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Review Article

Non-sexually transmitted bacterial infections of the vulva

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ABSTRACT

Infections of the vulva are an important health concern among women. Vulvar infections may be caused by bacteria, viruses, fungi, or parasites. Based on the mode of transmission, they are classified into sexually transmitted and non-sexually transmitted infections. Sexually transmitted infections such as herpes genitalis, syphilis, chancroid, donovanosis, and lymphogranuloma venereum are well known to dermatologists and venereologists. This review focuses on the non-sexually transmitted, bacterial infections of the vulva.

Keywords: Vulva, Infections, Non-sexually transmitted, Bacterial

INTRODUCTION

Infections of vulva are produced by various pathogens including bacteria, virus, fungi, and parasites. The infections that affect the vulva may be broadly classified into sexually and non-sexually transmitted infections [Table 1]. In this review, we try to give an overview on the non-sexually transmitted, bacterial infections of the vulva, which range from mild forms such as impetigo, folliculitis and furuncle to abscesses, erysipelas, and cellulitis to severe life-threatening forms such as necrotizing fasciitis and progressive synergistic gangrene, as seen in any other body site.[1] Table 1 shows the important bacteria that cause vulvar infections.[2]

The most common cutaneous infections of the vulva are caused by streptococci and staphylococci [Table 2].[2-6]

A meeting of experts by Centers for Disease Control and Prevention (CDC) has recommended incision and drainage (I & D) as the first line of treatment for skin lesions such as furuncles and abscesses. It is advised to send the drained pus for culture. When the patient manifests systemic symptoms, severe local symptoms, immunosuppression, or failure to respond to I & D, additional antimicrobial therapy with coverage against methicillin-resistant *Staphylococcus aureus* (MRSA) is advised.[7]

The treatment outlined for cellulitis without abscess is antibiotics with coverage against streptococci. An antibiotic effective against MRSA is added in case of inadequate response or lack of response.[7]

The United States Food and Drug Administration (US FDA) recommends clindamycin (450 mg, 4 times daily per orally for 10 days) or doxycycline (a loading dose of 200 mg twice a day for

2 days followed by 100 mg twice a day for 10 days per orally) for infections due to *Staphylococcus*, but not specifically for MRSA. In India, clindamycin is given in the dose of 300–600 mg 8th hourly. FDA has approved linezolid 600 mg twice a day for 10 days for skin infections by MRSA.[7]

RECURRENT FURUNCLES AND ABSCESSES

Obesity and drugs or conditions producing immunosupression (including uncontrolled diabetes mellitus) may predispose an individual to recurrent infections by streptococci or staphylococci.[6] Another cause identified for recurrent furuncles of buttocks and vulva is vaginal colonization by MRSA.[8] In the past few decades, vaginal colonization by *Staphylococcus aureus (S. aureus)* has shown a rise (from 30% in 1980 to 40% in 2005).[9] A previous study reported that patients with vaginal colonization by *S. aureus* also showed colonization of anterior nares and labia.[10] It is suggested that hygienic and contraceptive practices that require insertion of fingers into the vagina increase the risk of vaginal colonization by *S. aureus*. A higher risk of vaginal colonization by *S. aureus* was noted in diaphragm users in comparison to those who used intrauterine device. Use of Rely tampons before 1980 and previous history of herpes genitalis (weak association) were the other risk factors noted for staphylococcal colonization of vagina.[10,11]

It is advised to carry out a vaginal swab study in patients with recurrent furuncles and abscesses of buttocks or genital area to identify those showing vaginal colonization by *S. aureus*. No standard treatment guidelines are available for decolonizing the organism from the vagina. Simor *et al*. found that about 75% of patients colonized with MRSA (defined as isolation of the organism by culture of samples from one or more body sites at two separate time points within a period of 2 weeks in a patient with no evidence of infection) remained decolonized for a period of 3 months following a treatment regimen that included a 7-day course of daily washes with 2% chlorhexidine gluconate, 2% mupirocin ointment applied to the anterior nares with a cotton-tipped applicator 3 times a day, rifampin 300 mg twice a day, and doxycycline 100 mg twice a day.[12]

