ABSTRACT

Objective: To describe a case of granulomatous hypophysitis occurring after treatment with interferon alfa-2b and ribavirin for hepatitis C.

Methods: Clinical, radiologic, laboratory, and pathologic assessments of a woman with granulomatous hypophysitis and interferon-induced thyroiditis are presented.

Results: A 42-year-old woman with hepatitis C was treated with interferon alfa-2b and ribavirin for 5 months. She was referred after symptoms of thyrotoxicosis developed, in conjunction with laboratory and radiographic evidence of thyroiditis. During the initial evaluation, she was weak and hypotensive; biochemical evaluation showed undetectable plasma cortisol and corticotropin concentrations. Magnetic resonance imaging revealed diffuse enlargement of the pituitary gland, which encroached on but did not compress the optic chiasm. Treatment with supraphysiologic doses of prednisone resulted in clinical and radiographic improvement. Once physiologic doses of glucocorticoids were instituted, however, follow-up magnetic resonance imaging showed substantial progression of the diffuse pituitary enlargement and mild compression of the optic chiasm. Surgical debulking of the mass and histologic evaluation showed chronic, noncaseating granulomatous hypophysitis. An extensive evaluation for secondary causes of granulomatous inflammation of the pituitary revealed only an elevated angiotensin-converting enzyme level; no organisms were identified. After 2 courses of high-dose glucocorticoids, she had radiographic evidence of decreased size of the pituitary lesion but continued to have multiple anterior pituitary hormone deficiencies.

Conclusion: Granulomatous hypophysitis and sarcoidosis of the pituitary are rare disorders. Hypophysitis should be considered in patients receiving interferon and ribavirin therapy who have symptoms consistent with pituitary dysfunction. (Endocr Pract. 2007;13:169-175)

INTRODUCTION

Interferon is a well-established therapy for chronic hepatitis C. The addition of ribavirin to interferon has considerably improved virologic and histologic responses (1,2). The attachment of a polyethylene glycol moiety extends the half-life of interferon (peginterferon) allowing once-weekly dosing and has been shown to be effective in the treatment of chronic hepatitis C (3). Although these treatments are highly effective for many patients, the side effects can cause substantial morbidity. Autoimmune thyroid disease resulting in hypothyroidism or hyperthyroidism is a well-established complication of interferon treatment. In an appreciable number of hepatitis C-infected patients given interferon alone or in combination with ribavirin, antithyroid peroxidase or antithyroglobulin antibodies will develop (4,5). Although hypothyroidism seems to be more common, several authors have reported the development of thyrotoxicosis after initiation of interferon therapy (6-9). Subacute thyroiditis has also been described in patients treated with interferon either with or without ribavirin (6,7,10).

In addition to thyroid abnormalities, the development or reactivation of sarcoidosis has been associated with interferon therapy in patients with hepatitis C and other diseases (11,12). Both systemic and localized granulomatous reactions after treatment with interferon (with or without ribavirin) have been described and include involvement of the lungs, liver, skin, parotid gland, and uterus (11-22).
Although sarcoidosis affecting many organ systems has been associated with interferon therapy, central nervous system involvement appears to be rare. Miwa et al (23) described a patient treated with interferon for hepatitis C in whom symptoms consistent with neurosarcoidosis developed. This patient also demonstrated pulmonary lesions and an elevated angiotensin-converting enzyme (ACE) concentration. Her condition improved after discontinuation of interferon therapy and initiation of glucocorticoid treatment. Sakane et al (24) have also reported the occurrence of hypopituitarism in a patient treated with interferon. An autoimmune phenomenon was proposed, and 11 months after discontinuation of the interferon treatment, the patient’s pituitary function was restored. No histologic data were provided.

In this report, we describe a woman with hepatitis C in whom thyroiditis and granulomatous disease of the pituitary developed after treatment with interferon alfa-2b and ribavirin. To our knowledge, this is the first such reported case in the literature.

