8.6.10 Intracellular klebsiella infections (donova

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8.6.10 Intracellular klebsiella infections (donovanosis and rhinoscleroma) 1051 Vaccines The greatest need for typhoid vaccination is among infants, children, and young adults in endemic areas, especially where the burden of disease is high and antibiotic resistance is increasing, and among la- boratory workers handling the organisms. In practice, vaccines are given mostly to travellers to endemic areas. The currently available vaccines are the parenteral Vi vaccine, given as a single injection, and the live attenuated Ty21a vaccine, given as three or four oral doses. The Ty21a vaccine should not be given to immunosuppressed persons or those taking mefloquine or antibiotics. A new Vi conjugate vaccine has recently been approved by WHO for use as a public health tool to control typhoid in endemic areas. This new vaccine is considered to be more effective than the standard Vi vaccine and has the potential to be delivered as part of the EPI programme. Current typhoid vaccines do not protect against paratyphoid infection and the protection afforded by vaccination can be overcome by large inocula of bacteria. Efficacy figures derive largely from trials conducted in partly immune popula- tions and overestimate the benefit in persons without prior exposure. The risks of typhoid in travellers are low (3–30 cases per 100 000) and the precise efficacy of currently recommended doses in previously un- exposed adults remains unknown. Circumstantial evidence indicates that the typhoid vaccines afford protection to travellers visiting endemic areas. Travellers without the vaccine seem more susceptible to the dis- ease, and this is true for even short-term (less than 1 week) travellers to endemic areas. New vaccines are being developed including several variants of the Vi conjugate vaccine and single dose oral vaccines. Paratyphoid fever S. Paratyphi A is the main serovar causing paratyphoid in Asia. S. Paratyphi B and S. Paratyphoid C are sporadically reported world- wide. Paratyphoid A has recently been increasing in South Asia and China, including drug-resistant disease. The minimum inhibitory concentrations of S. Paratyphi to the commonly used antibiotics are often higher than those of S. Typhi. Outbreaks of paratyphoid are more often food-borne than water-borne, probably because

larger inocula are needed to establish infection. Paratyphoid has a shorter incubation period (4–5 days). The clinical syndromes can be indis- tinguishable and Paratyphi A may be as severe as Typhi. The man- agement of paratyphoid is the same as that of typhoid. Efforts are being directed at the development of a paratyphoid vaccine. Areas of uncertainty and controversy The best recommendation for first-line antibiotic therapy in endemic areas has been an area of uncertainty. Many practitioners have used fluoroquinolones for first-line therapy where multidrug resistance is common. The spread of S. Typhi with low and high-level resistance to fluoroquinolones, particularly the H58 lineage in South Asia, means that approach can no longer be universally recommended. The op- timum treatment for such infections is undefined. The extended- spectrum cephalosporins, such as ceftriaxone, and azithromycin are available options but the recent outbreak of ceftriaxone resistant typhoid is a major concern. In some areas isolates have regained sen- sitivity to the older agents and chloramphenicol and cotrimoxazole are being used. New laboratory breakpoints for the fluoroquinolones and azithromycin have been recently introduced. Whether isolates with extended-spectrum cephalosporin or azithromycin resistance become common in the next decade remains to be seen. Another area of controversy is the use of vaccination as a public health tool in endemic areas. The case for vaccination is hampered by the lack of knowledge of the true burden of enteric fever in Asia and Africa, in particular the burden of severe and fatal disease. It is possible the increases in antimicrobial resistance may swing the cost–benefit ratio in favour of vaccination. Recent Vi vaccine trials have demonstrated the potential cost-effectiveness of vaccination. The realization that typhoid is common in children under 5 years has also focused attention on the development of vaccines appro- priate for this age group. WHO now recommends the usage of the Vi conjugate typhoid vaccine in countries with the highest burden of disease or high levels of antibiotic resistance in S. Typhi. Finally, reliable rapid diagnostics for undifferentiated febrile illness, including enteric fever, after malaria has been excluded are needed for low income countries. Targeted antibiotic therapy based on rapid diag- nostics could help decrease the rapid spread of antibiotic resistance. FURTHER READING Basnyat B, et al. (2005). Enteric fever (typhoid) fever in travellers. Clin Infect Dis, 41, 1467–72. Crump J, et al. (2015). Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance and antimicrobial management of invasive Salmonella infcetions. Clin Microbiol Rev, 28, 901–37. Hoffman SL, et al. (1984). Reduction of mortality in chloramphenicol- treated severe typhoid fever by high-dose dexamethasone. N Engl J Med, 310, 82–8. Mogasale, et al. (2014). Case fatality rate and length of hospital stay among patients with typhoid intestinal perforation in developing countries: a systematic literature review. PLoS One, 9, e93784. Waddington CS, et al. (2014). An out-patient, ambulant design, con- trolled human infection model using escalating doses of Salmonella Typhi challenge delivered in sodium bicarbonate solution. Clin Infect Dis, 58, 1230–40. Wong V, et al. (2015). Phylogeographical analysis of the dominant multidrug-resistant H58 clade of Salmonella Typhi identifies inter- and intracontinental transmission events. Nature Genet, 47, 632–37. 8.6.10 Intracellular klebsiella infections (donovanosis and rhinoscleroma) John Richens and Nicole Stoesser ESSENTIALS Two rare intracellular species of Klebsiella, a Gram-negative bacillus, cause granulomatous disease in humans that is found in small en- demic foci in warm climates, linked to poverty and poor hygiene.

