The Testicular Feminisation Syndrome

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Summary:
FOUR CASES OF testicular feminisation syndrome are reported with a discussion of the various peculiar features of this rare and interesting condition, in which an individual is genetically a male but is physically and mentally a female.

Introduction

One of the most interesting clinical curiosities in medicine is the condition of testicular feminisation syndrome in which the individual is essentially female in physical appearance and mental attitude but possesses gonadal testes. The following cases seen in the University Hospital, Kuala Lumpur are reported to illustrate the main features associated with this condition.

Case No. 1

Personal and family history:

TGT, a 21 year-old Chinese girl was referred from a district hospital in June 1974 with a history of primary amenorrhea. She was the sixth of a family of eight children, consisting of five girls and three boys. The eldest sister had seven children (four boys and three girls), the next sister had six children (all were girls), the third was 24 years old and had her menarche at the age of 14, and the younger sister was 17 years old and had her menarche at 15 years of age. The last two sisters and the patient were not married. There were two elder brothers and one younger brother. The mother had only one brother and no sister.

The patient had an apparently normal healthy childhood. There was no history of cyclical abdominal pain. Her breasts were noticed to develop at the age of 14 years. She had never felt any lump in her abdomen or her groins. She was average in her performance in school.

Physical examination:

She was generally thin-built and eunuchoid, 160 centimetres (five feet three inches) in height with normal proportions and weighed 39.7 kilograms (87.5 pounds).

She had an attractive feminine appearance with a fair complexion. There was no hirsuitism. She had long scalp hair but there was no axillary hair and only a few strands of hair in the pubic region. Her voice was high pitched. The breasts were fairly well-developed and the areolae and nipples were of normal size and pigmentation.

The thyroid gland was not palpable. Vision was normal. The heart and lungs were clinically normal. Examination of the abdomen and the groins did not reveal any lumps or tenderness.

The external genitalia were characteristically female with well-developed labia majora and minora and a normal-sized clitoris. The hymen was still intact. Examination per rectum did not reveal any cervix, uterus or palpable gonads. Further examination under anaesthesia showed a vagina of five centimetres in depth ending in a blind pouch.

Investigations

The routine blood and urine analysis, blood urea and serum electroloytes were normal. Radiographs of the chest and skull were unremarkable. The intravenous urogram showed both the kidneys

