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Somatotropinoma Infarction During Octreotide Therapy Leading to Bilateral Cavernous Sinus Syndrome

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Abstract. **The cyclic somatostatin analog, octreotide, forms the mainstay of medical treatment for acromegaly. In addition to lowering circulating growth hormone levels and shrinking tumor size, octreotide may provide symptomatic relief of headaches associated with growth hormone secreting tumors. The majority of reported complications of octreotide therapy are gastrointestinal and metabolic. The present case illustrates the development of acute bilateral cavernous sinus syndrome with loss of eye movement bilaterally during octreotide therapy. Serial MRI examination suggest tumor infarction as the etiology. The symptoms resolved over 2 months as the tumor shrunk in size and growth hormone was dramatically reduced.**

Keywords. **acromegaly, cavernous sinus syndrome, (CSS) pituitary adenoma, octreotide**

Introduction

While transsphenoidal surgical removal of growth hormone secreting pituitary adenomas remains the treatment of choice, medical care of acromegaly both pre and post-operatively is focused on octreotide treatment [1]. Octreotide, a long-acting somatostatin analog, lowers elevated growth hormone (GH) and insulin-like growth factor-I (IGF-I) levels in patients with acromegaly [2], and reduces the size of GH secreting tumors [2,3]. Because of this, octreotide has been proposed as a primary pharmacological treatment for patients with GH secreting tumors, including tumors with extensive involvement of the cavernous sinus [3]. The mechanism for octreotide's reduction in tumor size is hypothesized to be a reversible reduction in the size of individual tumor cells rather than cell death [4].

Symptoms of acromegaly including soft tissue enlargement, increased perspiration, fatigue, joint pain, cardiomyopathy, and sleep apnea may respond to octreotide therapy. The mechanism whereby octreotide effects most of these changes is linked to reduced GH and IGF-I levels. However, the mechanism of octreotide induced headache relief remains controversial, because analgesia occurs rapidly and occasionally without any reduction in hormone levels [5,6]. It is possible that octreotide acts therapeutically through mechanisms other than GH and IGF-I reduction. Some authors have proposed an opiate receptor mediated mechanism [7] while others have proposed vasoactive mechanisms of analgesia [8]. However, several authors have dismissed an opiate mediated mechanism both because octreotide acts pharmacologically as an opioid antagonist and because naloxone fails to influence octreotide induced headache reduction [9,10].

Octreotide therapy has been reported to cause gastrointestinal side effects such as flatulence, nausea, abdominal cramping, diarrhea, malabsorption, and gallstone formation [11,12]. The following case report is, to our knowledge, the first association of octreotide with somatotropinoma infarction resulting in bilateral cavernous sinus syndrome (CSS).

Case Report

A 12-year-old girl presented in July 1999 with gradually progressive headaches over a 3 month period. Her headaches were intermittently accompanied by emesis and subjective visual changes described as "eye shadowing." In addition, the patient had experienced a dramatic growth spurt with an accompanying enlargement of shoe size. A brain MRI scan revealed a pituitary macroadenoma extending bilaterally into the cavernous sinuses and the suprasellar cistern. Formal visual field testing revealed no deficit. Endocrine studies revealed GH of 33.5 ng/ml (normal < 5 ng/ml), plasma IGF-I of 924 ng/ml (normal = 116–270 ng/ml), and a prolactin (PRL) of 8142 ng/ml (normal = 1–17 ng/ml).

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On a regimen of 1 mg of cabergoline twice per week, the patient had experienced a decrease in headache intensity with persistent episodes of emesis and a reduction in PRL to 4156 ng/ml at 4 weeks and to 2892 ng/ml at 6 weeks. Repeat MRI (Figure 1A) revealed no reduction in tumor size, and the GH level remained elevated at 54 ng/ml (Table 1). Persistence of headaches prompted addition of narcotic analgesia.

A transnasal transsphenoidal resection of the adenoma was attempted on December 8, 1999. The fibrous consistency of the tumor prevented substantial resection and only a limited subtotal resection was obtained. The patient tolerated the procedure well. Post-operative physical examination revealed intact cranial nerve function with grossly intact visual fields. There was no evidence of cerebrospinal fluid nasal drainage. The patient continued to complain of severe headache and nausea, and was treated with narcotic analgesics, antiemetics, and hydrocortisone. There was no evidence of postoperative diabetes insipidus or SIADH. Postoperative MRI revealed no change in the size of the macroadenoma (Fig. 1B).

On the evening of December 13, the patient was begun on a regimen of 200 μg subcutaneous octreotide every 8 hours. Headaches vanished within 3–5 minutes but recurred within 4 hours. As a result, octreotide was continued at 200 μg every 4–6 hours. Nonetheless, headaches continued to recur between the injections. GH levels on the following morning were noted to be substantially elevated to 258 ng/ml immediately preceding the 9 AM dose of octreotide and increasing to 388 ng/ml four hours later (Table 1).