MENUSTRUAL TOXIC SHOCK SYNDROME (mTSS)

Although menstrual toxic shock syndrome is not a condition originating from or strictly confined to vulva, we have included it considering the clinical relevance and the propensity for the initial lesion to appear as vulvar erythema. mTSS is caused by superantigen-producing *S. aureus*. The incidence ranges from 0.03 to 0.5 cases per 100,000 population, and the mortality rate is 8%. mTSS is an entity different from non-menstrual-associated TSS, though the clinical features are similar. CDC has put forth a criteria to define TSS (other than streptococcal).[13]

Table 1: Non-sexually transmitted bacterial infections of the vulva.

Infection by *Streptococcus*
Infection by *Staphylococcus*
Infection by *Corynebacterium*
Infection by *Mycobacterium tuberculosis*
Infection by Actinomyces
Infection by *Mycoplasma*

To classify as mTSS, the disease onset should be less than 4 days before the onset of menses. However, it is advised to consider mTSS when a temporal relation exists between the disease and menses and it has been cautioned that a stringent adherence to the criteria may result in delay in diagnosis since all the features may not be present initially [Table 3].[13]

Pathogenesis

In 1978, Todd *et al*. described toxic shock syndrome as a disease entity associated with phage Group-I *Staphylococcus.* The organism produced an epidermal toxin, which was named enterotoxin F. This was later came to be known as toxic shock syndrome toxin-1 (TSST-1).[14] The association between mTSS and toxin producing *Staphylococcus* strains was identified in early 1980s.[15,16]

Recent understanding points to a complex interplay between pathogenic factors of *S. aureus*, immunological mechanisms of the host, and changes in the vaginal ecosystem during menstruation.[17]

Colonization of vagina by *S. aureus* increases during menses, probably due to altered vaginal environment. Rarity of mTSS is postulated to be due to colonization by TSST-1 negative strains (nose, vagina, or anus) in majority of the women. It was proposed that positive antibody titers against TSST-1 offer protection against mTSS. Low levels of anti-TSST-1 antibody are identified as a risk factor for the development of mTSS. Co-colonization with *Escherichia coli (E. coli)* promotes growth of TSST-1-positive *S. aureus* and the production of TSST-1. Hormonal contraceptives are mentioned to play a protective role against mTSS.[17]

Intravaginal devices (tampons, diaphragms, vaginal contraceptive sponges, and cervical caps) may serve as the initial trigger. A rise in mTSS was noted in late 1970s and 1980s with the use of new synthetic materials in tampons. More patients with mTSS in comparison to controls had the habit of using tampons day and night throughout the menstrual period. The link between tampons and mTSS has been somewhat delineated. It was demonstrated that tampons and other hygiene products promote the growth of *S. aureus* and favor the production of TSST-1 by increasing the viscosity as well as the surface area for adsorption and absorption. Moreover, absorbent tampons bind magnesium ions and the absence of magnesium has a promoting effect on TSST-1 production. Highly absorbent tampons lead to longer wearing times, which

Table 2: Infections of vulva caused by streptococci and staphylococci.

