Case Report

Occurrence of Klinefelter Syndrome Mosaic 45,X/46,XY/47,XXY/48,XXYY/48,XXXY and Primary Hyperparathyroidism

César Ernesto Lam-Chung, MD 1, Larissa López Rodríguez, MD 2, Yayoi Segura Kato, MSc 3, Iván Josué Jiménez González, MD 2, Lourdes Mena-Hernández, MD 4, Renata Rivera-Juárez, Chem 2, Paloma Almeda-Valdes, MD, PhD 1, Jazmín Arteaga Vázquez, MD, PhD 2.*

1 Department of Endocrinology and Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, México
2 Department of Genetics, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, Mexico
3 Unit of Molecular Biology and Genomic Medicine, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, Mexico
4 Department of Dermatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, México

Abstract

Objective: The presence of primary hyperparathyroidism (PHPT) and Klinefelter syndrome (KS) is rare, and its association with KS mosaicism is even rarer. We report an unusual combination of these entities.

Methods: The patient was a 44-year-old male with a history of PHPT who had recurrent urolithiasis despite being treated with a successful parathyroidectomy. On examination, he had axillary hair growth, bilateral gynecomastia, a large port-wine stain at the right hemithorax and upper right limb, and genitalia and pubic hair corresponding to Tanner IV classification with normal consistency and its association with PHPT remains to be elucidated.

Results: Laboratory findings were unremarkable except for a slightly elevated luteinizing hormone, which was normal on repeat testing. Because of the picture of unexplained gynecomastia, laboratory findings, and low-volume tests, a diagnosis of KS was considered. Chromosomal analysis revealed a rare 45,X/46,XY/47,XXY/48,XXYY/48,XXXY KS mosaic.

Conclusions: KS phenotypes are largely variable, and their association with PHPT remains to be elucidated.

© 2021 AACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Despite being described in 1942, the diagnosis of Klinefelter syndrome (KS) remains a significant challenge. Nearly 75% of the cases will never obtain the correct diagnosis, resulting in unfavorable repercussions in morbidity and mortality, but this percentage could be higher in countries with less favorable health care services. Small testes, gynecomastia, hypergonadotropic hypogonadism, and infertility are the classic features of KS; however, the absence of apparent signs complicates the identification of affected individuals.

KS is the most frequent cause of male primary hypergonadotropic hypogonadism. A 47,XXY karyotype occurs in 90% of cases, whereas the remaining cases comprise various grades of mosaicism or abnormal structure of the X chromosome. On rare occasions, KS variants can present as higher-grade X chromosome aneuploidies (48,XXXY or 48,XXYY polisomies) and can be associated with severe phenotypes, including cognitive and behavioral disorders.

Primary hyperparathyroidism (PHPT) is a common endocrine derangement with a prevalence of up to 1 to 4 per 1000 in the general population. It is characterized by hypercalcaemia and inappropriately normal or elevated levels of parathyroid hormone (PTH). The vast majority of PHPT cases are caused by a single parathyroid adenoma; the remaining causes

Keywords:
hyperparathyroidism
Klinefelter syndrome
mosaicism
nephrolithiasis
include 4-gland hyperplasia, multiple adenomas, and parathyroid cancer. Only 20% to 30% of patients with PHPT have symptoms, nephrolithiasis being the most common. The presence of PHPT and KS have not been reported in the same patient very often, and its association with KS mosaicism is even rarer. We report an unusual case of a young Hispanic male with a mosaic KS and PHPT.

Case Report

A Mexican mestizo man aged 44 years was referred to our endocrinology department for management of recurrent urolithiasis. He presented with complaints of episodic pain bilaterally in the lumbar region since age 19 and had been using nonsteroidal analgesic drugs to reduce his pain for the past 20 years. He had undergone subcutaneous mastectomy at age 15 for gynecomastia but was not evaluated for its cause. At age 39, he underwent transurethral lithotripsy with the removal of a 2-cm stone from the left ureter, and he was reportedly diagnosed under the surgery and did not reveal abnormalities. He affirmed that he has several uncles on both the paternal and maternal sides of his family with urinary calculi but could not provide any details (Fig. 1).

At the time of his visit, the patient appeared old for his age. He had a height of 164 cm, a weight of 77.3 kg (body mass index, 29 kg/m²), and an arm span of 158 cm. Physical examination was remarkable for bilateral gynecomastia (Grade IV), without masses or discharge, and a giant hemangioma on the right hemithorax and upper right limb (Fig. 2). Axillary hair growth was present. He had a height of 164 cm, a weight of 77.3 kg (body mass index, 29 kg/m²), and an arm span of 158 cm. Physical examination was remarkable for bilateral gynecomastia (Grade IV), without masses or discharge, and a giant hemangioma on the right hemithorax and upper right limb (Fig. 2). Axillary hair growth was present.

