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CASE REPORT

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Pasireotide: A new option for treatment of acromegaly

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Abstract

Acromegaly is characterized by excess production of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Although surgery is the first treatment option, somatostatin receptor analogs (SSRAs) can be used in selected cases which surgery is contraindicated. A patient who has been diagnosed as acromegaly was admitted to our hospital. Hypophyseal adenomectomy had been performed one year ago. The patient was taking lanreotide for 6 months and disease was not under control. She had loss of vision. Although she had a residual tumor, second surgery couldn't be performed due to the location of tumor. The patient was followed for 6 years. Radiotherapy and other medical treatment options were tried but none of them were successful. At the end of six years, pasireotide was started. At the third month of treatment, biochemical control was achieved. Pasireotide may be a treatment option for some patients with acromegaly that are inadequately controlled by first generation SSRAs.

Keywords: Acromegaly, pasireotide, somatostatin analog

Introduction

Acromegaly is a rare endocrine disease caused by excess secretion of growth hormone (GH) and, subsequently, hypersecretion of insulin-like growth factor I (IGF-I). In the majority of cases, a benign tumor on the pituitary gland leads to the excess production of growth hormone (GH). Beside this, hypothalamic tumors that release Growth hormone releasing hormone (GHRH) and neuroendocrine tumors that secrete ectopic GHRH and GH are the other rare causes of acromegaly [1].

Acromegaly has an annual incidence of 3-4 cases per million. It is most commonly diagnosed at 40-45 years of age. It is associated with two- to three-fold increased mortality rates. Uncontrolled disease causes serious health complications including cardiovascular disease, cerebrovascular disease, diabetes mellitus, hypertension and malignancy [2]. Mortality rate can be decreased by reaching targeted GH (GH <2.5 µg/L-Radioimmunoassay or <1 µg/dL-immunoluminometric and immunoradiometric assays) and IGF-1 levels (matched for age and gender). The goals of treatment are to stop tumor growing or to decrease tumor size besides biochemical control of disease.Transsphenoidal surgery (TSS) is the primary treatment option in most patients especially in those including a microadenoma or intrasellar macroadenoma. In experienced centers, biochemical remission rates can be achieved by surgery up to 80%. However, most of patients have macroadenomas with suprasellar extension and the postoperative remission rates are much lower in these cases [3].

Although medical therapies are the secondary choice of treatment, they can be preferred priorly in patients for whom surgery is contraindicated. These medical therapies can also be preferred in patients who do reject surgery or in cases that additional treatment is needed when postoperative remission is not achieved [4].

The standard medical treatment options are as follows: The first-generation long-acting SSRAs, dopamine agonists (e.g., cabergoline), the GH receptor antagonist pegvisomant (PEGV). Although there are various medical treatment options, control of the disease could not been achieved properly in approximately 30-60% of the patients [5,6]. The tailor-made approach has been suggested in recent trials for treatment. By using newly determined biomarkers, patients can be identified who could benefit from a particular pharmacological agent. This type of treatment strategies increases the success rates eventually [7,8].

We aim to present a case with acromegaly that biochemical control was achieved by second-generation SSRA(pasireotide) in the third month of treatment which was uncontrolled by all other treatment alternatives including first-generation long-acting SSRAs,

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cabergoline, PEGV and radiotherapy throughout six years period of disease.

Case

A 44-year old female patient was admitted to our hospital with the complaint of decreased visual acuity and growing of hands and feet. She had diabetes mellitus for five years which was regulated by insulin treatment. On her medical history, she was diagnosed as acromegaly 12 months ago and she was operated transcranially for 3-cm sized pituitary macroadenoma. She was taking medications for panhypopituitarism postoperatively. According to her medical records; preoperative GH and IGF-1 levels were 40 ng/ml and 3985ng/ml respectively. But we couldn't have her postoperative pathological report. On admission, she has been treated with lanreotide 90 mg for 6 months and her serum GH and IGF-1 levels were 6.66 ng/ml and 1291 ng/ml respectively. Magnetic resonance imaging (MRI) of pituitary has revealed a residual mass with two parts. One of it was 12x8x6 mm in size with suprasellar extension, neighboring to optic chiasma and extracting it caudally and posteriorly. The other part of residual tumor was in 15x10 mm in size, located in right cavernous sinuses and surrounds the internal carotid artery. Her visual field analysis was compatible with bitemporal hemianopsia.

