PREFACE

I enjoy seeing patients, as I think most endocrinologists do. One of the things I believe we enjoy most is seeing patients who provide challenges to us, so that we have to think a little harder to find the diagnosis and to be creative in our disease management. Going to the literature and textbooks—often via the computer—to look up the latest information, discussing cases with colleagues, reaching for help by way of telephone or email from more distant colleagues with greater expertise, are part of what we do on an everyday basis to provide the best care for our patients and also to provide intellectual stimulation for ourselves. This continued desire on our part to meet such challenging cases head-on and to stimulate ourselves intellectually are the reasons I am confident readers will like *Challenging Cases in Endocrinology*.

I have asked experts in their fields to provide for us accounts of those difficult cases that have required of them extra effort and creative thinking in diagnosis and management. You will be able to follow with them how they did what they did, and why. They have also provided detailed, up-to-date, referenced discussions to put their cases into context. In this way, you will be able to bring much of this information into daily use in your own practices, and the references we have provided will allow you to look up additional material as needed. As editor, I have read all of these cases and have personally picked up information and a number of tips that I have already put to use in my own practice.

This, therefore, is a book for the *practicing endocrinologist*, whether a fellow still in training, a full-time clinician out in practice for 25 years, or a clinician/academic who only sees patients one-half day per week. You can take it on the airplane with you or read a case at a time when you can fit it in. Very few of the cases are straightforward and many provide twists or turns—almost as if you were reading a novel.

I wish to thank the authors of these chapters for taking the time out of their busy schedules to write up their cases and for sharing their clinical expertise with us. I also wish to thank Ms. Joella Ackerman for helping me keep things organized and helping with the editing. Mr. Paul Dolgert and the editorial and production staff at Humana Press have been very supportive. Finally, I would like to thank my family—Susan, Tamara, Ethan, and Michael—who are used to seeing me at home working at the computer in the evenings and on weekends, for supporting me in this endeavor.

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Hypopituitarism

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CASE #1: SARCOIDOSIS

Case Description

A 44-yr-old African-American woman presented with a 7-yr history of amenorrhea, tiredness, unexplained fatigue, weakness, dry skin, and thinning of the hair. She remained healthy until age 37, when she developed oligomenorrhea and thinning of axillary and pubic hair, with loss of hair over the parietal area. Serum thyroid-stimulating hormone (TSH) levels done on two separate occasions were reported to be "normal." Three years before her presentation, and at the age of 41, she was admitted to a hospital with headaches, lethargy, and nausea. The diagnosis of obstructive hydrocephalus was made. She had an emergency ventriculostomy, followed by a right-sided V-P shunt, which she continues to have. Work-up at that time included a lumbar puncture (WBC = 6/mL, glucose = 64 mg/dL, protein = 17 mg/dL, VDRL = nonreactive) and a MRI of brain without contrast, which revealed an empty sella and postoperative changes. Other findings during that admission included hyponatremia (Na = 122 mmol/L), normocytic anemia, and leukopenia (WBC = 2500/μL, Hct = 33 %). A bone marrow biopsy revealed noncaseating granulomas. The diagnoses of collagen vascular disease, not otherwise specified and the syndrome of inappropriate antidiuretic hormone (SIADH) were made. She was discharged home on oral sodium supplements (NaCl, 2 g/d), fluid restriction, and phenobarbital for seizure prophylaxis. The latter was discontinued because of increasing lethargy.

She remained chronically unwell, with exacerbating illnesses requiring several hospitalizations. Six months prior to this evaluation, she was admitted to the hospital for abdominal pain, nausea, vomiting, and weight loss of 15 lbs. Ultrasound of the gall bladder and liver enzymes were normal. At that time, morning serum cortisol levels were measured on two occasions and were in the "low-normal range" of 6 to 8 μg/dL.

An outpatient endocrine consult was requested in view of the following thyroid function studies done at that time: a serum TSH of 0.94 mU/L, a total thyroxine level of 4.1 µg/dL (normal 5–11) and a calculated free thyroxine index of 4.0 (normal 5–11). Additional complaints included several years of history of dyspareunia and lack of libido.

In the clinic, she appeared tired and fatigued. Her exam was notable for a blood pressure of 90/70, a heart rate of 75/min, and a weight of 122 lbs. (baseline approximately 140). The thyroid was barely palpable. The skin was dry and there was sparse axillary and pubic hair. She had normal eye motility, full visual fields, and normal fundi. Her neurologic exam was remarkable for significant delay in the relaxation phase of the deep tendon reflexes.

Based on the past medical history and available clinical biochemical and pathological data, the diagnosis of hypopituitarism secondary to neurosarcoidosis was entertained. Additional studies were performed to assess pituitary function and confirm the etiology of hypopituitarism. Studies included the following serum levels: total thyroxine of 2.1 µg/dL, a free thyroxine index of 3 (normal 5–11), prolactin of 39 µg/L, an FSH of 1.1 IU/L, an LH of 0.9 IU/L, an estradiol of <10 ng/L, a total testosterone of 11 ng/dL, an AM cortisol of 5.5 µg/dL, a total calcium of 8.8 mg/dL, an albumin of 3.8 gm/dL, a Na^+ of 132 mmol/L, a K^+ of 4.2 mmol/L, and a normal ACE level.

A lumbar puncture revealed the following cerebrospinal fluid (CSF) data: WBC = 26/mL (70% lymphocytes and 15% monocytes, RBC = 0/mL, protein of 270 mg/dL, a glucose of 20 mg/dL, and negative stains and growth for bacteria, myobacteria, or fungi). Urinalysis showed a specific gravity of 1.015. Pulmonary function tests and chest X-ray were unremarkable. The electrocardiogram was reported as low voltage with sinus bradycardia. MRI of the pituitary with contrast showed meningeal enhancement in the region of the optic chiasm and a normal-appearing pituitary stalk. Neuroophthalmologic evaluation revealed granulomas in the tarsal conjunctiva but no uveitis.

