Successful response to pegylated interferon alpha in a patient with recurrent paraganglioma

Dear Editor,

Pheochromocytoma (PHEO) and extra-adrenal paraganglioma (PGL) are neuroendocrine tumors that arise from chromaffin cells of the adrenal medulla and the autonomic nervous system, respectively. These neoplasms are malignant in approximately 20% of cases (malignant PHEO and PGL and MPPs) (Baudin et al. 2014). Prospective trials are ongoing including the FIRSTMAPP (First International Randomized Study in Malignant Progressive Pheochromocytoma and Paraganglioma) trial.

Here, we describe a patient with recurrent PGL who showed significant response (based on anatomical and functional imaging) to one year of medical treatment with pegylated interferon alpha.

The patient, a 52-year-old male, had a history of isolated, secreting, left retroperitoneal PGL located in the lateroaortic region, close to the renal pedicle. In 2005, the patient had undergone a surgical resection that led to complete removal of a well-delineated, partially hemorrhagic tumor (60 × 50 × 30 mm) with no evidence of necrosis. Histopathology revealed clustered oval or fusiform acidophilic cells with variable shapes and nuclear sizes. There was no evidence of lymphatic or vascular invasion. On immunohistochemistry, cells were negative for the keratin antigen KL1 and positive for the epithelial membrane antigen, vimentin, synaptophysin and chromogranin. The mitotic index was <2 mitotic figures per 10 high-power fields (HPF) and the percentage of Ki67-positive cells was 13.5%. The Pheochromocytoma of the Adrenal Gland Scale Score (PASS) was unavailable. Three months after surgery, both plasma and urinary normetanephrine (NMN) concentrations were within the reference range. No abnormal findings were evident on 2-deoxy-2-[fluorine-18]fluoro-\( ^{-}\)D-glucose (FDG) positron emission tomography/computed tomography (PET/CT). The screening for germline mutations in SDHB/C/D and VHL genes was negative. The patient was asymptomatic, and biochemical monitoring yielded negative results until 2013, when the patient experienced symptom recurrence associated with an increase of urinary NMN. FDG PET/CT revealed a hypermetabolic uptake located close to the left renal pedicle with no evidence of systemic spread. The patient underwent surgery, and the pathological examination revealed the presence of two tumoral masses (50 × 40 × 20 mm and 17 × 13 × 19 mm in size) that exhibited tumor necrosis, lymphovascular invasion, extracapsular spread and peritumoral adipose tissue invasion. The presence of a poorly differentiated PGL was suspected, and microscopic resection was considered incomplete (R1). Immunostaining revealed that cells were positive for chromatogranin expression. The mitotic index was 3 mitoses per 10 HPF, and the percentage of Ki67-positive cells was 15%. The PASS score was 8. Three months after surgery, urinary NMN were again in the reference range. Because of the aggressive biological features of tumor recurrence, the screening for germline mutations was extended to other PGL susceptibility genes (i.e. MAX, FH and SDHAF2). Again, the results were negative. Immunohistochemical studies conducted on tumor samples obtained in 2005 and 2013 were positive for SDHA and SDHB and negative for SDHD expression, suggesting that the succinate dehydrogenase (SDH) enzymatic complex inactivation was unlikely in both tumor tissues. Histology and immunohistochemistry did not reveal an important T and/or B cells infiltrate. Finally, immunohistochemistry for HIF1-alpha yielded negative results. After approximately one year, the patient became symptomatic again and laboratory tests showed significantly increased urinary NMN concentrations. Contrast-enhanced CT identified an isolated 17-mm lesion in close contact with the surgical clips of the left renal pedicle (suggestive of local relapse). FDG PET/CT confirmed the pathological nature of that nodule and allowed the detection of two additional hypermetabolic lesions suggestive of metastases, in the left lumbar...
paravertebral region (L2–L3) and a left supraclavicular lymph node measured to 8 mm (Fig. 1). 123I-metaiodobenzylguanidine (123I-MIBG), 111In-pentetreotide scintigraphy and 18F-dihydroxyphenylalanine (18F-FDOPA) PET/CT yielded normal results. After discussion within the board of the French network for adrenal cancers (COMETE-Cancer), medical treatment with pegylated interferon alpha (Pegasys, Roche) at a dose of 180 µg/week was started. After one year, blood pressure remained uncontrolled and required both a higher prazosin dose (5 mg per day) and the addition of acebutolol (200 mg, twice a day). The instability of blood pressure suggested either an adverse effect of pegylated interferon alpha treatment or a consequence of uncontrolled NMN release from the tumor. A 30% decrease in urinary NMN levels was observed. A marked regression of the retroperitoneal tumor burden was clearly observed on both anatomical and metabolic imaging. The main lesion (located in the left renal pedicle) was barely detectable on FDG PET/CT (the tumor size was approximately 60% lower than that measured in the pretreatment period). Moreover, no significant tracer uptake was identified in the left supraclavicular region. Unfortunately, the patient developed typical signs of pegylated interferon alpha intolerance (e.g., fatigue, heartburn, muscle pain and two episodes of moderate neutropenia). Consequently, the dose was tapered off to 90 µg/week and ultimately discontinued. Unfortunately, 6 months after pegylated interferon alpha discontinuation, urinary NMN levels were found to be increased. In addition, there was a marked anatomical and metabolic relapse of the parapelvic renal nodule accompanied by an elevated metabolic activity within the retroperitoneal and the left supraclavicular lesions. The results of laboratory and imaging studies during the 1-year treatment and after discontinuation are detailed in Table 1.

