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PATHOLOGY OF THE MALE GENITAL TRACT

General overview

- Production of a normal ejaculate depends on a combination of factors:
  - normal spermatogenesis, spermatozoa maturation and transport
  - normal accessory genital gland function
  - nervous, musculoskeletal and psychological factors.
- Reproductive differentiation requires appropriate sequential development and regression of the gonadal mesenchyme, paramesonephric (Mullerian) and mesonephric (Wolffian) tubules and ducts, and the tissues of the gonadal ridge.
- When all steps occur normally, genotypic, gonadal, and phenotypic sex is matched.
- Males normally have an XY genotype, which is the testis-determining factor (TDF), the production of which is governed by the sex-determining region (SRY) of the Y chromosome.
- Male differentiation is dependent on the production of testosterone hormones.
- The male phenotype depends on the production (by the Sertoli cells) of Mullerian duct inhibitory substance (MIS), which causes the paramesonephric (Mullerian) duct to regress.
- Interstitial endocrine cells produce testosterone that inhibits further female differentiation, prevents the mesonephric (Wolffian) ducts from regressing, and induces development of the penis and scrotum.
- The mesonephric ducts give rise to the epididymides, deferent ducts, and vesicular glands.
- Developmental abnormalities of the male genital system include Klinefelter's syndrome, persistent Mullerian syndrome, and androgen insensitivity (testicular feminization).
- These manifested clinically as ambiguity in phenotype and/or infertility.

1. SCROTUM

- **Structure and function** - The scrotum is an outpouching of perineal skin and is lined by evaginations of the peritoneum.
- The structure of the scrotum is adapted to its function of maintaining the testis at a temperature less than core.
- The scrotal skin is thinner than skin elsewhere and is well supplied with apocrine sweat glands with little or no subcutaneous fat or connective tissue.
- The contractility of the scrotum is a property of the dermal dartos that consists of fibroelastic tissue and smooth muscle.

- Thermoregulatory function is shared by the cremaster muscle, which regulates the proximity of the testis to the body, and the pampiniform plexus of veins, which ensures maximum contact of cooled venous circulation with the warmer arterial blood.
- If the testes are maintained at or above normal body temperature, degeneration or arrest of development of the seminiferous epithelium occurs.
- **Pathological conditions** - The formation of the scrotum and its full development at puberty, requires gonadotrophin-induced androgens, and is dependent therefore on the development of testes.
- Apparent absence of the scrotum has been observed in cryptorchidism.
- Because of its delicacy, scrotal skin is especially vulnerable to inflammation called scrotal dermatitis ("Wash leather scrotum").
  - Scrotal dermatitis can be caused by nonspecific environmental irritants.
  - Repeated rubbing and scratching or both can result in lichen simplex chronicus (LSC), a common chronic, usually solitary plaque of thickened skin.
  - Patients with LSC clinically have pruritus out of proportion to the appearance of lesions. The lesions of LSC are characterized by pigmentation and exaggeration of the normal skin markings. The central area becomes scaly, thickened and pigmented. This can cause infertility due to testicular degeneration.

2. PENIS

- The penis can be affected by congenital anomalies, inflammations, and tumors.
- The venereal infections (e.g., syphilis and gonorrhea) usually begin with penile lesions.

CONGENITAL ANOMALIES

Hypospadias and Epispadias

- Malformation of the urethral groove and urethral canal may create abnormal openings
  - either on the ventral surface of the penis (hypospadias) – more common
  - or on the dorsal surface (epispadias).
- **Hypospadias**
- Occurs in 1 in every 300 male children.
- Although a familial pattern of hypospadias has been recognized, no specific genetic traits have been established.
- The abnormal opening is often constricted, resulting in urinary tract obstruction and an increased risk of ascending urinary tract infections.
- There are several forms of hypospadias, classified according to location:
  - (1) **glandular** - opening on the proximal glans penis
  - (2) **coronal** - opening at the coronal sulcus
  - (3) **penile shaft** – opening along the shaft
  - (4) **penoscrotal** – opening near the beginning of the scrotum

- (5) **perineal** – opening at the back of the scrotum

- When the orifices are situated near the base of the penis, normal ejaculation and insemination are hampered or totally blocked.
- Clinical presentation
  - Difficulty directing the urinary stream and stream spraying.
  - Chordee (curvature of the penis).
  - Perineal or penoscrotal hypospadias necessitates voiding in the sitting position, and can contribute to infertility.
  - Hooded appearance of the penis.
  - There is an increased incidence of cryptorchidism.
- Concomitant anomalies
  - Any degree of hypospadias is an expression of feminization.
  - Perineal and scrotal urethral openings should be carefully evaluated to ascertain that the patient is not a hermaphrodite.

