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Abstract

Vulvovaginal infective diseases encompass a spectrum of primary and secondary bacterial, viral, fungal, and parasitic, including protozoal, infections that variably affect females of different age groups and in varying global, geographic locations. In addition, the disease spectrum is also influenced by the underlying immune status of the patients. The primary vulvovaginal infections are dominated by the sexually transmitted diseases that are grouped under the rubric “genital ulcer disease” and encompass syphilis, chancroid, donovanosis, lymphogranuloma venereum, and herpes simplex virus infection. Syndromic medical management of genital ulcer disease has not only decreased the need for diagnostic biopsies but has also limited the exposure of pathologists to the wide range of histopathological features, mimicry, and pitfalls of these ulcerative entities and the associated diagnostic challenges. Hence, familiarity with the spectrum of features that characterize the disease is critical to avoid misdiagnosis of other inflammatory disease mimickers. The histopathological diagnosis of vulvovaginal involvement by systemic infections is plagued by clinical underrecognition of vulvovaginal involvement by systemic infections and the attendant-altered clinicopathological morphology because of exposure of the vulvovaginal area to friction, moisture, and pruritus. The biopsy therefore plays a pivotal diagnostic role in the confirmation of an increasing range of infections, including those that are unsuspected clinically.

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Introduction

A spectrum of primary and secondary infective processes may involve the vulvovaginal area. While some of these infections represent primary genital tract infections, other vulvovaginal infections are acquired, either by contiguous spread from adjacent organs or as part of system dissemination. The primary vulval infections are

dominated by sexually transmitted diseases that are grouped under the rubric “genital ulcer disease.” While the vulvovaginal manifestations of systemic infections may share phenotypic features of the diseases in extravulvovaginal locations, the exposure of the vulvovaginal area to friction, moisture, and pruritus may alter the morphological diagnostic features. The clinical phenotype of vulval infections overlaps with those of noninfective vulval dermatoses, posing clinical diagnostic challenges. Vulvovaginal infections may be assessed, for the first time, by a spectrum of health-care professionals including family practitioners, venereologists, dermatologists, gynecologists, or infectious disease specialists. Hence, clinical suspicion of vulvovaginal infections varies as no single practitioner oversees the spectrum of diseases. The biopsy may therefore be pivotal in the diagnostic confirmation of many vulvovaginal infections, including those that are not suspected clinically.

Predominantly Primary Vulvovaginal Infections

Genital Ulcer Disease

Syphilis

Syphilis, caused by *Treponema pallidum*, is a predominant sexually transmitted infectious disease of worldwide distribution [1]. Congenital and acquired forms of syphilis are characterized by cutaneous involvement, including vulval manifestations [2]. Acquired syphilis is divided into primary, secondary, latent, and tertiary stages [3]. *Clinical features:* The manifestations of primary syphilis occur 10–90 days postinfection as a painless “chancre” at the site of inoculation in association with local lymphadenopathy [3]. Rarely, more than one chancre may be present. Although resolution of the chancre occurs, vascular invasion facilitates the secondary stage, 2–6 months later [3]. In addition to mucocutaneous lesions, visceral and constitutional symptoms occur. The cutaneous clinical phenotype of secondary syphilis is heterogeneous and includes maculopapular, annular, psoriasiform, lichenoid, pustular, and

ulcerative lesions [4]. In flexural and anogenital skin, fleshy verrucous papules referred to as “condylomata lata” may be present. Tertiary syphilis occurs many years after disease onset but this may be accelerated in the setting of HIV infection [5, 6]. Cutaneous lesions, described in 70% of patients, include nodular tertiary and benign gummatous syphilis. Classical serologic testing for syphilis encompasses nontreponemal (rapid plasma reagin or Venereal Disease Research Laboratory) and treponemal tests (*T. pallidum* hemagglutination assay or *T. pallidum* particle agglutination) [7]. These tests may be negative in primary syphilis, and the serological tests are limited by low sensitivity and specificity [8].

Interactions between HIV and *T. pallidum* cause an accelerated disease course of both infections, altered clinical and laboratory profiles, increased risk for complications, and a decreased response to antisyphilitic treatment [9–11]. Serological confirmation of syphilis in HIV-infected patients may be hampered by an increased rate of negative serological tests in primary and secondary syphilis, increased false-negative nontreponemal antibody tests due to the prozone phenomenon [12], failure to clear nontreponemal antibody after treatment, and seroreversion of specific treponemal antibody tests to a negative state after treatment [13]. The accelerated cutaneous syphilitic lesions manifest as lues maligna with severe cutaneous ulceration and pseudolymphomatous mycoses-fungoides like lesions [14, 15]. The curative treatment schedule should include higher doses of penicillin [16, 17].

Microscopic features: Primary syphilis (chancre): The initial microscopic features of primary syphilitic encompass endothelial swelling and proliferation and an associated superficial and deep perivascular mononuclear inflammatory cell infiltrate. There is subsequent luminal occlusion as a result of endothelial hyperplasia and endarteritis obliterans and increased density of the mononuclear inflammatory cell in infiltrate, variable ulceration, and associated pseudoepitheliomatous hyperplasia. *Secondary syphilis:* Two main reactional patterns characterize secondary syphilis: psoriasiform (Fig. 2.1a, b) and lichenoid (Fig. 2.2a) [9]. The psoriasiform pattern (Fig. 2.1a,

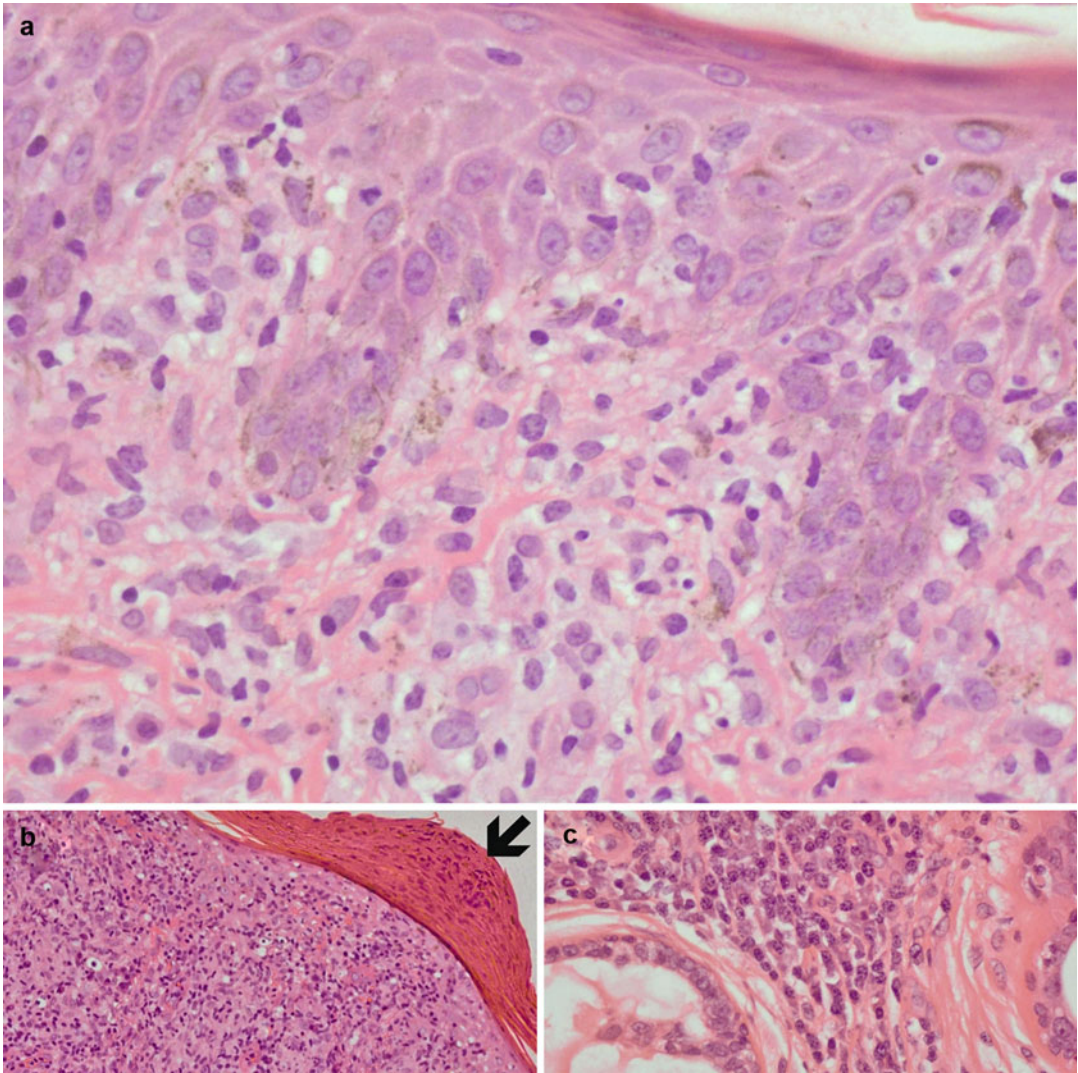


Fig. 2.1 Secondary syphilis: psoriasiform epidermal hyperplasia (a) with confluent parakeratotic crust (b, arrow) and plasma cells within eccrine secretory coil (c)

b) demonstrates epidermal acanthosis and club-shaped elongation of the rete ridges while the lichenoid pattern is typified by a band-like interface inflammatory infiltrate (Fig. 2.2a). The epidermis also demonstrates variable parakeratosis, apoptosis, erythrocyte extravasation, and transepidermal neutrophils and eosinophils (Figs. 2.1a, b and 2.2a, b). The dermal inflammatory cell infiltrate, composed mainly of CD8⁺ T lymphocytes, plasma cells, and macrophages, may extend deep into the dermis in perivascular and periappendageal locations (Fig. 2.1c) [18]. Other vari-

able findings include the presence of nonnecrotizing granulomas (more common in older lesions) and neutrophilic eccrine hidradenitis and the absence of plasma cells. Condylomata lata demonstrate more pronounced epidermal hyperplasia and intraepidermal microabscesses [19]. Lues maligna is characterized by thrombotic endarteritis obliterans (Fig. 2.2c), most pronounced at the dermal-subcutaneous junction, cutaneous infarction, ischemic ulceration, and a dense plasmacytic and histiocytic infiltrate. Pustular syphilis is characterized by folliculocentric

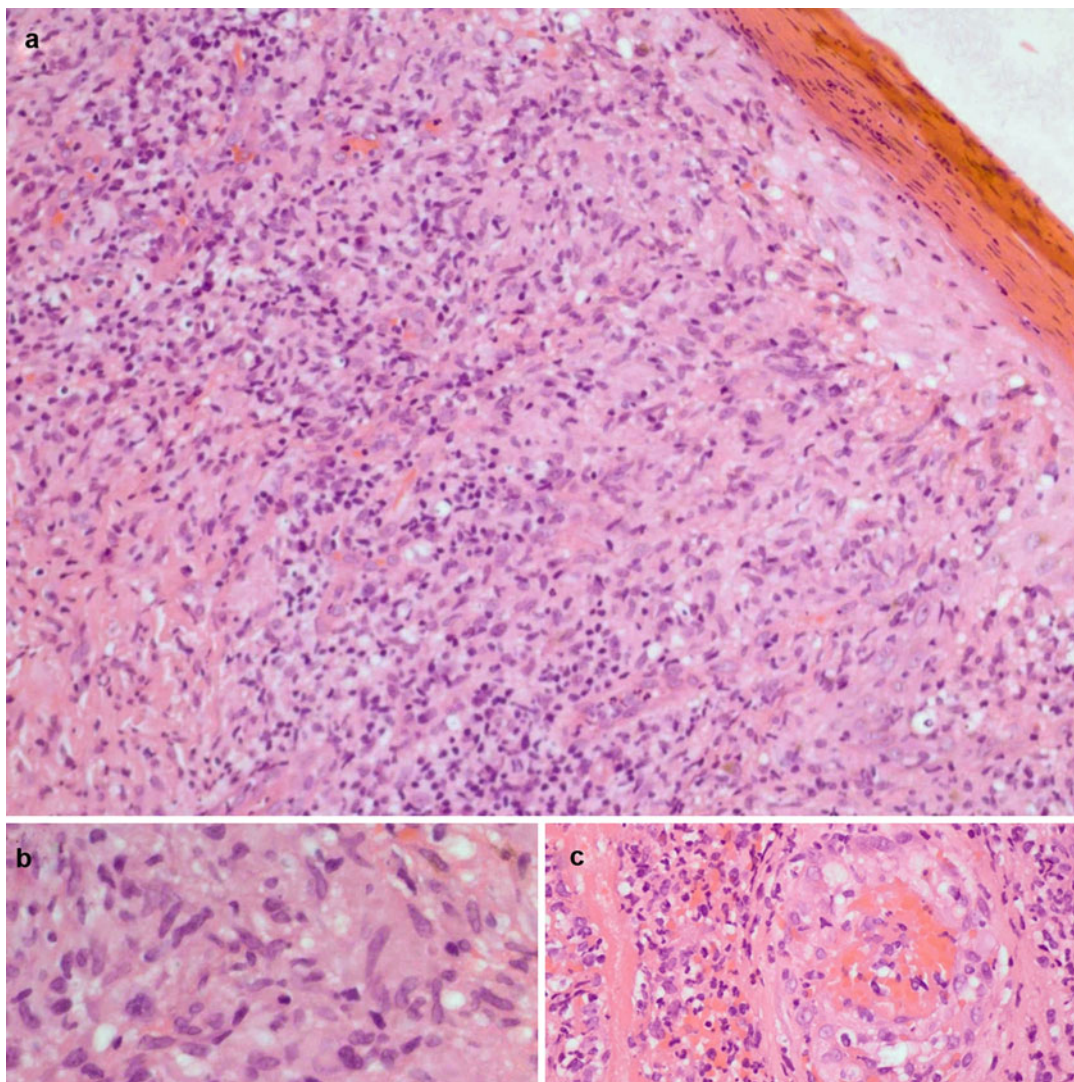


Fig. 2.2 Secondary syphilis: lichenoid inflammatory reaction pattern (a) with granulomatous inflammation (b). Thrombotic vasculitis in lues maligna (c)

suppurative inflammation and a surrounding perivascular lymphoplasmacytic infiltrate. Spirochetes are easily identified on silver stains. *Tertiary syphilis*: nodular tertiary syphilis is characterized by a dermal and subcutaneous perivascular plasmacytic infiltrate, variable granulomatous inflammation, and endarteritis obliterans (Fig. 2.3a). Benign gummatous syphilis is characterized by necrotizing granulomatous inflammation in which broad, irregular, acellular debris is surrounded by epithelioid histiocytes, multinucleate giant cells of Langhans type, lymphocytes, plasma cells, and fibroblasts (Fig. 2.3b).

