surface was smooth and shiny with partly greyish partly violet coloration. When cut, a lesion of a mostly brown or copper coloration with areas of softening and central cavitation which replaced the normal prostatic parenchyma was found. An abrupt or clear separation between the pathological and normal prostate tissue was not observed, but rather a gradual transition.

The histological analysis of the specimen revealed a neoplasm with imprecise limits and a epithelioid appearance with predominant growth by nests constructed of cuboidal cells ("Zellballen") with granular basophilic cytoplasms and small sized nuclei, mostly homogenous, and of a rounded-ovoid morphology. Peppered in and among them, appear cells with bizarre nuclei

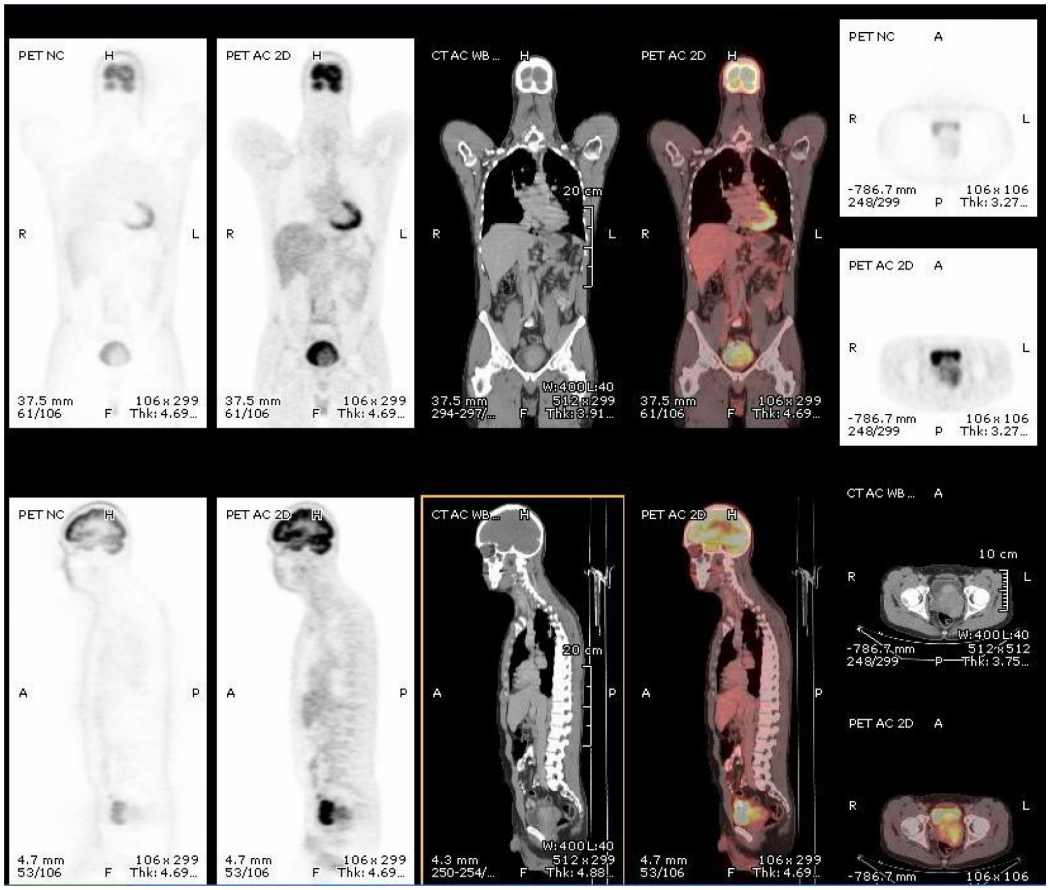

Figure 2. PET-TC scan.

