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KLINEFELTER'S SYNDROME ASSOCIATED WITH URETERAL POLYPS, RENAL PELVIC STONE AND PRIMARY HYPERPARATHYROIDISM

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Herein is reported a case of 47 XXY-Klinefelter's syndrome associated with ureteral polyps, renal pelvic stone and primary hyperparathyroidism. To the best of our knowledge, this is the second patient reported to have Klinefelter's syndrome coexisting with primary hyperparathyroidism. Frequent endocrinological disorders in the patients with Klinefelter's syndrome and diagnostic problems for hyperparathyroidism and ureteral polyps are discussed.

Key words: Klinefelter's syndrome, Primary hyperparathyroidism, Ureteral polyp.

According to the classical description, Klinefelter's syndrome is distinguished by small testes, gynecomastia and increased urinary gonadotropin activity¹⁾. Concepts of this syndrome have been modified and expanded to include a variety of additional physical characteristics, such as sparse body hair, eunuchoidal body habitus and feminine distribution of adipose tissue, which reflect the lack of androgen effects. Various other endocrinological disorders are reported to occur among the patients having this syndrome. These include diabetes mellitus²⁾, low radioactive iodine uptake by thyroid gland³⁾, low response of the gland to thyroid-stimulating hormone (TSH)^{3,4)}, and abnormal pituitary response to thyrotropin releasing hormone (TRH)⁵⁾.

Herein we report on a patient with Klinefelter's syndrome, who had right ureteral polyps, a stone in the ipsilateral renal pelvis and primary hyperparathyroidism. Review of the literature revealed only one similar case of primary hyperparathy-

roidism coexisting with Klinefelter's syndrome⁶⁾.

CASE REPORT

A 55-year-old Japanese male was hospitalized, because of right flank pain and gross hematuria. The past medical record disclosed several episodes of stone passage mainly from the right kidney and bilateral mastectomy that had been done for gynecomastia 16 years previously. The patient experienced no penile erection nor ejaculation. Physical examination revealed eunuchoidal body habitus with a height of 171 cm and an arm span of 177.8 cm. The patient weighed 71 kg. The beard, pubic hair and axillary hair were all scanty. Nasal cavities were free of polyps. Vague pain was noted on the right costovertebral angle, radiating to the right lower abdomen. The penis was small, measuring 5 cm in length and the bilateral testes were palpated to be small and firm, measuring about 1.5×2×2 cm. The prostate was normal in size and consistency. There was no evidence of hypospadias. The patient was normotensive and, psychologically, shy and

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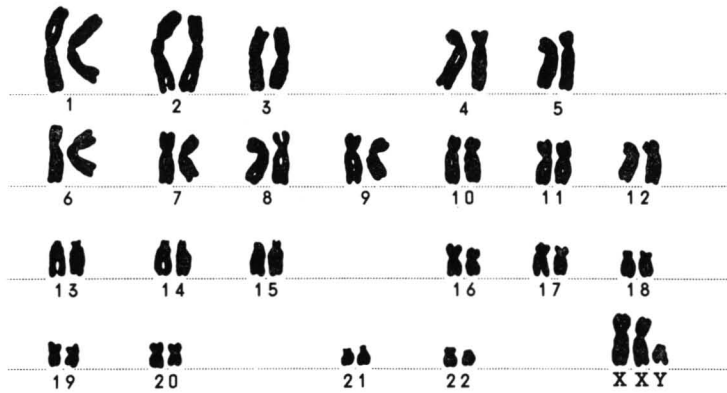


Fig. 1. Chromosomal analysis showing 47 XXY pattern (Giemsa stain).

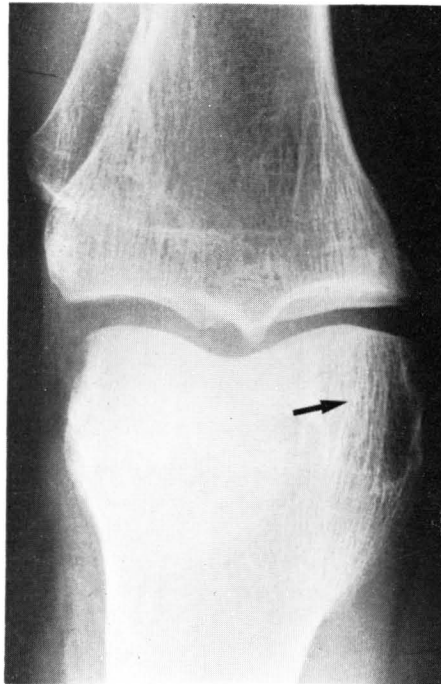


Fig. 2. Plain film of the left femur. Note cystic changes of the bone (arrow).

withdrawn, but of average intelligence.