Traditionally, *T. pallidum* has been identified using silver-impregnation staining, including Warthin Starry, Steiner, and Levaditi stains (Fig. 2.3c) [20]. The introduction of direct and indirect immunofluorescence and immunohistochemical spirochetal detection methods on fresh or archival wax block tissue has decreased the diagnostic challenges associated with nonspecific artefactual argyrophilia of cutaneous elements, including melanin pigment and connective tissue elements [20–22]. While spirochetes are demonstrated in primary and secondary, and to a lesser extent, tertiary, syphilis, significantly different

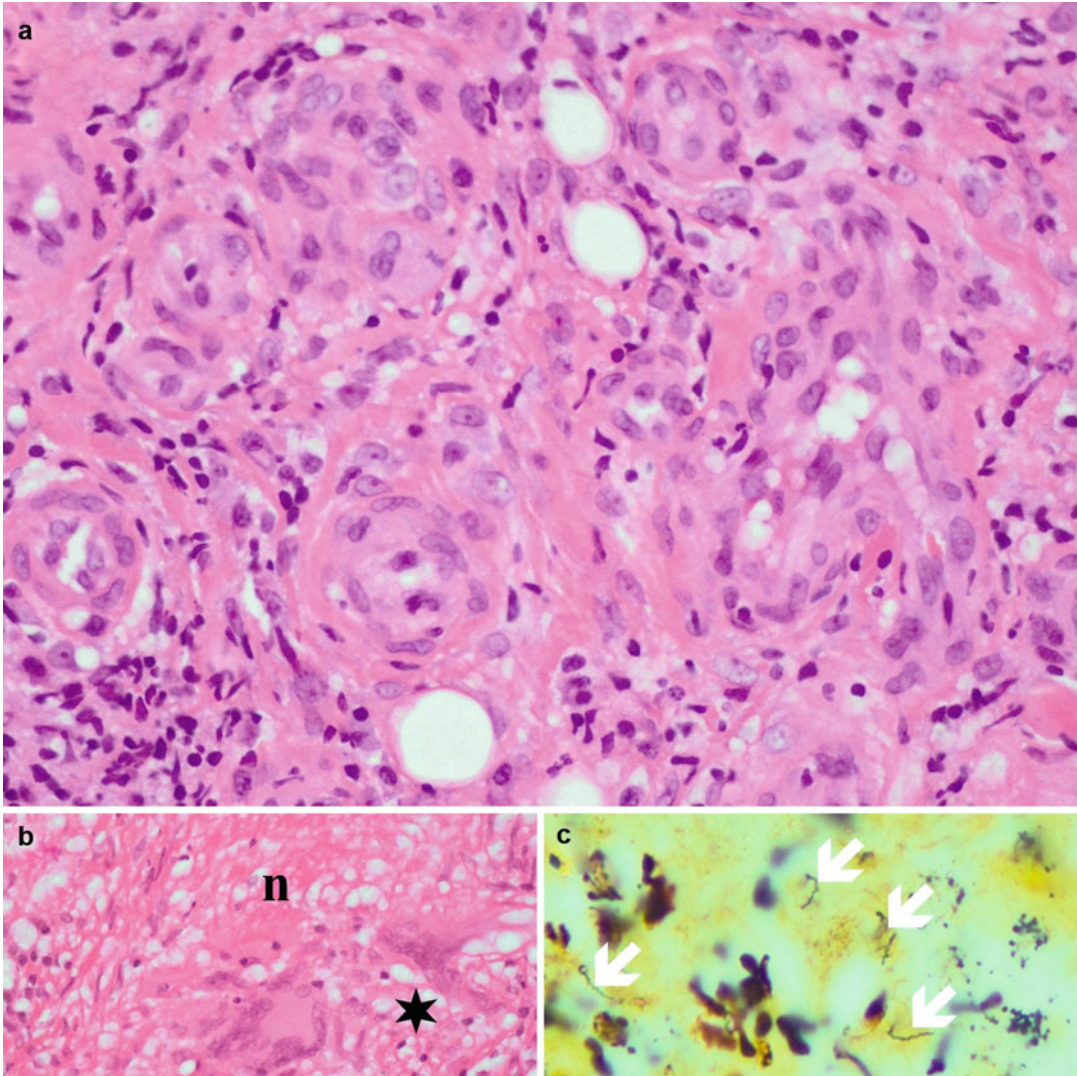


Fig. 2.3 Endarteritis obliterans (a) in nodular tertiary syphilis and necrotizing (n) granulomatous inflammation (asterisk) in syphilitic gumma (b). Warthin Starry silver stain demonstrating spirochetes (c, arrows)

distribution patterns have been documented in immunohistochemical and ultrastructural studies [20]. An epitheliotropic pattern typified by abundant spirochetes in an intercellular location in the lower epidermis has been described in secondary syphilis. Primary syphilis displays a mixed epitheliotropic and vasculotropic pattern with spirochetes being identified in and around blood vessels. The immunohistochemical detection of *T. pallidum* is hampered by false positivity for other spirochetal infections and borreliosis [7]. Molecular detection of *T. pallidum* using the polymerase chain reaction technique appears

more specific [23–25]. Amplification products specific to the *tp47* gene have been confirmed by the *tp47* hybridization probe; *tp47* lacks homology with other bacteria [7].

Differential diagnosis: While the lichenoid infiltrate of secondary syphilis mimics lichen planus, lichenoid drug eruptions, and pityriasis lichenoides chronica, the psoriasiform epidermal pattern mimics psoriasis and psoriasiform drug reaction. The inflammatory infiltrate extends deeper into the dermis in a predominant perivascular location in secondary syphilis. Marked spongiosis and dyskeratosis are not associated

with lichen planus or psoriasis vulgaris. While granulomatous foci may mimic sarcoidosis, granuloma annulare, and leprosy [26], a dense inflammatory component may mimic cutaneous lymphoma. Perifollicular pustular syphilis may resemble folliculitis. Gummatous syphilis may mimic gummatous tuberculosis, but the central necrotic zone of the former has an acellular appearance in which ghost outlines of cells are seen without the characteristic caseative nature of tuberculosis [27]. In addition, the large numbers of plasma cells are not a typical feature of tuberculosis. The syphilitic gumma differs from sarcoidosis by the presence of necrosis and the plasma cell-rich inflammatory background.

Chancroid

Chancroid, caused by *Haemophilus ducreyi*, a Gram-negative, facultative, anaerobic coccobacillus and strict human pathogen, is associated with suppurative lymphadenitis (buboes) [28, 29]. It is endemic in developing countries where a high HIV infection and AIDS prevalence coexist [28–30]. Chancroid causes a 25-fold increased HIV acquisition and transmission rate [30]. After entering the skin through microabrasions, the organism incites a local reaction. After 3–5 days, an erythematous papule develops at the entry site. This subsequently evolves into a pustule that undergoes necrosis to form a tender ulcer.

Clinical features: The ulcer has a necrotic, dirty appearance with an undermined edge and perilesional erythema. The ipsilateral lymph nodes form fluctuant masses that may rupture and result in draining inguinal sinuses. Clinical variants include dwarf, giant, follicular, transient, serpiginous, and phagedenic chancroid [31, 32]. While early studies documented atypical manifestations of chancroid in HIV-infected patients, subsequent studies have reported little difference in the clinical course, histomorphology, and response to therapy between HIV-naïve and HIV-seropositive patients [30]. **Diagnosis:** Apart from the histopathological diagnosis, *H. ducreyi* infection may be confirmed by culture, immunofluorescence tests, and PCR. *H. ducreyi* is a fastidious organism and is difficult to isolate from culture because it requires

immediate inoculation on enriched medium, such as chocolate horse blood agar [31, 33]. 16S rDNA sequencing techniques may allow definitive diagnosis [23, 29]. The potential virulence factors of *H. ducreyi* include pili, lipopolysaccharide, iron-regulated proteins, cytotoxins and hemolysins, heat shock proteins, and outer membrane proteins [29]. Antiphagocytic mechanisms, critical to the survival of *H. ducreyi* because it is an extracellular pathogen, are mediated by two homologous, large supernatant proteins, LspA1 and LspA2 [34], and fibrinogen binder A. *H. ducreyi* resistance to serum-mediated bactericidal activity occurs through the outer membrane protein, ducreyi serum resistance protein A.

Pathological features: Biopsy of the ulcer bed demonstrates a typical triple zonation phenomenon characterized by a superficial, necrotic zone that contains fibrin, neutrophils, erythrocyte, and necrotic debris (Fig. 2.4a); an edematous granulation tissue zone dominated by proliferating capillaries, display with thromboses or fibrinoid necrosis; and a third deep layer containing lymphocytes and plasma cells [35]. Pus aspirates or biopsies of the ulcer edge demonstrate coccobacilli on Giemsa (Fig. 2.4b), silver, or Gram stains. The arrangement of the organisms in clusters, and in parallel rows, is referred to as “school of fish,” “railroad,” or “chaining.” [35, 36] Ultrastructurally, *H. ducreyi* is largely extracellular and contains a trilaminar cell wall, typical of Gram-negative bacteria. B and T lymphocytes are preferentially located perivascularly in the middle and third zones, respectively [36]. Biopsies of the ulcer edge lack a zonation phenomenon but demonstrate a cell-mediated response dominated by CD4 and CD8 T lymphocytes, NK cells, macrophages, and plasmacytoid dendritic cells [34].

Donovanosis

Granuloma inguinale is caused by *Calymmatobacterium granulomatis*, a Gram-negative facultative, obligate intracellular pleomorphic bacterium [37, 38]. The natural history, treatment, disease classification, and nomenclature are controversial [37]. While originally labeled “serpiginous ulcer” in 1882, “granuloma inguinale” was introduced

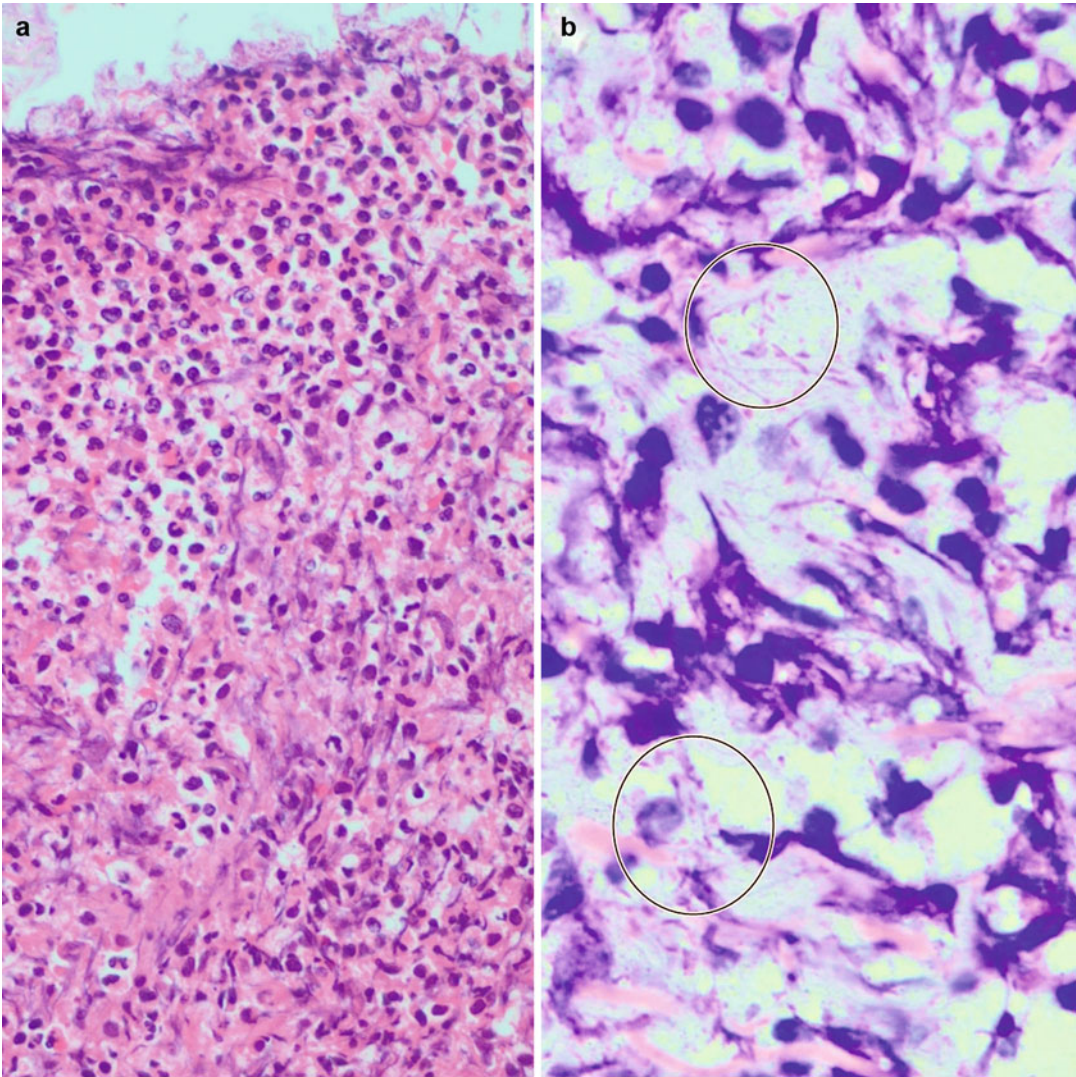


Fig. 2.4 Chancroid: ulcer with superficial necrotic debris and acute and chronic inflammatory cells (**a**) and “school of fish” appearance of coccobacilli (**b**, encircled)

thereafter to incorporate granulation tissue and the frequent localization of granuloma inguinale to the inguinal area [39]. The rubric “donovanosis” was coined in 1950 in honor of Donovan, who, in 1905, pioneered the discovery of the causative infective agent [39]. The name of the organism mirrors its pseudoencapsulated appearance in tissue sections (“Kalymma”: Greek for “hood” or “veil”). It has been proposed that the organism be reclassified as *Klebsiella granulomatis* because of the approximate 99% phylogenetic similarity with *K. pneumoniae* and

K. rhinoscleromatis [37]. Granuloma inguinale occurs in New Guinea, the Caribbean, South Africa, Southeast Asia, Australia, Brazil, and parts of India [40]. Granuloma inguinale is generally regarded as a sexually transmitted infection with an incubation period of 2 weeks to 6 months [41, 42].

