Int J Biol Med Res.2015;6(4):5336-5340

Contents lists available at BioMedSciDirect Publications

International Journal of Biological & Medical Research

Journal homepage: www.biomedscidirect.com

Case report

An Uncommon Case of Persistent Hypercalcaemia following Parathyroid Surgery

Indrajit Talapatra, Ian Patrick Michael O'Connell

Department of Medicine and Endocrinology, Royal Albert Edward Infirmary, Wigan, WN12NN (UK)

ARTICLE INFO

Keywords:
Hypercalcaemia
Primary Hyperparathyroidism
Parathyroidectomy
Vitamin D deficiency
Cinacalcet

ABSTRACT

A 67 year old woman was referred by her GP for raised serum calcium and raised Parathyroid hormone (PTH) to the clinic in June 2011. The patient had high calcium with raised PTH for six years, since 2005, prior to been seen in the clinic. The patient's renal function was normal and was diagnosed with Primary Hyperparathyroidism. Urinary calcium over 24 hours was mildly elevated and there was no evidence of kidneys stones on imaging. However a DEXA scan showed evidence of osteoporosis. The patient's Vitamin D level was normal and she was referred to a tertiary hospital for Parathyroidectomy. However the patient's serum calcium and PTH levels continued to remain high despite Parathyroid surgery. Subsequently for failed Parathyroidectomy the patient underwent a CT scan of thorax which suggested the presence of an ectopic mediastinal Parathyroid adenoma. The patient was not thought to be suitable for thoracic surgery and hence kept under monitoring for her serum calcium. The patient's recent Vitamin D level was found to be low and was commenced on Vitamin D supplementation. The calcium level became quite high and Vitamin D supplementation had to be withheld briefly. The decision was taken to treat the patient later with low dose Vitamin D simultaneously with Cinacalcet.

Introduction

Primary hyperparathyroidism is present in approximately 1 in 500 people and occurs predominantly in post-menopausal women. The condition occurs in approximately 85% cases as adenoma, 14% cases as Parathyroid Hyperplasia and in 1% cases as Parathyroid Carcinoma (1) . Rarely it can occur as part of MEN (Multiple Endocrine Neoplasia) Type 1 and Type 2a and Familial Hyperparathyroidism. There is also often concomitant Vitamin D deficiency in Primary Hyperparathyroidism which needs to be replenished. Serum calcium is raised together with raised urinary calcium. Serum PTH should be >3pmol/l (N: 1.1-6.9 pmol/l). Approximately 20% patients will have PTH at the upper part of the normal range (2). Cinacalcet, a calcium sensing receptor agent, is now licensed for use in Primary Hyperparathyroidism. It decreases serum calcium but not urinary calcium. However the definitive treatment is in the form of Parathyroid surgery. Localization of abnormal Parathyroid glands with Ultrasound and 99m Tc-sestamibi scan is imperative before minimally invasive Parathyroidectomy. Parathyroid surgery is to be carried out by experienced Surgeons who carry out >20 operations per year and includes minimally invasive surgery for adenoma and Partial Parathyroidectomy in hyperplasia (2). The operation is successful in 95% cases. However in a small number of cases ectopic Parathyroid adenomas may be present and unless removed continue to cause persistent hypercalcaemia.

Case report

A 67 year old woman was referred to us by her General Practitioner with raised serum calcium and raised Parathyroid hormone (PTH). Her serum calcium adjusted for albumin was 2.66 mmol/l (N: 2.20-2.60) and PTH level was 12.2 pmol/l (N: 1.1-6.9). Her renal function was normal. The patient had low mood, some bone pain, constipation and mild abdominal pain. The patient had similar biochemical results in 2005 but was not followed up by any Consultant in our hospital since then. The initial diagnosis was Primary Hyperparathyroidism, but there was no previous urine test to exclude FHH (Familial Hypocalciuric Hypercalcaemia). Her urine calcium done at this stage was mildly increased at 7.78 mmol over 24 (N: 2.5-7.5 mmol/24 hours). An X ray KUB ruled out urinary stones. Her DEXA (Dual Energy Xray Absorbimetry) scan showed T score (<-2.5 indicates osteoporosis) of -3.0 at the mid left forearm, -3.7 at the distal left forearm and -3.1 at the total left forearm, -2.3 at L1-L4 and -1.1 at left femoral neck . Thus the patient had Primary Hyperparathyroidism with osteoporosis and had one criterion for referral for Parathyroid surgery. She was commenced on a bisphosphonate, Alendronic acid 70 mg once weekly,

