MAYO CLINIC

Endocrinology Update

Endocrinology News From Mayo Clinic Vol. 16, No. 2, 2021

OCTOBER 2021

In this issue

Diagnosis of a Rare Endocrine Disorder in Adulthood: A Case From the Endocrine Teaching Clinics

A 39-year-old man presented for evaluation of recurrent fractures associated with extensive fibrous dysplasia of bone. His initial fracture occurred at the tibia at age 10 with minimal trauma. During childhood he sustained multiple additional fractures, including:

- His right humerus on four occasions
- A traumatic right hip fracture in grade school requiring treatment with an intramedullary rod and interlocking screws

The patient's puberty started at age 12. Following high school, he noted a gradual increase in facial asymmetry with prominence of his forehead and left check. He denied prior chronic glucocorticoid or anti-epileptic medication use and had no history of nephrolithiasis or hearing loss. The patient had no other known medical comorbidities and was taking no medications.

Family history was notable for hypothyroidism in his mother and hyperthyroidism in his paternal grandfather. His brother and sister are healthy, and the patient has no children.

On examination, the patient had a BMI of 24.6 kg/m^2. He was alert and in no distress. He had prominence of the right brow and

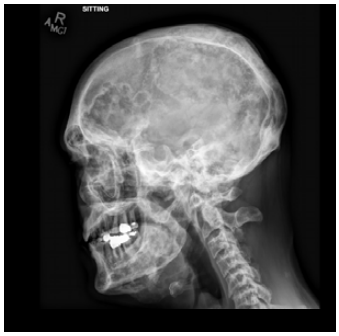

Figure 1. Polyostotic fibrous dysplasia involving the calvaria and mandible. Skeletal survey demonstrates extensive, advanced changes of polyostotic fibrous dysplasia involving multiple bones, including the calvaria and mandible. Typical imaging features include lucent intramedullary lesions with ground-glass opacity and mild bone expansion.

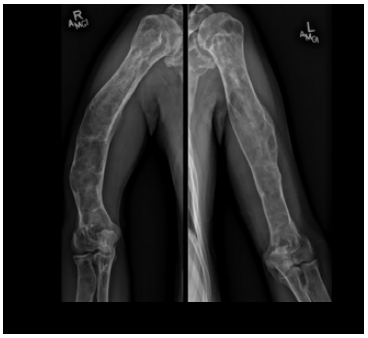

Figure 2. Polyostotic fibrous dysplasia involving the humeri. Skeletal survey demonstrates extensive, advanced changes of polyostotic fibrous dysplasia involving multiple bones, including the humeri.

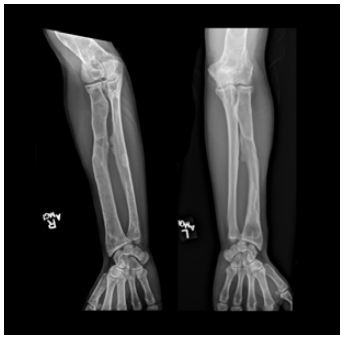

Figure 3. Polyostotic fibrous dysplasia involving the forearms. Skeletal survey demonstrates extensive, advanced changes of polyostotic fibrous dysplasia involving multiple bones, including the forearms.

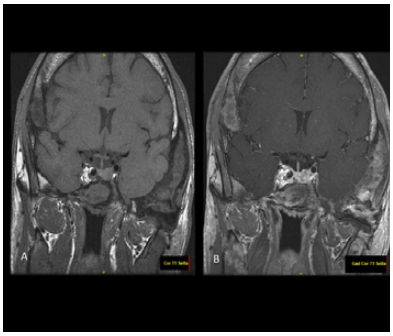

Figure 4. MRI pituitary without (A) and with (B) intravenous contrast. Post-contrast imaging demonstrates a focus with heterogeneous enhancement involving either the left side of the pituitary or the left side of the sella just lateral to the mildly displaced pituitary gland. This may represent a microadenoma, but the findings are not entirely characteristic of an adenoma and the changes may simply be lateral to the pituitary gland itself.

Peter J. Tebben, M.D.

left cheek and significant bony deformities of all extremities. No dental abnormalities, cushingoid features or tremors were noted.