At 6 PM on December 14th, the patient's urine output increased to one liter over an hour and she was noted to develop acute bilateral CSS. Physical examination revealed near complete bilateral sixth and third nerve palsies with severe bilateral ptosis as well as fixed and constricted pupils. The patient remained at her baseline mental status with intact facial sensation. Systolic blood pressure preceding the onset of CSS remained in the range of 120 to 130 mmHg, with no hypotensive or hypertensive episodes. Prior to or during the onset of these symptoms, the patient was not exposed to agents known to affect platelet function or coagulation (aspirin or estrogen therapy) with the exception of ibuprofen 800 mg every 6 hours. PT (9.7 sec), INR (1.0), and PTT (24.6 sec) levels were all within the normal range. An emergent MRI revealed an increase in the tumor size from 4.3 to 4.8 cm in transverse dimension (Fig. 1C), and the tumor was noted to herniate through the diaphragma sellae extending up the right sylvian fissure with a slight elevation of the right lateral ventricle. Moreover, there was a dramatic loss of homogenous contrast enhancement throughout the bulk of the lesion. No evidence of acute hemorrhage was noted. The patient was given 100 mg hydrocortisone to reduce suspected tumor edema and 10 U of subcutaneous dDAVP to control diabetes insipidus. The cranial nerve palsies remained unimproved. Cabergoline was continued at 1 mg twice a week, but octreotide was temporarily stopped.

Two days following the onset of CSS, on December 16th, the patient experienced partial resolution of her left VIth nerve palsy, but a noticeable decrease in facial sensation in the V2 distribution bilaterally. Her plasma GH had fallen to 11.3 ng/ml and her prolactin was 111 ng/ml. To control severe recurrent headaches, she was restarted on 200 μg subcutaneous octreotide every four hours, and continued on this regimen throughout the remainder of her hospital stay. By the time of her discharge on December 20th, GH and PRL levels had fallen to 2.9 ng/ml and 51.4 ng/ml respectively (Table 1). An MRI obtained prior to discharge (Figure 1D) revealed interval changes in the tumor consistent with necrosis and inflammation around the carotid arteries.

Following discharge, the patient was placed on a

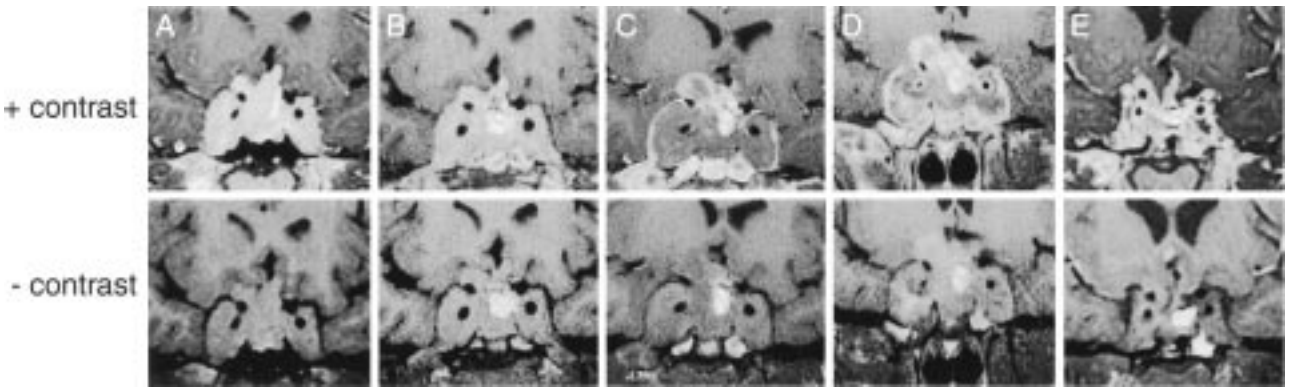

Fig. 1. *Serial coronal MRI scans of the sella tursica and cavernous sinuses with and without gadolinium contrast. A. Preoperative MRI from September 30. B. Postoperative MRI from December 9. C. MRI scan obtained during the acute onset of CSS and DI following octreotide therapy on December 15. D. MRI scan from December 19. E. MRI scan from January 13 following long-acting octreotide therapy.*

Table 1. *Summary of laboratory test results*

Date	Growth hormone ng/ml	Prolactin ng/ml	IGF-I ng/ml	MRI
7/19/99	33.5	8142	924	yes
7/21 treatment initiated				
		49	8000	
8/23		4156		
9/17		2350		
9/30				yes
10/8	54	2958		yes
12/8 transsphenoidal surgery				
12/9				yes
12/11				yes
12/13 octreotide treatment begins				
12/14 9am	258			
12/14 1pm	388			
12/15				yes
12/16	11.3	111		
12/17	2.5	72.3		
12/18	3.1	56.8		
12/19	2.9	51.4		yes
12/21	2.5	35.2		
1/6	2.9	260		yes
1/13				yes
2/11	3.9	564	1173	
3/24	8.9		1208	

long-acting octreotide formulation (Sandostatin LAR) at a dose of 20 mg per month. The cavernous sinus syndrome continued to gradually improve with resolution of diplopia and a return to normal cranial nerve function by February of 2000. Follow-up GH and PRL levels were 2.9 ng/ml and 280 ng/ml respectively (Table 1). An MRI obtained at that time revealed marked involution of the macroadenoma (Fig. 1E).

