An unusual somatotropin and thyreotropin secreting pituitary adenoma efficiently controlled by Octreotide and Pegvisomant

T. Meas, E. Sobngwi, P. Vexiau, P. Boudou

Departments of Endocrinology and Hormonal Biology, Hospital Saint-Louis, Assistance-Publique Hôpitaux de Paris, 1, avenue Claude Vellefaux 75010 Paris, France.

Correspondence: T. Meas, address see above.
e-mail: taly.meas@lrb.ap-hop-paris.fr

We describe the case of a 36-year-old male patient with a mixed-secreting pituitary macro adenoma. The diagnosis was evoked by the medical staff of his company in May 2002, during the annual medical check-up. At that time, the patient presented features of acromegaly with the dysmorphic syndrome of the extremities. He complained from fatigue, headaches, joint pains, and cyphosis. In addition, his medical record mentioned a history of the carpal tunnel syndrome four years before. A complementary investigation consisting of a MRI and endocrine check-up was performed in June 2002, and showed a macroadenoma of 18 millimeters with an extension in the right cavernous sinus, and circulating levels of GH at 7 ng/ml (normal <10ng/ml), IGF1 at 1430 ng/ml (normal range: 177-381 ng/ml), TSH at 1.54mUI/ml (normal range: 0.50-3.50mUI/ml) and FT4 at 39 pmol/L (normal range: 8-20) as shown in table I.

The patient attended a neurosurgical department in August 2002 to be treated by transphenoidal selective adenomectomy. The presence of a multi-secreting adenoma was histologically confirmed by immunostaining which revealed a majority of cells that expressed GH (60%), Prolactin (PRL) (25%), TSH (15%) and alpha sub-unit.

Three months after surgery the secreting adenoma was still present as shown by a new MRI and high circulating levels of IGF1 (945 ng/ml), GH...
(4.9 ng/ml) and FT4 (29 pmol/l) were measured. At this time, the patient was addressed to our department where he was admitted for the first time in May 2003. Clinical and hormonal investigations were performed. Normal blood pressure and cardiac ultrasonography were recorded, no sleep apnea syndrome was reported and no malignant colic, sigmoidal and rectal polyposis was found. The patient was glucose intolerant. Basal circulating levels of IGF1, GH, and FT4 remained clearly elevated. Free T3 levels were at the upper limit of the normal range. In addition, GH levels were imperfectly suppressed during OGTT, as shown in Table I. In contrast,