of greater cytological atypia, and other rounded nuclei with reinforced nuclear membranes, with evident central nucleolus. These cells have higher density polygonal eosinophyllic cytoplasm with a ganglionic habit. Immunostaining revealed expression for Vimentin, Synaptophysin, chromogranin and ENE, being negative for PSA and AE1/AE3. The proliferation index (MIB.1) of the cells is very low. In addition, and in a characteristic way, the nests appear surrounded by fibrous septa, with sustentacular cells (S.100+), with elongated nuclei and badly defined spindles and cytoplasm. The growth of the lesion causes hyaline fibrosis in the prostatic stroma, with focal neural (multifocal perineural growth) and glandular preservation. The rest of the prostatic parenchyma had its habitual structure without a well-defined transition with the neoplasia. The seminal vesicles showed neither infiltration nor histological lesions. These characteristics allow the classification of the lesion as a neuroendocrine tumor with histological and immunostaining characteristics compatible with prostatic paraganglioma (Figs. 3 and 4).

Three months after surgery the patient has got urinary continence and normal blood pressure but suffers from erectile dysfunction. A scan with Octreotide In-111 showed no pathological tracer deposits expressing Somatostatin receptors in the planar body images and SPECT-CT of abdomen at 6 and 24 hours after the administration of a dose of radio-medical tracer were observed. One year after surgical treatment he has normal micturition and blood pressure but persistent erectile dysfunction.

Discussion

Paragangliomas are slow growing neoplasms derived from the paraganglion tissue.[1] They consist of neuroendocrine cells derived from the neural crest along the autonomic nervous system and associated with abundant vascularization. According to the anatomical location they can be grouped into branchiomeric, intravagal, aortic-sympathetic and autonomous-visceral paragangliomas.[2]

Approximately 90% grow in the adrenal gland and are called pheochromocytomas. The other 10%

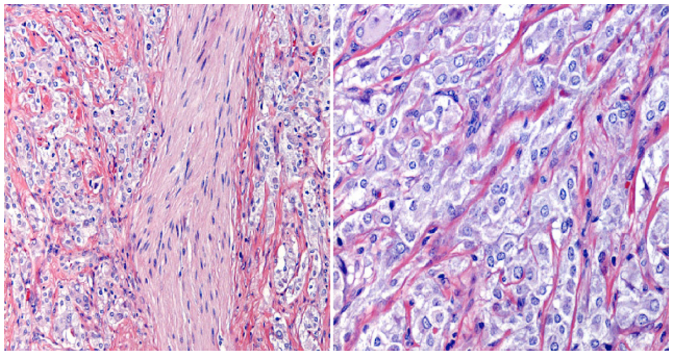

Figure 3. Hematoxylin-eosin 10× and 20×.

are non-adrenal paragangliomas, of which 85% are abdominal. Of these last, approximately 88% are para-aortic (next to the adrenal gland and the renal hilum, and at the Zuckerkandl organ and are more frequent in adults) and the rest, almost all are found in the bladder, mostly in pediatric patients.[3,4] There are 10 cases of prostatic paraganglioma documented in medical literature which arise in the sympathetic paraganglionic tissue located in the soft tissue besides and behind the gland.[5–7] (Table 1).

Generally, paragangliomas affect young adults of both sexes equally, although cases of prostatic paraganglioma have been encountered in children.[10] The symptoms are varied and are related to the size and location of the lesion, as well as to the tumor's capacity to secrete catecholamines. In the case of prostate paragangliomas, the most frequent local symptoms are hematuria and moderate perineal pain, but other associated symptoms are derived from the production of vasoactive amines such as treatment-resistant hypertension, as well as the presentation of hypertensive crisis triggered by micturition, defecation or a digital rectal examination.[18]

It should be taken into consideration that up to 50% of paragangliomas are hereditary and can be associated with diseases like type 1 neurofibromatosis, familial paraganglioma, von Hippel-Lindau disease and the Carney's triad.[19]

Diagnostic confirmation is accomplished through the determination of catecholamine and its derivatives in serum or urine of 24-hours and body scintigraphywithI^{123}-meta-iodobenzylguanidine(I^{123}-MIBG).[20] Other image tests such as CT, PET-CT or MRI can help to establish the diagnosis and locate the lesion.

