Radioisotopic and anatomical imaging approach of a primary non functioning liver paraganglioma

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Keywords: Paraganglioma
- Octreoscan
- MIBG scintigraphy
- Structural imaging

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Received:
24 November 2010
Accepted revised:
8 February 2011

Abstract

Paragangliomas, also described as ectopic pheochromocytomas are infrequent neuroectodermal neoplasms that could be found wherever paraganglionic tissue exists. We present a rare case of a manifold non-functional primary hepatic paraganglioma in a 71 years old female. The combination of structural computed tomography and magnetic resonance imaging and of a functional modality, octreotide scan supported diagnosis. The role of nuclear medicine is crucial because it may help to determine future treatment in cases where there is suspicion of this tumour. However it has certain limitations, largely related to the physiological radionuclidic biodistribution. This case is described because of its relative rarity and also to emphasize the need to be studied by multidisciplinary collaboration.

Hell J Nucl Med 2011; 14(2): *Published on line: 16 June 2011*

Introduction

Paraganglioma (PG), as an "alternative" type of pheochromocytoma (PC), usually appears parallel to the autonomous nervous system from the cervix to pelvis. It can also arise intra-abdominally from the para-aortal chromaffin tissue, from the remnants of the organ of Zuckerkandl or be found incidentally in unusual locations such as the gallbladder, the biliary tree or the urinary bladder. The diagnosis of PG and its management require multidisciplinary collaboration between laboratory physicians, surgeons and oncologists [1]. We report this case of PG because of its relative rarity and to emphasize the need to be examined cooperatively.

Case report

A 71 years old white female was referred to "Metaxa" Cancer Hospital with the diagnosis of liver paraganglioma. One year before, the patient was admitted to "Tzanio" General hospital with hypogastric pain radiating to the lumbosacral area. Pain was gentle but paroxysmal. The patient had a history of asthma, while her family's medical history was not significant.

During her initial examination, chest and abdominal computed tomography (CT) showed a large abdominal mass (approximately 12cm in diameter) arising from the left ovary and multiple low attenuation foci in the liver of less than 4cm in diameter. These findings were confirmed by abdominal magnetic resonance imaging (MRI). Numerous gallstones were also present within the gallbladder. Thorax CT was negative.

Initially, the liver lesions were attributed to metastatic disease of unknown origin. Nevertheless, there was neither positive gastroscopy or colonoscopy nor abnormalities of the hematology tests. The patient underwent laparoscopic surgery, the abdominal mass was removed and the liver lesions were biopsied. Biopsy specimens showed that the abdominal mass was an ovarian fibroma, whilst the liver parenchyma samples showed immunohistochemical features of paraganglioma.

More specifically, the biopsy specimens revealed diffuse (>50% of tumor cells) and intense immunohistochemical positivity of the tumor cells for synaptophysin (SYP) and vimentine (VIM). The test of S-100 protein highlighted the sustentacular cells, while inhibin (INH) and calretinin (CaR) were negative. Immunostaining for chromogranin A (CgA) was paradoxically but not unprecedentedly negative [2]. Less than 2% of tumor cells showed positive Ki67 nuclear staining, indicating low cellular proliferation (for certification of high cellular proliferation in PC/PG, Ki67 must be >3%) [3]. It is important to note that the incidence of immunohistochemical expression for the above markers in a "typical" PC/PG is 100% for SYP, 95% for CgA, 70% for S-100P and about 50% for VIM, while for INH and CaR are less than 2% [4]. Besides, the presence of cytokeratin in relation to some tissue culture studies, indicate immunoblot confirmation [5] (Fig.1).