Clinical features: Cutaneous and subcutaneous papules and nodules form at the site of inoculation. They may then evolve into large ulcers that bleed easily to touch [37, 39]. Hypertrophic, verrucous, or foul-smelling destructive, deep

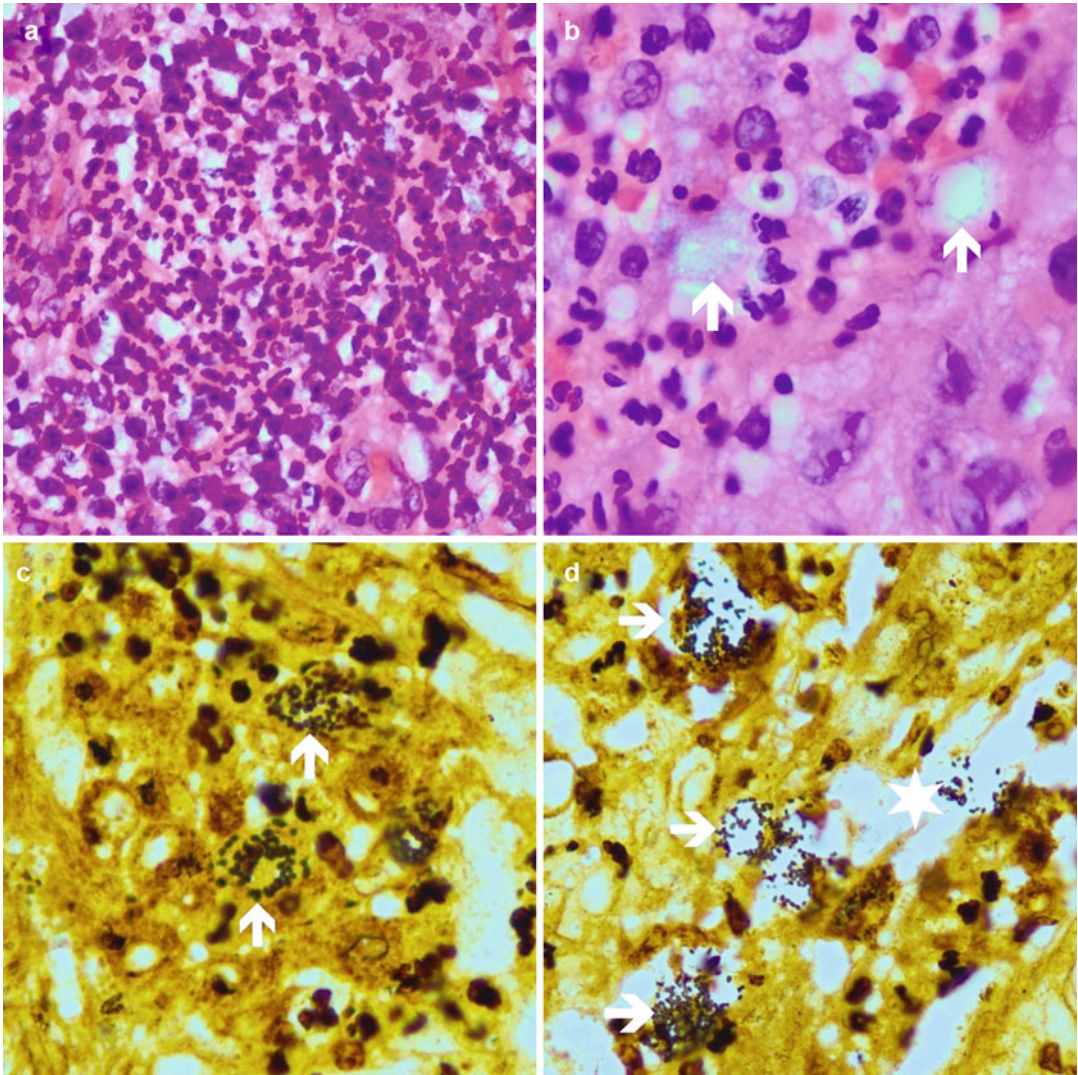


Fig. 2.5 Dense inflammatory infiltrate composed of neutrophils and plasma cells (a), Donovan bodies (b, arrows), highlighted with Warthin Starry silver stain (c, arrows).

Transepidermal (asterisk) elimination of Donovan bodies (d, arrows)

ulcers; deformative, fibrosing, cicatrizing lesions; abscesses; or fistulae are documented [37, 39, 41]. *Treatment and outcome:* Granuloma inguinale resolves if appropriate treatment is instituted promptly. Doxycycline, azithromycin, cotrimoxazole, erythromycin, and aminoglycosides are effective. Treatment delays may result in significant morbidity [38]. HIV coinfection may result in persistent ulcers with greater tissue destruction that may require more aggressive and prolonged therapy [38]. Smears and histopathological

assessment of lesional tissue will demonstrate the presence of Donovan bodies. However, in partially treated lesions, Donovan bodies may be elusive. In such settings, PCR studies are helpful in confirming the diagnosis [42].

Histopathology: The diagnostic features of granuloma inguinale include a granulation tissue response with a dense inflammatory component composed of plasma cells, macrophages, aggregates of neutrophils, and few, if any, lymphocytes (Fig. 2.5a). The macrophages are large with

voluminous, vacuolated cytoplasm in which 1–2- μ m bacilli, the Donovan bodies, are seen on routine stains (Fig. 2.5b). The organisms are demonstrated to better effect on Warthin Starry (Fig. 2.5c) or Giemsa-stained sections where they have the typical bipolar appearance of safety pins because of the bipolar condensation of the stain. Transepidermal elimination of the organisms is described (Fig. 2.5d). The edge of the ulcer may demonstrate pseudoepitheliomatous hyperplasia. *Differential diagnosis*: The extent of neutrophilic infiltration in a background of granulation tissue and chronic inflammation mimics the chronic suppurative prototypical inflammatory response of an abscess. This may be particularly important in deep subcutaneous nodules. More superficial biopsies with pseudoepitheliomatous hyperplasia may mimic squamous cell carcinoma. Squamous cell carcinoma coexists with granuloma inguinale rarely [40]; strict criteria for malignancy must be adhered to, to avoid misdiagnosis. In patients who have received symptomatic treatment, Donovan bodies may be elusive. In such instances, when the inflammatory background is compelling for granuloma inguinale, PCR testing and nucleotide sequencing investigations will confirm the histopathological suspicion. Fungal (histoplasmosis, cryptococcosis, and pneumocystosis) [43] and protozoal (toxoplasmosis, leishmaniasis) [44] infections also contain intracytoplasmic organisms within histiocytes, but these infections are typified by a granulomatous response, the histiocytes may have a foamy appearance, and the infecting agents are larger and have a round to oval rather than elongated bacillary shape.

Lymphogranuloma Venereum

Although lymphogranuloma venereum (LGV) was described as early as 1786 [45], it was only established as a distinct clinicopathological entity in 1913. Reported uncommonly, LGV accounts for 2–10% of genital ulcers in India and Africa [46]. It is caused mainly by one of three invasive LGV biovar strains of *C. trachomatis* serotypes L1, L2, and L3. *C. trachomatis* is an obligate intracellular parasite. The L1, L2, and L3 serotypes parasitize histiocytes [47, 48]. Three stages

typify the life cycle of *C. trachomatis*. In stage 1, elementary particles, referred to as the infective particles, penetrate the host cell. In stage 2, the elementary particle evolves into a reticulate body. The reticulate body exists exclusively intracellularly, is metabolically active, and divides by binary fission. Eventually, in stage 3, reticulate bodies transform into elementary bodies that leave the host cell by exocytosis [45].

Clinical features: LGV also occurs in three clinicopathological stages. Following an incubation period of 3–30 days, a small papule, ulcer, or herpetiform lesion develops at the site of inoculation [38, 45, 48]. The secondary or inguinal stage evolves over an average of 10–30 days after the primary stage [45, 49]. Inguinal, femoral, and deep pelvic lymphadenopathy occurs and is followed by necrosis and subsequent chronic edema, ulcers, and sclerosing fibrosis. The tertiary stage, referred to as the genitoanorectal syndrome, encompasses proctocolitis, perirectal abscesses, fistulae, stenosis, and strictures of the rectum [38]. Lymph stasis results in severe vulval edema, known as esthiomene [50]. *Diagnosis*: Is based on the isolation of *C. trachomatis* by culture and cell typing of the isolate [38]. Isolation is undertaken in a coculture system or in the yolk sac of eggs. LGV also induces a strong immune response. In the presence of clinical clues of LGV, a complement fixation antibody titre of >1:64 or a fourfold increase in titer is diagnostic of chlamydial infection. Molecular confirmation of LGV using PCR techniques and DNA sequencing of the variable segments of the *OMP1* gene is used to determine the serovars/serotype [51].

Microscopic features: The ulcer of the first stage is characterized by superficial fibrin and neutrophils and deep mixed inflammation, including neutrophils, mononuclear cells, and giant cells [45, 50, 52]. The features at this stage are nonspecific [35]. The lymph nodes demonstrate follicular hyperplasia and foci of necrosis that evolve into stellate abscesses with a zone of palisaded epithelioid cells, giant cells, and lymphocytes (Fig. 2.6a, b). The foci of central necrosis become eosinophilic, acellular, and homogeneous. Fibrosis supervenes. *Differential diagnosis*: The

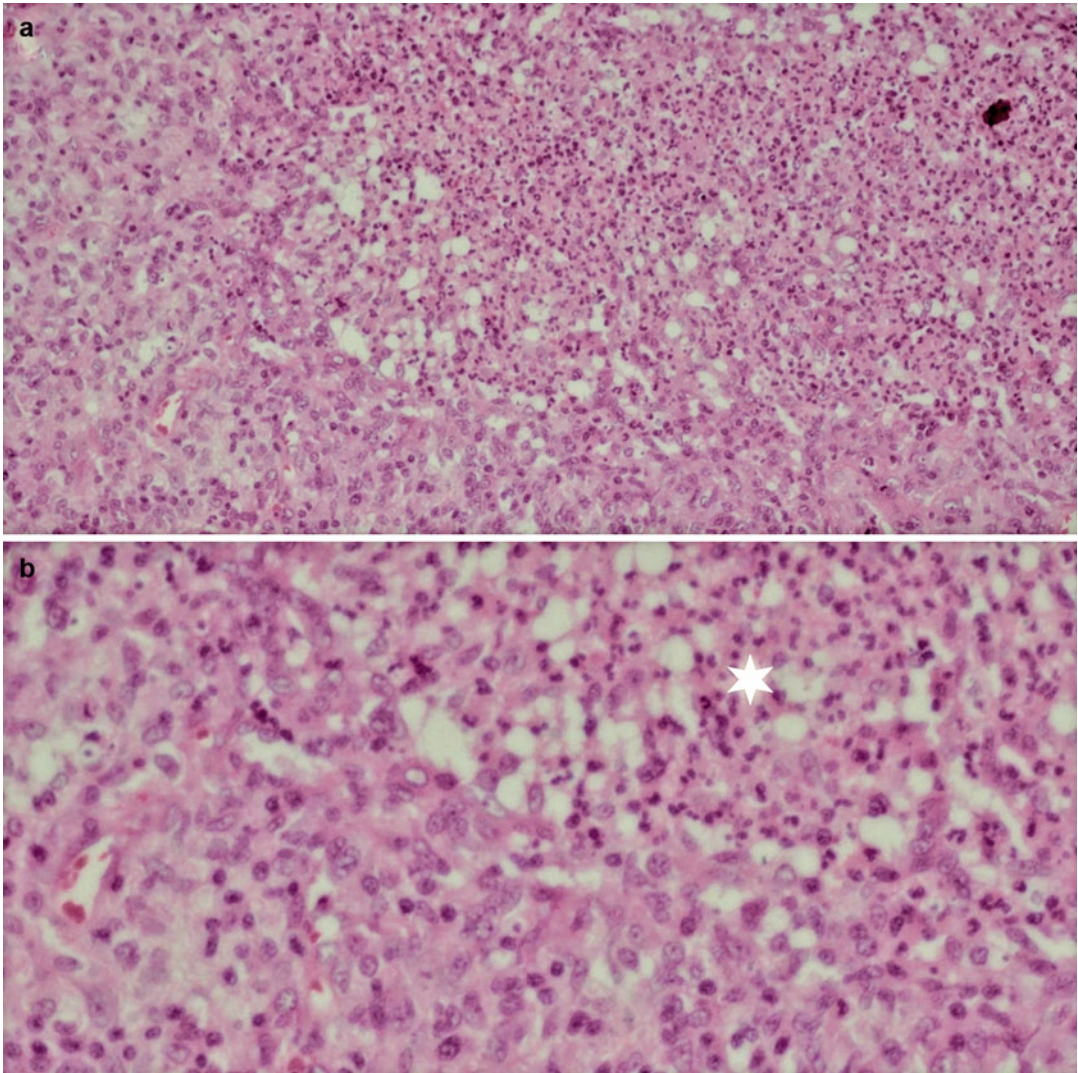


Fig. 2.6 Lymphogranuloma venereum: part of a stellate abscess in an inguinal lymph node (**a**, low power) and high power (**b**) demonstration of central suppuration (*asterisk*) and adjacent histiocytic response

microscopic features of the genital ulcer mimic an abscess, early cat scratch disease, syphilis, and herpetic and aphthous ulcers.

Herpes Simplex Virus Infection

Derived from the ancient Greek word meaning to crawl or creep, “*herpes*” refers to the family of viruses of which the ubiquitous, immunologically distinct *herpes simplex virus-1* (HSV-1) and *herpes simplex virus-2* (HSV-2) are the most aggressive human pathogens [53]. Genital

herpes is the most common cause of genital ulceration worldwide [38]. While HSV-2 is the more common cause of genital herpes, an increasing prevalence of HSV-1-induced genital ulcers is being recognized [54]. The virus spreads during asymptomatic and symptomatic viral shedding. Viral replication at the site of inoculation is followed by neural transmission to the dorsal root ganglia, where the virus remains in a latent state, until reactivation occurs. The latter may be a consequence of

fever, stress, immunosuppression, or immunocompromise [55–57]. HSV-1 infections are less likely to recur than HSV-2 infections [58].

Clinical features: Primary genital herpes ulcers and vesicles are typically asymptomatic, occurring within 3 days to 2 weeks, with an average of 5 days, after HSV exposure. However, a systemic prodrome, inclusive of fever, myalgia, and headache, occurs. Secondarily infected or recurrent herpetic lesions are very painful. The recurrent lesions manifest as vesicles on an erythematous base with variable crusting, pustulation, and erosions. These lesions heal with scarring. Recurrent disease is typified by systemic spread, prominent regional lymphadenopathy, and adjacent skin and soft tissue involvement of the buttock, perineum, and cervix. Unusual clinical appearances include nodular vulvitis and a Well's syndrome (eosinophilic cellulitis), presentation with vulvar edema [59, 60], and exophytic masses. Genital herpes in HIV-infected patients may have severe and atypical clinical presentations, including an increased number and size of lesions, increased pain, slower healing, and a verrucous clinical appearance [54]. *Diagnosis:* HSV infection can be confirmed by their direct identification in cultures, direct immunofluorescence, immunohistochemistry, in situ hybridization, and PCR techniques. Viral culture involves the inoculation of lesional tissue into HeLa cells, amnion, or fibroblasts with resultant demonstration of viral cytopathic effects. Appropriate primers or pyrosequencing can be employed to subtype the herpesvirus [61]. *Outcome:* Topical, oral, or intravenous antiviral agents (acyclovir, valaciclovir, famciclovir) are effective in primary or recurrent disease. Intravenous use may be effective in immunocompromised hosts. HSV may develop acyclovir resistance because of mutations in the viral *thymidine kinase* gene [53]. HSV may thus be either deficient in thymidine kinase or may contain thymidine kinase that is incapable of phosphorylating acyclovir.

Pathologic features: The epithelium undergoes ballooning and reticular degeneration to form an intraepithelial vesicle. Ballooning

degeneration is characterized by intense eosinophilia of the cytoplasm with loss of intracellular cohesion and attachment, resulting in secondary acantholysis [62]. Molding of these cells may be prominent. Reticular degeneration is characterized by hydropic swelling and rupture of the epidermal cells and ulceration (Fig. 2.7a). Eosinophilic intranuclear inclusions are an important diagnostic feature. They measure 3–8 μm in diameter, are surrounded by a halo, and may be identified in epidermal cells, endothelium, sebaceous and eccrine, epithelium, fibroblasts, macrophages, and endoneurial cells [62, 63]. Multinucleation may be present (Fig. 2.7a). Neutrophils, sebaceous gland involvement, folliculitis, and neuritis may be variably noted. The neural alterations include neuronal atrophy and Schwann cell hypertrophy [62, 63]. Herpetic syngitis, associated with eccrine epithelial necrosis and syringosquamous metaplasia, is documented rarely, mainly in immunocompromised patients [64, 65]. HSV-2-associated eosinophilic cellulitis (Well's syndrome) has been documented in biopsies of acute, edematous blistering vulval dermatitis [60]. In this setting, epidermal spongiosis, massive eosinophil infiltration of the dermis, and eosinophilic flame figures partially surrounded by histiocytes are observed [60]. Biopsies of exophytic or nodular masses demonstrate variable ulceration and pseudoepitheliomatous hyperplasia of the epidermis and a dense inflammatory dermal response [66, 67]. Pseudolymphomatous features that are observed include a dense lymphoid infiltrate with atypical lymphocytes, angiotropism and a variable eosinophilic component (Fig. 2.7b, c) [68, 69]. The immunophenotype of the lymphoid infiltrate is predominantly CD3⁺, with variable of CD4, CD8, CD30, CD56, and T1A1 immunopositive cells. A wedge-shaped infiltrate with atypical lymphocytes, some CD30 positive, may resemble lymphomatoid papulosis. The infiltrate may demonstrate polyclonality or monoclonality on molecular investigation of the TCR- γ gene [69]. Ultrastructural examination demonstrates virus particles, 90–130 μm in diameter, in the nuclei of basal epidermal cells [62].