In the revised literature, it is not recommended to perform a diagnostic biopsy due to the possibility of triggering a hypertensive crisis both in prostate and bladder pargangliomas,[21] although the frequent scarcity of symptoms and indicators of this pathology mean that on occasion we can't meet this criteria.

The treatment of choice in the case of localized and solitary tumor is the complete surgical resection under adrenergic blockage and volume expansion, in a similar fashion as in adrenal pheochromocytomas.[22] Radiotherapy has also been recommended, although its best indication is in the palliative treatment of the pain associated with bone metastases lesions.[1]

All paragangliomas share the same histological characteristics independent of the site of origin.[23] They show a pattern of nests and cords (Zellballen) surrounded by fine fibrovascular tracts. Other less frequent patterns exist and they are usually focal such as angiomatoid, spindle-cell, clear cell and sclerosing.

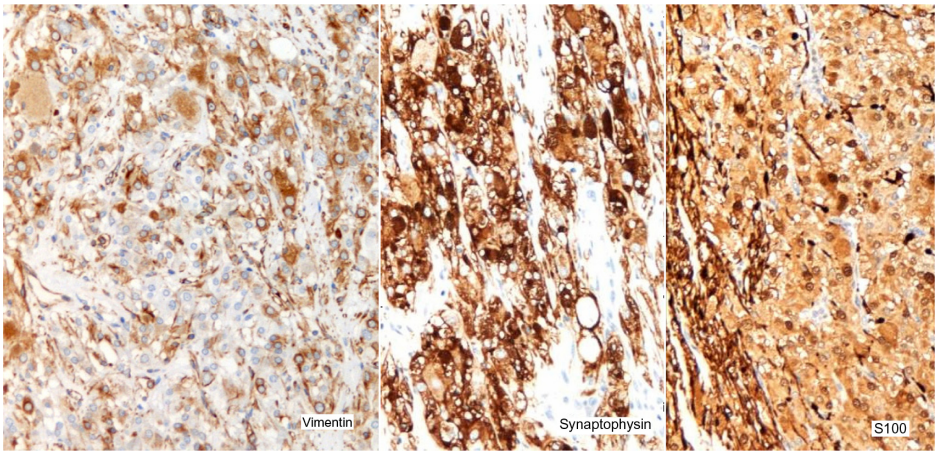

Figure 4. Inmunostaining (Vimentin, Synaptophysin, S100 10×).

Table 1. Summary of current and past cases.

	Age	Location	Presentation	Diagnosis	Treatment	Follow-up
Mehta[8]	29	Pelvis	Edema of the right leg + asymmetric enlargement of the prostate on the right side	BP, urography, cystoscopy, cystogram, biopsy, aortogram	Exploratory celiotomy + chemotherapy (vincristine, cyclophosphamide, doxorubicin, carboxamine, actinomycin)	6 months: no recurrent disease
Nielsen[9]	37	Pre-prostatic, adrenal, para-aortic, sigmoid meso-colon	Hypertension, headaches, sweetening, DM	BP, US, aortography	Adrenalectomy, excision of the other lesions	–
Dennis[7]	35	Prostate	Hypertension, post-micturitional headache, dizziness and pallor	BP, CT, MIBG, angiography, MRI, cystoscopy	Radical retropubic prostatectomy + lymph node resection	12 months: no recurrent disease
Voges[10]	8	Prostate, left interior iliac artery	Hypertension, severe headaches, blurred vision	BP, CT, US, MIBG, voiding cystourethrogram	Radical prostatectomy (right bundle preservation) + resection of the tumor next to the left internal iliac artery	3 months: asymptomatic; no recurrent disease
Shapiro[11]	17	Prostate	Painless hematuria	BP, US, CT, MRI, MIBG	Chemotherapy: unresponsive. Surgical exploration: unresectable	–
Hasselager[12]	29	Prostate	Hematuria, dysuria, hemospermia	BP, urography, US, cystoscopy, biopsy, CT, MRI, MIBG	PTUR	18 months: no recurrent or metastatic disease
Jimenez[13]	17	Prostate	Perineal pain during defecation and urination	BP, US	Radical retropubic prostatectomy + lymph node resection + adjuvant chemotherapy (vincristine, cyclophosphamide, cisplatin)	5 years: no recurrent disease
Parwani[14]	35	Prostate	Gross hematuria, flank pain	BP, CT, US, prostate biopsy	–	–
Campodonico[15]	33	Prostate	Epigastralgia, heartburn	BP, US, CT, MIBG, prostate biopsy	Nerve-sparing radical prostatectomy with right pelvic lymphadenectomy	24 months: no recurrent disease
Perlmutter[16]	63	Peri-prostatic	Hypertension	BP, US, MRI, MIBG, prostate biopsy	Resection sparing the prostate + lymphadenectomy	–
Chen[17]	36	Prostate	Hemospermia, bloody stool, constipation	BP, US, MRI, prostate biopsy	Radical retropubic prostatectomy	40 months: asymptomatic; no recurrent disease
Current	34	Prostate	Perineal pain	BP, US, CT, PET-CT with FDG, MIBG, prostate biopsy	Radical retropubic prostatectomy	12 months: no recurrent disease; normal micturition, erectile dysfunction