A new screening for germline as well as somatic mutations was then performed and extended to additional genes (SDHA, EGLN1, EGLN2, MDH2, NF1, RET, TMEM127 and EPAS1). A SDHA nonsense variant (c.91C>T, p.(Arg31Ter)) was identified in the heterozygous state,

Figure 1
Results of FDG PET/CT imaging in a patient with recurrent PGL at 3 (A, D), 6 (B, E) and 12 (C, F) months after the beginning of pegylated interferon alpha treatment. There was a progressive reduction of tracer uptake in the retroperitoneal relapsed lesion (arrows) located close to the surgical clips of the left renal pedicle, in the left lumbar paravertebral region (L2–L3) as well as in a left supraclavicular lymph node (arrowhead). Upper panel: anterior whole-body maximum intensity projection images. Lower panel: coronal fused PET/CT images.
both in the germline and the tumor DNA. Additional SDHA mutations or deletions were lacking in the contralateral allele, suggesting the absence of loss of heterozygosity (LOH) at the SDHA locus in the analyzed tumor.

Complete surgical removal remains the gold standard for treating recurrent isolated PGL with curative intent. Here, we describe a patient with an apparently sporadic retroperitoneal PGL who showed multiple recurrences after surgery and was successfully treated with pegylated interferon alpha and relapsed after discontinuation. This drug has been proposed as a second-line treatment (either alone or in combination with octreotide) in certain neuroendocrine tumors (Santhanam et al. 2002). However, its potential clinical usefulness in PGL/PHEO has not been previously reported. Our therapeutic approach was motivated by a number of reasons, including (1) the patient's high surgical risk (as reflected by the need of left nephrectomy aimed at removing the lesion close to the renal pedicle), (2) the aggressive tumor phenotype, (3) the morphological progression and (4) the suspected metastatic nature of the supraclavicular lymph node. All of these aspects – rather than uncontrolled or not fully controlled clinical symptoms (e.g., isolated hypertension) – prompted the use of medical treatment rather than a watchful waiting strategy. Pegylated interferon alpha was initiated due to slow morphological progression, as defined by RECIST (Response Evaluation Criteria In Solid Tumors) progression below 20% over a year. Although published data on medical treatments for recurrent PHEO/PGL remain scanty, a higher number of studies on MPPs are available. The main management strategies for MPPs include watchful waiting, targeted internal radiotherapy, chemotherapy and molecular targeted therapies (Baudin et al. 2014). However, prospective assessments of their effectiveness are lacking. In addition, their efficacy can be hampered by the need to decrease dosing or even discontinue treatment because of the adverse effects that may have a negative impact on the quality of life. Two distinct molecular pathways leading to abnormal cell growth and apoptosis inhibition (i.e., increased angiogenesis and abnormal activation of kinase signaling pathways)

Table 1  Biochemical, imaging and metabolic characteristics of the patient with recurrent paraganglioma before and after treatment with pegylated interferon alpha.