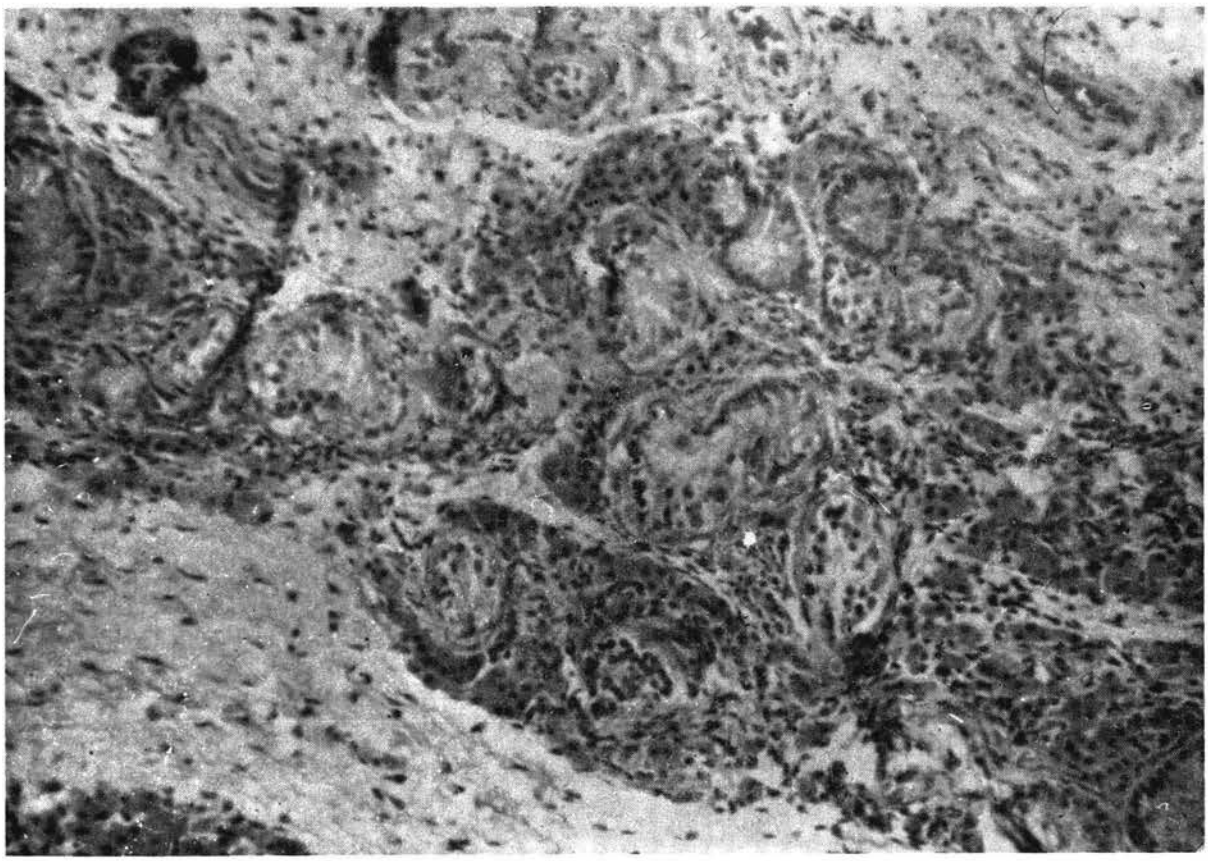

Photo 1.
(Low power) Dysgenetic testis with lobulated clumps of tubules lined by immature Sertoli cells separated by loose connective tissue stroma.

being normal in size, shape and position with no abnormalities seen in the pelvicalyceal system, ureters or the bladder. The total 24-hour urinary 17-ketosteroids was 14.4 milligrams and urinary cortisol was 730 micrograms (Normal limits).

The buccal smear did not show any Barr body and the blood leucocytes showed the drumstick in less than three per cent. Chromosome culture of peripheral leucocytes showed a 46 (XY) karyotype.

Psychosexual History

She was positively female-orientated. She used face powder and dressed in women's clothes. She mixed socially with both sexes but she had no special boyfriend as she felt that she was too young to get married. She admitted however that some boys had been interested in her but she did not reciprocate as she thought she was "abnormal". To quote her, "All I am interested is to have periods. All women have periods. I have no period. I am not normal."

Histopathology

A laparatomy with a small abdominal incision was done. No uterus or tubes were seen. A vestigeal ligament-like structure stretched from behind the bladder to end in small cysts, adjacent to the two gonadal swellings. Each gonad measured about two and a half by three by one centimetres and had a white capsule. A wedge biopsy of both gonads was made.

The histology of the biopsy specimens showed the structure of dysgenetic testes with Sertoli cell

