THYROIDITIS DEVELOPING POST INITIATION OF OCTREOTIDE IN A CASE OF TSH SECRETING TUMOR

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Abstract

Thyroiditis developing post pituitary surgery in a case of TSH secreting tumor has been reported, albeit rarely. A 46 year old female was treated as a case of hypothyroidism for almost five years, however, TSH levels remained unsuppressed in spite of increasing thyroxine doses. A cyclic pattern of TSH with T3 secretion was observed after stopping thyroxine, though T4 levels were normal. T3 suppression test revealed a non suppressed TSH and MRI sella revealed a pituitary mass with Grade 1 cavernous sinus invasion. With a diagnosis of TSH secreting tumor, the patient was initiated on octreotide therapy. TFT normalized within 4 days of initiation of octreotide, tumor size reduced by about 30% within 2 months of therapy and goiter size reduced to almost half with octreotide therapy. Anti TPO levels which were initially negative became positive within a month of octreotide therapy and FNAC thyroid revealed thyroiditis. To the best of our knowledge, this is the second case report of development of thyroiditis after octreotide therapy. The immunomodulatory role of TSH and somatostatin may have a role in the development of thyroiditis in this case.

Key words: TSH Secreting Tumor, Somatostatin, Thyroiditis.

INTRODUCTION

TSH secreting tumours are an infrequent cause of thyrotoxicosis and account for less than 1% of all pituitary adenomas (1, 2). Autoimmune thyroid disease in association with TSH secreting tumor has been described, though rarely (3-6). The prevalence of circulating antithyroid autoantibodies is similar to that found in the general population. However, there are anecdotal case reports of patients developing Graves' disease after pituitary surgery (7, 8). The immunomodulatory role of TSH with the decline in TSH levels post surgery has been implicated for autoimmune thyroid disease. We describe here a 46

year old female where inappropriate TSH secretion was recognised due to pituitary tumor. She developed autoimmune thyroiditis post initiation of octreotide therapy. The possible role of somatostatin and TSH in immunomodulation and thyroiditis is briefly discussed.

CASE DESCRIPTION

A 46 year old female treated as a case of hypothyroidism since 2014 presented one year later with high TSH and goitre. She had no symptoms related to thyrotoxicosis and was clinically euthyroid at this initial visit. She lived in a two storey house and did all household chores on her own. Her FT4 was normal and TSH 13.8 mU/L while on 125 mcg of thyroxine. A marginally high FT3 was missed at this time point. She had a nodular goitre, anti TPO was negative and FNAC thyroid revealed a colloid goitre. With a provisional diagnosis of hypothyroidism, in subsequent visits to different doctors, she was followed up with TSH only. However, her TSH continued to remain high (ranging from 8-13 mIU/L) and her thyroxine dose was gradually increased to 225 mcg per day. She started complaining of occasional palpitations for which she was started on atenolol. Because of high requirements of thyroxine doses and a non suppressed TSH, she was investigated for malabsorption and her celiac serology was found to be negative. She was then considered as a case of ITSH (inappropriate TSH) and thyroxine was stopped. Thyroid function tests (TFT) done on multiple occasions over 3 months after stopping thyroxine revealed a normal FT4 but a variably high FT3 (Table 1). TFT levels in our laboratory were done by chemiluminescence (Vitros, EciQ, Beckmann Coulter DXI-600). Total T3 levels were also high ranging from normal to 50% above the upper limit of normal T3 levels. TSH levels also variably ranged from 10-20 mIU/L (Fig. 1). Anti TPO levels were negative. Our patient was regularly

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menstruating and had 4 children, the youngest was 14 years old, all lactated till 3 years of age. There were no complaints of headache or visual symptoms. She had been diagnosed as a case of hemofacial spasm in 2002 for which she was not taking any treatment.

Her other investigations including hemogram, LFT and KFT were normal except for osteopenia documented in DEXA scan. MRI contrast enhanced sella revealed a pituitary tumor (15x10x19 mm) with Grade I cavernous sinus invasion. T3 suppression test with 100 mcg of T3 given for 8 days resulted in a non suppressed TSH (decrease from 14.3 to 6.3 mIU/L, 58% reduction) in spite of T3 levels rising to 9.6 pg/mL.