Laboratory Findings

Table

| Values (normal range) | Before parathyroidectomy | After parathyroidectomy | On admission | At follow-up |
|-----------------------|---------------------------|-------------------------|--------------|--------------|
| **Blood**             |                           |                         |              |              |
| Sodium (136-146 mmol/L) | ...                      | ...                     | ...          | ...          |
| Potassium (3.5-5.1 mmol/L) | ...                      | ...                     | ...          | ...          |
| Chloride (98-107 mmol/L) | ...                      | ...                     | ...          | ...          |
| Calcium (8.6-10.3 mg/dL) | 10.3                     | 10.2                    | 9.12         | ...          |
| Phosphorus (2.5-5 mg/dL)  | 2.3                      | 3.63                    | 2.64         | ...          |
| Magnesium (1.9-2.7 mg/dL) | 2.29                     | 2.20                    | 2.00         | ...          |
| Creatinine (0.3-0.7 mg/dL) | 1.03                     | 0.99                    | 0.94         | ...          |
| Albumin (3.5-5.7 g/dL)   | 5.3                      | 4.75                    | 5.20         | ...          |
| Intact parathyroid hormone (12-88 pg/mL) | 128.33                   | 58.9                    | 70.0         | ...          |
| 25 (OH) vitamin D (30-100 ng/mL) | 17.6                     | ...                     | 22.1         | ...          |
| 1, 25-dihydroxyvitamin D (19.6-54.3 pg/mL) | ...                      | ...                     | 45.7         | ...          |
| Follicle-stimulating hormone (1.27-19.26 mIU/mL) (men) | ...                      | 13.09                   | 7.98         | ...          |
| Luteinizing hormone (1.24-8.62 mIU/mL) (men) | ...                      | 9.37                    | 4.12         | ...          |
| Estradiol (<60 pg/mL) (men) | ...                      | 19.0                    | ...          | ...          |
| Testosterone (1.75-7.81 ng/mL) | ...                      | ...                     | 4.27         | ...          |
| Thyrotopin (0.3-5 mIU/L)  | ...                      | 0.98                    | 1.75         | ...          |
| Prolactin (3.9-29.5 mg/mL) | ...                      | 8.30                    | 33.11        | ...          |
| Insulin-like growth factor 1 (78-230 ng/mL) | ...                      | ...                     | ...          | ...          |
| Growth hormone (0-3 ng/mL) | ...                      | 0.03                    | 0.031        | ...          |
| Corticotropin (10-100 pg/mL) | ...                      | 70                      | 35           | ...          |
| Free thyroxine (0.63-1.34 ng/dL) | ...                      | 0.95                    | 1.1          | ...          |
| Cortisol 8AM (6.7-22.6 mcg/dL) | ...                      | 11.86                   | 12.59        | ...          |
| Glycated hemoglobin (<5.7%) | ...                      | 4.9                     | 4.8          | ...          |
| Total cholesterol (<200 mg/dL) | ...                      | 207                     | 174          | ...          |
| High-density lipoprotein (40-60 mg/dL) | ...                      | 49                      | 45           | ...          |
| Low-density lipoprotein (<130 mg/dL) | ...                      | 151                     | 111          | ...          |
| Triglycerides (<150 mg/dL) | ...                      | 97                      | 113          | ...          |
| Fasting plasma glucose (70-105 mg/dL) | ...                      | 104                     | 81           | ...          |
| Alkaline phosphatase (34-104 U/L) | 105                     | 69                      | 73           | ...          |
| Alanine aminotransferase (5-52 U/L) | ...                      | 18.5                    | 25           | ...          |
| Aspartate aminotransferase (13-39 U/L) | ...                      | 17.0                    | 20           | ...          |
| 24-h Urine excretion |                           |                         |              |              |
| Sodium (mmol/100 ml) | ...                      | 136                     | 197          | ...          |
| Potassium (mmol/100 ml) | ...                      | 40                      | 32           | ...          |
| Calcium (<300 mg/100 ml) | 330.8                    | 403                     | 32           | ...          |
| Phosphorus (<1000 mg/100 ml) | ...                      | 260                     | 209          | ...          |
| Creatinine (mg/100 ml) | ...                      | 1792                    | 1497         | ...          |
| Citrate (250-1000 mg/100 ml) | 490.3                    | 343                     | 475          | ...          |
| Oxalate (7-44 mg/100 ml) | 20.2                     | 21.52                   | 23.22        | ...          |
Additional work-up tests included a urine amino acid panel, which did not reveal any abnormalities. Considering recurrent urolithiasis despite the absence of biochemical etiology and under the patient’s consent, a nephrolithiasis multigene panel (Invitae) was performed, which reported 2 variants of uncertain significance: c.569 T>C (p.Met190Thr) in the SLC3A1 gene and c.2359C>T (p.Arg787Trp) in the XDH gene, both in the heterozygote state.