The patient's reflexes were normal and symmetric. The thyroid gland was estimated at 25 grams with a prominent right thyroid lobe without discrete nodularity. The patient had a flat hyperpigmented brown circular lesion with irregular borders immediately distal to the right knee.

Laboratory studies (Table) identified elevated bone-specific alkaline phosphatase and fibroblast growth factor 23 (FGF23) as a result of extensive fibrous dysplasia. In addition, mild hyperthyroidism with negative thyrotropin receptor antibody and elevated insulin-like growth factor-1 (IGF-1) were present. An oral glucose suppression test confirmed growth hormone excess.

Serum creatinine	0.61	0.74-1.35 mg/dL
Serum calcium	10.0	8.6-10.0 mg/dL
Serum albumin	4.2	3.5-5.0 g/dL
Serum phosphorus	2.7	2.5-4.5 mg/dL
25-OH vitamin D	35	20-50 ng/mL
Bone-specific alkaline phosphatase	116	0-20 mcg/L
Fibroblast growth factor 23 (C-terminal assay)	398	< or = 180 RU/mL
Parathyroid hormone	48	15-65 pg/mL
1,25-(OH)2 vitamin D	32	18-64 pg/mL
24-hour urine calcium	115	< 250 mg/24 h
24-hour urine phosphorus	653	< 1100 mg/24 h
Thyroid-stimulating hormone	0.02	0.3-4.2 mIU/L
Free T4	1.8	0.9-1.7 ng/dL
Total T3	141	80-200 ng/dL
Thyrotropin receptor antibody	< 1.00	0.00-1.75 IU/L
Growth hormone (random)	3.24	0.01-0.97 ng/mL
Insulin-like growth factor-1 (IGF-1)	470	48-292 ng/mL
IGF-1 Z-score	> 3.00	-2.0-2.0 SD
AM cortisol	14	7-25 mcg/dL
Prolactin	8.6	4.0-15.2 ng/mL

Table. Laboratory work-up is significant for severe hyperthyroidism and elevated thyrotropin receptor antibody.

Skeletal survey identified diffuse polyostotic fibrous dysplasia (Figures 1, 2 and 3, page 1) . MRI pituitary demonstrated extensive changes of fibrous dysplasia involving the calvaria and skull base and a possible pituitary microadenoma (Figure 4, page 1).

Neck ultrasound revealed confluent nodularity in the right lobe with multiple small solid isoechoic nodules. Thyroid uptake and scan were consistent with autonomously functioning thyroid nodules without any cold nodules.

Dual-energy X-ray absorptiometry demonstrated:
- Left distal 1/3 radius Z-score of -1.5
- Left femoral neck Z-score of -1.5
- Left total hip Z-score of -1.3
- L1-L4 Z-score of -1.1

DIAGNOSIS: MCCUNE-ALBRIGHT SYNDROME

The patient was diagnosed with McCune-Albright syndrome (MAS), given his polyostotic fibrous dysplasia, café au lait macule (skin lesion distal to the right knee), growth hormone excess and autonomously functioning thyroid nodules.

"Remarkably, despite his severe imaging findings, our patient denied significant bone pain; we thus did not pursue treatment with a bisphosphonate. He received definitive hyperthyroidism treatment with 20 millicuries of I-131, which proved successful with subsequent development of hypothyroidism requiring levothyroxine replacement," says Peter J. Tebben, M.D., a pediatric endocrinologist at Mayo Clinic in Rochester, Minnesota. "We recommended medical therapy for acromegaly using intramuscular octreotide acetate depot injections, which eventually achieved normal IGF-1 levels."

DISCUSSION

MAS occurs due to post-zygotic gain of function alterations in the *GNAS* gene, which encodes the *a*-subunit of the Gs signaling protein. These mutations ultimately lead to constitutive cyclic apical membrane proteins signaling. Patients with *GNAS* variants have significant phenotypic variability ranging from asymptomatic monostotic fibrous dysplasia (FD) to severe bone disease with multiple endocrinopathies.

