



Steroid Induced Hyperglycemia

THE UNIVERSITY OF TEXAS
MD Anderson
Cancer Center
Department of Endocrine Neoplasia
and Hormonal Disorders
Making Cancer History[®]



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Due to their inhibitory effect on the immune system, glucocorticoids (corticosteroids) are an essential component of various chemotherapeutic regimens and are commonly used in treatment of leukemias and lymphomas [1]. In addition, they play an important role in cancer pain management [2] and prevention and treatment of chemotherapy induced nausea and vomiting [3]. However, due to their systemic effects, they are associated with an adverse impact on various organ systems [4]. Among these and of particular concern in cancer patients include uncontrolled hyperglycemia, increased risk of fractures, and systemic infections.

Prevalence of steroid induced hyperglycemia among various patient populations

Glucocorticoids are known to precipitate new-onset diabetes or exacerbate pre-existing diabetes. To date, there is sparse literature on the prevalence of steroid induced hyperglycemia (SIH) or steroid induced diabetes mellitus (SDM), specifically among cancer patients. In patients treated with glucocorticoid therapy, the odds ratio of development of Type 2 DM has been reported from 1.36-2.31 [5]. Another study in non-cancer population evaluating patients receiving high doses of corticosteroids documented hyperglycemia in 64% of patients with multiple hyperglycemic episodes occurring in 52% of patients [6]. At MD Anderson Cancer Center, in patients with Acute Lymphocytic Leukemia (ALL) treated with induction chemotherapy which included high dose dexamethasone, 37% were noted to have hyperglycemia, while 7% had a previous diagnosis of diabetes [7]. In another study evaluating children with ALL, overt hyperglycemia, was seen in up to 56% of children receiving induction chemotherapy [8]. The true incidence of SIH is difficult to diagnose given the prevalence of undiagnosed Type 2 Diabetes in many patients. And while steroids play an important role in causing hy-

perglycemia in cancer patients, other contributing factors include infection, decreased activity, parental and enteral nutrition, and emotional stress.

Definition of steroid induced hyperglycemia and indications for screening

Various studies use the standard definition for the diagnosis of diabetes to define SIH as a fasting glucose ≥ 126 mg/dL or at least 2 random values ≥ 200 mg/dL [7, 8]. Hemoglobin A1c (HbA1c) has not been validated in the use of SIH diagnosis as it is not indicated for monitoring of short term hyperglycemia; however, if elevated, it can be useful in the diagnosis of previously unidentified Type 2 DM, if the patient has normal red cell turnover, absence of hemoglobinopathies, or recent blood transfusion [9]. The American Diabetes Association (ADA) Standards of Medical Care in Diabetes guidelines recommend glucose monitoring in all patients without known diabetes who receive high-dose glucocorticoid therapy [10].

Mechanism of how steroids cause hyperglycemia

Steroids cause hyperglycemia through direct stimulation of enzymes in the hepatic gluconeogenesis pathway. Furthermore, they increase peripheral insulin resistance resulting in decreased glucose uptake by muscle and adipose tissue.

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(Thosani, continued)

Preclinical studies have demonstrated that steroids affect both β cell function and mass. For example, in mice, dexamethasone has been shown to induce direct apoptosis of β cells [11]. T

Rationale and Goals for Treatment

Hyperglycemia due to steroid therapy is correlated with worse disease-specific outcomes and greater risk of progression to diabetes. A study done at MD Anderson in patients with ALL found shorter remission, increased risk for complicated infections, and increase in overall mortality for patients with untreated hyperglycemia during induction chemotherapy[7]. Subsequently, a randomized controlled trial done by our group did not show improvement in clinical outcomes of patients despite improved glycemic control, though the study was limited by significant baseline differences among the control and intervention arm[12].