Discussion

Primary transsphenoidal resection has been reported to achieve GH levels <5 ng/ml in 78% of patients and adequate glucose suppression tests in 58% [13]. However, radiation and octreotide remain the principal means of reducing the function of the residual GH secreting tumor that is not amenable to resection. In addition, octreotide is an important treatment for persistent severe headaches in these patients.

The major portion of a macroadenoma that is not accessible to transsphenoidal resection is that which invades dura, including the cavernous sinus. Tumor extension into the cavernous sinus allows the tumor to encase the IIIrd, IVth, and VIth cranial nerves as well as the 1st and 2nd divisions of the Vth cranial nerve. CSS, a combination of palsies in this group of cranial nerves, has been reported to result from cavernous sinus tumors, but occurs most commonly in association with neurovascular abnormalities of the cavernous sinus, neurosurgical intervention in this region, or the Tolosa-Hunt syndrome. Commonly, the nerves of the cavernous sinus will tolerate gradual encasement by tumors, while abrupt changes in pressure associated with phenomena like carotid-cavernous sinus fistulas will invariably compromise the function of these nerves [14].

In the present case, the acute onset of diabetes insipidus and CSS followed the initiation of octreotide therapy. MRI scans obtained before and after onset of CSS during the postoperative period showed a dramatic change in the adenoma in response to octreotide. These studies demonstrate an interval increase in size of the adenoma involving the sella turcica, cavernous sinuses, and suprasellar region resulting in increased mass effect on the optic chiasm, hypothalamus, and cavernous sinus contents. In addition, the lesion's enhancement abruptly changed from a homogenous pattern to a pattern of peripheral enhancement with no internal tumor enhancement. Subsequent MRI obtained 4 days later continued to show loss of tumor enhancement and evidence of enhancement around the carotid arteries. The MRI scan one month later showed progressive tumor involution with long acting octreotide treatment. These imaging changes are consistent with tumor infarction.

In addition to MR findings, plasma GH levels are consistent with tumor infarction. GH dramatically increased immediately after the initiation of octreotide therapy, likely as a reflection of tumor necrosis. GH and Prolactin levels then declined significantly within three days of octreotide initiation, and plasma GH remained low despite temporary withdrawal of octreotide. The necrosis of the tumor is further suggested by a dramatic decline in serum prolactin despite unchanged cabergoline dosage. Another case report presenting the endocrine findings of a patient with a growth hormone and prolactin producing pituitary adenoma showed that treatment of acromegaly with a single dose of bromocriptine caused pituitary hemorrhagic infarction [15]. Like the patient in the present case, this patient showed significantly lowered GH and PRL levels after bromocriptine administration.

It is generally assumed that octreotide reduces tumor volume by a mechanism that involves shrinkage of tumor cells [7]. This hypothesis that tumor shrinkage is noncytolytic rests largely on morphometric studies and on the evidence that tumor mass recurs when octreotide therapy is discontinued [4]. In the present case, tumor size reduction may have resulted from a combination of ischemic necrosis and noncytolytic tumor cell shrinkage. Hemorrhagic pituitary infarction usually occurs after acute hypotension in pregnancy (Sheehan's syndrome) or in large pituitary tumors as a result of "outgrowth" of blood supply. Several cases of tumor infarction following acute stimulation have been reported [16]. Thus, pituitary infarction may occur when tumor blood demand exceeds blood supply. Oc-

treotide might induce infarction through a direct effect on tumor vessels.

Vasoconstriction may represent a mechanism whereby octreotide might induce tumor ischemia. A double blind controlled trial has shown octreotide to be effective in 100 μg doses against migraine headaches raising the possibility of direct cerebrovascular effects [17]. Octreotide is also known to reduce bleeding in patients with variceal bleeding [18]. Other investigators have documented improvement in various vascular parameters in portal hypertension with octreotide treatment [19]. Yamashita has demonstrated effects of octreotide on phosphatase activity in endothelium [20].

Previous case reports have documented an association of head trauma with pituitary hemorrhage [21,22]. These reports suggest the possibility that subtotal resection of the tumor may have induced trauma sufficient to cause infarction and subsequent necrosis. However, in both of these cases the pituitary apoplexy reported was hemorrhagic. More importantly, the apoplectic event always occurred in close temporal proximity to the trauma. In the current case, tumor infarction happened on post-operative day 6. Delayed pituitary infarction following subtotal resection has not been reported.

In summary, administration of octreotide is common in acromegalic patients with cavernous sinus involvement due to the surgical inaccessibility of such tumors. The present case illustrates the possibility of CSS complicating such treatment. In addition, the elevation in GH levels and tumor size immediately following initiation of octreotide therapy argues for a mechanism other than GH reduction through noncytolytic tumor cell shrinkage. A vascular effect of octreotide on somatotrophic tumors is one possible mechanism for such an effect.

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