**Table I**

Patient medical follow-up and data from his hormonal investigation at baseline and under dynamic tests, before and following several treatments.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological data</td>
<td>Before surgery</td>
<td>After surgery</td>
<td>Without any treatment</td>
<td>Under Octreotide 20 mg every 4 weeks since May</td>
<td>Under Octreotide 30 mg every 3 weeks since October</td>
<td>Under pegvisomant 10 mg per day since April</td>
<td>Under pegvisomant 10 mg per day since April</td>
<td>Under cotreatment with pegvisomant 10 mg per day and Octreotide 20 mg every 4 weeks since November</td>
</tr>
<tr>
<td>IGF1 (ng/ml)</td>
<td>1430</td>
<td>945</td>
<td>610</td>
<td>648</td>
<td>661</td>
<td>405</td>
<td>338</td>
<td>228</td>
</tr>
<tr>
<td>GH under OGTT (ng/ml)</td>
<td>7.0</td>
<td>4.9</td>
<td>14.4</td>
<td>7.0</td>
<td>4.6</td>
<td>4.0</td>
<td>5.7</td>
<td>2.9</td>
</tr>
<tr>
<td>TRH</td>
<td>0.0</td>
<td>1.54</td>
<td>0.87/2.7</td>
<td>2.1/4.2</td>
<td>1.4</td>
<td>1.1/2.6</td>
<td>1.73/6.6</td>
<td>1.30/4.9</td>
</tr>
<tr>
<td>TSH/PRL (mU/ml)/PRL (ng/ml) under TRH</td>
<td>15</td>
<td>1.67</td>
<td>1.02/4.1</td>
<td>6.8/10.5</td>
<td>1.7/8.3</td>
<td>7.5/9.9</td>
<td>6.8/5.3</td>
<td>6.8/5.3</td>
</tr>
<tr>
<td>FT3 (pmol/L)</td>
<td>7.6</td>
<td>5.8</td>
<td>3.1</td>
<td>5.8</td>
<td>5.4</td>
<td>5.4</td>
<td>5.4</td>
<td>2.7</td>
</tr>
<tr>
<td>FT4 (pmol/L)</td>
<td>39.0</td>
<td>29.0</td>
<td>35.0</td>
<td>15.5</td>
<td>21.0</td>
<td>34.5</td>
<td>36.0</td>
<td>18.9</td>
</tr>
<tr>
<td>LH/FSH (IU/L) under GnRH</td>
<td>0</td>
<td>4.3/11.9</td>
<td>1.9/5.9</td>
<td>9/7.4</td>
<td>2.2/7.2</td>
<td>2.3/5.7</td>
<td>3.5/4.1</td>
<td></td>
</tr>
<tr>
<td>ACTH (pmol/L)</td>
<td>14.9</td>
<td>18.0</td>
<td>26.7</td>
<td>55.5</td>
<td>53.6</td>
<td>53.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol 8 h (nmol/L)</td>
<td>386</td>
<td>223</td>
<td>386</td>
<td>166</td>
<td>254</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
gonadal and adrenal axes were not altered (table I). Based on these data, he was treated by 20 mg of a long-acting releasing somatostatin analog (Octreotide) every four weeks. In October 2003, during a new clinical visit, no modifications were observed in circulating IGF1 levels or RMI (fig. 1a), and GH levels remained unsuppressed after an OGTT. In contrast, FT4 levels normalized. Thus, the posology was increased to 30 mg Octreotide every three weeks. In April 2004, circulating IGF1 levels were still highly elevated and very similar to those measured one year before. Thus, Octreotide was discontinued and replaced by a GH receptor antagonist (Pegvisomant) at the dose of 10 mg SC per day. After seven months of treatment by Pegvisomant, IGF1 and testosterone levels improved. In contrast, FT3 and FT4 levels worsened, and MRI remained unchanged (fig. 1b). Thus, a co-treatment by Octreotide 20mg every 4 weeks and Pegvisomant 10 mg per day was initiated in November 2004, in order to control both thyreotropin and somatotropin secretions.

Four months after bi-therapy was initiated, the patient complained about gastro-intestinal disturbances (flatulence, abdominal pain) and against repeated number of injections, although, no side effects were observed at the injection site. We detected asymptomatic gallstones and sludge. In addition, circulating IGF1 levels were normalized, free T4 and T3 levels returned to normal values as shown in table I. The liver enzymes were normal, and no change was noted in the size of the tumor by MRI.

DISCUSSION

We report the first case of a multi-secreting pituitary macroadenoma normalization of which was obtained after combined treatment by Octreotide and Pegvisomant. The tumor was GH, TSH, PRL and alpha-subunit secreting. Only, GH and TSH secretions had a clinical expression.

TSH secreting adenoma is a rare disorder, representing less than 1% of all pituitary tumors [1]. In contrast, pituitary adenomas that express and secrete more than one hormone are not uncommon. Approximately 25% of GH-secreting adenomas also produce PRL, and other associations, among which TSH, GH, PRL, alpha subunit and ACTH have been reported but are less frequent. The initially treatment of TSH-secreting tumors should be surgery. Radiotherapy can be used as an adjuvant therapy, but the percent of remission is low (60%) either after radiotherapy or stereotactic radiosurgery. Native somatostatin acts as a neurotransmitter, neuromedulator and inhibitor of GH and TSH release in pituitary. As the native form, somatostatin analogs such as Octreotide or Lanreotide elicit their biological effects by activating somatostatin receptors. To date, five subtypes are described among which subtypes 2 and 5 are mainly concerned with respect to analogs affinity. In addition, the detection of these subtypes by “in vitro” and “in vivo” techniques in TSH-secreting pituitary adenomas has allowed treatment of these patients with somatostatin analogs [2]. Indeed, Octreotide or Lanreotide controlled

Figure 1: Pictures of MRI. a) MRI after surgical intervention and six months of treatment with an Octreotide 20 mg every 4 weeks. b) MRI after seven months of Pegvisomant 10 mg per day.