section 8 Infectious diseases 1052 Donovanosis—caused by Klebsiella granulomatis (previously named Calymmatobacterium granulomatis); presumed to be sexually trans- mitted; presents with genital ulcers or growths, often accompanied by an inguinal ‘pseudobubo’ (granuloma inguinale). Diagnosed by demonstrating Donovan bodies (vacuoles containing capsulated coccoid bacteria) lying within histiocytes in material taken from a typical lesion. Treatment is with azithromycin;

surgery may be needed for complications. Rhinoscleroma—caused by Klebsiella rhinoscleromatis; transmission believed to occur from person to person; following a period of rhinitis most typically manifests with bulky growths in the upper respiratory tract. Diagnosed by demonstrating intracellular organisms in typical lesions, combined with culture. Treatment is with ciprofloxacin; sur- gical debulking of lesions and/or reconstruction may be required. Donovanosis Introduction and epidemiology Donovanosis was first described in Calcutta by Donovan in 1905. It is an infection endemic in certain areas of India, Papua New Guinea, the Caribbean, southern Africa, and parts of South America, including Brazil. An important focus among Australian aborigines has recently been eliminated. Donovanosis seems to be retreating, raising hopes of eventual eradication. Dark-skinned people appear to have greater susceptibility. The predilection of lesions for the anogenital region of sexually active adults and the frequent asso- ciation with other sexually transmitted infections point strongly to sexual transmission. In the past, epidemics of donovanosis in New Guinea were linked to ritual homosexual and heterosexual practices. Perinatal transmission has been observed in a few cases. Aetiology An unusual Gram-negative bacillus can be isolated in HEp-2 cells or human peripheral blood mononuclear cells from patients with the characteristic lesions of donovanosis. This organism will not grow on conventional solid media. Previously named Donovania and subsequently Calymmatobacterium by Aragão and Vianna in 1913, it has now been classed as Klebsiella granulomatis on the basis of close DNA homology with other Klebsiella species. K. granulomatis shows morphological identity with Donovan bodies observed within clinical lesions of donovanosis and pa- tients with characteristic lesions have high levels of antibody that react equally with Donovan bodies and with K. granuloma- tis. K. granulomatis is pathogenic only to humans. Experimental transmission has been reported with lesion material, but to date not with a pure culture of this organism. Donovanosis shows a close macroscopic and microscopic similarity to rhinoscleroma which produces granulomatous lesions of the upper airways. These lesions contain intracellular clusters of the closely related organism Klebsiella rhinoscleromatis. Pathogenesis The organism has a special tropism for dermal macrophages. The response to infection is characterized by vigorous granulomatous inflammation that damages the skin and subcutaneous tissues. Extension of the infection is a local process of spreading ulcer- ation. The inguinal lesions are probably seeded by lymphatic spread. Haematogenous dissemination and spread to the upper genital tract of women are exceptional. Lesions in women tend to be more exten- sive and may progress rapidly during pregnancy. Clinical features After an incubation period of 1–360 days (median 50 days), the dis- ease usually starts with a small genital papule or nodule which rapidly progresses into a painless ulcer displaying a deep red colour, contact bleeding, and a rolled edge. Hypertrophic lesions that pout outwards from the surrounding skin are frequent. Other presentations include verrucous, necrotic, or sclerotic lesions. Local lymphoedema is seen commonly in women. Chronic lesions tend to expand gradually along skin folds forming a large continuous area of ulceration with a characteristic serpiginous outline (Fig. 8.6.10.1). Inguinal lesions are common (Fig. 8.6.10.2). They start as a firm, subcutaneous swellings and often ulcerate. The term ‘pseudobubo’ tends to be applied to any inguinal lesion in donovanosis although it was originally coined to describe a subcutaneous inguinal abscess, which is a rare event. Such lesions have even given rise to suspicion of bubonic plague when Donovan bodies in the aspirate were misinterpreted. Primary lesions of the cervix simulate carcinoma of the cervix. Upper genital tract in- volvement in women might simulate pelvic inflammatory disease or malignancy and hydronephrosis can ensue. Anal lesions have been de- scribed in homosexual men. Involvement of the rectum seldom occurs. Oral lesions of donovanosis with extension to cervical nodes have been described. Haematogenous dissemination is associated with pregnancy and causes lesions of bone,