Table 1. TFT values while off thyroxine

TSH (0.5-5.0)	Free T4 (0.7-2.0) (ng/mL)	Free T3 (2.0-4.4) (pg/mL)
19.41	-	-
13.8	1.1	5.6
10.4	1.60	2.68
16.79	0.97	5.12
14.3	1.63	6.76

Figure 1. Trend of TSH (μ IU/mL) and T3 (pg/mL) levels before and after initiation of Octreotide therapy.

Pituitary Macroadenoma (15x10x19mm) before Octreotide

With a provisional diagnosis of TSH secreting tumor, the patient was initiated on injection octreotide 50 mcg thrice daily; 4 days after the initiation of octreotide, TSH levels and T3 levels normalised (TSH decreased from 6.3 to 1.8 mIU/L and T3 decreased from 9.6 to 4.3 pg/dL). Injection octreotide 20 mg LAR was given on the eighth day of initiation of short acting octreotide followed by another octreotide LAR preparation 28 days later. Two months after initiation of octreotide, patient continued to be euthyroid with normal T3 and T4 levels (Table 2). There was also a 50% decrease in the size of the nodular goitre documented with ultrasound thyroid. The MRI of the sella revealed a marked decrease in pituitary tumor size from 15x10x19 mm to 9x9x7 mm after 2 months of octreotide therapy (Fig. 2).

A patient underwent FNAC of the thyroid 18 days after initiation of octreotide, which revealed lymphocytes infiltrating sheets of thyroid follicular cells suggestive of thyroiditis (Fig. 3). Anti TPO levels which were initially negative on two occasions, were now positive [anti TPO 109.5 U/mL (normal <60 U/mL)] almost a month after initiation of octreotide therapy.

DISCUSSION

TSHomas are rare pituitary tumors characterized by goiter, excess of circulating of T3 and T4 along with inappropriately elevated TSH levels (1, 2). The present case was treated as a case of hypothyroidism for almost 4 years before being diagnosed as a TSH secreting tumor. Our patient was asymptomatic (except for goiter), had normal T4 levels and subtle elevations in T3 levels making diagnosis

Pituitary Macroadenoma with reduction of size (9x9x7mm) 2 months after Octreotide

Figure 2. Response of pituitary tumor to octreotide therapy.

Groups of thyroid follicular epithelial cells showing marked Hurthle cell change (arrow) lying in a background of abundant colloid admixed with blood (400x)

Prominent lymphocytic infiltration into the thyroid follicular epithelial cell clusters (200x)

Figure 3. FNAC thyroid showing lymphocytes infiltrating sheets of thyroid follicular cells suggestive of colloid goiter with chronic lymphocytic thyroiditis (Bethesda-II) (18 days post octreotide).

Table 2. TFT during T3 suspension test and post octreotide therapy

Test	TSH (mIU/L) (0.5-5.0)	FT4 (ng/mL) (0.6-1.2)	FT3 (pg/mL) (2.0-4.4)
On admission	14.3	1.63	6.76
After T3 Suspension Test	6.3	1.45	9.61
4 days after Inj. Octreotide	1.8	1.48	4.32
1 Month after Inj. Octreotide	2.61	1.47	2.83
1.5 Months after Inj. Octreotide	2.9	0.67	3.51

difficult. A recent review by Beck Peccoz *et al.* observed that around 20% patients with TSH secreting tumors may not have thyrotoxic symptoms (1).

The normal T4 levels in our patient eluded the diagnosis for a long period of time. The reason for normal circulating T4 in our patient and subtle T3 elevations could be a relatively bio-inactive TSH secreted by the pituitary tumor. There have also been anecdotal case reports of normal T4 levels in patients with TSH secreting tumors who had coexisting thyroiditis (3-6). Our patient developed thyroiditis after therapy, so this cannot be the cause of normal T4 levels in our patient. Our patient hailed from an iodine deficient area of Western Bihar and had used uniiodinised rock salt till 30 years of age. It is also possible that deficient iodine stores may have contributed to normal T4 levels in our patient since iodine is required for conversion of T4 to T3.