Dynamic studies of pituitary hormone secretion were done, as shown in the Fig. 1. Briefly, they showed an elevated serum prolactin level on multiple occasions, associated with partial hypopituitarism, with loss of gonadal, thyroidal, and adrenal functions. Antidiuretic hormone (ADH) secretion was considered to be normal. The pattern of response to the administration of hypothalamic releasing hormones was consistent with deficiency of hypothalamic releasing hormones. Thus, despite the presence of clinical hypothyroidism and peripheral hypothyroxinemia, serum TSH levels were inappropriately in the "normal" range and increased further after thyrotropin-releasing hormone (TRH) was administered. The pattern of response to GnRH administration was similar and consistent with partial deficiency of the latter hypothalamic releasing factor. The patient had partial adrenocorticotropic hormone (ACTH) deficiency as evidenced by the subnormal rise in serum cortisol following insulin-induced hypoglycemia (nadir glucose of 22 mg/dL). The cortisol response to cortrosyn in this patient was considered "normal." Such discordance in cortisol responses is seen in 40–50% of patients with ACTH deficiency, particularly when the latter is partial.

The diagnosis of neurosarcoidosis and hypothalamic hypopituitarism was made and the patient was started on prednisone therapy (40 mg/d) as well as physiologic thyroid hormone replacement. Two weeks later, she felt like 'she was given a new life'. Premarin and provera were subsequently added with further improvement in her well being.

She did relatively well over the years, requiring careful monitoring. Seven years after the diagnosis was made, she developed cervical and brachial plexus neuritis, and was given high-dose steroids. As a result of steroid therapy, she had hypertension, weight
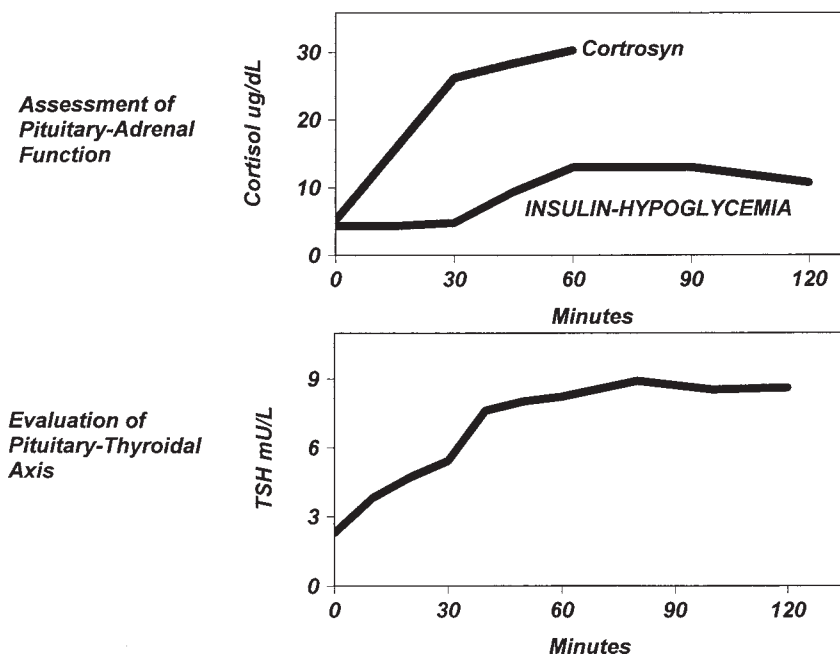
Fig. 1. Dynamic testing of pituitary function in a patient with hypopituitarism is shown. The upper graph shows evaluation of pituitary–adrenal function using cortrosyn stimulation test (250 µg, IV) and insulin-induced hypoglycemia (nadir glucose of 22 mg/dL). The lower panel of the graph shows the response to TRH administration in a patient with clinical and biochemical (low thyroxine) features of hypothyroidism.

gain, and developed cataracts and avascular necrosis of the hip, requiring total hip replacement. Currently, she is 54 yr old, doing very well with minimal neurologic sequale. She is an active housewife and a baby sitter. She continues to be on prednisone (7.5 mg/d), thyroxine, and premarin as hormone replacement. Although she was documented to have GH deficiency, she declined physiologic replacement therapy.

Discussion

This case illustrates many of the difficulties and problems encountered in establishing the diagnosis of hypopituitarism and in defining its etiology. The long duration of symptoms and their "nonspecific nature" clearly contributed to the delay in diagnosis. The patient had signs and symptoms of, at least, partial hypopituitarism 7 yr before her presentation. In addition, she had histologic findings 3 yr before presentation that were consistent with systemic sarcoidosis. At that time, she had anemia, hyponatremia, and noncaseating granulomas on bone marrow biopsy. She also had clinical features suggestive of adrenal insufficiency (tiredness, fatigue, hypotension, hyponatremia, loss of axillary and pubic hair) as well as hypogonadism (amenorrhea and dyspareunia).

Repeated assessment of thyroid function using TSH as a marker expectedly revealed normal values. The original thyroid function tests done a few months before endocrine evaluation were interpreted to be consistent with euthyroid-sick syndrome. It was not until the clinical and biochemical data were looked at together, that the diagnosis of hypopituitarism was entertained.

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology *(1)*. Its prevalence varies from 5–50/100,000 depending on the population studied. In the United States, there is a 3.8-fold increased risk among African-Americans, with a slight female preponderance. The peak incidence of sarcoidosis is in the fourth decade of life. There seems to be a threefold higher incidence of family history of sarcoidosis among African-Americans. It is interesting to note that the patient's mother and sister had the disease. In these respects, our patient's presentation and background were typical.

Despite extensive epidemiological studies, there is incomplete understanding of the etiology of this disease. Both a genetic/immunologic predisposition and an environmental trigger seem involved in the pathogenesis. The hallmark of the disease is the presence of noncaseating granulomas. The clinical manifestations range in severity and in spectrum, depending on the specific organs involved. Whereas some symptoms can also be related to the products of granulomas such as vitamin D and the resulting hypercalcemia *(1)*, others are related to tissue and organ destruction such as the case with pulmonary manifestations. The following organ systems *(1)* are involved in sarcoidosis: pulmonary (90%), ocular (20%), dermatological (20%), reticuloendothelial (20%), gastrointestinal, salivary and hepatic (20%), musculoskeletal (10%), cardiac (5%), and nervous system (5%).