Currently, there are no clear guidelines delineating when therapy should be initiated and what agents are most effective. Thus, the decision to initiate treatment rests on the clinical presentation of the patient, and the prognosis of the cancer or other comorbid conditions. For outpatients and inpatients, therapy is generally initiated when 2 random glucose measurements are ≥ 200 mg/dL and the choice of treatment depends on the dose and duration of steroid therapy. The consensus guidelines from American Association of Clinical Endocrinology (AACE) and ADA recommend glucose targets of 140 mg/dL to 180 mg/dL in critically ill patients and 100 mg/dL to 180 mg/dL for patients admitted to general medical-surgical wards[13]. For cancer patients with a poor prognosis and shorter survival, higher glucose ranges are permissible with a goal to prevent symptomatic hyperglycemia and avoid hypoglycemia.

Treatment options for SIH

The initial consideration for therapy includes a diet low in carbohydrates and processed sugars, which may be difficult in cancer patients with anorexia, cachexia, and/or nausea in whom limiting food choices may not be an option. For patients on tube feed therapy, lower carbohydrate containing formulas such as Diabetisource can be used to help improve glycemia. In patients receiving parenteral nutrition therapy, regular insulin can be added into TPN typically starting at an insulin: carbohydrate ratio of 1 unit:8 grams dextrose and titrating according to glycemic response.

The use of oral agents to control hyperglycemia in cancer patients can be challenging due to the adverse effects, duration of action, and co-existing contraindications. Metformin, which combats insulin resistance, is frequently used but can cause nausea and diarrhea and does not specifically target the postprandial rise of glucose seen with steroid therapy. Also, it is contraindicated in patients with renal and liver failure due to the increased risk of lactic acidosis. Sulfonylureas have to be used with caution in cancer patients as there is a significant risk for hypoglycemia if patient has poor appetite or skips meals. Non-sulfonylurea secretagogues, which are

only taken with meals, can help control postprandial hyperglycemia; however, their use is limited due to cost. Thiazolidinediones have a significant longer onset of action, which makes them ineffective for short term control of hyperglycemia with steroid therapy; additionally, side effects of weight gain, edema, decrease in bone mineral density [14] and reported association with bladder carcinoma[15], limit their use in cancer patients.

DPP-IV inhibitors have a moderate effect on postprandial glucose and are generally well tolerated with minimal side effects. GLP-1 agonists have been studied in both preclinical and clinical models for treatment of steroid induced hyperglycemia, with some promising results. In a mouse model, Zhao et al., showed that a single subcutaneous dose of exenatide improved glycemia in oral glucose tolerance test after dexamethasone administration[16]. In humans treated with high dose oral prednisolone, treatment with exenatide reduced hyperglycemia during a mixed meal challenge [17]. For both DPP-IV inhibitors and GLP-1 agonists, postmarketing case reports suggest an increased risk of acute pancreatitis and pancreatic cancer with this agent, which raises concern about their use in the cancer population[18].

In most patients with steroid induced hyperglycemia, insulin therapy provides optimum glycemic control which can be adapted to the variability of the patient's clinical scenario. In the intensive care setting, insulin infusion is commonly used to achieve glycemic targets. For patients who are in the non-ICU setting, subcutaneous insulin distributed as basal and bolus regimen is effective in managing steroid induced hyperglycemia.

While there are no clear guidelines for the dosing and distribution of insulin therapy in patients receiving glucocorticoids, a recent study comparing basal/bolus regimen as compared to regular insulin sliding scale in patients receiving high dose dexamethasone showed that the former regimen was more effective in achieving glycemic targets in cancer patients[19]. Though there was no effect in length of stay or infection rates among these groups, three patients in the sliding scale group developed diabetic ketoacidosis or hyperosmolar hyperglycemia. The authors initiated insulin therapy at 0.66 units/kg which was titrated up to 1.2 units/kg/day without any evidence of hypoglycemia. In a retrospective chart review of leukemia patients seen at our institution who received Dexamethasone 40 mg daily during chemotherapy, we noticed an improvement in glycemic control when initiating insulin therapy at 1.2 units/kg. Severe hypoglycemia (glucose <40 mg/dL) was not observed in any patients and only 6% of patient days were noted to have glucose values <70 mg/dL with no adverse events (data not yet published). Another analog insulin which has proven effective with steroids is NPH. In a pilot study done in 20 patients with cystic fibrosis related diabetes receiving high dose methylprednisone, who were treated with basal glargine and premeal lispro, improvement in glycemic control was noted with NPH insulin dosing concomitant with methylprednisone administration[20].

