Management of patients with thyroid cancer does not end when the medical signs of disease have disappeared. Physical, psychological and day-to-day adjustments have to be made by many patients, similar to adjustments made by other cancer survivors. Therefore, Mayo Clinic has created the thyroid cancer survivorship program. The program is designed for patients with well-differentiated thyroid cancer who have completed curative-intent treatment. Eligible patients are seen in a nurse practitioner-led survivorship clinic.

Michele M. Merten, APRN, C.N.P., D.N.P., with Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic’s campus in Rochester, Minnesota, says: “We founded our thyroid cancer survivorship program in April 2017 in response to two publications: the 2006 report *From Cancer Patient to Cancer Survivor: Lost in Transition*; and the 2015 publication *Cancer Program Standards: Ensuring Patient-Centered Care*.

“As part of the survivorship visit, patients receive a survivorship care plan (SCP), which is an individualized plan summarizing the patient’s treatment (such as surgery, radioactive iodine or percutaneous ethanol injection), cancer staging, thyroid hormone replacement goals, potential short- and long-term side effects from treatment, and an outline regarding expected future follow-up. The SCP also documents the care team, which includes the patient’s primary care provider, surgeon, endocrinologist and endocrine nurse practitioner.

“Health promotion is reviewed with the patient in regard to limiting alcohol use, abstaining from tobacco, being physically active and aiming for a healthy weight. Resources for achieving these goals are also discussed and reviewed with patients, and may include the Mayo Clinic Cancer Education Center, the YMCA Livestrong Program, and information on the American Cancer Society, which can help offset costs incurred by patients with cancer.”

Mabel Ryder, M.D., with Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, comments: “As many patients with well-differentiated thyroid cancer tend to do well clinically following surgery with or without radioactive iodine, these patients are followed in Endocrinology instead of Medical Oncology. As a result, many patients with well-differentiated thyroid cancer were not receiving survivorship support or resources prior to implementing the SCP. At one point or another, many patients have
been told they have the ‘good cancer.’

“After delivery of the SCP in a survivorship visit along with a review of their laboratory tests and imaging studies, many patients have voiced that although they have been told they have the ‘good cancer,’ they still have fears of recurrence and uncertainties about the future. Others have expressed feeling unvalidated in seeking cancer resources as they have the ‘good cancer.’”

Merten adds: “Receiving the SCP with resources validates their diagnosis and empowers these patients to move forward in their cancer journey and lessens their uncertainty — something we hope to measure in a future study. At the end of the visit, patients receive two copies of their SCP (one for them and one to share with their primary care provider), with a third copy scanned into the electronic health record. Data taken during the six-month pilot following implementation of survivorship care plans in April 2017 demonstrated that those patients nearer to diagnosis required more time in a face-to-face visit, compared with those further out from diagnosis and treatment. During the six-month pilot, 84 percent of eligible patients received an SCP.”

It has taken a team effort to successfully identify patients eligible for an SCP, as these patients are not seen in an oncology practice and are intermixed in the scheduling of patients with other thyroid diseases.

Marius N. Stan, M.D., with Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, explains: “Initially, our scheduling office and desk staff worked meticulously to assist in identifying eligible patients. As another real-time means to identify eligible patients, endocrinologists seeing patients can order a future appointment in the thyroid cancer survivorship program clinic. Once patients are identified and scheduled in a survivorship appointment type, an automatically generated message is sent to our nursing staff, who then begin the pre-visit manual preparation of populating the SCP with the patient-specific information.

“Our institution has recently transitioned to a new electronic health record. Our next phase will be automating this process further through that record.”

For more information


Hypertriglyceridemic Pancreatitis

Severe hypertriglyceridemia is the third most common cause for acute pancreatitis, and has been estimated to account for nearly 9 percent of patients with acute pancreatitis. Vinaya Simha, M.B.B.S., M.D., with Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic’s campus in Rochester, Minnesota, says: “Limited evidence suggests that hypertriglyceridemic pancreatitis is more severe than other forms of acute pancreatitis and that the severity depends on the degree of hypertriglyceridemia. While this is not established, it is quite clear that the risk of pancreatitis increases with higher serum triglyceride (TG) levels.

“While the risk of acute pancreatitis in the general population is about 0.5 to 1 percent, and about 5 percent in people with alcoholism, the risk increases to 10 percent in those with serum TG above 1,000 mg/dL. The risk increases further, to above 50 percent, when serum TG is greater than 5,000 mg/dL. Hypertriglyceridemic pancreatitis is unlikely when serum TG is below 1,000 mg/dL, and in a large study of people with acute pancreatitis, the median TG level at presentation was around 2,600 mg/dL. It is, however, important to recognize that even extreme elevations of serum TG can occur as an epiphenomenon in patients with other forms of acute pancreatitis as well.”