Fig. 1. Patient’s pedigree. The proband (III.2) is marked by a black arrow.

Fig. 2. Clinical manifestations in the propositus. A, Prominent gynecomastia and a violaceous spot (10 cm at its greatest dimension) in the right pectoral area with well-defined boundaries. B, A large port-wine stain was also observed in the right scapular area, with well-defined irregular borders of vascular origin. C, Vascular spots with the same characteristics were observed on the right arm and forearm. Note that it is a dermatosis that only affects the right hemibody and does not cross the midline.
Because of the picture of unexplained gynecomastia, slightly high LH, and inability to palpate the left testicle, a diagnosis of KS was considered. A direct spermatobioscopy was carried out that revealed oligo-terato-asthenozoospermia (semen volume $= 1.7$ mL [normal $> 1.5$ mL], total sperm number $= 16 \times 10^6$ ejaculate [normal $\geq 39 \times 10^6$]). Ultrasonography of the testis showed the absence of both parenchymal alterations and hypervascularization; the right and left testicle volume was $8.1$ mL and $10.4$ mL, respectively. Chromosomal analysis was performed (GTG banding at 550 band resolution), which revealed low-grade mosaicism: mos $45,X,-Y[3]/48,XXXY[1]/46,XY[46]$. Interphase fluorescence In Situ hybridization was performed on lymphocytes and buccal epithelial cells, using the Vysis-ABBOTT® LSI probes: CEPX (DXZ1) and LSI CEPY (DYZ1), which also revealed a low-grade mosaicism: nuc ish(DXZ1,DYZ1)x2[6/1000]/[DXZ1x3,DYZ1x1][11/1000]/[DXZ1x1][40/1000]/[DXZ1x2,DYZ1x1][77/1000] and nuc ish(DXZ1,DYZ1)x2[6/1000]/[DXZ1x3,DYZ1x1][8/1000]/[DXZ1x2,DYZ1x1][61/1000]/[DXZ1x1][128/1000], respectively, according to the International System for Human Cytogenetic Nomenclature ISCN (2013) [11] (Fig. 3).

At the present time, our patient continues to have recurrent episodes of urolithiasis and irregular compliance with the treatment recommendations (including low sodium intake and potassium citrate supplementation), despite our efforts.

**Discussion**

We report the occurrence of a rare case of mosaic KS associated with PHPT and a variant of uncertain significance in the SLC3A1 gene. Only 2 cases of the coexistence of KS and PHPT have been reported. [9,12] Both cases had typical clinical and biochemical findings of KS. None of them were mosaic KS. To our knowledge, this is the first report of a mosaic KS case with normal gonadotropin levels at an adult age with mild clinical manifestations of KS, like gynecomastia, and with this unique pattern of mosaicism.

Unelevated serum gonadotropin levels in nonmosaic KS have been reported before. [13] It has been associated with different grades of mosaicism, [14] homogenous 47,XXY, [13] and trisomy Xq, [15] which indicate no obvious association between cytogenetic compositions and phenotypes. Typically, testosterone levels start to decline in late adolescence, and by early adulthood, overt hypergonadotropic hypogonadism ensues. [16] In addition, testosterone levels start to decline as normal testicular tissue is destroyed. [17] Because our patient had repeat PTH values that were normal with higher levels of vitamin D, we speculate that our patient could also have secondary hyperparathyroidism.

