Methodic elaboration for practical lesson in

Dermatovenerology

for students of Medicine Faculty nr.2

Topic N10

Gonorrhea and non gonococcal urogenital infections
Cutaneous Manifestations of HIV Infection

GONORRHEA

Key features:

- Gonorrhea is the most common reportable STI in the industrialized world and is caused by *Neisseria gonorrhoeae*, a microorganism that infects the mucous membranes of the human genital tract (as well as the anus, rectum or mouth) after direct–usually sexual–contact with the mucosal surface of an infected person
- Cutaneous pustules and systemic symptoms such as arthritis and fever result from hematogenous dissemination; sepsis occurs in only a very small percentage of infected individuals
- The incidence of gonorrhea has declined over the past several decades, and in some countries it has become a disease concentrated in minority populations. There has been a recent increase in reported gonococcal cases in many parts of Europe, especially in the Russian Federation and other former Eastern Block countries
- Over the past few decades, resistance of N. gonorrhoeae to various antimicrobials, especially penicillin, tetracyclines and quinolones, has continued to rise to the point that fluoroquinolones are no longer effective for the treatment of gonorrhea in a number of geographic regions

Transmission -*N. gonorrhoeae* is a pathogen restricted to humans as its only host and transmitted primarily by sexual contact. The most efficient transmission occurs by vaginal or anal intercourse where there is physical contact with the mucosal surface of a sexual partner with asymptomatic or mildly symptomatic infection. An exception is indirect contact among prepubescent girls sharing contaminated objects. There is no evidence that gonococci can be spread by air droplet transmission as occurs with meningococci. Vertical transmission occurs from an infected mother to the newborn during parturition, and this may lead to gonococcal conjunctivitis, pneumonia or even vulvovaginal infection.

Biology of *N. gonorrhoeae* - Gonococci are Gram-negative diplococci that typically grow in pairs. They exhibit multiple colony types when grown on hemoglobin-containing media in a 3% CO_2 atmosphere. The outer membrane structure of *N. gonorrhoeae* is typical for Gram-negative bacteria but, in contrast to *N. meningitidis,* it lacks the polysaccharide capsule that is responsible for the virulence of meningococci. Surface molecules of the outer membrane are involved in attachment, invasion and injury of the host and they are important antigenic structures, especially the pili. The microorganism cannot tolerate drying or low temperatures and its growth is optimal at 35–37°C in a 5% CO_2 atmosphere on a complex growth medium, containing inorganic iron, glucose, vitamins and cofactors as well as antibiotics.

Pathogenesis - Although there is increasing knowledge about the pathogenicity of this microorganism, the exact molecular mechanisms of invasion of gonococci into the host cell are still unknown. Several virulence factors are involved in the processes of adherence, inflammation and mucosal invasion. Because pili increase adhesion to the host cell, they also play an important role in pathogenesis; this may explain why non-piliated gonococci have a reduced ability to cause infections in humans. Gonococci are able to multiply and divide intracellularly, where they are immune to host defense mechanisms. Gonococci have the ability to cause tissue damage by production of a variety of peptides and lipids such as phospholipase, peptidases, lipid A and peptidoglycans. They seem to play a role in the damage of fallopian tubes and the development of postinflammatory arthritis.

Clinical Features - There is a broad spectrum of clinical manifestations of gonorrhea in both men and women, including asymptomatic infections, local symptomatic mucosal infections (with or without local complications), and systemic dissemination. Symptoms vary according to sites of infection and the different strains.

The incubation period for gonorrhea is relatively short; it only takes 2-5 days until signs and symptoms of an infection with *N. gonorrhoeae* appear.

- **Gonococcal infection in men** - While up to 10% of infected men remain asymptomatic, the most common clinical presentation of gonococcal infection is an acute anterior urethritis with dysuria and a urethral discharge that is mostly purulent and profuse and spontaneously appears at the urethra. In about one-quarter of infected men, the urethral symptoms are less pronounced, similar to those of non-gonococcal urethritis, and appear only after urethral manipulation (stripping). Without treatment, the clinical symptoms disappear in most patients after about 6 months. ***Local complications include***

inflammation of the Cowper's and Tyson's glands and gonococcal pyoderma; ascension may lead to epididymitis, prostatitis and vesiculitis. Patients with gonococcal epididymitis present with unilateral testicular pain and swelling accompanied by urethritis.