Bacterial infection	Common pathogen	Clinical features	Management
Impetigo	*Staphylococcus aureus* or β-hemolytic *Streptococcus*	Superficial, non-follicular pustules	Topical 2% mupirocin/ 2% fusidic acid/ 1% retapamulin/ 2% clindamycin twice a day for 5–7 days Extensive impetigo/ impetigo with a predominant bullous component/ impetigo with palpable lymphadenopathy — oral antibiotics like flucloxacillin (250–500 mg 6th hourly)/ cephalexin (250 mg 6th hourly or 500 mg 12th hourly)/ co-amoxiclav (500/125 mg 8th hourly)/ cloxacillin (500 mg 6th hourly)/ clindamycin (300–450 mg 6th hourly or 8th hourly) for 5–7 days
Ecthyma	*Staphylococcus aureus, Streptococcus pyogenes*	Small bullae or pustules on an erythematous base, lesions show a hard crust of dried exudate and an indurated base	• Steps to improve hygiene and nutrition, treatment of any underlying condition like scabies • Topical 2% mupirocin/ 2% fusidic acid twice a day for 5–7 days or more • Multiple lesions/ immunocompromised patients — oral antibiotics like flucloxacillin (250–500 mg 6th hourly)/ clindamycin (300–600 mg 8th hourly)/ doxycycline 100 mg 12th hourly) for 1–2 weeks
Folliculitis	*Staphylococcus aureus* (usually Panton Valentine Leukocidin producing), community acquired methicillin-resistant *Staphylococcus aureus*	Follicular pustule	Topical 2% mupirocin/ 2% fusidic acid/ 2% clindamycin twice a day
Furuncle	*Staphylococcus aureus*	Infection of hair follicle and perifollicular tissue, involves deep dermis	Incision and drainage, oral antibiotics when indicated.
Carbuncle	*Staphylococcus aureus*	Painful, tender swelling that develops pus discharging sinuses with necrosis of intervening skin	Incision and drainage or saucerization under local anesthesia, oral antibiotics like flucloxacillin (250–500 mg 6th hourly)
Recurrent toxin mediated perineal erythema	Superantigen toxins produced by strains of *Staphylococcus* and *Streptococcus*	Preceding an impetigo or a streptococcal throat infection, the patient develops erysipelas like macular erythema that subsides with desquamation, not associated with systemic features, may also affect hands, feet and axillae, throat swabs may isolate *Staphylococcus aureus* or *Streptococcus pyogenes*, swabs from perineal area do not show any organism	Oral antibiotics like cloxacillin 250–500 mg 6th hourly or erythromycin 250–500 mg 6th hourly for 5–7 days
Perianal streptococcal dermatitis	Group A β-hemolytic *Streptococcus,* Group B β-hemolytic *Streptococcus*	More common in children, occasionally seen in adults, may affect vulva, manifests as erythematous, sharply demarcated, pruritic lesion, occasional fissuring of perianal skin	Oral antibiotics based on pus culture and sensitivity reports

(Contd...)

Table 2: *(Continued).*

Bacterial infection	Common pathogen	Clinical features	Management
Bartholin abscess	*Staphylococcus aureus*, *Streptococcus faecalis*	Tender swelling on either side of vaginal opening, associated with constitutional symptoms	Warm water sits bath, simple aspiration of cyst, incision and drainage Two or more recurrences — marsupialization Indications for antibiotics — recurrence, pregnancy, immunosuppression, methicillin-resistant *Staphylococcus aureus* risk, widespread surrounding cellulitis, and gonorrhea or chlamydia infection Preferred antibiotics — ceftriaxone, ciprofloxacin, doxycycline, or azithromycin (based on the indication)
Erythrasma	*Corynebacterium minutissimum*	Red or brown, hyperpigmented patches or plaques with scaling and central hypopigmentation, may mimic candidiasis, dermatophytosis, pityriasis versicolor, erysipelas, Paget's disease, or terra firma-forme dermatosis	Topical 2% fusidic acid cream/ topical erythromycin More severe infection — oral erythromycin 250 mg 4 times a day for 2 weeks
Erysipelas	β-hemolytic *Streptococcus*	Sharply demarcated, shiny, erythematous plaque of sudden onset associated with pain, swelling, and fever	Flucloxacillin 500 mg 6th hourly/ clindamycin 500 mg 12th hourly/ clarithromycin 500 mg 12th hourly/ benzylpenicillin 600–1200 mg 6th hourly I/V/ flucloxacillin and benzyl penicillin I/V/ clindamycin 600 mg 8th hourly I/V for 5–10 days
Cellulitis	β-hemolytic *Streptococcus*	Acute spreading infection, extends more deeply than erysipelas, involves the subcutaneous tissues, complications like necrosis more common than in erysipelas	Flucloxacillin 500 mg 6th hourly/ clindamycin 500 mg 12th hourly/ clarithromycin 500 mg 12th hourly/ benzylpenicillin 600–1200 mg 6th hourly I/V/ flucloxacillin and benzyl penicillin I/V/ clindamycin 600 mg 8th hourly I/V for 7–10 days
Menstrual toxic shock syndrome	Superantigen producing *Staphylococcus aureus*	Fever, diffuse macular erythroderma, desquamation 1–2 weeks after the onset of rash, hypotension, multisystem involvement, negative results of blood, throat and cerebrospinal fluid cultures, negative serology for Rocky Mountain spotted fever, leptospirosis or measles.	Methicillin susceptible *Staphylococcus aureus*- clindamycin (900 mg 8th hourly) and oxacillin/ nafcillin (2 g 4th hourly) I/V Methicillin-resistant *Staphylococcus aureus* – clindamycin (900 mg 8th hourly I/V) and vancomycin (15–20 mg/kg every 8–12 hours I/V, not to exceed 2 g per dose)/ linezolid (600 mg 12th hourly orally or I/V) alone or in combination with vancomycin
Necrotizing fasciitis	Group A *Streptococcus*	Starts as a painful skin lesion that rapidly progresses with destruction of fascia and necrosis of subcutaneous tissue	Emergency surgical debridement, systemic antibiotics based on swab culture reports