Abbreviations: BP, biochemical profile; BTUR, bladder transurethral resection; CT, computed tomography; US, ultrasonography; MRI, urological magnetic resonance imaging; MIBG, ^{131}iodine metaiodobenzylguanidine; PET, positron emission tomography.

The lesions are composed of two types of cells: the principal and sustentacular cells. The majority of the cells have a rounded and ovoid nucleus with finely granular chromatin and occasional nucleolus, with a salt-and-pepper appearance. Their cytoplasm is large, polygonal, eosinophilic and finely granular, and can occasionally be pigmented. Immunostaining is positive for neuroendocrine markers (synaptophysin, chromogranin A, neural-specific enolase CD 56 and serotonin). The sustentacular cells have a hyperchromatic nucleus and a flattened and elongated cytoplasm; they are characteristically positive for S100.[23]

The principal differential diagnosis for this pathology is high grade adenocarcinoma of the prostate. Negative results in inmunostaining for PSA, prostate-specific acid phosphatase, cytokeratin 7, cytokeratin 20, cytokeratin 903 and thrombomodulin, along with positive results for chromogranin, synaptophysin and S100 are clear differential diagnostic criteria.[14]

In general they are tumors of benign nature, but 10% of cases have been reported as malignant neoplasms with extensive local infiltration and a high tendency towards the development of distant metastases in bones, lymph nodes and heart, therefore life-long follow-up is needed.[10,24] In addition, its insidious course with a lack of specific symptoms in many patients makes the diagnosis of the tumor difficult until an advanced stage.[14] Given that the size and location of these tumors stand out as important prognostic factors, its early diagnosis is fundamental.[1] However histological features predicting paragangliomas' behavior have not been defined, but possibly the presence of a high level of mitotic activity, large areas of necrosis and evidence of vascular invasion might be useful to predict their evolution.[23,25]

Conclusions

Prostatic paraganglioma is an unusual pathology, generally benign, which should be considered in the differential diagnosis of prostate tumors in young males.

Its diagnosis is based on the determination of catecholamine in 24-hour blood and urine and in imaging techniques mainly body scintigraphy with MIBG I-123. Diagnostic confirmation is achieved through a histopathological study.

Treatment consists of radical resection of the pelvic mass under adrenergic blocking and volume expansion. Radiotherapy is useful in palliative treatment.

Given the scarcity of documented cases, it is difficult to establish the prognosis for patients affected by this pathology. Its malignancy is defined by clinical criteria, which indicates life-long follow-up to eliminate the possibility of relapses.

Author Contributions

Wrote the first draft of the manuscript: BPF, MRG. Contributed to the writing of the manuscript: MFLG, PAP. Agree with manuscript results and conclusions: JMSA, AMR. Jointly developed the structure and arguments for the paper: BPF, MFLG. Made critical revisions and approved final version: PAP, MFLG, JMSA. All authors reviewed and approved of the final manuscript.

Conflicts of Interest

There is no actual or potential conflict of interest in relation to this article.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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