Our patient had gonadotropin levels that were virtually within normal ranges. Central hypogonadism is the result of the exhaustion of LH and follicle-stimulating hormone secondary to chronic
stimulation. On the other hand, it is feasible that variable levels of gonadotropin in KS represent different phenotypes. Numerous findings on slight neuroendocrine variations have been reported in KS, including increased secretion of prolactin and growth hormone and increased levels of daily pulsatility of LH. Androgen sensitivity also has an important role in influencing the KS phenotype. The SLC3A1 gene (located at chromosome 2p16.3-p21) protein product is involved in the transportation of cystine and dibasic (ornithine, lysine, and arginine) and neutral amino acids. It encodes the neutral and basic amino acid transport protein rBAT, which forms a heterodimer with the gene product of SLC7A9, and its mutation results in cystinuria. Cystinuria caused by defects in SLC3A1 is inherited in a true autosomal recessive manner in which heterozygotes have normal urinary cystine excretion. The absence of cystine in the kidney stone analysis and the urine amino acid panel support this notion. However, there have been cases of type II and type III heterozygotes that suffer from calcium oxalate urolithiasis. A variant has a minor allele frequency of <0.01, and In-Silico predictors (MutationTaster) describe it as disease-causing. Nevertheless, the status remains unchanged.

Up to 30% of recurrence of nephrolithiasis after parathyroidectomy has been reported after an average follow-up of 5 years. The cause of recurrent urolithiasis despite being treated with successful parathyroidectomy remains unclear because hypercalciuria is the main lithogenic factor associated with stone formation in PHPT. Few studies have attempted to elucidate the increased risk of kidney stone formation despite successful parathyroidectomy. It has been hypothesized that young age, higher body mass index, persistent hypercalciuria, low urine citrate: and high urine phosphate, oxalate, and sodium may explain this occurrence. Our patient had none of these risk factors of kidney stone formation other than young age.

Conclusion

Until now, no syndromic or pathogenic connection has been established between PHPT and KS. As in the other 2 reported cases, the coexistence of these 2 entities may be coincidental. We are unaware of any reasons why the presence of KS should alter the prevalence of PHPT in patients with KS or why either of these entities should alter the features of the other. Because PHPT is detected earlier in life, mild symptoms, such as depression, fatigue, and mood disorder, can be easily overlooked, as is the case with hypogonadism. We hope that this case sheds light on the phenotypic variation of KS and contributes to the existing literature.

Acknowledgments

We thank the Department of Endocrinology and Metabolism and the Department of Dermatology of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