liver, and spleen. Lesions in infants tend to involve the ears and nearby lymph nodes. Patients coinfected with HIV tend to have lesions that heal more slowly and are associated with more significant tissue destruction. Complications of donovanosis include extensive scar formation, lymphoedema of the genitalia, penile autoamputation, and the de- velopment of squamous carcinoma in active or healed lesions. Secondary infection with fusospirochaetal organisms can cause rapid, extensive, and sometimes fatal tissue destruction. Fig. 8.6.10.1 Characteristic serpiginous ulcer in female patient with long-standing donovanosis.

8.6.10 Intracellular klebsiella infections (donovanosis and rhinoscleroma) 1053 Differential diagnosis and clinical investigations Klebsiella granulomatis is difficult to culture and the diagnosis is made by demonstrating Donovan bodies lying within histiocytes in material taken from a typical lesion. Donovan bodies show well with Giemsa's, Leishman's, and Wright's stains but poorly with haema- toxylin and eosin. Histology typically shows a heavy plasma cell infiltrate and epithelial hyperplasia in addition to histiocytes con- taining Donovan bodies (Fig. 8.6.10.3). Differential diagnoses in- clude squamous carcinoma of cervix, vulva, or penis, secondary syphilis, and conditions that produce genital lymphoedema such as filariasis and lymphogranuloma venereum. Molecular diagnostic tests for the detection of K. granulomatis DNA have been developed but are not validated or approved for diagnostic use by the United States Food and Drug Authority (FDA). Serology has no role in diagnosis. Patients should be screened for other sexually transmitted infections. Treatment In 1913, Aragão and Vianna described the value of trivalent antimony in treating donovanosis (Fig. 8.6.10.2). The British Association for Sexual Health and HIV (BASHH) (2018), United States CDC (2015), and European guidelines (2016) recommend azithromycin 1 g orally once per week or 500 mg daily until lesions have healed (and a min- imum of three weeks [BASHH, CDC]). Alternative regimens include doxycycline (100 mg orally twice daily) or ciprofloxacin (750 mg or- ally twice daily) or erythromycin (500 mg orally four times daily) or co-trimoxazole (960 mg orally twice daily). Combination therapy or the addition of an aminoglycoside (e.g. gentamicin 1 mg/kg every 8 hours) can be considered if there is no improvement within a few days of treatment. Erythromycin is safe and gives good results in pregnant women. Women in labour found to have untreated lesions of the cervix should be delivered by caesarean section to reduce known risks of haematogenous dissemination and transmission to the neonate. A week of prophylactic treatment can be offered to healthy contacts to abort incubating infections. Patients with genital deformity might benefit from plastic surgical procedures. Patients with HIV should be managed with the same treatments, although the duration required might be longer. Rhinoscleroma Introduction, aetiology, and epidemiology Rhinoscleroma is a chronic granulomatous infection, predomin- antly of the upper respiratory tract. It is endemic to Mexico, Central and South America; Africa (especially Egypt and Uganda); Central and Eastern Europe (e.g. Siberia, Turkestan), the Middle East, India, China, the Philippines, Indonesia, and Papua New Guinea. The disease was first described in Austria and Germany by Hebra and Kaposi in 1870; the histological features by Johann von Mickulicz in 1877; and the causative organism, Klebsiella rhinoscleromatis, first identified by von Frisch in 1882. The term 'scleroma respiratorium' was proposed by Belinov in 1932 as it was found to affect both upper and lower respiratory tracts. Although limited epidemiological data are available, young adults appear to be most commonly affected. Pathogenesis Transmission is believed to occur through the inhalation of contam- inated droplets or material. The infection probably begins in areas of epithelial transition, such as the nasal vestibule. The nasal cavity is the most affected part of the body, but infection can spread to the larynx, nasopharynx, oral cavity, sinuses, soft tissues of the lips/ nose, trachea, and bronchi.