Phimosis

- Phimosis is a condition in which the contracted foreskin cannot be retracted (pulled) over the glans. This can also occur when the orifice of the prepuce is too small to permit its normal retraction.
- This condition is a normal occurrence in the newborn boy.
- **Causes**
- Chronic infection from **poor local hygiene** is its most common cause.
- Most cases occur in **uncircumcised males**.
- Phimosis can also occur if the foreskin is forced back before it is ready.
- **Presentations**
- Phimosis can occur at any age.
- It causes bulging of the foreskin during urination.
- Edema, erythema, tenderness of the prepuce, purulent discharge usually cause the patient to seek medical attention. Inability to retract the foreskin is a less common complaint.
- In diabetic older men, chronic balanoposthitis may lead to phimosis and may be the initial presenting complaint.
- Clinical importance:
  - interferes with cleanliness
  - permits the accumulation of secretions and detritus under the prepuce
  - favours the development of secondary infections and possibly carcinoma.

Paraphimosis

- Paraphimosis occurs when the foreskin is retracted behind the corona (or crown) of the penis and cannot be returned (pushed back) to the unretracted position. This can cause entrapment of the penis and impairing the drainage of blood.
- **Causes**
- This is due to chronic inflammation under the redundant foreskin, which leads to contracture of the preputial opening (phimosis) and formation of a tight ring of skin when the foreskin is retracted behind the glans.

- Iatrogenic causes: during penile examination or penile cleaning.
- Pathology
- The skin ring causes venous congestion leading to edema and enlargement of the glans, which make the condition worse.
- As the condition progresses, arterial occlusion and necrosis of the glans may occur.

Note: This is a medical emergency: Paraphimosis usually can be treated by firmly squeezing the glans for 5 minutes to reduce the tissue edema and decrease the size of the glans. The skin can then be drawn forward over the glans. Occasionally, the constricting ring requires incision under local anaesthesia.

INFLAMMATION

- A significant number of inflammatory conditions of the penis are caused by STIs.
- Local inflammatory processes unrelated to STIs may also involve the penis.
  - Specific sexually transmitted infections include syphilis, gonorrhea, genital herpes, etc.
- Several other systemic inflammatory diseases may produce penile lesions.
- Inflammations of the penis almost invariably involve the glans and prepuce.
- **Balanoposthitis** is nonspecific inflammation of the glans and prepuce caused by a wide variety of organisms (*Candida albicans*, anaerobic bacteria, *Gardnerella*, and pyogenic bacteria).
- Fungi may infect the skin of the penis and scrotum, because growth of fungi is favoured by warm, moist conditions at this site and poor local hygiene.
- Genital candidiasis may occur in otherwise normal individuals, but it is particularly common in patients with diabetes mellitus.
- Candidiasis typically presents as an erosive, painful, intensely pruritic lesion involving the glans penis, scrotum, and adjacent areas.
- Scrapings or biopsy specimens of the lesions reveal characteristic budding yeast forms and pseudohyphae within the superficial epidermis.
- Most cases of balanoposthitis occur as a consequence of poor local hygiene in uncircumcised males.
  - This causes accumulation of desquamated epithelial cells, sweat, and debris, termed **smegma**, which acts as local irritant.
- In such cases, the distal penis is typically red, swollen, and tender; a purulent discharge may be present.
- Persistence of such infections leads to inflammatory scarring and leading to phimosis.

TUMORS

- Tumors of the penis are uncommon. The most frequent neoplasms are carcinomas and a benign epithelial tumor (condyloma acuminatum)

3. TESTIS & EPIDIDYMIS

CONGENITAL ANOMALIES

- Except undescended testes (cryptorchidism), congenital anomalies are extremely rare and include absence of one or both testes and fusion of the testes (*synorchism*).