TSH levels in our patient varied widely from 10 to 20 mIU/L. Okuma *et al.* similarly reported the first case of a cyclic production of TSH from a TSH secreting pituitary tumor (9). The authors observed an increase in T3 and T4 levels with cyclic rise in TSH and normalization of thyroid hormones with

fall of TSH. However, in our patient there was no clear rise or fall of T4 with changes in TSH thereby indicating that TSH secreted by the tumor was largely bioinactive. It is surprising to note that our patient did not develop thyrotoxic symptoms until the dose of thyroxine was increased to 200 mcg per day. Langlois *et al.* similarly observed no evidence of thyrotoxic symptoms in a patient of TSH secreting tumor treated as hypothyroidism until the thyroxine doses were increased to 150 mcg per day (6). They were unable to provide an explanation for the same. Brucker Davis *et al.* in a series of 25 patients with TSH secreting tumors observed that 3 of 25 had no thyrotoxic symptoms in spite of high T3 and T4 (10). They performed estimation of various T3 responsive parameters during the T3 suppression tests and concluded that there was no evidence of acquired thyroid resistance in these patients. They hypothesized that the apparent tolerance to elevated thyroid hormone in some patients may be linked to the gradual development of hyperthyroidism, leading to compensatory mechanisms, such as desensitization or down regulation of thyroid hormone receptors.

The diagnosis of TSH secreting pituitary

tumor in our patient was considered on the basis of an inappropriately elevated TSH, T3 suppression test, pituitary tumor on MR imaging and prompt clinical response to octreotide. Normalization of T3 levels with octreotide therapy, reduction in tumor and goiter size established the diagnosis of TSH secreting tumor in our patient. Octreotide therapy for TSH secreting tumors is known to be effective in normalizing TFT and reducing tumor size in most patients (1, 11,12,13). A cavernous sinus invasion by the tumor precluded complete surgery, therefore, the patient was given octreotide as primary therapy. While TSH levels show a prompt response within few hours of octreotide injection, however, normalization of T3 (from 9-4 pg/mL) within 4 days of initiation of octreotide in our patient is surprising. Fukuhara *et al.* noticed that the median time to normalization of TFT was 20 days in patients who were given preoperative octreotide therapy for control of TFT prior to surgery (14). However, in their series, the time to normalization of TFT ranged from 5-30 days indicating possibly differing octreotide responsiveness and metabolism of T3 and T4 in patients with TSH secreting tumors. The tumor reduced in size by about 30% within 2 months of octreotide therapy in our patient. Atkinson *et al.* reported a case of TSH secreting tumor who also showed an almost 50% reduction in tumor size post octreotide initiation (15).

Our patient developed thyroiditis after initiation of octreotide. Both FNAC thyroid and anti TPO levels had been normal prior to therapy. There have been few cases of thyroiditis reported in patients with TSHoma earlier (3-6). However, in all these cases thyroiditis was diagnosed at presentation alongwith TSH secreting tumors and not during the course of either medical or surgical therapy. It is unlikely that thyroiditis contributed to reduction in T3 levels post therapy in the present case since TSH levels also declined.

Our patient developed thyroiditis after initiation of octreotide therapy. Somatostatin is involved in immunomodulation, such as the regulation of proliferative responses to antigens or mitogens in different types of immune cells, or the balance between Th1 and Th2 patterns of cytokine secretion by CD4 T-lymphocytes (7). Koriyama described a patient who showed increase in the levels of anti TPO, anti thyroglobulin and TSH receptor antibodies when octreotide was administered in a patient with TSH secreting tumor (7). An increase in titres of these antibodies was observed within one month of octreotide administration. We also similarly observed high titres

of anti TPO antibodies and histological evidence of thyroiditis within a month of octreotide administration. Thyroiditis in our patient developed post therapy when the TSH levels declined from above 10 mIU/L to 1.8 mIU/L post therapy. Previously, anecdotal cases of development of Graves' disease after surgery of pituitary tumor have been described (when TSH levels declined) (7, 8, 16, 17). The immunomodulatory role of TSH was implicated for the development of Graves' disease post surgery in these cases. TSH is known to have an important role in regulation of immunomodulatory gene expression in the thyrocytes (18). Rapid reductions in TSH levels after tumor resection could induce Fas-mediated apoptosis as a result of cell surface Fas expression and expression of both ICAM 1 and MHC class II molecules on the cell surface of thyroid cells (7). Consequently, autoimmune responses against the thyroid gland may be activated. Kageyama *et al.* described a case where TSH and TRH antibodies were detected 2 weeks post trans-sphenoidal surgery of the pituitary tumor, rose for 3 months and then declined (8). We did not perform TSH receptor antibodies in the present case since T3 levels showed a decline unlike previously reported cases.

In conclusion, this was a rare case of TSH secreting tumor. The prompt response to octreotide and development of thyroiditis after octreotide injection make it a uniquely rare case of TSH secreting tumor.

Conflict of interest

The authors declare that they have no conflict of interest.

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