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Case Report

Gout in Primary Hyperparathyroidism, Connecting Crystals to the Minerals

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Abstract

Musculoskeletal manifestations in primary hyperparathyroidism (PHPT) range from 13% to 93% encompassing pseudogout, vertebral fracture, myopathy, and cord compression. Though pseudogout has been the most prevalent musculoskeletal condition in PHPT, rarely reports of acute gouty attacks in large joints including the knee have been reported in the literature. Here we detail a unique case of PHPT presenting with acute severe bilateral knee joint inflammatory arthritis accompanied by occasional abdominal pain. Joint aspiration fluid study revealed extracellular monosodium urate crystals exhibiting strong negative birefringence on polarized light microscopy suggestive of acute gouty arthritis. Hypercalcemia and hypophosphatemia with high intact parathyroid hormone (iPTH) confirmed the diagnosis of PHPT and a right inferior parathyroid adenoma was localized. Parathyroidectomy resulted in statistically significant clinical improvement of the debilitating joint manifestations, and the patient was able to walk again without support. Although the incidence of gout is increasing because of an overall increase in metabolic syndrome prevalence, a higher prevalence than in the general population is reported in PHPT. Serum uric acid levels positively correlate with serum iPTH levels in PHPT, and parathyroidectomy leads to a reduction in levels. Acute inflammatory joint pain due to urate crystal deposition in a large joint like the knee is an uncommonly reported condition in PHPT. Identifying the correct etiology in such a case can result in marked clinical improvement in the joint manifestations following surgical cure of hyperparathyroidism.

Key Words: hyperparathyroidism, parathyroid, gout, arthritis, hyperuricemia, uric acid

Abbreviations: iPTH, intact parathyroid hormone; MSU, monosodium urate; NHANES, National Health and Nutrition Examination Survey; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; SHPT, secondary hyperparathyroidism; SUA, serum uric acid; TSH, thyrotropin; UA, uric acid.

Musculoskeletal manifestations in primary hyperparathyroidism (PHPT) range from 13% to 93% in primary hyperparathyroid patients. It encompasses a variety of pathological conditions starting from pseudogout to back pain, arthralgia, vertebral fracture, generalized bone pains, muscle weakness, pseudoclubbing, shoulder rotator cuff tear, to sacral fracture, cord compression, gout, paraplegia, myotonic dystrophy, erosive spondyloarthropathy, and ankylosis of the sacroiliac joint [1-3]. Neuropsychiatric and rheumatological manifestations are lesser recognized associations in PHPT. PHPT presenting primarily as a joint complaint is rare. In this case report we present a patient with a unique case of PHPT presenting as acute large-joint inflammatory arthritis (bilateral knee joints) ultimately diagnosed to have acute gout that resolved with surgical removal of the parathyroid tumor.

Case Presentation

A 30-year-male patient presented with complaints of bilateral knee pain and swelling for 10 days. Further enquiry revealed a history of recurrent flank pain with passage of stones in the urine. The patient was diagnosed to have right renal calculi a few months back. There was no history of fever, hematuria, oral or genital ulcerations, redness of the eyes, altered bowel habits, blood in the stool, or fractures. No similar illness was reported in the family. The initial examination suggested a case of inflammatory large-joint arthritis without any involvement of small joints or axial skeleton. The involved knee joints were swollen, warm, red, and so exquisitely tender that the patient had difficulty walking without support (Fig. 1).

The laboratory parameters (Table 1) were significant for anemia, hypercalcemia, hypercalciuria, mild renal dysfunction, elevated intact parathyroid hormone (iPTH) values with vitamin D in the insufficient range. Ultrasonography of the abdomen showed bilateral renal calculi with mild hydronephrosis. Bone mineral density by dual-energy x-ray absorptiometry showed *Z* scores of –3.3 at the lumbosacral spine, –3.8 at the femoral neck, and –6.8 at the distal 1/3 radius.