Cryptorchidism

- Cryptorchidism is found in approximately 1% of 1-year-old boys. It is one of the most common abnormalities of the male reproductive system.
- This anomaly represents a complete or incomplete failure of the intra-abdominal testes to descend into the scrotal sac.
- Individual cases of cryptorchidism may be due to genotypic or environmental causes.
- In most patients the undescended testis is palpable in the inguinal canal.
- Descent of the testes, epididymides, and spermatic cord (including the testicular artery and vein and the deferent duct) is a complex series of events that requires hormonal, constitutive, and nervous control.
- Testicular (and therefore epididymal) descent occurs in three main stages: the relative trans-abdominal migration phase, the intra-inguinal phase, and extra-inguinal migration.
- The condition is completely asymptomatic, and it is found by the patient or the examining physician only when the scrotal sac is discovered not to contain the testis.
- Retained testes lack spermatogenesis, and fertility may be compromised.
- Testicular torsion is found almost exclusively in maldescended testes.
- **Morphology**
- Cryptorchidism is unilateral in most cases.
- Cryptorchid testis is small in size and is firm in consistency as a result of fibrotic changes.
- Histologic changes in the malpositioned testis begin as early as 2 years of age.
- The seminiferous tubules are smaller than normal and often present with the "Sertoli cell only" pattern.
- Changes are characterized by an arrest in the development of germ cells associated with marked hyalinization and thickening of the basement membrane of the spermatic tubules.
- When the testis lies in the inguinal canal, it is particularly exposed to trauma and crushing against the ligaments and bones.
- A concomitant inguinal hernia accompanies the undescended testis in about 10% to 20% of cases.
- In addition, the undescended testis is at a greater risk of developing testicular cancer than is the descended testis.
- During the first year of life the majority of inguinal cryptorchid testes descend spontaneously into the scrotum.
- Those that remain undescended require surgical correction, preferably before histologic deterioration sets in at around 2 years of age.

Other testicular anomalies

Monorchia is the presence of only one testis.

- Monorchism is the result of cryptorchidism, severe unilateral testicular degeneration or agenesis.

VARIATION IN TESTICULAR AND EPIDIDYMAL SIZE

- **Testicular hypertrophy -** Enlargement of an otherwise normal testis is rarely a primary disorder.
- Secondary or compensatory hypertrophy is a unilateral condition that indicates an underlying disease such as orchitis or neoplasia in the contralateral testis.
- Underlying conditions include hemicastrates, hypoplasia, cryptorchidism, or atrophy of the contralateral testis.
- The increase in size can be due to an increase in the size of Sertoli cells and in the number of germinal cells per Sertoli cell.
- It can also be due to an increase in the number of Sertoli cells and spermatogonia, and an increase in diameter and length of seminiferous tubules.
- **Testicular hypoplasia -** Hypoplastic testes don't grow to normal size.
- Testicular hypoplasia occurs in cryptorchidism or genetic abnormalities such as Klinefelter's syndrome.
- An affected testis is grossly similar to a normal testis in almost every way, except size.
- The small size is because of an abnormally small number, length, or diameter of tubules, or one or more combinations of these.
- Microscopic abnormalities include a total lack of germ cells, arrested spermatogenesis in all tubules, or arrested spermatogenesis that varies from tubule to tubule.
- **Atrophy**
- Atrophy is a regressive change that affects the scrotal testis and can be caused by:
  - progressive atherosclerotic narrowing of the blood supply in old age
  - the end stage of an inflammatory orchitis
  - cryptorchidism
  - hypopituitarism
  - generalized malnutrition or cachexia
  - irradiation
  - prolonged administration of antiandrogens (treatment for advanced carcinoma of the prostate)
  - exhaustion atrophy (due to persistent stimulation produced by high levels of follicle-stimulating pituitary hormone)
- The gross and microscopic alterations follow the pattern as for cryptorchidism.
- Clinical conditions include decreased fertility due to hypospermatogenesis, maturation arrest and vas deferens obstruction.

INFLAMMATION

Mumps

- Mumps is a systemic viral disease that most commonly affects school-aged children.
- Testicular involvement is extremely uncommon in this age group.
- In postpubertal males, however, orchitis may develop and has been reported in 20% to 30% of male patients.
- It can lead to sterility.

Tuberculosis

- Tuberculosis almost invariably begins in the epididymis and may spread to the testis.
- The infection invokes the classic morphologic reactions of caseating granulomatous inflammation characteristic of tuberculosis elsewhere.

