Title

A Case of Tertiary Hyperparathyroidism and Parathyromatosis

Journal

Proceedings of UCLA Health, 24(1)

Authors

Day, Andrew J.
Praw, Stephanie Smooke

Publication Date

2020-04-23

CLINICAL VIGNETTE

A Case of Tertiary Hyperparathyroidism and Parathyromatosis

Andrew J. Day, MD and Stephanie Smooke Praw, MD

Case

A 53-year-old male presented to Transplant Nephrology after five days of fatigue, dizziness, nausea, vomiting, and loss of appetite. He received a deceased donor renal transplant 6 weeks prior to this presentation. His past medical history was significant for end stage renal disease due to IgA nephropathy, nephrolithiasis, atrial fibrillation, and mood disorder. He also reported total parathyroidectomy with autotransplantation in the right forearm seven years prior at an outside hospital. The operation had been complicated by left vocal cord paresis. While in clinic, his serum calcium returned at 14.4 mg/dL (8.6-10.3) and he was directly admitted to the hospital. The patient was not taking exogenous calcium or calcitriol. Despite intravenous hydration, intravenous furosemide, intramuscular calcitonin, and cinacalcet, his serum calcium levels remained elevated. Further diagnostic evaluation was significant for elevated serum parathyroid (PTH) level of 900 pg/mL (normal 11-51). Nuclear medicine parathyroid scan revealed a focus of increased tracer uptake posterior to the inferior pole of the left thyroid lobe as well as another focus of increased tracer uptake in the right forearm. Ultrasound showed a 3.3 cm lobulated hypoechoic nodule posterior to the inferior pole of the left thyroid lobe. Additional ultrasonographic findings included multiple peri-centimeter thyroid nodules as well as prominent right level 2 cervical lymph nodes.

Given the inability to control serum calcium levels despite aggressive medical therapy, surgical intervention was recommended during his hospitalization. Because of his left vocal cord paralysis, he underwent a focused left side parathyroidectomy on hospital day 7. Intraoperative findings and pathology were consistent with parathyromatosis in addition to incidentally discovered metastatic papillary thyroid carcinoma. Following his operation, intravenous hydration was discontinued, and he was discharged on cinacalcet. He returned to the operating room two months later for total thyroidectomy, bilateral modified radical neck dissection, and left central neck dissection for further management of his metastatic papillary thyroid carcinoma. Following this operation, he received radioiodine remnant ablation. He is now 18 months from his hospitalization with calcium and parathyroid hormone levels elevated but reasonably controlled with cinacalcet. He has abnormal neck lymph nodes, suspicious for thyroid cancer, that are being closely monitored.

Discussion

Secondary hyperparathyroidism can be defined as increased PTH production and secretion in response to a biochemical abnormality caused by a condition external to the parathyroid glands. While there are many stimuli for parathyroid hormone release, secondary hyperparathyroidism is classically associated with chronic kidney disease. Progressive renal injury results in phosphate retention, elevated fibroblast growth factor 23 (FGF23) levels, decreased calcitriol production, and hypocalcemia—all of which contribute to the development of secondary hyperparathyroidism. Many of these biochemical abnormalities can be observed after a relatively mild reduction in glomerular filtration rate, though the prevalence of secondary hyperparathyroidism increases as kidney function declines.[1] Over time, this biochemical abnormality may be associated with parathyroid gland hypertrophy and hyperplasia.

Initially, elevated PTH levels are adaptive, and patients with mild to moderate renal insufficiency rarely have symptoms related to these biochemical abnormalities. As the disease progresses, hyperparathyroidism becomes associated with increased risk of metabolic bone disease, bone fracture, heterotopic calcification, parathyroid autonomy, and mortality. The phrase, Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) is now used to describe this clinical syndrome. CKD-MBD is a systemic disorder due to CKD that may include either one or a combination of the following: 1) Biochemical abnormalities of calcium, phosphorus, PTH, or vitamin D, 2) Abnormalities in bone turnover, mineralization, volume, linear growth, or strength, previously called renal osteodystrophy, and 3) Heterotopic calcification.[2] Management recommendations include routine assessment and monitoring of serum PTH, vitamin D, phosphate, and calcium levels in all patients with chronic renal dysfunction.[2,3] Although the frequency of monitoring and goal values may vary, it is important to maintain neutral phosphorus balance, adequate vitamin D supplementation, and controlling PTH levels to prevent progression to tertiary hyperparathyroidism while maintaining bone health.[1] Dietary phosphate restriction and oral phosphate binders can help achieve neutral phosphate balance. Medical management of PTH levels can include active vitamin D analogues, such as calcitriol, calcimimetics, such as cinacalcet, or a combination of the two.