- **Gonococcal infection in women** - In about 50% of infected women, gonococcal infection is asymptomatic and therefore remains unnoticed. The primary site of gonococcal infection in women is the endocervical canal, with associated clinical symptoms consisting of increased vaginal discharge, dysuria, intermenstrual bleeding, and menorrhagia. Clinical inspection shows a typical purulent cervical discharge with erythema and edema; swabbing of the endocervical canal results in a characteristic yellow swab, indicating gonococcal cervicitis. Urethral colonization is present in 70-90% of infected women and is the usual site of infection in women who have had a hysterectomy. Occasionally, inflammation of Bartholin's glands is observed, with acute swelling of the labial folds and a discrete purulent discharge that appears when pressure is applied to the gland.***The most common local complication in women*** is acute salpingitis or pelvic inflammatory disease (PID) due to ascension of the microorganisms. It occurs in approximately 10-20% of infected women and may result in the long-term consequences of infertility, chronic pelvic pain, and ectopic pregnancy. Clinically, symptoms of PID vary and include lower abdominal pain, adnexal tenderness, elevation of the ESR, leukocytosis and fever. Gonorrheic perihepatitis (Fitz–Hugh–Curtis syndrome), an inflammation of the adjacent peritoneal area, is an infrequent complication in which symptoms of PID are accompanied by pain in the right upper quadrant, mimicking acute cholecystitis.
- **Extragenital gonorrhea**
  - Pharyngeal gonorrhea
  - Rectal gonorrhea
  - Gonococcal ophthalmia
- **Disseminated gonococcal infection**
  - Arthritis–dermatosis syndrome (gonococcemia)
  - Gonococcal endocarditis and meningitis

Laboratory Diagnosis Laboratory diagnosis is based on the identification of *N. gonorrhoeae* from infected mucous membranes by stained smears, cultures or molecular biologic detection of the microorganism in genital, rectal, pharyngeal or ocular secretions.

In women, samples for smears and cultures are obtained from the endocervical canal (after cleansing of any external exudate of vaginal secretions) and from the urethra. In the case of diagnosis by nucleic acid amplification methods (see below), urine, vulvovaginal or introital specimens can also be tested. In men, specimen collection from the urethra is performed by using a small swab or bacteriologic loop. In the case of molecular biologic detection of gonococcal DNA or RNA, urine is also an appropriate and non-invasive specimen type. Anorectal specimens should be obtained under direct vision using anoscopy. Swabs of the posterior pharynx, including the tonsillar area, can be plated directly onto supplemented selective media. In the case of clinical symptoms in extragenital areas or a history of oropharyngeal or anal intercourse, as well as in high-risk groups, routine sampling of the pharyngeal and anorectal areas is recommended.

- **Staining methods -** Direct detection of the microorganism (as diplococci within polymorphonuclear cells) in stained smears using a Gram or methylene blue stain provides an immediate provisional diagnosis, especially in symptomatic individuals.
- **Culture techniques -** Isolation of *N. gonorrhoeae* by culture is the gold standard for the diagnosis of gonococcal infections in men and women, and positive results obtained by stained smears should be confirmed by gonococcal culture. elective medium that are used for isolation of *N.gonorrhoeae* are Muller-Hinton and antibiotic-containing selective media Thayer–Martin. Incubation is recommended at 35–37°C in a 5% CO_2 environment.
- **Non-amplified DNA hybridization** - The non-amplified DNA probe test (Gen-Probe PACE 2®) is still the most common non-culture test for gonorrhea and is based on the hybridization of gonococcal RNA. It has a sensitivity and specificity comparable with culture.
- **Nucleic acid amplification techniques** - the strand displacement amplification assay (ProbeTec™), can detect gonococcal DNA or RNA, alone or in addition to chlamydial DNA, from a single collected specimen.

Differential Diagnosis - Other causes of urethral and cervical discharge in men and women must be considered. Among them, infections with *Chlamydia trachomatis*, *Trichomonas vaginalis*, yeasts and anaerobic bacteria have to be included in the routine differential diagnosis.

Treatment of localized, uncomplicated gonococcal infection:

- Single dosage of any of the following:
  - Cefixime, 400 mg PO
  - Ceftriaxone, 125 mg IM
  - Ciprofloxacin, 500 mg
  - Ofloxacin, 400 mg PO
  - Levofloxacin, 250 mg PO
  - Patients allergic to cephalosporins or quinolones may be treated with spectinomycin, 2 g in a single IM dose.

CHLAMYDIA

Etiology and Pathogenesis -The Greek-derived word chlamys means "cloak draped around the shoulder." This refers to the draping of intracytoplasmic inclusions containing C. trachomatis around the nucleus of an infected cell.[16] C. trachomatis is a nonmotile, Gram-negative, obligate intracellular organism with 15 serotypes: A through C cause chronic conjunctivitis and are endemic in Africa and Asia, D through K cause urogenital tract infections, and L1 though L3 cause lymphogranuloma venereum (see Chap. 203). The bacteria have a two-phase life cycle. The infectious form is known as the elementary body, which enters host cells through endocytosis. Replication through binary fission occurs inside the host cell, using host-derived adenosine triphosphate, with formation of reticulate bodies. Large intracytoplasmic inclusions inside cells are made up of hundreds of reticulate bodies, which then convert back to infectious elementary bodies to be released from the cell.