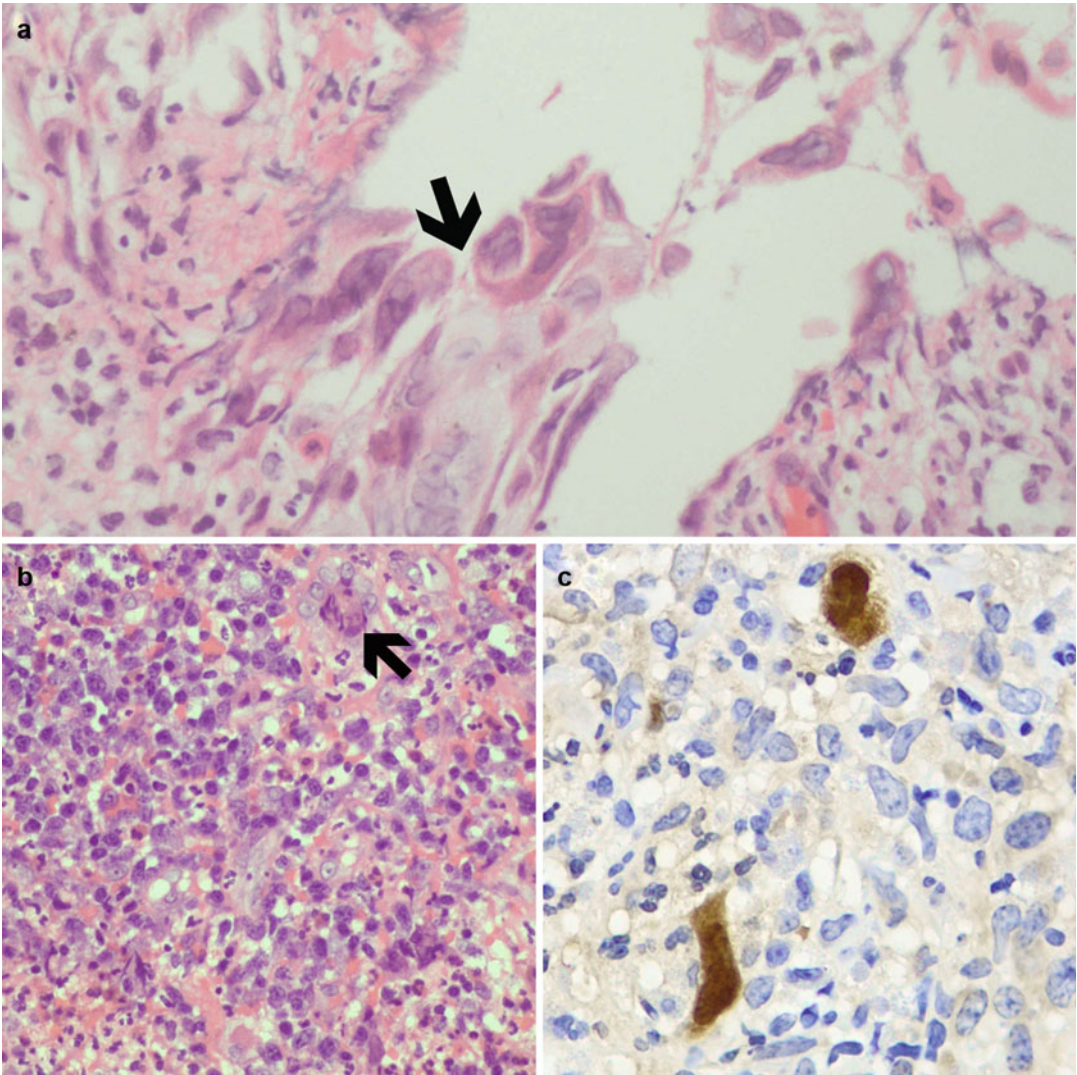


Fig. 2.7 *Herpes simplex virus* infection: Epithelial ulceration with intranuclear inclusions (**a**, arrows) and giant cell transformation. Pseudolymphomatous response

around *herpes simplex virus*-infected cell (**b**, arrow), highlighted by *herpes simplex virus* immunostain (**c**)

Other Predominantly Primary Genital Infections

Other Bacterial Infections and Malakoplakia

Bacterial vaginosis is typified by a decrease in the quantity and prevalence of hydrogen peroxide-producing lactobacilli; the microecologic imbalanced replacement by *Gardnerella vaginalis*, anaerobes, and *Mycoplasma hominis*; and the consequent production of malodorous vaginal

discharge, vulvovaginal pruritus, and irritation [70, 71]. The diagnosis is usually made by the presence of clue cells on vaginal smear (Fig. 2.8a) and a positive whiff test. The latter refers to the production of a fishy odor when the vaginal discharge is exposed to potassium hydroxide [72].

Superficial and deep staphylococcal folliculitis and abscess formation, occurring secondary to physical trauma or chemical injury, are characterized by perifollicular erythema and variable follicular suppuration, destruction, and granulomatous

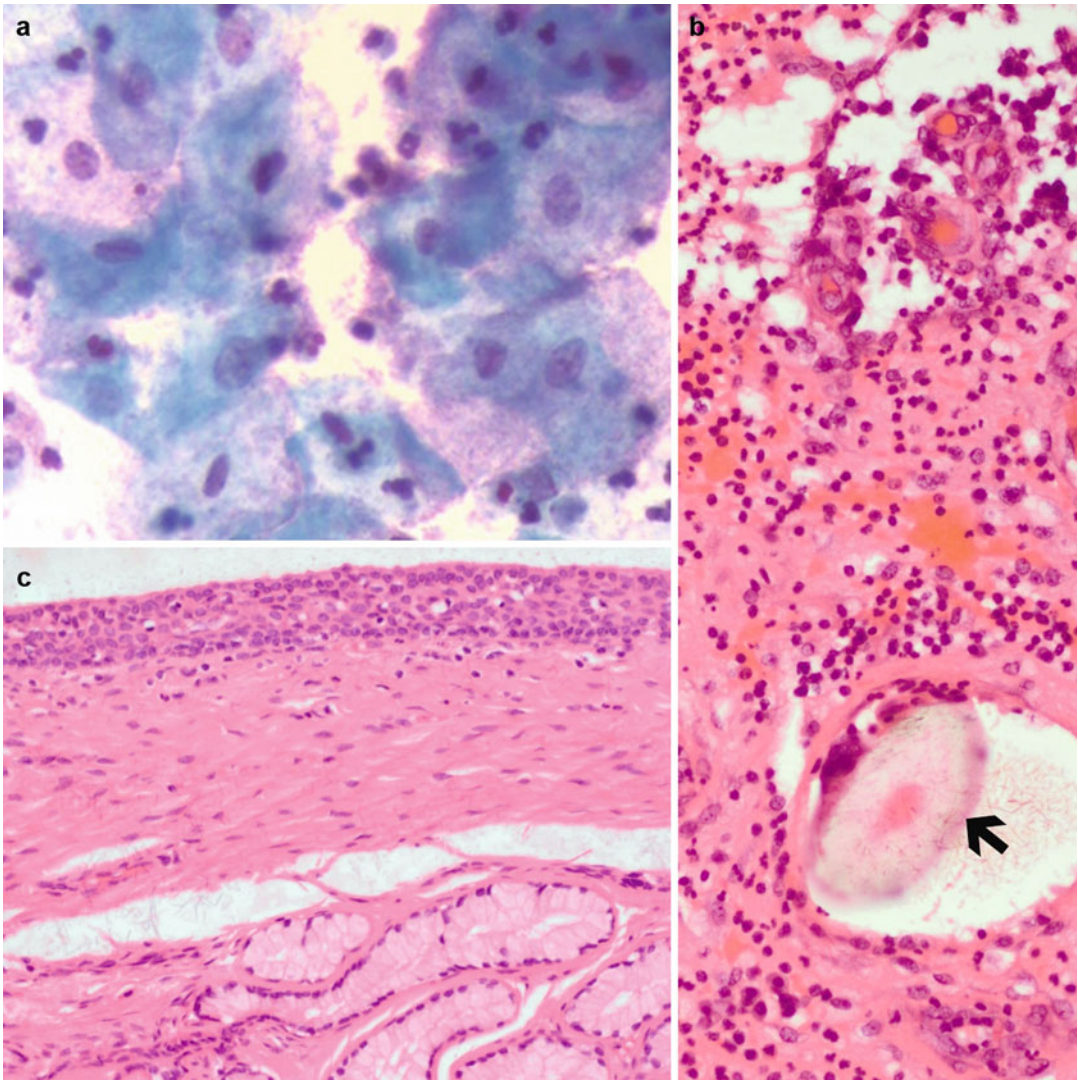


Fig. 2.8 Bacterial vaginosis (a) characterized by squamous epithelial cells covered by coccobacilli (clue cells). Bartholin duct cyst (b) with superficial epithelium

and mucous glands in wall. Pilonidal sinus (c) with a granulation tissue-lined tract with suppuration and hair shafts (arrow)

inflammation, similar to that in other anatomic sites. Bullous impetigo and staphylococcal scalded skin syndrome are typified by flaccid bullae. Rupture of the bullae in staphylococcal scalded skin syndrome results in exfoliation of confluent areas of the epidermis. In patients with recurrent vulvovaginal abscesses, infection caused by methicillin-resistant *S. aureus* should be considered as an etiological agent [73–75]. Abscesses in the vulvovaginal area may arise in dilated and inflamed Bartholin (Fig. 2.8b), Gartner, or Skene

ducts, hidradenitis suppurativa, pilonidal sinuses (Fig. 2.8c), and urethral diverticula. *S. aureus* is implicated in most of these settings but *Bacteroides*, *E. coli*, *N. gonorrhoea*, *K. pneumoniae*, and *Chlamydia* have been implicated in Bartholin abscess [76–79].

Streptococcal infections of the vulvovaginal area are heterogeneous. Superficial streptococcal disease encompasses a perianal dermatitis with vulvovaginal spread. Necrotizing gangrene, a fulminant life-threatening condition, is caused by a

wide range of organisms, including *C. perfringens*, *S. aureus*, *P. mirabilis*, *P. aeruginosa*, and *S. viridans*. Occurring in patients with diabetes mellitus, peripheral vascular disease, and immunocompromised states, extensive surgical debridement is the gold standard of management [80, 81]. Microscopic appraisal of debrided tissue demonstrates extensive tissue necrosis including fascial necrosis, thrombosis, and obliterative endarteritis of subcutaneous vessels and leukocytic infiltration [80].

Erythrasma, a superficial cutaneous infection that is caused by *Corynebacterium minutissimum*, involves the intertriginous spaces most commonly [82]. It occurs mainly in diabetic, obese, elderly, and other immunocompromised patients and those with excessive sweating [83]. Patients usually present with large, slowly spreading, confluent, slightly raised, reddish-brown macular patches with variable central clearing and poorly defined borders [82]. A superficial scale maceration is present in dry and moist areas, respectively. While the cutaneous lesions may be asymptomatic, moderate itching or discomfort is recorded [82]. *C. minutissimum* is a Gram-positive, aerobic diphtheroid rod that invades the upper third of the stratum corneum and proliferates in warm and humid conditions [83]. The diagnosis of erythrasma is confirmed by coral-pink fluorescence under Wood's lamp and by the presence of Gram-positive rods on smears or in the superficial stratum corneum in biopsy sections [82–84]. Methylene blue-stained smears demonstrate the presence of dark blue granules. Erythrasma may be confused with seborrheic dermatitis and may coexist with *Malassezia* species [82–85]. However, the latter is characterized by spores and thick hyphal forms that demonstrate green autofluorescence under Wood's lamp.

Malakoplakia, initially described by Michaelis and Gutmann in 1902, is a chronic inflammatory disease that is associated with a range of bacterial infections [86]. While malakoplakia involves the mucosa of the urinary tract most commonly and a wide range of extraurinary sites may be involved, vulvovaginal involvement is documented rarely [86, 87]. However, of the genital organs, vaginal

involvement is most common [87]. The pathogenesis of malakoplakia is controversial, but an infective basis, altered histiocytic activity, altered immune response, and abnormal gut flora have been implicated [88–90]. *E. coli* is implicated in more than two-thirds of cases, but other known infective associations include *Klebsiella*, *Mycobacterium tuberculosis*, *Staphylococcus aureus*, *Proteus* species, and *Rhodococcus equi* [88–90]. Malakoplakia is characterized by the presence of solitary or widespread soft plaques and nodules [90]. Microscopically, sheets of swollen histiocytes with eosinophilic granular or vacuolated cytoplasm, referred to as von Hansemann cells, containing periodic acid Schiff-positive and diastase-resistant inclusions and Michaelis-Gutmann bodies are seen.

Vulvovaginal Candidiasis

Vulvovaginal candidiasis affects approximately 75% of women in the reproductive age at least once in their lifetime, with approximately 50% experiencing ≥ 1 recurrence and 5–8% experiencing multiple annual episodes [91, 92]. Occurring in association with a normal vaginal pH (pH range = 4.0–4.5), vulvovaginal candidiasis is caused most commonly by *Candida albicans* [91, 93]. Risk factors for vulvovaginal candidiasis include diabetes mellitus, antibiotic use, high reproductive hormone levels, and genetic predisposition [94, 95]. Clinically, patients have a white, curd-like vaginal discharge, vulvovaginal erythema, edema, and fissures. Microscopically, there is epidermal hyperkeratosis, parakeratosis, and hyperplasia with subcorneal or spongiotic pustules (Fig. 2.9a) and periodic acid Schiff-positive budding yeasts, 3–6 μm diameter, round to oval in shape, and pseudohyphae, 2–4 μm in length (Fig. 2.9b). In biopsies, the epidermal alterations may resemble that of psoriasis vulgaris, lichen simplex chronicus, and eczematous dermatitis. Periodic acid Schiff identification of the fungal forms is pivotal to the diagnosis.

