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Primary hyperparathyroidism and Klinefelter's syndrome in a young man

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Summary

We report the association of primary hyperparathyroidism (PHPT) and Klinefelter's syndrome (KS) in a 22-year-old male complaining of worsening fatigue. PHPT was asymptomatic at the diagnosis, but the patient had worsening hypercalcemia and osteoporosis, and developed acute renal colic. He then underwent parathyroidectomy with resection of a single adenoma and normalization of calcium and parathyroid hormone levels. Clinical and therapeutic implications of this rare association are discussed.

Learning points:

- The coexistence of KS and PHPT is very uncommon.
- Patients with mild PHPT often have nonspecific symptoms that may be confused and superimposed with those of hypogonadism.
- KS patients, especially when young and already osteoporotic at diagnosis, should be screened for other causes of secondary osteoporosis, in particular PHPT.

Background

Klinefelter's syndrome (KS) is the most common genetic cause of human male infertility, with a reported prevalence of 0.1–0.2% in the general population. The disease is widely underdiagnosed and the suspicion is usually driven by symptoms of hypogonadism (1). The typical endocrine derangements include decreased secretion of androgens and elevated gonadotropin levels.

Hypogonadism represents one of the most important causes of male osteoporosis; early onset of testosterone deficiency, as observed in KS, is an important risk factor for precocious osteoporosis (2). Signs of osteoporosis are detected in up to 40% of KS patients. The reduction in bone mineral density (BMD) affects morbidity risk and mortality from fractures in KS patients (3). Longitudinal studies in KS patients on testosterone replacement treatment yielded contradictory results as for BMD.

Low vitamin D and high parathyroid hormone (PTH) levels are frequent findings in KS patients (4). On the contrary, the coexistence of KS and primary hyperparathyroidism (PHPT) is very uncommon (5). We report herein the second case of this rare association.

Case presentation

A 22-year-old male was referred to our Endocrine Unit for worsening of fatigue. There was no family history of endocrine malignancy or endocrinopathy.

Personal history was uneventful. Physical examination disclosed small testes (8 ml) and sparse beard growth. He was tall (180 cm) and not obese (BMI 18 kg/m^2) with eunuchoid proportion (arm span 184 cm).

Investigation

Hypergonadotropic hypogonadism (follicle-stimulating hormone 45.7 UI/l, luteinizing hormone 26.5 U/l, testosterone 2.87 μg/l; 10,3 nM/l) and azoospermia were detected.

The karyotype was 47,XXY, thus pointing to the diagnosis of KS.

Routine laboratory profiles displayed normal complete blood count and renal function, but elevated serum calcium levels, both total (10.9 mg/dl, normal range 8.2–10.2; 2.7 nM/l, normal range 2.1–2.6) and ionized (1.35 mmol/l, normal 1.13–1.32), while phosphate and alkaline phosphatase (ALP) were within normal limits.

The serum PTH level was increased (95 ng/l, normal 15–65; 10 pM/l, normal range 2–7), 25-hydroxyvitamin-D3 (25OH-D) was decreased (10.2 μg/l, recommended >20 and 25.5 nmol/l, recommended >50), and calciuria was low (73 mg/24 h).

Ultrasonography (US) did not disclose pathological findings at the heart and kidney levels.

The patients refused microscopic testicular sperm extraction and androgen replacement therapy (ART) was started (transdermal testosterone, 40 mg/day), along with vitamin D repletion with cholecalciferol (10 000 U/week).

Three months later, 25OH-D was 21 μg/l (52.4 nM/l) and PHPT was confirmed (serum calcium 10.9 mg/dl, 2.7 nM/l; ionized calcium 1.41 mmol/l; PTH 98 ng/l, 11 pM/l). The resulting urine calcium-to-creatinine excretion ratio was >0.02 in two determinations.

Neck US and parathyroid scintigraphy were negative for enlarged parathyroid glands.

Dual-energy X-ray absorptiometry scan revealed osteoporosis at the forearm (BMD 0.526 g/cm^2; *z*-score: −3.1) and osteopenia at the femur (BMD 0.777 g/cm^2; *z*-score, −1.7).

Genetic tests for MEN and familial hypocalciuric hypercalcemia were found to be negative from the results.

On considering the young age of the subject, a genetic evaluation was required to rule out syndromic PHPT. *HRPT2* (*CDC73*), and *CASR* gene mutations were ruled out by sequencing the whole genes. As for menin, no mutation was found in exons 2, 3, 4, 5, 6, 7, 8, 9, and 10, whereas two new heterozygotic variants were disclosed in intron 2, namely c.445+70C>A and c.445+58G>A. The effect on splicing was null for the former but can reach 77% for the latter (Ref Seq: NM_130799.2). However, RNA extraction, RT, and cDNA sequencing of exons 1, 2, 3, and 4 did not disclose alternative splicing near the intronic variants, thus ruling out MEN1.

Six months later, while on vitamin D supplementation and ART with testosterone normalization (5.41 μg/l; 18.8 nM/l), the patient reported an increase in beard growth but no improvement in well-being. He still complained of asthenia and anxiety.