I/V: Intravenously.

cause a longer growth phase for the organism and increase the risk for mTSS.[17]

Treatment

Treatment of mTSS includes removal of any potential intravaginal or intrauterine device and careful evaluation to detect any focus of infection like abscesses, which may necessitate investigations such as computed tomogram or magnetic resonance imaging. Patients may need intensive medical treatment for organ failure and hypotension. Antibiotics may be chosen as outlined in Table 2.[13]

Eradication measures are recommended for those patients identified as nasal carriers of *S. aureus*. The patient should be advised to avoid vaginal devices in future to avoid recurrences.[17]

Table 3: Case definition of menstrual toxic shock syndrome by CDC

Clinical criteria	Laboratory criteria for diagnosis
An illness with the following clinical manifestations: Temperature greater than or equal to 102.0°F (greater than or equal to 38.9°C) Rash: diffuse macular erythroderma Desquamation: 1–2 weeks after onset of rash Hypotension: Systolic blood pressure less than or equal to 90 mmHg for adults or less than fifth percentile by age for children aged less than 16 years **Multisystem involvement (three or more of the following organ systems):** 1. Gastrointestinal: Vomiting or diarrhea at onset of illness 2. Muscular: Severe myalgia or creatinine phosphokinase level at least twice the upper limit of normal 3. Mucous membrane: Vaginal, oropharyngeal, or conjunctival hyperemia 4. Renal: Blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (greater than or equal to 5 leukocytes per high-power field) in the absence of urinary tract infection 5. Hepatic: Total bilirubin, alanine aminotransferase, or asparate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory 6. Hematologic: Platelets less than 100,000/mm^3 7. Central nervous system: Disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent	Negative results on the following tests, if obtained: 1. Blood or cerebrospinal fluid cultures (blood culture may be positive for *Staphylococcus aureus*) 2. Negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles Probable case: A case that meets the laboratory criteria and shows 4/5 clinical features Confirmed case: A case that meets the laboratory criteria and shows all the five clinical features, including desquamation, unless the patient dies before desquamation appears.

CDC: Centers for Disease Control and Prevention

NECROTIZING FASCITIS OF THE VULVA

Group A *Streptococcus* is the most common cause for necrotizing fasciitis.[2] Many other bacteria including *Vibrio vulnificus*, *Clostridium perfringens,* and *Bacteroides fragilis (B. fragilis)* are also identified as pathogens.[2] Starting at the site of trauma (which could be severe, minor, or inapparent), the infection extends to the subcutaneous tissue with progressive destruction of fat and fascia.[18] It is a life-threatening condition characterized by rapid progression and a case fatality rate of up to 40%.[18] Emergency surgical debridement could be life saving. Acute onset, rapid progression, sites affected (commonly involves the extremities or abdomen), and presence of risk factors such as diabetes mellitus, prior history of trauma, or intravenous drug use may help to diagnose the condition early.[19] Laboratory risk indicator for necrotizing fasciitis score is a validated diagnostic tool with a positive predictive value of 92.0%.[19]