Laboratory examinations revealed normal blood cell counts and a normal range of serum chemistry and electrolytes except for elevated serum alkaline phosphatase level (204 U/L) and borderline serum calcium level (10.8 mg/dl). Oral glucose tolerance test (G.T.T.) showed a diabetic curve of blood sugar, although the fasting blood sugar level was within normal range.

Urinalysis showed numerous red blood cells in the sediment and the urine culture was negative. Repeated urinary cytology showed findings suggestive of malignancy. Plasma hormonal study by radioimmunoassay revealed elevated levels of luteinizing hormone (LH) (100 mIU/ml) and follicle stimulating hormone (FSH) (170 mIU/ml), but a low level of testosterone (133 ng/dl). Urinary 17-ketosteroid and 17-hydroxysteroid were

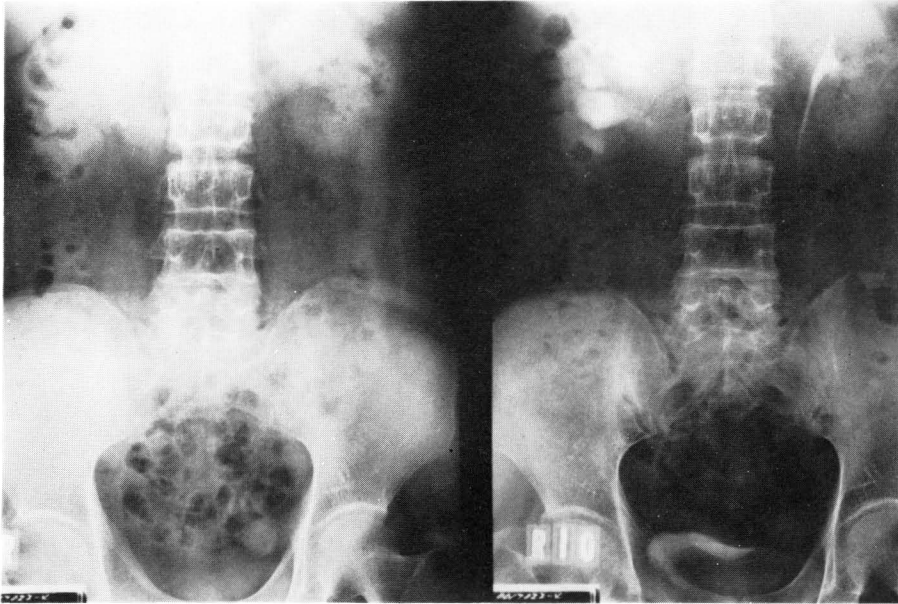


Fig. 3. Excretory urogram demonstrating a stone in the right pelvis and ipsilateral hydronephrosis. Right: Plain film. Left: 10 minutes urogram.

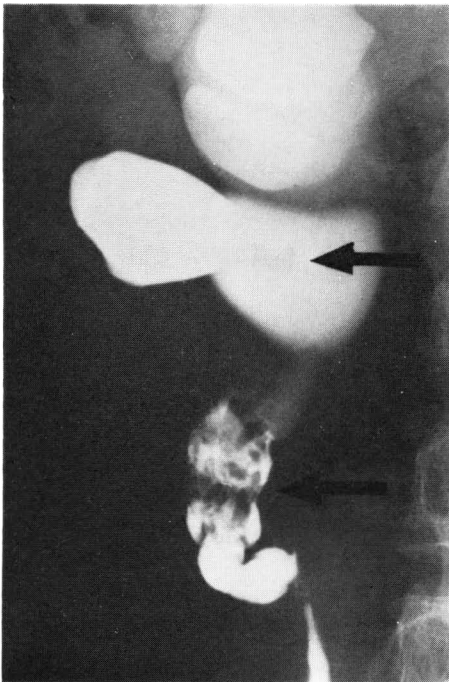


Fig. 4. Retrograde pyeloureterogram showing multiple vermiform filling defects in the upper ureter (lower arrow) and the right renal stone (upper arrow).