Urogenital tract infection is the area most commonly affected in men and women. Transmission is through oral, anal, or vaginal intercourse with symptoms occurring 1 to 3 weeks after exposure. However, asymptomatic infection occurs in up to 80 percent of women and 50 percent of men. Co-infection with other STDs occurs frequently, most commonly with gonorrhea. Serotype G has been associated with an increased risk of squamous cell carcinoma. Newborns can be infected from passage through the birth canal of an infected mother.

Clinical Findings: History and Physical Findings - The most common manifestation of disease is urethritis, characterized by a watery or mucoid discharge from the urethra that may be accompanied by dysuria in both men and women. Rectal infection may result in proctitis in both men and women. Infection may also present as lymphogranuloma venereum .

- **In men** younger than age 35 years, C. trachomatis is the most common cause of epididymitis. Besides urethral discharge, men may also present with unilateral scrotal pain and swelling. It remains questionable whether chlamydia causes prostatitis. Some studies have linked chronic prostatitis to C. trachomatis infection.
- **In women**, the columnar epithelium of the endocervix is commonly affected. Other symptoms beside those of urethritis include intermenstrual or postcoital bleeding and lower abdominal pain. As with gonococcal infection, a severe complication in women that can result in sterility is PID, with ascending infection to the uterus and fallopian tubes. Symptoms may include fever, lower abdominal pain, back pain, vomiting, vaginal bleeding, dyspareunia, and adnexal or cervical motion tenderness on physical examination. Sequelae of untreated infection include tubo-ovarian abscesses, ectopic pregnancies, chronic pelvic pain, and infertility due to chronic inflammation with resultant scarring. Five percent to 10 percent of women with PID may develop perihepatitis (Fitz-Hugh-Curtis syndrome).
- **Newborns** may develop conjunctivitis and pneumonia after being infected from passage through the birth canal of an infected mother. Signs of ophthalmia neonatorum may include injected conjunctivae, purulent discharge, or swollen eyelids. Pneumonia as a consequence of neonatal chlamydial infection can first present after 1 to 3 months. Symptoms may include cough and fever with wheezing or crackles on pulmonary ascultation.

Laboratory Tests - Traditionally, chlamydial infection was diagnosed by tissue culture with specimens obtained from the endocervix in women, urethra in men, rectum, or conjunctivae. More rapid and sensitive tests have replaced culture in the past few years.

- ***A direct fluorescent antibody test***, which is highly specific, can be performed on cervical and penile urethral specimens with rapid results.
- ***Enzyme immunoassays***, which are less specific than the direct fluorescent antibody test, can be used to detect chlamydial antigens through the formation of a color change.
- Less invasive tests involving ***nucleic acid amplification***, such as PCR and ligase chain reaction, are more commonly being used to detect even small amounts of chlamydial DNA in urine samples.

Complications - Reactive arthritis can occur up to 1 month after symptoms of non-gonococcal urethritis (NGU). The classic triad associated with this syndrome is NGU, arthritis, and conjunctivitis. Additional symptoms may include fever, malaise, myalgias, asymmetric joint stiffness, lower back pain, cutaneous lesions involving the genitals, and aortic regurgitation as a result of inflammation around the aortic valve. Individuals with the haplotype HLA-B27 are at increased risk of developing the reactive arthritis syndrome.

Prognosis and Clinical Course -Early treatment with appropriate antibiotic therapy results in excellent prognosis and reduces the risk of long-term complications, such as infertility from PID. It is important to complete an appropriate course of antibiotics. First-time therapy with antibiotics has been shown to be up to 95 percent effective in eradicating infection. It is important to counsel patients on the risks of co-infections with other STDs and to arrange for partner referral. Sexual contact should be avoided until treatment is completed.

Treatment of Chlamydia infection:

- Azithromycin, 1 g PO in a single dose
- Doxycycline, 100 mg PO twice a day for 7 days
- Recommended treatment for pregnant women:
    - Erythromycin, 500 mg PO four times a day for 7 days
    - Amoxicillin, 500 mg PO three times a day for 7 days

TRICHOMONAS VAGINALIS

Epidemiology - Trichomonas vaginalis causes a condition called trichomoniasis, which affects about 2 million to 3 million women annually in the United States. Worldwide, it has been estimated to affect more than 180 million women. It is difficult to estimate the number of men infected because most infections in men are asymptomatic. Yet, 30 percent to 40 percent of men who are exposed have detectable organisms. It is currently not a reportable disease.