Necrotizing fasciitis originating in the vulva is a rare occurrence and most of the cases reported are in postpartum women or associated with diabetes mellitus.[20,21] In a case series of six patients who manifested progressive synergistic bacterial gangrene involving the vulva (arising from vulvar abscesses and Bartholin gland abscess), all were diabetic and the mortality rate was 50%.[22]

Patel *et al*., have reported vulvar necrotizing fasciitis in a healthy woman.[18] Mohammed and Mohammed reported a 7-year-old child who developed necrotizing fasciitis following female genital mutilation (the partial or total removal of the female external genitalia or other injury to the female genital organs for cultural or other non-therapeutic reasons).[23,24]

Stephenson *et al*., in a study of 29 patients with necrotizing fasciitis of vulva, cautioned against the possible innocuous appearance of the initial lesion.[25] In their series, two patients with a fatal outcome had initially developed pustules with mild induration which were treated with hot compresses. It was pointed out that even when deep tissue necrosis is underway, superficial skin changes could be minimal. The authors found a delay of >48 hours between presentation and surgical

debridement as a poor prognostic factor. Wound culture of 23/29 (79%) patients in their study yielded more than 1 organism, which included *Peptostreptococcus*, *B. fragilis*, *E. coli*, *Enterococcus*, and 13-hemolytic *Streptococcus*. The culture report favored a polymicrobial etiology and underscored the need for broad spectrum antibiotics, in addition to surgical debridement. All the 29 patients received broad-spectrum antibiotics that included a penicillin or a cephalosporin, an aminoglycoside, and clindamycin or metronidazole. The authors reported a mortality rate of 48.3% (14/29).[25]

TRICHOMYCOSIS PUBIS

Trichomycosis pubis is also referred to as trichobacteriosis pubis. The causative agents are *Corynebacterium* species (*Corynebacterium tenuis*, *Corynebacterium propinquum*, and *Corynebacterium flavescens*) and *Serratia marcescens* and affects pubic as well as axillary hair, especially in individuals with poor hygiene, hyperhidrosis, and obesity.[26] Yellowish to reddish to gray-black concretions are seen attached around the pubic hair. Treatment involves shaving off the affected hair and topical antibiotics such as clindamycin 1% or fusidic acid 2%.[27]

MYCOBACTERIAL INFECTION OF THE VULVA

Tuberculous infection of vulva is rare. Tuberculosis (TB) of vagina/vulva contributes to 1% of genital tract TB.[28] The most commonly affected site for genital TB is the fallopian tube (95–100%), followed by uterine endometrium (50–60%), ovaries (20–30%), cervix (5–15%), and uterine myometrium (2.5%).[28] Tuberculous infection of the vulva can occur through hematogenous spread from other body foci (most commonly lungs), lymphatic spread, contiguous spread from upper genital tract, or rarely as a primary infection through contact with an infected partner (partner with tuberculous epididymitis).[28]

TB of the vulva commonly presents with small shallow ulcers and multiple sinuses.[28] Other manifestations include hypertrophic lesions, nodules with sinuses, fungating masses, and infection of Bartholin gland.[29-31]

Jiménez-Gallo *et al.*, reported a 78-year-old woman who presented with a painful ulcer of labia minora of long duration.[32] She was a renal transplant recipient on immunosuppressive treatment with oral corticosteroids, tacrolimus, and mycophenolate mofetil. Histopathology showed tuberculoid granulomas and some of them showed caseation necrosis. Cultures from ulcer and urine specimens isolated *Mycobacterium tuberculosis*. There was no evidence of TB elsewhere in the body including lungs and upper genital tract. Authors made a final diagnosis of periorificial cutaneous TB.[32]