Fig. 5. Gross specimen shows multiple worm-like masses, attached to the upper ureter by slender stalks.

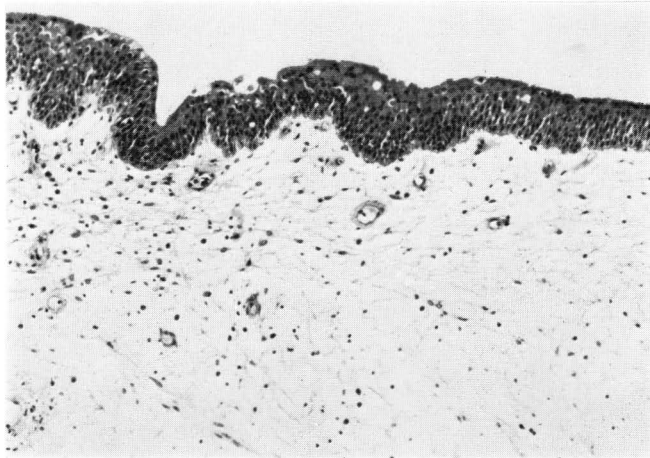


Fig. 6. Microscopic examination shows abundant fibrous stroma covered by normal transitional epithelium. Low magnification, reduced from X20.

4.6 and 8.1 mg per 24 hours, respectively. The uptake of radioactive iodine (T₃,T₄) by thyroid gland was normal. Chromosomal analysis, which revealed a 47 XXY pattern (Fig. 1), confirmed the clinical impression of Klinefelter's syndrome. Testicular biopsy revealed abundant fibrovascular connective tissue and few seminiferous tubules with no evidence of spermatogenesis.

X-ray bone study demonstrated significant, diffuse osteolytic changes of the skull, ribs, hands and long bones, and cystic changes of the femur, which indicated signs of osteitis fibrosa cystica (Fig. 2). An excretory urogram outlined severe right hydronephrosis and a tiny stone-like shadow in the ipsilateral renal pelvis (Fig. 3). A retrograde ureteropyelogram demonstrated multiple vermiform filling defects in the right upper ureter, which caused significant ureteral obstruction (Fig. 4). Because of the clinical impression of urothelial malignancy and severe hydronephrosis, a right radical nephroureterectomy was done. Macroscopically, the resected kidney had atrophic parenchyma and a small brownish stone in the renal pelvis, which was loosely attached to the posterior wall. On dissection multiple vermiform masses extruded out of the ureter, each measuring about 3 × 1 cm (Fig. 5). Microscopic examination of this ureteral lesions revealed fibrous

stroma lined with normal transitional cell epithelium, and the nature of the lesion was confirmed to be of typical benign ureteral polyps (Fig. 6). The postoperative convalescence was uneventful. The stone was composed of mixtures of calcium oxalate with calcium phosphate in the form of hydroxyapatite.

In spite of the normal or borderline high serum calcium levels, repeated measurements of daily urinary calcium demonstrated constant hypercalciuria (more than 300 mg/24 hr) under the regimen of low calcium diet. The rate of renal tubular reabsorption of phosphate was decreased to 54 per cent. On the basis of these clinical observations, a presumptive diagnosis of primary hyperparathyroidism was made. The repeated peripheral plasma levels of parathyroid hormone were constantly higher than normal (0.87 ng/ml, 0.77 ng/ml, normal: less than 0.5 ng/ml). A selective catheterization of the cervical veins was performed to collect multiple blood samples for parathyroid hormone assay, by the method described by Nadalini et al⁷⁾. The levels of the hormone were similar, high in all the blood samples from several places on the cervical veins, suggesting the presence of diffuse parathyroid hyperplasia (Fig. 7). Selective cervical angiography demonstrated no apparent enlargement of the glands.