Table 1 summarizes the patient's biochemical results at presentation and her results 6 years ago.

Table1: Patient's biochemical results at presentation in 2011 and earlier in 2005

* Corresponding Author : **Dr I Talapatra**
indra_tala@hotmail.com

Parathyroid hormone (N: 1.1-6.9 pmol/l)	2/6/2011 12.2	24/10/2005 13.86	21/10/2005 15.96	3/10/2005 11.29	21/09/2005	17/08/2005		
Ionized Calcium (N: 1.05-1.30 mmol/l)			Ionized Calcium: 1.39	Ionized Calcium: 1.36				
Calcium adjusted for albumin (N: 2.2-2.6 mmol/l)	2.66	2.80	2.60	2.56	2.55	2.50		
Phosphate (0.87-1.45 mmol/l)	0.70	1.00	1.01	0.73	0.83	0.87		
Magnesium (0.7-1.0 mmol/l)	0.87	0.93	0.85					
Alkaline Phosphatase (N: 30-130 U/l)	77	137	137	140	130			

The patient's Vitamin D was normal at 67.7 nmol/l (N: 50-125). The patient continued to have high serum calcium and was referred to a tertiary centre for Parathyroidectomy where in June 2012 the patient had Parathyroid surgery following imaging of her Parathyroid glands. She was followed up regularly following parathyroid surgery but continued to have elevated serum calcium and PTH levels. Her blood results pre-surgery and following Parathyroidectomy are summarized in Table2.

Table2: Patients biochemical results prior to surgery and following Parathyroidectomy

	7/3/12 (prior to parathyroidectomy)	23/11/12 (after parathyroidectomy)	19/6/13	04/12/13	28/11/14	15/12/14	16/2/15	18/5/15
PTH	9.7		9.8	11.4	9.6			
Calcium	2.64	2.67	2.65	2.72	2.89	2.67	2.44	2.63
Calcium adjusted for albumin	2.75	2.78	2.78	2.76	2.93	2.74	2.59	2.80
Phosphate	0.69	0.73	0.88	0.92	0.84	0.83	0.75	0.83
Albumin	44	44	42	44	44	42	42	41
Magnesium	0.87							
Alkaline Phosphatase	74	66	87	75	82	81	94	94

A subsequent scan suggested an ectopic mediastinal Parathyroid adenoma in the left aorto-pulmonary window. Repeat DEXA scan showed osteoporosis (T score of middle-third of left forearm was -3.5, and of left hip was -1.2) and the patient remained on weekly oral Alendronic acid. The options thought of were medical treatment with Cinacalcet, possible radiologically assisted embolization or thoracic surgery. The Thoracic Surgeons were not keen on video assisted thoracic surgery (VATS) and a sternotomy was thought to be a large incision for a small lesion. However it was thought that the intervention would be influenced by her serum calcium level and bone density. She remained under medical follow up. A recent blood test showed her Vitamin D to be low at 33.3 nmol/l and was commenced on Vitamin D supplement (Cholecalciferol) 20,000 units every week. It has been agreed that if her serum calcium reaches close to 3mmol/l, she would be treated simultaneously with Cinacalcet. Her latest blood results showed a raised adjusted serum calcium of 2.89 mmol/l, normal phosphate level of 0.91 mmol/l and normal alkaline phosphatase of 98 U/l. Her latest Vitamin D level was 47.5 nmol/l. Her recent DEXA scan from April 2015 showed osteoporosis at the wrist with a T score of -3.7 at the distal one-third left forearm; the other T score figures were -1.7 at lumbar spine, -1.3 at left femoral neck and -1.2 at the total left hip. The patient was maintained on weekly Alendronic acid. The Vitamin D supplementation was withheld for a few days followed by its recommencement at a lower dose of 800 IU/day with a plan to simultaneously treat the patient with Cinacalcet..

