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Solid Tumour Section

Mini Review

Endocrine/neuroendocrine glands: Phaeochromocytoma

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Identity

Alias
Catecholamine-secreting paraganglioma; Functional paraganglioma.

Note
Usually, the term "phaeochromocytoma" designe secreting adrenal medulla tumor. An extraadrenal tumor is indicated by the term "catecholamine-secreting paraganglioma".

Clinics and pathology

Note
Neuroendocrine tumours arise from neuroecto-dermal chromaffin tissue, usually develop within the adrenal medulla but could develop in extraadrenal sympathetic ganglia in 10 % of cases. Phaechromocytomas secrete catecholamines (epinephrine, norepinephrine, dopamine) in the circulation and could induce severe lethal cardiovascular and cerebrovascular complications.
They are located in the abdomen and in the pelvis (adrenal medulla, organ of Zuckerkandl, urinary bladder, paraganglia chromaffin cells in association with nerves and plexus). In rare cases, they could develop in the mediastinum (chest, pericardium, thorax) or in the neck (carotid body) and in the head (glomus jugulare and tympanicum). Usually, the paragangliomas located in the neck and in the head are non functional.

Phenotype / cell stem origin

Crest neural cells.

Etiology

Phaeochromocytoma is an inherited form of cancer in 10% to 25% of cases. In familial cases, pheochromocytoma is a component of one of the four following autosomal dominant syndromic diseases, Multiple Endocrine Neoplasia type 2 (MEN2), Von-Hippel-Lindau disease (VHL), Hereditary paraganglioma syndrome (PGL) and Neurofibromatosis type 1 (NF1). In 75 to 90% cases, it is a sporadic or a non syndromic disease of an unknown etiology.

Epidemiology

The annual incidence is estimated at 1/10 000.

Clinics

The clinical manifestations are commonly paroxystics and result from catecholamine secretion: blood pressure changes (hypertension ± hypotension, orthostatic hypotension, hypertension induced by postural change or by the palpation of the mass), tachycardia, excessive sweating, pallor of face, headaches, etcŠ. The diagnosis is given by the elevation of the 24-hour urinary total metanephrine-(metanephrine plus normeta-nephrine)-to-creatinine ratio and by the location of the tumor by imagery tests (computed axial tomography, magnetic resonnance imaging, scintigraphy with 131I-MIBG, somatostatin receptor scintigraphy).

Treatment

The treatment is the surgical removal of the tumor in a reference center. The patient must be prepared by a preoperative alpha blockade in order to prevent severe hypertensive crises and complications at the time of surgery. The treatment of recurrence or metastases is

surgery to reduce tumor mass and/or alternative therapy as irradiation with large doses of 131I-MIBG or radiotherapy of bones metastases.

Evolution

Usually phaeochromocytomas are benign tumors but they could be malignant (lymph nodes, bone or visceral metastases) in 10% of cases with recurrence and distant metastases. Tumor recurrence may occur months or years following the initial surgery.

Cytogenetics

Cytogenetics Morphological

Allelic losses at chromosome 1p, 3p, 17p, and 22q have been reported in sporadic and familial forms of phaeochromocytomas and at chromosome 11q in head and neck paragangliomas.

Genes involved and proteins

Note

271 patients with an apparently sporadic phaeochromocytoma, and identified 66 patients with a germline mutations (24%) have been tested. Of these 66, 11 patients had mutations of SDHD (4%), 12 of SDHB (4.5%), 13 of RET (4.8%) and 30 of VHL (11.3%) genes. The genetic testing of all patients with phaeochromocytoma is important to identify genetic defects which are relatively frequents even in apparently sporadic tumours, to organize the clinical management of the patients with an inherited form of the disease and to propose a presymptomatic familial genetic testing.

SDHB

Location

1p36.1-p35

DNA / RNA

8 exons, 1100 bp, 35.45 kb.

Protein

The subunit B protein or iron-sulfur protein (280 amino acids, 31.62 kDa), which binds three different iron-sulfur clusters, is directly involved in the catalytic activity of succinate dehydrogenase (mitochondrial complex II).