Etiology and Pathogenesis - T. vaginalis is an STD caused by parasitic protozoa, which infect vaginal and urethral epithelium, causing microulcerations. In women, organisms may be isolated from the vagina, urethra, cervix, Bartholin and Skene glands, and bladder. In men, organisms may be found in the external genital area, anterior urethra, epididymis, prostate, and semen. The incubation period before symptomatic infection is usually between 4 and 28 days. In women, manifestation of infection ranges from an asymptomatic carrier state to inflammatory vaginitis. Due to the increase in vaginal acidity, symptoms tend to occur during or after menstruation. Most men are asymptomatic carriers.

Clinical Findings: History and Physical Findings - Women who are infected may complain of a malodorous, yellow-green vaginal discharge, vulvar pruritus and erythema, dyspareunia, lower abdominal discomfort, or dysuria. Infection tends to occur in sexually active women and men. Men are usually asymptomatic, yet some may complain of urethral discharge and burning on urination with increased frequency. Both men and women may be asymptomatic carriers. Newborns may become infected from passage through the birth canal of an infected mother. Infection in a child may be a sign of sexual abuse.

On physical examination, punctate hemorrhages may be seen on the vaginal wall and cervix. A term commonly associated with such hemorrhages is colpitis macularis or strawberry cervix. This is a specific sign of trichomoniasis, yet is only seen in 1 percent to 2 percent of women during a regular pelvic exam. It may be visualized in up to 45 percent of cases through the use of colposcopy. Findings of balanitis, epididymitis, and prostatitis may be present in men. Co-infection with other STDs may produce a more complex case.

Laboratory Tests -Vaginal pH tends to be elevated above 5.0 in trichomoniasis. A saline wet mount of a vaginal swab specimen is a common diagnostic test.

- The ovoidshaped protozoa can be visualized microscopically, best by phase contrast or dark-field examination.
- The most sensitive test is anaerobic culture, which usually is positive within 48 hours, and is the preferred method for diagnosing infection in men.
- PCR methods have been shown to have high sensitivity and specificity; however, availability of these tests is limited.

Complications - Recently, studies have shown a link between T. vaginalis infection and complications in pregnancy, such as premature delivery, early rupture of membranes, and low birth weight in newborns. Trichomoniasis has also been associated with an increased risk of HIV transmission. Less commonly, it has been linked to atypical PID.

Prognosis and Clinical Course -Prognosis is excellent with resolution of infection occurring after appropriate treatment. Treatment of sexual partners is important to avoid re-infection. Persistent infection despite appropriate treatment with metronidazole may require susceptibility testing.

Treatment of Trichomoniasis:

- Metronidazole, 2 g PO in a single dose
- Metronidazole, 500 mg PO twice a day for 7 days[a]
- Alternative recommendations
    - Tinidazole, 2 g PO in a single dose

CUTANEOUS MANIFESTATIONS OF HIV INFECTION

Key features:

- Cutaneous disorders in the setting of HIV infection represent a vast spectrum of diseases. As immunity deteriorates, variable presentations, opportunistic infections, mixed infections and potential adverse drug reactions are increasingly likely
- Because the cutaneous findings often correlate with immune status, a more focused differential diagnosis may be generated if the viral load and $CD4^+$cell count are known. For example, seborrheic dermatitis and oral hairy leukoplakia first appear in patients with $CD4^+$counts >500 cells/mm^3, whereas giant mollusca and large non-healing perirectal ulcers due to herpes simplex virus are seen in patients with counts of less than 50 cells/mm^3
- With the advent of *h*ighly *a*ctive *a*nti *r*etroviral *t*herapy (HAART), skin disorders such as herpes zoster and *Mycobacterium avium intracellulare* infection may become clinically apparent or worsen when the immune status improves, a phenomenon known as the immune reconstitution syndrome
- Unusual skin eruptions, skin diseases with exaggerated presentations (e.g. seborrheic dermatitis, molluscum contagiosum), sudden acute exacerbations (e.g. psoriasis), and treatment failures (e.g. refractory dermatophyte infection) should alert the clinician to the possibility of underlying HIV infection
- Several of the drugs employed in HAART can lead to significant drug–drug interactions, e.g. ritonavir inhibits cytochrome P450