(Continued on Page 3)

Upcoming Events

ThyCa Conference 2013. 16th International Thyroid Cancer Survivors' Conference September 27-29, 2013. Philadelphia, PA. (www.thyca.org)

American Society for Bone and Mineral Research (ASBMR) 2013 Annual Meeting. Oct 12-15, 2013. Baltimore, MD. (www.asbmr.org)

83rd Annual Meeting of the American Thyroid Association October 16-20, 2013. San Juan, Puerto Rico (www.thyroid.org)

Pediatric Endocrine Society PES 2014 May 3-6, 2014, Vancouver, Canada. (www.lwpes.org)

American Association of Clinical Endocrinologists (AACE) 23rd Annual Meeting and Clinical Congress May 14-18, 2014 Las Vegas, NV. (www.aace.com)

American Society of Clinical Oncologists (ASCO) Annual Meeting 2014. May 30-June 3, 2014. Chicago, IL. (<http://chicago2014.asco.org/>)

American Diabetes Association (ADA) 74th Scientific Sessions. June 13-17, 2014. San Francisco, CA. (www.scientificsessions.diabetes.org)

ICE/ENDO: The International Congress of Endocrinology?The Endocrine Society Annual Meeting 2014. June 15-18, 2014. San Francisco, CA. (www.endo-society.org)



(Thosani, continued)

Long term outcome of steroid hyperglycemia

There is no data on the long term outcome of steroid induced hyperglycemia. Prospective studies are needed to evaluate the lingering effect of steroids on glucose metabolism, and to determine which therapeutic agents are most effective in controlling hyperglycemia while minimizing side effects in cancer patients.

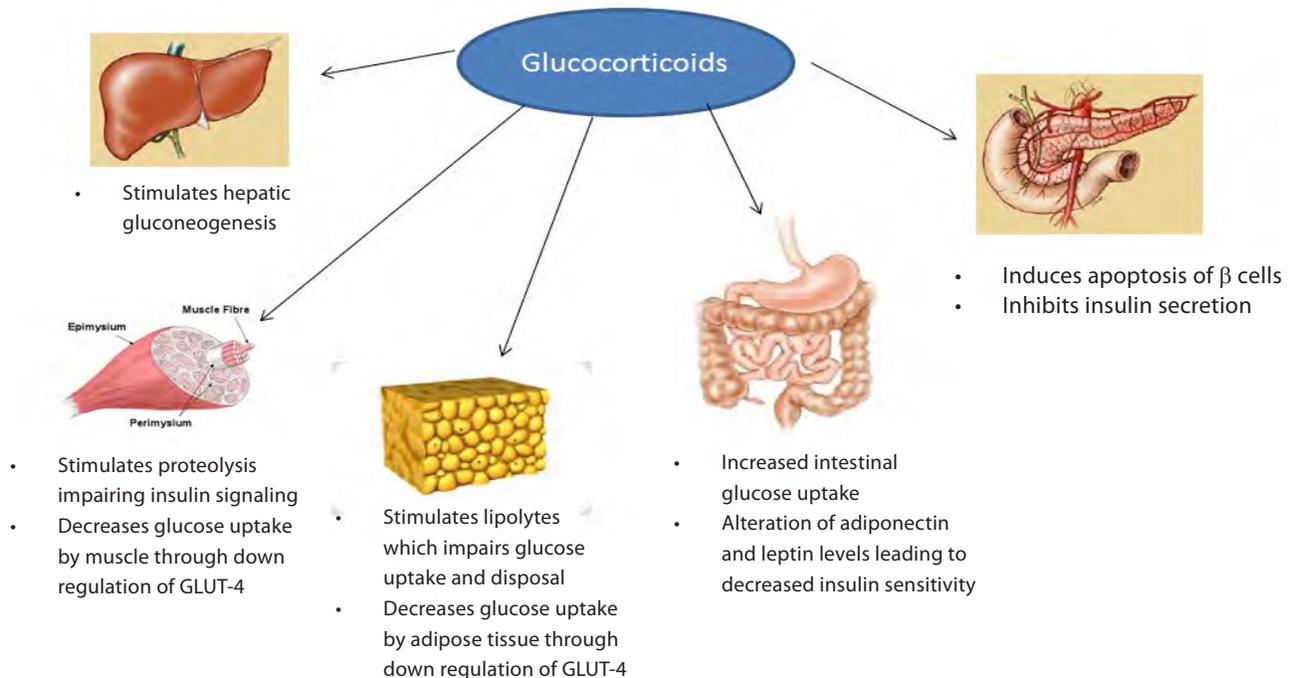
Acknowledgements: I would like to thank Victor Lavis, MD for his critical review and contributions to this manuscript.