High-resolution ultrasound revealed a hyperechoic linear margin of the articular cartilage indicating crystal deposition as a double contour sign involving the knee and ankle joint (Fig. 2). Hyperechoic gouty tophaceous deposits were also detected along the peritendinous aspect of the tendo Achilles and patellar tendon on ultrasound. Bilateral knee magnetic resonance imaging revealed moderate joint effusion along with synovial thickening. There were changes of grade IV

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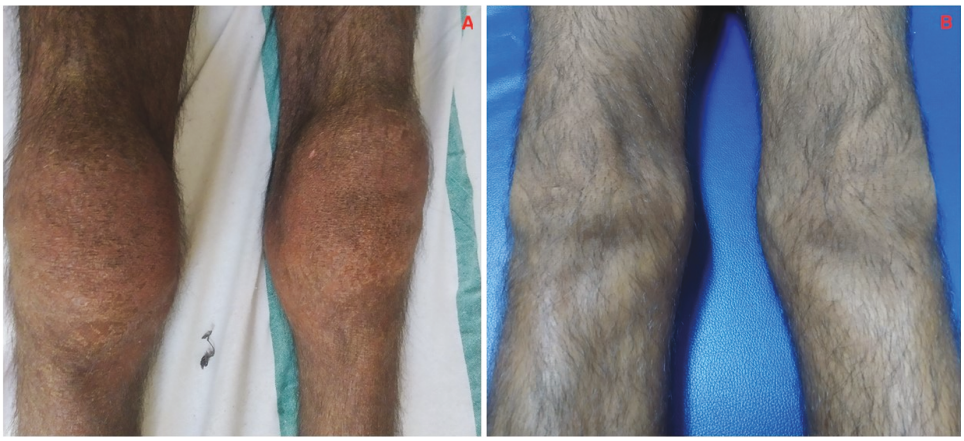

Figure 1. Clinical images of bilateral knee joints. A, Bilateral knee joint swelling. B, Resolution of swelling in both knee joints after parathyroid surgery.

Table 1. Laboratory parameters of patient at baseline

Parameter	Value	Reference range
Hemoglobin, g/dL	8.1	13.5-16.5
TLC, /cu mm	8250	4000-11000
MCV, fl	86.6	82-98
Platelet count, /cu mm	2.45×10^5	$1.5\text{-}4.0 \times 10^5$
Creatinine, mg/dL	1.4	0.84-1.25
Sodium, meq/L	135	135-145
Potassium, meq/L	3.5	3.5-5.5
Iron, µg/dL	75	70-180
Ferritin, ng/mL	815.3	18-341
TIBC, µg/dL	173	240-450
Fasting plasma glucose, mg/dL	90	70-100
Uric acid, mg/dL	5.4	3.5-7.2
TSH, mIU/L	1.94	0.5-3.5
Prolactin, ng/dL	11.6	4.02-18.14
Calcium, mg/dL	10.4, 10.4	8.2-10.2
Phosphorus, mg/dL	2.74, 2.86	2.5-4.5
25(OH)D, ng/mL	28.4	< 20 deficiency 20-29 insufficiency 30-100 sufficiency
iPTH, pg/mL	1404	18.5-88
ALP, IU/L	467	52-171
24-h urinary calcium, mg/d	353.24	100-300
24-h urinary uric acid, mg/d	480	250-750

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; iPTH, intact parathyroid hormone; MCV, mean corpuscular volume; TIBC, total iron-binding capacity; TLC, total leukocyte count; TSH, thyrotropin.

chondromalacia patella with multifocal areas of chondral loss along the patellofemoral and tibiofemoral joints.

Knee joint aspirated synovial fluid was turbid in appearance. The string test was less than 5 cm. The improved Neubauer chamber count showed 1600 WBC/cumm. Smears showed predominantly acute inflammatory cells along with extracellular monosodium urate (MSU) crystals both in groups and singly scattered. These crystals were needle shaped with sharp edges and exhibited strong negative birefringence on polarized light microscopy suggestive of acute gouty arthritis. The crystals that were parallel to the polarizer were yellow in appearance, whereas those that were perpendicular appeared blue (Fig. 3).

