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Kyoto University
KLINFELETER'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 hyperparathyroidism coexisting with Klinefelter's syndrome5.

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
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. 1. Chromosomai analysis showing 47 XXY pattern (Giemsa stain).

Fig. 2. Plain film of the left femur. Note cystic changes of the bone (arrow).
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.
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 hydro nephrosis and a tiny stone-like shadow in the ipsilateral renal pelvis (Fig. 3). A retrograde ureteropyelogram demonstrated multiple vermiliform 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 vermiliform masses extruded out of the ureter, each measuring about 3 x 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 al. 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.
A cervical exploration was performed through a suprasternal 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.\textsuperscript{8}. Diabetes mellitus is one of the most frequently reported endocrinological disorders. Nielsen\textsuperscript{2} 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.\textsuperscript{9} ex-
amiined 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. 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 al. 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 literature. 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 Gagne reviewed 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 Pollack 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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