**CASE REPORT**

A 42-year-old woman with hepatitis C presented to our institution for evaluation of hyperthyroidism thought to be related to interferon therapy. Before initiation of treatment with interferon alfa-2b and ribavirin, she was biochemically euthyroid and otherwise healthy. Interferon and ribavirin therapy had been initiated 5 months before the current presentation, and symptoms of fatigue and poor appetite developed about 2 months preceding presentation. Subsequently, she lost 8 kg and complained of dizziness and tachycardia. Results of thyroid function tests performed immediately before her referral were consistent with thyroiditis, with a low level of thyroid-stimulating hormone (TSH), elevated level of free thyroxine (FT$_4$), high concentration of total triiodothyronine, and low $^{125}$I uptake. Despite discontinuation of the interferon alfa-2b and ribavirin therapy and initiation of β-adrenergic blocking treatment, her symptoms persisted.

During the patient’s initial assessment at our institution in January 2002, she displayed signs and symptoms of thyrotoxicosis, which was confirmed biochemically (Table 1). Because of substantial loss of weight, poor appetite, and orthostatic hypotension, an evaluation of her hypothalamic-pituitary-adrenal axis was performed and demonstrated secondary adrenal insufficiency, with low serum cortisol and corticotropin concentrations (Table 1). The patient was admitted to the hospital for further investigation and intravenous treatment with glucocorticoids. Magnetic resonance imaging (MRI) of the sella turcica showed diffuse enlargement of the pituitary, which abutted but did not displace the optic chiasm (Fig. 1 A). A partial right superior quadrantanopia due to an old occipital infarct was present, with no new visual field deficits.

The patient experienced a dramatic improvement in symptoms after initiation of prednisone therapy in a daily dose of 40 mg. Supraphysiologic doses were chosen because of the presumed interferon-induced thyroiditis. We also thought that the higher dose of prednisone may be therapeutic if her pituitary disease was due to hypophysitis that had resulted in secondary adrenal insufficiency, hypogonadotropic hypogonadism, and a mildly elevated serum prolactin level (Table 1).

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient data</th>
<th>Reference range</th>
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<tbody>
<tr>
<td>Thyroid-stimulating hormone (μIU/mL)</td>
<td>&lt;0.01</td>
<td>0.3-5.0</td>
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<tr>
<td>Free thyroxine (ng/dL)</td>
<td>2.6</td>
<td>0.8-1.8</td>
</tr>
<tr>
<td>Triiodothyronine (ng/dL)</td>
<td>279</td>
<td>80-180</td>
</tr>
<tr>
<td>Thyroperoxidase antibodies (IU/mL)</td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Thyrotropin receptor antibodies (%)</td>
<td>&lt;5</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Morning cortisol (μg/dL)</td>
<td>&lt;1.0</td>
<td>7-25</td>
</tr>
<tr>
<td>Corticotropin (pg/mL)</td>
<td>&lt;4</td>
<td>10-60</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>54.3</td>
<td>4-30</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>&lt;35</td>
<td>&lt;400</td>
</tr>
<tr>
<td>Luteinizing hormone (mIU/mL)</td>
<td>2.0</td>
<td>…</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (mIU/mL)</td>
<td>4.3</td>
<td>…</td>
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During the subsequent 4 weeks, symptomatic hypothyroidism developed with a low level of FT₄ of 0.5 ng/dL (normal, 0.8 to 1.8) and a TSH of 4.7 μIU/mL (normal, 0.3 to 5.0). Treatment with levothyroxine was begun at a dosage of 100 μg daily. Her prednisone dose was slowly tapered and eventually substituted with hydrocortisone, 10 mg in the morning, 10 mg at noon, and 5 mg in the evening. Her appetite had improved, and she regained 9 kg.

A repeated MRI in May 2002 demonstrated a slight decrease in the size of her pituitary gland since the initial examination 4 months previously (Fig. 1 B). By this time, her TSH was undetectable and her FT₄ level was normal (1.4 ng/dL). Therefore, the levothyroxine dosage was reduced to 50 μg daily. In July 2002, the levothyroxine therapy was discontinued because her TSH level remained low (0.03 μIU/mL) in conjunction with a normal FT₄ concentration. This decision was made because the patient did not display overt signs of clinical hypothyroidism or hyperthyroidism, and it was unclear whether she had exogenous subclinical hyperthyroidism or secondary hypothyroidism attributable to the presence of a pituitary lesion.