Syphilis

- The testis and epididymis are affected in both acquired and congenital syphilis.
- The morphologic pattern of the reaction takes two forms:
  - the production of gummas (soft, non-cancerous growth)
  - or a diffuse interstitial inflammation characterized by edema and lymphocytic and plasma cell infiltration.

VASCULAR DISORDERS

Torsion

- Twisting of the spermatic cord typically cuts off the venous drainage of the testis.
- Torsion results from an anatomic defect where the testis has increased mobility.
- If the torsion is corrected within 6 hours, the testis may remain viable.

TESTICULAR TUMOURS

- Testicular neoplasms are divided into two major categories: germ cell tumours (about 95%) and sex cord-stromal tumors.
- Most germ cell tumors are aggressive cancers.
- Sex cord-stromal tumors, in contrast, are generally benign.

Pathologic Classification of Common Testicular Tumors

Germ Cell Tumors

- **Seminomatous tumors**
  - Seminoma
  - Spermatocytic seminoma
- **Non-seminomatous tumors**
  - Embryonal carcinoma,
  - Yolk sac (endodermal sinus) tumor
  - Choriocarcinoma

- Teratoma

Sex Cord-Stromal Tumors

- Leydig cell tumor
- Sertoli cell tumor

GERM CELL TUMORS

- For unexplained reasons there is a worldwide increase in the incidence of germ cell tumors.
- In the 15- to 34-year age group, they constitute the most common tumor of men and cause approximately 10% of all cancer deaths.
- **Environmental factors and genetic predisposition**
- Environmental factors play a role in the incidence of testicular germ cell tumors.
- Testicular germ cell tumors are associated with a spectrum of disorders known as testicular dysgenesis syndrome (TDS).
- This syndrome includes cryptorchidism (most important risk factor), hypospadias, and poor sperm quality
  - some of these conditions might be influenced by in-utero exposures to pesticides and nonsteroidal estrogens
- There is a strong family predisposition associated with the development of testicular germ cell tumors.

Seminoma

- Seminomas are the most common type of germ cell tumors.
- The peak incidence is the third decade and they almost never occur in infants.
- An identical tumor arises in the ovary, where it is called *dysgerminoma*.
- Seminomas produce bulky masses, sometimes ten times the size of the normal testis.
- The typical seminoma has a homogeneous, gray-white, lobulated cut surface, usually devoid of hemorrhage or necrosis.
- Extension to the epididymis, spermatic cord, or scrotal sac occurs.

Yolk sac tumor (non-seminomatous germ cell tumor)

- It is the most common testicular tumor in infants and children up to 3 years of age.
- In this age group it has a very good prognosis.
- Grossly, the tumor is nonencapsulated, and on cross-section it presents a homogeneous, yellow-white, mucinous appearance.

Teratoma (non-seminomatous germ cell tumor)

- The designation *teratoma* refers to a group of complex testicular tumors having various cellular components from more than one germ layer.
- Pure forms of teratoma are fairly common in infants and children, second in frequency only to yolk sac tumors.
- Grossly, teratomas are usually large, ranging from 5 to 10 cm in diameter.
- Because they are composed of various tissues, the gross appearance is heterogeneous with solid, sometimes cartilaginous, and cystic areas.

TUMORS OF SEX CORD-GONADAL STROMA

Interstitial (Leydig) cell tumor

- Interstitial cell tumors are derived from the endocrine cells of the testicular interstitium.
- They are grouped with Sertoli cell tumors as they are derived from tissue of the sex cords or stroma.
- Interstitial cell tumors may be multiple (multicentric) or solitary and unilateral or bilateral.
- They may arise at any age, although most cases occur between 20 and 60 years of age.
- **Gross features**
- These neoplasms form circumscribed nodules, usually less than 5 cm in diameter.
- They are rarely large enough to increase the size of the organ, but the rounded bulge of the tumor can be visible in a small, soft, atrophic testis.
- They are well demarcated but only lightly encapsulated.
- The tumor is predisposed to hemorrhage which causes dark discoloration, and to cyst formation in areas.
- Approximately 10% of the tumors in adults are invasive and produce metastases; most are benign.