Skeletal survey revealed changes of hyperparathyroidism in the form of subperiosteal resorption along the radial aspect of the second and third distal phalanges in bilateral hand radiographs along with salt and pepper appearance of the skull. Ultrasound of the neck detected a well-defined homogenous hypoechoic solid nodule with mildly increased vascularity posterior and inferior to the right lobe of thyroid suggestive of a parathyroid adenoma (Fig. 4). Four-dimensional computed tomography (4D-CT) of the neck showed a single right inferior parathyroid adenoma which was confirmed in the ^{99}mTc Sestamibi SPECT-CT and a final diagnosis of primary hyperparathyroidism (PHPT) with a right inferior parathyroid adenoma.

For the joint symptoms, the patient was put on nonsteroidal anti-inflammatory drugs and colchicine was added. There was some relief in pain although the antalgic gait persisted. The patient successfully underwent a right inferior parathyroidectomy with intraoperative PTH monitoring (PTH values of 1210 pg/mL at incision, 168 pg/mL at 5 min, 122 pg/mL at 15 min).

The patient's postsurgical course was largely uneventful and he did not experience any tetany. On follow-up at 8 weeks, there was marked clinical improvement with considerable reduction in pain and knee joint swelling (see Fig. 1). iPTH values on follow-up were 23.1 and 59.5 pg/mL with serum calcium 9.37 mg/dL, phosphorus 4.2 mg/dL, alkaline phosphatase 103 IU/L, and 25-hydroxyvitamin D 37.5 ng/mL. The anemia improved with hemoglobin 13.5 g/dL (bone marrow biopsy was not performed), serum uric acid (SUA) 4.6 mg/dL, and creatinine 1.3 mg/dL. Currently the patient can walk without any functional limitation and is on vitamin D and calcium supplementation.

Discussion

PHPT, the disease of "bones, stones, and groans" has become a "silent" disease in most populations. Asymptomatic PHPT is the most common presentation of the disease [4-7]. In developed nations, about 15% of patients with PHPT present with overt symptoms (kidney stones and osteoporotic fractures) [8], whereas this figure is higher in countries where

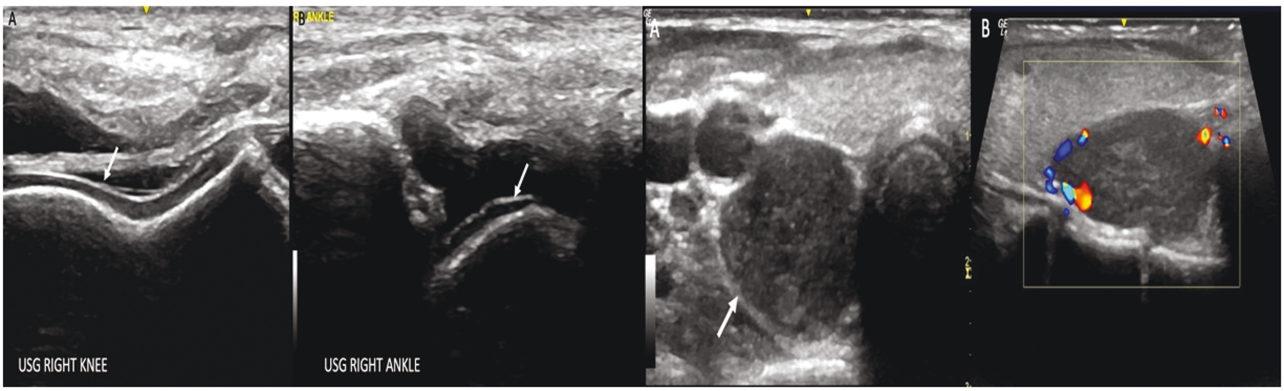

Figure 2. (Left): Ultrasound images of joints. A, Knee joint. B, Ankle joint: Arrows show the hyperechoic band at the cartilage-synovial interface due to monosodium urate crystal deposition on the cartilage surface. Knee and ankle joint effusion is also evident. (Right). Ultrasound imaging of the neck. A, Transverse image showing a well- circumscribed hypoechoic solid mass lesion (arrow) posterior to the right lobe of the thyroid. B, Color Doppler image, longitudinal view shows peripheral vascularity in the solid nodule.

