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RESEARCH LETTER

Acromegaly can be cured by first-line pasireotide treatment?

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Pasireotide long-acting release (LAR) is a new generation long-acting somatostatin multi-receptor ligand, with an increased affinity for the five subtypes of the somatostatin receptor compared with first-generation somatostatin analogues (SSAs) [1]. Several studies have proven the efficacy of pasireotide LAR in reaching the biochemical control of acromegaly, both in medically naive and in patients resistant to conventional SSA [2–7]. We report here the case of a patient with acromegaly who was successfully treated with first-line pasireotide LAR.

Case report

The patient's medical history concerning the present case started on April 2009, at the age of 68 years, when the patient underwent urologic specialist evaluation for a recent occurrence of nocturia, pollakiuria, and dysuria. The specific prostate antigen (PSA) value was normal. However, the ultrasound evaluation of the prostatic gland showed an increased volume of the gland with a transversal diameter of 57 mm. The patient was encouraged by the urologists to undergo an endocrine evaluation. In September 2009, the patient was admitted at our Unit of Pituitary Disease. The patient did not suffer from any specific symptoms (weight: 75 kg; body mass index: 25 kg/m^2). His face and habitus were suggestive of acromegaly. The patient underwent a basal pituitary hormonal test that documented an impaired secretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-I), 8.7 ng/ml and 584 ng/ml (age and gender-adjusted range: 80–200 ng/ml), respectively. During suppression test with glucose (75 g), GH nadir during oral glucose tolerance test (OGTT) was 8.14 ng/ml. None pituitary deficits occurred.

Remaining pituitary function was conserved. Contrasted pituitary and brain magnetic resonance (MR) showed the presence of a 7-mm nodular expansive formation in the right half of the pituitary, compatible with a small pituitary adenoma (Fig. 1a, b). Consequently, the diagnosis of acromegaly due to the presence of a pituitary adenoma was conducted.

The patient underwent a clinical evaluation for acromegaly-associated comorbidities, and was documented with multinodular thyroid goiter, liver steatosis, hip osteopenia with cervical spine spondyloarthritis and dorsal spine right-sided convex rachis, slight left ventricular hypertrophy, chronic bronchitis, and obstructive sleep apnea syndrome. Moreover, the patient underwent a gastroscopy and colonoscopy, with the removal of a polypoid lesion of the hepatic flexure, diagnosed as tubular adenoma with low-grade dysplasia. Due to the patient's clinical condition and the potential neurosurgical radicality, neurosurgery treatment of the pituitary lesion was suggested but the patient refused this option. Therefore, the patient was directed to medical therapy with long-acting SSAs. Particularly, at the time, the patient was proposed to participate in a randomized, double-blind arm (pasireotide LAR vs octreotide LAR) Phase III clinical trial (NCT00600886) [2]. The patient was screened, enrolled, and randomized in the pasireotide LAR arm. At the screening visit, the IGF-I value was 612 ng/ml, mean GH was 10.78 ng/ml, and GH nadir were 8.03 ng/ml. The prolactin value was within the normal range. At the 12th month of pasireotide LAR treatment (end of trial core phase), IGF-I resulted as normalized within normal age- and gender-adjusted ranges, mean GH level resulted lower than 2.5 µg/l. Consequently, the patient was

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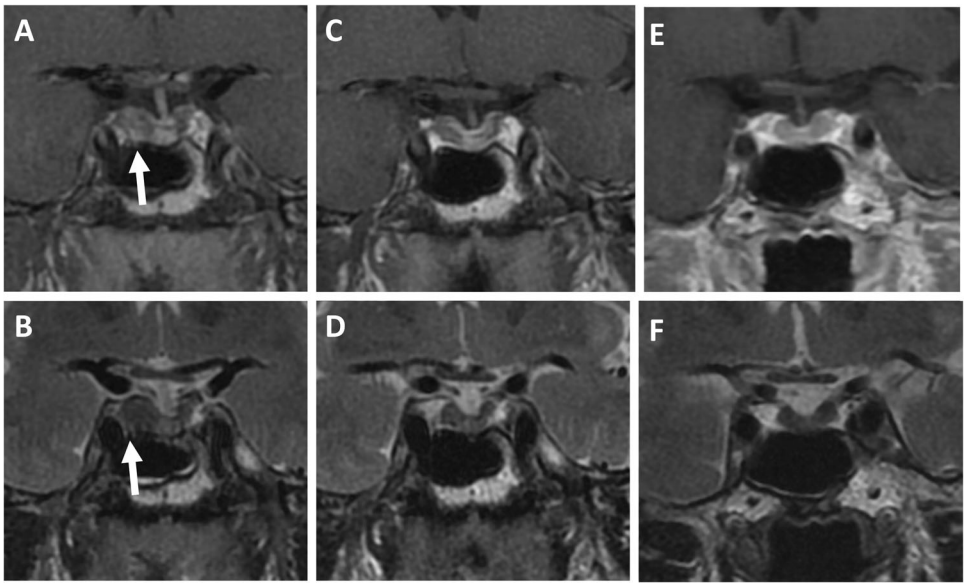