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Figure 1



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Website: <http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/endocrine-neoplasia-and-hormonal-disorders/index>.

Sialendoscopy: Treatment for Salivary Gland Dysfunction Following Radioiodine Therapy



Stephen Y. Lai, M.D., Ph.D., FACS, Associate Professor, Department of Head and Neck Surgery

Radioactive iodine-131 (RAI) is frequently used to ablate remnant thyroid tissue in patients who have had a thyroidectomy for the treatment of thyroid cancer. The use of RAI has been described as a single most important adjuvant treatment for ensuring a favorable outcome for disease-free survival. However, the use of radioactive iodine is associated with significant side effects. With regard to the head and neck, these side effects include

sialadenitis, xerostomia, dysguesia (altered taste sensation), facial palsy, stomatitis, oral candidiasis and the potential development of salivary gland neoplasms. These side effects can have a significant effect on a patient's quality of life.

The most common of these side effects is the development of sialadenitis and xerostomia which can occur early or late following RAI treatment. While RAI preferentially targets thyroid cells, salivary gland cells and salivary duct cells also absorb RAI. This can lead to decreased saliva production and stenosis of salivary ducts. Approximately 80% of saliva is generated by the major salivary glands, which include the parotid, submandibular and sublingual glands. The parotid gland is located on the side of the face and has a duct (Figure 1: Stensen's duct) that enters the oral cavity and the level of the second maxillary molar on each buccal surface. The submandibular gland empties into the mouth under the tongue through Wharton's duct (Figure 2) on each side of the frenulum. The sublingual gland has 15-20 small ducts (Figure 3: Bartholin's ducts) that open into the floor of the mouth. The parotid gland tends to be more susceptible to RAI damage. Additionally, RAI causes more damage to the salivary gland ducts than external beam radiation therapy, which causes more salivary gland cell injury.