Germinal mutations

Germline mutations cause hereditary paraganglioma, non-familial paraganglioma, familial and sporadic pheochromocytomas. Different germline mutations have been reported. Mutations in SDHB have been also published in cases of sporadic and familial malignant pheochromocytomas. Some tumors display a second hit with the loss of 1p chromosome containing the wild type allele of SDHB gene. As in SDHD-inherited tumors, the inactivation of SDHB protein induces a complete loss of succinate deshydrogenase activity in the tumoral tissues and an activation of hypoxic-angiogenic pathway.

VHL

Location

3p25-p26

DNA / RNA

3 exons, 4862 bp, 12,37 kb.

Protein

The pVHL (213 amino acids, 24.15kDa) is a tumor suppressor protein which forms a multimeric complex with elongin B, elongin C and cullin 2. It is involved in several processes including cell cycle control, control of extracellular matrix, mRNA stability but its main function is the regulation of hypoxia-inducible gene expression and the negative regulation of angiogenesis via VEGF, HIF and EPAS. The VHL disease predispose to the development of various tumors. Pheochromo-cytoma occurs in the type 2 of the disease.

Germinal mutations

Germline mutations of VHL gene have been identified in >500 kindreds. For the Von Hippel-Lindau (VHL) type 2, the mutations are missense mutations with recurrent mutations at codon 98 (Y98H), 167 (R167Q) and188 (L188V).

RET

Location

10q12.2

DNA / RNA

21 exons, 53.3kb.

Protein

The RET protein (1114 amino acids, 124.32 kDa) is a receptor tyrosine kinase which is expressed in derivatives of neural-crest cells. The first identified ligand is the glial-derived neurotropic factor (GDNF). The activating mutations of proto-oncogene RET, which constitutively activate the kinase receptor, induce three different subtypes of multiple endocrine neoplasia II (MEN2). Phaeochromocytoma occurs in MEN2A (in association with medullary thyroid carcinoma and hyperparathyroidism) and in MEN2B (in association with medullar thyroid carcinoma, marfanoid habitus, mucosal neuromas and ganglioneuromatosis of the gastrointestinal tract). In MEN2A, the mutations are principally located in the cystein-rich domain in affecting one important cystein residue (in exon 10 the Cys609, Cys610, Cys618 and Cys620) in particular the codon Cys634 in exon 11, which are significantly associated with phaeochromocytoma development, and induce a RET homodimerization. The MEN2B is caused by mutation in the tyrosine kinase domain and principally by the M918T mutation (95% of cases) which activates the

kinase activity. The identification of a MEN2 carrier by genetic testing is an indication to propose a prophylactic thyroidectomy.

SDHD

Location
11q23

DNA / RNA
4 exons, 1313 bp, 131.25 kb.

Protein
The complex II (succinate-ubiquinone oxido-reductase) is a key component of the mitochondrial respiratory chain and the tricarboxylic acid cycle. It is involved in the oxidation of succinate (succinate + ubiquinone = fumarate + ubiquinol) and carries electrons from FADH to CoQ. It is composed of four nuclear-encoded subunits. The subunit D protein or small subunit (cybS) (159 amino acids, 17.43 kDa) is one of the two integral membrane proteins anchoring the complex to membrane. The inactivation of SDHD protein in tumors, resulting of a germline SDHD mutation and a 11q LOH at tumoral level, induces the complete loss of succinate deshydrogenase activity.

Germinal mutations
Germline SDHD mutations are mainly associated with head and/or neck paragangliomas but several SDHD mutations have been reported in non familial and familial pheochromocytoma. Different types of mutations are described: false-sense mutations, insertions and deletions leading to protein truncation and missense mutations.

NF1

Location
17q11

DNA / RNA
57 exons, 8959 bp, 279.3 kb.

Protein
The neurofibromin 1 (2839 amino acids, 319.4 kDa) is a GTPase activating protein. In Von Recklinghausen neurofibromatosis or neurofibro-matosis type 1, the risk of phaeochromocytoma is very low (<1%). The diagnosis of NF1 is essentially clinical (café au lait spots, neurofibromas, Lisch nodules, Crowe's sign, glioma of optic nerve, bone anomalies, positive family history, Š). The genetic testing is difficult due to the large size of the gene and the absence of an hot-spot region of mutations.

Germinal mutations
Nucleotide substitutions, deletions or insertions have been described.

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