Laboratory results indicated worsening of hypercalcemia (total calcium 11.3 mg/dl, 2.8 nM/l and ionized calcium 1.46 mmol/l) with increased bone turnover (bone ALP 59 μg/l, osteocalcin 75 μg/l, and CTX 0.99 ng/ml) (Table 1).

Imaging studies were repeated. An oval, avascular mass, smaller than 10 mm, was shown in the lower left thyroid pole at US, but ^{99}Tc-sestaMIBI scan and neck and mediastinal magnetic resonance imaging were negative.

The patient was referred to surgery. Before parathyroidectomy (PTX), he was hospitalized for an acute renal colic with left hydronephrosis. A stent was inserted and ureteroscopy was negative for lithiasis.

Treatment

Bilateral neck exploration was then performed, with resection of the lower left parathyroid gland. Intraoperatively, PTH dropped by more than 50%. Pathological examination disclosed a parathyroid adenoma (diameter 1 cm and weight 240 mg).

Outcome and follow-up

Two days after operation, normalization of serum calcium level, ionized calcium, and PTH levels was confirmed, with persistence until the last follow-up visit (at 3 months).

Table 1 Biochemical data at diagnosis and after 6 months on ART+cholecalciferol.

Analyte	At diagnosis	After 6 months on ART+cholecalciferol
Hematocrit (%)/ hemoglobin (g/dl)	38.9/13.4	42.3/14.1
Creatinine (mg/dl)	0.7	0.8
Testosterone (μg/l–nM/l)	2.87–10	5.41–18.8
Weight (kg)	58.5	59.5
Serum calcium (mg/dl–nM/l)	10.9–2.7	11.3–2.8
Ionized calcium (mM/l)	1.35	1.46
Urinary calcium (mg/24 h)	73	267
25OH-D (μg/l–mM/l)	10.2–25.5	23.5–58.7
PTH (ng/l–pM/l)	95–10	98–11

25OH-D, 25-hydroxyvitamin-D3; PTH, parathyroid hormone.

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Discussion

We report herein the association of PHPT and KS in a young adult patient. This is the second case reported thus far, and the first one was with asymptomatic PHPT at diagnosis.

The first case of this rare association was reported more than 50 years ago, in a white 21-year-old male, diagnosed with KS on the basis of typical clinical features, decreased urinary excretion of 17-ketosteroids, and increased pituitary gonadotropins (5). Oral smear showed a female chromatin pattern. It turned out that he had also PHPT with hypercalcemia and hypophosphatemia due to a left parathyroid adenoma. At that time, PHPT was considered a rare disease.

Over the last decades, the clinical profile of PHPT has shifted from an overtly symptomatic disorder with nephrolithiasis and overt bone disease to a disorder with few or no symptoms at all. Patients with mild PHPT often have nonspecific symptoms, such as fatigue, mood disorders, anxiety, depression, and irritability (6). These complaints may be confused and superimposed with those of hypogonadism (1).

KS is a common cause of hypogonadism in men. Testosterone regulates male bone metabolism both through direct action at the androgen receptor on osteoblasts and, indirectly, after aromatization to estradiol. The low concentrations of insulin-like factor 3 found in most adult men with KS have also been related to low bone mass. Early-onset reduced bone mass in subjects with KS is due to both reduced bone formation and increased bone reabsorption (2), with decreased pubertal peak bone mass attainment and accelerated bone loss during adulthood. KS patients have typically lower BMD at the spine, hip, and forearm compared with healthy subjects, and signs of osteoporosis are detected in up to 40% of patients. Reduced BMD might also be present in KS men when testosterone levels are still normal and, in addition, ART does not always restore BMD in KS patients. Epidemiological studies have demonstrated that increased morbidity and mortality in KS (7) are also due to fragility fractures.

Vitamin D deficiency may play a role in worsening of bone mass. It is very common in KS, mainly if abdominal obesity and sedentary lifestyle are additional contributing factors. Data about the effects of vitamin D supplementation on calcium levels in PHPT are still controversial; nonetheless, supplementation is considered safe in patients with mild/asymptomatic PHPT and vitamin D deficiency (8).

Osteoporosis is a key feature of overt PHPT, preferentially located at sites rich in cortical bone, such as the distal forearm (9). Our patient was osteoporotic with greater impairment of BMD at the forearm, as typically observed in PHPT.

Currently, no pathogenic link can be hypothesized between KS and PHPT, even in the syndromic forms of the latter. It is therefore reasonable to regard this connection as merely accidental. Nonetheless, the association seems particularly ominous as PTHP does worsen bone damage induced by KS, thus further increasing the risk of fracture. PTX may promote bone mass recovery (10), hence lowering the risk of fracture.

Our patient was asymptomatic for PHPT at presentation, but became actually symptomatic for nephrolithiasis. International guidelines on asymptomatic PHPT recommend PTX for patients under 50 years of age (8) owing to the 25–40% risk of progression to symptomatic PHPT over the years (10), as well as the efficacy of curative PTX in reducing the long-term risk of lithiasis recurrence (11).