Fig. 1 **a**, **b** FSE T2-weighted and contrast-enhanced T1-weighted images at diagnosis of GH secreting pituitary adenoma. **c**, **d** FSE T2-weighted and contrast-enhanced T1-weighted images at the time of myasthenia gravis diagnosis. **e**, **f** FSE T2-weighted and contrast-enhanced T1-weighted images at last evaluation (8 years after the diagnosis). MRIs obtained at diagnosis show a small lesion in the right portion of pituitary gland, isointense on T2-weighted image and hypointense on T1-weighted contrast-enhanced image (arrows in **a** and **b**). In the last examination obtained 8 years later, the lesion is not yet identifiable

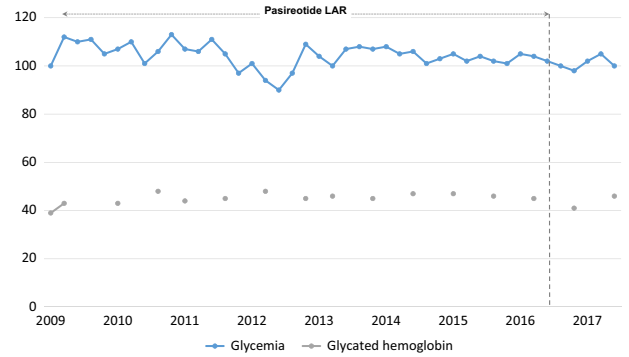

Fig. 2 Dosage of glycemia (mg/dl) and glycated hemoglobin (mmol/mol) during and after pasireotide long-acting release (LAR) treatment

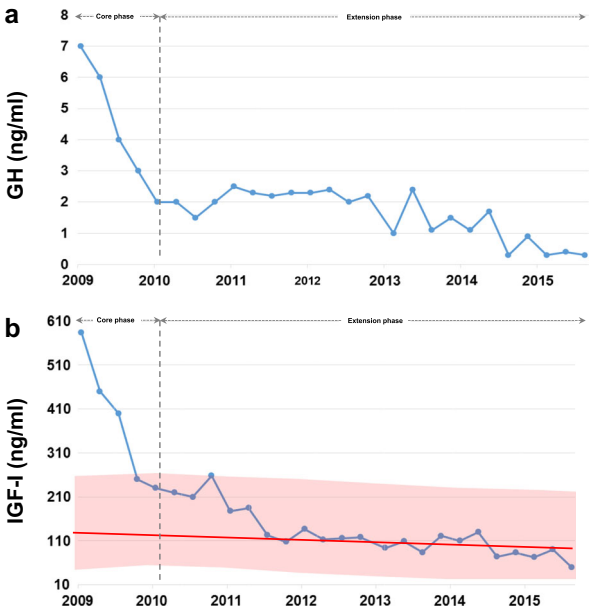

Fig. 3 Dosage of IGF-I and mean GH during the study period. **a**, **b** The blue graphs represent the values of GH and IGF-I of the patient during the treatment, respectively. The red line represents the physiological value of IGF-I adjusted for age. The transparent red area represents the range of physiological value of IGF-I adjusted for age

allowed to participate in the extension phase of the study, undergoing treatment with pasireotide LAR 40 mg monthly. During the study period, the patient developed an impaired glucose tolerance (IGT), which was perfectly managed only through a hypoglucidic diet. In Fig. 2, the trend of glycemia and glycated hemoglobin during pasireotide LAR treatment are represented. During the study extension phase, owing to the quarterly dosage of IGF-I and mean GH, a progressive reduction of both GH and IGF-I was documented (Fig. 3) and, in parallel, a progressive reduction of the volume of the known pituitary adenoma was also observed. However, in May 2016, the patient was referred to the Emergency Department of our hospital for the occurrence of diplopia. The biochemistry blood test resulted normal. A brain computed tomography excluded the presence of intracranial bleeding, acute ischemic focal lesion, and pituitary apoplexy. The patient was admitted to our Department of Endocrinology for further diagnostic investigations. The serious adverse event (SAE) was reported at the Safety Unit of the Clinical Trial. The endocrine assessment revealed IGF-I: 50 ng/ml (range: 22–212). The brain and pituitary MR documented that the known pituitary adenoma was only just visible and confirmed the absence of pituitary apoplexy (Fig. 1c, d). Due to the low IGF-I value and because of the onset of dyspnea, dysphagia, and rhinolalia, treatment with pasireotide LAR was withdrawn. Anti-muscle-specific kinase (MuSK) resulted above the normal range, instead anti-acetylcholine receptor autoantibodies were negative.