In *Orphanet Journal of Rare Diseases* in 2019, the FD/MAS international consortium defined MAS as the combination of FD (monostotic or polyostotic) and at least one extra-skeletal manifestation or the presence of at least two extra-skeletal features. Extra-skeletal manifestations include:

- Hyperpigmented skin lesions with irregular borders that typically do not cross the midline (café au lait macules)
- Gonadal involvement that may manifest as peripheral (gonadotropin-independent) precocious puberty, recurrent ovarian cysts in girls and women, or testicular lesions in boys and men
- Thyroid disease with multiple thyroid nodules that can be autonomously functioning
- Growth hormone excess
- Hypercortisolism in the neonatal period

"MAS is a clinical diagnosis and in cases of diagnostic uncertainty genetic testing can be pursued. It is important to note that because MAS is a mosaic disorder, affected tissue is required to identify variants in the *GNAS* gene," says Dr. Tebben. The estimated prevalence of MAS is between 1/100,000 and 1/1,000,000, as reported in research published in *Orphanet Journal of Rare Diseases* in 2008.

Polyostotic fibrous dysplasia
In MAS, FGF23 associated hypophosphatemia is a surrogate measure of the severity of fibrous dysplasia and renal phosphate wasting is a predictor of future fracture. Bone pain may be present due to FD itself or due to FGF23 mediated hypophosphatemia or both. To treat bone pain, it is essential to address hypophosphatemia if present and optimize the serum 25-hydroxyvitamin D concentration.

First line pharmacologic therapy for bone pain is acetaminophen. For persistent moderate to severe bone pain, an intravenous bisphosphonate such as pamidronate or zoledronate can be used. However, it is unclear if bisphosphonates reduce FD lesion size or progression.

Acromegaly
The prevalence of acromegaly in patients with MAS is 20% to 30%. In patients with MAS, the primary change underlying acromegaly is somatotroph hyperplasia involving the entire pituitary gland, with or without a somatotroph adenoma. Notably, acromegaly is typically associated with skull base FD, which carries an increased risk of hemorrhage due to increased vascularity.

A review of 112 patients with MAS and acromegaly published in *The Journal of Clinical Endocrinology & Metabolism* in 2014 reported that a pituitary adenoma was present in 54% of patients. Postoperative control was achieved in only three of 25 (12%) patients who received surgery: One received radiotherapy preoperatively and the other two received a large or total hypophysectomy.

Because somatotroph hyperplasia involves the entire pituitary gland and surgery can be technically challenging and generally requires performing a total hypophysectomy, medical therapy is preferred as first line treatment. Dopamine agonists may be minimally effective and somatostatin analogues (either as monotherapy or in combination with a dopamine agonist) were effective in lowering GH/IGF-1 in about one-third of patients. Pegvisomant has been reported to successfully normalize IGF-1 in most patients. Limited data suggests that pituitary radiation is often unsuccessful. Furthermore, malignant transformation of FD has been reported in a small number of cases, which also limits the utility of radiotherapy.

Thyrotoxicosis due to a toxic multinodular goiter
In MAS, patients can have a toxic multinodular goiter and there is an increase in deiodinase activity with an increase in the T3 to T4 ratio.

LEARNING POINTS

- Patients with fibrous dysplasia, whether monostotic or polyostotic, should be evaluated for possible endocrinopathy and MAS.
- Bone pain can be due to chronic FGF23 mediated hypophosphatemia or the fibrous dysplasia lesions. After correction of hypophosphatemia and vitamin D deficiency (if present) an intravenous bisphosphonate may be helpful for some with moderate to severe bone pain.
- In MAS, the primary etiology underlying acromegaly is somatotroph hyperplasia involving the entire pituitary gland, with or without a somatotroph adenoma. Therefore, medical therapy is preferred as first line treatment.

FOR MORE INFORMATION

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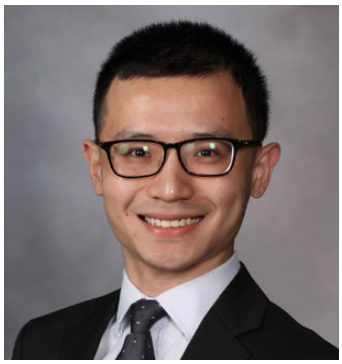
Jacob D. Kohlenberg, M.D.