Kristen M. Gonzales, M.D., a clinical fellow with Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, explains: “The pathogenesis of hypertriglyceridemic pancreatitis is not clear, but likely involves free fatty acid-mediated cellular damage. Large TG-rich lipoprotein particles, primarily chylomicrons, impede capillary circulation and cause ischemic damage to pancreatic acinar cells. Damaged cells release lipase and other enzymes into the interstitium, leading to TG hydrolysis and free fatty acid release. Free fatty acid aggravates cellular damage through
a variety of mechanisms, including endothelial damage, vascular leak, mitochondrial toxicity, platelet aggregation and activation of coagulation cascade.”

Maria (Daniela) D. Hurtado Andrade, M.D., Ph.D., a clinical fellow with Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, adds: “Homozygous deficiency of lipoprotein lipase causing familial chylomicronemia syndrome is the most common primary monogenic disorder responsible for hypertriglyceridemic pancreatitis. Many other genetic defects involving lipoprotein lipase-mediated TG hydrolysis, such as mutations in apolipoproteins C-II and A-V, LMF1, and GPIHBP1, also have been described in a few pedigrees. However, these are extremely rare disorders, including lipoprotein lipase deficiency, which has an estimated prevalence of one in a million. Secondary exacerbating factors in patients with an underlying lipid disorder, often polygenic, are more commonly responsible for hypertriglyceridemic pancreatitis. It is therefore very important to seek and address these secondary causes for elevated TG, which include uncontrolled diabetes, alcohol use, weight gain, and high intake of saturated fats and refined carbohydrates. Drug-induced hypertriglyceridemia is another important cause for acute pancreatitis. The list of offending agents includes estrogen, retinoic acid derivatives, sirolimus, L-asparaginase, capetabidine, protease inhibitors and propofol.”

Tiffany M. Cortes, M.D., a clinical fellow with Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic’s campus in Minnesota, highlights: “Treatment of hypertriglyceridemic pancreatitis, similar to other forms of acute pancreatitis, primarily involves intravenous hydration and other supportive measures, adequate analgesia, and fasting. The NPO state not only helps decrease pancreatic secretion and inflammation but also decreases further generation of chylomicrons. Pharmacotherapy to lower serum TG with fibrates is unlikely to be beneficial in the initial stages, and attention has focused on other measures to achieve this. Therapeutic plasma exchange is clearly effective in rapidly decreasing serum TG by nearly 60 to 80 percent, but it is not clear if this results in significant clinical benefit.

Small uncontrolled studies and retrospective analysis have shown only minimal improvement in scores assessing pancreatitis severity with no change in mortality or complications. Similarly, a randomized controlled trial showed no benefit of high-volume hemofiltration, which reduced serum TG to below 500 mg/dL in less than 12 hours, when compared with intravenous (IV) insulin and low molecular weight heparin. In fact there was a higher incidence of organ failure in the hemofiltration group with no difference in mortality, local complications or length of stay.”

Dr. Simha adds: “IV insulin infusion is an effective but underutilized intervention to reduce serum TG. Insulin is not only an activator of lipoprotein lipase but also suppresses free fatty acid release, thus limiting further generation of TG-rich lipoproteins from the liver. It is also the optimal therapy for hyperglycemia and should clearly be the treatment of choice for patients with hypertriglyceridemic pancreatitis secondary to uncontrolled diabetes.

“Drs. Gonzales, Hurtado Andrade, Cortes and I retrospectively reviewed the clinical course of 94 adult patients with hypertriglyceridemic pancreatitis admitted to Mayo Clinic in Rochester, Minnesota, from 2001-2016, to gain insight into the role of IV insulin therapy. Sixty-four patients received IV insulin infusion. Nine patients were additionally treated with plasma exchange therapy and 21 patients received only conservative treatment. Plasma exchange therapy was associated with a more rapid decline in serum TG as expected, but there was no difference in the length of hospital stay or overall complications between IV insulin and plasma exchange therapy. Baseline TG and pancreatitis severity were comparable between the two groups. Of the 64 patients who received IV insulin, nine did not have diabetes. Serum TG declined more rapidly in these patients, but overall clinical outcomes were similar.

“These limited observations on the benefits of IV insulin infusion in hypertriglyceridemic
pancreatitis need to be confirmed by larger clinical trials. The optimal dose and duration of IV insulin infusion also need to be determined. Meanwhile, it is important for clinicians to recognize IV insulin infusion as a safe, effective and economical therapeutic option compared with plasma exchange therapy when treating hypertriglyceridemic pancreatitis.”

Dr. Simha advises: “To prevent hypertriglyceridemic pancreatitis, it is reasonable to target fasting serum TG below 500 mg/dL, employing both pharmacologic and lifestyle interventions. Strict adherence to a diet low in saturated fat and refined carbohydrates is likely to be beneficial in most patients. There is considerable interest in novel TG-lowering therapies involving anti-sense oligonucleotides targeting apolipoprotein C-III and ANGPTL3-4, but their safety and long-term efficacy need to be established.”

