Cancer Treatment Reviews 37 (2011) 111–119

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

Malignant pheochromocytomas and paragangliomas – The importance of a multidisciplinary approach

Kim Francis Andersen [a,*], Rahim Altaf [b,1], Anders Krarup-Hansen [b,1], Bjarne Kromann-Andersen [c,1], Thomas Horn [d,1], Niels Juel Christensen [e,1], Helle Westergren Hendel [a,1]

[a] Department of Clinical Physiology and Nuclear Medicine, Herlev Hospital, University Hospital of Copenhagen, DK-2730 Herlev, Denmark
[b] Department of Oncology, Herlev Hospital, University Hospital of Copenhagen, DK-2730 Herlev, Denmark
[c] Department of Urology, Herlev Hospital, University Hospital of Copenhagen, DK-2730 Herlev, Denmark
[d] Department of Pathology, Herlev Hospital, University Hospital of Copenhagen, DK-2730 Herlev, Denmark
[e] Department of Endocrinology and Internal Medicine, Herlev Hospital, University Hospital of Copenhagen, DK-2730 Herlev, Denmark

ARTICLE INFO

Article history:
Received 14 February 2010
Received in revised form 6 July 2010
Accepted 8 July 2010

Keywords:
Pheochromocytoma
Paraganglioma
Adrenal mass
Multi-modality imaging
MIBG
SSTR
PRRT

SUMMARY

Approximately 10% of the pheochromocytomas and 20% of the paragangliomas are malignant with poor survival. As the biological behaviour of these tumours cannot be predicted with certainty from pathology the diagnosis of malignancy is difficult. Genetic testing is gaining impact as mutations in the tumour suppressor gene Von Hippel-Lindau and the mitochondrial succinate dehydrogenase enzyme complex subunit B (SDHB) are associated with malignancy. Excess release of catecholamines is characteristic for pheochromocytomas. High levels of chromogranin A, that is co-stored and co-secreted with catecholamines, may indicate tumour mass and malignancy and can be used to monitor response and relapse. The secretory and non-secretory tumours can be visualised with functional (specific and non-specific) imaging as SPECT and PET using ^{123}I-MIBG, somatostatin analogues, ^{18}F-DOPA, and ^{18}F-FDG. These modalities are recommended in patients with extra-adrenal and suspected metastatic/malignant disease, in case of distorted post-operative anatomy, and when suspected recurrence. The sensitivities of ^{123}I-MIBG scintigraphy or ^{18}F-DOPA PET are relatively low in SDHB mutated tumours, but high using ^{18}F-FDG. Specific PET imaging with somatostatin analogues generally has high sensitivity in malignant disease. There are no curative therapeutic options for malignant, metastatic pheochromocytomas/paragangliomas, wherefore consolidation of quality of life is essential. Adjuvant radionuclide treatment with beta-emitting isotopes coupled to MIBG or somatostatin analogues have shown response in approximately 30%. Chemotherapy is restricted to patients not accessible for surgery and resistant to radionuclide therapy. Novel targeted therapies, which mainly through a cytostatic effect interfere with specific targeted molecules needed for carcinogenesis and tumour growth show encouraging results.

Introduction

Pheochromocytomas and paragangliomas are rare tumours arising from chromaffin tissue either in the adrenal medulla (pheochromocytomas) or cells derived from the embryonic neural crest (paragangliomas). The latter may be located at any place from the cervical region to the lower pelvis cavity. Even though autopsy incidences probably are significantly higher, clinical incidences of pheochromocytomas have been estimated to range from 0.4 to 9.5 per million per year,[1–5] and approximately 1.5 per million per year in terms of paragangliomas.[6–8] As some of the tumours may be malignant the clinical course is potentially life-threatening. Therefore early diagnosis – including staging – is essential in order to initiate an optimal treatment strategy.

This review dealing with malignant pheochromocytomas and paragangliomas focuses especially on the multi-modality approach in diagnosis and treatment provided by the introduction of new radionuclides and the increasing availability of positron emission tomography (PET).

Clinical presentation

Chromaffin tumours may be divided into several groups based on malignant potential, secretory status, or genetic profile. The

* Corresponding author. Tel.: +45 44883408; fax: +45 44883411.
E-mail addresses: kifran02@heh.regionh.dk (K.F. Andersen), altafdk@hotmail.com (R. Altaf), ANKHA@heh.regionh.dk (A. Krarup-Hansen), BJAKRO@heh.regionh.dk (B. Kromann-Andersen), THOHO@heh.regionh.dk (T. Horn), nijc@heh.regionh.dk (N.J. Christensen), HEHEW@heh.regionh.dk (H.W. Hendel).
[1] Tel.: +45 44884488.

0305-7372/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ctrv.2010.07.002

tumours may be present at all ages, with a peak around 30–50 years. There are no sex differences. The largest group of patients presents with a solitary tumour located to the adrenal medulla. Approximately 10% of these tumours are malignant.[9,10] More than 20% of the abdominal paragangliomas are malignant. Paragangliomas of the head and neck are benign in the majority of cases.[11]

The clinical presentation depends on several factors: (a) symptoms related to malignancy (weight loss, fatigue, and tumour mass related symptoms) (b) symptoms and signs due to an increased secretion of catecholamines (c) mutations in specific genes associated with symptoms from other organs. Most patients with pheochromocytoma – either malignant or benign – have attacks with symptoms like headache, tachycardia, and sweating, but the most important objective sign is episodes of – or further increment of existing – arterial hypertension. The presentation of symptoms and signs may differ considerably from patient to patient.