Thymic Hyperplasia in Severe Graves' Hyperthyroidism: A Case From the Endocrine Teaching Clinics

A 58-year-old woman presented to the Endocrine Clinics at Mayo Clinic in Rochester, Minnesota, with symptoms of chest pressure, palpitations, insomnia and an unintentional weight loss of 20 kg over five months. She had a smoking history of 20

John C. Morris III, M.D.



Dingfeng Li, M.D.

pack-years. There was no known family history of thyroid dysfunction, autoimmune disease or malignancy.

Physical examination revealed a diffusely enlarged thyroid gland (estimated weight of 50 grams), irregularly irregular heartbeats with a resting rate of 150 beats per minute, fine tremors of her fingers and brisk deep tendon reflexes.

An electrocardiogram showed atrial fibrillation. The patient's laboratory work-up was significant for severe hyperthyroidism and elevated thyrotropin receptor antibody (Table 1, page 5).

Chest computerized tomography (CT) angiogram to rule out pulmonary embolism was obtained prior to the thyroid function test results, which incidentally revealed an anterior mediastinal mass (Figure A). The iodine 123 uptake scan demonstrated a symmetrically enlarged thyroid with diffuse homogeneous uptake (71% at 24 hours, reference range: 8% to 29%), without ectopic uptake in the chest.

Graves' disease was diagnosed and the patient was started on methimazole, 20 mg three times daily, and propranolol immediately. She was treated with radioactive iodine ablation (iodine 131, 20 millicuries) at seven-month follow-up. Her symptoms and thyroid function gradually improved. The patient eventually developed hypothyroidism and required thyroid hormone replacement at 15-month follow-up.

Repeat chest CT at three months and 12 months demonstrated significant decrease of the thymic volume (Figures B and C).

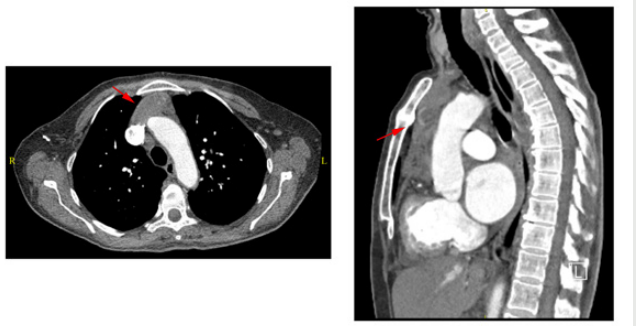


Figure A. CT scan of chest at initial presentation. Computerized tomography (CT) scan of the chest shows a homogenous anterior mediastinal mass (red arrows) at initial presentation.

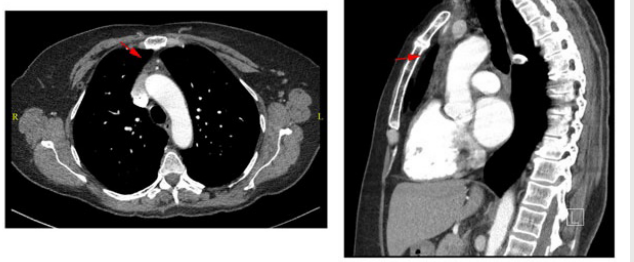


Figure B. CT scan of chest at three-month follow-up. Computerized tomography (CT) scan of the chest shows a homogenous anterior mediastinal mass (red arrows) at three-month follow-up.

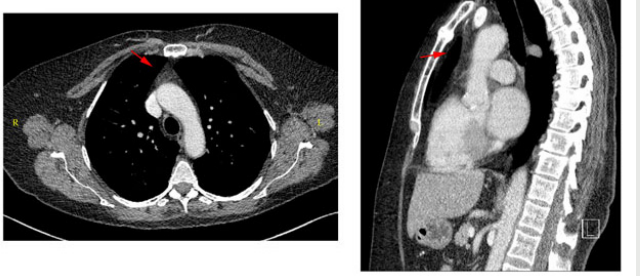


Figure C. CT scan of chest at 12-month follow-up. Computerized tomography (CT) scan of the chest shows a homogenous anterior mediastinal mass (red arrows) at 12-month follow-up.