Trichomoniasis

Trichomoniasis, caused by the flagellate protozoan *T. vaginalis*, is believed to be the most frequent sexually transmitted infection and is a risk

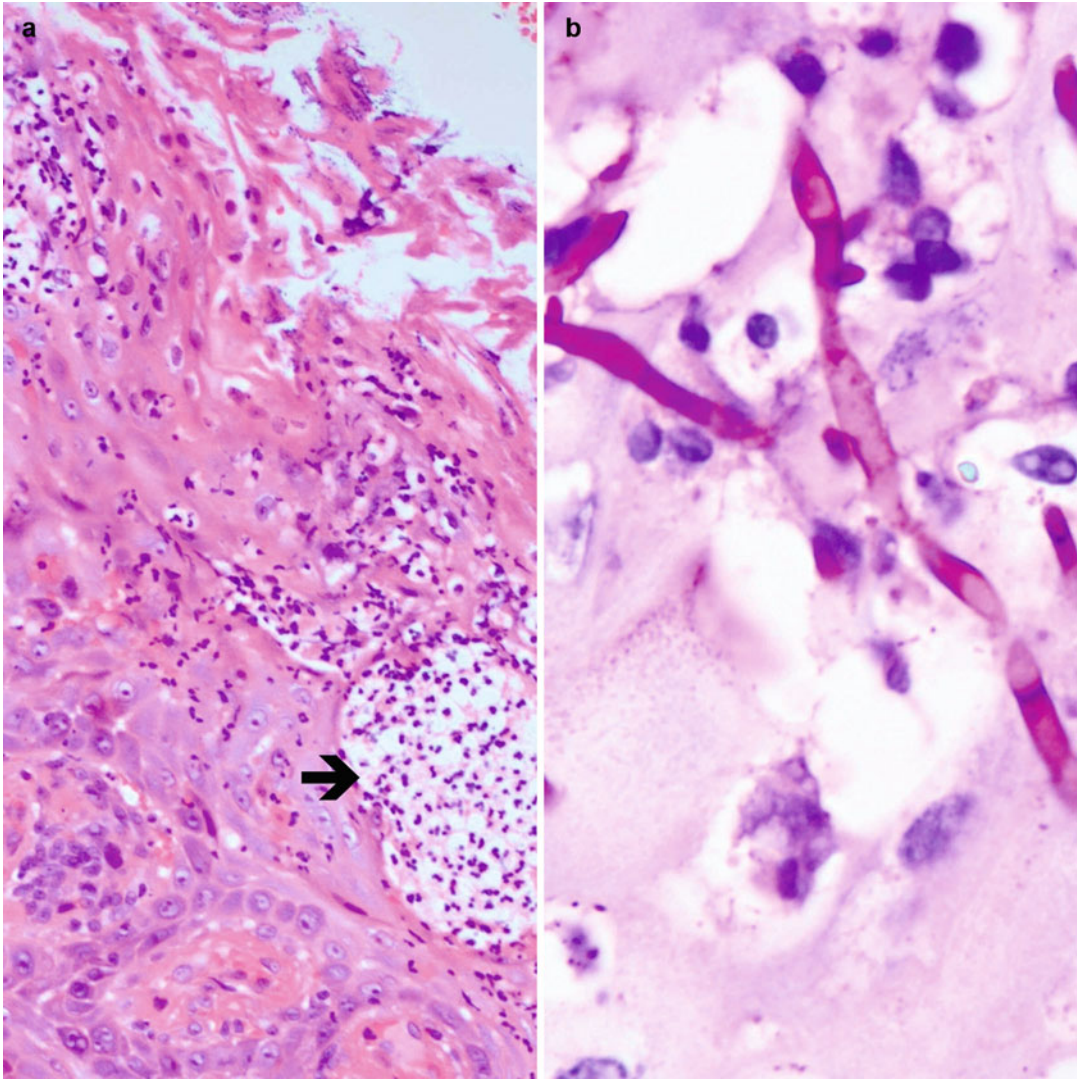


Fig. 2.9 Vulvovaginal candidiasis: Hyperparakeratotic, acanthotic epithelium (a) with pustules (arrow) and superficial debris. Periodic acid Schiff-positive pseudohyphae (b)

factor for HIV transmission [96, 97]. It usually parasitizes the vagina, prostate gland, and urethra [98]. *T. vaginalis* trophozoites are 23–39 μm in length and 5–8 μm wide. They contain four anterior flagella and a fifth flagellum that is present within the undulating membrane [98, 99], spanning approximately two-thirds of the distance to the posterior end of the body [98, 99]. Patients present with a foul-smelling, yellow-green vaginal discharge, acute vaginitis, and vulvovaginal tenderness [100]. The vulvovaginal mucosa demonstrates intense erythema and edema [98,

101]. Diagnosis is made on direct wet mount examinations of vaginal secretions (Fig. 2.10a), culture, Papanicolaou smears, and serologic and PCR investigation; the latter has been found to be 100% specific and sensitive [102]. Oral metronidazole is the current drug of choice.

Pediculosis Pubis

Pubic lice (pediculosis pubis, crab lice) infest over 10% of human populations worldwide [103]. Caused by *Phthirus pubis*, crab louse disease is usually transmitted sexually in association with

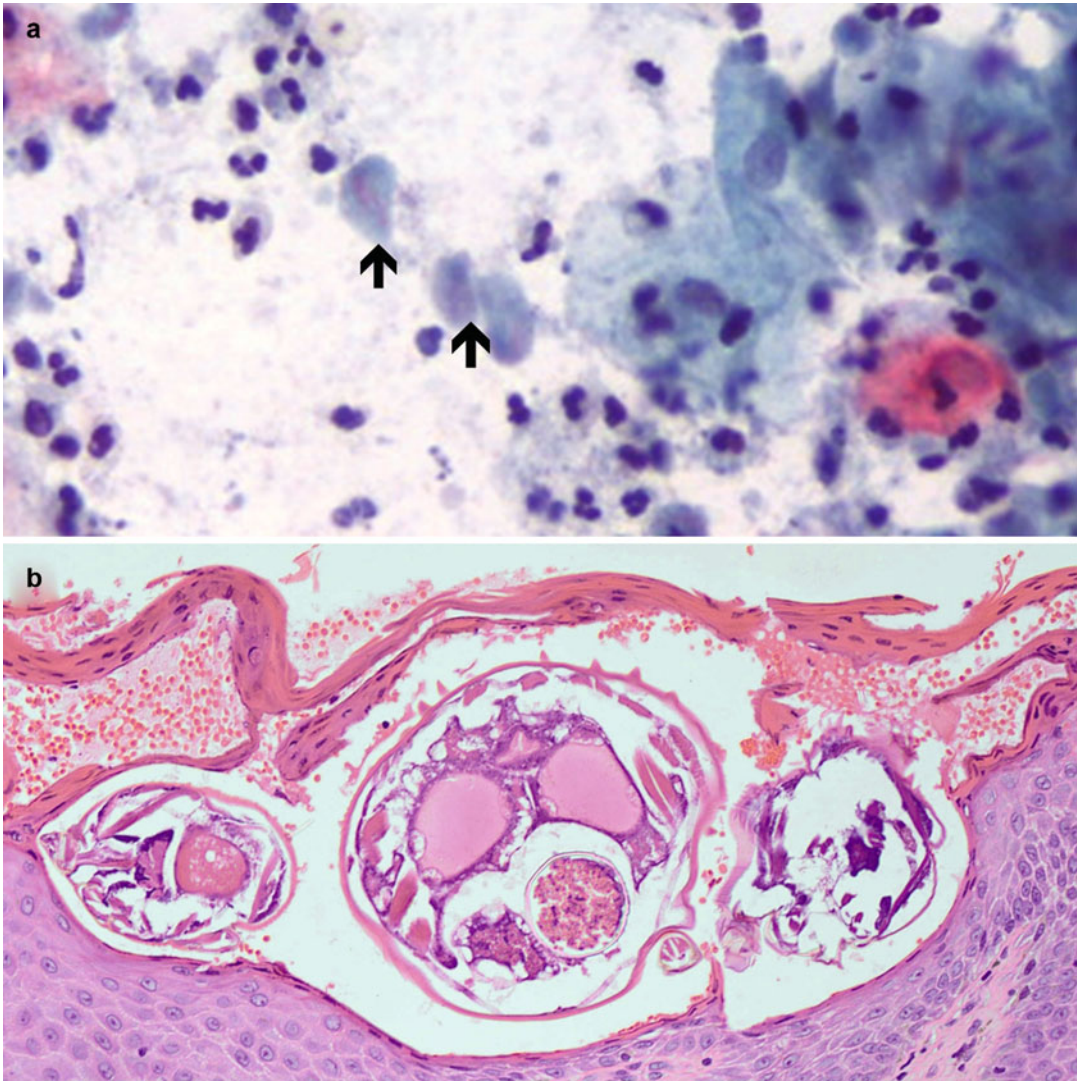


Fig. 2.10 Trichomoniasis: pear-shaped organisms (a, arrows) on a Papanicolaou-stained smear. Hyperparakeratotic, acanthotic epidermis with *S. scabiei* mites (b)

another concomitant sexually transmitted disease in 30% of patients [104]. Crab louse infestation is typified by their attachment to pubic hairs. Established infestation is accompanied by bluish-gray macules on the thighs and lower abdomen that are a consequence of hemorrhage and hemosiderin deposition. Excoriations may be present as a consequence of pruritus. Diagnosis depends on the identification of the 0.8- to 1.2-mm long adult organisms and viable eggs (nits) on hair shafts [103].

Scabies

Scabies is caused by the female mite of the genus *Sarcoptes scabiei* var *hominis*. It is spread by close human contact. The female mite lives in epidermal burrows. Norwegian or crusted scabies is associated with immunosuppression. Microscopically, scabies is associated with intraepidermal mites or scabietic fecal material or ova, epidermal spongiosis, intraepidermal eosinophils, and a lymphoeosinophilic infiltrate around the superficial and deep vascular plexuses.

Norwegian scabies is characterized by a psoriasiform epidermal reaction pattern with epidermal hyperkeratosis, parakeratosis, and large numbers of organisms (Fig. 2.10b) [54, 105].

Secondary Vulvovaginal Infection

Contiguous Spread from Adjacent Organs

Amoebiasis

Cutaneous amoebiasis is a rare disease [106, 107]. Caused by *Entamoeba histolytica*, it may be the exclusive expression of amoebiasis, or it may represent contiguous spread from a local site. *E. histolytica* has phagocytic, proteolytic, and cytolytic capabilities [108, 109]. Cytolysis is induced by amoebapores, small peptide that form pores in lipid bilayers [110]. Cytokines and chemokines released by disrupted epithelial cells attract neutrophils and macrophages to the site of disease [111, 112]. Neutrophil lysis and cysteine proteinases released by *E. histolytica* exacerbate the tissue damage [113]. Despite the proximity of the vulva to the gastrointestinal tract, vulval amoebiasis is reported rarely [114]. The cutaneous manifestations include painful ulcers with necrotic bases and variably raised edges, fistulae, abscesses, sinuses, and polypoid and warty outgrowths. Cutaneous amoebiasis occurs by direct or indirect routes. The former comprises contiguous spread from an adjacent visceral amoebic focus in the colon, rectum, or liver. Indirect cutaneous involvement occurs by vascular invasion and hematogenous and lymphatic spread. *Outcome*: If diagnosed and treated in a timely manner, healing of cutaneous lesions occur. Intravenous or oral metronidazole is the drug of choice.

Pathologic features: While the biopsy findings may differ based on the pathogenesis of the disease, the hallmark of the disease is liquefactive necrosis and trophozoites with ingested erythrocytes, hematophagous trophozoites (Fig. 2.11a). Pseudoepitheliomatous hyperplasia, atrophy, sinuses, and fistulae are variable findings. Vascular invasion and intraluminal amoebae may be identified, especially in lesions with deep

involvement. Neutrophils with leukocytoclasia may be prominent. The periodic acid Schiff stain highlights hematophagous amoebic trophozoites (Fig. 2.11b) but degenerate trophozoites do not stain, and amoebae may be missed in densely neutrophilic foci. *Differential diagnosis*: The clinical differential diagnosis includes tuberculosis, syphilis, herpetic ulceration, Crohn's disease, and carcinoma, all of which are microscopically distinctive.

Schistosomiasis

Blood flukes of the genus *Schistosoma* are the infective agents of schistosomiasis that afflicts >200 million people worldwide [115]. The three major pathogenic species include *S. mansoni*, *S. japonicum*, and *S. haematobium*. *S. haematobium* is most commonly associated with female genital tract schistosomiasis [116]. Schistosomiasis is endemic in Egypt, Middle East, and Africa and is transmitted by freshwater snails [44]. Cercariae swim through fresh water and penetrate human skin with the aid of proteolytic enzymes [117]. Schistosomes form, shed off a surface glycocalyx and become schistosomules. These migrate to the lung and then settle in the pelvic or hepatic venous plexuses [117]. Cutaneous disease, in general, assumes four forms: cercarial dermatitis, urticarial lesions, papular granulomatous or warty lesions, and extragenital cutaneous lesions. Vulvar schistosomiasis is typified by papules, nodules, ulcers, polyps, warty outgrowths, exophytic tumor masses, and vulval edema. The lesions may be pruritic and painful [118, 119]. It has been suggested that genital schistosomiasis may be a risk factor for HIV transmission [116]. Sequestration of ova in the mucocutaneous epithelium of the genitalia causes friable contact bleeding foci. At these points, genital schistosomiasis is hypothesized to expose the deeper mucocutaneous tissue to HIV. *Diagnosis*: If patients have hematuria, microscopic examination of a midday or filtered terminal urine specimen may demonstrate ova. *S. haematobium* has a characteristic terminal spine, in contrast to *S. mansoni* ova that have lateral spines. *S. japonicum* does not possess a spine. While the entire wall of *S. mansoni* and

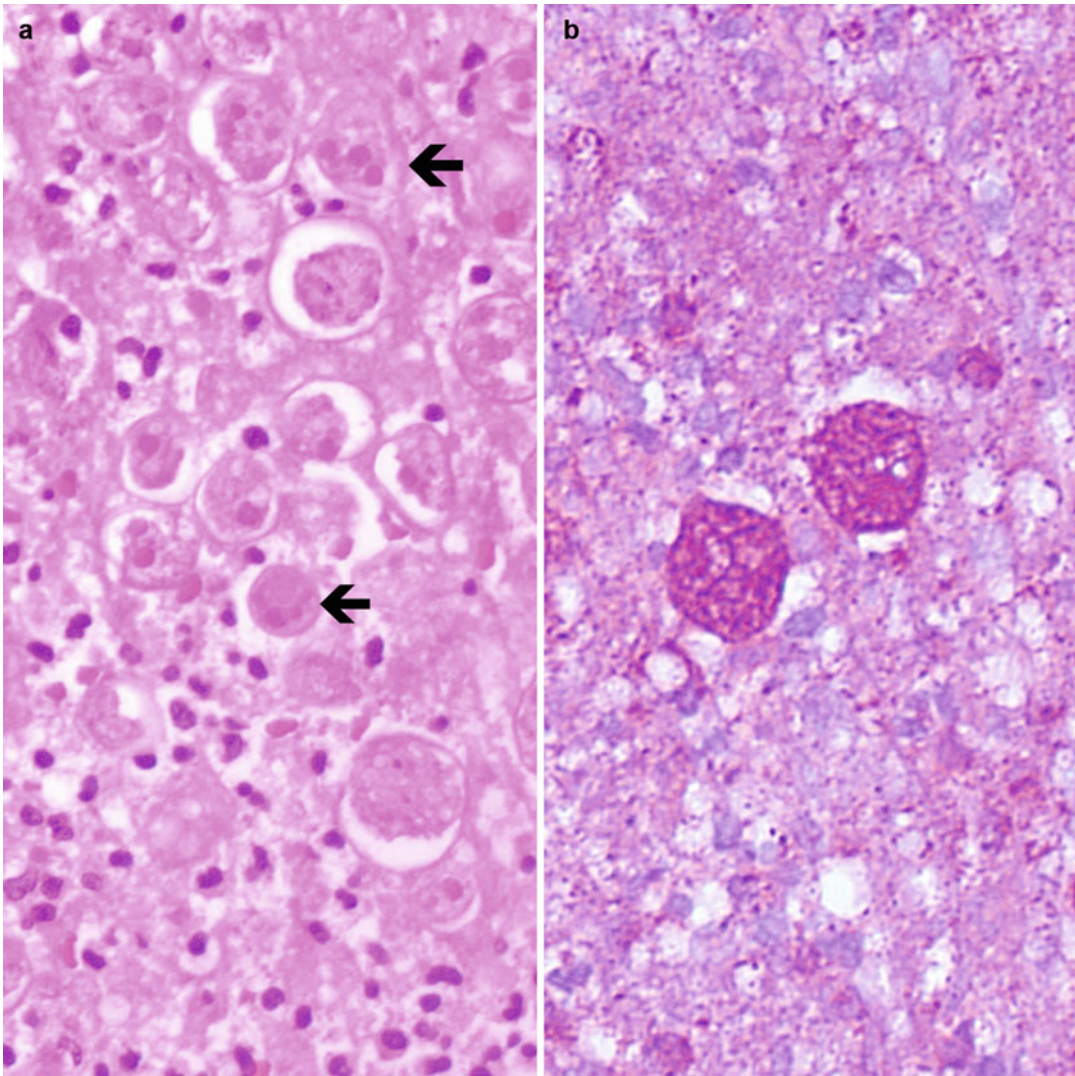


Fig. 2.11 Amoebiasis: hematophagous amoebic trophozoites (a, arrows) highlighted by periodic acid Schiff stain (b)