Sertoti cell tumor

- These tumors often cause enlargement of the affected testis and there is, sometimes, the development of a **feminization** syndrome in the host.
- The feminizing effect of these tumors is due to either their high content of estrogen or to secretion of inhibin.
- Increased inhibin secretion by the neoplastic Sertoli cells inhibits the secretion of FSH and LH by the pituitary, which, in turn, inhibits testosterone production and presumably alters the ratio of estrogen to testosterone.
- Recovery may follow castration and supportive therapy.
- Larger tumors are irregularly ovoid, lobulated and enclosed in a tense tunica albuginea.
- The cut surface bulges and usually is white and quite firm or even hard, although sometimes it may be discolored or cystic.
- The firmness of the tumor is due to the abundance of its stroma (thus different from the other tumors).

PATHOLOGY OF THE PROSTATE

- The prostate is a retroperitoneal organ encircling the neck of the bladder and urethra, and is devoid of a distinct capsule.
- Testicular androgens control the growth and survival of prostatic cells. Castration leads to atrophy of the prostate caused by widespread apoptosis.
- Lesions include inflammation, hyperplasia, neoplasia, etc.

BENIGN ENLARGEMENT

Benign Prostatic Hyperplasia (BPH) or Benign Nodular Hyperplasia (BNH)

- Benign prostatic hyperplasia (BPH), also known as benign prostatic hypertrophy, is a histologic diagnosis characterized by proliferation of the cellular elements of the prostate.
- BPH is an extremely common disorder in men around the age of 50.
- The surface is irregularly nodular (BNH) and may obscure the normal bilobed appearance.
- It is characterized by hyperplasia of prostatic stromal and epithelial cells, resulting in the formation of large, fairly discrete nodules in the periurethral region of the prostate.
- Etiology is not clear but an overall reduction of the rate of cell death, resulting in the accumulation of old cells in the prostate could be the cause.
- The prostate nodular enlargements may encroach on the lateral walls of the urethra to compress it to a slit-like orifice.
- Chronic bladder outlet obstruction (BOO) may lead to urinary retention, renal insufficiency, recurrent urinary tract infections, gross hematuria, and bladder calculi.
- The increased resistance to urinary outflow leads to bladder hypertrophy and distension, accompanied by urine retention.
- The inability to empty the bladder completely creates a reservoir of residual urine that is a common source of infection.
- Patients experience increased urinary frequency, nocturia, difficulty in starting and stopping the stream of urine, straining (valsalva manoeuvre) overflow dribbling, dysuria, and have an increased risk of developing bacterial infections of the bladder and kidney.
- Enlargement of the prostate is also frequently associated with constipation due to pressure on the rectum.
- **Diagnosis**

- Digital rectal examination (DRE) - During this portion of the examination, prostate size and contour can be assessed, nodules can be evaluated, and areas suggestive of malignancy can be detected.
- Urinalysis - to assess for the presence of blood, leukocytes, bacteria, protein, or glucose
- Urine culture - to exclude infectious causes of irritative voiding and is usually performed if the initial urinalysis findings indicate an abnormality
- Prostate-specific antigen - Although BPH does not cause prostate cancer, men at risk for BPH are also at risk for this disease.
- Electrolytes, blood urea nitrogen (BUN), and creatinine - These evaluations are useful screening tools for **chronic renal insufficiency**.
- Ultrasonography (abdominal, renal, transrectal) - to determine bladder and prostate size and the degree of hydronephrosis (if any) in patients with urinary retention or signs of renal insufficiency.
- Endoscopy of the lower urinary tract – Cystoscopy.

TUMORS

Adenocarcinoma

- Adenocarcinoma of the prostate is the most common form of cancer in men.
- Cancer of the prostate is typically a disease of men over the age of 50, screening for prostate cancer is recommended to begin at the age of 40.
- Several factors, including age, race, family history, hormone levels, and environmental influences can influence the development of prostate cancer.
- **Clinical course**
- Localized prostate cancer is asymptomatic, and is usually discovered by the detection of a suspicious nodule on rectal examination or elevated serum PSA level.
- Most prostatic cancers arise peripherally away from the urethra, and therefore urinary symptoms occur late.
- Back pain caused by vertebral metastases is common.
- Digital rectal examination may detect some early prostatic carcinomas because of their posterior location.
- PSA is the most important test used in the diagnosis and management of prostate cancer.