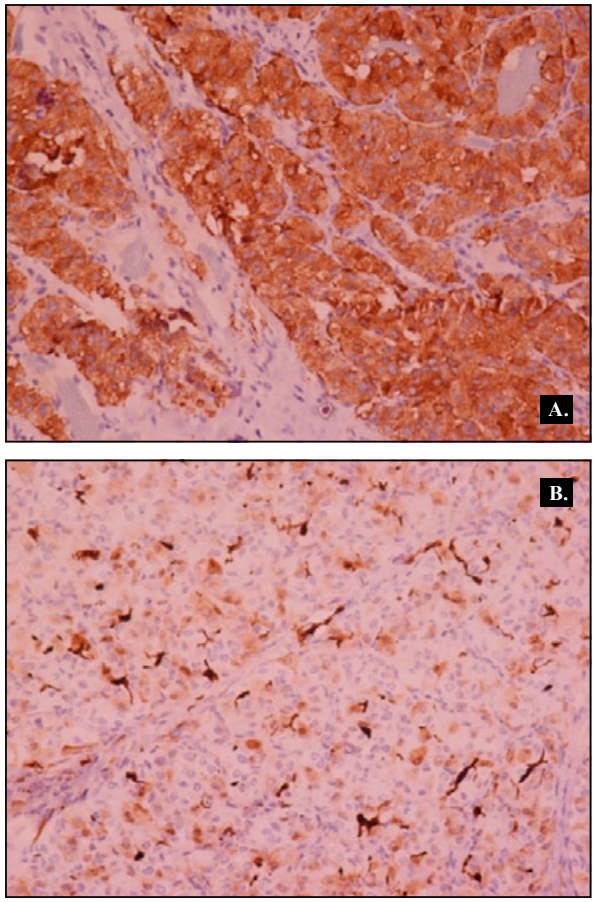

Figure 1. Liver paraganglioma: the histopathological study revealed diffuse immunostaining for synaptophysin (**A**). Also delicate sustentacular network was outlined for S100p (**B**) and diffuse stain for vimentine (**C**).

Later on, the patient was referred to "Metaxa" Cancer Hospital for further evaluation and definition of the subsequent therapeutic manipulations. On admission, the patient received "cold" octreotide treatment with depot long-acting somatostatin analog (sandostatin LAR). At one year's follow-up, the patient's condition was constant, suggesting that she suffered from a benign form of a non-functioning PG.

Discussion

Consistent with previous assessments, it is now considered that 10% of all pheochromocytomas are recognized at extra-adrenal sites. Others estimate this percentage as 15% for adults and 30% for children [6]. As far as liver localisation is concerned, there have been only few cases reported in the english literature [7-9].

It should be pointed out that in cases of non functional paragangliomas, as the one presented here, serum and urinary levels of catecholamines and their metabolites are in the normal range. Additionally, their complications might be mild and non specific.

Once a biochemical diagnosis of paraganglioma is made, CT or MRI structural imaging is usually performed. Although these techniques have an excellent sensitivity for detecting most catecholamine-producing tumors, modern guidelines emphasize the pivotal importance of functional imaging. Radionuclide-based modalities such as ^{131}I -meta-iodobenzylguanidine (^{131}I-MIBG) scan and ^{111}In-diethylenetriaminepentaacetic acid-octreotide (octreoscan), are the main procedures used for this purpose. Other methods, like dynamic imaging using ^{99m}Tc-DTPA, have incidentally been described [10]. More recently, positron emission tomography with ^{68}Ga-AM3/^{177}Lu-AM3 peptides as radiotracers are used for the differential diagnosis of pheochorocytomas/paragangliomas and for indicating the extent of the disease [11-13].

According to recent literature, in some cases there are variations and/or discrepancy between conventional radiology and scintigraphic findings or between the different radionuclidic procedures [14, 15]. Furthermore, there is an increased percentage of false negative results in non functioning paragangliomas, when sensitivity is examined by ^{131}I -meta-iodobenzylguanidine (^{131}I-MIBG) scintigraphy the reason of which is not clear [16]. Lack of localization could result from alterations in biodistribution (for example increased focal physiological activity) or from the small size of the tumors. Nevertheless, a direct proportional correlation was found between the percentage of uptake of the radiotracer and the number of neurosecretory granules in the tissue sections [17, 18].

In our case, the ^{131}I-MIBG scan was normal, taking into account that the patient did not use tricyclic antidepressants, sympathomimetics or antihypertensives during the period of the examination. On the contrary, planar views of octreoscan scintigraphy at 4, 24 and 48h post the intravenous administration of 222MBq of indium-111 (^{111}In-pentetreotide) were strongly positive [19].

Molecular imaging permits functional characterization of tissues by identifying specific receptors via targeted agents. Indium-111-pentetreotide is the radiolabelled form of octreotide, a shortened version of somatostatin. Neurondocrine tumors (NET) comprise of somatostatin receptors (SSTR), a kind of membrane glycoproteins. There are 5 subtypes of SSTR, while octeotride has a high affinity for SSTR 2, 3 and 5 subtypes. Paragangliomas over-express these receptors, therefore are well imaged by octreoscan [20]. In comparison to ^{131}I-MIBG, better renal excretion of octreoscan, allows a clearer visualization of the abdominal tumor sites, by decreasing background activity.