S. japonicum ova is acid fast by Ziehl Neelsen staining, only the terminal spine of *S. haematobium* is acid fast [117]. ELISA methods have been developed to confirm schistosomal infection. *Outcome/treatment*: Praziquantel is the current drug of choice for schistosomiasis with a cure rate of 60–90% in individuals from endemic areas and 100% for those in nonendemic areas [120, 121]. High pretreatment schistosomal load, high rate of reinfection, drug resistance, the circulation of immature parasitic organisms unaffected by drugs, and noncompliance are causes for a suboptimal response to praziquantel

[120, 121]. Current molecular investigational tools include the Taq Man real-time PCR assay for early detection of *Schistosoma* species, the role of increased CD23⁺ B lymphocytes in drug-resistant schistosomiasis, genotypic analyses for the monitoring of mass drug administration campaigns, and the role of the phosphotyrosine signaling network in the development of novel antischistosomal therapy [115, 122, 123].

Pathology: Genital or perineal biopsies demonstrate ulceration, sinuses, and pseudoepitheliomatous hyperplasia. Free-lying, variably calcified ova may be accompanied by a florid granulomatous

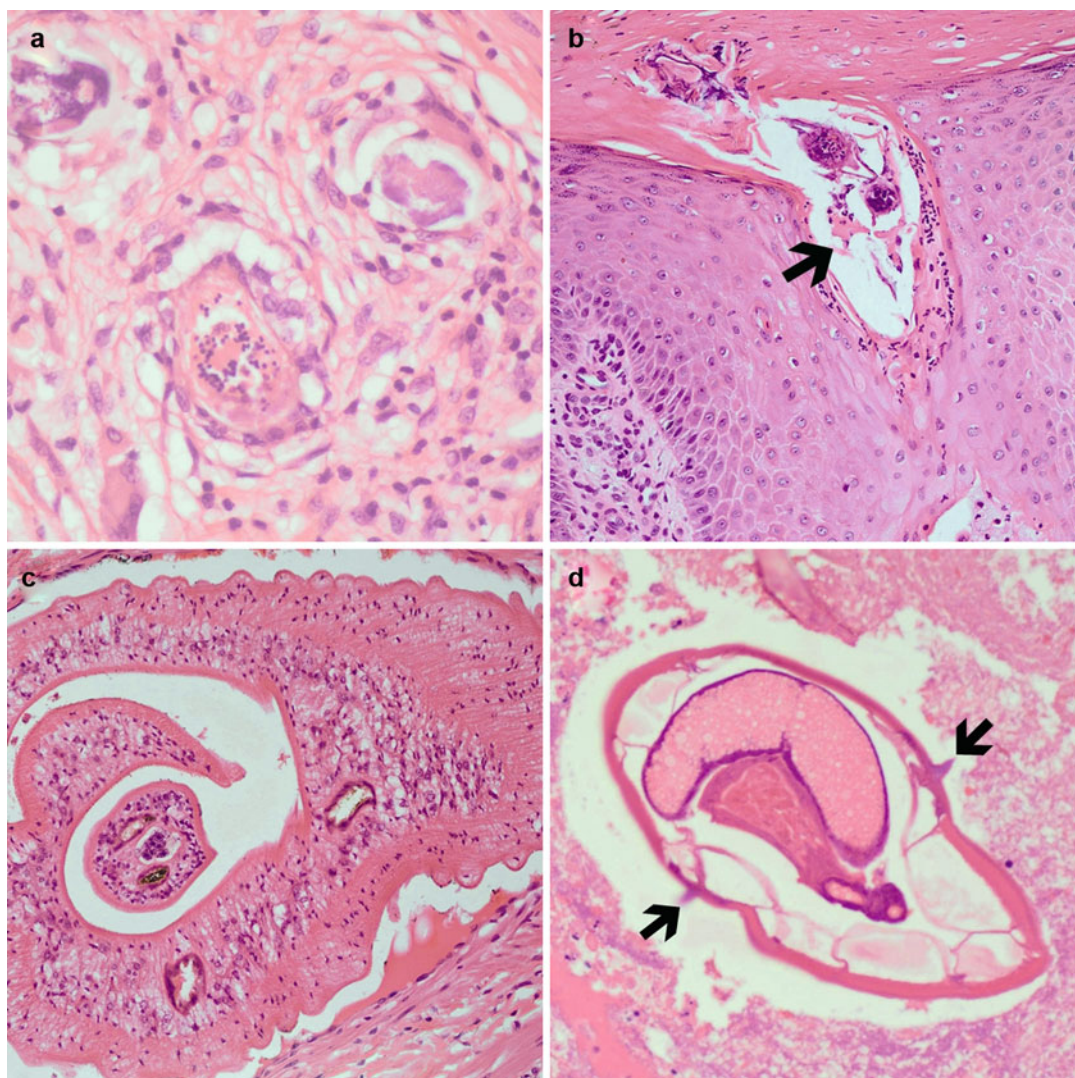


Fig. 2.12 *S. haematobium* ova within a dermal granuloma (a). Transepidermal elimination of viable ova (b, arrow) and intravenous schistosomal worms (c). *E. vermicularis* with lateral alae (d, arrows)

reaction (Fig. 2.12a) with eosinophils, eosinophil flame figures, and the Splendore-Hoeppli phenomenon [44, 118]. The ova may be degenerate or viable with identifiable miracidia. Transepidermal elimination of schistosomal ova may be present (Fig. 2.12b), especially in biopsies demonstrating pseudoepitheliomatous hyperplasia [123]. Fibrosis and intravenous worms (Fig. 2.12c) are a variable finding.

Enterobiasis

Enterobiasis, a worldwide infection, caused by *Enterobius vermicularis*, is spread by overcrowd-

ing and the sharing of clothing. *E. vermicularis* is an intestinal parasite, residing mainly in the ileocecal area, colon, rectum and vermiform appendix [124]. Following copulation in the colonic lumen, the adult male worm dies. The gravid female migrates to the anal region where ova are deposited, causing intense pruritus ani and serving as a nidus for ano-oral transmission of the organism. The ingested ova that contain first-stage larvae hatch in the duodenum and are carried to the colon where they develop into adult worms [124, 125]. Retrograde infection may

occur when ova hatch on the skin of the buttocks and larvae migrate through the anus to the colon [124]. Because of the proximity of the vulva to the anus, adult worms migrate to the vulva, vagina, cervix, endometrium, ovaries, and peritoneal cavity, with resultant deposition of ova. Vulval involvement by *E. vermicularis* is rare, with patients presenting with vulvovaginitis or a vulval mass [125–127].

Microscopic features: There is pseudoepitheliomatous epidermal hyperplasia that mimics squamous cell carcinoma. An inflammatory response to subepithelial ova or worms is present. This may be granulomatous in nature with a variable eosinophilic component. The inflammatory component can assume a lichenoid pattern [124]. The ova are approximately 50–60 μm by 20–30 μm in dimension and contain a thick two-layered shell. The cuticle of adult worms is expanded into alae that extend along each side (Fig. 2.12d). The uterus of the female adult worm fills the body cavity and is distended with ova [124, 125].

Vulvovaginal Involvement by Systemic Infection

Tuberculosis

Although tuberculosis has afflicted mankind throughout recorded and archeological history, it remains among the leading causes of morbidity and mortality worldwide [128, 129]. Caused by *M. tuberculosis*, a member of the *M. tuberculosis* complex that includes six other closely related species, cutaneous tuberculosis accounts for 1.5% of extrapulmonary disease [130]. Less than 2% of genital tuberculosis occurs in the vulva and vagina, with the vulva being the least common site for genital tuberculosis [131, 132]. Primary vulval inoculation tuberculosis, first described in 1888 [132], is rare. Vulval tuberculosis is usually associated with systemic disease, especially pulmonary tuberculosis or tuberculosis higher in the genital tract, including the fallopian tubes, uterus, and ovaries [130].

Clinical features: Vulval tuberculosis presents as ulcers with variable sinus formation, hypertrophic lesions, id reactions, or rarely,

esthiomene [133–137]. Lupus vulgaris and scrofuloderma have been described, the former more commonly [130, 138, 139]. Vulval tuberculids are documented rarely. While lichen scrofulosorum and papulonecrotid tuberculid may involve the vulva, the latter is the only documented vulval tuberculid, described as part of localized or more widespread disease [140, 141]. Lichen scrofulosorum, a widely disseminated rash composed of 2-mm-diameter, variably scaly, folliculocentric papules, may involve the vulva as part of a generalized process [142]. **Differential diagnosis:** Ulcerative manifestations may resemble sexually transmitted diseases including LGV, chancroid and syphilis, schistosomiasis, Crohn's disease, and amoebiasis. Hypertrophic lesions may resemble carcinoma while the papular tuberculids may resemble sarcoidosis. **Diagnosis:** Apart from the histomorphological confirmation of tuberculosis, mycobacterial PCR can be employed for diagnosis [143]. Microbiological culture not only allows genotypic analysis of the culture isolates but also facilitates drug sensitivity testing. **Treatment:** The first-line drug schedule includes isoniazid, rifampicin, ethambutol, and pyrazinamide. Patients with multidrug- and extreme-drug-resistance tuberculosis require alternate schedules.

Microscopic features: Necrotizing granulomatous inflammation with caseative necrosis and a surrounding histiocytic, palisaded, or granulomatous inflammatory response with Langhans giant cells is the prototypical reaction pattern. Ziehl Neelsen staining demonstrates acid fast bacilli. In scrofuloderma, tuberculous lymphadenitis ruptures more commonly to the skin and to the surface with resultant sinus formation. The center of the lesion demonstrates suppurative or abscess-like morphology. The deep aspect of the lesion is composed of the prototypical necrotizing granulomatous histomorphology with identifiable acid fast bacilli. Papulonecrotic tuberculid is characterized by a wedge-shaped zoned inflammatory reaction pattern. Superficial crust, acute inflammatory exudate, coagulative necrosis, granulomatous inflammation, and vasculitis are stratified from the superficial to deepest location (Fig. 2.13a). Acid fast bacilli are not identified on special

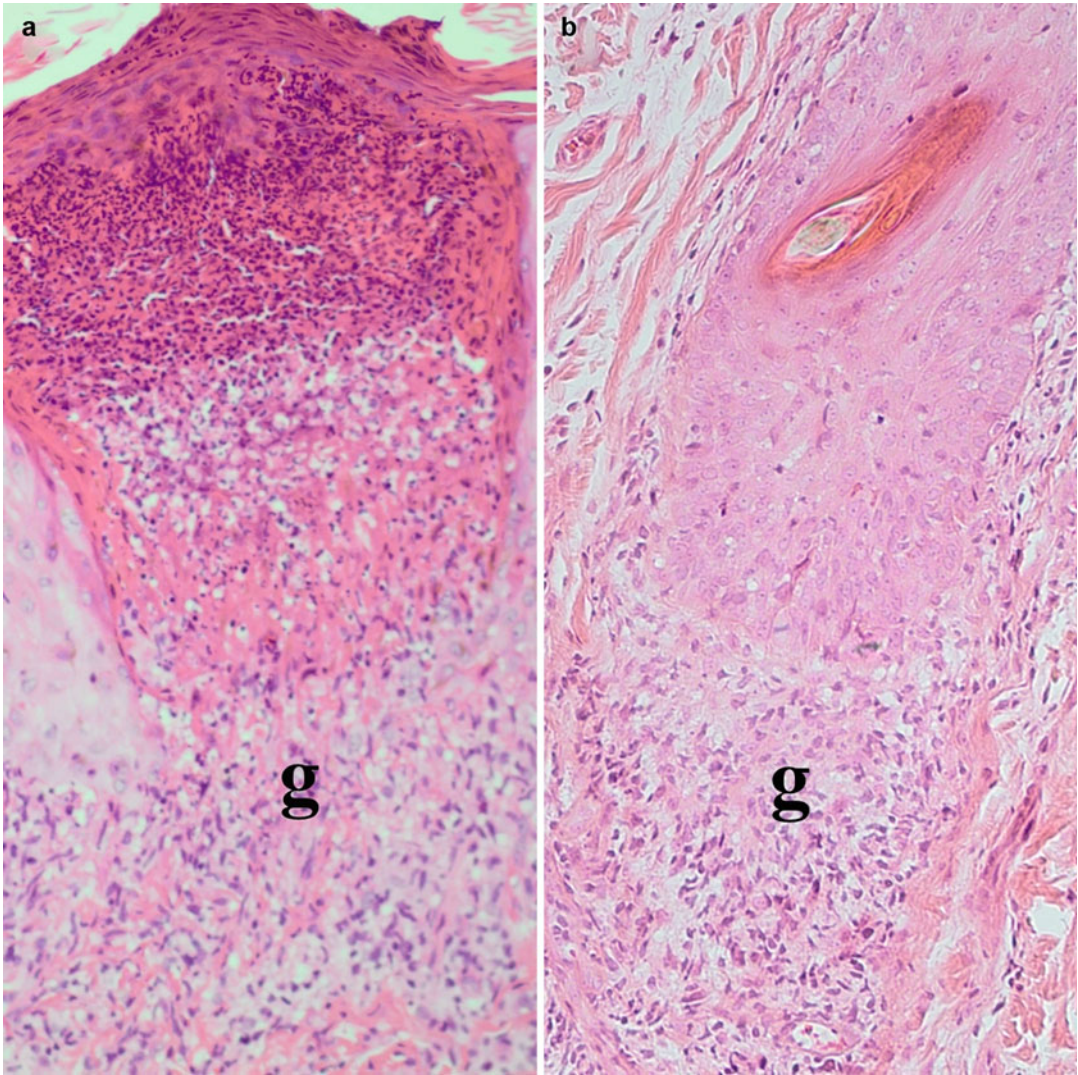


Fig. 2.13 Papulonecrotid tuberculid (a) with a “zoned” inflammatory, including deep granulomatous (g), response. Nonnecrotizing perifollicular granulomatous inflammation (g) in lichen scrofulosorum (b)

mycobacteria stains. Biopsy of lichen scrofulosorum demonstrates subepidermal, periappendageal, and interstitial microgranulomas (Fig. 2.13b).

