Case Report

The First Ethnic Asian Case Report of Paget's Disease with Concomitant Primary and Secondary Hyperparathyroidism

Nantaporn Siwasaranond MD[1], Vorachai Sirikulchayanonta MD[2], Suphaneewan Jaovisidha MD[3], Hataikarn Nimitphong MD[1]

[1] Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[2] Faculty of Science, Rangsit University, Pathum Thani, Thailand

[3] Department of Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

The authors report a case of Paget's disease [PD] with concomitant primary hyperparathyroidism [PHPT] in a 63-year-old Thai female who presented with elevation of alkaline phosphatase [ALP] from the routine annual check-up. The plain film and bone scintigraphy revealed a solitary Paget's lesion, characterized by osteolytic area, thicken cortex and prominent trabeculations in the right proximal femur. Further investigations revealed low level of 25-hydroxyvitamin D [25-(OH)D], elevation of calcium and parathyroid hormone [PTH] levels. A nodule in the right parathyroid gland was found. The serum calcium and PTH turned to normal after removal of the nodule, which was histologically diagnosed as parathyroid adenoma. Bisphosphonate was then given for treatment of Paget's disease to prevent fracture. The case of Paget's disease with concomitant parathyroid adenoma has not been previously reported in ethnic Asian groups. It is important to address that this concomitance is possible even in the countries where Paget's disease is rare, so that appropriate management is not overlooked.

Keywords: Paget's disease, Primary hyperparathyroidism, Hypercalcemia, Elevated alkaline phosphatase

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The co-existence of Paget's disease [PD] of bone and primary hyperparathyroidism [PHPT] was previously described many years ago[1,2]. The chance of occurrence of both entities in the same patients is extremely rare and entirely found in western countries where PD is quite common. To our knowledge, there has not been any report regarding such co-existence in Asian patients; in addition, our case possesses more puzzle feature of having secondary hyperparathyroidism, which was probably due to vitamin D deficiency.

Case Report

A 63-year-old woman was found to have persistently elevated alkaline phosphatase [ALP] (range from 150 U/L up to more than 300 U/L) by the routine annual check-up in 2012. Meanwhile, she was uneventful until a year later when she developed abdominal discomfort and had weight loss about 5 kilograms within two months. She denied of having loss of appetite, bowel habit change, and bone pain. Her medication was notably only acetaminophen for osteoarthritis. There was no history of diabetes, hypertension, tuberculosis, polyarthritis, or any other significant illness. She completed the vaccination program in her childhood. In addition, there is no known family history of bone diseases. Fecal occult blood test and ultrasonography of upper abdomen were performed from the other hospital and revealed unremarkable finding.

The physical examination at the out-patient clinic revealed unremarkable finding except for patello-femoral crepitus of both knee-joints due to osteoarthritis. The esophagogastroduodenoscopy and computed tomography colonoscopy were performed to investigate for her abdominal symptoms and revealed negative findings. Plain radiographs (Figure 1) of hips and femurs showed osteolytic lesion with cortical thickness and coarse trabeculations of the right proximal femur, compatible with PD of bone. No abnormality was seen in the left femur. Bone scan (Figure 2) and magnetic resonance imaging [MRI] (Figure 3) also supported the diagnosis of solitary PD. Bone biopsy of the lesion in the right proximal femur was taken from the soft part of the lesion and reported as consistent with lytic

Correspondence to:

Nimitphong H, Division of Endocrinology and metabolism, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.
Phone: +66-2-2011647, **Fax**: +66-2-2011715
Email: hataikarnn@hotmail.com

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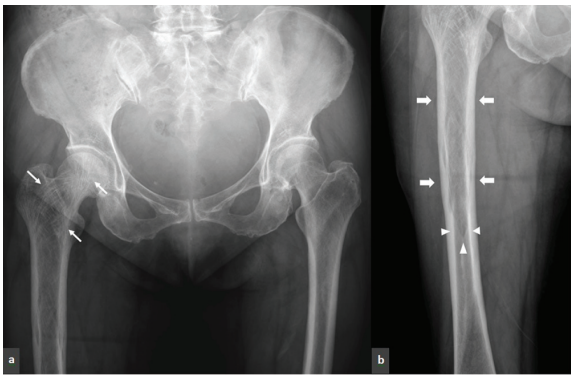