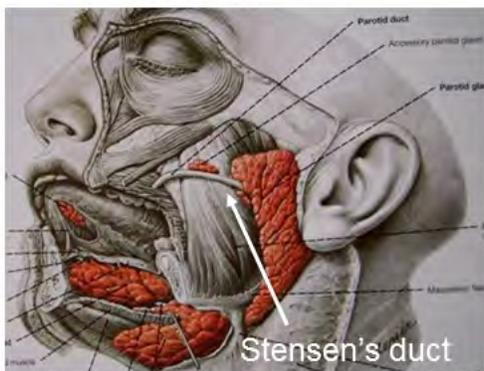


Figure 1

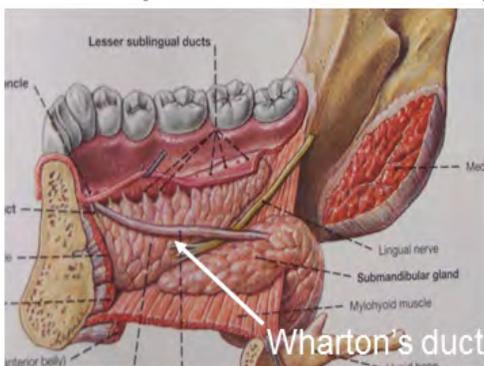


Figure 2

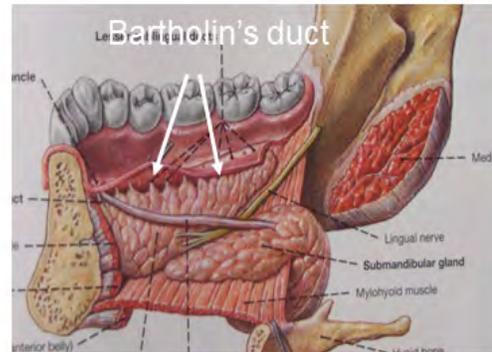


Figure 3

Approximately 10 to 60% of patients treated with RAI report acute or chronic saliva dysfunction related symptoms. Patients treated with RAI frequently complained of oral discomfort/pain, increased rate of dental caries and oral infection, dysphagia, decreased nutritional intake and consequently reduced body weight. The likelihood of developing salivary gland related side effects from RAI therapy are related to cumulative dose received. The onset of these symptoms may be immediate or several years following treatment. Conservative management of sialadenitis typically involved adequate hydration, external massage, warm compresses and sialogogues (agents that stimulate saliva production). More aggressive treatment may involve the use of systemic steroids to reduce inflammation or cholinergic medications to try to stimulate saliva production. Unfortunately, these approaches do not often provide satisfactory relief.

In the early 1990s, endoscopic equipment was developed to allow clinicians to evaluate salivary gland ducts that may only be 2-3 mm in diameter. A semi-rigid endoscope has been created that allows for visualization of the salivary duct as well as irrigation and instrumentation (Figure 4: sialendoscope). Sialendoscopy was initially developed to address salivary gland stones (sialoliths), which most commonly occur in the submandibular gland. Forceps and basket devices have been developed to retrieve stones and thus avoid a surgical procedure for the removal of an affected gland. Sialendoscopy has also been used to diagnosis and treat other disorders of the salivary glands, including recurrent parotitis of childhood and autoimmune disorders such as Sjogren's syndrome.

RAI-treated patients with sialadenitis and xerostomia may also be examined and treated with sialendoscopy. This is performed in the operating room as an outpatient procedure. Patients are intubated through the nose in order to leave the oral cavity widely accessible. The opening to the duct of the affected gland is then examined and dilated. The opening of the duct in the oral cavity is frequently narrowed following RAI therapy. Once the sialendoscopy is introduced into the duct, the duct can be examined and irrigated with saline. Typically, the duct of an RAI-treated patient is narrower and paler than untreated subjects. The hydraulic pressure opens the entire duct system and also helps to wash out mucus and debris (Figure 5 – Intraoperative findings). Specific segments of duct that are narrowed can be physically dilated with the endoscope or with a balloon. The duct can also be irrigated with steroid solution to reduce inflammation reducing the side effects associated with systemic doses of steroids. Finally, a stent can be temporarily placed in the parotid duct and secured to the lining of the oral cavity. The stent is usually left in place for two weeks and removed during the post-operative clinic visit. For each patient, the affected glands are serially examined during the procedure.

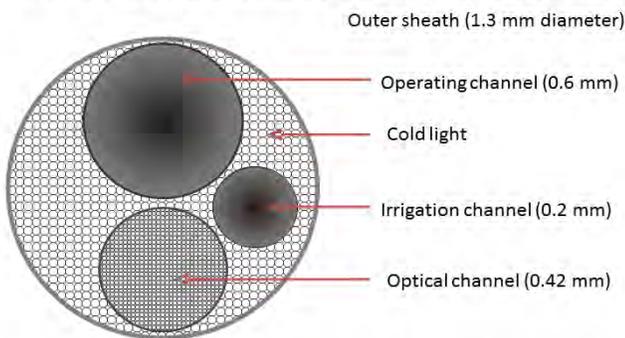
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Figure 4