Bacillary Angiomatosis

Bacillary angiomatosis is caused by members of the *Bartonella* spp., *B. quintana*, and *B. henselae* [144–146]. Although known for more than 100 years, *Bartonella* spp. are still considered emerging infectious agents [147, 148]. *B. henselae* that also causes cat scratch disease

and peliosis hepatitis is transmitted mainly by cat fleas. *B. quintana*, residing in humans, also causes trench fever and is transmitted by body lice, cat fleas, and ticks. It is associated with poor living conditions and homelessness. Bacillary angiomatosis is associated with clinical heterogeneity, presenting as solitary or multiple lesions. Ulcers, papules, nodules, and pyogenic granuloma-like and warty lesions are documented in the skin. Vulval bacillary angiomatosis is documented rarely [149–151].

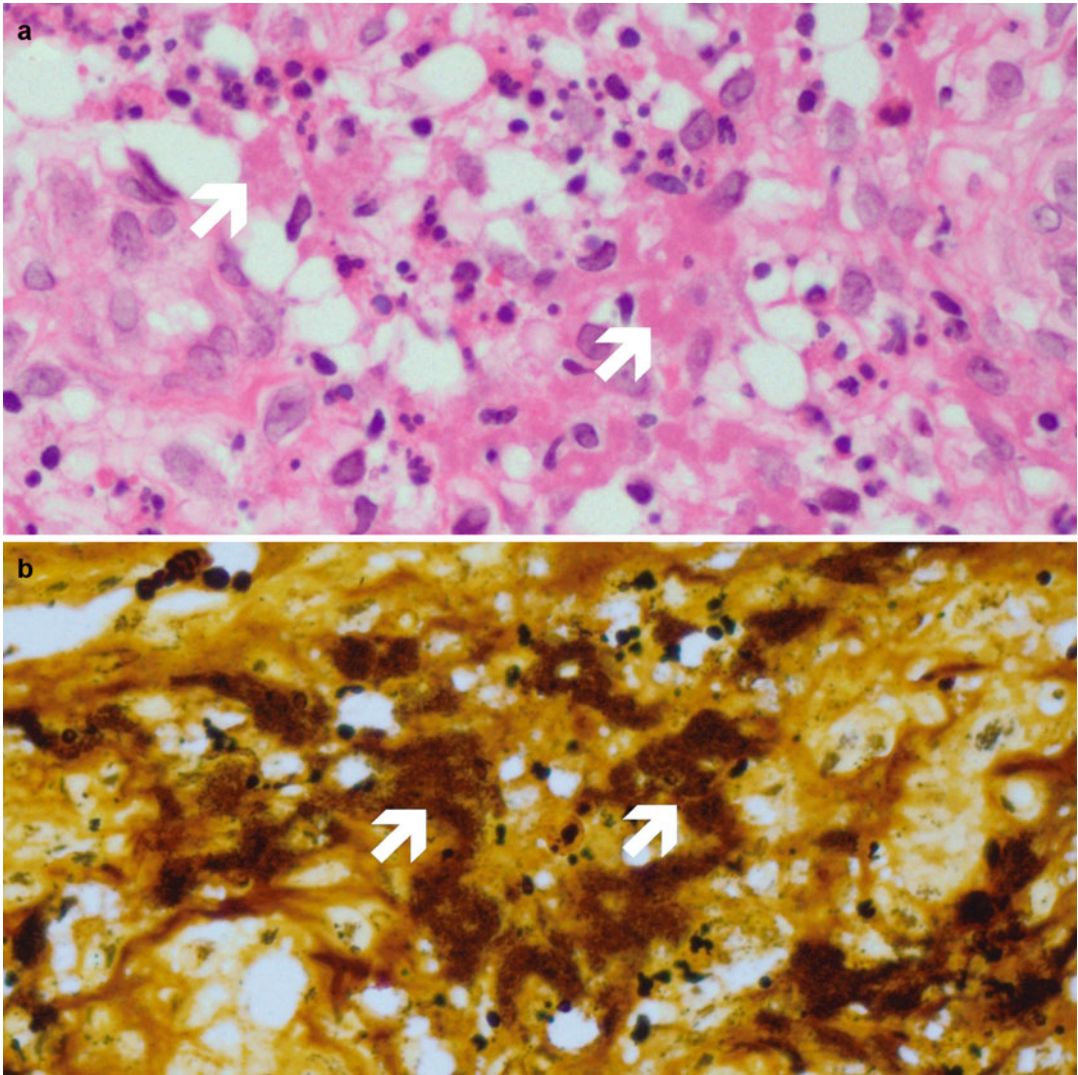


Fig. 2.14 Bacillary angiomatosis: vasculature lined by plump endothelial cells (**a**), intervascular neutrophils, karyorrhectic debris, and paravascular eosinophilic

material (*arrows*), confirmed to be argyrophilic organisms on Warthin Starry stain (**b**, *arrows*)

Microscopic features: Bacillary angiomatosis is characterized by lobular vascular proliferation, interstitial neutrophils, and karyorrhectic debris (Fig. 2.14a). The vascular channels are lined by epithelioid endothelial cells. Paravascular clumps of argyrophilic organisms are present (Fig. 2.14b). Ulceration, pseudoepitheliomatous hyperplasia, and a confluent neutrophilic infiltrate are less common microscopic findings. **Differential diagnosis:** Deep lesions may mimic abscess because

of confluent suppuration or they may have a solid appearance with minimal debris, resembling tumors with an epithelioid endothelial phenotype, including angiosarcoma, epithelioid hemangioendothelioma, and cutaneous epithelioid angiomatous nodule. Bacillary angiomatosis with spindle cells mimic Kaposi sarcoma. The diagnosis may be confirmed on a biopsy, with exact bacillary confirmation being obtained by molecular investigation. Serological and microbiological studies,

the latter typified by specialized techniques, may also aid the diagnosis.

Cytomegalovirus Infection

Cytomegalovirus (CMV) is a member of the Herpesviridae family of DNA viruses [152]. A major cause of mortality and morbidity in immunocompromised individuals, it is one of the most common fatal systemic infections in patients with AIDS [153].

Clinical features: Cutaneous manifestations, documented rarely, include a generalized maculopapular rash, ulcers, indurated hyperpigmented nodules, vesicles, petechiae, plaques, and pseudoangiomatous lesions that mimic a range of dermatoses [153]. Nonpathognomonic ulcers involve the genital, perineal, and perianal areas [152, 154]. They may be single or multiple and vary in size [155]. The significance of CMV in the cutaneous lesions is controversial [156, 157]. While CMV may be pathogenic, it may also be an epiphenomenon and colonizer of endothelial cells during CMV viraemia [157]. It has been questioned why localized CMV ulceration has a propensity for genital or perineal involvement [155]. It has also been suggested that these anatomic locations serve as latency sites for CMV. The intraneural location of CMV inclusions in genital and perineal skin, similar to shingles, has supported such a view. *Diagnosis:* According to some workers, light microscopy of routine hematoxylin-and-eosin-stained sections is the most sensitive diagnostic tool [157]. Immunohistochemistry, in situ hybridization, and molecular investigations may be employed for diagnostic confirmation. *Outcome:* Localized infection has a better outcome than disseminated disease. Ganciclovir, foscarnet, and valganciclovir are used for treatment.

Microscopic features: There is capillary dilatation with endothelial localization of large, eosinophilic intranuclear inclusions, approximately 10 μm in size (Fig. 2.15a) [62, 158]. These inclusions may be present within the granulation tissue in the ulcer base, with resultant leukocytoclastic vasculitis and thrombosis [62, 155, 157]. Inclusions are also present in

keratinocytes, eccrine epithelium, macrophages, and fibroblasts [157].

Epstein-Barr Virus Infection

While Epstein-Barr virus (EBV)-associated genital ulcers were first documented in 1977, in 1913 Lipschütz described an acute disease with fever, genital ulcers, and lymphadenopathy in young women that was labeled “Lipschütz syndrome” [159]. It is possible that some patients with Lipschütz syndrome have primary EBV infection. EBV-associated genital ulcers occur in patients with a mean age of 14.5 years (range=2–51 years) [159].

Clinical features: The ulcer may be single and >1 cm in diameter or multiple and small [160]. The ulcers are deep and necrotic with irregular edges and a yellow adherent membrane. Pain is the main presenting symptom, but a prodrome of fatigue, headache, and fever precedes the ulcer symptoms. Signs of infectious mononucleosis may also be present, including lymphadenopathy and tonsillitis [159, 160]. The ulcers respond to systemic corticosteroid therapy or may resolve spontaneously within approximately 2 weeks [160]. *Diagnosis:* Clinical suspicion is pivotal to diagnostic confirmation. The initial presence of IgM in the absence of antibody to EBV nuclear, and a subsequent identifiable IgG antibody response to viral capsid, confirms a primary EBV infection. The genital ulcers may therefore be a manifestation of a viremia [159]. PCR testing of the ulcer may be helpful to confirm the diagnosis. *Differential diagnosis:* The differential diagnosis includes primary syphilis, which is painless in comparison to the EBV ulcer. Aphthous ulcers can be excluded by the results of clinical serological tests. Other infective ulcers, including those due to herpes simplex virus infection and candidiasis, demonstrate identifiable organisms.

Microscopic features: Biopsies demonstrate nonspecific features including granulation tissue with mixed acute and chronic cells and debris, similar to that seen in aphthous ulcers. Thrombosis and lymphocytic vasculitis may be present.

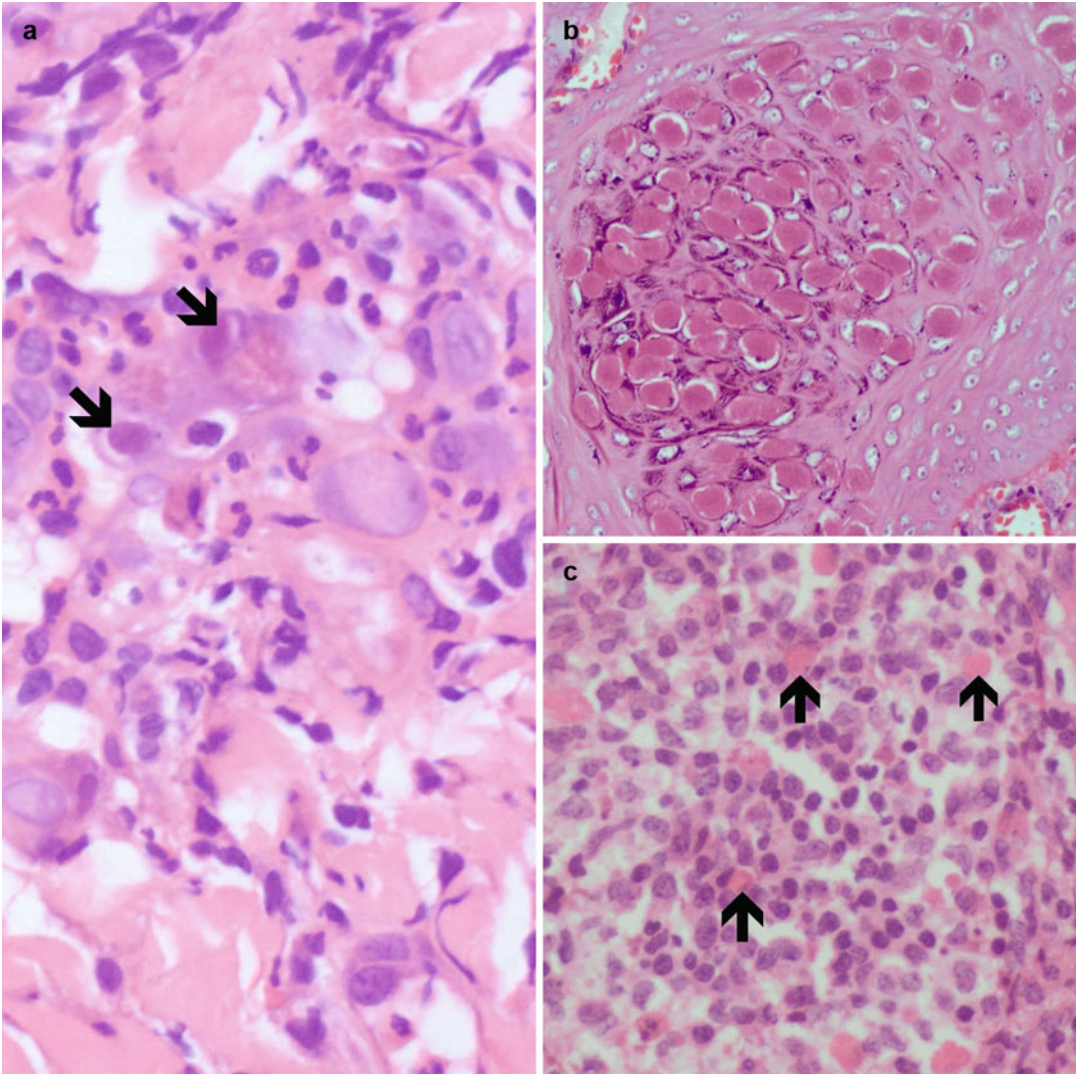


Fig. 2.15 Cytomegalovirus infection: vasculitis and “owl’s eye” inclusions in endothelial cells (**a**, arrows). Inclusions of *Molluscum contagiosum virus* within epi-

thelial crater (**b**). Pseudolymphomatous inflammatory reaction to degenerate dermal molluscum bodies (**c**, arrows)

Molluscum Contagiosum

Molluscum contagiosum, a worldwide infection, is caused by *Molluscum contagiosum virus*, the most common poxvirus that infects humans [161]. It occurs in individuals of all ages, but it commonly affects children, sexually active adolescents, and immunocompromised persons [162]. Molluscum contagiosum in women is usually a sexually transmitted disease, but spread through fomites, direct bodily contact, or minor abrasions also occurs. It manifests as waxy, skin-

colored papules, 2–5 mm in dimension, in multiple anatomical locations on the labia majora, labia minora, and mons pubis as a sexually transmitted disease [163, 164]. In patients with AIDS, giant molluscum contagiosum often measuring more than 1 cm occurs. In children, vulval involvement usually occurs as part of disseminated disease. Exclusive vulval molluscum contagiosum in children is unusual [165]. In adult women, exclusive vulval molluscum contagiosum occurs as a sexually transmitted infection

[164]. While molluscum contagiosum is a self-limited disease, curettage or cryosurgery may be used as physical treatment modalities. Topical application of 5% imiquimod cream may also be effective.

Microscopic features: A cup-shaped lesion composed of acantholytic epidermis with viral inclusion bodies is seen. In the lower epidermis, ovoid, eosinophilic inclusion bodies, the molluscum, or Henderson-Patterson bodies are seen in a peripheral location. At the granular layer level, the molluscum bodies appear basophilic. Central disintegration of the stratum corneum results in crater formation and the release of molluscum bodies therein. While the dermis is usually uninvolved, rupture of the crater discharges molluscum bodies and keratinous debris into the dermis (Fig. 2.15b). In this setting and when the molluscum contagiosum undergoes spontaneous involution, intense dermal inflammation, including a pseudolymphomatous response (Fig. 2.15c), is seen.