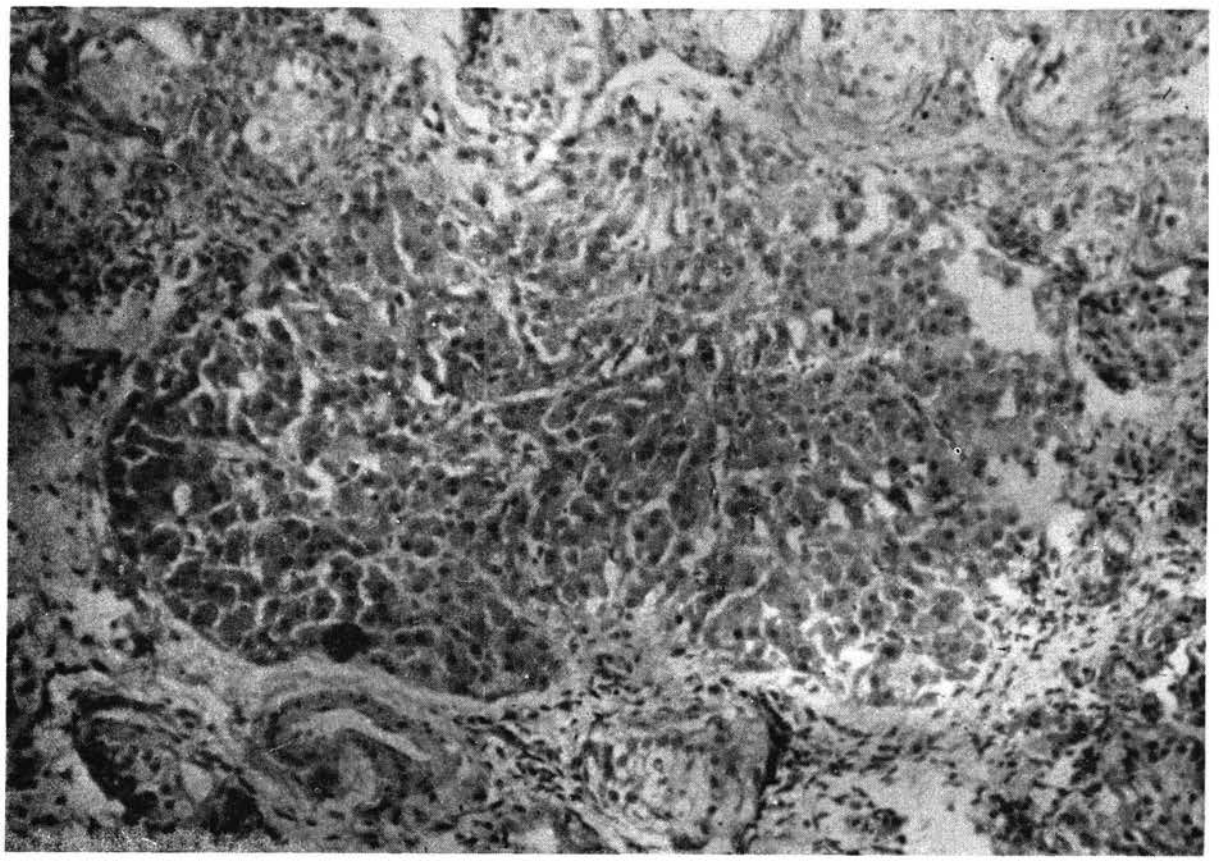

Photo 2.
(Low power) Dysgenetic testis showing hyperplastic Leydig cells.

adenoma. There was normal tunica albuginea. There were lobulated clumps of tubules lined by immature Sertoli cells separated by loose connective tissue stroma. Spermatogenesis was absent. Focal Leydig cell hyperplasia was evident. There was no evidence of any ovarian tissue or malignancy seen.

Management

When the patient was informed that there was no cure for her she became very depressed. However subsequent interviews with her managed to dispel her depressive mood. We convinced her that her amenorrhea had not affected her health or her feminity. She was told that her problem was not her fault or that of her parents. There were other women with amenorrhoea and infertility. She was reassured that she could lead a normal happy life as a wife as her sexual function would not be affected. She was encouraged to continue her usual activities. The decision whether to tell her future husband about her condition would be left to her. At NO time was she or her relatives ever told that she was a "male" and had testes. The ward staff were instructed to avoid discussing her condition in her presence.

She was advised gonadectomy but she only agreed to this after about six months. At the subsequent laparatomy, total excision of both gonads was done. Further histological examination did not reveal any malignancy. She was given stilboesterol one milligram daily as hormone maintenance therapy after gonadectomy.

Case No. 2

TML, a 14 year old Chinese girl who happened to be the niece of the first patient described was referred a year later as she had bilateral inguinal swellings and was suspected to have the same condition. She had not reached her menarche yet.