Figure 1. Plain radiographs of both hips (a) and the right femur (b) in anteroposterior [AP] views show osteolytic lesion involving the right proximal femur. The advancing inferior edge is "blade of grass or flame" appearance (thin white arrows in a). Slight bone expansion and thickened cortex is observed (thick white arrows in b). Course and prominent trabeculation from femoral head down to intertrochanteric region is seen (white arrowheads in b).

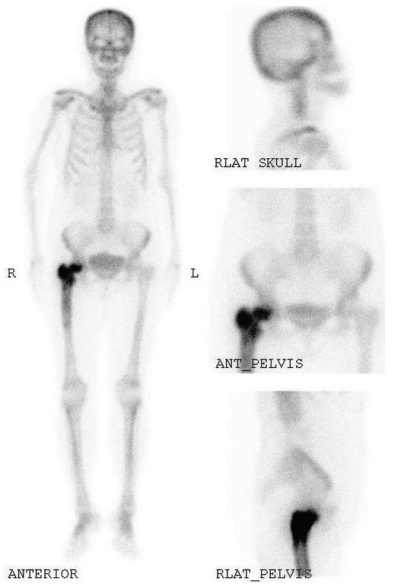

Figure 2. Bone scan reveals solitary increased uptake at the right proximal femur, most intense at the femoral head and neck. The rest of skeletal system shows no abnormal increased uptake.

component of PD illustrating mainly active osteoblasts and osteoclasts that have myriads of nuclei intermingling with trabeculae of woven bone and fibroblastic stroma (Figure 4).

All laboratory results were summarized as in Table 1. The diagnosis of PD in the present case was made primarily based on the elevation of ALP, typical radiographic findings, and supported by

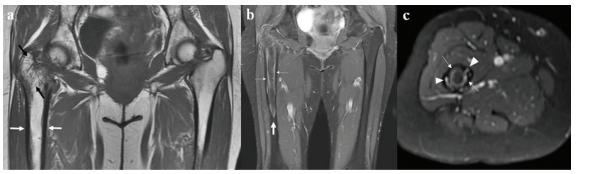

Figure 3. (a) Coronal T1-weight MR image of the hips reveals course trabeculation at the proximal femur (black arrows), slight contour expansion and thickened cortex (white arrows). (b) Coronal and (c) axial T1-weighted MR images with fat-suppression of the thighs after intravenous gadolinium injection reveal faint enhancement of the marrow cavity. The endosteal area shows intense enhancement down along the diaphysis (thin white arrows in b and c), with "blade of grass" appearance at inferior margin (thick white arrow in b), corresponding with plain radiograph. Intracortical enhancement is also observed (white arrowheads in c). The enhancement suggests area of active disease.

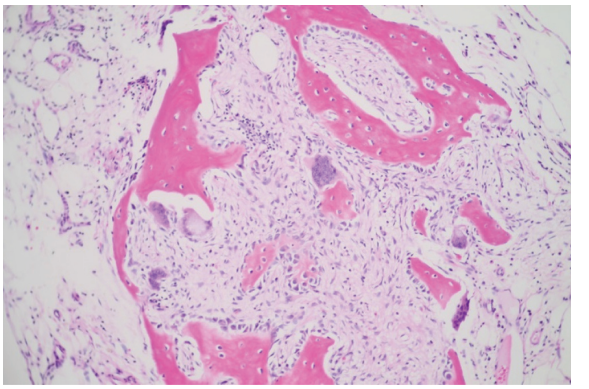

Figure 4. Bone biopsy at right femur in this patient shows mainly trabecular bone surrounded with fibroblastic stroma intermingling with several osteoclasts having numerous nuclei.