All-in-one Sialendoscope: Cross-section



Sialendoscopy: Intraoperative Findings

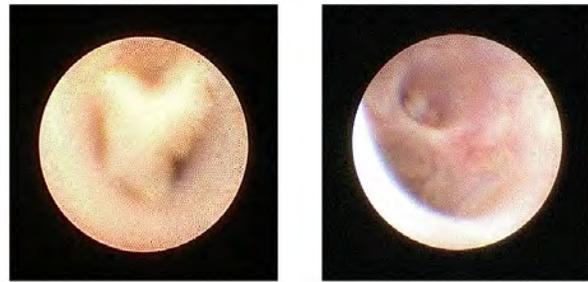


Figure 5

we see with sialadenitis and/or xerostomia related to RAI treatment do not do well with conservative management. These patients elect to have the sialendoscopy procedure. Patients have tolerated the procedure very well and there have been no major complications or issues. The great majority of our patients have reported improvement of their symptoms. We find that there seems to be more improvement of the duct-related issues (e.g., pain and swelling) than xerostomia. This may be because sialendoscopy can open narrowed salivary gland ducts, but does not help injured salivary gland cells. We are continuing to collect data regarding patient symptoms, length of time for symptom relief and saliva production. We will formally report this experience in the clinical literature soon.

Summary

The use of RAI is very effective in the treatment of patients with thyroid cancer. However, significant oral side effect, including sialadenitis and xerostomia, may occur. When patients do not find relief with conservative measures, sialendoscopy may improve these symptoms through dilation and irrigation of the salivary gland ducts.

We have been studying our experience with sialendoscopy for patients treated with RAI. We have found that approximately half of the patients that

For a complete list of reference, please contact Charles Stava at cstava@mdanderson.org.

Thyroid Nodule Clinic



Do you need a resource for the evaluation of a thyroid nodule?

Thyroid nodules are fairly common, representing the most common endocrine problem in the United States, but effective evaluation is extremely important to rule out thyroid cancer.

Dr. Naifa Busaidy, Director of the Thyroid Nodule Clinic at MD Anderson Cancer Center says, "The clinic serves as a resource for our physicians and all patients with thyroid nodules. We want to be a part of your team in providing an exceptional experience for the community physician and their adult and pediatric patients."

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All patients receive within one day:

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- Thyroid ultrasound
- Thyroid biopsy, if needed
- Multidisciplinary conference to discuss treatment options, if needed.

The Thyroid Nodule Clinic is located inside the Endocrine Center at The University of Texas MD Anderson Cancer Center at 1515 Holcombe Blvd in Houston, Texas.

For more information or to refer a patient for an appointment:

New Patient Referral Coordinators: 713-563-4400, and 713-792-5410 for patients under 18 years of age.

Physician to Physician Referrals: 713-792-2841

Online Referrals: <https://my.mdanderson.org/>

The Thyroid Cancer Survivorship Clinic



The Department of Endocrine Neoplasia and Hormonal Disorders is proud to feature the Thyroid Cancer Survivorship Clinic at The University of Texas MD Anderson Cancer Center. The mission of the Thyroid Cancer Survivorship Program is to address the outcomes of thyroid cancer and its therapy, and improve survivors' health and quality of life through integrated programs in patient care, research, prevention and education.

A Specialty-trained dedicated nurse practitioner and Endocrinologist are here to monitor cancer survivors for recurrence of thyroid cancer. Additionally, our team works closely with other specialized physicians and nurses to look for and manage late effects related to thyroid cancer and its therapies. We are uniquely able to coordinate care related to speech and swallowing problems, bone and heart health, dry mouth, tearing, and dental complications, as well as fatigue.

Finally, an important mission of our Thyroid Cancer Survivorship Program is to ensure that all of our patients are receiving adequate cancer prevention screening for all malignancies, whether at MD Anderson or in the community.

To refer a patient, please call our New Patient Referral Coordinators at 713-563-4400. For physician to physician referrals, please call 713-792-2841.



