Malignant phaeochromocytoma – a challenge in diagnosis and therapy

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Abstract

Phaeochromocytoma is an endocrine tumour that originates in catecholamine producing chromaffin cells of the adrenal medulla. Approximately 10% are malignant but there are no precise histological or biochemical markers to distinguish these from benign ones. The presence of metastases at distant sites is the most reliable clue but histologic features utilized in several scoring systems aid in predicting malignancy. Malignant phaeohromocytoma predominantly secrete noradrenaline and there may be high dopamine levels. Increased levels of chromogranin A, negative staining for inhibin/activin beta subunit and presence of SDHB mutation are the other factors associated with malignant potential. Multi modality evaluation with combination of CT, MRI, SPECT and radionuclide scintygraphy augments the diagnostic yield. Recent advance in molecular diagnostic markers further improved the knowledge in predicting malignant potential. Currently available therapeutic options are surgical debulking, pharmacological therapy for excess catecholamines, radionuclide therapy, antineoplastic therapy and external radiotherapy. These modalities provide symptomatic relief and biochemical control, but with no significant survival benefit. The development in the field of molecular pathway responsible for the malignant potential of phaeochromocytoma gives a hope to future therapy.

Abbreviations: CT- computed tomography, MRI- magnetic resonance imaging, SPECT- single photon emission computed tomography, PET- positron emission tomography, SDHB- succinate dehydrogenase B, ETA and ETB-endothelin receptors, mTOR- mammalian target of rapamycin, HIF- hypoxia inducible factors, ERBB2- erythroblastic leukemia viral oncogene homolog 2

Key words: malignant phaeocromocytoma, catecholamines, tumour markers

Introduction

Catecholamine secreting tumours are rare neoplasms that arise from chromaffin cells of the adrenal medulla (phaeochromocytoma) and the sympathetic ganglia (paraganglioma). The majority of pheochromocytomas are sporadic, but increasing prevalence of hereditary forms have been demonstrated recently (1). Around 10% of these tumours are malignant (2,3) and despite advanced diagnostic methods prediction of malignancy is difficult. Histologically and biochemically malignant tumours cannot be differentiated from benign ones. The presence of tumour spread to distant sites where chromaffin tissue is normally absent such as lymph nodes, liver, lung and bones is the only reliable clue to the presence of malignancy (4). Standard therapies for malignant phaeochromocytoma are non specific and the rarity of this condition makes it difficult to gather knowledge regarding outcomes of new forms of therapy. Since malignant phaeochromocyoma carries a poor prognosis and the occurrence of metastasis even years after the primary surgery, improvement in diagnostic and therapeutic measures are crucial (5,6).

Diagnostic clues for malignant phaeochromocytoma

Classically the diagnosis of phaeochromocytoma is achieved by measurement of urinary and plasma metanephrines. Methylation of noradrenaline to adrenaline requires phenylethanolamine-N-methyl transferase, which is a cortisol dependent enzyme. This explains the predominant production of adrenaline by phaeochromocytoma and noradrenaline by paraganglioma (7). Malignant phaeocromocytomas secrete predominantly noradrenaline. It is possibly due to the large tumour size which gets direct blood supply rather than corticomedullary. Therefore low cortisol concentration causes lack of methylation to adrenaline (7,8). In addition, increased levels of plasma dopamine or its metabolite methoxytyramine due to less differentiated catecholamine biosynthetic pathway may suggest malignancy (9,10).

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Chromogranin A is a protein released from storage granules of neuroendocrine cells and is elevated in 80% of patients with phaeochromocytoma, though it is not specific, malignancy is usually associated with very high rates (9,11). Some studies show normal adrenal medulla and benign phaeochromocytomas strongly stained for inhibin/activin beta subunit whereas it is negative in malignant tumours which may be used as an indicator of malignant potential (12). The other most important predictor of malignancy is the presence of SDHB mutation (13).