histologic diagnosis. In addition, this case also developed hypercalcemia and vitamin D deficiency (25-hydroxyvitamin D [25(OH)D] = 14 ng/ml). Intact parathyroid hormone [PTH] was found to be elevated and might be due to primary or secondary (from either PD or vitamin D deficiency) hyperparathyroidism (Figure 5). Bone survey was performed and surprisingly did not reveal typical changes of bone as manifested in hyperparathyroidism, i.e., salt-and-pepper appearance of the calvarium, subperiosteal bone resorption of fingers. However, bone mineral density [BMD] was performed and T-score at distal 1/3 of wrist, femoral neck, and lumbar spine were -3.2, -1.5, -0.7, respectively, and suggested greater cortical bone loss than trabecular bone loss, which is a typical finding in PHPT. Therefore, this patient was categorized as asymptomatic PHPT and met the criteria for

Table 1. The initial laboratory investigations

Blood tests	Results	Unit	Normal reference range
Complete blood count [CBC]			
Hemoglobin	11.5	g/dl	12 to 16
Hematocrit	35.1	%	36 to 48
White blood cell count	6,650	cell/mm^3	4,000 to 10,000
Platelet	254,000	cell/mm^3	140,000 to 450,000
Blood chemistry			
Blood urea nitrogen [BUN]	19	mg/dl	7 to 18
Creatinine	0.77	mg/dl	0.55 to 1.02
Estimated glomerular filtration rate [eGFR]	82.2	ml/minute/1.73 m^2	-
Sodium	140	mmol/L	136 to 145
Potassium	4.16	mmol/L	3.5 to 5.1
Chloride	110	mmol/L	98 to 107
Carbondioxide	20.7	mmol/L	22 to 29
Calcium [Ca]	12.7	mg/dl	8.5 to 10.1
Phosphate [P]	2.3	mg/dl	2.5 to 4.9
Parathyroid hormone [PTH]	290.5	pg/ml	15 to 65
Total 25-hydroxyvitamin D [25(OH)D]	14.6	ng/ml	≥30
Liver function test [LFT]			
Aspartate aminotransferase [AST]	24	U/L	15 to 37
Alanine aminotransferase [ALT]	31	U/L	30 to 65
Alkaline phosphatase [ALP]	293	U/L	50 to 136
Gamma glutamyl transferase [GGT]	22	U/L	5 to 55
Total bilirubin [TB]	0.3	mg/dl	0 to 1.0
Direct bilirubin [DB]	0.1	mg/dl	0 to 0.3

parathyroid surgery[3]; serum calcium of more than 1 mg/dl above the upper limit of normal (range from 11 to 15 mg/dl), and osteoporosis. Parathyroid scan was subsequently performed and revealed remaining uptake in lower pole of the right thyroid lobe on second hour image, compatible with the presence of parathyroid adenoma at the right lower gland. At that time, the authors were in doubt as to whether parathyroidectomy (for the treatment of PHPT) or medical treatment with bisphosphonates (for the treatment of PD) should be the first step of treatment. The authors decided to perform parathyroidectomy of right lower pole as primary approach on the basis that the authors might be able to cure PHPT and reduce high bone turnover activity, which might secondarily improve Paget's lesion. The nodule from parathyroidectomy revealed parathyroid adenoma by histological diagnosis. Post-operatively, the patient was quite uneventful. She had neither hypocalcemia nor hungry bone syndrome. The serum calcium turned to normal level immediately while serum ALP gradually declined and returned to normal level in the following three months (Figure 6,