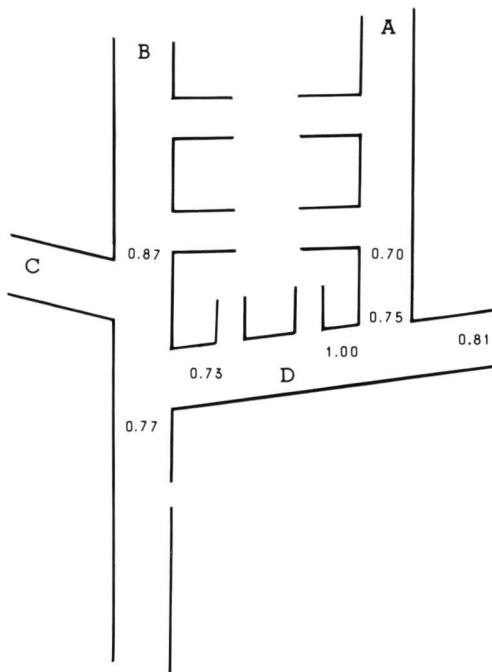


Fig. 7. Levels of P.T.H. (ng/ml) in veins of neck and thorax. P.T.H. levels are similarly high in all sampling site. A: Left internal jugular vein, B: Right internal jugular vein, C: Right brachial vein, D: Left brachiocephalic vein.

A cervical exploration was performed through a supra sternal notch incision. By the operation, the preoperative diagnosis of

hyperplasia was confirmed and a three quarter parathyroidectomy in addition to thymectomy was performed. Microscopically, the parathyroid glands showed findings compatible with water-clear cell type hyperplasia (Fig. 8). Serial sections of the excised thymus revealed no ectopic parathyroid tissue. The plasma level of parathyroid hormone became normal after the parathyroidectomy and convalescence was uneventful.

DISCUSSION

Aside from the well-known abnormality of pituitary-gonadal function, many interesting endocrinological disorders have been reported to occur among patients having Klinefelter's syndrome. The endocrinological disorders in Klinefelter's syndrome were recently reviewed by Hsueh et al.⁸⁾ Diabetes mellitus is one of the most frequently reported endocrinological disorders. Nielsen²⁾ reviewed 157 cases of this syndrome and found a diabetic G.T.T. pattern in 29 per cent and frank diabetes in 8 per cent. The incidence of an abnormal G.T.T. in patients with Klinefelter's syndrome seems apparently higher than the incidence in a random population. As noted in the present patient, most of these cases show no clinical manifestation of diabetes mellitus. Engelberth et al.⁹⁾ ex-

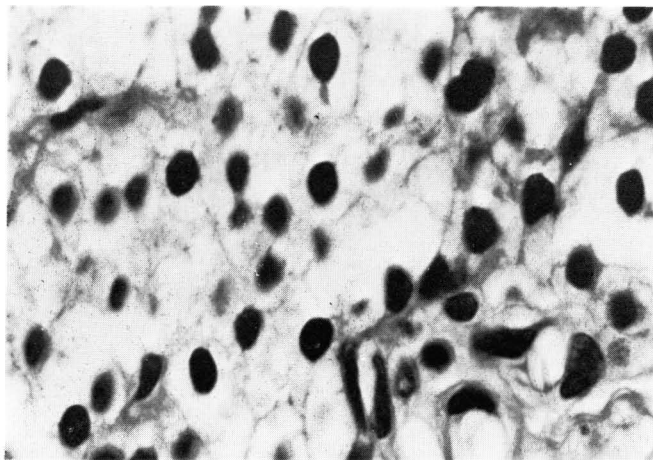


Fig. 8. Microscopic examination shows diffuse hyperplasia of the parathyroid glands without evidence of malignancy. Note abundant water-clear cells. High magnification, reduced from $\times 100$.

amed 36 chromatin-positive men, including 15 patients with Klinefelter's syndrome and found high levels of autoantibodies against cerebral tissue, testicle, thyroid, liver, kidney as well as insulin. These autoantibodies against various homologous tissues and hormone might be considered to be one of the causes of the endocrinological disorders noted in the patients of this syndrome, although the genotypic influence of the extra X chromosome may have an important role at the cellular level. Thyroid dysfunction has been reported to be frequently associated with Klinefelter's syndrome^{3,4}. In spite of the relatively high incidence of this disorder, radioactive iodine uptake was normal in the present patient. An increased incidence of breast cancer in Klinefelter's syndrome has been reported and this incidence was calculated by Scheike et al¹⁰. to be one fifth the incidence in females and 20 times the incidence in normal males. Because of the higher incidence of breast cancer in this syndrome, prophylactic mastectomy has been recommended. As for the association of primary hyperparathyroidism with Klinefelter's syndrome, only one case report exists in the past literature⁶. This patient is a 21-year-old white male with Klinefelter's syndrome and a stone at the left ureteropelvic junction; the diagnosis of hyperparathyroidism was based on hypercalcemia and hypercalciuria. The patient was confirmed to have a parathyroid adenoma by cervical exploration. Because of the rarity in the association of hyperparathyroidism among the patients with Klinefelter's syndrome, this association is considered to be incidental.