While the imaging features of this entity are variable, the use of coupled multi modality evaluation with CT, MRI, SPECT and radionuclide scintigraphy augment the diagnostic yield. In MRI these tumours have classically been described to have a "light-bulb" hyperintensity on T2-weighted sequences, due to a cystic component, and are hypointense on T1 sequences (14). The signal intensity on T2-weighted images may be low in malignant lesions due to haemorrhagic and necrotic areas though not a sufficient discriminating feature (15). The most specific radiotracer used is I^{123} or I^{131} labeled metaiodo benzyl guanidine (MIBG), which has chemical similarities to norepinephrine and is concentrated in chromaffin tissue. It permits evaluation of extra adrenal, metastatic and multiple tumours and has the ability to perform whole body scan. But dopamine secreting tumours usually do not take up MIBG and its sensitivity is low in malignanay (16). As these chromaffin tumours express somatostatin receptors, Indium-11-DTPA-octreotide, a somatostatin analog can be useful in MIBG negative cases with sensitivity of nearly 90% (17). Detecting small lesions which express low density somatostatin receptors, PET imaging with gallium labeled octreotide (^{68}Ga-DOTATOC) is superior and identification of lung or bone metastases is better with this modality (18). PET imaging with ^{18}F-FDG has higher sensitivity in detecting glucose avid metastatic lesions (19).

There are no precise histological features to predict malignant potential, but cytologic features, mitotic activity, pattern of growth and invasion are utilized to develop scoring systems. The Phaeochromocytoma of the Adrenal gland Scale Score (PASS) is the most commonly used system and score of more than 6 suggest a malignant lesion (20). In addition the growing development of molecular diagnostic markers provides supplementary information. Studies show Ki 67 index, a marker of proliferation, if >4% and absence of pS100 staining have significant correlation with high risk of maliganancy and recurrence (21). Up regulation of heat shock protein 90 (HSP90), telomerase activity and the telomerase catalytic subunit (hTERT) are closely linked with malignant phaeochromocytoma (22). It seems overexpression of angiogenic molecules such as vascular endothelial growth factors (VEGF), angioprotein-2, and endothelin receptors ETA and ETB are also associated with malignant phenotype (23).

Management

No randomized clinical trials are available regarding the treatment of this rare condition. The treatment goals are surgical debulking of primary tumour and metastases if possible, pharmacological control of hormone mediated symptoms, radiometabolic treatment and external radiotherapy, antineoplastic agents and the novel molecular targetted therapy. For large tumours transabdominal approach is preferred over laparoscopic resection and total adrenalectomy with loco regional lymph node clearance is recommended (24). Though surgery alone hardly cures the malignant phaeo-chromocytoma, it reduces the symptoms of catecholamine excess and improves the response to other therapeutic modalities such as MIBG. Arterial chemo-embolization, radiofrequency ablation and stereotactic radiotherapy are the valuable tools for control of metastases (25). Radionuclide treatment with I^{131}MIBG is the most widely studied non surgical therapy for tumors which are not resectable and considered as a good option in patients with high uptake on scintigraphy as 60% of metastases are MIBG avid (26,27). Combination with radiolabelled somatostatin analogues has synergistic effect. External radiotherapy might help bone metastases, but the patient needs proper preparation and monitoring to avoid crisis related with excessive release of catecholamine from radio induced inflammation (28). Chemotherapy with combination of cyclophosphamide, vincristine, and dacarbazine (CVD) is the most effective option for lesions which are resistant to both surgery and radionuclide therapy (26). But the tumour has the tendency to recur once the chemotherapy is stopped and becomes unresponsive to the same regimen (29).

Currently available therapeutic modalities provide symptomatic relief and biochemical control, but with no significant survival benefit. The development in the field of molecular pathway responsible for the malignant potential of phaeochromocytoma gives a hope to future therapy. One of the pathways is inhibition of HSP 90 since overexpression of this molecules play an important role in malignant phenotype (30). Therapies targeting angiogenic molecules is the other promising option and sunitinib, a tyrosine kinase inhibitor which acts on these targets shows good results (23,31). Combination of thalidomide (targeting VEGF) and temozolamide seems to have a good response in malignant phaeochromocytoma (32). There are clinical trials assessing the efficacy of other targeted therapies (mTOR inhibitors, HIF inhibitors, prolyl hydroxylase activators and ERBB2 inhibitors) on the horizon (26).

Conclusion

At present, no definite pathological or biochemical markers are available to distinguish malignant phaeochromocytoma from a benign tumour. Currently existing therapeutic modalities mostly offer symptomatic control rather than a cure. The recent development of molecular biology has improved the understanding of

pathways involved in malignant transformation of phaeochromocytoma and led to discovery of novel tumour markers. Advances in imaging techniques, nuclear medicine, chemotherapy and radiotherapy provide considerable impact in the management of patients, though limitations still exist. The novel molecular targeted therapies are promising strategies but the development of evidence based approach from large international trials is needed for the successful management.

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