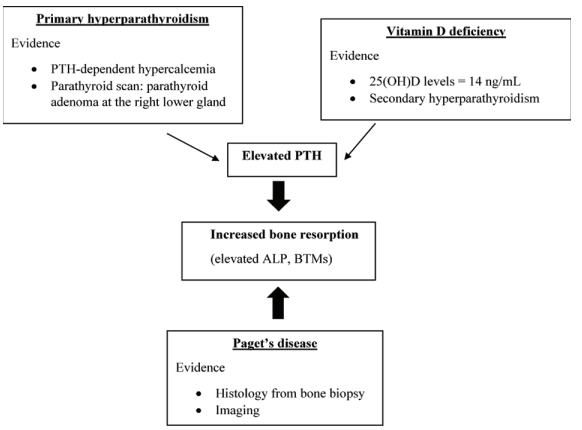

Figure 5. Relationship among clinical manifestations of primary hyperparathyroidism, secondary hyperparathyroidism, and Paget's disease of bone in this patient.

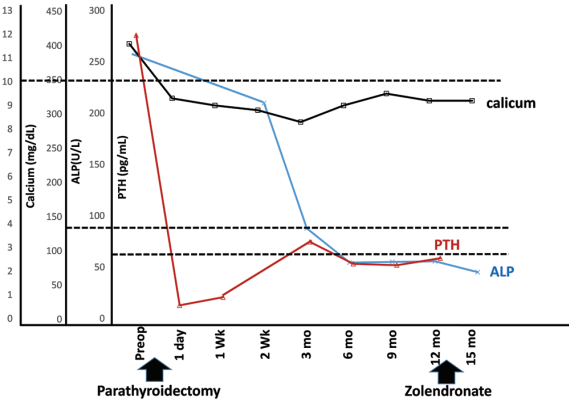

Figure 6. The time course of changes in serum calcium, ALP, and PTH after parathyroidectomy and bisphosphonate treatment; dashed lines represent the upper limit of normal levels of calcium, parathyroid hormone [PTH] and alkaline phosphatase [ALP].

Table 2. Serum Ca, phosphate, alkaline phosphatase, and parathyroid hormone level during follow-up

Blood tests	Before surgery	Post-operative duration							
		Day 1	1 week	2 weeks	3 months	6 months	9 months	12 months	15 months
Calcium (8.5 to 10.1 mg/dl)	11.6 (range 11 to 15)	9.3	9.0	8.8	8.3	9.0	9.5	9.2	9.2
Phosphate (2.5 to 4.9 mg/dl)	3.2	2.6	2.9	3.8	2.8	3.5	-	3.7	-
ALP (50 to 136 U/L)	389	-	-	316	133	83	84	85	69
PTH (15 to 65 pg/dl)	276	12.9	20.8	-	74.7	53.3	52	58.8	-
P1NP (16.27 to 73.87 ng/mL)	287.70	-	-	-	-	-		33.75	20.66
CTX (0 to 0.704 ng/mL)	1.210	-	-	-	-	-		0.223	0.103

ALP = alkaline phosphatase; PTH = parathyroid hormone; P1NP = N-terminal propeptide of type 1 procollagen; CTX = C-terminal cross-linking telopeptide

Table 2). She received vitamin D treatment (60,000 units per week) after the parathyroid surgery until the last follow-up. One year after surgery, plain radiograph still revealed an unchanged lesion of PD in the right proximal femur. Correspondingly, an increased uptake at the right proximal femur from bone scan still existed with some improvement. When compared with the pre-operation, N-terminal propeptide of type 1 procollagen [P1NP] and C-terminal cross-linking telopeptide of type I collagen [CTX-I] levels were lower and fell to the normal range of those levels in postmenopausal women (Table 2). Since the lesion had persisted and located at a femur, which might lead to a high-risk for fracture, bisphosphonate (zolendronic acid 5 mg intravenous) was given once. At six months post bisphosphonate administration, she was still uneventful.