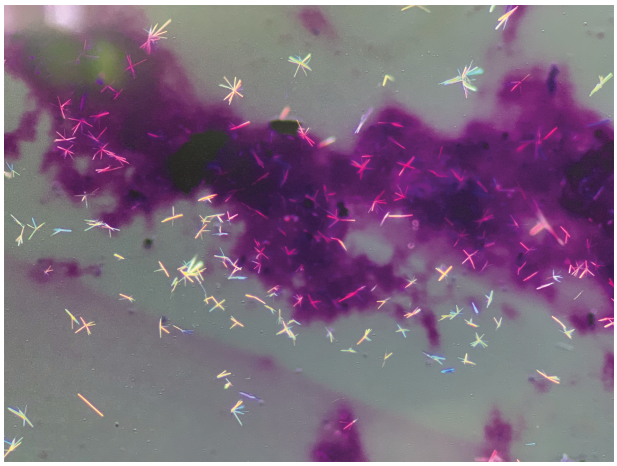

Figure 3. Synovial fluid showing needle-shaped monosodium urate crystals exhibiting strong negative birefringence on polarized light microscopy.

routine laboratory screening is less common [9-13]. The "nontraditional" aspects of PHPT are attracting particular attention, including risk factors for cardiovascular disease such as hypertension, phenotype IV lipoproteinemia, insulin resistance, and cardiovascular dysfunction, and lesser recognized associations like neuropsychiatric and rheumatological manifestations. Our case highlights such an uncommon presentation of large-joint gouty arthritis in PHPT.

The usual presentation of PHPT in Europe and North America is asymptomatic, whereas in India "symptomatic" PHPT is seen in more than 90% cases, with higher indices of the disease (fractures, renal calculi, pancreatitis), observed iPTH values, and tumor weight. Vitamin D deficiency being highly prevalent also contributes to the burden of disease and higher iPTH levels.

In addition to the skeletal manifestations (classic bone disease, osteitis fibrosa cystica—degranulation of the skull [so-called salt and pepper appearance], distal tapering of the clavicles, subperiosteal bone resorption, brown tumors, and bone cysts), rheumatological symptoms of excess PTH have been described [14-16]. PHPT is associated both with calcium pyrophosphate crystal deposition disease [17, 18] and hyperuricemia or gout [19]. The most prevalent joint manifestation in PHPT has been pseudogout. PHPT presenting as acute monoarticular or oligoarticular arthritis is rare in the literature. Moreover, surgical cure of hyperparathyroidism has also been associated with pseudogout [20-22].

Gout as a complication of hyperuricemia is an increasingly prevalent inflammatory arthritis in recent times in the midst of increasing individuals with metabolic syndrome and obesity [23]. Hyperuricemia and gout have been described in anecdotal case reports and case series of PHPT [1, 24-26]. Data from a randomized trial based on men older than 40 years [27] and another community population study of men aged 70 years and older [28] have shown a statistically significant association between PTH and SUA levels. This suggests that a substantial biological influence of PTH on SUA level may exist. In a cross-sectional study, serum PTH level was positively correlated with SUA level, and the PTH level was statistically significantly higher in patients with hyperuricemia than normouricemia [29]. Data from 8316 participants in the National Health and Nutrition Examination Survey (NHANES) 2003 to 2006 using weighted logistic regression showed that serum PTH levels were independently associated with SUA levels and frequency of hyperuricemia at the population level [30]. The increase of UA was in parallel with the increase of PTH, and PTH in the highest quartile had statistically significantly higher serum UA than those in the lowest quartile. Chen et al [31] also concluded from the NHANES data that serum UA was positively correlated with elevated PTH levels, especially at an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2.