INFECTIOUS HIV-RELATED CUTANEOUS DISORDERS

VIRAL INFECTIONS

- Exanthem of primary HIV infection (acute retroviral syndrome) -The earliest cutaneous manifestation of HIV infection may be an exanthem occurring as a manifestation of primary HIV infection. The latter is defined as the presence of HIV-1 in the plasma (based on detection of viral RNA by PCR and/or p24 antigen) *prior* to the development of HIV-1 antibodies (as determined by ELISA or Western blot). Primary HIV infection may be asymptomatic, but up to 80% of newly infected individuals will report a history of a 'viral illness'. Also referred to as acute retroviral syndrome, the most common signs and symptoms include fever, lymphadenopathy, pharyngitis and a cutaneous eruption, reminiscent of acute mononucleosis. The generalized morbilliform exanthem (that typically spares the palms and soles) usually lasts 4-5 days. Additional manifestations are outlined in Figure 77.3. Due to an initial burst of HIV replication, a decline in $CD4^+$T cells can be observed (see Fig. 77.3), occasionally to levels that allow the development of opportunistic infections[12, 13]. The acute illness occurs 2-4 weeks after HIV exposure; symptoms are self-limited, but the duration varies from a few days to over 10 weeks. The acute retroviral syndrome may be confused with a drug reaction or other infections (e.g. Epstein–Barr virus, hepatitis B virus, enteroviruses, cytomegalovirus, secondary syphilis). The diagnosis therefore requires a high degree of clinical suspicion (not just in high-risk groups) and is confirmed by specific laboratory tests for HIV RNA and p24 antigen.
- **Herpes simplex virus (HSV)** Oral, labial and genital HSV infections in relatively immunocompetent HIV-infected individuals are typical in appearance and severity, with recurrence rates similar to those observed in the general population. Once significant immune suppression develops, lesions may progress to chronic, non-healing, deep ulcerations involving the perianal region, genitalia and tongue. More frequent recurrences are also observed when the $CD4^+$count falls to <100 cells per cubic millimeter
- **Varicella zoster virus (VZV)** - In HIV-infected individuals, primary varicella may follow a benign course or it may be complicated by fatal pulmonary involvement. HIV-infected patients have a 7-15 times greater relative risk of developing herpes zoster, a disease that is predictive of progression to severe immune suppression, especially if associated with fever. As cell-mediated immunity declines, reactivation of latent virus can occur. Although the classic dermatomal eruption may be seen, HIV-associated zoster can also be multidermatomal, ulcerative, chronic, verrucous and/or widely disseminated with systemic involvement. Bacterial superinfection, acyclovir resistance, therapeutic failure, and multiple recurrences are not uncommon[24]. Vasculitis with bone necrosis and exfoliation of teeth may develop if the blood supply to the mandible and maxilla are compromised[25].
- **Poxvirus** Molluscum contagiosum commonly affects children (especially those with atopic dermatitis) and immunosuppressed individuals, particularly patients with HIV infection and significantly reduced $CD4^+$cell counts[27]. HIV-infected patients may develop classic dome-shaped umbilicated papules as well as larger (>1 cm) coalescent and disfiguring lesions that are often resistant to treatment. Although any part of the body can be affected, the lesions favor the face, neck and intertriginous areas.
- **Human papillomavirus (HPV)** - is transmitted by close, repeated contact that can be sexual in nature (including genital–genital and digital–genital) as well as by fomite contact. HPV-induced lesions are common in the general population but even more prevalent in HIV-infected individuals. Lesions may be widespread with multiple verrucae on the face, limbs and genitalia that may coalesce into large plaques. In addition, HIV-infected patients have a higher risk of developing cervical intraepithelial neoplasia (CIN) and anal intraepithelial neoplasia (AIN).
- **Epstein–Barr virus (EBV)** -Oral hair leukoplakia is an early sign of HIV infection that develops in approximately 25% of infected individuals. In the absence of antiretroviral therapy, development of oral hairy leukoplakia is a predictor of rapid decline and progression to AIDS. The usually asymptomatic lesions appear as corrugated white plaques with hair-like projections along the lateral aspect of the tongue. Lesions have no malignant potential and are usually not treated unless they are unsightly or cause dysphagia. Antiretroviral therapy may lead to regression of the plaques[34].
- **Cytomegalovirus (CMV**) - Despite the high frequency of CMV viremia, cutaneous disease is relatively uncommon; presentations vary from ulcers and verrucous or purpuric papules to

vesicles, morbilliform eruptions and hyperpigmented indurated plaques. Ulcers may also develop within any mucosal surface and are usually a sign of disseminated disease. Demonstration of intranuclear CMV inclusions within dermal endothelial cells usually proves to be a more sensitive assay than viral cultures.

Bacterial Infections - *Staphylococcus aureus* is the most common bacterial pathogen in patients infected with HIV, especially those with indwelling catheters. Infections respond to antibiotic therapy, but recurrences are common owing to nasal colonization[23, 37]. Pyogenic bacterial infections generally respond to antibiotics but unusual presentations, e.g. botryomycosis, may be quite refractory. Topical antibiotics and chlorhexidine gluconate washes of the skin may temporarily eradicate bacterial colonization, although it usually recurs. **Other Bacterial Infections** - Other bacterial infections that have been observed in association with HIV infection include *Pseudomonas* bacteremia and hot-tub folliculitis, aggressive head and neck infections with *Haemophilus influenzae*, and periodontal disease caused by complex oral flora (*Mycoplasma salivarium*, *Bacteroides fragilis*, *Fusobacterium varium*, *F. necrophorum* and *Enterobacter cloacae, B. henselae* , *Mycobacterium avium intracellulare*, *M. haemophilum* and *M. Fortuitum*, *Treponema pallidum*.