Case Files From The Department: Hypophysitis Due to Ipilimumab Therapy for Metastatic Melanoma

Steven G. Waguespack, MD, F.A.AP., F.A.C.E., Associate Professor and Deputy Department Chair, Department of Endocrine Neoplasia and Hormonal Disorders

A 64-year-old man with a stage IV metastatic melanoma presented for further evaluation of possible hypophysitis. He had been receiving therapy with ipilimumab (Yervoy®) and one week after his third ipilimumab infusion, he developed severe headaches followed by profound fatigue, decreased exercise tolerance, decreased appetite, and cold intolerance. Three weeks after the last ipilimumab infusion, he was found to have extremely low free T4 and TSH levels, which prompted an endocrinology consultation. Additional testing, including a low dose cosyntropin stimulation test, confirmed central hypothyroidism, central adrenal insufficiency, and hypogonadotropic hypogonadism. A pituitary MRI (Figure 1) showed new enlargement of the pituitary gland, and the diagnosis of ipilimumab-induced hypophysitis was confirmed. The patient began routine testosterone, glucocorticoid, and levothyroxine replacement therapy with a dramatic improvement in his well-being. The pituitary size returned to baseline two months after diagnosis (Figure 2).

Ipilimumab is a novel immunotherapy that was FDA-approved in 2011 for the treatment of unresectable or metastatic melanoma and is being investigated in other malignancies. It is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody that up-regulates the immune system. As an unintended consequence, immune-mediated endocrinopathies can occur, including hypophysitis, thyroiditis, and rarely primary adrenal insufficiency. Patients receiving ipilimumab should be routinely monitored for these acquired endocrinopathies during treatment. Hypophysitis typically presents with headaches and sign/symptoms of multiple anterior pituitary hormone deficiencies. After diagnosis, routine hormone replacement therapy should be initiated, and based upon our anecdotal clinical experience, high-dose steroids are typically not required. Pituitary function should be intermittently evaluated because recovery can occur, although the natural history and long-term outcomes of ipilimumab-induced hypophysitis remain largely unknown.

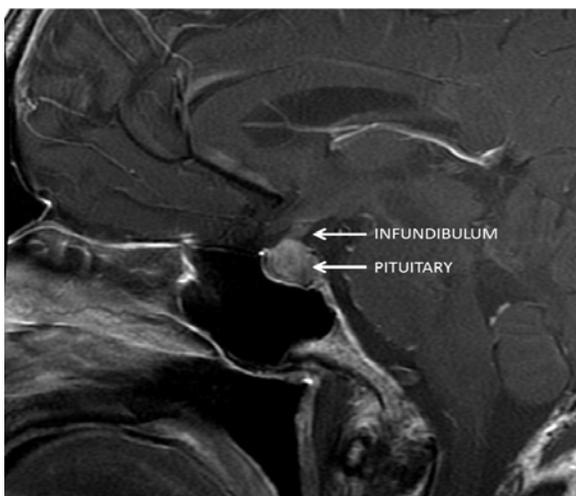


Figure 1

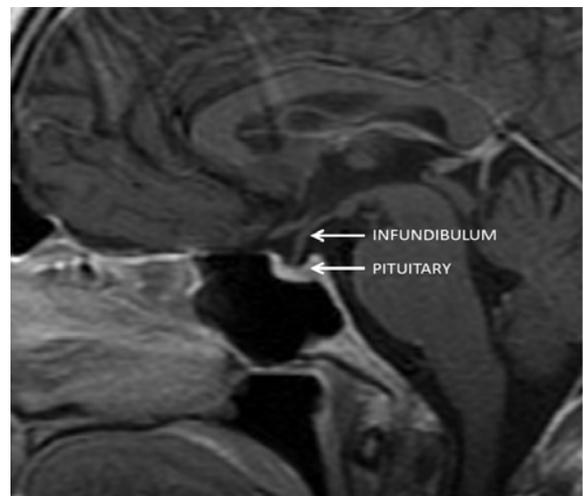


Figure 2

Notes from the Endocrine Faculty Team

Recognitions:

• Congratulations to Dr. Camilo Jimenez-Vasquez for being appointed as co-chair of the International Society for Pheochromocytoma and Paraganglioma Research Support (PRESSOR)

Publications:

- Chae YK, **Hu MI**, Katz RL, Chavez-Macgregor M, Haluska P, Meric-Bernstam F, Gonzalez-Angulo AM, Melhem-Bertrandt A. Two Birds with One Stone: Octreotide Treatment for Acromegaly and Breast Cancer. *J Clin Oncol*. 2013 Jun 24 [Epub ahead of print].
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Presentations:

The following were presented at the American Society of Clinical Oncologists' (ASCO) Annual '13 Meeting from May 30 to June 3, 2013, in Chicago IL:

- Devine CE, Hernandez M, **Busaidy NL**, **Waguespack SG**, **Ying AK**, **Habra MA**, **Thosani S**, **Hu MI**, **Cabanillas ME**. Is 2nd line targeted therapy beneficial in patients with differentiated thyroid cancer (DTC) after 1st line sorafenib (SOR) failure?: The team's research is focused on efficacy of molecular targeted therapies in advanced differentiated thyroid cancer, especially salvage therapy after first line sorafenib failure. They have demonstrated that patients who fail first line sorafenib will continue to respond to salvage TKIs despite similar mechanisms of action. Their study is the first to report overall survival in patients treated with first line sorafenib and in patients receiving multiple TKIs.
- **Cabanillas ME**, Holsinger FC, Sturgis EM, **Habra MA**, Davies MA, Munsell MF, French J, **Busaidy NL**, **Hu MI**, **Sherman SI**. Pharmacodynamic study of neoadjuvant vemurafenib (VEM) in patients (pts) with BRAF mutated, locally advanced papillary thyroid cancer (PTC). This was to announce that the team has initiated the study to determine the efficacy of vemurafenib (VEM) in patients with BRAF-mutated PTC.
- **Hu MI**, Glezerman I, Leboulleux S, et al. Denosumab for the Treatment of Bisphosphonate-refractory Hypercalcemia of Malignancy (HCM)
- **Sherman SI**, Cohen EE, Schoffski P, Elisei R, Schlumberger M, Wirth LJ, Mangeshkar M, Aftab DT, Clary DO, Brose MS. Efficacy of cabozantinib (Cabo) in medullary thyroid cancer (MTC) patients with RAS or RET mutations: Results from a phase 3 study.
- Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK, **Sherman SI**, Smith JWA, Chung J, Siedentop H, Molnar I, Schlumberger M. Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The phase 3 DECISION trial.
- Wilky BA, Ahmed SR, Ball DW, Rudek MA, Nelkin B, Cosgrove D, Gong J, Finkelstein D, Zahurak M, Janku F, O'Connor A, Markus S, Carducci MA, **Sherman SI**, Kurzrock R, Zinner R, Azad NS. A phase I study of combination therapy with pazopanib, a VEGF/PDGFR/raf inhibitor, and GSK-1120212, a MEK inhibitor, in advanced solid tumors with expansion cohorts in differentiated thyroid carcinoma, cholangiocarcinoma and soft tissue sarcoma.

The following were presented at The Endocrine Society's (ENDO) 95th Annual Meeting and Expo13 from June 15 to June 18, 2013, in San Francisco, CA:

- Carhill AA, Litofsky DG, **Sherman SI**. "Unique Characteristics and outcomes of patients diagnosed with both primary thyroid and primary renal cell carcinoma"
- Dadu D, **Hu MI**, **Habra MA**, **Waguespack SG**, **Ying AK**, **Busaidy NL**, **Cabanillas ME**. Salvage therapy with tyrosine kinase inhibitors (TKIs) for differentiated thyroid carcinoma (DTC) after first line sorafenib failure.
- Dadu R, **Waguespack SG**, **Cabanillas ME**. Should presence of RAS mutation change management?
- Ali SK, Dadu R, Lu C, Grubbs E, Blevins D, **Cabanillas ME**. Peculiar Presentation of Papillary Thyroid Cancer.
- Shawa H, **Habra MA**. Adrenal Ganglioneuroma.
- Deniz F, **Habra MA**. HDL changes with mitotane therapy. • **Habra MA**. Incidental pituitary microadenomas in ectopic Cushing's patients: Collaborative project with Cleveland Clinic. • **Jimenez-Vasquez C**. Honorary session for the Endocrine Society Fellows Workshop: "How I got here? A personal journey"
- **Sherman SI**. Thyroid Cancer Year in Review
- **Waguespack SG**. The Patient with a Neuroendocrine Tumor: When is Genetic Testing Recommended?

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