Lower and upper extremities electromyography analysis showed a postsynaptic block of the neuromuscular transmission. Consequently, anti-MuSK-positive myasthenia gravis was diagnosed, and the patient was treated with steroid therapy (prednisone 25 mg/day) and apheresis. In September 2016, steroid therapy was switched to azathioprine. During 12 months of follow-up, no medical therapy for the acromegaly was prescribed. IGF-I resulted always within normal age- and gender-adjusted ranges and GH nadir during OGTT 0.3 ng/ml. In November 2017, pituitary and brain MR only demonstrated a slight prominence of the pituitary gland in the absence of focal lesion within the pituitary gland. Consequently, at present, the patient is considered cured for acromegaly, in the absence of residual of the previous pituitary lesion (Fig. 1e, f).

Discussion

Several studies have recently documented the efficacy of pasireotide LAR in the normalization of GH and IGF-I secretion and in the reduction of pituitary mass, both in medically naive patients with active acromegaly after prior pituitary surgery and in de novo diagnosed patients with no history of medical or neurosurgical treatment (treatment-naive patients) [1–7]. Particularly, data derived from the Phase III trial CSOM230C2305 [3] proved a rate of biochemical control of acromegaly of 25.7% of de novo/treatment-naive acromegaly patients, after 12 months of treatment. In that study, the biochemical control of disease was defined as GH ≤ 2.5 µg/l and age- and sex-matched normalization of IGF-I. Moreover, in that study, the normalization of IGF-I was achieved in 30.5% of de novo/treatment-naive acromegaly patients and reduction of pituitary volume (≥20% from baseline) was documented in 80.8% of both medically naive or treatment-naive patients, with a mean reduction of 40% of baseline tumor volume [3].

To our knowledge, our case was the first described treatment-naive patient cured with first-line therapy with pasireotide LAR, with a long-term follow-up (longer than 8 years): in our case, in fact patient achieved the normalization of the IGF-I and GH secretion and the complete regression of the pituitary adenoma, during pasireotide LAR treatment and during wash-out follow-up. Until now, in fact, only in a single patient on treatment with pasireotide LAR as primary therapy [8], an effective normalization of GH and IGF-I secretion and a reduction of tumor volume was described. Moreover, our case emphasizes the safety of pasireotide: despite the long-term treatment with pasireotide LAR, the patient developed a slight IGT, perfectly managed only through a hypocaloric and hypoglucidic diet. Moreover, the occurrence of myasthenia gravis in our patient is considered an event unrelated neither with acromegaly nor with pasireotide LAR treatment, as no other cases have been previously described.

In this patient, the diagnosis of myasthenia gravis was conducted by a neurologist, neuroradiologist, neuro-endocrinologist, and a neurosurgeon. This multidisciplinary management of diplopia allows us to exclude the diagnosis of pituitary apoplexy. In fact, high volumes of anti-MuSK were detected, as well as a postsynaptic blockade of the neuromuscular transmission at the lower and upper extremities at electromyography analysis. Moreover, the neuroradiological follow-up from the initial diagnosis of acromegaly to the pituitary MR conducted at the occurrence of diplopia allows the exclusion of pituitary apoplexy (Fig. 1) due to the absence of MR signs of pituitary apoplexy, such as the enlargement of the pituitary gland, its hypointense sign in T2-weighted images and the presence of dural thickening [9]. At least, pituitary apoplexy is characterized by the so-called "apoplexy triad" [10], which occurs in approximately 85% of patients and consists of visual impairment, headache, and nausea or vomiting. Instead, in our patient the diplopia was an isolated event, which occurs in the absence of headache, nausea, or vomiting. In conclusion, according to the current consensus, acromegaly first-line medical treatments are the conventional SSAs (octreotide LAR and lanreotide autogel) [11], our case suggests a potential role of pasireotide LAR as primary therapy. However, to better define the outcome of pasireotide LAR in medically or treatment-naive patients, studies with large series of cases are required, also for identifying prognostic markers of response to the treatment, as proven for conventional SSA-resistant acromegaly patients [12].

Compliance with ethical standards

Conflict of interest Medical writing and editorial assistance were provided by Luca Giacomelli, PhD, and Aashni Shah, on behalf of Content Ed Net; this assistance was funded by Novartis Farma (Origgio, Italy). MS is Novartis Farma employee. The remaining authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from the individual participant included in the study.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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