Fungal Infections

- **Candidiasis** is the fungal infection most frequently encountered in association with HIV infection and its incidence correlates with lower $CD4^+$cell counts. Ninety percent of patients with AIDS will develop candidiasis of the oropharynx. Perlèche with painful fissures at the oral commissures and persistent candidal infections of intertriginous zones are also seen in HIV-infected individuals. Other signs suggesting immune suppression include chronic paronychia, onychodystrophy, and refractory vaginal candidiasis. Disseminated candidiasis has been reported and is often fatal in those with HIV infection.
- **Dermatophytoses** - The incidence of superficial dermatophyte infections is increased in immunosuppressed hosts. In such patients, these usually minor infections may serve as a source of morbidity as they can provide portals of entry for serious pathogenic bacteria. Cutaneous involvement can be atypical in appearance, and lesions may be more widespread and resistant to therapy. Spread of interdigital tinea pedis onto the dorsal foot, fungal folliculitis (Majocchi's granuloma) and proximal white onychomycosis have all been observed in HIV-infected patients.
- **Systemic fungal infections** - Cryptococcosis and any of the dimorphic fungal infections, including histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, sporotrichosis and penicilliosis, may become widespread in HIV-infected patients. In affected individuals, the $CD4^+$counts are usually <250 cells/mm^3. These infections present with a wide range of morphologies, including pustules, papulonodules, and less often, patches, plaques and mucocutaneous ulcerations.

Parasitic Infections:

- Leishmaniasis - Multiple organs may be parasitized, and, when the skin is involved, the lesions typically present as ulcerated nodules (up to 2 cm in diameter) on the extremities; in atypical presentations, the lesions are disseminated. Erosions and ulcerations of the lips, palate and nasal mucosa can also be seen. If left untreated, destruction of cartilaginous structures may result in disfigurement. Fever, hepatosplenomegaly, and varying degrees of pancytopenia may also be present. The diagnosis of cutaneous leishmaniasis is established via microscopy, *in vitro* culture or PCR of lesional tissue.
- *Strongyloides stercoralis* is an intestinal helminth endemic to the tropical and subtropical regions of the world. Dissemination (i.e. hyperinfection) may occur in immunosuppressed individuals, and, when the skin is affected, lesions mimic a number of other conditions such as urticaria and livedo reticularis; on the lower trunk, they may resemble purpuric 'thumbprints'. Eosinophil counts are commonly elevated. Identification of larvae in biopsy specimens as well as sputum, duodenal or gastric contents, or CSF confirms the diagnosis, as does identification of eggs in stool specimens. *S. stercoralis* hyperinfection is almost universally fatal and response to treatment with ivermectin or thiabendazole is extremely poor.

Ectoparasitic Infestations

- **Scabies,** an infestation with the mite *Sarcoptes scabiei* var. *hominis*. Severe infestation may develop as a consequence of diminished cell-mediated immunity. Cutaneous lesions vary from the 'classic' crusted papules to pruritic dermatitis to keratotic and crusted plaques[56] (Fig. 77.9);the latter may or may not be pruritic. Burrows, commonly found on the hands, wrists, ankles and interdigital areas, are less apparent in HIV-infected patients. Also, the ears, face and scalp (sites not usually affected in immunocompetent hosts) are commonly involved in immunosuppressed patients. In crusted (Norwegian) scabies, lesions may be generalized with subungual debris and gross nail thickening due to an extraordinary mite load; thousands to millions may be present on a single patient. Secondary infection with bacteremia and fatal septicemia has been reported in HIV-infected patients with scabies.
- **Demodicosis** is caused by the mites *Demodex folliculorum* and *D. brevis* and has been reported in association with HIV infection. Rosacea-like demodicosis may be more frequent in HIV-positive patients. These eruptions, usually found in the head and neck region, are similar in morphology to, and must be differentiated from, other pruritic papular eruptions.

NON-INFECTIOUS HIV-RELATED CUTANEOUS DISORDERS

A number of non-infectious dermatoses have been described in association with HIV infection. The development of one or more of these conditions should alert the clinician to consider HIV infection as a possible underlying etiology.