Discussion

Table 3 summarizing the proposed guidelines in asymptomatic patients for Parathyroidectomy:

Criteria	NIH Guidelines fom 1990	NIH Guidelines from 2002	NIH Guidelines from 2008
Serum Calcium above the upper limit of normal range	1.0-1.6 mg/dl	1.0 mg/dl	1.0mg/dl
Urine Calcium over 24 hours	400 mg/24 hours	400 mg/24 hours	No longer a criterion
X ray abdomen	Renal stones	Renal stones	Renal stones
Renal function	Creatinine Clearance reduced by 30%	Creatinine Clearance reduced by 30%	eGFR <60 ml/min
Bone Density Scan (DEXA)	Z score < −2.0 in forearm	T score < −2.5 at any site	T score < −2.5 at any site, and/or previous fracture
Age	< 50 years	< 50 years	< 50 years

The guidelines of referral for Parathyroid surgery were first introduced in 1990 by NIH (National Institute of Health (NIH) and were modified in 2002 and 2008. The initial Guidelines proposed for Parathyroidectomy are summarized below (3) :

(1) Markedly raised serum calcium of 1.0-1.6 mg/dl above the upper limit of normal (>12 mg/dl)

(2) History of an episode of life threatening hypercalcaemia

(3) Creatinine clearance reduced by <30%

(4) Urine calcium > 400 mg/day

(5) Nephrolithiasis

(6) Age <50 years

(7) Osteitis fbrosa cystica

(8) Bone mass reduced by > 2 SD as compared to controls matched for age, gender and ethnic group

(9) Neuromuscular weakness inclusive of proximal weakness, atrophy, hyperreflexia and Gait disburbance

The guidelines proposed in asymptomatic patients by NIH over different years are summarized in Table 3 (4).

The corresponding figures in SI units for referral for Parathyroidectomy are serum calcium >0.25 mmol/l above the upper limit of normal and 24 hours urine calcium > 10 mmol (N: 2.5-7.5 mmol/24 hours). The recent referral Criteria of the UK include serum calcium >3 mmol/l and still include 24 hours urinary calcium of >10 mmol. The patients fulfilling one or more Criteria are to be referred. Our patient had osteoporosis and therefore met at least one Criterion for referral for surgery. The symptoms of hypercalcaemia can be summarized in the form of a mnemonic: "stones, bones, groans and moans". The patients can have kidney stones, bone pain from osteitis fibrosa cystica (the patients can also have osteoporosis), abdominal groans from constipation, peptic ulcer and pancreatitis and psychic moans. Our patient had a few of these symptoms.