Although hypercalcemia has been most commonly seen in the patients with primary hyperparathyroidism, the serum calcium levels in the present case were normal or at the upper borderline. Yendt and Gagne¹¹ examined 55 patients with proven primary hyperparathyroidism and found 5 patients to have "normocalcemic hyperparathyroidism." Because all of these 5 patients were women, they ascribed this finding to the lower mean calcium level for normal women than for normal men. The effect of gonadal

steroids on the serum calcium level, however is not clearly understood at present. Determination of tubular reabsorption of phosphate is considered to be helpful in the diagnosis of hyperparathyroidism, when minimum hypercalcemia and normal serum phosphate level are obtained. To locate the tumor preoperatively, multiple cervical venous samplings were obtained to measure the concentration of the parathyroid hormone. This procedure was considered to be the most effective aid not only to confirm the diagnosis preoperatively, but also to discriminate between parathyroid adenoma and diffuse hyperplasia before the operation.

Fibrous (fibroepithelial) ureteral polyps are rare benign mesodermal tumors occurring in the upper urinary tract. In reviewing previously reported fibrous polyps, Banner and Pollack¹² reported that the male to female ratio is 3 to 2. The etiology of benign ureteral polyps has not been established. The proposed causes are obstruction, infection, trauma, chronic irritation, hormonal imbalance and developmental defects. The mechanical irritation caused by recurrent stone passage in our patient might have predisposed the minimum mucosal change to the formation of multiple ureteral polyps. Angiography does not seem to be suitable for the diagnosis of ureteral polyps, because both of the benign ureteral polyps and malignant epithelial tumor have poor vascularity. On excretory urography, ureteral polyps mostly demonstrate long, smooth, cylindrical filling defects, whereas epithelial neoplasms usually show a short, irregular and shaggy appearance. When the diagnosis of benign ureteral polyp is established, a partial ureterectomy, polypectomy, or simple fulguration may be indicated. However, if the kidney is severely damaged or the diagnosis is doubtful, nephroureterectomy should be considered.

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和文抄録

原発性副甲状腺機能亢進症，尿管ポリープおよび腎盂結石を伴った Klinefelter 症候群の 1 例

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副甲状腺機能亢進症，右尿管ポリープ，および右腎盂結石を合併した Klinefelter 症候群の 1 例を経験し，その臨床経過を報告するとともに文献的考察を加えた。

〔症例〕 55歳男性で右側腹部痛を主訴として来院した。理学的所見で外陰部は男性型であるが發育不良で両側睾丸は小さく eunuchoidal habitus を呈した。既往歴に右尿管結石で 5 回自然排石が認められたほかに，16年前 gynecomastia のため mastectomy を受けた事がある。身長 171 cm，arm span 177.8 cm で体毛は少なく染色体検査は 47 XXY で Klinefelter 症候群と診断した。血清 LH，FSH は高値でテストステロン値は低値を示した。排泄性腎盂造影で右水腎症と右腎盂結石が認められ，逆行性腎盂造影により右尿管上部に水腎症の原因となる腫瘍による多発性陰影欠損がみられ，尿細胞診も悪性腫瘍を疑わせたため，右

尿管全摘術を施行した。尿管腫瘍は組織学的には多発性の尿管ポリープであった。血清 Ca，P は正常範囲内であるが hypercalciuria がみられ，% TRP も 54 % と低値で副甲状腺ホルモン値も高いため，原発性副甲状腺機能亢進症を疑い cervical exploration を施行した。副甲状腺は，diffuse hyperplasia を呈し 3/4 副甲状腺全摘術と胸腺摘出術を行った。摘出した胸腺内には異所性副甲状腺組織は認められなかった。文献的に本症候群には糖尿病，甲状腺機能不全，下垂体性腺機能不全などのいくつかの内分泌機能障害が報告されている。しかし本症候群に副甲状腺機能亢進を合併した報告は過去に 1 例をみるにすぎない。副甲状腺機能亢進症の診断上，% TRP と静脈カテーテルによる頸部静脈血の multiple sampling による副甲状腺ホルモン測定の意味について言及した。