Figure 1 : Reproduction de l’IRM. a) IRM après la chirurgie et 6 mois de traitement par Octreotide 20 mg toutes les 4 semaines. b) IRM après 7 mois de Pegvisomant 10 mg par jour.
biochemical disease activity in 80% of the patients, and tumor shrinkage occurred in 52% of these patients [1, 3]. Otherwise, these subtypes of receptors are found in GH—secreting pituitary adenomas, and somatostatin analogs controlled IGF1 and GH secretion in about 55-70% of patients with acromegaly [4]. In addition, tumor shrinkage and tumor size reduction were reported in 30% of these patients [4]. Thus, in patients with both secretions, treatment by a somatostatin analog seems to be relevant.

In the present case, Octreotide succeeded to control TSH- but not GH-secreting adenoma, and had no effect on the tumor size as measured by MRI. Octreotide induced only mild gastrointestinal and biliary side effects. The main goal of the treatment of acromegaly is to achieve GH levels under 1 μg/l after OGTT, and to normalize age and gender adjusted IGF1 levels [5].

Pegvisomant, a novel genetically GH-receptor antagonist who inhibits GH action rather than secretion, is available in France since April 2004. Pegvisomant is administrated by daily subcutaneous injection, and is well tolerated, although, liver enzymes should be monitored, and tumor size should be closely followed to detect possible growth of adenoma [6]. Thus, we decided to evaluate this drug in our patient who failed to be cured after surgery, and maintained abnormally high circulating levels of IGF1 and GH after treatment by somatostatin analogs. Pegvisomant does not attempt to lower circulating GH levels which may increase during treatment [6]. In contrast, Pegvisomant normalized circulating IGF1 levels in 82 to 97% of the patients [7]. In the present case, circulating IGF1 levels decreased by 49% after 7 months of treatment by 10 mg per day of Pegvisomant, but were not completely normalized. GH levels increased (table I) as expected as well as free T3, free T4 and TSH levels. In addition, no side effects were noticed, and the tumor size remained unchanged. Based on these results, we decided to initiate a co-treatment by Octreotide 20mg every 4 weeks plus Pegvisomant 10mg SC daily. After 4 months of co-treatment, IGF1, free T3 and free T4 levels were normalized, GH levels decreased, other endocrine functions remained in the normal range and no modification in the tumor size was noted by MRI.

The association of both therapies was already reported in the literature but only in cases of acromegaly. One case concerned a 34-yr-old male with acromegaly whose tumor size increased, and extended to the chiasma with bitemporal visual defects [8]. The main goal consisted to control the tumor size and to complete the normalization of circulating IGF1 levels. The authors succeeded in both goals, including improvement in visual field defects. These results were achieved with 40 mg of Pegvisomant and 30 mg of Octreotide. To date, there is limited experience comparing Pegvisomant in association with somatostatin analogs, as 90% of the patients with acromegaly normalized their circulating IGF1 levels using Pegvisomant alone. But because of the cost of Pegvisomant some authors proposed combined therapy in acromegaly when patients are not controlled by Octreotide alone [9]. They concluded that combined therapy with Octreotide monthly and Pegvisomant weekly is as effective as daily pegvisomant monotherapy.

In the present case, the existence of a co-secreting pituitary adenoma allowed us to propose such association which revealed synergistic effects, as shown previously [9]. Overall, this co-secreting pituitary adenoma uncontrolled by Octreotide (20 or 30mg) or Pegvisomant (10 mg) alone, normalized his somatotropic and thyreotropic secretions using low doses of both drugs (Octreotide 20 mg every four weeks and Pegvisomant 10 mg per day). This combined therapy was well tolerated with no change on the tumor size.

REFERENCES