The association between PTH and UA is further supported by the use of cinacalcet (allosteric activator of the calcium-sensing receptor and acts to suppress PTH level) in secondary hyperparathyroidism (SHPT). Cinacalcet can substantially reduce the increase of serum UA levels in SHPT without affecting renal function. After 12 weeks of cinacalcet treatment, serum UA level decreased together with the reduction of PTH in patients with SHPT undergoing dialysis [32]. It is interesting to note that hyperuricemia-induced vitamin D deficiency and hyperparathyroidism can further aggravate bone remodeling disturbances in UA-related bone loss and dramatically increase fracture risk [33]. A possible explanation for the association of gout and hyperparathyroidism is the increased levels of serum urate that have been described in some cohorts of patients with PHPT [14]. Though hyperuricemia has been known to be associated with hyperparathyroidism, as far as we are aware the kind of

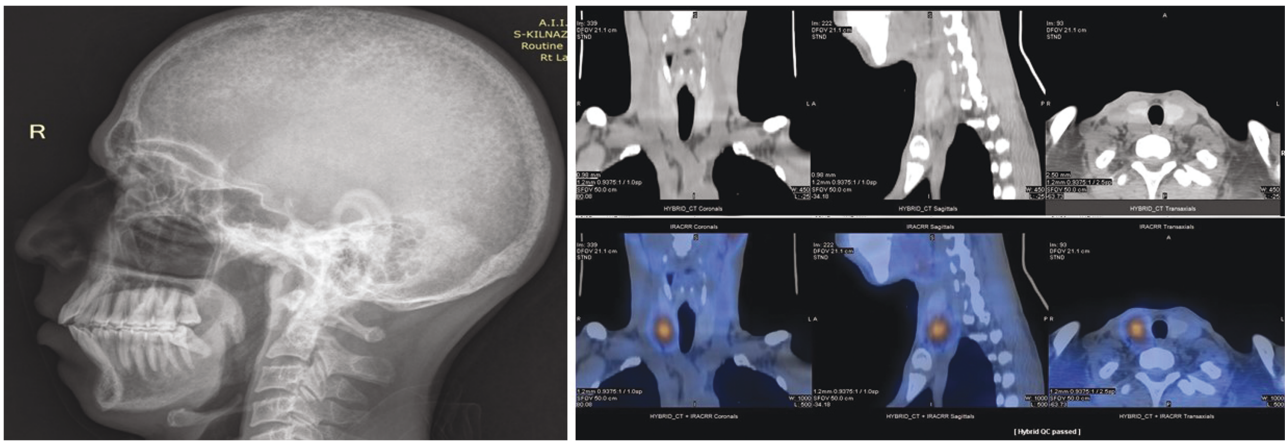

Figure 4. A, X-ray of the skull right lateral view showing classical "salt and pepper" appearance. B and C, Single-photon emission computed tomography (SPECT)-CT imaging of the neck showing a radiotracer avid well circumscribed soft tissue density lesion 1.8 × 2.0 × 3.6 cm, lying posterior and medial to the inferior pole of right lobe of thyroid gland suggestive of single right inferior parathyroid adenoma.

acute gouty knee arthritis seen in our patient has not been previously reported. In one report, a lytic lesion initially assumed to be a brown tumor was found on joint aspiration to contain urate deposits [34]. Singly scattered needle-shaped extracellular MSU crystals with sharp edges and exhibiting strong negative birefringence on polarized light microscopy were seen from the knee joint aspirate and synovial fluid analysis in our patient (see Fig. 4). During acute gout arthritis attacks, crystallization of needle-shaped MSU and infiltration of neutrophils are characteristic features in the synovial fluid.

