editorial article

Urology pertinent neuroendocrine tumors: focusing on renal pelvis, bladder, prostate located sympathetic functional paragangliomas

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SUMMARY: **Urology pertinent neuroendocrine tumors: focusing on renal pelvis, bladder, prostate located sympathetic functional paragangliomas.**

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Urology pertinent neuroendocrine neoplasias are more and more driving to research attractive contributions mainly as regards the urinary tract paragangliomas, besides the prostate cancer neuroendocrine differentiation. About such visceral sympathetic paragangliomas, a considerable attention is aroused by those concerning the renal pelvis, urinary bladder and, particularly, the prostate gland. Essential catecholamine/adrenergic signal-mediated pathophysiological implications and outlined diagnostic approaches are here taken into consideration. Particularly, to reach an accurate functional diagnostic assessment, both plasma and urine catecholamine level tests are required together with ^{123}I or ^{131}I-meta-iodobenzylguanidine (MIBG) scan while ^{131}I-,

instead of ^{123}I-, labeled MIBG, proving to be also useful to targeted radionuclide therapy of sympathetic paragangliomas. Nevertheless, a thorough diagnostic confirmation should be obtained by a proper histologic/ immunohistochemical study, so that it respectively highlighting the typical "zellballen" cell setting and neuroendocrine tumor cell specific biomarkers such as chromogranin-A, synaptophysin, neuron-specific enolase. Open/laparoscopic/robot-assisted surgical procedures are performed under α_1 (doxazosin, prazosin) - and β(propranolol)-adrenergic blockade to avoid the risk of an intraoperative adrenergic signal-triggered hypertensive crisis, what moreover may occur also during cystoscopy and biopsy in case of bladder or prostate paraganglioma. Given a conceivable likeness, about some adrenergic-mediated pathophysiological implications, between prostate paraganglioma and prostate cancer neuroendocrine transdifferentiation – although as regards two obviously different diseases – a reliable pathogenetic matter concerning prostate paraganglioma is requiring novel research approaches.

KEY WORDS: Paragangliomas - Prostate - Bladder - Renal pelvis - Neuroendocrine tumors - Prostate cancer neuroendocrine differentiation.

About urology pertinent neuroendocrine tumors, the literature has been enriched, in the last decade, with intriguing contributions concerning the urinary tract sympathetic paragangliomas, particularly renal pelvis, bladder, prostate or periprostatic locations.

Paragangliomas

Paragangliomas, as neuroendocrine tumors arising from embryonic neural crest cells of either sympathetic or parasympathetic paraganglia – groups of cells near nervous system-derived respective ganglia – may be of two types, *functional* (sympathetic chromaffin paragangliomas/pheochromocytomas), as catecholamine-secreting tumors, hence appearing with typical symptoms such as paroxysmal hypertension, heart palpitations, headache attacks, sweating or, instead, parasympathetic *non-functional* neoplasias as lacking in chromaffin cells (1-5).

Sympathetic functional paragangliomas – outside adrenal gland chromaffin cell-derived neoplasias – are commonly found in the abdomen, within shaped paraganglia, along the aorta lenght, also including the area between renal arteries and aortic-iliac bifurcation, besides the so-called or-

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gan of Zuckerkandl as a large source of catecholamines in foetus and infants, or, otherwise, within visceral organs – autonomous-visceral paragangliomas – like the renal pelvis, urinary bladder, prostate/periprostatic locations. Parasympathetic non-functional paragangliomas occur, instead, as branchiomeric and intravagal tumors, on the head and neck regions – so as tympano-jugular paraganglioma, carotid body chemosensor tumor/chemodectoma, vagal paraganglioma – without hormone production, thus their occurrence resulting found on the basis of possible tumor mass-effects symptomatology (coughing, hearing loss in one ear, swallowing difficulties) or quite incidentally during imaging examinations (1, 3, 6).

Generally, paragangliomas may occur in both sexes young adults. About 30% of the sympathetic paragangliomas/pheochromocytomas are hereditary tumors because of mutations, under epigenetic imprinting effects, of the succinate dehydrogenase (SDH) gene whose the codified mitochondrial enzyme acts, within a proper oxygen level sensor process, to convert succinate to fumarate as a step of cell citric acid cycle (Krebs cycle) and electron transport chain, the lack of such enzyme-mediated conversion leading to send-out pseudosignals of low-oxygen environment with hypoxia like condition-induced (HIF-1α role indeed implied) abnormal cell growth/tumor promotion (3, 6-8).