Importance of Prompt Treatment for Severe Hypercortisolism Secondary to Ectopic Cushing Syndrome: Cases From the Endocrine Teaching Clinics

Case 1
A 69-year-old man presented to the nephrology clinic for evaluation of rapidly progressing hypertension, hypokalemia and lower extremity edema over one month. He had a 20-year history of well-controlled hypertension on two medications. Despite multiple medication adjustments prior to evaluation, his hypertension remained poorly controlled. An endocrine work-up for secondary hypertension was performed, excluding pheochromocytoma and primary aldosteronism. However, the serum cortisol concentration after an overnight 1-mg dexamethasone suppression test was markedly abnormal at 88 mcg/dL, prompting referral to Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic’s campus in Rochester, Minnesota. In addition to hypertension, the patient complained of a two-month history of progressive weakness, muscle mass decline, severe fatigue necessitating wheelchair use, difficulty concentrating and mood changes. During this time, he had an episode of severe cellulitis requiring hospitalization. On physical examination, the patient did not have moon facies, supraclavicular pads, dorsocervical pad or striae.

Prior to the Mayo Clinic evaluation, the patient had an abdominal CT scan performed for resistant hypertension. The scan revealed prostate enlargement with seminal vesicle invasion and multiple areas of intraperitoneal metastases (Figure 1). Prostate biopsy showed two distinct diagnoses of small cell carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
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<tr>
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<td>Fasting glucose, mg/dL</td>
<td>116</td>
<td>175</td>
<td>70-100</td>
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<td>8 a.m. cortisol, mcg/dL</td>
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<td>140</td>
<td>7-25</td>
</tr>
<tr>
<td>8 a.m. cortisol after 1-mg dexamethasone suppression, mcg/dL</td>
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<td>-</td>
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<tr>
<td>Corticotropin, pg/mL</td>
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<td>626</td>
<td>10-60</td>
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<tr>
<td>24-hour urine-free cortisol, mcg</td>
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<tr>
<td>Pituitary MRI</td>
<td>No pituitary mass seen</td>
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Table. Laboratory studies confirm severe ACTH-dependent hypercortisolism.

Figure 1. Contrast-enhanced CT scan sagittal image showing prostatic mass and multiple metastases (arrows).
and prostate adenocarcinoma. Further laboratory studies confirmed severe corticotropin (ACTH)–dependent hypercortisolism (Table, see page 4), which was determined to be due to ectopic ACTH production from prostate small cell carcinoma.

Given the unresectable nature of the prostatic small cell carcinoma and the severe clinical and biochemical presentation, the decision for bilateral adrenalectomy was made and performed seven days after the initial abnormal dexamethasone suppression result. Perioperatively, the patient was initiated on glucocorticoid and mineralocorticoid replacement therapy. Anticoagulation was started given the increased thrombosis risk, and antibacterial prophylaxis was initiated. One week after surgery, the patient was discharged to a skilled nursing facility to continue rehabilitation with a plan to follow up with Medical Oncology for management of the underlying malignancy.

**Case 2**

A 51-year-old woman presented to an outside facility for evaluation of acute abdominal pain. Imaging showed a 9.5-cm pancreatic mass, innumerable hepatic metastases and a bowel perforation. She had immediate abdominal surgery, and the intraoperative liver biopsy demonstrated a well-differentiated neuroendocrine tumor with positive immunohistochemical staining for gastrin. During her hospital stay, the patient was observed to have hyperglycemia, hypokalemia, muscle weakness and delirium. These new symptoms were concerning for abnormal cortisol secretion and further hormonal evaluation was performed. She was found to have severe hypercortisolism secondary to ACTH hypersecretion with a morning serum cortisol concentration of 140 mcg/dL (normal, 7 to 25 mcg/dL), serum ACTH concentration of 626 pg/mL (normal, 10 to 60 pg/mL) and 24-hour urine cortisol excretion of 4,360 mcg (normal, < 45 mcg). Her pituitary MRI showed no tumor.

The patient was transferred to Mayo Clinic for further management. Given the severity of her clinical and biochemical presentation as well as the unresectable nature of her tumor, the decision for bilateral adrenalectomy was made and was completed on the second day of her hospitalization. The patient’s hospital course was complicated by *Escherichia coli* bacteremia (identified on admission blood cultures), postoperative hemorrhage requiring another surgical intervention and continued delirium. She was discharged 10 days after bilateral adrenalectomy with a plan to follow up with Medical Oncology for management of the metastatic neuroendocrine tumor. A postoperative gallium-68 (Ga-68) DOTATATE PET scan demonstrated the diffuse nature of her hepatic metastases (Figure 2, see page 6).