Finally, it should be considered that, despite the correction of hypogonadism with ART, our patient still complained of asthenia and anxious-depressive symptomatology. Randomized studies (10) demonstrated a moderate improvement in the quality of life after PTX; moreover, it has been recently reported that there is clinical improvement of symptoms in patients with asymptomatic PHPT after surgery, mostly in younger patients and in those with higher preoperative calcium levels (6). Expected bone recovery and decrease in nonspecific symptoms might have not yet been achieved in our patient due to the short follow-up.

There are no data about the effects of ART on serum calcium in hypogonadal patients with coexisting PHPT. Anyway, previous experimental studies demonstrated that testosterone increases oxalate urinary excretion and calcium oxalate crystal deposition in the kidney; furthermore, no relationship has yet been demonstrated between testosterone levels and nephrolithiasis (12).

In conclusion, this is the second case of a highly uncommon and probably accidental association between two endocrine diseases that are now considered relatively frequent. Both can expose patients to serious complications. It is therefore appropriate to recommend PTX, because it can cure PHPT in over 98% of patients. We suggest that patients with KS, especially when young and already osteoporotic at diagnosis, should be screened for other causes of secondary osteoporosis, in particular PHPT,

in order to implement therapeutic actions able to improve bone health.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

The authors confirm that written informed consent was obtained from the patient for publication of the submitted article.

Author contribution statement

E Castellano, R Attanasio, and G Borretta contributed to literature search and the writing of the manuscript. A Maffè and V Guarnieri provided the DNA analysis report. M Pellegrino and G Borretta contributed toward patient care and finalizing the draft.

References

1 Lanfranco F, Kamischke A, Zitzmann M & Nieschlag E 2004 Klinefelter's syndrome. *Lancet* **364** 273–283. (doi:10.1016/S0140-6736(04)16678-6)

2 Ferlin A, Schipilliti M, Vinanzi C, Garolla A, Di Mambro A, Selice R, Lenzi A & Foresta C 2011 Bone mass in subjects with Klinefelter syndrome: role of testosterone levels and androgen receptor gene CAG polymorphism. *Journal of Clinical Endocrinology and Metabolism* **96** E739–E745. (doi:10.1210/jc.2010-1878)

3 Bojesen A, Juul S, Birkebaek N & Gravholt CH 2004 Increased mortality in Klinefelter syndrome. *Journal of Clinical Endocrinology and Metabolism* **89** 3830–3834. (doi:10.1210/jc.2004-0777)

4 Bojesen A, Birkebaek N, Kristensen K, Heickendorff L, Mosekilde L, Christiansen JS & Gravholt CH 2010 Bone mineral density in Klinefelter syndrome is reduced and primarily determined by muscle strength and resorptive markers, but not directly by testosterone. *Osteoporosis International* **22** 1441–1450. (doi:10.1007/s00198-010-1354-7)

5 Spalding J, Morrow GW, Jr & Scholz D 1962 Coexisting Klinefelter's syndrome and primary hyperparathyroidism: report of case. *Metabolism* **11** 732–734.

6 Blanchard C, Mathonnet M, Sebag F, Caillard C, Hamy A, Volteau C, Heymann MF, Wyart V, Drui D, Roy M *et al*. 2013 Surgery for 'asymptomatic' mild primary hyperparathyroidism improves some clinical symptoms postoperatively. *European Journal of Endocrinology* **169** 665–672. (doi:10.1530/EJE-13-0502)

7 Swerdlow AJ, Higgins CD, Schoemaker MJ, Wright AF & Jacobs PA 2005 Mortality in patients with Klinefelter syndrome in Britain: a cohort study. *Journal of Clinical Endocrinology and Metabolism* **90** 6516–6522. (doi:10.1210/jc.2005-1077)

8 Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C & Potts JT, Jr 2014 Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *Journal of Clinical Endocrinology and Metabolism* **99** 3561–3569. (doi:10.1210/jc.2014-1413)

9 Rao DS, Phillips ER, Divine GW & Talpos GB 2004 Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism. *Journal of Clinical Endocrinology and Metabolism* **89** 5415–5422. (doi:10.1210/jc.2004-0028)

10 Ambrogini E, Cetani F, Cianferotti L, Vignali E, Banti C, Viccica G, Oppo A, Miccoli P, Berti P, Bilezikian JP *et al*. 2007 Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial. *Journal of Clinical Endocrinology and Metabolism* **92** 3114–3121. (doi:10.1210/jc.2007-0219)

11 Elkoushy MA, Yu AX, Tabah R, Payne RJ, Dragomir A & Andonian S 2014 Determinants of urolithiasis before and after parathyroidectomy in patients with primary hyperparathyroidism. *Urology* **84** 22–26. (doi:10.1016/j.urology.2014.01.016)

12 Afsar B & Karaca H 2014 The relationship between insulin, insulin resistance, parathyroid hormone, cortisol, testosterone, and thyroid function tests in the presence of nephrolithiasis: a comprehensive analysis. *Central European Journal of Urology* **67** 58–64. (doi:10.5173/ceju.2014.01.art13)

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