Among the paraganglioma (PGL) multiple syndromes, the PGL1 is associated with mutation of SDH gene complex subunit D (SDHD, chromosome 11q23), quite regarding the parasympathetic tumors located in head/neck, whereas PLG3 and PLG4 are respectively linked with mutation of subunit C (SDHC, chromosome 1q21) or subunit B (SDHB, chromosome 1p36.1), both concerning the sympathetic paragangliomas. The PGL2, instead, would seem to be due to SDHAF2 (succinate dehydrogenase complex assemblying factor 2) gene mutation. Hereditary paragangliomas may sometimes belong to neurofibromatosis 1 (NF1), multiple endocrine neoplasia-2 (MEN2), von Hippel-Lindau syndrome or even very rare Carney's triad that includes paraganglioma, gastrointestinal stromal tumor, pulmonary chondroma (1, 6-11).

Paragangliomas of the urinary tract

The extremely rare, among the viscero-autonomic sympathetic paragangliomas, *renal pelvis* chromaffin cell tumor shows typical symptomatology including paroxysmal blood pressure rise, sweating, hearth palpitations and headache attacks. To reach an accurate functional diagnosis (Table 1), both plasma and urine catecholamine level tests are required together with ^{123}I- or ^{131}I-metaiodobenzylguanidine (MIBG) scan while ultrasonography, CT and MRI are useful to provide morphological data about primary tumor and its metastases. It has to be pointed out that ^{131}I-, instead of ^{123}I-, labeled MIBG, besides supplying the functional diagnosis, may be also used for targeted radionuclide therapy of sympathetic paragangliomas (10, 12, 13).

Previous preoperative both α_1- and β-adrenergic blockade – respectively by administration of prazosin/ doxazosin and propranolol – and also plasma volume expansion with saline infusion, to prevent possible postoperative hypotension due to chronic volume contraction, the open/laparoscopic/robot-assisted radical excision of diseased kidney or, if it is possible, the only removal of the tumor (especially in case of *renal hilar* paraganglioma with compression-mediated renal artery stenosis) are suitable surgical procedures (12, 14, 15).

The *bladder* sympathetic paraganglioma, amounting to 6% of all extra-adrenal pheochromocytomas, accounts for 0.06-0.1% of all bladder tumors (2, 6). Given that it arises from sympathetic nervous system-derived chromaffin cells within the bladder wall layers, its reliable idenfication may pointed out on the basis of typical histological features and, particularly, by resorting to suitable immunohistochemical assessment in addition to specific blood plasma/urine labor tests and imaging approaches (Table 1) (2, 5, 7, 10, 13, 16).

However the clinical appearance is quite characteristic as including episodic headache, paroxysmal arterial hypertension and, particularly, micturition/bladder contraction due α_1 adrenergic/catecholamine-mediated, typical symptoms such as syncope, sweating and heart palpitation attacks, what may also occur during cystoscopy and biopsy (1, 2, 6, 9, 13, 16).

Management of such tumor includes transurethral resection or open/laparoscopic either partial or total cystectomy with pelvic lymph node dissection, nevertheless every surgical measure after preoperative antihypertensive-adrenergic blocker approach. Possible adjuvant external beam radiation the-

TABLE 1 - UROLOGY-PERTINENT SYMPATHETIC PARAGANGLIOMAS: OUTLINED DIAGNOSTIC APPROACHES.

Laboratory tests

Blood plasma
- Tyrosine-derived catecholamine family: - norepinephrine
                                                           - epinephrine
                                                           - dopamine

  The methylation of norepinephrine to epinephrine is significantly lower, because of phenylethanolamine N-methyltransferase gene mutation-induced downregulation, in malignant paragangliomas (31).

- Catecholamine metabolites: - normetanephrine
                                        - metanephrine
                                        - metoxytyramine, as novel plasma biomarker for SDHB gene mutation-dependent chromaffin paraganglioma (32).

- Chromogranin-A

Urine
(24 h collection)
- Catecholamine family: - norepinephrine   • Metabolites: - normetanephrine
                                 - epinephrine   - metanephrine
                                 - dopamine   - vanillylmandelic acid

Imaging

CT, MRI, Ultrasonography   to identify primary tumor site and metastatic locations, size and morphological features. Particularly, MRI (T1-, T2-, water diffusion-weighted and contrast-enhanced imaging) can play a reliable role in the preoperative diagnosis (5).

Nuclear medicine functional tests: - [123]I- or[131]I-meta-iodobenzylguanidine(MIBG) SPECT. Such compound, given its noradrenaline-like guanethidine derivation, is endowed with particular tropism for α_1-adrenergic receptors (7). ^{131}I-MIBG may be concurrently used as imaging means and targeted therapeutic measure (that is a theranostic procedure) of malignant paragangliomas(10,33,34)
                                         - ^{18}F-fuorodeoxyglucose (FDG) PET, lacking in specific tumor-targeting.
                                         - ^{18}F-fuorodihydroxyphenilalanine(FDPA) PET
                                         - ^{68}Ga-Dotatoc (DOTA-Phe-Tyr-octreotide) PET, useful to properly identify somatostatin cell receptor-endowed neuroendocrine tumors.

