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Diagnosis—this can be difficult as clinical symptoms, radiographic, or histopathological signs, and the results of serological tests may all be misleading. The finding of so-called sulphur granules is pathog- nomonic: these are macroscopically visible, yellowish, or reddish to brownish particles that exhibit a cauliflower-like appearance under the microscope at low magnifications, and which may be found as free structures in pus or embedded in affected tissue. Reliable diag- nosis chiefly rests on bacteriological culture but the introduction of MALDI-TOF technology has allowed better identification in some instances. Treatment and prognosis—antibacterial drugs used for treatment should be active against both the causative actinomycetes and all concomitant bacteria. For cervicofacial actinomycoses, the rare cutaneous processes, and most thoracic forms of the disease, this requirement is best fulfilled by amoxicillin plus clavulanic acid in medium to high doses: abdominal cases and the presence of un- usually resistant concomitant bacteria may require the addition of further antimicrobials (e.g. an aminoglycoside plus either metronida- zole or clindamycin). The prognosis of cervicofacial and cutaneous actinomycoses is good provided that treatment is adequate; thoracic and abdominal forms are more serious, with grave prognosis without proper treatment. Definition Actinomycoses are sporadically occurring endogenous polymicrobial inflammatory processes in which fermentative (facultatively an- aerobic or capnophilic) actinomycetes of the genera Actinomyces and Propionibacterium, but rarely also Bifidobacterium, may act as the principal pathogens. Clinically, the subacute to chronic, granu- lomatous as well as suppurative disease tends to progress slowly and usually gives rise to multiple abscesses and draining sinus tracts. Because the term ‘actinomycosis’ denotes a polyaetiological inflam- matory syndrome rather than a condition attributable to a single actinomycete species, it should only be used in the plural. Aetiology of human actinomycoses Actinomyces israelii and A. gerencseriae are by far the most frequent and most characteristic pathogens aetiologically involved in the human form of the disease. A. gerencseriae emerged from the former sero- and biovariety 2 of A. israelii in 1990. A third species of fila- mentous fermentative Gram-positive bacteria, Propionibacterium propionicum (formerly Actinomyces propionicus, Arachnia propi- onica), is a much less common cause of actinomycotic infections (Table 8.6.30.1). Several other fermentative actinomycetes have occasionally been isolated from actinomycosis-like lesions (Table 8.6.30.1). In a given

 case, however, it is often difficult to decide whether these organisms are primary pathogens or merely contaminants, especially when the specimen has had contact with mucosal secretions or when two different actinomycete species have been isolated from the same specimen (Table 8.6.30.1). Nevertheless, A. naeslundii, A. odonto- lyticus, A. viscosus, A. meyeri, and Bifidobacterium dentium (for- merly Actinomyces eriksonii) have all been reported to be capable of producing human infections clinically identical to those caused by A. israelii, A. gerencseriae, or P. propionicum, while A. bovis, the classic agent of bovine actinomycosis, has never been recovered with certainty from human infective processes (Table 8.6.30.1). Fermentative actinomycetes previously termed A. naeslundii and A. viscosus underwent considerable taxonomic and nomenclatural changes recently (Henssge et al., 2009). According to these changes, organisms now named A. viscosus only occur in animals, particu- larly in hamsters. Human isolates of the former species A. naeslun- dii and A. viscosus have been assigned to A. naeslundii sensu stricto and the new species A. oris and A. johnsonii, but it is difficult to dis- criminate between these three species by routinely used diagnostic procedures. Epidemiology Actinomycoses are not transmissible and cannot be brought under control by vaccination or by measures that prevent spread. Sporadically, they occur worldwide. In Germany, the incidence of

the disease was estimated to range from 1 in 40 000 (acute and chronic cases together) to 1 in 80 000 (chronic cases alone) per year, but appears to be decreasing in recent years. Men are affected 2–4 times more frequently by cervicofacial actinomycoses than are women. However, the male to female ratio appears to vary with age. Although actinomycoses may be found in patients of any age, men are predominantly affected between their 20th and 50th years and women in the second to fourth decade of their lives. Before puberty and in old age, actinomycoses occur spor- adically in patients of both sexes without the pronounced predispos- ition of men. Pathogenesis and pathology Most of the fermentative actinomycetes pathogenic to humans are found regularly and abundantly in the mouths of healthy adults. However, these microbes occur only sporadically or in low numbers in the digestive, respiratory, and genital tracts, as well as in the mouths of babies before teething and of adults without any natural teeth or tooth implants. Therefore, these actinomy- cetes may be considered facultatively pathogenic commensals of the human mucous membranes, which, apart from the very rare actinomycotic wound infections following human bite or fist fight traumata, produce disease exclusively as endogenous pathogens. For active invasion of the tissue, the classic pathogenic fermen- tative actinomycetes apparently require a negative redox potential, which may result either from insufficient blood supply (caused by circulatory or vascular diseases, crush injuries, or foreign bodies) or from the reducing and necrotizing capacity of other microbes in the lesion. Defective functions of the immune system do not spe- cifically predispose to actinomycotic infections. Synergistic polymicrobial infection True actinomycoses are essentially always synergistic mixed infections, in which the actinomycetes act as the specific com- ponent, the so-called guiding organisms that decide on the characteristic course and the late symptoms of the disease. The so-called concomitant microbes (Table 8.6.30.2), which may vary considerably in composition (about 100 aerobic and anaer- obic species) and number (up to 10 per case) of species from case to case, are often responsible for the clinical picture at the begin- ning of the infection and for certain complications; they are also part of the resident or transient surface microflora of the mucous membranes of humans. Particularly pronounced synergistic interactions appear to exist between pathogenic fermentative actinomycetes, espe- cially Actinomyces israelii and A. gerencseriae, and Actinobacillus actinomycetemcomitans, which has recently been reclassified as