Periorificial TB involves the oral, perianal, or genital mucosae and the periorificial skin. Auto-inoculation of *M. tuberculosis* from a pulmonary, intestinal, or genitourinary focus by direct spread causes periorificial TB. If not diagnosed and treated promptly, periorificial TB may lead to military dissemination.[32]

TB of the vulva is often mistaken for sexually transmitted infections (STIs), Lipschütz ulcer, subcutaneous mycosis, or malignancy.[29-32]

Management of vulvar TB

Management of vulvar TB is according to the World Health Organization (WHO) guidelines for extra-pulmonary tuberculosis (EPTB).[33] The WHO defines bacteriologically confirmed case of EPTB as a patient with a microbiological diagnosis of EPTB, based on positive microscopy, culture, or a validated polymerase chain reaction (PCR)-based test.[33]

A patient with a strong clinical suspicion and other evidence of EPTB such as compatible imaging findings, histological findings, ancillary diagnostic tests (organ system-specific tests such as pleural fluid adenosine deaminase activity in pleural TB, or cerebrospinal fluid biochemistry and differential cell count in TB meningitis), or response to anti-TB (ATT) treatment and with negative microbiological tests for TB (microscopy, culture, and validated PCR-based tests), is classified as clinically diagnosed EPTB.[33] A presumptive case (a patient with symptoms and signs of EPTB, who needs to be evaluated), started on ATT empirically, without microbiological testing should also be considered as a clinically diagnosed case. A clinically diagnosed case, if subsequently found to be bacteriologically positive, should be reclassified as bacteriologically confirmed.[33]

The evaluation in a suspected case of vulvar TB includes investigations to rule out the probable differential diagnoses, investigations to confirm the diagnosis of tuberculous infection of the vulva, and the investigations to detect any primary focus in lungs or other organs [Table 4]. A tuberculin skin test, erythrocyte sedimentation rate, and complete blood count may be done at baseline in all the patients. These may give a clue towards the possibility of a tuberculous focus, though tuberculin skin test has only limited significance in a population with a high burden of TB and who undergo universal Bacillus Calmette and Guerin (BCG) vaccination. Serology for human immunodeficiency virus (HIV) infection should be carried out in all suspected cases of EPTB, since the former increases the risk of TB.[28,33]

Treatment of vulvar TB is with ATT (rifampicin, isoniazide, pyrazinamide, and ethambutol for the first 2 months followed by rifampicin, isoniazide, and ethambutol for subsequent 4 months) as per standard guidelines.[33]

Often the lesions respond to medical management, but at times surgical reduction may be required.[29]

Table 4: Evaluation of a patient with suspected tuberculosis of vulva.

To rule out the probable differential diagnoses for vulvar tuberculosis	To confirm the diagnosis of tuberculosis of the vulva	To detect any tuberculous focus of infection in any other body site
Ulcerated lesion Smear from ulcer-Tzanck smear, Gram stain, dark field microscopy Serology — Venereal disease research laboratory test, *Treponema pallidum* hemagglutination test, *Treponema pallidum* particle agglutination test, ELISA/Western Blot for type 2/ type 1 herpes simplex virus Molecular methods — polymerase chain reaction (PCR) test for type 2/ type 1 herpes simplex virus Histopathology **Hypertrophic/fungating masses with/ without discharging sinuses** Tissue smear from the lesion Histopathology Culture — fungal culture, bacterial culture	Microscopy for acid fast bacilli Histopathology examination Molecular methods — nucleic acid amplification test, polymerase chain reaction, GeneXpert/MTB/RIF (a cartridge-based nucleic acid amplification test that can identify *Mycobacterium tuberculosis* DNA and resistance to rifampicin)	Chest radiography Microscopy for acid fast bacilli in sputum and urine PCR/GeneXpert/MTB/RIF of sputum and urine Hysterosalpingography – to evaluate the internal structure of the female genital tract and tubal patency Ultrasonogram of abdomen and pelvis – to assess abdominal organs, ovary and uterus Ultrasonogram of kidney, ureter, and bladder Intravenous pyelogram Computed tomogram and magnetic resonance imaging, when indicated Histopathology analysis of any suspicious lesion