In the CNS, sarcoidosis has a predilection to the base of the skull and manifests clinically as cranial neuropathy (most commonly optic and facial nerves), lymphocytic meningitis, hydrocephalus (obstructive and nonobstructive), hypothalamic dysfunction, and hypopituitarism *(2–5)*. The patient under discussion has most of these manifestations.

The diagnosis of sarcoidosis in general is established based on three criteria: a) the recognition of the characteristic clinical findings; b) histologic evidence of noncaseating granulomas; and c) ruling out other causes of granulomas, particularly tuberculosis *(1)*. In the case of CNS involvement, the search for extraneurological manifestations should be undertaken, as these are present in 90% of patients and are easier to biopsy *(2,3)*. Lumbar puncture and gadolinium-enhanced MRI of brain are useful adjuncts in the diagnosis, especially in the absence of apparent systemic pathology *(2,3)*. CSF abnormalities are present in 80% of cases and most commonly include an elevated protein level and increased lymphocytes. MRI abnormalities are also detected frequently. The most specific finding for hypothalamic involvement is pituitary stalk thickening and leptomeningeal enhancement in the optic chiasm area. The latter helps to differentiate neurosarcoidosis from hypothalamic disease resulting from other causes such as multiple sclerosis and lymphocytic hypophysitis *(2,3)*. Products of granulomas such as ACE levels and IL-2 are nonspecific and depend on disease activity *(2,3)*. However, the finding of an elevated ACE level in the CSF fluid is indicative of active neurosarcoidosis.

The cause of hypopituitarism in neurosarcoidosis was demonstrated to be hypothalamic insufficiency by dynamic endocrine testing *(5)*. The general principles of testing outlined in earlier studies remain the mainstay of the diagnosis, and were applied to our patient. As shown in Fig. 1, the administration of TRH to our patient with clinical hypothyroidism resulted in a delayed and sustained release of TSH that is typically described in patients with tertiary or hypothalamic hypothyroidism. The latter pattern of response is also seen in patients with pituitary stalk section or compression. It is not surprising to note that such patients just as ours had mild hyperprolactinemia. Other dynamic studies using other stimulatory hypothalamic factors or hormones such as CRH and GnRH (performed on our patient, but not shown) can demonstrate the similar phenomena. In the study by Stuart et al., 6 out of 10 patients with neurosarcoidosis had a normal LH rise

(greater than three- to six-fold basal) following GnRH infusion, and a lack of response after clomiphene citrate was observed in all 10 patients *(5)*.

After establishing the diagnosis, management of patients with sarcoidosis requires comprehensive and meticulous care. Attention to the details of specific organ involvement and management of problems arising from the disease itself (e.g., hypopituitarism, anemia), or as a complication of therapy (e.g., ulcer, weight gain, osteoporosis, fluid retention, and so on), represent some of the challenges encountered. Patients with neurosarcoidosis are often managed by multiple specialists with variable areas of interests and expertise, who should regularly interact and communicate with each other.

Even with steroid therapy, recovery of hypothalamic function is extremely unusual and, therefore, hypopituitarism necessitates permanent hormone replacement. Physiologic steroid replacement is roughly the equivalent of 5 mg prednisone per day. Most patients with neurosarcoidosis receive therapeutic doses of prednisone, and may therefore exhibit relative adrenal insufficiency at physiologic doses. Management of hypothyroidism is these patients is similar to that of patients with hypopituitarism, regardless of its etiology and relies primarily on oral thyroxine. Sex hormone replacement is crucial because of the high risk for osteoporosis. Similarly, GH therapy may be beneficial, but was refused by our patient. Diabetes insipidus, when present, is usually central and would respond well to oral or intranasal DDAVP. However, occasionally it may be partially nephrogenic when hypercalcemia is a complicating feature.

Chronic steroid therapy requires as much monitoring as hypopituitarism itself. Our patient developed cataracts, avascular necrosis of the hip, hypertension, and kidney stones. She is on prophylactic therapy for peptic ulcer disease.

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CASE #2: HYPOPHYSITIS

Case Presentation

A 25-yr-old woman was referred to our institution for evaluation of increasing fatigue, tiredness, sleepiness, decreased appetite, nausea, and a 5-kg weight loss over a 3-mo period. The patient noted gradual loss of libido, a decrease in axillary and pubic hair over the 2 mo preceding her evaluation. Six months before her visit, she underwent an eventful vaginal delivery after a full-term uncomplicated pregnancy. Menses resumed several weeks postpartum and remained regular since. The patient did not breastfeed her infant and she was treated briefly with bromocriptine. The patient denied having headaches or visual symptoms. Her past medical history was otherwise unremarkable. The family

Table 1
Pituitary Hormone Response to Dynamic Testing

Dynamic test	At Presentation		38 Months After Biopsy	
	Baseline level	Peak	Baseline peak	Level
Insulin-Induced Hypoglycemia*				
GH (µg/L)	2	8.9	0.1	6.9
ACTH (ng/L)	<3	3.1	<3	<3
Cortisol (µg/dL)	0.5	1.1	0.5	0.6
TRH Stimulation Test				
TSH (mU/L)	1.2	8.2	1.7	9.9
Prolactin (µg/L)	2.1	1.9	1.3	1.4
GnRH- Stimulation Test				
FSH (IU/L	3.5	11.8	4.9	12
LH (IU/L)	4.6	23.5	6.7	33

*Nadir glucose of 25 mg/dL

history revealed a mother with Grave's disease and a maternal aunt with systemic lupus erythematosus (SLE).

On physical examination, pertinent findings included a recumbent blood pressure of 116/74 mmHg, which decreased to 100/60 upon assuming upright posture. She appeared tired, exhausted, and pale. The skin was not dry and the thyroid was not enlarged. Axillary and pubic hair were diminished. There was no increased pigmentation over mucous membranes or the skin. Eye exam revealed normal extraocular movement, pupillary reactions, visual fields, and fundi. Deep tendon reflexes were normal.