**Discussion**

Ectopic ACTH production accounts for up to 20 percent of ACTH-dependent Cushing syndrome. Patients with ectopic ACTH secretion typically present with a much more rapid progression compared with those who have a pituitary-dependent Cushing syndrome. Frequently, patients with ectopic ACTH syndrome have muscle weakness, hypokalemia, hypertension and hyperglycemia that progresses over a short period of time. This rapid onset and marked production of ACTH, as well as the underlying malignancy, make significant weight gain and obesity less likely, which can cause a delay in the diagnosis of Cushing syndrome. Although these patients may lack some of the more obvious clinical features of cortisol excess, they are at high risk of life-threatening complications such as infections and thrombosis. In the journal *Cancer* in 2011, clinical investigators at The University of Texas MD Anderson Cancer Center reviewed a 30-year experience with outcomes of 43 patients with ectopic ACTH secretion and found that 10 patients had infections and six patients had symptomatic venous thromboembolism, with two who died from pulmonary embolism. Follow-up of these patients showed a mortality rate of 62.8 percent with a median overall survival of 32.2 months.
In an article from the National Institutes of Health published in *The Journal of Clinical Endocrinology and Metabolism* in 2000, investigators showed that all patients who had ectopic ACTH production and severe infection had 24-hour urine-free cortisol excretion of more than 500 mcg (with most more than 1,000 mcg). Although medical therapy can decrease cortisol secretion or block its effect, these agents may take weeks for maximum effect, and even then may not be fully effective in correcting the clinical impact of hypercortisolism. Whereas, as documented in a report from Mayo Clinic published in *Clinical Endocrinology* in 2008, bilateral adrenalectomy is a relatively safe, prompt and extremely effective treatment option for ACTH-dependent Cushing syndrome that cannot be cured by resecting the source of ACTH.

These cases illustrate the importance of prompt recognition, diagnosis and treatment of ectopic Cushing syndrome. Both patients had 24-hour urinary cortisol excretion of more than 1,000 mcg — reflecting an endocrine emergency that required immediate treatment. In cases where a complete and prompt resection of the ACTH-secreting neuroendocrine tumor is not possible, bilateral adrenalectomy should be considered.

**For more information**


Figure 2. Ga-68 DOTATATE PET scan showing the primary pancreatic neuroendocrine tumor and diffuse liver metastases.
Melanie L. Lyden, M.D., program director, Comprehensive Endocrine Surgery Fellowship at Mayo Clinic, Rochester, Minn., and Veljko Strajina, M.D., 2018 graduating Endocrine Surgery fellow. Dr. Strajina’s new appointment is in the Mayo Clinic Surgical Critical Care Fellowship at Mayo Clinic in Rochester, Minn.
Education Opportunities

Endocrine Update 2019
Feb. 11-15, 2019, at Fairmont Orchid, Kohala Coast, Big Island, Hawaii

Designed for endocrinologists and interested internists and surgeons, this annual Endocrine Update addresses gaps in medical knowledge and barriers in clinical practice to improve the outcomes of patients with endocrine and metabolic disorders. Topics span the full range of endocrinology through lectures, panel discussions, clinicopathologic sessions, clinical pearls sessions, informal breakfast roundtable discussions and small-group discussions with experts. Attendees have plenty of opportunity for interaction with course faculty selected for their expertise and clinical acumen. For more information, visit https://ce.mayo.edu/internal-medicine/content/21st-annual-endocrine-update-2019 or call 800-323-2688 (toll-free).

19th Annual Nutrition and Wellness in Health and Disease 2019
Sept. 22-24, 2019, at Swissotel, Chicago

This course is designed for physicians, advanced practice clinicians, dietitians, nurses, and health and wellness specialists. Many physicians and other clinicians have had limited training in nutrition, yet nutrition is key to the management of many endocrine disorders, such as diabetes, obesity and lipid disorders. In addition, physical activity and other healthy lifestyle behaviors are vital components in the promotion of health and the treatment of disease. Physicians, bariatric surgeons, psychologists, dietitians, and health and wellness specialists will discuss situations commonly encountered in the ambulatory setting. Topics include obesity in adults and children, individual and group-based weight management strategies, and dietary, behavioral change, activity, pharmacological and bariatric approaches. Additional topics will include nutrition and physical activity management of common obesity-associated conditions, plus physical activity and wellness topics for attendees and their patients. Presentations offer practical clinical management pearls, interactive case studies and panel discussions. For more information, visit https://ce.mayo.edu/internal-medicine/content/19th-annual-nutrition-wellness-health-and-disease-2019#group-tabs-node-course-default2 or call 800-323-2688 (toll-free). Course hashtag: #MayoNutrCME.