Fusion imaging techniques : PET/CT , PET/MRI, SPECT/CT, SPECT/MRI may be useful to carefully pick out metastases or multiple concomitant paragangliomas.

Histology and immunohistochemistry

Histologic features consist in either typical "zellballen" (small nest-like clusters of spindle-to-polygonal chief cells enveloped by thin vascular-fibrous septa and sustentacular cells) or more rare ribbon-like cell growth patterns, with frequent tumor necrosis besides muscularis propria/detrusor invasion (6).

Immunohistochemical staining of paraganglioma cells, as well as of neuroendocrine tumor cells, shows positivity for specific biomarkers, such as chromogranin-A, synaptophysin, neuron-specific enolase, in comparison with pan-cytokeratin (PCK) negativity.

rapy can improve median survival in patients suffering from malignant paraganglioma (1, 4, 6, 9).

As regards the *prostate* or *periprostatic* sympathetic paragangliomas, the symptomatology, in addition to that generally prostatism-related, consists in catecholamine hypersecretion-due typical expressions such as heart aberrant palpitations, palaness, headache and sweating attacks besides mic-

turition-triggered possible cardiac arrhythmia and syncope, sometimes occurring also after defecation and digital rectal examination (17-22).

Usually such neoplasias, often found in young males, are of benign nature, only about 10% of cases resulting to be malignant. From the literature emerges that some cases of prostatic paraganglioma have been encountered too in children (22, 23).

Tumor discovery is morphologically achieved through digital rectal examination, ultrasonography, contrast-enhanced CT and MRI and, in addition, ^{18}F-fuorodeoxyglucose PET/CT fusion imaging, but to reach, given the symptom features, its functional diagnosis, it is timely the resort to body ^{123}I-MIGB scanning, even though the laboratory findings – plasma and 24-hour urine catecholamine high level positivity compared with prostate-specific antigen (PSA) test negativity – obviously referring to a sympathetic paraganglioma.

Extremely accurate diagnostic confirmation could be obtained by histologic-immunohistochemical study but it is advisable to refrain from prostatic biopsy given the chance of triggering above mentioned hypertensive crise-linked problems (Table 1).

The surgical procedure for intraprostatic paraganglioma consists of radical prostatectomy under preoperative both α_1- and β-adrenergic blockade together with plasma volume expansion. External beam radiation- or radionuclide ^{131}I-MIBG- or even ^{223}Ra-therapy may be carried-out particularly for palliative treatment of painful symptoms of malignant paraganglioma-related bone metastatic lesions (10, 17, 18, 22).

As regards a possible identified *periprostatic* – prostate closely located – sympathetic paraganglioma, the surgical treatment is usually confined to open/laparoscopic only tumor excision, still with previous both adrenergic blockade and plasma volume expansion (17, 18, 21).

Emerging remarks and conclusions

In the field of urology pertinent neuroendocrine tumors, the above mentioned sympathetic pargangliomas, are just interesting particularly as regards their pathophysiological conditions and resultant symptomatology, with consequent resort to specific diagnostic measures (Table 1).

Among such tumors, that prostatic one is lately arousing attractive research works given its conceivable pathogenetic correlations – on the basis of involved similar *adrenergic mechanisms* – with prostate cancer beginning to neuroendocrine conversion, even though it regarding two different pathological conditions.

As regards the *prostate paraganglioma*, indeed, the tumor chromaffin cells just clustering near intraprostatic sympathetic nerves, can induce whole adrenergic signal-mediated pathogenetic effects. In the same way, as far as the *prostate carcinoma* is concerned, particularly the cancer cells proximal to intraprostatic sympathetic nerve ramifications may undergo possible – because of androgen deprivation, prolonged adrenergic agent treatment, long-term chemo/radiation therapy – transdifferentiation to neuroendocrine-like cells, via β_2 adrenergic-mediated molecular mechanisms just starting from cancer cell β_2-receptors (24-26). Quite hence, the activation by cAMP – 3',5'-cyclic adenosine-monophosphate derived, through adenyl-cyclase catalytic conversion, from ATP, adenosine triphosphate – of PKA (cAMP-dependent protein kinase) signaling pathway, leads, together with production of anti-apoptotic and pro-angiogenic factors, up to phosphorilation of CREB (cAMP responsive element binding) protein, so that driving prostate cancer cells to be provided with neuroendocrine features among which various neuroendocrine markers, such as neuron specific enolase, synaptophysin, chromogranin-A (24, 27-30).

In conclusion, given such conceivable likeness about *adrenergic-mediated* pathophysiological implications of both prostate paraganglioma and prostate cancer neuroendocrine transdifferentiation – although as regards two different pathologic conditions – the properly set up pathogenetic matter concerning prostate sympathetic paraganglioma is more and more rousing novel suitable research approaches.

Conflict of interest statement
The Author declares that such article has been carried out without any potential conflict of interests.

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