Initial laboratory data revealed the following: Na^+:127 mmol/L; K^+: 4.0 mmol/L; Cl^-:101 mmol/L; HCO_3^-: 28 mmol/L; BUN: 23 mg/dL, and a creatinine of 0.6 mg/dL. The hematocrit was 33% and the WBC was 3800/µL.

Initial endocrine data included the following: Am cortisol of 0.6 µg/dL, which increased to 3.5 µg/dL after IV cortrosyn (250 µg), a morning plasma ACTH level of <3 ng/L (10–52), DHEA-S of 5 µg/dL (50–400), free thyroxine of 0.8 ng/dL (0.6–1.5), a TSH of 1.7 mU/L, a prolactin of 2.0 µg/L, an FSH of 10 mU/L, an LH of 11 mU/L, an estradiol of 65 ng/L, a total testosterone of 15 ng/dL (10–70), and a free testosterone of 0.2 ng/dL (0.2–7).

A magnetic resonance imaging scan (MRI) of the sella turcica showed an enhancing sellar mass that extended into the suprasellar area, and was close to, but not in contact with the optic chiasm or the cavernous sinus.

The diagnosis of adrenal insufficiency was clinically suspected and biochemically confirmed. The patient was started on physiologic hydrocortisone replacement therapy (20 mg daily, in three divided doses), with prompt clinical improvement in symptoms. The treatment was discontinued for 2 d a week later when pituitary dynamic studies were performed. The results are illustrated in Table 1. Briefly, FSH and LH responses to GnRH were normal. Similarly, serum TSH increased normally after TRH administration. In contrast, baseline serum prolactin levels were low and did not increase after stimulation with TRH. Plasma cortisol and ACTH levels were low or undetectable and failed to increase after insulin-induced hypoglycemia (Nadir glucose level of 25 mg/dL). In contrast, serum GH levels increased appropriately after insulin-induced hypoglycemia.

Because of the unusual nature of mass, its proximity to the optic chiasm, and the endocrine data, biopsy of the mass was recommended. A transsphenoidal biopsy of the sellar mass showed findings consistent with lymphocytic hypophysitis, with scattered normal pituitary cells. Multiple sections throughout the specimen were immunostained and showed cells staining positive for prolactin, TSH, FSH, LH, GH, but not for corticotropin. The lymphocyte population consisted of a mixture of B and T cells. The B-cell population was composed of a polyclonal mixture of cell types by immunohistochemical staining for immunoglobulin heavy and light chains.

Postoperatively, corticotropin deficiency persisted and physiologic hydrocortisone replacement therapy was continued. A repeat MRI scan of the sella performed 6 mo after the biopsy showed no interval changes in the appearance of the pituitary mass. A MRI done 38 mo after the biopsy showed spontaneous resolution of the pituitary mass. Shortly thereafter, pituitary dynamic studies were repeated and were unchanged (see Table 1). Ten months later (i.e., 4 yr after initial presentation, she developed signs and symptoms of primary hypothyroidism). She was found to have a goiter, an elevated serum TSH level, as well as a positive antithyroid peroxidase antibody. Treatment with thyroxine reversed all symptoms of hypothyroidism. Currently, she continues to do well, 6 yr after the diagnosis of hypophysitis was made. She continues to have normal menses while receiving chronic physiologic hydrocortisone and thyroxine replacement.

Discussion

The current case has many of the features that have been reported in most cases of hypophysitis, particularly the temporal relationship to pregnancy. The pattern of pituitary hormone losses (ACTH and prolactin) with sparing of the gonadotropins is also typical of hypophysitis. The presence of a family history of autoimmune diseases and the subsequent development of such a disease (Hashimoto's thyroiditis) in our patient are consistent features of patients with adenohypophysitis *(1–3)*.

Lymphocytic hypophysitis is one of the recently appreciated entities that can cause a pituitary mass and hypopituitarism. It is an inflammatory process, likely to be autoimmune in nature that involves the pituitary gland. Even though the inflammatory process is diffuse, corticotrophs appear to be the most susceptible, whereas gonadotrophs are the least affected by the inflammatory process. Thus, in patients with hypophysitis, ACTH deficiency is the most commonly impaired axis, whereas gonadal function is often normal *(1–3)*. Lactotrophs are often affected by the inflammatory process, as reflected by the fact that serum prolactin levels are low in approximately one-half of the patients *(1,2)*. A variant of this disease entity involves predominantly the posterior lobe of the pituitary and/or the stalk and, as expected, results in diabetes insipidus *(4)*. Most patients with hypophysitis or their relatives have other autoimmune illnesses such as Grave's disease, Hashimoto's thyroiditis, vitiligo, lupus, and inflammatory arthritis *(1,2)*.

A few of the reported cases have been noted to have serum antibodies against pituitary tissue as well as other autoantibodies *(1,2)*. The latter finding in addition to the described histologic changes suggest that the disease is autoimmune in nature. In a study of sera from patients with biopsy proven lymphocytic hypophysitis, Crock *(5)* found that 70% had antibody to a 79-Kd cytosolic protein. Antibodies to the same antigen were seen in some patients with Addison's disease suggesting that the antigen is not restricted to the pituitary *(5)*.

Precise diagnosis of this entity can only be made by biopsy. Definitive data on the long-term natural history of the disease are sparse. This case and a few others reported in the literature indicate that such patients can have spontaneous regression of the inflammatory process (1–3). The natural course of the disease as constructed by the various presentations and manifestations suggest progressive fibrosis and loss of pituitary cells after an initial episode of edema, inflammation, and associated mass lesion. Depending on the stage of the disease at the time of diagnosis, patients may present with a large pituitary mass lesion as a result of the inflammatory process or with an atrophic and fibrotic gland. Although lymphocytic adenohypophysitis has been described in men and women of all age groups, the typical patient is a young woman presenting during pregnancy or within 1–2 yr after delivery. Despite the well-recognized tendency of gonadotropin secretion in these patients to be spared, subsequent fertility was not well appreciated. A few reports have indicated that such patients can get pregnant after the first episode of hypophysitis without unusual complications (3).