Papulosquamous Disorders

- **Seborrheic dermatitis** is the most common skin disorder to affect HIV-infected individuals (up to 85%) and is seen in all stages of the disease. Clinical findings may be similar to those seen in the general population, i.e. erythema and yellowish scale on the face as well as involvement of extrafacial locations such as the central chest and inguinal creases. However, exaggerated presentations with obvious facial plaques can also occur and should raise the possibility of HIV infection, as should a sudden onset or acute worsening of seborrheic dermatitis.
- **Psoriasis -** The overall incidence of psoriasis is probably not increased in the setting of HIV infection, although its clinical presentation can be dramatic. It may develop at any stage of HIV infection and, as with seborrheic dermatitis, a rapid onset of 'eruptive' psoriasis can serve as an important clue to an underlying HIV infection. An 'inverse' distribution involving inguinal creases and genitalia may be observed. The psoriasis is often severe and may be associated with significant nail dystrophy, arthritis and Reiter's disease; it tends to worsen with declining immune status. Secondary bacterial infection with sepsis has been reported.
- **Papular pruritic eruption (PPE) of AIDS** is characterized by marked pruritus and a greater involvement of the extremities than the trunk or face. It is more prevalent in Africa as compared to North America or Europe. Some authors believe PPE represents a spectrum of pruritic disorders, including eosinophilic folliculitis, while others have raised the possibility that it is an exaggerated response to arthropod antigens. Clinically, the lesions are symmetrically distributed, non-follicular papules, often with secondary changes (e.g. excoriations, formation of prurigo nodularis).
- **Eosinophilic folliculitis** is one of the most characteristic and common pruritic dermatoses associated with HIV disease. One theory is that it is an exaggerated reaction to *Malassezia* yeast or other organisms normally present within the follicular infundibula in HIV-infected patients and is a reflection of abnormal Th2/Th1 immune responses. Excoriated follicular papules and rare intact pustules are found primarily on the face and upper trunk. Cultures are negative and peripheral eosinophilia may be present. $CD4^+$counts are usually <200 cells per cubic millimeter.

NEOPLASTIC HIV-RELATED CUTANEOUS DISORDERS

A number of different neoplasms may develop in patients with HIV infection. Diagnosis is established primarily by clinical appearance and histologic examination. Aggressive treatment and heightened awareness are imperative for improving prognosis.

Primary Cutaneous Neoplasms

- Squamous and basal cell carcinoma. In HIV-infected individuals, as compared with the general population, these tumors appear earlier and more often in sites such as the trunk and extremities; metastases of BCC have been recorded. The SCC:BCC ratio is reversed in those with HIV infection, similar to that observed in organ transplant recipients.

Lymphomas

- Lymphomas of both B- and T-cell lineage may develop in HIV-infected adults and children, often in the setting of significant immune suppression with $CD4^+$counts <200 cells/mm^3. Clinically, pink to violaceous papules are usually seen when the skin is affected; the lesions often ulcerate and sometimes simulate panniculitis. Unlike in immunocompetent patients, most lymphomas are non-Hodgkin B-cell type, high or intermediate grade. Additional differences include a younger age of onset, more advanced stages and, most importantly, extranodal involvement at presentation, in particular the CNS, intestine and skin. Approximately one-half of the non-Hodgkin lymphomas are associated with EBV infection.

Kaposi's Sarcoma

- Development of AIDS-related Kaposi's sarcoma (KS) has not been shown to correlate with the degree of immunosuppression and can be seen at any stage of HIV infection. Clinically, skin lesions vary from small violaceous papules to large plaques to ulcerated nodules. Initially, the upper body is involved, often along skin lines in a pityriasis rosea-like pattern and at sites of local trauma. Lesions develop on the face, in particular the nose, and on oral mucosal surfaces, including the gums and hard palate. The most common sites of internal involvement are the gastrointestinal tract and lymphatics, the latter leading to occlusion with secondary lymphedema. As a general rule, one internal lesion develops for every five cutaneous lesions.

DIAGNOSIS

In HIV-infected patients, the diagnosis of cutaneous disorders is established in the context of the clinical appearance coupled with confirmatory studies such as scrapings, biopsies and serologic assays. Given their immunocompromised state, these patients can have mixed infections or combination infectious–neoplastic or inflammatory– neoplastic lesions. Finally, other factors such as age, sex and anatomic distribution assist in narrowing the differential diagnosis.

HIV serologic testing should be performed in any patient who requests it. Testing should also be considered for individuals in high-risk groups, such as men who have sex with men, intravenous drug users and commercial sex workers, as well as for patients who have sexually transmitted infections, active tuberculosis or are pregnant. Herpes zoster in a young person, refractory candidiasis, generalized lymphadenopathy, unexplained dementia, aseptic meningitis, peripheral neuropathy, chronic unexplained fever or diarrhea, weight loss, extranodal lymphoma, chronic HSV infection or multidermatomal herpes zoster infection should prompt the clinician to recommend testing for HIV. Generalized pruritus without a primary eruption should also prompt HIV testing in at-risk individuals.