Our patient had presented with features of bilateral inflammatory knee arthritis that initially were thought to be of rheumatological origin (possibilities included seronegative rheumatoid arthritis, psoriatic arthropathy, or acute rheumatic fever) or infectious origin (septic arthritis).

The patient's associated nonspecific abdominal pain initially gave us some clue about the possibility of hypercalcemia and hyperparathyroidism. Maddegedara et al [35] reported a case of atypical oligoarthritis primarily involving the small joints of hands initially treated as rheumatoid arthritis but disease-modifying anti-rheumatoid drugs were ineffective. The patient was eventually diagnosed with PHPT and the symptoms resolved after successful parathyroidectomy. As we know in gout, the metatarsophalangeal joint is the most common joint to be involved but the knee joint may also be affected. Our patient did not have any particular precipitating factors like hypouricemic therapy, any surgery, excess alcohol consumption, or any kind of trauma. SUA was normal. UA levels can be normal or low in acute episodes because of the uricosuric nature of inflammatory cytokines, which actually limits the diagnostic value of SUA measurements during acute attacks [36].

Imaging plays a vital role in the assessment and evaluation of patients with suspected hyperparathyroidism and the identification of the cause and related complications. In our case, ultrasound and magnetic resonance imaging played a crucial role in identifying the pattern and the extent of the arthritis and the pattern of crystal deposition that supported the diagnosis of gouty arthritis. The double contour sign on ultrasound indicates a hyperechoic band over the articular cartilage due to deposition of MSU crystals along the joints [37].

In a National Institutes of Health case series, 20 of 56 patients with hyperparathyroidism had SUA levels greater than 7 mg/dL; after parathyroidectomy, SUA levels decreased by more than 1 mg/dL in 64% of these patients [38]. Randomized controlled trials have also found that hyperuricemia or gout is associated with the use of teriparatide (recombinant human PTH) [39, 40]. In data from the Fracture Prevention Trial, use of teriparatide in a large sample size of more than 17 000 postmenopausal women increased the incidence of hyperuricemia episodes in a dose-dependent manner, although the attack of gout did not reach clinical significance [41]. Notable advances have been made in the physiology of proximal tubular urate transport. Elevated PTH levels are thought to reduce renal UA transport in proximal renal tubules and excretion leading to hyperuricemia in PHPT patients, although the exact mechanism remains unclear [42]. Multiple transporters (both secretary and absorptive) at both the basolateral and apical membrane have been identified [43-46]. PTH would be expected to have more-negative effects on net proximal tubular urate reabsorption, given that proximal tubular salt (Na+-Cl–) and urate transport are regulated in parallel and PTH is a potent inhibitor of NHE3, a critical apical transporter for proximal tubular salt absorption [47]. Thus, PTH would be expected to have more inhibitory effects on net proximal tubular urate reabsorption. Another factor could be downregulation of ABCG2 expression in renal proximal tubules and intestines, resulting in decreased excretion of UA via the kidneys and intestines.

Parathyroidectomy in PHPT results in the improvement of UA levels and eliminates the biochemical risks of hyperuricemia including gout [48]. Similarly Yoneda and colleagues [49] demonstrated serum UA was statistically significantly higher in patients with PHPT and improved after parathyroid adenoma removal. Our patient has now been on more than 6 months of follow-up after parathyroid surgery and his knee joint swelling has dramatically improved with no recurrence of acute gouty attacks.

Conclusion

Gout in PHPT is a rare entity. However, the association of hyperuricemia in PHPT cannot be denied and has been reported in various case series and larger studies with a pathophysiological basis. This is probably the first case report illustrating large knee joint acute gouty arthritis due to PHPT. A detailed history, thorough clinical examination, and a sim-

ple calcium and phosphate levels pointed to the diagnosis. A high index of suspicion in bone-joint rheumatology clinics would serve to correctly identify PHPT as an underlying pathology in such cases. It would be interesting to screen for PTH levels in gout patients in a larger data set to get a truer picture of this association.

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Disclosures

The authors have nothing to disclose.

Data Availability

Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

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