The diagnosis is often difficult without a biopsy because of the variable mode of presentation and the lack of a serologic marker for the disease (1,2,6). A few clues to the diagnosis include presentation during or within 2 yr after pregnancy in a woman who has other autoimmune diseases. The pattern of pituitary hormone deficit can also be very helpful in suspecting the diagnosis. ACTH and prolactin deficiencies associated with normal gonadotropin secretion are very likely to be caused by hypophysitis because impairment of pituitary-gonadal function is one of the earliest manifestation of hypopituitarism caused by mass lesions or vascular necrosis. Surgery is sometimes necessary at the time of first presentation especially in patients with mass lesions compressing the optic apparatus. When the clinical presentation, radiological and endocrine manifestation are all consistent with the diagnosis, tissue diagnosis may not be essential as long as the patient is followed closely. Although some advocate high-dose glucocorticoid therapy, there are no data to support efficacy of such treatment (6). Hormone replacement therapy is the main form of treatment and should thoroughly address individual needs.

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CASE #3: PITUITARY APOPLEXY

Case Presentation

A 46-yr-old man presented to the emergency room of a community hospital with a 6-h history of a sudden, severe, frontal headache that awakened him from sleep. He denied having similar episodes or frequent headaches. Evaluation by the emergency room physi-

cian was reported to have shown a temperature of 38.1°C, a blood pressure of 150/80, and a pulse of 99/min. He was described to have tenderness over the frontal and maxillary sinuses. His neck was supple and the remainder of his physical exam was reported to be unremarkable. He was discharged home on antibiotics and decongestants for presumed acute sinusitis. He returned to the same emergency room the next morning with persistent headaches and new onset of diplopia. He reported that he was unable to take the antibiotics he was previously prescribed because of nausea and vomiting. Evaluation by the emergency room physician showed a temperature of 39.4°C, a blood pressure of 120/68 and a pulse of 110/min. He was suspected by the emergency room physician to have meningitis and was transferred to our institution for further management.

On arrival to our institution, the patient appeared ill, but was alert and oriented, complaining of headaches, diplopia, and photophobia. He reported to have been previously healthy except for diminished libido and potency, for which he was prescribed Viagra® for 1 yr. He denied having chronic headaches or visual symptoms. On examination, the patient was slightly overweight with normal features. His vital signs were similar to those obtained at the emergency room. He had ptosis of the right eye, right abducen palsy, as well as bitemporal hemianopsia. Fundoscopic exam showed normal venous pulsation and mild, bilateral temporal disk pallor. The patient had minimal tenderness over maxillary and frontal sinuses, whereas his neck showed minimal stiffness. He was noted to have a slight bilateral gynecomastia, without a nipple discharge. The rest of the physical exam was negative.

After blood samples were drawn, iv fluids were administered. The patient had a non-contrast CT scan in the emergency department that showed a 2-cm hyperintense sellar mass with suprasellar extension. Following iv contrast, the mass became more intense. The endocrine team was consulted when the presumptive diagnosis of pituitary tumor apoplexy was made. Intravenous hydrocortisone (100 mg) was administered, a lumbar puncture was done followed by wide spectrum antibiotic therapy. The patient was admitted to the neurological intensive care unit for monitoring. Studies on the CSF specimens showed 15 WBC/mL, mostly lymphocytes, a normal glucose of 79 mg/dL, and an elevated protein concentration to 220 mg/dL. Cultures done on a CSF specimen showed no bacterial growth.

Pertinent laboratory studies done on arrival showed normal values for electrolytes, calcium, BUN, and creatinine. Total WBC was 15,500/μL with 75% neutrophils, 5% bands, 5% basophils, and 10% lymphocytes. Endocrine studies on blood samples drawn before therapeutic intervention showed the following: a serum cortisol of 6.5 μg/dL, a plasma ACTH of 13 ng/L, a free T4 of 1.1 ng/dL (0.6–2.0), a serum TSH of 1.9 mU/L (0.5–5.0), a free testosterone of 1 ng/dL (2.5–10), an FSH level of 0.7 mU/L (2–10), an LH level of 0.2 mU/L (2–10), and a prolactin of 2 μg/L (4–18).

In the intensive care unit, the patient was monitored and continued on hydrocortisone (25 mg IV, every 6 h), iv fluids and iv antibiotics. Clinical improvement was noted within a few hours of admission such that he became afebrile and noted some relief from the headaches. On repeated examinations, the third and sixth nerve-palsies were noted to persist. Twenty-four hours after admission to the ICU, the patient had transsphenoidal decompression of the necrotic tumor. Immunostaining of the resected tissue was limited because of the extensive necrosis. However, available viable tumor tissue showed a few prolactin-staining cells. Twenty-four hours after surgery, hydrocortisone therapy was discontinued while the patient continued to be clinically monitored. Resolution of the

headaches and improvement of eye motility were noted within 24 h of surgery. Plasma ACTH and cortisol levels measured >36 h after hydrocortisone therapy was discontinued were appropriately elevated (55 ng/L, 33 µg/dL, respectively), indicating normal pituitary–adrenal function.

The patient continued to do well postoperatively and was discharged home on the fourth postoperative day only on pseudoephedrine for congestion. At the time of discharge, he had normal eye motility and visual fields. When tested 4 wk after discharge, his pituitary function was considered normal, including a free testosterone of 6.9 ng/dL (2.5–10), an AM cortisol of 27 µg/dL and a serum prolactin of 4.5 µg/L. A MRI scan done 6 mo after surgery showed no residual tumor. The patient continued to do well with normal pituitary function and no recurrence of the tumor, 7 yr after surgery.