Discussion

PD is relatively common in Europe, Australia, Canada, New Zealand, South Africa, and the United states. Although this disease is considered to be uncommon in Asian people, the recent report in New Zealand found that there was a decline of PD in the European population, in conjunction with the emergence of the disease in the Asian population[4]. PD is characterized by focal area of increased and disorganized bone remodeling affecting one (monostotic) or more bones (polyostotic) throughout the skeleton. Examination of bone-biopsy specimens indicates an evolution of the lesions, with the earliest abnormality being a focal increase in bone resorption by very large osteoclasts, followed by increased osteoblastic activity producing a high rate of bone formation resulting in bone that is less well organized than normal. Finally, a burned-out phase in which bone cell activity is markedly reduced and the bone structure is abnormal, with chaotic lamellar bone interspersed with woven bone. The abnormal bone structure may be associated with enlarged affected bones. This disease preferentially involves in the axial skeleton, i.e., the pelvis (70%), femur (55%), lumbar spine (53%), skull (42%), and tibia (32%)[5-10]. Typical presentation of PD, as in our case, is an incidental finding of abnormal radiograph and/or biochemical testing in a healthy patient who underwent investigation for other reasons. Five to 40% of patients came to medical attention present with symptoms and complications, for example bone pain, bone deformity, osteoarthritis, hearing loss, spinal stenosis[5]. Until recently, there were only six cases of PD reported in Thailand and all of them were Chinese descent[11-13]. However, this case report would alert the physicians to be aware of PD in Thai patients presented with asymptomatic elevated in ALP as well as hyperparathyroidism, which can present as coexistence.

PD does not commonly affect calcium level. When concomitant hypercalcemia developed in patient suspected of PD, one of the followings should be considered, immobilization hypercalcemia in PD or co-existing of PHPT[14]. Unlike the co-existing of PHPT and PD, the pathophysiological relationship between PD and secondary HPT (elevated PTH develops with normal or borderline low in serum calcium) is well described[15,16]. The prevalence of secondary HPT was about 12% to 18% of moderately active PD, a setting of skeletal metabolic balance favoring bone formation[1,2]. Active PD causes increasing in calcium demand during period of active new bone formation and may fluctuate with time, secondarily causing secondary HPT[1]. Furthermore, exogenous causes of disequilibrium between bone resorption and formation in PD include several antiresorptives treatments, vitamin D deficiency/inadequacy, and low calcium intake with the diet[14] exaggerate secondary HPT. This implies that dietary supplement with calcium and vitamin D in subjects with PD, especially who receive bisphosphonates treatment, is desirable to prevent this condition. Secondary HPT from vitamin D deficiency

was mostly reported in subjects with 25(OH)D of less than 20 to 30 ng/ml[17,18]. In our patient, 25(OH)D was 14 ng/ml, thus possibly contributed to secondary HPT. However, vitamin D replacement was initiated after the successful parathyroidectomy because of concerning for aggravated hypercalcemia. On the other hand, the less common co-existing condition, PD and PHPT, is much more debated[19]. The estimated prevalence of PHPT together with PD is 2.2% to 6.0% based on each study[19,20]. Coexisting PHPT in patient with PD is difficult to distinguish in clinical practice. That is both of them can alter bone remodeling, causing a stage of high bone turnover and increasing in bone markers and ALP as seen in this case (Figure 5). One disorder may stimulate the other[21], excess PTH should be likely to have an exaggerated impact at skeletal sites affected by PD, causing osteolytic lesions, elevated ALP levels. PD bone formation further secondary increase PTH levels as describe above. Up to date, there are few case reports of coexisting PD and PHPT, which had different presentations (Table 3)[22-24]. For example, our patient was diagnosed asymptomatic monostotic PD and PHPT at the same time, one of them was diagnosed symptomatic monostotic PD and PHPT at the same time, and two of them were diagnosed polyostotic PD prior to PHPT. Most of cases had asymptomatic PHPT (same as in ours), and one of them had normocalcemic HPT. For the treatment, parathyroidectomy was performed in all patients, and then followed with bisphosphonates. In our case, the authors hypothesized that both primary (from parathyroid adenoma) and secondary HPT (from vitamin D deficiency) caused elevated PTH. Of note, PTH and ALP were all normal when the authors prescribed vitamin D after successful parathyroidectomy.