DISCUSSION

First described by Dr. William Halsted in Transactions of the American Surgical Association in 1914, thymic hyperplasia in Graves' disease is not uncommon, although the true incidence is unclear because chest imaging is not routinely obtained in every patient who is newly diagnosed with Graves' disease. The pathogenesis is thought to be related to a direct trophic effect from excess thyroid hormones, as well as autoimmunity from thyrotropin receptor antibody, leading to increased proliferation of cortical epithelial cells and medullary lymphoid follicles.

When considering the etiology of an anterior mediastinal mass, the list of differential diagnoses is extensive (Table 2). Overall, in cases unrelated to thyroid disease, the risk of malignancy of an anterior mediastinal mass is reportedly as high as 59% in patients ages 20 to 40, and 30% in other age groups. Therefore, obtaining a tissue biopsy or diagnostic thymectomy is often warranted.

However, in the setting of untreated thyrotoxicosis, this intervention should be strictly avoided as it is associated with critical complications such as triggering thyroid storm and leading to morbidity and mortality. Therefore, it is recommended that, in the absence of suspicious radiographic features (that is, heterogeneous enhancement, invasion of surrounding structures, calcification), medical treatment of Graves' disease with the goal of euthyroidism should be the next step and biopsy or thymectomy should be deferred in the acute setting.

Thymic hyperplasia in Graves' disease is a benign condition and often reversible to various degrees with treatment. Various studies have reported a significant decrease (33%

to 90%) in thymic volume after successful treatment of hyperthyroidism using anti-thyroid drugs with a follow-up ranging from six weeks to two years. Therefore, a repeat chest image six months after achieving euthyroidism is recommended. If there is less than 50% regression of the mass, biopsy or thymectomy should be reconsidered to rule out malignancy.

KEY POINTS

- Thymic hyperplasia in Graves' disease is related to excess thyroid hormones and thyrotropin receptor antibody.
- It is a benign condition and usually improves after successful treatment of Graves' disease.
- Biopsy and thymectomy should be deferred in the setting of thyrotoxicosis and be reconsidered if thymus fails to regress on repeat imaging.

Laboratory data	At diagnosis	3-month follow-up	12-month follow-up	15-month follow-up	Reference range
Thyroid-stimulating hormone (mIU/L)	< 0.01	< 0.01	< 0.01	23.5	0.3-4.2
Free thyroxine (ng/dL)	> 7.7	1.8	1.4	0.5	0.9-1.7
Total triiodothyronine (ng/dL)	> 525	220	100	170	80-200
Thyrotropin receptor antibody (IU/L)	> 40	—	—	—	0.00-1.75

Table 1. Laboratory work-up is significant for severe hyperthyroidism and elevated thyrotropin receptor antibody.

Differential diagnosis	Subtype
Thymus	Thymoma Thymic cyst Thymic hyperplasia Thymic carcinoma
Lymphoma	—
Germ cell tumor	Teratoma or dermoid cyst Seminoma Nonseminoma: Yolk sac tumor Embryonal carcinoma Choriocarcinoma
Intrathoracic thyroid	Substernal goiter Ectopic thyroid tissue
Intrathoracic parathyroid	Parathyroid adenoma Ectopic parathyroid gland
Hemangioma Lipoma	— —
Liposarcoma	—
Fibroma	—
Fibrosarcoma	—
Foramen of Morgagni hernia	—

Table 2. Differential diagnosis of anterior mediastinal mass. When considering the etiology of an anterior mediastinal mass, the list of differential diagnoses is extensive.

Bariatric Surgery in Children and Adolescents at Mayo Clinic

Severe obesity is affecting increasing numbers of youth, leading to the emergence of conditions previously considered adult diseases, such as type 2 diabetes, hypertension, hyperlipidemia, obstructive sleep apnea, fatty liver disease, and bone and joint dysfunction during adolescence. Despite plateauing in the rates of childhood obesity overall, the prevalence of severe obesity is on the rise: Nearly 10% of 12- to 15-year-olds and 14% of 16- to 19-year-olds have severe obesity. Unfortunately, it is highly likely that obese children and adolescents will carry their obesity into adulthood.