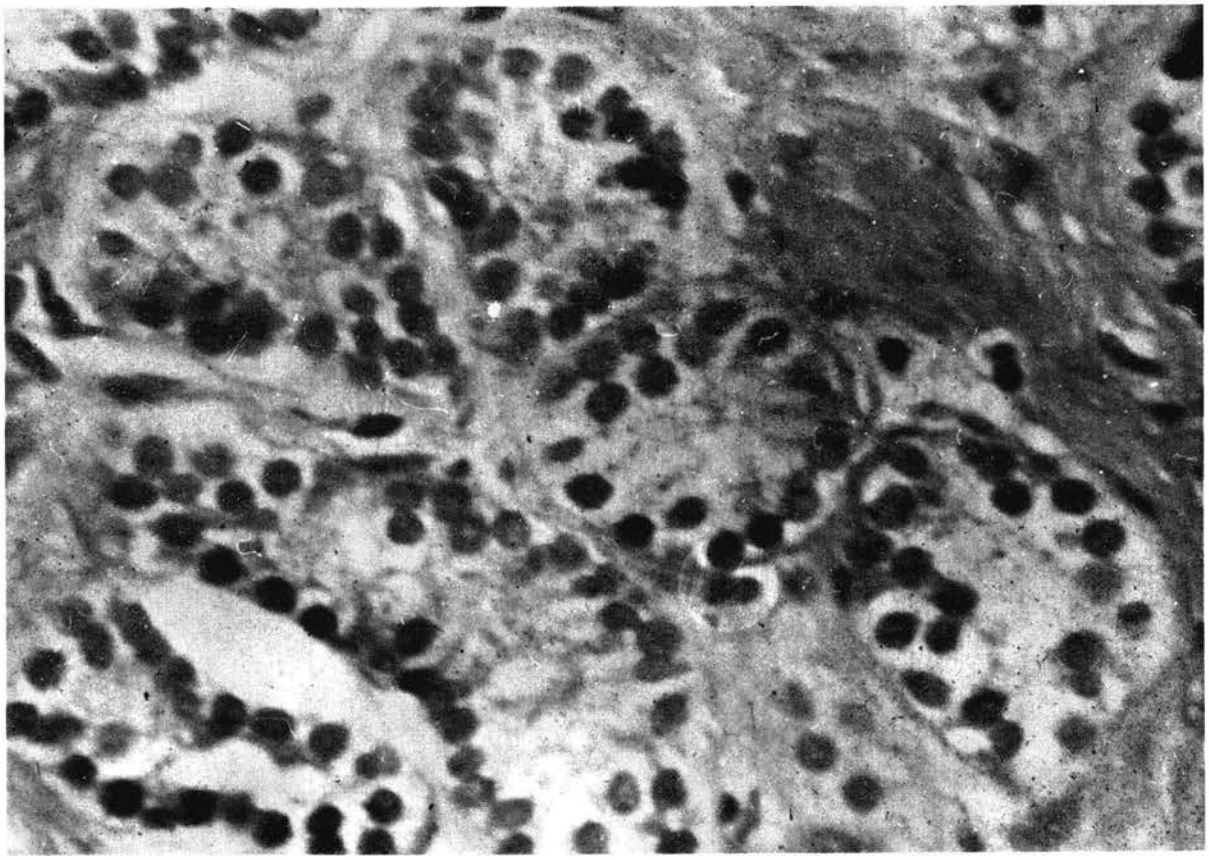

Photo 3.
(High power) Dysgenetic testis with Sertoli cell adenoma.

Otherwise she was feminine in other ways. Breast development was appropriate to her age. At the right inguinal region, there was a 3 by 2 cm soft, non-reducible swelling while on the left side, there was a similar swelling which was however reducible. The genitalia were female in appearance but the vagina which was about 8 cm deep, ended in a blind pouch. No cervix or uterus was felt. Neither the uterus nor the adnexal organs were present on laparascopic examination. Biopsy of the gonad showed infantile testicular tissue. Chromosome culture showed 46 XY karyotype.

Case No. 3

Z.I., a 16 year old Malay girl was referred for primary amenorrhoea. She was fair-complexioned with a typical female appearance. Her breasts were first noticed to develop at the age of 14 years. She also had bilateral inguinal swellings, which were tender on deep palpation. The right swelling was reducible while the left was not. Biopsy of the swellings showed hypoplastic testes and Leydig cell hyperplasia. The external genitalia were female although the vagina was only 4 cm deep and ended in a blind pouch. No uterus or ovaries was seen at laparascopy.

There were 4 other sisters in her family but all had normal menses.

Case No. 4

Z.B., a 22 year old Malay girl had been married for two years when she came to us with history of primary amenorrhoea and infertility. She was rather attractive with normal breast development and feminine voice. There was however no axillary or pubic hair. The labia and clitoris were normal and the depth of the vagina was about 6 cm. There was no cervix, uterus or tubes. She admitted to have occasional dyspareunia.

On laparascopy, the two gonads were seen within the abdominal cavity just at the internal inguinal ring. Chromosome culture showed 46 XY karyotype.

Discussion

These patients presented as a problem of intersex, a term which has replaced the old terms of pseudohermaphroditism. The sex of an individual is a composite of several factors: sex chromosomes, gonads, hormones, external genitalia, sex of rearing and sex of psychological orientation. Any anomaly in one or more factors will lead to a problem of intersex. Although the manifested sex is dependant on the dominating factor, the sex of rearing and the sex of psychological orientation are important for the individual's role in society. The other factors may be altered or ignored, if necessary, to suit this role.