<table>
<thead>
<tr>
<th></th>
<th>2014 Before treatment</th>
<th>2015 After 3 months of treatment</th>
<th>2015 After one year of treatment</th>
<th>2016 At 6 months after treatment discontinuation</th>
<th>2016 At 12 months after treatment discontinuation</th>
<th>Normal range</th>
</tr>
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<tbody>
<tr>
<td>Blood NMN (nmol/L)</td>
<td>9.9</td>
<td>7.6</td>
<td>4.94</td>
<td>9.3</td>
<td>24.6</td>
<td>&lt;10.96</td>
</tr>
<tr>
<td>Urinary NMN (nmol/24 h)</td>
<td>5916 NA</td>
<td></td>
<td>3993 NA</td>
<td>4730 NA</td>
<td>6730 NA</td>
<td>600-2293</td>
</tr>
<tr>
<td>Urinary 3-methoxytyramine (nmol/24 h)</td>
<td>NA</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>442</td>
<td>88-320</td>
</tr>
</tbody>
</table>

Abdominopelvic CT

| Lesion located between the surgical clips of the left renal pedicle (mm) | 17 | 7 | 7 | 13 | NA |
| Left renal pedicle surrounding the surgical clips | 22 | 3.8 | 2.8 | 3.4 | NA |
| Lesion located over the above-mentioned region, below the left adrenal gland | 5.7 | 3.8 | 2.6 | 5.2 | NA |
| Left supraclavicular node (8 mm in size) | 4.9 | 2.7 | 1.9 | 3.5 | NA |
| Left mesenteric lesion less than 1 cm in size close to the L2–L3 vertebral level | 10 | 10 | 5 | 20 | NA |

Bold values indicate abnormal biochemical findings.

CT, computed tomography; FDG, 2-deoxy-2-[fluorine-18]fluoro-D-glucose; NA, not available; NMN, normetanephrine; PET, positron emission tomography; SUVmax, maximum standardized uptake value.
have been implicated in the pathogenesis of PGL/PHEO (Parenti et al. 2012). Vascular endothelial growth factor (VEGF)-mediated angiogenesis has been reported in both human (Zielke et al. 2002) and rat PHEO cell lines (PC12) (Zielke et al. 2002). Interferon alpha is a pleiotropic cytokine that exerts a variety of direct and indirect anticancer effects including angiogenesis inhibition (Decatris et al. 2002). Moreover, it has been shown to inhibit PC12 cell growth by inducing apoptosis and cell cycle arrest likely through VEGF inhibition (Motylewska et al. 2013).

SDHA is one of the four mitochondrial succinate-coenzyme Q reductase subunits (complex II). SDHA gene can act as a tumor suppressor gene, and mutations have been implicated in the predisposition to PHEO/PGL (Burnichon et al. 2010, Korpershoek et al. 2011). Functional studies demonstrated that a germline SDHA mutation associated with a LOH at the SDHA locus results in a loss of SDH enzymatic activity in the tumor, leading to an increased angiogenesis via a pseudo-hypoxic mechanism (Burnichon et al. 2010). Negative SDHA immunohistochemistry may reveal the presence of SDHA mutations and allows the identification of SDHA-related tumors in at least 3% of patients affected by apparently sporadic PHEO/PGL (Korpershoek et al. 2011). However, a recent study in a PHEO/PGL cohort reported a case of SDHA-mutated tumor showing a positive SDHA/SDHB immunostaining (Papathomas et al. 2015). In the current study, the observed discordance between positive SDHA immunostaining and the presence of a SDHA variant may be explained by the absence of LOH.

Based on our current results, interferon alpha holds promise as a potential therapeutic alternative for patients with aggressive PGL/PHEO. Our case highlights the clinical utility of functional nuclear imaging in patients with aggressive PGL/PHEO. Molecular imaging techniques are highly sensitive and capable of detecting disease at early stages. They can also help to optimize tumor delineation, ultimately improving both patient staging and treatment strategies. Although FDG PET/CT continues to represent the most common molecular imaging modality for the management of malignant PGL/PHEO (particularly SDHB-related PGL), the use of 68Ga-labeled somatostatin analogues PET/CT is gaining momentum (Jansen et al. 2015). In addition, PET/MRI hybrid imaging is increasingly being used for the assessment of therapeutic response in PHEO.
Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this article.

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References