Case report

Functional imaging as an aid to decision-making in metastatic paraganglioma

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Abstract. Malignant paraganglioma is a rare and slow growing tumour of neuroendocrine origin. At the time of diagnosis, the tumour is usually widespread, with limited therapeutic options. A variety of functional imaging studies are available for staging the disease, guiding therapy and monitoring treatment response. These include 123I-MIBG or 131I-MIBG, 111In-pentetreotide or 111In-lanreotide (somatostatin analogues), and 18F-FDG positron emission tomography. Various radionuclides, including 131I and 90Y, can be targeted to the tumour using MIBG or pentetreotide. Such targeted radionuclide therapy may provide valuable long-term palliation in such patients. We present two cases with metastatic paragangliomas who had widespread soft tissue and bone metastases. One patient was treatment naive and the second had received previous chemotherapy. The functional imaging work-up performed and the targeted radionuclide therapies considered in these patients are described. Both patients were treated with 131I-MIBG. Partial tumour response and complete symptomatic and hormonal response was achieved in one patient; in the second patient there was no change.

Paragangliomas are rare tumours of neural crest origin. They are thought to arise from chemoreceptor cells, hence the alternative name of chemodectoma. They are also called glomus tumours. Primary sites include the medial aspect of the carotid bulb (carotid body tumour), the vagus nerve ganglion (glomus vagale), the middle ear (glomus tympanicum) and the jugular bulb (glomus jugulare). About 50% of tumours are malignant and develop metastases, usually to lungs, liver, lymph nodes, bone and spleen [1]. Some malignant paragangliomas secrete catecholamines and serotonin. In most cases the disease is sporadic, but a familial form is rarely seen.

Metaiodobenzylguanidine (MIBG) is structurally similar to noradrenaline and is taken into chromaffin cells by an active transport mechanism and concentrated in storage granules. More than 90% of paragangliomas concentrate MIBG, a property that allows these tumours to be imaged with 123I-MIBG [2] and subsequently treated with 131I-MIBG [3–6]. Another feature of these tumours is that they express somatostatin receptors, enabling imaging with radiolabelled somatostatin analogues such as 111In-pentetreotide [7] and subsequent treatment with 90Y-somatostatin analogues (90Y-DOTATOC) [8]. Because of the rarity of malignant paraganglioma, there are only limited data about targeted radionuclide therapy and there is very little guidance about appropriate investigations to guide treatment and to assess response.

Functional imaging was used in the initial assessment and follow-up of two patients with metastatic paragangliomas.

Case 1

A 46-year-old man presented in December 1997 with proptosis of the right eye and diplopia. He also gave a history of pain in the left hip for several months. CT showed a lytic lesion in the right lateral orbital wall, with a soft tissue mass extending into the back of the right orbit intracranially and indenting the anterior right temporal lobe (Figure 1). A metastasis in the left iliac crest and an abdominal mass were also detected on CT. He received urgent palliative radiotherapy to the right eye prior to full investigation. His blood chemistry was unremarkable. Biopsy of the left iliac crest lesion showed a metastatic paraganglioma. The urinary noradrenaline level was 1791 nmol 24 h⁻¹ (normal range 120–590 nmol 24 h⁻¹). A diagnostic 123I-MIBG...
scan to map the full extent of disease and to assess the possibility of $^{131}$I-MIBG therapy showed intense uptake in the right orbital region and the left iliac bone. The scan also showed widespread disease involving the skull vault, spine, pelvis and chest region (Figure 2A). Owing to marked avidity for $^{123}$I-MIBG, the patient was considered for $^{131}$I-MIBG therapy. The initial plan was to give a total of 33.3 GBq (900 mCi) of $^{131}$I-MIBG in three cycles at approximately 10 week intervals, assuming there was no significant myelosuppression.

The first therapy dose of $^{131}$I-MIBG was given in March 1998 (Figure 2B). The thyroid gland was blocked with oral potassium iodide 60 mg given twice daily, which was started 2 days prior to treatment and continued for 17 days after the infusion. 12.1 GBq (327 mCi) of $^{131}$I-MIBG was infused intravenously over 30 min. A complete blood count was done weekly to monitor any myelosuppression. No immediate adverse effect was observed, apart from nausea 8 h post infusion. Mild thrombocytopenia was noted by the third week, but this recovered within 1 week. The patient reported marked improvement in leg pain 2 months after treatment. A second dose of 12.2 GBq (329 mCi) of $^{131}$I-MIBG was given in May 1998. The third dose of 12.5 GBq (337 mCi) was given in September 1998. The patient tolerated these doses well and only after the third dose did he develop a significant haematological nadir. His haemoglobin (7.6 g dl$^{-1}$) and platelets count ($22 \times 10^9$ l$^{-1}$) dropped and three units of blood were transfused. He made an uneventful recovery and remained well and asymptomatic without further treatment. His $^{123}$I-MIBG scan in February 1999 showed partial remission of disease (Figure 2C). He remained asymptomatic and returned to work. His most recent scan in November 1999 showed progression of disease (Figure 2D). A $^{99}$Tc$^{m}$-methylenediphosphonate (MDP) bone scan showed uptake in only the iliac crest (Figure 3A) and an $^{111}$In-pentetreotide study was negative (Figure 3B). $^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography showed glucose-avid metastases with a similar distribution to the $^{123}$I-MIBG scan (Figures 3C,D). The disease continued its progress and the patient died in October 2000.
Case 2