We increased the lanreotide dose to 120 mg. At 20th months of follow up period postoperatively, neither biochemical control nor decreasing in tumor size were achieved. We decided to perform conventional radiotherapy with 180 Gray. After radiotherapy, the disease was not controlled and lanreotide was switched to octreotide. The starting dose of octreotide was 30 mg and increased to 40 mg in follow up period. At that time, cabergoline was added and the dose was increased to 3 mg /week. Approximately 2 years after radiotherapy, a small decrement in suprasellar part of the lesion was detected but IGF-1 level was not normalized.

Despite these treatments, disease was active biochemically. Possible debulking surgery had high risk for carotid artery injury due to the invasion of tumor. For this reason the second surgery was not performed. At the fourth year of disease, pegvisomant was started 2 times/week initially and increased 3 times/week at 6th weeks. After one year of pegvisomant treatment, the target level of GH and IGF-1 couldn't be reached. At the fifth year on follow up, by the approval of Ministry of Health, pasireotide 0.6 mcg /day was initiated to the patient. Before starting pasireotide, the IGF-1 level was 383 mg/ml. After 3 months of pasireotide treatment, the IGF-1 level was normalized. The IGF-1 levels of the patient during treatment are shown in figure 1. The patient has been using pasireotide for 1 year. Neither improvement on visual acuity nor decreament in size of tumor were detected but disease was under control biochemically from the third month of pasireotide treatment. The magnetic resonance imagings taken at the initiation of the treatment and at the sixth year revealed no significant difference as shown in figure 2.

The patient was scanned for comorbidities of acromegaly. She was treated for Diabetes Mellitus one year before diagnosis of acromegaly. On follow up period, GLP-1 agonists were added to insulin treatment. After the disease was under controlled, insulin therapy stopped and she continued to use GLP-1 agonist for regulation of blood glucose level. As the risk of increased malignancy in acromegaly patients, thyroid ultrasonography was performed. A thyroid nodule 3 cm in size was detected and the result of fine needle aspiration biopsy was suspicious for malignancy. Total thyroidectomy was performed and histopathological examination revealed multifocal papillary carcinoma. The patient had 100 mCİ radioiodine treatment and follow-up continued in the Deparment of Nuclear Medicine.

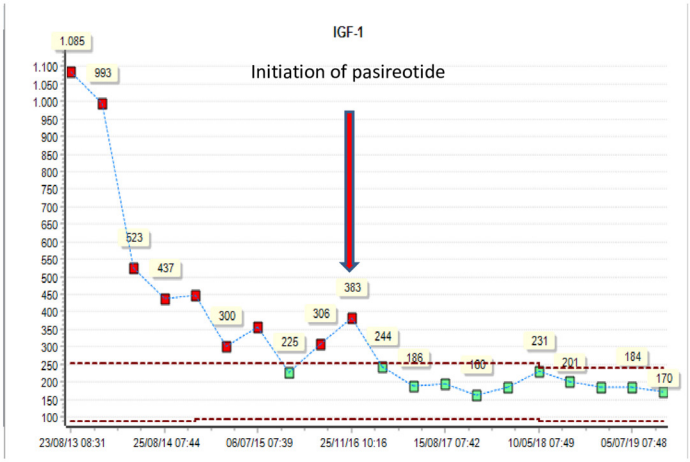

Figure 1. Variation of serum IGF-1 levels during the course of disease (Reference Range for IGF-1:94-252 ng/mL)

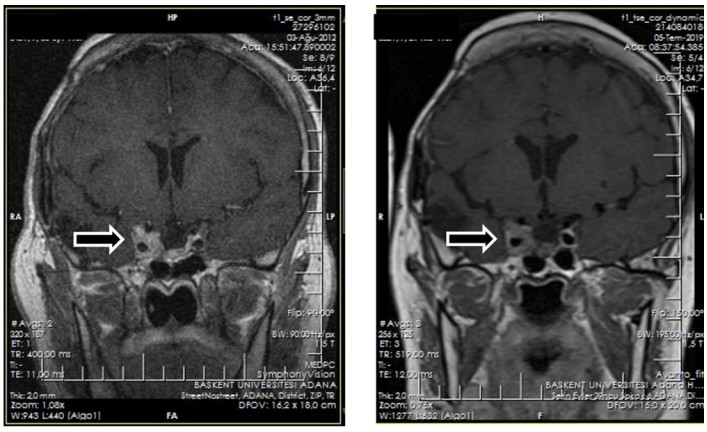

Figure 2. Pituitary MRI:T1 weighted post-contrast images taken A) in 2012 and B) in 2019