C.L., L.R., and J.A. acquired the data. R.R. contributed by performing the analysis of the conventional and molecular cytogenetic studies. C.L. wrote the manuscript. All authors contributed to the article and approved the submitted version.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Klinefelter Jr HF, Reifenstein Jr EC, Albright Jr F. Syndrome characterized by gynecomastia, aspermatogenesis without a-leydigism, and increased excretion of follicle-stimulating hormone. J Clin Endocrinol Metab. 1942;2(11):1327–1337.
2. Herlihy AS, Halliday J, Cock ML, McLachlan RI. The prevalence and diagnosis rates of Klinefelter syndrome: an Australian comparison. Med J Aust. 2011;194(1):24–28.
3. Gravholt CH, Chang S, Wallentin M, Fedder J, Moore P, Skakkebæk A. Klinefelter syndrome: integrating genetics, neuropsychology, and endocrinology. Endocr Rev. 2018;39(4):389–423.
4. Kanakis GA, Nieschlag E. Klinefelter syndrome: more than hypogonadism. Metabolism. 2018;86:135–144.
5. Frühmesser A, Kotzot D. Chromosomal variants in Klinefelter syndrome. Sex Dev. 2011;5(3):109–123.
6. Tartaglia N, Ayari N, Howell S, D’Epagnier C, Zettler P, 48,XXXY, 48,XXYY, and 49,XXXXXY syndromes: not just variants of Klinefelter syndrome. Acta Paediatr. 2011;100(6):851–860.
7. Bilezikian JP, Cusano NE, Khan AA, Li J-M, Marcocci C, Banderia F. Primary hyperparathyroidism. Nat Rev Dis Primers. 2016;2:16033.
8. Fraser WD. Hyperparathyroidism. Lancet. 2009;374(9684):145–158.
9. Castellano E, Pellegrino M, Attanasio R, Guarneri V, Maffe A, Borretta G. Primary hyperparathyroidism and Klinefelter’s syndrome in a young man. Endocr Diabetes Metab Case Rep. 2015:2015, 150019.
10. Invitae Nephrolithiasis Panel. Invitae Corporation. https://www.invitae.com/en/physician/tests/720337/. Accessed January 18, 2021.
11. Shaffer LG, McGowan-Jordan J, Schmid M, eds. ISCN 2013: an international system for human cytogenetic nomenclature. Basel, Switzerland: S. Karger; 2013.
12. Spalding M, Morrow Jr GW, Scholz DA. Coexisting Klinefelter’s syndrome and primary hyperparathyroidism: report of case. Metabolism. 1962;11:732–734.
13. Cangiano B, Indiri R, Proffka E, et al. Central hypogonadism in Klinefelter syndrome: report of two cases and review of the literature. J Endocrinol Invest. 2021;44(3):459–470.
14. Shirai M, Matsuda S, Mitsukawa S. A case of hypogonadotropic hypogonadism with an XY/XXY sex chromosome mosaicism. Tokohu J Exp Med. 1974;114(2):131–139.
15. Sabbaghan M, Meybodi AM, Rahimian M, Sadighi Gilani MA. Occurrence of 47,X,i(X)(q10),Y Klinefelter variant with hypogonadotropic hypogonadism. Fertil Steril. 2011;96(2):e115–e117.
16. Aksglaede L, Skakkebæk NE, Alsmurf K, Juul A. Clinical and biological parameters in 166 boys, adolescents and adults with nonmosaic Klinefelter syndrome: a Copenhagen experience. Acta Paediatr. 2011;100(6):793–806.
17. Lanfranco F, Kamischke A, Zittmann M, Nieschlag E. Klinefelter’s syndrome. Nat Rev Endocrinol. 2004;364(9434):273–283.
18. Cherian KE, Jeebhasingh FK, Kapoor N, Paul TV. Klinefelter syndrome with low gonadotropin levels. BMJ Case Rep. 2015;2015, bcr2015213333.
19. Rabinowitz D, Cohen MM, Rosenberg E, et al. Chromatin-positive Klinefelter syndrome with undetectable peripheral FSH levels. Am J Med. 1975;59(4):584–590.
20. Carter JN, Wiseman DG, Lee HB. Klinefelter’s syndrome with hypergonadotropic hypogonadism. Br Med J. 1977;1(6055):212.
21. Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. J Clinical Endocrinol Metab. 2003;88(2):622–626.
22. Bonomi M, Rochira V, Pasquali D, et al. Klinefelter syndrome (KS): genetics, clinical phenotype and hypogonadism. J Endocrinol Invest. 2017;40(2):123–134.
23. Giusti M, Mortara R, Bolognesi F, Mignone D, Giordano G. Sleep-wake behavior and integrated values of LH, FSH, PRL, FH, and TSH in Klinefelter’s syndrome: a national registry study. J Endocrinol Invest. 1997;20(4):355–359.
24. Aksglaede L, Jensen RB, Scholz DA. Coexisting Klinefelter’s syndrome and primary hyperparathyroidism? J Med Genet. 2001;38:16033.
25. Pras E, Arber N, Akessonovic I, et al. Localization of a gene causing cystinuria to chromosome 2p. Nat Genet. 1994;14(6):415–419.
26. Calonge MJ, Gasparini P, Chillariego R, et al. Localisation of a gene causing cystinuria to chromosome 2p. Nat Genet. 1994;158(6):803–810.
27. Ptas E, Arber N, Akessonovic I, et al. Localization of a gene causing cystinuria to chromosome 2p. Nat Genet. 1994;158(6):803–810.
28. Deaconson TF, Wilson SD, Lemann Jr J. The effect of parathyroidectomy on the recurrence of nephrolithiasis. Surgery. 1987;102(6):910–913.
29. Kong X, Shen I, Gu X. Current opinions on nephrolithiasis associated with primary hyperparathyroidism. Urolithiasis. 2018;46(5):453–457.
30. Islam AK, Holt S, Reich J, Nwariaku F, Antonelli J, Maalouf NM. What predicts recurrent kidney stone after parathyroidectomy in patients with primary hyperparathyroidism? J Am Coll Surg. 2020;231(1):74–82.
32. Tran H, Grange JS, Adams-Huet B, et al. The impact of obesity on the presentation of primary hyperparathyroidism. J Clin Endocrinol Metab. 2014;99(7):2359–2364.

33. Spivacow FR, Negri AL, del Valle EE, Fradinger E, Martinez C, Polonsky A. Persistence of hypercalciuria after successful surgical treatment for primary hyperparathyroidism. Int Urol Nephrol. 2012;44(3):857–863.

34. Marchini GS, Faria KVM, Torricelli FCM, et al. Sporadic primary hyperparathyroidism and stone disease: a comprehensive metabolic evaluation before and after parathyrodeectomy. BJU Int. 2018;121(2):281–288.

35. Blanchard C, Mathonnet M, Sebag F, et al. Surgery for ‘asymptomatic’ mild primary hyperparathyroidism improves some clinical symptoms post-operatively. Eur J Endocrinol. 2013;169(5):665–672.