ACTINOMYCOSIS OF THE VULVA

Actinomycosis is a rare infection caused by obligate anaerobic, gram-positive bacteria that are common commensals of mucosae of oral cavity, digestive tract, and genitourinary tract. *Actinomyces odontolyticus*, *Actinomyces meyeri*, *Actinomyces israelii*, and *Actinomyces gerencseriae* are responsible for more than 90% of clinically significant infections in humans. In 40–60% of the affected, the cervicofacial region or the central nervous system (40–60%) is involved. Abdominal (20–30%), thoracic/pulmonary (20–30%), pelvic (3–5%), and cutaneous (3–5%) manifestations are also reported.[34]

The clinical picture can resemble malignancy or infections produced by Mycobacteria or *Nocardia* due to its propensity to cause contiguous and progressive spread and tendency to produce cold abscess. The lesion may appear as a swelling with sinuses discharging yellowish sulfur granules. Sulfur granules are conglomeration of bacteria trapped in biofilm.[34,35]

Soft-tissue infections have been reported on face, gluteal region, extremities, breast, and vulva following trauma or human bite. There are occasional reports of actinomycosis manifesting as vulvar mass with discharging sinuses.[36,37] Marcovici had reported a 14-year-old girl who manifested vulvar abscess due to *A. meyeri*, which responded to incision and drainage followed by a 4-week course of amoxicillin 875 mg orally, every 12 hours.[38]

Diagnosis is based on the clinical picture and by the identification of *Actinomyces* from the lesion. Since the organism is a normal colonizer in several body sites, isolation of the same in the absence of suggestive clinical features (such as sinuses discharging sulfur granules) is of little significance.[35] However, identification of the bacteria from a lesional isolate is possible only on occasions. Prior treatment with antibiotics, growth of concomitant or contaminant microorganisms, microaerophilic/anaerobic character of the organism warranting strict anaerobic processing, and need for prolonged culture in appropriate media in appropriate conditions are the factors that often lead to failure to culture the organism.[35] The ideal specimen for culture is a tissue from a surgical biopsy or pus, while swabs are not preferred.[32] Since it is a slow-growing organism, a negative culture report should not be issued before at least 10 days of incubation; hence, it becomes important to convey the clinical suspicion of actinomycosis to the microbiologist to receive an accurate report.[35]

The media used for *Actinomyces* are chocolate blood agar media at 37°C, enriched media like brain heart infusion broth or *Brucella* blood agar with hemin and Vitamin K1 and semi-selective media such as phenylethyl alcohol or mupirocin-metronidazole blood agar.[35] A clue to the identity of the species isolated is obtained from the characteristic colony formed (e.g., molar tooth colony of *A. israelii* and rust-brown or red-colored colonies *by A. odontolyticus*).[35]

Gram staining of pus or histopathology of tissue is more sensitive than culture (which remains sterile in 50% of cases) in diagnosis. Typical histopathology features of necrosis with yellowish, sulfur granules are seen in about 75% of cases. On hematoxylin and eosin staining, sulfur granules appear as basophilic masses with eosinophilic terminal clubs. Gram staining revealing gram-positive, filamentous, branching

bacteria at the periphery of the granule is highly suggestive of actinomycosis.[35]

PCR, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, and 16S RNA gene sequencing are the advanced diagnostic tests found useful in actinomycosis.[34] Immunofluorescence techniques have poor sensitivity but are highly specific in the diagnosis.[35]

Treatment

Drug of choice is penicillin G or amoxicillin, since *Actinomyces* spp. are usually extremely susceptible to beta-lactams. High doses (to ensure drug penetration in abscesses and infected tissues) of penicillin G or amoxicillin are required for prolonged (6–12 month) periods. However, a shorter duration treatment of about 3 months could be effective in patients who had undergone optimal surgical resection of infected tissues.[35]

LIPSCHÜTZ ULCERS

Benjamin Lipschütz, in 1913, described acute, non-venereal ulcers and termed them Lipschütz ulcers.[39]