Occasionally PTH levels cannot be kept in acceptable ranges with medical therapy. This severe form of hyperparathyroidism is often called refractory hyperparathyroidism. Refractory

hyperparathyroidism along with hypercalcemia suggests tertiary hyperparathyroidism. It is thought that prolonged stimulation of the parathyroid gland by chronic hypocalcemia, hyperphosphatemia, and calcitriol deficiency can lead to parathyroid autonomy. Anatomically, parathyroid gland autonomy is characterized by diffuse hyperplasia as well adenomatous transformation resulting in nodular and hyperplastic glands. These transformed cells may not respond appropriately to the usual suppressive stimuli. Tertiary hyperparathyroidism often becomes apparent after a patient undergoes renal transplantation.[1]

Surgery may be required for these most severe forms of hyperparathyroidism that cannot be controlled with medical therapy. Despite advances in medical therapy, a sizeable number of patients require surgery for refractory hyperparathyroidism.[4] Commonly accepted indications for parathyroidectomy include symptomatic or severe hypercalcemia or hyperphosphatemia, symptomatic bone disease or spontaneous fracture, calciphylaxis, and persistent hyperparathyroidism more than one year after renal transplantation.[1] The decision to proceed with parathyroidectomy for asymptomatic hyperparathyroidism prior to renal transplantation can be difficult with limited evidence to assist with decision-making. Hyperparathyroidism resolves in a majority of patients following renal transplantation, so parathyroidectomy is not routinely necessary in asymptomatic patients regardless of PTH levels. Some will develop severe, persistent hyperparathyroidism after transplantation. Persistent hyperparathyroidism can result in hypercalcemia, hypercalciuria, hypophosphatemia, and nephrolithiasis.[5] In addition, persistent hyperparathyroidism after transplantation has been associated with decreased graft function and increased mortality.[6] Because of these concerns, some recommend parathyroidectomy prior to transplant if PTH is >800 pg/mL despite medical therapy.[2]

When surgery is required to manage refractory hyperparathyroidism, subtotal or total parathyroidectomy with or without autotransplantation can be performed.[7-9] Cervical thymectomy and parathyroid tissue cryopreservation can also be utilized if possible. Postoperative complications of parathyroidectomy include recurrent laryngeal nerve injury, hypoparathyroidism, hematoma formation, and wound infection. After parathyroidectomy for tertiary hyperparathyroidism, patients are at increased risk for Hungry Bone Syndrome, characterized by hypocalcemia and hypophosphatemia. Persistent or recurrent parathyroid disease is common when surgery is performed in patients with end stage renal disease. This possibility should be discussed with patients prior to surgery. For this reason, routine monitoring of blood mineral levels after surgery is recommended.[2]

Parathyromatosis is a rare, serious cause of persistent hyperparathyroidism, occurring after parathyroid surgery. Patients with parathyromatosis usually have several nodules and/or nests of benign parathyroid tissue scattered in the neck and mediastinum. This was first described in 1975.[10] A review published in 2012 identified only 36 cases that met their inclusion criteria.[11] Two theories have been proposed regarding the pathogenesis of parathyromatosis.[12] One proposes parathyromatosis is the consequence of gland rupture and subsequent seeding of the surgical field during an operation. The second theory proposes embryological parathyroid rest tissue undergoes hyperplasia when exposed to physiological stimuli. Parathyromatosis appears to be more common in women than in men, most common in the 5th and 6th decade of life, and also more common in patients with end-stage renal disease when compared to those who do not.[11] Preoperative imaging does not appear to be helpful as parathyromatosis is most often diagnosed interoperatively.[11] Pathological review of tissue is important to help differentiate this from parathyroid carcinoma.[13] The disease appears to be unrelenting and treatment strategies rarely result in cure. A combination of surgical and medical therapy is usually required for disease control.[11]

This case illustrates the importance of monitoring mineral metabolism in patients with chronic kidney disease as well as the importance of appropriate management of hyperphosphatemia and PTH levels. Occasionally, despite improvements in the medical management of this condition, parathyroidectomy is needed for refractory hyperparathyroidism, and should be considered prior to renal transplantation. During surgery, care should be taken to avoid parathyroid gland rupture and seeding of the surgical field. This vignette also demonstrates the importance of routine monitoring after parathyroidectomy given the risk of both Hungry Bone Syndrome and persistent/recurrent disease. Parathyromatosis is a rare but serious disease that can be exceedingly difficult to manage.