As noted in research by Armstrong and others in *Pediatrics* in 2019, lifestyle modifications remain a cornerstone for weight reduction in all children with obesity. However, lifestyle modifications have only modest success, particularly in youth with severe obesity. The role of medications in achieving weight loss in adolescents with severe obesity still needs to be defined due to scarcity of data on short- and long-term efficacy of weight-loss medications in children.

In adults with obesity, bariatric surgery has been shown to be the most effective option to achieve weight loss and remission of several comorbid conditions. Recent studies in adolescents also demonstrate good efficacy of bariatric procedures (laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass) in achieving weight loss in adolescents with severe obesity.

Seema Kumar, M.D., chair of Pediatric Endocrinology and Metabolism at Mayo Clinic in Rochester, Minnesota, says, "Bariatric surgery in adolescents has been associated with remission or improvement of several obesity-related comorbidities, including type 2 diabetes, hypertension and dyslipidemia. In fact, bariatric surgery in adolescents leads to higher rates of resolution of type 2 diabetes and hypertension in comparison with this surgery in adults."

In view of the available data on weight loss and resolution of cardiovascular risk factors among adolescents, the American Society for Metabolic and Bariatric Surgery (ASMBS) and the American Academy of Pediatrics

Seema Kumar, M.D.

Todd A. Kellogg, M.D.

Bridget K. Biggs, Ph.D., L.P.

have developed more-recent guidelines that recommend bariatric surgery to be considered for youth with body mass indexes (BMIs) of 35 kg/m^2 or more with concurrent severe comorbid disease, or for those with BMIs of 40 kg/m^2 or more, even in the absence of any comorbid diseases. The guidelines, published in *Surgery for Obesity and Related Diseases* in 2018, no longer recommend using linear growth and Tanner staging to determine eligibility for surgery. The guidelines also suggest consideration of surgery in special cases such as in children with syndromic obesity, those with hypothalamic obesity and patients with limited decision-making capacity.

Todd A. Kellogg, M.D., Breast, Endocrine, Metabolic, and Gastrointestinal Surgery at Mayo Clinic in Rochester, Minnesota, elaborates: "Helping children and adolescents to manage their severe obesity through surgery should be viewed no differently than the treatment of other medical conditions with an operation. It's as safe as gallbladder surgery. It helps to level the playing field toward achieving the necessary weight loss and staving off chronic and debilitating weight-associated medical diseases, which then lead to a healthier lifestyle and improved quality of life."

Dr. Kumar continues: "It has been gratifying and extremely rewarding to see some of these adolescents come out of their shells after undergoing surgery."

Bridget K. Biggs, Ph.D., L.P., co-chair of Child and Adolescent Psychiatry and Psychology at Mayo Clinic in Rochester, Minnesota, notes: "I love seeing the young people in our program blossom in self-confidence with gradual successes in building a healthy lifestyle before and after surgery and witnessing the marked improvements in quality of life they experience, particularly after surgery."

The adolescent bariatric surgery program at Mayo Clinic in Rochester, Minnesota, is accredited by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program and staffed by a multidisciplinary team comprising Drs. Biggs, Kellogg, and Kumar and Rose J. Prissel, M.S., RDN, LD. Through this program, patients receive education and support to facilitate lifestyle modifications before surgery and receive close follow-up after surgery.

Weight regain remains a challenge in adolescents as in adults, and therefore close follow-up is necessary to achieve long-term efficacy. The team has used telemedicine widely to maintain contact with adolescents in the program both before and after surgery, particularly during the COVID-19 pandemic.

FOR MORE INFORMATION

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Immune Checkpoint-Induced Hypoparathyroidism: A Case From the Endocrine Teaching Clinics

The introduction of immune checkpoint inhibitor (ICI) drugs has revolutionized cancer therapy. The drugs target immune checkpoint molecules, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), that contribute to cancer pathogenesis. Immune checkpoints are closely involved in maintenance of immunological tolerance to self-antigens; ICIs have, thus, been associated with immune-related adverse events (irAEs). Endocrinopathies including hypothyroidism and hyperthyroidism, hypophysitis, primary adrenal insufficiency, and autoimmune diabetes mellitus are among the more commonly reported events. Hypoparathyroidism with ICI use is an exceedingly rare endocrine complication.