HIV seroconversion usually occurs 6 weeks after initial infection. Criteria for HIV seropositivity include repeatedly positive ELISA results confirmed by a positive Western blot study (usually requiring reactivity against at least two of the viral protein markers p24, gp41 or gp120/160). Non-reactive results are obtained during a seronegative 'window' that usually lasts 1-3 months after the initial infection. Thus, if HIV infection is strongly suspected, methods for detection of viral antigens rather than anti-HIV antibodies need to be employed. Fourth-generation HIV screening assays have been developed that attempt to shorten the seronegative window by simultaneous detection of anti-HIV antibodies and p24 antigen.

Seroconversion, advanced HIV disease, HIV-2 infection, the presence of alloantibodies (seen with pregnancy, blood transfusions or organ transplantation) or autoantibodies (seen in autoimmune connective tissue diseases, other autoimmune diseases or malignancy) may lead to an indeterminate test result in which both the ELISA and Western blot studies are positive but with reactivity against only one protein marker

present. Repeat tests should be performed in 2-6 months for confirmation. Individuals with an indeterminate test result who are in the process of seroconverting will usually become seropositive within 1 month.

If necessary, HIV RNA PCR and/or isolation of the virus by culture can be used to confirm the diagnosis in questionable cases. However, the specificity of a single plasma viral load test is only about 97% and false-positive results, particularly in the range of <5000 copies/ml, have been described. Importantly, HIV postexposure prophylaxis may hamper detection of the virus by culture or PCR and delay seroconversion.

Virtually any cutaneous lesion in an HIV-infected patient may be caused by a potentially treatable infectious agent. Histologic examination of biopsy specimens and cultures of dermal tissues may be required for diagnosis. In addition, there is an armamentarium of ancillary serologic and histologic studies that may be necessary. Special growth requirements for fastidious opportunistic organisms need to be anticipated. It should be remembered that mixed infections may also be present.

TREATMENT

Although major advances in the treatment of HIV infection have been made in the past 15 years, the most important was the development of a combination drug regimen known as HAART. Of the various HAART regimens, the most common ones comprise two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs; NtRTIs, respectively) combined with either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. HAART has the capability of profoundly suppressing viral replication, leading to the reconstitution of $CD4^+$lymphocyte counts with a concomitant drop in morbidity and mortality. As a consequence, the annual mortality from AIDS has declined by 75% since 1995 in developed countries.

The three main classes of antiretroviral agents target different aspects of the HIV life cycle. Protease inhibitors inhibit the protease enzyme that participates in viral processing and assembly. NRTIs, NtRTIs and NNRTIs terminate DNA chain synthesis by inhibiting the reverse transcriptase enzyme. Enfuvirtide, the first representative of the fusion inhibitors, was recently approved; it blocks HIV from entering target cells by inhibiting the gp41-mediated fusion of the viral envelope with human cell membranes. Enfuvirtide has to be administered subcutaneously and often causes painful injection site reactions. As a result, it is usually reserved for patients with limited treatment options.

While the decision to institute antiretroviral therapy is based primarily on the $CD4^+$cell count (as it correlates with expected disease-free survival), response to therapy is monitored by quantitative HIV RNA PCR (as plasma viremia is a strong prognostic indicator of HIV disease progression)[94]. Suppression of HIV replication to below the limit of quantification for as long as possible is therefore a critical goal of HAART. When HIV replication is adequately suppressed (i.e. below 50 copies/ml plasma), evolution of viral resistance to antiretroviral drugs is minimal. However, continuous replication in the presence of antiretroviral drugs, whether due to patient non-adherence, pre-existent drug resistance and/or iatrogenic low drug levels, can rapidly exhaust currently available treatment options.

In addition to increasing life expectancy in those with HIV infection, HAART has resulted in a significant decrease in the incidence of several of its cutaneous manifestations, including candidiasis, KS, eosinophilic folliculitis, opportunistic deep mycoses and mycobacterioses, as well as oral hairy leukoplakia. Surprisingly, the prevalence of papillomavirus and poxvirus infections has increased. There are also studies that demonstrate that HAART does not cause reversal of AIN, and, as such, patients who live longer with this complication may be at even greater risk of developing anal SCC. It is also possible that other cutaneous neoplasms may be seen with greater frequency as patients survive longer. Paradoxically, flares of several infectious skin diseases (due to inflammatory immune reactions) have been observed following institution of HAART, especially when $CD4^+$cell counts rise at least twofold from depressed levels (usually <50 cells/mm^3). Examples include herpes zoster, leprosy, and disseminated *Mycobacterium avium* and CMV infections. These represent manifestations of the so-called immune recovery syndrome or immune reconstitution inflammatory syndrom. Distinguishing these flares of inflammation from active opportunistic infections or from drug toxicity may be difficult.