By October 2002, the patient had diffuse enlargement of the pituitary gland, displacing the optic chiasm (Fig. 1 C). In the interim, she had also gained weight, had devel-

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**Fig. 1.** Serial magnetic resonance images of the head of the study patient. **A,** At initial presentation in January 2002. **B,** In May 2002, after several months of prednisone therapy. **C,** In October 2002, several months after high-dose glucocorticoid therapy had been discontinued. **D,** Initial postoperative image in February 2003. **E,** In June 2003 (7 months after a debulking surgical procedure and 4 months of treatment with high-dose glucocorticoids). **F,** In May 2005, after surgical intervention and 2 courses of high-dose prednisone therapy.
oped symptoms of clinical hypothyroidism, and had a low level of FT₄ (0.4 ng/dL) and an inappropriately normal TSH (1.0 μIU/mL), indications that secondary hypothyroidism had developed (which was addressed therapeutically). Because of the dramatic pituitary enlargement and a threat to her vision, a transphenoidal surgical procedure through a transnasal endoscopic approach was performed for diagnostic and therapeutic purposes. During exenteration of the pituitary, yellow-gray adenohypophysial tissue was resected, which histologically showed chronic, noncaseating granulomatous adenohypophysitis (Fig. 2). Accompanying lymphocytes were cytologically benign and consisted primarily of T cells. Stains for fungi (methenamine silver) and tubercle bacilli (auramine-rhodamine fluorescent method) were negative. Because granulomatous disease of the pituitary can be primary or secondary (Table 2), several additional studies were performed. Cerebrospinal fluid and pituitary tissue cultures, stains, and serologic studies were negative for bacterial, fungal, and mycobacterial disease. Serum IgG against syphilis was detected, consistent with a previously treated infection of the patient; however, a cerebrospinal fluid Venereal Disease Research Laboratory (VDRL) test was negative. Cytoplasmic-staining antineutrophil cytoplasmic autoantibodies were negative, and perinuclear-staining antineutrophil cytoplasmic autoantibodies were positive (low titers), but no additional signs of vasculitis were apparent. An ACE level was elevated at 80 U/L (normal, 7 to 46). Chest radiography and chest computed tomogra-

phy revealed no findings consistent with pulmonary sarcoidosis.

A diagnosis of granulomatous adenohypophysitis due to isolated pituitary sarcoidosis was made. Despite surgical intervention, residual sellar disease extending into the suprasellar space, right cavernous sinus, and further along the planum sphenoidale was evident on a postoperative MRI (Fig. 1 D). High-dose systemic glucocorticoid therapy was initiated with prednisone (60 mg every other day), alternating with physiologic doses of hydrocortisone. Alternate-day dosing was chosen because the patient had previously developed exogenous Cushing’s syndrome and severe depression during high-dose glucocorticoid therapy.

By June 2003, after 4 months of treatment, a notable reduction in size of the pituitary lesion was evident on MRI (Fig. 1 E). The prednisone dose was slowly tapered, and the patient was eventually given a total of 25 mg of hydrocortisone per day. Despite an initial slight enlargement in the lesion after the dose of prednisone was tapered, the patient had progressive yet incomplete resolution of the suprasellar lesion (Fig. 1 F).

At the time of her most recent follow-up in July 2006, the patient continued to have several anterior pituitary hormone deficiencies that necessitated replacement with glucocorticoids, levothyroxine, and estrogen. In addition, a low serum level of insulin-like growth factor-I developed; however, in the setting of an ongoing inflammatory process, growth hormone replacement was not yet initiat-

Fig. 2. Histologic appearance of the removed suprasellar tissue, showing a well-formed, noncaseating granuloma (arrow). (Hematoxylin-eosin; original magnification x200.)
ed. Her hepatitis C has not required additional pharmacologic treatment, and she is clinically doing well.

**DISCUSSION**

Inflammatory conditions of the pituitary are rare lesions than can result in considerable morbidity and even death if not recognized and treated properly. Hypophysitis can manifest with a variety of symptoms, including headache, visual disturbances, and various anterior and posterior pituitary deficiencies (41-44). Some patients will also have mild to moderate elevations of the serum prolactin level (42-46). In the current report, we described a woman with thyroiditis and granulomatous disease of the pituitary gland associated with interferon and ribavirin therapy. Although her initial symptoms were attributable to excess circulating thyroid hormone, signs and symptoms of adrenal insufficiency and hypogonadism quickly developed.