Discussion

Acromegaly is a serious disease and surgery is considered as first-line treatment. When surgery is contraindicated or in cases with inadequate surgery, the first generation somatostatin receptor analogs (lanreotide, octreotide) can be used in treatment. If these treatments fail, dopamine agonists or GH receptor antagonists (pegvisomant) can be added to treatment. Unfortunately, 30-60% of cases do not obtain biochemical or tumoral control despite these therapies [9]. In recent years, the use of second-generation somatostatin multi-receptor ligand pasireotide is becoming a current issue in resistant cases of acromegaly.

Somatostatin receptor analogs are used as first drug in the medical treatment of acromegaly.

Although earlier studies show that the first generation SSRAs (lanreotide and octreotide) seem to be effective in treatment, the results of recent studies are not satisfactory. Biochemical control could be sustained in only 40% of cases.

Octreotide and lanreotide show the efficacy by binding to somatostatin receptor subtype (SSTR) SSTR2, SSTR5, SSTR3, SSTR1. But they have the highest binding affinity to SSTR2. Pasireotide has also binding capacity to SSTR1, SSTR2, SSTR3. Unlike first generation SSRAs, the second-generation somatostatin multi-receptor ligand pasireotide has the highest binding affinity to somatostatin receptor subtype 5 (SSTR5). The disease control had been achieved 20% more in cases which first generation SSRAs fail [10].

Neither biochemical control nor decrease in tumor size have been achieved although surgery, radiotherapy and various other medical treatments in our case. The biochemical and/or tumoral resistance in acromegaly treatment have been reported in the literature. Biochemical resistance is identified as uncontrolled IGF-1 and GH levels [11]. Tumoral resistance is identified as increasing in size of tumor or < 20% decrease in tumor size with treatment. The resistance to somatostatin receptor analogs is defined as unresponsiveness to drug with maximum dose during 12 months period of treatment [11].

A number of factors might predict a response to somatostatin receptor analogs. Somatostatin receptor subtype expression of adenoma is attributed as one of the reason of resistance to medical treatment in acromegaly. Somatostatin analogs seem to be more effective in some cases. Female gender, older age, lower GH and IGF-1 levels at the time of diagnosis, densely granulated adenoma histopathologically and hypointensity in T2 weighted images of MRI are predictors for somatostatin receptor analog responsiveness. Unlike these, male gender, histopathologically sparsely granulated adenoma or GH/prolactin secreting adenoma are all factors related with a poor response to first generation SSRAs.

The absence or scarcity of SSTR2 is related to the resistance to octreotide and lanreotide. Whereas octreotide and lanreotide has the highest binding afinity to SSTR2, pasireotide has the highest binding capacity to SSTR5 [12]. In the ACRONIS study, after 6-months of treatment with pasireotide [13], biochemical control was obtained in patients resistant to first-generation SSRAs. In accordance with this result, the PAOLA study has shown significant decrease in GH and IGF-1 with six-month treatment with pasireotide 40 mg monthly, in patients resistant to first-generation SSRAs [12]. There are some reports that show the efficacy and safety of combination therapies with pasireotide and pegvisomant. In PAPE study, patients using first-generation SSRA and pegvisomant combination, have > 50% reduction in the dose of pegvisomant necessary to achieve similar control when switching to pasireotide instead of first-generation SSRA [14].

According to studies, beside the number of receptors, there are some proteins which are related to the function of receptors. The lower expression of Beta- arrestin seems to increase the response to medical treatment. This protein binds to G-protein receptor, inhibits signalization of SSTR2s and increases the effects of these medical therapies. FLNA (Protein filamin A) is another protein that provides transduction and matching of SSTR2. Although it is not shown in human studies yet, the lower expression of this protein resulted to the resistance to medical drugs in acromegaly. Except the number of expression SSTR2, the lower expression of SSTR5 is considered to be important in resistance [15].

As a result, the second-generation somatostatin multi-receptor ligand pasireotide having the highest affinity to SSTR5, seems to be effective in cases of acromegaly which biochemical control and/or decrease in tumor size could not been achieved by other drugs. Immunohistochemically-obtained receptor profiling or adhesion molecules may be helpful in deciding choice of treatment. But we need further trials to manage appropriate treatment.

Conflict of interest

The authors declare that they have no competing interest.

Financial Disclosure

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