Parathyroidectomy is successful in >95% cases. The commonest cause of unsuccessful Parathyroidectomy is a missed abnormal parathyroid gland; however ectopic location of Parathyroid adenoma and variable anatomy of the Parathyroid glands may also be responsible for failed Parathyroid surgery(5,6). In our patient the cause of failed Parathyroiectomy was an ectopic mediastinal Parathyroid adenoma. In about 6-16 % of cases, the Parathyroid gland(s) may be present in an ectopic location namely in the thymus, retro-oesophageal region and can be intrathyroidal (1) and can develop adenomas. The various surgical procedures available include Video Assisted Minimally Invasive Thoracic surgery (VATS), Endoscopic Parathyroidectomy, Minimally Invasive Radionucleotide Guided Surgery (MIRP), Thoracoscopic Excision and Open Thoracic approach. Excision of ectopic mediastinal Parathyroid adenomas has over the years been done by open techniques including median sternotomy, manubrial split or thoracotomy(7,8). Some studies showed thoracoscopic excision of mediastinal ectopic Parathyroid adenomas has low complication rates and may decrease the duration of stay in the hospital(9). NICE Guidelines though published in December 2007 suggested limited evidence in favour of thoracoscopic removal of ectopic mediastinal Parathyroid adenomas (10). Parathyroid adenomas located below the aortic arch are very rare and open surgery can be safe with minimal risk of torrential bleeding from damage to aortic arch(10). NICE also stated that if Parathyroid malignancy is suspected then it may influence the choice of surgical procedure (10). An article in 2013 suggested that 95% of Parathyroid adenomas in the chest could be removed through a small neck incision. Thoracoscopic attempt to remove the adenoma in some cases can result in the tumour being broken down with further growth of tumour tissue in the chest and lungs (11). In our patient the location of the ectopic Parathyroid adenoma influenced the Thoracic Surgeons not to operate on it. Parathyroid adenomas are occasionally found within the aortopulmonary window, lateral to the ductus arteriosus and are extrapericardial in location. One embryologic theory links their development to migration with the recurrent laryngeal nerve (12).

Patients with Primary Hyperparathyroidism are at risk of vitamin D deficiency because of accelerated catabolism and inactivation of 25-hyroxy vitamin D. There is increased clearance and biliary excretion of the degradation products of 25-hydroxy vitamin D. Patients with Primary Hyperparathyroidism and co-existent Vitamin D deficiency have higher levels of PTH, larger Parathyroid adenomas and more frequent fractures than patients with a normal level of Vitamin D . The reduction in PTH levels following Vitamin D supplementation in patients with PHPT may improve bone mineral density and reduce fracture risk (13). Also, Vitamin D-deficient patients undergoing Parathyroidectomy are at increased risk of hungry bone syndrome and post-operative hypocalcaemia and hence supplementation of vitamin D is needed in all patients with Primary Hyperparathyroidism and co-existent Vitamin D deficiency (14). Vitamin D replacement can be done reasonably safely in Primary Hyperparathyroidism till the corrected calcium is 3mmol/l. Most authors recommend measurement of Vitamin D in all patients with PHPT, and its supplementation if 25(OH)D is <50 mmol/(15). Adverse effects include hypercalcuria and, less commonly, exacerbation of hypercalcemia.

Patients with Primary Hyperparathyroidism should drink plenty of water and should avoid thiazide diuretics and Lithium. Bisphosphonates have no effect on serum and urine calcium but preserve bone mass. Cinacalcet is a calcimimetic drug which increases sensitivity of calcium- sensing receptor to activation by extracellular calcium and reduces PTH secretion and serum calcium but not urinary calcium. It is licensed for patients in whom Parathyroid surgery is inappropriate and if Parathyroid adenoma is not found on neck exploration (2, 16). Cinalcalcet is also licensed for Parathyroid carcinoma and Secondary Hyperparathyroidism in patients with chronic kidney disease and undergoing dialysis.

There has been no previous case report of simultaneous administration of Vitamin D and Cinacalcet in a patient with persistent hypercalcaemia following failed Parathyroidectomy (carried out to cure Primary Hyperparathyroidism), although there have been reports of treating patients with low dose Vitamin D and Cinacalcet in Secondary Hyperparathyroidism. We report the first such case.

Conclusions:

(1) Parathyroidectomy should be undertaken in all patients with Primary Hyperparathyroidism who fulfil one or more criteria for Parathyroid surgery

(2) Parathyroidectomy is successful in 95% cases. Failed Parathyroidectomy resulting in persistent hypercalcaemia occurs commonly from a missed abnormal Parathyroid gland but can result from variable anatomy of Parathyroid glands and ectopic Parathyroid adenoma.

(3) Vitamin D should be estimated and supplemented in all patients with Primary Hyperparathyroidism and co-existent Vitamin D deficiency. Some Consultants though are sceptical of the use of Vitamin D supplementation (Cholecalciferol) as there is a possibility of the elevation in serum calcium level. Vitamin D supplementation should be stopped once the calcium reaches close to 3 mmol/l or may be continued together with Cinacalcet.