In our case, three foci of intense accumulation and one of low tracer activity were recorded within the liver, corresponding to the lesions seen on the MRI examination (Fig. 2 and 3). None of the scintigraphic techniques showed any other paraganglionic lesions. It is commonly accepted that neither the immunohistochemical nor the imaging techniques can predict the benign or malignant behavior of a paraganglioma. This can be defined only by the presence or absence of metastases. On the basis of these data, our patient is under close surveillance, in order to detect and treat any possible future relapse of the disease.

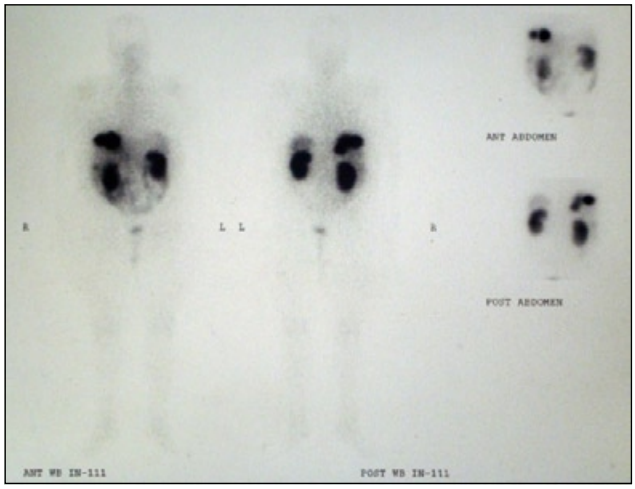

Figure 2. Whole body somatostatin receptor scintigraphy (octreoscan) accompanied with planar static views of the abdomen demonstrating 2-3 foci of intense increased radiopharmaceutical uptake and one focus of mild accumulation to the seventh and eighth segment of the liver respectively. There was no evidence of distant metastases.

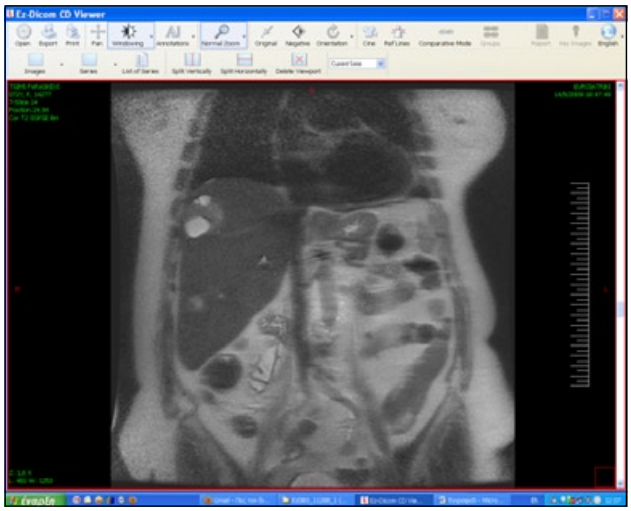

Figure 3. Abdominal MRI (BH-FRFSE sequence). Multiple liver focal lesions ranging from 1.3-4.2cm in diameter, with heterogeneous signal due to the presence of liquid and solid components. The lesions showed enhancement within the solid part on post gadolinium images.

Radionuclidic examinations in general, ^{131}I-MIBG and octreotide scintigraphy in particular, are of decisive importance in cases where the presence of paragangliomic cells are suspected and differential diagnosis with other solid tumors is necessary. However these modalities present some restrictions, which are associated to variable tumour differentiation and heterogeneous expression of SSTR's or to insufficient knowledge of physiological radioisotopic biodistribution. For reliable results, we should consider these restrictions and examine the patient also with anatomical imaging.

In conclusion, we present this case of liver paraganglioma because it is rare, and in order to underline the need for a multidisciplinary study.

Acknowledgement
Our special thanks to Prokopios I. Vogiatzis, MD, Histopathology Laboratory, General Hospital of Rhodes, Dodecanese-Greece, for his useful contribution.

Authors declare that they have no conflicts of interest

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