Patients with rhinoscleroma have impaired cellular immunity with a decrease in the CD4+ T-lymphocyte count, poor activation of Fig. 8.6.10.2 Inguinal lesion: from Aragão and Vianna's paper on the value of trivalent antimony in treating donovanosis. From Aragão H, Vianna G (1913). Resquizas sobre o Granuloma venereo. Mem Inst Oswaldo Cruz, 5, 211–38. Fig. 8.6.10.3 Donovan bodies: Giemsa-stained smear from donovanosis lesion demonstrating the characteristic 'closed safety pin' appearance of encapsulated organisms within a large histiocyte.

section 8 Infectious diseases 1054 macrophages, and inhibition of phagocytosis. A Mexican study has shown that the HLA DQA1*03011-DQB1*0301 haplotype is associ- ated with the development of rhinoscleroma. Clinical features Rhinoscleroma typically presents in three progressive, overlapping stages, and runs a slow, fluctuating course over several years. Symptoms of the first stage mimic those of the common cold, although usually with a malodorous, purulent discharge persisting over several months. The second stage, which lasts months to years, represents the proliferative stage, during which the granulomas form. These cause deformity, and in some cases, breathing difficulties, due to occlusion of affected parts of the respiratory tract. The usual clinical presentations at this stage are with nasal obstruction and bleeding and nasal deformity (splaying of the lower nose, often with a visible growth ex- tending down to the upper lip, known as Hebra nose) (Fig. 8.6.10.4). The granulomatous process can extend into and destroy neighbouring soft tissues, cartilage, bone, and skin. The third, fibrotic, stage is char- acterized by extensive scarring and stricture formation. A rare case of pneumonia and systemic sepsis has been reported. Differential diagnosis and clinical investigations Histology shows a dense infiltrate of plasma cells among which are large foamy histiocytes (Mikulicz cells) containing Gram-negative bacteria and Russell bodies, which are thought to be aggregated, un- released immunoglobulin components within plasma cells (Fig. 8.6.10.5). The diagnosis is usually made by demonstrating intracellular organisms in Giemsa-stained or silver-stained sections taken from typical lesions, combined with culture for *K. rhinoscleromatis*. Culture is only positive in 50–60% of cases. Differential diagnoses include fungal infections, mucocutaneous leishmaniasis, tuberculosis, leprosy, granulomatosis with polyangiitis (Wegener's granulomatosis), and car- cinoma. Computed tomography (CT) scanning and endoscopic tech- niques provide useful ways to define the extent of the disease. Treatment Treatment with ciprofloxacin 500 mg twice daily for 4–12 weeks ap- pears to be substantially superior to previously used antibiotic re- gimens (rifampicin, streptomycin, tetracyclines, ampicillin, and co-trimoxazole). Long-term follow-up might be required to monitor for recurrent disease. Debulking operations might be needed for obstructing nasal and tracheal disease, and tracheostomy can be required as a temporary measure. Reconstructive surgery might be needed to deal with late fibrotic stenosis. FURTHER READING Borgstein J, Sada E, Cortes R (1993). Ciprofloxacin for rhinoscleroma and ozena. Lancet, 342, 122. Bowden FJ, et al. (1996). Pilot study of azithromycin in the treatment of genital donovanosis. Genitourin Med, 72, 17–9. Canalis RF, Zamboni L (2001). An interpretation of the struc- tural changes responsible for the chronicity of rhinoscleroma. Laryngoscope, 111, 1020–6. Carter JS, et al. (1999). Phylogenetic evidence for reclassification of Calymmatobacterium granulomatis as Klebsiella granulomatis comb. nov. Int J Syst Bacteriol, 49, 1695–700. Centers for Disease Control and Prevention (2010). Sexually transmitted diseases treatment guidelines. MMWR, 59 (No. RR-12), 1–109. Mackay IM, et al. (2010). Detection and discrimination of herpes simplex viruses, Haemophilus ducreyi, Treponema pallidum, and Calymmabacterium (Klebsiella) granulomatosis from genital ul- cers. Clin Infect Dis, 42 1431–8. O'Farrell N (2002). Donovanosis. Sex Transm Infect, 78, 452–7. O'Farrell N, Hoosen A, Kingston M (2018). 2018 UK national guideline for the management of donovanosis. Int J STD AIDS, 29, 946–8. Richens J (1991). The diagnosis and treatment of donovanosis (granu- loma inguinale).

Sex Transm Infect, 67, 441–52. Velho PE, Souza EM, Belda Jr W (2008). Donovanosis. Braz J Infect Dis, 12, 521–5. Fig. 8.6.10.4 Rhinoscleroma with characteristic nasal splaying (Hebra nose) and obstruction of the left nostril in a 30-year-old man from Papua New Guinea. From Cooke R and Stewart B (2004). Colour atlas of anatomical pathology, Third edition, p. 37. Churchill Livingstone, Edinburgh, with permission. Fig. 8.6.10.5 Rhinoscleroma. Silver-stained preparation showing bacteria. Copyright J Richens.

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