The syndrome of testicular feminisation is diagnosed when an individual has all the external characteristics of a female, including psychological orientation, and yet has a male chromosomal and gonadal sex pattern.

This unusual condition was first reported in 1815 by Steglehner while performing an autopsy on a female, discovered, in his own words, "something wonderful and unheard of, the testes". However it was only in 1953 that Morris reviewed 82 cases in the literature and labelled the term "testicular feminisation syndrome". By 1963 there were 160 recorded in the literature with the incidence quoted as 1:60,000 (Morris 1963). However only 40 of these had complete chromosomal analysis (Pion 1965).

From the Malaysia/Singapore region, there has been only one family reported so far. (Wong and Salmon 1966)

Pathophysiology

Attempts to explain this syndrome on the hormonal status have been made in several experiments. Simmer et al (1965) have summarised their findings in their monograph:

1) the level of oestrogens in the urine is higher than that in the normal male and lower than that in the female (Wilkins 1957) but may fall to almost zero when the testes are removed,

2) the level of androgens have been found by most workers to be similar to most men,

3) the level of gonadotrophins is also of normal level but is sometimes increased especially after gonadectomy.

There have been several theories to explain the discrepancy between male gonads and female phenotype. One theory is that there was testicular insufficientcy in foetal life (Jost 1958) which is probably inherited as sex-linked recessive. Thus there is failure of the hormonal influence of the Mullerian system which is thus allowed to develop. A more acceptable theory is that there is failure of the end-organ response to the testicular hormones. This is supported by experimental evidence that showed that the level of androgens is normal with no increase in oestrogens. Even when exogenous androgens are given orally or percutaneously as an ointment, there is no response from the hair follicles or the clitoris. Thus Morris (1963) has also termed it the "androgen insensitivity" syndrome.

Recent work has shown that there is deficiency of 5-alpha steroid reductase which is necessary to convert testosterone in target cells to dihydrotestosterone which is the active compound (Wilson & Walker 1969). However, administration of dihydrotestosterone did not show any clinical response.

Other theories include those of Bardin (1970) who postulated that there was defective nuclear binding and uptake of the dihydrotestosterone; Dorfman who felt that there could be anti-androgenic substances in the peripheral tissues; and Wilkins who thought that there was rapid conversion of androgens into oestrogens in the end-organs.

The testes are found in the abdomen in 21 per cent of cases, in the inguinal region in 60 per cent, and in the labia majora in 19 per cent (Hauser 1963). There is rarely any evidence of spermatogenesis or the presence of normal Sertoli cells. The uterus and tubes are never present. However the vulva is essentially female. The pubic and axillary hair are usually absent. The breasts develop at the usual age and reach normal adult size. If the testes were removed, breast development would be affected (Hain & Schofield 1957). Jeffcoate (1968) however disagree with this.

The behaviour of these patients is undoubtedly feminine orientated and lead to normal sex lives complete with orgasm (Morris 1963, Wilkins 1957). Libido has been reported to be normal (Hauser 1963). Although they are sterile, they show normal instincts of motherhood.

The mode of inheritance has not been finally settled though most workers believe it to be sex-linked recessive manifesting in males.

Patients with this condition do not usually present problems at birth. Some may present with inguinal swellings and/or hernias in childhood.

Most of them present in adulthood with complaints of primary amenorrhea and sterility. Male nuclear sexing and chromosome karyotype of 46 XY from buccal smears and blood cultures in an otherwise normal female is characteristic and histology showing testicular tissue in the gonads is confirmatory. A few patients possess mosaicism of XY/XO and may manifest as incomplete testicular feminisation.

Some workers routinely perform gonadectomy after puberty for fear of the risks of malignancy in the intra-abdominal testes. Morris (1963) found that in a series of 50 patients who were more than 30 years, 22 per cent showed malignancy in the gonads. Other workers such as Jones and Scott (1958) found the incidence to be only five per cent. Hauser (1963) found ten cases of seminomas out of 128 cases of which eight were cured and only two died. Thus they advocate gonadectomy only if there is evidence of neoplasia. If gonadectomy is performed, it is necessary to treat these patients with small maintenance doses of oestrogens.

As there is no confusion in the sex identity, psychological workup is less indicated. It is stressed that it is not revealed to the patient or the relatives the existence of male gonads. They can be reassured of a normal sex life ahead and that amenorrhea and infertility are no bar to a happy married life.

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