A 28-year-old male presented in 1993 with a carotid body tumour and pulmonary metastases. A diagnosis of metastatic paraganglioma was made. The carotid body mass was surgically resected and he received chemotherapy in 1995, with no response. In March 1999 he re-presented with weight loss, haemoptysis and excessive sweating. CT showed progression of the lung metastases. An $^{123}$I-MIBG scan in April 1999 showed mild tracer uptake in the hilar region, thoracic and lumbar spine, and left sacroiliac region (Figure 4A), and a lesion in the left orbital area. $^{111}$In-pentetreotide scan showed poor uptake in the lung metastases, normal but pronounced uptake in the kidneys and faint marrow activity. The orbital lesion was not visualized (Figure 4B). A similar pattern was observed with $^{111}$In-lanreotide.

A $^{99}$Tc$^{99m}$-MDP bone scan showed the characteristic appearance of multiple and widespread bony metastases involving the skull and spine, the right coracoid process, several ribs and both iliac bones (Figure 4C). $^{18}$F-FDG positron emission tomography delineated multiple foci of increased uptake in the hilar lymph nodes, both lung fields and virtually the whole spine (Figures 4D,E).

In spite of the poor $^{123}$I-MIBG uptake observed on the diagnostic scan, it was decided to give a single therapy dose of $^{131}$I-MIBG. This judgement was based on past experience when we have occasionally observed relatively higher uptake and longer duration of activity in metastatic sites. In this case, post-therapy scans on Days 2 and 7 showed a similar distribution pattern to the diagnostic study, but the biological half-life of the therapeutic dose was less than the time expected from the diagnostic test. No further active anticancer treatment was given. The patient died in September 2000.

Discussion

These two cases show the nature of the disease in its treated and naive form. Radiolabelled MIBG has a sensitivity of over 90% for detecting metastatic paragangliomas. Uptake by the metastases is high and this provides an ideal opportunity to carry out targeted radionuclide therapy with $^{131}$I-MIBG. In Case 1 there was no prior systemic treatment and the tumour showed marked avidity for $^{131}$I-MIBG. The proptosis was treated successfully by a combination of external beam radiotherapy and targeted radionuclide therapy. While only a partial response was
achieved in terms of tumour mass, a complete hormonal response was obtained. The patient was able to continue his employment and enjoy a normal quality of life until December 1999.

It was not surprising that we were unable to eradicate MIBG-avid disease completely. Our past experience, and that of other groups [3–6], indicates that approximately 73% of patients show at least partial tumour response, hormonal response or symptomatic improvement. Complete remission is rare. Tumour shrinkage is achieved in metastatic disease, and small lesions tend to resolve while larger ones usually persist. Our reluctance to pursue tumour eradication further should be viewed against a background of having already given 36.7 GBq (993 mCi) of 131I-MIBG over a period of 6 months, by which time myelosuppression developed. Other therapeutic options include surgical debulking and chemotherapy. In this case surgery was not a viable option and we opted for a “wait and see” approach. This may permit marrow recovery and allow the possibility of further treatment with 131I-MIBG if the patient relapses and becomes symptomatic or a hormone secretor. Chemotherapy could also be considered if escape from 131I-MIBG therapy occurs [9].

The extent of radiopharmaceutical avidity by relapsed disease is poorly understood and the progress of disease may be variable. Our second patient was a case in point. His presentation 4 years after initial chemotherapy suggests that the progress of disease was slow. However, the spread was extensive at presentation. Most of the radionuclide diagnostic tests were initiated in this patient with a view to palliative radionuclide therapy. It was clear that his treated disease showed poor avidity for 123I-MIBG and 131I-MIBG. Furthermore, there was no uptake of 111In-pentetreotide and 131I-lanreotide. No histological evidence of somatostatin receptors was sought to explain this lack of uptake. It can only be speculated that tumour dedifferentiation may have led to these findings. Painful bone metastases may be treated with rhenium-186-HEDP. However, this treatment was not carried out as pain was not the major complaint and the risk of serious myelosuppression would have been high. In addition, the extensive soft tissue metastases would have escaped treatment. Despite these findings, we decided to give a trial of 131I-MIBG therapy in the hope that some palliation may be achieved in spite of weak uptake of MIBG. Unfortunately, this was not the case and the patient died in September 2000.

It is concluded that, in view of the aggressive nature of the disease and the poor response to other treatments, 131I-MIBG may be a useful therapeutic modality for patients with metastatic paraganglioma.

References