CASE PRESENTATION

A 76-year-old male presented to the emergency department with one-weeklong complaints of weakness, anorexia and confusion. He started a combination immunotherapy of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) seven months prior for widespread metastatic melanoma to the pericardium, lung, liver and lymph nodes. Two months after the initiation of this regimen, he developed irAEs of colitis and pneumonitis. His immunotherapy was put on hold. Approximately four months later, he was switched to nivolumab

monotherapy. He received two infusion cycles with the last dose given 28 days prior to our evaluation.

On presentation, the patient's physical examination was remarkable for a blood pressure of 93/48 mm Hg. Chovestek sign and Trousseau sign were not present. Laboratory test results from his initial evaluation in the emergency department included:

- Total serum calcium: 5.7 mg/dL on presentation; reference range 8.8 to 10.2 mg/dL
- Serum albumin: 3.0 g/dL on presentation; reference range 3.5 to 5.0 g/dL
- Serum phosphorus: 5.1 mg/dL on presentation; reference range 2.5 to 4.5 mg/dL
- Serum magnesium: 1.7 mg/dL on presentation; reference range 1.7 to 2.3 mg/dL
- Serum ionized calcium: 3.01 mg/dL on presentation; reference range 4.57 to 5.43 mg/dL
- Serum sodium: 118 mmol/L on presentation; reference range 135 to 145 mmol/L

An electrocardiogram was remarkable for prolonged QT corrected interval of 492 milliseconds. The patient was immediately treated with a total of 3 grams intravenous calcium gluconate and normal saline infusion.

Further work-up showed an undetectable serum parathyroid hormone (PTH < 6.0 pg/mL; reference range 15 to 65 pg/mL) and a normal serum total 25-hydroxyvitamin D of 31 ng/mL.

The patient was diagnosed with primary hypoparathyroidism. Notably, he denied any history of previous neck surgery or head and neck radiation. Anti-parathyroid antibody, for which a clinically available test is performed by radiobinding assay, previously recognized in some cases of autoimmune hypoparathyroidism, was undetectable in this case.

A review of the patient's record showed that calcium levels had been within the normal range until the index presentation, with a median total serum calcium of 9.3+/-0.23 mg/dL over a period of five years prior to any ICI therapy and median creatinine of 1.29+/-0.27 mg/dL. PTH was normal at 49 pg/mL six years prior to presentation (Figure).

Additional testing performed due to concerns for other endocrinopathies, particularly adrenal insufficiency due to noted hyponatremia, included a morning cortisol that was low at 2.0 mcg/dL (reference range 7 to 25 mcg/dL) and a serum ACTH that was inappropriately normal at 8.3 pg/mL (reference range 7.2 to 63 pg/mL). MRI of the brain did not reveal any pituitary or hypothalamic abnormalities. Both thyroid stimulating hormone and free T4 were normal at 2.9 mIU/L (reference range 0.3 to 4.2 mIU/L) and 1.1 ng/dL (reference range 0.9 to 1.7 ng/dL), respectively.

OUTCOME AND FOLLOW-UP

The patient was started on 500 mg of oral calcium carbonate (elemental calcium) three times daily and 1,000 IU of cholecalciferol daily, along with 0.25 mcg of calcitriol twice daily. His serum calcium level showed improvement over the course of three days. Hydrocortisone replacement was initiated with good clinical response in blood pressure, sodium levels and symptoms. After 22 days of starting this regimen, serum calcium was 8.1 mg/dL with serum albumin of 4.0 g/dL and a 24-hour urinary calcium of 198 mg every 24 hours.

DISCUSSION

"Given the lack of other associated causes of hypoparathyroidism, late age of onset and absence of other autoimmune polyglandular syndrome features — combined with the temporal relationship between ICI therapy and other associated irAEs including hypophysitis with secondary adrenal insufficiency — we believe this case illustrates hypoparathyroidism as a rare complication associated with ipilimumab and nivolumab therapy," says Robert A. Wermers, M.D., chair of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota.