(4) Cinacalcet should be used in patients with Primary Hyperparathyroidism and hypercalcaemia who cannot have parathyroid surgery

(5) Cinacalcet should also be considered for failed Parathyroidectomy from ectopic mediastinal Parathyroid adenoma, who cannot have removal of such a Parathyroid adenoma

References:

(1) Roy M , Mazeh H, Chen H, Sippel RS. Incidence and localization of ectopic parathyroid adenomas in previously unexplored patients. World J Surg. 2013 Jan;37(1):102-106.

(2) Wass J, Owen K. 2014. Calcium and bone metabolism. Oxford handbook of Endocrinology and Diabetes. Oxford University Press, UK: 449-468

(3) Eigelberger M S, Cheah W K, Ituarte P H G, Streja L, Duh Q Y and Clark OH. The NIH Criteria for Parathyroidectomy in Asymptomatic Primary Hyperparathyroidism. Are They Too Limited? Ann Surg. 2004 Apr; 239(4): 528–535.

(4) Morris L G T and Myssiorek D. When is Surgery Indicated for Asymptomatic Primary Hyperparathyroidism? Laryngoscope. 2009 Dec; 119(12): 2291–2292(5)Gough I. Re-operativeparathyroid surgery: The importance of ectopic location andmulti-gland disease. ANZ J Surg 2006;76:1048-1050.

(6) Richards ML, Thompson GB, Farley DR, Grant CS. Re-operativeparathyroidectomyin 228 patients during the era of minimal-access surgery and intraoperativeparathyroid hormone monitoring. Am J Surg 2008;196:937-943.

(7) Russell CF, Edis AJ, Scholz DA, Sheedy PF, Van Heerden JA. Mediastinal parathyroid tumours: experience with 38 tumors requiring median sternotomy for removal. Ann Surg. 1981;193:805–809.

(8) Conn JM, Goncalves MA, Mansour KA, McGarity WC. The mediastinal parathyroid. Am Surg. 1991;57:62–66

(9) Sukumar MS, Komanapalli CB, Cohen JI. Minimally invasive management of the mediastinal parathyroid adenoma. Laryngoscope. 2006;116:482–487

(10) Parathyroid surgery – Introduction.EndocrineSurgeon.co.uk , August 18, 2015 (http://www.endocrinesurgeon.co.uk/index.php/parathyroid-surgery-introduction)

(11) Morgan J. Parathyroid Adenomas Located in the Chest: No Worries, Chest Parathyroid Tumors can be Very Easy to Remove! Hyperparathyroidism blog, August 5, 2013 (http://blog.parathyroid.com/parathyroid-adenoma-chest-mediastinum)

(12) Arnault V, Beaulieu A, Lifante JC, Serra AS, Sebag F, Mathonnet M, et al. Multicenter study of 19 aortopulmonary window parathyroid tumors: the challenge of embryologic origin. World J Surg. 2010;34:2211–2216

(13) Andrew Grey, Jenny Lucas, Anne Horne, Greg Gamble, James S. Davidson, and Ian R. Reid. Vitamin D Repletion in Patients with Primary Hyperparathyroidism and Coexistent Vitamin D Insufficiency. JCEM. DOI: http://dx.doi.org/10.1210/jc.2004-1772 . First Published Online: July 02, 2013

(14) Silverberg SJ. Vitamin D deficiency and primary hyperparathyroidism. J Bone Miner Res. 2007 Dec; 22 Suppl 2:V100-104

(15) Mikhail N. Clinical Significance of Vitamin D Deficiency in Primary Hyperparathyroidism, and Safety of Vitamin D Therapy. South Med J. 2011;104(1):29-33

(16) Rothe H M, Liangos O, Biggar P, Petermann A and Kettelar M. Int J Endocrin., 2011. v2011 Article ID 415719, 5 pages. http://dx.doi.org / 10.1155/2011 /415719