Superficial Dermatophytic Infection and Pityriasis Versicolor

The superficial dermatophytes include organisms of three genera: *Microsporum*, *Trichophyton*, and *Epidermophyton*. Tinea cruris, a dermatophytic infection of the groin, perineum, and perianal area, is caused by organisms of all three genera, but *T. rubrum* is the most common. Erythematous patches, plaques, pustules, and vesicles may be present. Biopsies demonstrate variable epidermal acanthosis, parakeratosis, spongiosis, and fungal yeasts and hyphae [43]. Majocchi granuloma, caused most commonly by *T. rubrum*, presents with perifollicular disease in immunocompetent and deep plaque/nodular lesions in immunocompromised patients [166]. It has been reported rarely in the vulva [166]. **Microscopically**, there is granulomatous perifolliculitis and an infiltrate of neutrophils, lymphocytes, and histiocytes. Vulval diseases caused by *Malassezia furfur* include pityriasis versicolor and folliculitis, both of which may occur in the vulva [167]. Pityriasis versicolor is characterized by reddish-brown to white scaly macules on the labia majora. **Microscopically**, fungal yeasts and hyphae are noted in the stratum corneum.

Histoplasmosis

Histoplasmosis is caused by *Histoplasma capsulatum*, a dimorphic fungus that exists worldwide but is endemic in the central United States, Latin American, and Caribbean countries [168–170]. Found in moist, acid soil with a high organic content, histoplasmosis is acquired by the inhalation of spores from soil contaminated by bird and bat guano [170, 171]. Ninety percent to ninety-five percent of new *H. capsulatum* infections are asymptomatic [172]. The rest present with symptomatic acute, disseminated, and chronic pulmonary forms of the disease [172]. Cutaneous histoplasmosis usually occurs in the setting of disseminated histoplasmosis, secondary to progression of primary pulmonary disease, in approximately 6% of patients with disseminated histoplasmosis [43, 168]. The patients who are afflicted are mainly patients with hematological malignancies, inborn errors of immunity, or AIDS. Mucocutaneous histoplasmosis of the female genital tract is rare, being reported twice to date, once as part of chronic disseminated histoplasmosis [173] and once as primary conjugal histoplasmosis [174].

Clinical appearance: The cutaneous spectrum of histoplasmosis includes ulcers, papules, nodules, plaques, molluscum-like lesions, purpura, erythroderma, and panniculitis [170, 175]. **Diagnosis:** Serological testing, fungal culture, histopathological appraisal, and PCR testing are useful diagnostic measures. Fungal morphologic in cultures at temperatures <35°C are those of a mycelial phase while at 37°C, the organism assumes a yeast-like form [168, 172]. **Differential diagnosis:** Organisms that reside in an intracellular location include those that cause donovansiosis, leishmaniasis, toxoplasmosis, and leprosy. *H. capsulatum* is the only microorganism that parasitizes histiocytes and stains with the usual fungal stains. **Treatment:** Oral itraconazole is effective for less severe forms of the disease and for maintenance therapy. Amphotericin-B is used in patients with severe disease and AIDS.

Microscopic features: Necrotizing or nonnecrotizing granulomatous (Fig. 2.16a) or diffuse histiocytic reaction patterns occur. The former

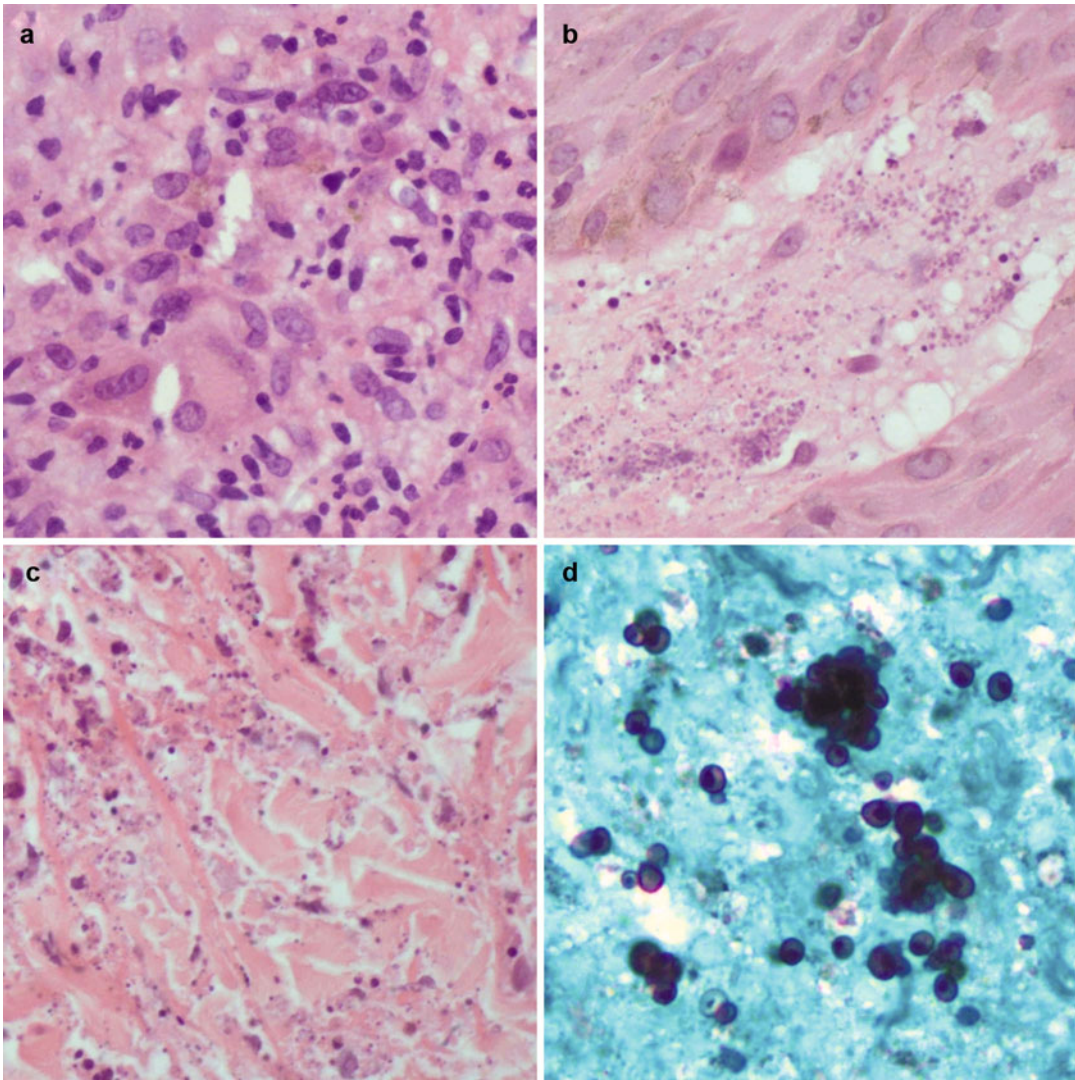


Fig. 2.16 Histoplasmosis: granulomatous response (a). Diffuse histiocytic infiltrate with intracytoplasmic microorganisms (b) and abundant dermal karyorrhexis

(c). Gomori-Grocott methenamine silver-stained *H. capsulatum* yeast forms (d)

is unusual in skin locations. The histiocytic reaction pattern is typified by sheets and nodular aggregates of dermal histiocytes in which abundant intracytoplasmic organisms are seen (Fig. 2.16b) [168, 170]. Karyorrhexis is variably present (Fig. 2.16c) [170, 176]. The individual organisms are round to oval 2–4-μm spores that are surrounded by a halo. The spores demonstrate variable narrow-necked budding and stain with periodic acid Schiff and silver stains (Fig. 2.16d).

Cryptococcosis

Cryptococcosis, caused by *C. neoformans*, is a fungal infection of worldwide occurrence [177]. It is a ubiquitous saprophyte of soil, being most abundant in environments contaminated by bird excreta [177]. Although usually acquired by inhalation of yeasts, primary cutaneous cryptococcosis occurs rarely [43]. Cryptococcosis occurs mainly in patients with malignancies, patients on immunosuppressive or corticosteroid therapy, and in transplant recipients [178]. Pulmonary

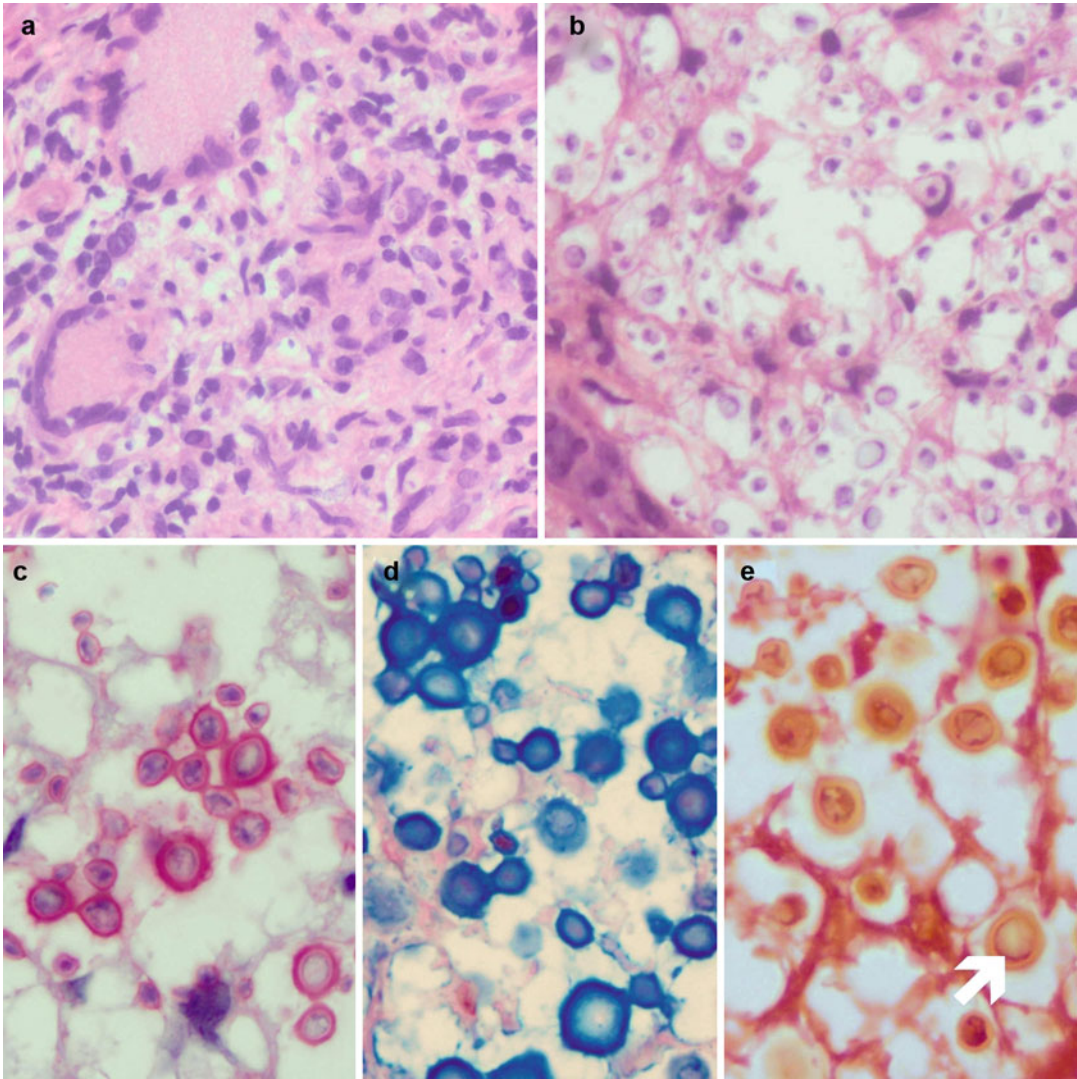


Fig. 2.17 Cryptococcosis: granulomatous (a) and paucicellular, “gelatinous” (b) patterns. Carminophilous organisms (c, Southgate mucicarmine), alcian blue-positive capsules (d), and Fontana-Masson-positive cell walls (e, arrow)

disease may be symptomatic or asymptomatic. The most important clinical manifestation is meningitis that is fatal if untreated [179]. Disseminated cryptococcosis occurs in 10–15% of immunocompromised patients [180]. Cutaneous disease, involving mainly the face, scalp, and neck, occurs in approximately 10% of patients with disseminated cryptococcosis [180]. Genital tract involvement by *C. neoformans* is rare [181, 182]. Cutaneous disease is heterogeneous with papules, ulcers, nodules, plaques, molluscum-like lesions, tumor-like swellings, and ecchymoses being

documented most commonly [43, 178]. They may be solitary or multiple. Vulvovaginal cryptococcus has been documented in less than five patients to date [181, 183, 184]. *Treatment:* Antifungal agents, including amphotericin B, fluconazole, and itraconazole form the backbone of therapeutic schedules, with fluconazole emerging as the drug of choice for maintenance therapy [178].

Microscopic features: The microscopic appearances include granulomatous (Fig. 2.17a) and paucicellular infiltrates (Fig. 2.17b–e). Paucicellular reactions are typified by aggregates of histiocytes,

parasitized by yeast forms, many in a narrow-necked budding state (Fig. 2.17b). The organism is a 4- to 12- μ m diameter round to oval yeast with a carminophilous, mucoid, capsule. Southgate mucicarmine (Fig. 2.17c), periodic acid Schiff, and alcian blue (Fig. 2.17d) stains highlight the capsule while Fontana Masson staining (Fig. 2.17e) highlights the cell wall. The latter is important when capsule-deficient forms are present. In biopsies with a necrotizing granulomatous appearance, the organisms are fewer and less readily visible than in those with a paucicellular, gelatinous appearance. Unusual appearances include those with abscess-like morphology and a pseudotumoral spindle cell-reaction pattern [182]. In biopsies from patients on antiretroviral therapy, immune reconstitution may result in an intense, including neutrophilic, inflammatory response with dense granulation tissue. In such biopsies, cryptococci may be elusive and require the full panel of infective stains for diagnosis.

Leishmaniasis

Leishmaniasis, caused by protozoa of the gender *Leishmania*, is one of the most common protozoan diseases worldwide [44]. Sandflies are the arthropod vectors of *Leishmania* species [185]. Sandflies belong to the genus *Phlebotomus* in the Old World and to *Lutzomyia* and *Psychodopygus* in the New World [44]. Mucocutaneous genital tract ulcers are documented in men more than in women [185–189]. Following a sting by the infected sandflies, promastigotes transform into amastigotes within macrophages. Leishmaniasis is classified into acute and chronic forms of the disease. The acute forms that may be localized or diffuse last approximately 3 months and are composed of a diffuse infiltrate of histiocytes with intracytoplasmic, 2–4- μ m-diameter, Leishman-Donovan bodies. Representing amastigotes, these Leishman-Donovan bodies are typified by a round, basophilic nucleus and a rod-shaped, paranuclear kinetoplast that is optimally demonstrated by the Giemsa stain [44]. Chronic cutaneous leishmaniasis refers to disease that remains unresolved after 1–2 years of symptomatic cutaneous disease. It is characterized by diffuse or nodular, tuberculoid-type granulomatous inflammation

with intracytoplasmic Leishman-Donovan bodies. *Differential diagnosis*: Includes diseases with intracytoplasmic organisms. The Donovan bodies of granuloma inguinale are smaller than Leishman-Donovan bodies and stain positively with silver stains, in contrast to Leishman-Donovan bodies that are not argyrophilic. *H. capsulatum* and *S. schenckii* lack a kinetoplast and demonstrate narrow-necked budding.

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Pathology of the Vulva and Vagina

Brown, L. (Ed.)

2013, XIII, 286 p., Hardcover

ISBN: 978-0-85729-756-3