Consideration for the treatment in our patient, parathyroidectomy was the definitive treatment of PHPT and would potentially improve biochemistry and bone lesions of PD[3]. On the other side, as our patient did not have any symptoms of PD, bisphosphonates therapy for PD would be a second step of treatment, aiming in prevention for future complication, for example bone pain, bone deformity, or fractures[5] as suggested in the current guideline of the Endocrine Society[6]. A decline in ALP level to normal range within three months after parathyroidemtomy implied that the PHPT mostly underlined elevated ALP in this patient. With regard to skeletal abnormality, bone scan of our patient demonstrated an improvement in an increased uptake at the right proximal femur after one year of parathyroid surgery. This improvement corresponded with many studies in PHPT[25]. However, the focal bone lesions at right femur persisted and could be explained by metabolically inactive disease. The location of bone involvement in this patient is at significant risk of further complication, such as fracture

Table 3. Comparison of clinical manifestations between this patient and others presented with coexisting PD and PHPT

	The present patient	Stathopoulos et al., 2013[22]	Brooks et al., 2011[23]	Mooney et al., 2003[24]
Patient's characteristic				
Age (years)	63	74	63	73
Gender	Female	Male	Female	Male
Race	Thai	Greek	American	Australian
Sequence of presentation	Concurrent	Concurrent	PD prior to PHPT (6 years)	PD prior to PHPT (2 years)
Detail of PD				
Characteristic	Asymptomatic, monostotic	Symptomatic, monostotic	Symptomatic, polyostotic	Symptomatic, polyostotic
Location	Right proximal femur	Right hip	Cavarium, right humeral head, mid thoracic spine, sacrum, right hemipelvis	Skull, lumbar and thoracic spine, ribs, pelvis, both femurs, humerus and tibia
ALP level (U/L) (normal reference range)	389 (50 to 136)	199 (40 to 129)	3,103 (38 to 126)	1,075 (30 to 115)
Detail of PHPT				
Characteristic	Asymptomatic	Normocalcemic	Asymptomatic	Asymptomatic
PTH level (pg/ml) (normal reference range)	276 (15 to 65)	86.9 (15 to 65)	307 (12 to 65)	84 (10 to 70)
Calcium level (mg/dl) (normal reference range)	11 to 15 (8.5 to 10.1)	9.1 (8.2 to 10.2)	11.1 (8.4 to 10.2)	10.6 (8.4 to 10.4)
25(OH)D level (ng/ml) (normal reference range)	14.6 (≥30)	22.1 -	Not applicable	Not applicable

PD = Paget's disease; PHPT = primary hyperparathyroidism; ALP = alkaline phosphatase; PTH = parathyroid hormone; 25(OH)D = 25-hydroxyvitamin D

and with the conjunction of no contraindication for bisphosphonates therapy, zolendronic acid 5 mg was given as single infusion.

Conclusion

This is the first case report of the concomitant of PHPT, secondary HPT from vitamin D deficiency and PD of bone in Thai. When hypercalcemia was found in patient suspected of PD, immobilization hypercalcemia in generalized PD or co-existing of PHPT should be considered. Serum calcium, phosphate and PTH should be an additional work up to determine the cause of hypercalcemia. One disorder may worsen another. The appropriate treatment as to whether parathyroidectomy (a treatment of choice for PHPT) or medical treatment with bisphosphonates (a treatment of choice for PD and an alternative treatment for PHPT), should depend on the severity and urgency of the disease.

Acknowledgement

Written consent was obtained from the patient for publication of the present study.

What is already known on this topic?

PD with coexistence of PHPT is rare and entirely reported from western countries where PD is common.

What this study adds?

PD with concomitant primary and secondary HPT disease could be found in clinical practice in Southeast Asia. Therefore, this case report would alert the physicians to be aware of combination of both diseases in patients presenting with elevated in ALP, hypercalcemia, and no history of immobilization.

Potential conflicts of interest

The authors declare no conflict of interest.

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