Discussion

This case illustrates many of the issues and difficulties encountered in the management of patients with pituitary tumor apoplexy. Although the patient had a 1-yr history of symptoms suggestive of hypogonadism, the pituitary adenoma was previously undiagnosed and apoplexy was the first manifestation of the tumor. This is seen in approximately 50% of patients with pituitary tumor apoplexy *(1–3)*. It is likely that the patient had a prolactin secreting pituitary adenoma although this could not be documented with certainty. The low serum prolactin level seen at presentation does not necessarily argue against the latter diagnosis. It is well known that serum prolactin levels decrease precipitously in patients with prolactinomas, after complete adenomectomy *(4)*, or after hemorrhagic infarction *(5)*, as was the case in this patient.

Pituitary tumor apoplexy represents a rare clinical syndrome usually resulting from hemorrhagic infarction of an existing large adenoma. Although many precipitating factors are known, most episodes occur spontaneously as was the case in this patient. Pituitary tumor apoplexy is a clinical, rather than a pathological diagnosis. The term should be used only when signs of compression of perisellar structures or meningeal irritation occur after hemorrhagic infarction of an adenoma *(1)*.

As illustrated by the current case, the diagnosis of pituitary tumor apoplexy can be difficult and is frequently missed because, in addition to its relative rarity, the existence of an adenoma is not often suspected at the time of ictus. The clinical manifestations at the time of presentation consist of neurological and endocrinological signs and symptoms *(1)*. The pathophysiology of the clinical manifestations of pituitary tumor apoplexy can be divided into any combination of the following mechanisms:

1. Hemorrhagic infarction of the tumor leading to sudden increases in intrasellar pressure. The latter results in compression of the normal pituitary tissue as well as its vascular blood supply, leading to hypopituitarism, particularly acute adrenal insufficiency. In addition, the increased intrasellar pressure contributes to the development of headaches which is described as sudden in onset, severe and persistent in nature and bifrontal or occipital in location.
2. Sudden increase in intrasellar contents leading to increased pressure on adjacent vascular and neural structures, laterally, superiorly, and inferiorly.
   a. Laterally, increased pressure leads to damage to cavernous sinus neural structures e.g. cranial nerves III, IV, V, and VI. The patient under discussion has both third and sixth nerve palsies that explain his clinical symptoms.

    b. Superiorly, increased pressure will lead to compression of the optic apparatus that can present clinically as decreased visual acuity as well as visual field deficit as was demonstrated in our patient.

    c. Inferiorly, increased pressure can lead to CSF leak. The patient under discussion did not have any evidence for a CSF leak.

3. Leakage of blood or necrotic tissue into the subarachnoid space; leading to signs and symptoms of chemical meningitis. The patient under discussion had a clinical picture consistent with meningeal irritation, photophobia and fever associated with negative bacterial cultures, a finding quite characteristic of patients with tumor apoplexy.

The diagnosis of pituitary tumor apoplexy can, at times, be difficult as it may mimic a number of other intracranial illnesses *(1)*. The two most important diseases that should be considered are aneurysmal subarachnoid hemorrhage and bacterial meningitis. Imaging studies are helpful in differentiating these illnesses.

Hypopituitarism often contributes to the morbidity and mortality of pituitary tumor apoplexy. Impaired secretion of all anterior pituitary hormones may be seen after pituitary tumor apoplexy. The most clinically important deficit is that of ACTH because it leads to acute glucocorticoid insufficiency at a time of severe physical stress. In that respect, the patient under discussion had what appeared to be a "normal " serum cortisol at a time when he was extremely stressed. Thus, he was presumed to have partial ACTH deficiency even though his serum levels were in the so-called "normal range." The vast majority of patients present with at least partial hypopituitarism *(1,2)*. It is important to point out that many patients would be expected to have hypopituitarism even before the apoplectic episode, because practically all have large tumors *(1,2)*. Our patient had clinical and biochemical features consistent with central hypogonadism at the time of presentation. It was not clear whether the hypogonadism in this patient was caused by a presumed long-standing hyperprolactinemia (not documented) or whether it was a component of the state of hypopituitarism. Even though GH secretion was not tested at presentation, it is more than likely that the patient had GH deficiency.

Management schemes for pituitary tumor apoplexy should address systemic, neurological, and endocrinological abnormalities. Patients presenting with clinical symptoms consistent with apoplexy require immediate medical attention, thorough clinical evaluation and continuous monitoring. Some of the most important interventions that must be urgently addressed in a patient with suspected pituitary tumor apoplexy are corticosteroid replacement and vigorous supportive measures to ensure hemodynamic stability *(1)*.

Once the diagnosis of pituitary tumor apoplexy is clinically suspected, routine blood studies as well as additional blood samples should be drawn for subsequent determination of all pituitary hormone levels. Urgent imaging studies such as CT or MRI scan should be obtained to confirm the diagnosis. Glucocorticoid deficiency, seen in the vast majority of patients, results in significant morbidity, if left untreated. As was demonstrated in our patient, once glucocorticoids are administered, clinical improvement is invariably noted and hemodynamic stability is easier to maintain. The glucocorticoids are administered in supraphysiological doses to serve not only as replacement for endogenous hormone deficiency, but also to help control the effects of swelling on parasellar structures. We recommend either 100 mg hydrocortisone administered intravenously every 6 h or 4–6 mg dexamethasone administered intravenously every 6 h as the initial choice of steroid therapy.

Documentation of any visual field defect is important and should be obtained if the clinical condition permits. Analysis of CSF fluid is usually not necessary, unless the diagnosis of meningitis can not be safely excluded on clinical grounds. When the patient's physiological status is stabilized, the decision regarding the best method for reversing or preventing further neurological compromise should be considered. Several reports have documented that spontaneous neurological recovery is possible despite unilateral ophthalmoplegia and partial visual field defects. Thus, nonoperative, conservative medical management of patients with pituitary tumor apoplexy has been recommended by some *(1–3,6)*. Even though improvement in neurological symptoms may be seen in patients treated conservatively, worsening of pituitary function is usually seen in such patients.

Because some patients may deteriorate rapidly *(1–3,6)* and the effects of continued compression on neural structures and endocrine function may be deleterious, we believe that urgent decompression should be undertaken by an experienced neurosurgeon, unless there are strong contraindications to surgical intervention. In view of the low morbidity and mortality associated with transsphenoidal surgical decompression, this approach is routinely used for the vast majority of patients.