Lipschütz ulcers manifest as acute painful, non-sexually transmitted ulcers and usually affect young females or girls (usually virgins). Accompanying systemic symptoms as reported in literature include fever, myalgia, headache, diarrhea, oral aphthae, enlarged lymph nodes, tonsillitis, or respiratory symptoms. Spontaneous healing is the rule, which may or may not be associated with scarring.[39]

A genital ulcer always needs prompt treatment, since it places the patient at a higher risk of acquiring STIs including HIV infection. The acute symptoms including pain associated with Lipschütz ulcers prompt the affected to seek emergency treatment. Although often self-limiting, an accurate diagnosis of Lipschütz ulcer may help to alleviate the psychological and marital stress that may follow the suspicion of a STI.

Epstein–Barr virus (EBV), cytomegalovirus (CMV), parvovirus, influenza virus, *Toxoplasma gondii*, and paramyxovirus are identified as causes for non-venereal vulvar ulcerative diseases.[39] Krapf *et al*., have described a 13-year-old girl who presented with acute ulcer of the vulva. Three days before the onset of vulvar ulcer, the patient developed fever, chills, sore throat, and loss of taste and tested positive for coronavirus disease 2019. The possible differential diagnoses including herpes simplex infection and Behcet's disease were ruled out by appropriate evaluation. She did not respond to corticosteroids, but improved with colchicine.[40]

Mycoplasmas are well known to produce cutaneous manifestations including Stevens-Johnson syndrome, toxic epidermal necrolysis, mucositis, erythema multiforme, non-specific cutaneous eruptions, Henoch-Schonlein purpura, and erythema nodosum.[39]

Mycoplasma pneumoniae (M. pneumoniae) was added to the list of etiological agents of non-venereal vulvar ulcers, when in 1979, Korting and Hinterberger reported the same, in a patient with atypical pneumonia, caused by *M. pneumoniae*.[39] There are occasional reports of *M. pneumoniae* induced genital ulcers in boys and young males as well.[41]

Only 3–10% of those infected with *M. pneumoniae* manifest overt pneumonia; hence, absence of systemic symptoms does not rule the possibility of *M. pneumoniae*-induced genital ulcers.[39]

The exact mechanism by which *M. pneumoniae* induces genital ulcers remains unknown. The proposed mechanisms include: (i) A type III hypersensitivity reaction in the acute phase of the infection, when immune complexes get deposited in localized sites, producing microthrombosis and necrosis, (ii) a direct cytolysis, due to multiplication of *M. pneumoniae* in keratinocytes, where it reaches by hematogenous dissemination or by autoinoculation or by exposure to the agent in the vaginal discharge, and (iii) a unipolar or bipolar major aphthosis induced by the infective agent.[39]

Diagnosis is reached by ruling out other causes including STIs and Behcet's disease. Tzanck smear analysis, tissue smear and gram stain of ulcer material, serology for HIV, syphilis, and herpes simplex virus (HSV) and PCR analysis of ulcer material for EBV, CMV, HSV, gonorrhea, and *Chlamydia* may help to rule out the common differential diagnoses. Serology and PCR may help to diagnose *M. pneumoniae* infection.[39]

Previous authors have identified *M. pneumoniae* in pharyngeal swab, but not from ulcer material, underscoring the possibility of a hypersensitivity reaction.[42] In doubtful cases, a histopathology may help to rule out other causes.

Though it is a self limiting condition, some clinicians prefer to treat with antibiotics. Topical steroids and analgesics may offer symptomatic relief.[43]

CONCLUSION

Non-sexually transmitted bacterial infections of the vulva include common infections caused by common pathogens such as streptococci and staphylococci, rare manifestations by common pathogens (*M. pneumoniae* induced Lipschütz ulcers) and rare infections like actinomycosis. Often the affected women hesitate to seek medical help since the diseases affecting genitalia are commonly perceived as STIs. Non-STIs of genitalia are often not discussed as much as their sexually transmitted counterparts. Through this review,

we have tried to draw attention to these important, but less discussed conditions.

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