"While this combination of drugs has been shown to improve progression-free survival in melanoma, it may be associated with an increase of irAEs compared with monotherapy. Moreover, endocrine complications present earlier, at 30 days, with combination therapy compared with 76 days for complication presentation in those treated with a single agent (ipilimumab)," Dr. Wermers notes.

The patient had also previously reported

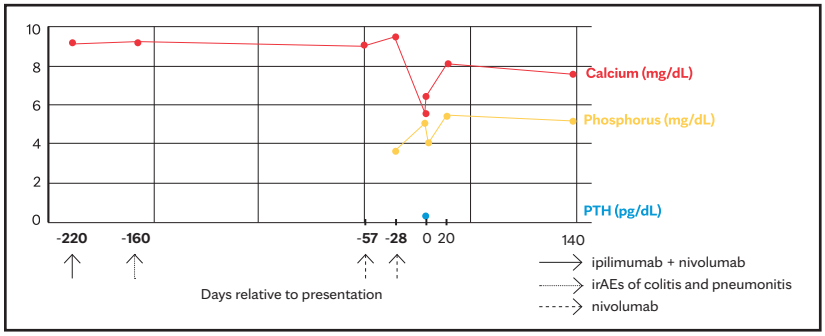

Figure. Serum calcium, phosphate and PTH levels relative to the ICI treatment regimen. PTH: parathyroid hormone; ICI: immune checkpoint inhibitor.

Robert A. Wermers, M.D.

Omar M. El Kawkgi, M.B., B.Ch., B.A.O.

irAEs (colitis and pneumonitis), which may be of significance as a predictor of developing additional irAEs. Whether or not this patient's course of combination therapy followed by nivolumab monotherapy created a cumulative toxicity effect is difficult to ascertain based on current literature.

"The mechanism of irAE-related hypoparathyroidism remains unclear, but it is postulated that autoantibodies may play a role," says Omar M. El Kawkgi, M.B., B.Ch., B.A.O., an Endocrinology, Diabetes, Metabolism, and Nutrition fellow, at Mayo Clinic in Minnesota. "Anti-parathyroid and activating calcium sensing receptor (CaSR) autoantibodies have been implicated in autoimmune hypoparathyroidism. Indeed, activating CaSR autoantibodies were detected in a patient with primary hypoparathyroidism receiving nivolumab.

"Anti-parathyroid antibodies have been described in patients with autoimmune endocrine conditions such as Addison's disease and Hashimoto's thyroiditis, as well as cases of idiopathic hypoparathyroidism and animal models of autoimmune hypoparathyroidism. Further research is needed to elucidate the role of these various antibodies and if ICI-associated hypoparathyroidism may be due to a destructive immune process as may occur in other endocrinopathies."

Unlike other irAEs, endocrinopathies often require lifelong treatment with permanent hormone replacement. The reasons for this difference are unclear. In this case, 77 days after ICI use, PTH remains undetectable and the patient continues to require 500 mg of elemental calcium three times daily and 0.25 mcg of calcitriol twice daily to maintain his serum calcium within a satisfactory range. Persistence of hypoparathyroidism despite discontinuation of ICI drugs has been previously recognized.

Dr. Wermers concludes: "In an era of novel immuno-oncology treatments, it is important to consider ICI blockade-mediated hypoparathyroidism in patients presenting with hypocalcemia. Particular attention may be needed for patients who received combination ICI and have had previous irAEs. Future studies should focus on understanding the mechanism of ICI-associated hypoparathyroidism, predicting factors and long-term outcomes with such events."

FOR MORE INFORMATION

El Kawkgi OM, et al. Hypoparathyroidism: An uncommon complication associated with immune checkpoint inhibitor therapy. *Mayo Clinic Proceedings: Innovations, Quality & Outcomes*. 2020;4:821.

2021 GRADUATING CLINICAL ENDOCRINOLOGY FELLOWS

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ENDOCRINE UPDATE 2022

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Mayo Clinic welcomes inquiries and referrals, and a request to a specific physician is not required to refer a patient.

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Endocrinology Update

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Cover Image:
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Endocrinology Update (MC5810-0821) is published by 200 First St. SW, Rochester, MN 55905. Periodicals postage paid at Rochester, Minn., and at additional mailing offices.

MC5810-0821