Conservative medical therapy is a reasonable alternative option, particularly in areas that lack expertise in this type of surgery. Similarly, patients who are poor surgical candidates and those who have strong contraindications for surgical intervention are treated conservatively. This would involve supportive therapy, continued use of supraphysiologic doses of glucocorticoids for several weeks and hormone replacement. Improvement in neurologic symptoms is often seen in the majority of patients treated conservatively and at times to a similar degree to that seen in surgically treated patients. The role of conservative, medical therapy in the immediate management of patients with this disorder, was recently investigated in a recent study by Maccagnan et al. *(6)*. The authors conducted a nonrandomized study on patients presenting with apoplexy and treated them all with dexamethasone. Patients who failed to improve after 1 wk of dexamethasone were surgically treated. The authors found that patients treated conservatively had a similar neurologic and neuroophthalmologic improvement when compared to surgically treated patients. However, it is obvious from the design of the study that surgically treated patients had more severe symptoms at presentation. Despite that limitation, it is clear that conservative therapy can be used in selected patients with minimal symptoms and those who improve dramatically after glucocorticoid administration.

Surgical decompression does not always result in complete resection of these infarcted macroadenomas, and routine postoperative radiological and endocrinological assessment is mandatory. Depending on the type of tumor, additional forms of therapy can be employed to control residual tumor growth.

Impairment in pituitary function may be reversed, in some patients, after surgery. Therefore, patients undergoing surgery are routinely monitored in the intensive care unit for several days after transsphenoidal decompression. We recommend that all patients should be continued on glucocorticoid therapy until the second postoperative day, at which time the dosage can be tapered or stopped abruptly. Once steroids are discontinued, serum cortisol levels are measured twice a day, and the patient is carefully monitored for any signs or symptoms of glucocorticoid deficiency *(1)*. As demonstrated by the patient under discussion, those with an intact pituitary-adrenal axis postoperatively will have high or high-normal serum cortisol levels, and several levels should be >15 µg/dL. Patients with equivocal (<10 µg/dL) or low (<5 µg/dL) levels should be restarted on physiologic

glucocorticoid therapy, particularly if they had symptoms. These patients can be tested later for further delineation of pituitary-adrenal function. In the authors' experience, most patients have high-normal serum cortisol levels within 24–36 h after discontinuing glucocorticoid therapy. As an alternative approach to rapid discontinuation of glucocorticoid therapy, steroids may be tapered slowly over several weeks, and then the patient's pituitary-adrenal axis should be tested. Although both approaches are reasonable, we favor the former method because it avoids the confounding effects of longer steroid therapy on evaluating the remaining pituitary function as well as the unnecessary use of medication with potential side effects.

The remainder of pituitary function should be assessed a few weeks after the episode. In our patient, this was done 4 wk after surgery and showed normalization of adrenal and gonadal functions. Growth hormone deficiency is the most commonly observed abnormality in patients with pituitary macroadenomas with or without apoplexy *(1,7)*. Current evidence indicates that physiologic replacement with GH is clinically beneficial.

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CASE #4: METASTASIS TO PITUITARY

Case Presentation

A 55-yr-old man presented to the neurology service with, a 2-d history of diplopia and headaches. Diplopia occurred primarily while the patient was looking sideways, although it was also reported on looking up. He had been unable to drive because of the new symptoms. The headaches came on gradually and were predominantly frontal and throbbing in nature. He had been previously healthy until approximately 2–3 mo prior to admission when he noted progressive tiredness and fatigue for no apparent reason. On further questioning, he also complained about diminished libido and potency for 2–3 mo prior to the onset of fatigue. He was reported by his wife to be more cold intolerant and to have started snoring only a few weeks before his presentation. His appetite has diminished, although the weight has not changed significantly. Two weeks prior to the hospital admission, the patient noted increasing thirst, polyuria, and nocturia of 4–6 times every night. At that time, he saw his primary physician who noted that a random glucose level was 195 mg/dL, whereas the urinalysis was unremarkable. The patient was told to have "borderline diabetes" and was advised to decrease carbohydrate and calorie intake. His symptoms persisted despite strict adherence to the latter recommendations.

The past medical history was significant for an episode of hemoptysis, 8 mo prior to admission and was otherwise unremarkable. The latter episode resolved spontaneously and the patient did not pursue further medical care. The patient was involved in an automobile accident 1 yr before the current presentation and apparently lost consciousness for several hours because of a concussion. A CT scan of the head (with and without contrast) then was reported to be negative. The patient had a 45 pack/year history of cigarette smoking and drinks only socially. The family history was remarkable for a father who had type 2 diabetes mellitus, as well as hypertension.

On physical exam, the patient appeared well nourished, yet fatigued while the left eye was covered with a patch to avoid diplopia. Vital signs were unremarkable as was the skin exam. He had mild ptosis of the left eye, left abducens nerve palsy, and an 8 mm minimally reactive left pupil. He also had upper-outer quadrianopsia in the left eye and normal fundi. There was no gynecomastia and the genital exam was normal. Except for a delayed relaxation phase of deep tendon reflexes, the rest of the exam was negative.

Initial laboratory studies revealed the following values; Na$^+$: 147 mmol/L, K$^+$: 4.8 mmol/L, Cl$^-$: 95 mmol/L, HCO3$^-$; 21 mmol/L, BUN:64 mg/dL, Creatinine: 1.8 mg/dL, total Ca: 12.9 mg/dL, albumin 4.5 gm/dL, total protein 8.5 gm/dL, alkaline phosphatase 289 IU/L with normal AST and ALT, urine specific gravity of 1.002 with negative dip stick for protein and glucose. A chest X-ray showed a 3-cm mass in the right upper lobe of the lung. A bone scan showed multiple areas of increased activity in the spine as well as the right femur. A CT scan of the head and a subsequent MRI scan demonstrated an enhancing, large suprasellar mass invading the left cavernous sinus and compressing the optic chiasm as well as the optic tracts. The sella turcica was not grossly enlarged. Review of the CT scan done 1 yr ago when the patient had a concussion confirmed the negative study, particularly in the suprasellar region.