REFERENCES

1. **Rosen CJ**, ed. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. Ames USA: John Wiley & Sons, Inc; 2013.
2. Erratum: Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*. 2017;7:1-59. *Kidney Int Suppl* (2011). 2017 Dec;7(3):e1. doi: 10.1016/j.kisu.2017.10.001. Epub 2017 Nov 17. PubMed PMID: 30681074; PubMed Central PMCID: PMC6341011.
3. **Eknoyan G, Levin A, Levin NW**. Bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42:1-201.
4. **Li S, Chen YW, Peng Y, Foley RN, St Peter WL**. Trends in parathyroidectomy rates in US hemodialysis patients from 1992 to 2007. *Am J Kidney Dis*. 2011 Apr;57(4):602-11. doi: 10.1053/j.ajkd.2010.10.041. Epub 2010 Dec 24. PubMed PMID: 21186072.
5. **Julian BA, Quarles LD, Niemann KM**. Musculoskeletal complications after renal transplantation: pathogenesis and treatment. *Am J Kidney Dis*. 1992 Feb;19(2):99-120. Review. PubMed PMID: 1739106.

6. **Pihlstrøm H, Dahle DO, Mjøen G, Pilz S, März W, Abedini S, Holme I, Fellström B, Jardine AG, Holdaas H**. Increased risk of all-cause mortality and renal graft loss in stable renal transplant recipients with hyperparathyroidism. *Transplantation*. 2015 Feb;99(2):351-9. doi: 10.1097/TP.0000000000000583. PubMed PMID: 25594550.
7. **Pitt SC, Sippel RS, Chen H**. Secondary and tertiary hyperparathyroidism, state of the art surgical management. *Surg Clin North Am*. 2009 Oct;89(5):1227-39. doi: 10.1016/j.suc.2009.06.011. Review. PubMed PMID: 19836494; PubMed Central PMCID: PMC2905047.
8. **Tang JA, Friedman J, Hwang MS, Salapatas AM, Bonzelaar LB, Friedman M**. Parathyroidectomy for tertiary hyperparathyroidism: A systematic review. *Am J Otolaryngol*. 2017 Sep - Oct;38(5):630-635. doi: 10.1016/j.amjoto.2017.06.009. Epub 2017 Jun 21. Review. PubMed PMID: 28735762.
9. **Anderson K Jr, Ruel E, Adam MA, Thomas S, Youngwirth L, Stang MT, Scheri RP, Roman SA, Sosa JA**. Subtotal vs. total parathyroidectomy with autotransplantation for patients with renal hyperparathyroidism have similar outcomes. *Am J Surg*. 2017 Nov;214(5):914-919. doi: 10.1016/j.amjsurg.2017.07.018. Epub 2017 Jul 17. PubMed PMID: 28736060.
10. **Palmer JA, Brown WA, Kerr WH, Rosen IB, Watters NA**. The surgical aspects of hyperparathyroidism. *Arch Surg*. 1975 Aug;110(8):1004-7. PubMed PMID: 1156145.
11. **Hage MP, Salti I, El-Hajj Fuleihan G**. Parathyromatosis: a rare yet problematic etiology of recurrent and persistent hyperparathyroidism. *Metabolism*. 2012 Jun;61(6):762-75. doi: 10.1016/j.metabol.2011.11.001. Epub 2012 Jan 4. Review. PubMed PMID: 22221828.
12. **Reddick RL, Costa JC, Marx SJ**. Parathyroid hyperplasia and parathyromatosis. *Lancet*. 1977 Mar 5;1(8010):549. PubMed PMID: 65648.
13. **Fernandez-Ranvier GG, Khanafshar E, Jensen K, Zarnegar R, Lee J, Kebebew E, Duh QY, Clark OH**. Parathyroid carcinoma, atypical parathyroid adenoma, or parathyromatosis? *Cancer*. 2007 Jul 15;110(2):255-64. PubMed PMID: 17559137.