Genetics

Currently, mutations in at least six different genes (the tumour suppressor genes VHL (Von Hippel-Lindau), NF1 (Neurofibromin 1), RET (' *rearranged during transfection*') proto-oncogene, and SDHB and SDHD (the mitochondrial succinate dehydrogenase enzyme complex subunit B and D)[12–15] have been associated with predisposition to pheochromocytomas and paragangliomas. The genetic component is most likely responsible for the tumour behaviour. It has been shown that VHL, SDHB, or SDHD mutated tumours and some sporadic tumours form a single cluster, as do RET and NF1.[16] Cluster 1 tumours have a hypoxia-driven angiogenesis, whereas increased metabolism and RNA synthesis characterises the cluster 2 tumours. VHL and SDHB mutated tumours are associated with malignancy in 5% and 50% respectively, whereas the other mutated tumours are rarely associated with malignancy.

Approximately 30% of all patients with pheochromocytoma harbour a germline mutation in one of the known susceptibility genes, and these patients often have a family history of pheochromocytoma or the presence of bilateral disease.[17]

Patients with Von Hippel-Lindau disease, neurofibromatosis, or multiple endocrine neoplasia (MEN) type 2 – caused by mutations in the above mentioned genes – more often present with signs/symptoms related to the primary disease than to pheochromocytoma. Neurofibromatosis type 1 is due to inactivation of neurofibromin, which plays a role in intracellular signalling. The RET protooncogene encodes a tyrosine kinase receptor, and mutations induce constitutive activity of the receptor, leading to multiple endocrine neoplasia (MEN) type 2. Patients with mutations in SDHB and SDHD genes have only symptoms related to the presence of an increased secretion of catecholamines and/or tumour mass. Gene analysis should be done first. It is especially important in younger patients or those with a positive family history, or in case of multi-focal tumours and/or the presence of specific tumour localisations (extra-adrenal abdominal, pelvic and thoracic location).[17] Except for SDHB mutations, which may be present at all ages, patients above 50 years do not need be screened.

Among patients with abdominal paraganglioma a substantial number have a mutation in a single susceptibility gene. Mutations in SDHB genes may also result in extra-adrenal pheochromocytomas, which often are malignant. In the case of mutations in SDHC and SDHD genes, the paragangliomas typically are located in the head and neck region. These tumours are benign. Mutation screening depends on the personal/family history and clinical findings as mentioned above.[17–19] Again, mutation screening in patients above 50 years is mainly relevant for the SDHB gene, as it may be present in all ages.

Biochemical diagnosis

Most laboratories recommend measurements of free normetanephrine and metanephrine in plasma or urine as the initial testing in patients suspected of having a secretory chromaffin tumour, as the sensitivity of the test (99% and 97%, respectively) is superior to measurements of catecholamines in plasma (86%) and urine (84%).[14,20,21] However, by applying this method there is a risk of overlooking tumours, which only produce small levels of catecholamines or exclusively secrete dopamine. In case of the latter, plasma measurement of dopamine or its metabolite methoxytyramine may have a role.[20] Drugs that increase catecholamine release, such as tricyclic antidepressants, trandate, and phenoxybenzamine, may lead to false-positive results.

Chromaffin tumours' different biochemical properties may be used to identify malignancy, as malignant pheochromocytomas have been shown to secrete predominantly noradrenaline.[22] As some malignant chromaffin tumours produce mainly dopamine,[23] malignancy may be indicated via the combination of elevated plasma dopamine and urinary dihydroxy-phenylalanine with the presence of preferentially noradrenaline producing tumours.[24,25] Finally, Amar et al.[26] demonstrated that the log urinary total metanephrine excretion could be used as an indicator of tumour burden.

Chromogranin A is a protein that is co-stored and co-secreted with catecholamines. Plasma levels of chromogranin A reportedly have a sensitivity of 83–89% for identifying pheochromocytomas.[27,28] Even though chromogranin A is elevated in both non-secretory and secretory pheochromocytomas/paragangliomas,[29] different patterns of expression may help to differentiate between benign and malignant disease.[30] High plasma levels of chromogranin A have been suggested to be indicative of malignancy,[22] and there is a proven correlation between chromogranin A levels and tumour mass as well as plasma metanephrines.[31] Chromogranin A also can be used to gauge tumour response and relapse.[22,32] Other biomarkers that have been applied to distinct malignant from benign chromaffin tumours are neuron-specific enolase and adrenocorticotrophin (increased in malignancy),[33,34] as well as secretogranin II and prohormone convertases I and II (over-expressed in benign tumours).[35] However, in patients with non-secretory tumours the best result may be obtained by imaging techniques.

Pathology

Several attempts have been made in order to predict the biological behaviour of chromaffin tumours. Recently a Pheochromocytoma of the Adrenal Gland Scaled Score (PASS)[36] was proposed. Based on 100 cases of adrenal pheochromocytomas (50 malignant and 50 benign), certain histological features, such as invasion (vascular, capsular, and/or periadrenal adipose tissue), large nests or diffuse growth, focal or confluent necrosis, high cellularity, tumour cell spindling, cellular monotony, increased and/or atypical mitotic figures, profound nuclear pleomorphism, and hyperchromasia, were suggestive of malignancy. The results on the validity of this scoring system are conflicting.[37] The expression of cell cycle/apoptosis related genes, such as P53 and Ki-67, might be of prognostic value,[10] but with the recent developments in molecular biology, one may expect analysis of DNA and RNA to be more promising. Some common histological features of chromaffin tumours are visualised in Fig. 1.

Imaging

Initial anatomical imaging with computed tomography (CT) and magnetic resonance imaging (MRI) are useful in the localisation of