There are 3 types of primary inflammatory pituitary lesions—lymphocytic, granulomatous, and xanthomatous hypophysitis. *Lymphocytic hypophysitis* is the most common form, usually occurring in women during their fourth decade of life and frequently during late pregnancy or in the postpartum state. The histologic characteristics include diffuse adenohypophysial infiltration by lymphocytes and plasma cells associated with variable fibrosis (41-44). Primary *granulomatous hypophysitis* is rare and seems to occur equally among male and female patients, although the age at onset is typically younger in the latter. Histologic examination reveals noncaseating lesions containing granulomas with multinucleated giant cells and histiocytes; however, lymphocytes and plasma cells may also be present. The least common form of primary hypophysitis is *xanthomatous hypophysitis*. We found only a single well-documented reported case (47). Although lymphocytes may be present, the defining inflammatory cells are lipid-rich histiocytes.

The histologic appearance of the pituitary lesion in our patient was that of noncaseating granulomatous adenohypophysitis. This finding along with (1) an elevation of the serum ACE level and (2) the administration of interferon and ribavirin, which has been associated with new or reactivated sarcoidosis, is consistent in our case with a diagnosis of sarcoidosis. Miwa et al (23) described a 56-year-old woman in whom neurosarcoidosis developed after treatment with interferon-β for chronic hepatitis C. The diagnosis was based on an elevated ACE level and multiple cranial nerve deficits. Her symptoms diminished after discontinuation of the interferon therapy and initiation of supraphysiologic doses of prednisolone. In contrast to our patient, she had no MRI abnormalities or evidence of pituitary dysfunction. Sakane et al (24) described a 44-year-old woman with hypopituitarism after treatment with interferon α-2b for chronic hepatitis C. This patient had no detectable pituitary abnormalities on MRI. Her anterior pituitary deficiencies resolved 11 months after discontinuation of the interferon therapy.

Ultimately, our patient’s lesion responded to surgical debulking and high-dose glucocorticoid treatment. This result in itself does not distinguish sarcoidosis from primary hypophysitis because some patients with the latter condition will also respond to corticosteroid therapy (46).

The imaging modality of choice for pituitary lesions is MRI, but it cannot reliably distinguish inflammatory disease from neoplasms and other sellar lesions. Radiographic evaluation of inflammatory pituitary lesions can reveal the appearance of a distinct pituitary mass (46,48). No pathognomonic clinical, biochemical, or radiographic criteria allow a clear distinction of adenohypophysitis from a nonfunctioning pituitary adenoma. A definitive diagnosis can be made only histologically. Histologic evaluation along with an elevated ACE level enabled us to postulate that our patient had sarcoidosis. Several reports have described adenohypophysitis being mistaken as a pituitary adenoma (46,48). This potential poses a problem in that operative management is not the treatment of choice in patients with hypophysitis, especially if the optic chiasm is not jeopardized. In our patient, surgical intervention was indicated for diagnostic purposes and because of the substantial enlargement of the sellar lesion with displacement of the optic chiasm, as shown in Figure 1 C. Several systemic diseases can mimic primary adenohypophysitis and should be considered in the differential diagnosis of a suspected inflammatory pituitary lesion (Table 2). Granulomatous lesions involving the pituitary may be due to various infectious agents (not demonstrated in our patient) as well as to sarcoidosis. Thorough clinical, biochemical, and microbiologic evaluations in our patient suggested the diagnosis of sarcoidosis associated with the use of interferon and ribavirin.

### Table 2

<table>
<thead>
<tr>
<th>Disease</th>
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<tr>
<td>Wegener’s granulomatosis</td>
<td>25-28</td>
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<tr>
<td>Neurosarcoidosis</td>
<td>29,30</td>
</tr>
<tr>
<td>Ruptured Rathke’s cleft cyst</td>
<td>31,32</td>
</tr>
<tr>
<td>Takayasu’s arteritis</td>
<td>33</td>
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<td>Crohn’s disease</td>
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<td>Syphilis</td>
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<td>Histiocytosis</td>
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</table>
CONCLUSION

The development or reactivation of sarcoidosis has been associated with the use of interferon and ribavirin therapy. Many causes of a sellar mass can manifest with multiple hormone deficiencies. Sarcoidosis is one of the possibilities that should be considered in patients treated with interferon and ribavirin for chronic hepatitis C who have symptoms consistent with pituitary disease.

DISCLOSURE

The authors have no conflicts of interest to disclose.

REFERENCES