Endocrine evaluation included the following: A free thyroxine of 0.45 ng/dL (0.6–2.0), a TSH level of 1.4 mU/L, a serum prolactin level of 43 µg/L, an AM cortisol of 1.9 µg/dL, a plasma ACTH of 11 ng/L, a total testosterone of 55 ng/dL (300–1000), a free testosterone of 0.7 ng/dL (2.5–10), an LH of 0.7 IU/L, and an FSH of 1.2 IU/L. Plasma PTH level was 5 ng/L (10–55), whereas that of PTH-rP was 18 pmol/L (normal : <5).

The patient was given iv saline and dexamethasone (6 mg every 6 h) and phenytoin for seizure prophylaxis. Oral thyroxine was started and then subcutaneous insulin was added 2 d later when glycemic control worsened. Slight clinical improvement was noted a few days later. Cranial irradiation was initiated after biopsy of the lung mass confirmed lung malignancy. The patient refused further treatment of the lung cancer and died within 2 mo of diagnosis. Postmortem examination confirmed the diagnosis of metastatic lung cancer to the bone, liver, as well as the suprasellar region.

Discussion

Although this was an unusually complicated clinical history, the diagnosis was not difficult to make on admission. The patient presented with third and sixth cranial nerve palsies as a result of tumor invasion into the cavernous sinus. In addition, the patient had headaches, perhaps as a result of rapid increase in the size of the suprasellar mass. From an endocrine standpoint, the patient also had clinical history suggestive of hypopituitarism, diabetes mellitus, as well as partial diabetes insipidus. Diabetes insipidus appears to

be both central (partial loss of ADH secretion) as well as nephrogenic (secondary to hyper-calcemia). The increased serum calcium level in this patient, was predominantly humoral in nature resulting from secretion of PTH-rP by the lung cancer, although osseous metasta-sis could have been an additional contributing factor. Biopsy of the lung mass confirmed the diagnosis of lung cancer. Thus, the patient presented with a newly discovered supra-sellar mass associated with clinical and biochemical evidence for hypopituitarism and diabetes insipidus. The mass was relatively fast growing, as it was not noted on a previous CT scan done 1 yr earlier for a different reason. The findings of abnormal uptake in the bones associated with the increased alkaline phosphatase and otherwise normal liver function tests clearly suggest metastatic cancer. In view of the convincing nature of the clinical history as well as the biochemical findings, a biopsy of the suprasellar mass was not attempted. The presence of a relatively large suprasellar mass associated with normal-size sella suggest a rapidly expanding mass, rather than a benign, slowly growing tumor.

The clinical setting in this patient was somewhat typical of metastatic disease to the pituitary and suprasellar region *(1–6)*. The rapid onset of symptoms and the associated ocular dysmotility at presentation favored the diagnosis of metastatic cancer rather than a pituitary adenoma. The large size of the suprasellar mass, particularly because it was not detected a year earlier, provided further support for the presumptive diagnosis *(4)*. In this patient with osseous metastasis with a strong clinical history consistent with the diagnosis, biopsy of the sellar lesion is not necessary. Biopsy may be necessary if there were doubts about the diagnosis or if the patient had no known primary cancer *(1–6)*.

Breast, prostate, lung, and gastrointestinal malignancies are the most common pri-mary tumors that are documented to have metastasis to the pituitary and parasellar region. Of the malignancies that metastasize to the pituitary, breast cancer appears to be the most common, accounting for approximately 50%, while lung (20%), GI (5–10%) and pros-tate (5–10%), and others representing the rest. It is estimated that up to 9% of patients with metastatic breast cancer have pituitary and/or perisellar involvements *(1–6)*. Other areas of distant metastasis are often recognized before pituitary involvement can be demonstrated.

Metastasis to the pituitary fossa is often not limited to the anterior lobe, as it commonly involves the posterior lobe of the pituitary and the hypothalamus. Consequently, diabetes insipidus is diagnosed in 35–70% of these patients *(1–6)*. In contrast, diabetes insipidus is seen in <5% of patients with pituitary adenomas or other benign growths in the region. In fact, the most common cause of diabetes insipidus in patients with adenomas and even those with benign growths in the perisellar region is secondary to surgical procedures. Furthermore, and for the same reason, the hypopituitarism seen in patients with metasta-tic cancer is associated with mild hyperprolactinemia. Similarly, patients with metastatic tumors to the pituitary often (40–50%) present with cranial nerve palsies as a result of inva-sion of the cavernous sinuses *(1–6)*. A mass lesion is often, but not always, seen in such patients, especially those with lymphoproliferative diseases. In patients with pituitary/perisellar metastasis, the bony sella turcica is often eroded, although its size is usually normal despite the presence of an intrasellar or suprasellar mass lesion *(1,3,4)*.

Overall management of patients with metastasis depends to some degree on the type of malignancy and extent of metastasis. Immediate management involves the use of large doses of glucocorticoids (usually dexamethasone) and initiating external irradiation. In addition, thyroxine replacement therapy should be initiated whenever the diagnosis of

hypothyroidism is confirmed. Oral or intranasal DDAVP are the mainstay in the management of diabetes insipidus, once confirmed. Other hormone replacement therapy (sex steroids, GH) is not warranted until the overall prognosis is appreciated. Most patients with metastatic cancer to the pituitary die within 3–6 mo *(1–6)*.

Despite some of the distinctive features, it is, at times, difficult to differentiate metastatic cancer to the pituitary from benign pituitary adenomas. Features that would favor the diagnosis of metastatic tumor rather than an adenoma include: rapid onset of symptoms and progression over a short period of time, known history of a malignancy, cranial nerve palsies, and the presence of diabetes insipidus. As discussed earlier, diabetes insipidus is very unusual in patients with pituitary adenomas who have not had surgery. Thus, even in patients with no known malignancies, metastatic cancer should be seriously considered in the differential diagnosis of a pituitary mass, particularly in those presenting with diabetes insipidus or ocular nerve palsies. Repeat imaging studies over several weeks often shows progression of metastatic cancer.

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