Table 8.6.30.1 Fermentative actinomycetes isolated from human cervicofacial actinomycotic lesions at the Hygiene-Institute of the University of Cologne and the Institute for Medical Microbiology and Immunology of the University of Bonn, Germany, between 1985 and 1999

Species identified	Number	Percentage of cases
One species per specimen:		
A. israelii	421	55.3
A. gerencseriae	111	14.6
A. naeslundii/A. oris/A johnsonii	122	16.0
A. odontolyticus	19	2.5
A. meyeri	5	0.7
A. georgiae	1	0.1
A. neuii subsp. neuii	1	0.1
P. propionicum	7	0.9
Bifidobacterium dentium	3	0.4
Corynebacterium matruchotii	12	1.6
Rothia dentocariosa	5	0.7
Not identified to species level	54	7.1
Two species per specimen:		
A. israelii + A. naeslundii/A. oris/A johnsonii	11	0.8
A. israelii + A. meyeri	2	0.1
A. israelii + A. odontolyticus	1	0.1
A. israelii + P. propionicum	2	0.1
P. propionicum + A. naeslundii/A. oris/A johnsonii	2	0.1
P. propionicum + A. neuii	1	0.1
Total number of isolates	761	100.0

Modified from Pulverer G, Schütt-Gerowitt H, Schaal KP (2003). Human cervicofacial actinomycoses: microbiological data of 1997 cases. Clin Infect Dis, 37, 490–7.

 Aggregatibacter actinomycetemcomitans. The latter organism, the species designation of which refers to its characteristic association with actinomycetes (Latin actinomycetem comitans = accompanying an actinomycete), may even sustain the inflammatory process under similar clinical symptoms after chemotherapeutic elimination of the causative actinomycete. Histopathology Initially an inflammatory granulation tissue develops, which usually

breaks down to form either an acute abscess or chronic multiple ab- scesses with proliferation of connective tissue. The pathognomonic sulphur granules are formed primarily in the infected tissue, but may also appear as free structures in abscess content or sinus dis- charge. They are then of the highest diagnostic importance. Sulphur granules, which were originally designated Drusen in Harz's first description of Actinomyces bovis in 1877, are macro- scopically visible (up to 1 mm in diameter) yellowish or reddish to brownish particles that exhibit a cauliflower-like appearance under the microscope at low magnifications. They consist of a conglom- erate of filamentous actinomycete microcolonies formed in vivo and surrounded by tissue reaction material, especially polymorpho- nuclear granulocytes (Fig. 8.6.30.1). At high magnification, a Gram- stained smear of the completely crushed granule reveals the presence of clusters of Gram-positive interwoven branching filaments with radially arranged peripheral hyphae and of a variety of other Gram-positive and Gram-negative rods and cocci, which represent the concomitant flora (Fig. 8.6.30.2). A club-shaped layer of hyaline material may be seen on the tips of peripheral filaments, which can aid in the differentiation of actinomycotic sulphur granules from Table 8.6.30.2 Concomitant actinomycotic flora isolated from cervicofacial actinomycotic lesions at the Hygiene-Institute of the University of Cologne and the Institute for Medical Microbiology and Immunology of the University of Bonn, Germany, between 1972 and 1999 Species/group identified Number Percentage of cases Aerobically growing organisms Coagulase-negative staphylococci 781 39.1 Staphylococcus aureus 99 5.0 α-Haemolytic streptococci 206 10.3 β-Haemolytic streptococci 85 4.3 Other aerobically growing bacteria 104 5.2 Candida spp. 22 1.1 No aerobic growth 943 47.2 Anaerobes and capnophils Aggregatibacter (Actinobacillus) actinomycetemcomitans 283 14.2 'Microaerophilic' and anaerobic streptococci 992 49.7 Bacteroides ureolyticus/Campylobacter gracilis/ Capnocytophaga spp./Eikenella corrodens 370 18.5 Black-pigmented Bacteroidaceae 501 25.1 Other Bacteroides spp. and Prevotella spp. 419 21.0 Fusobacterium spp. 753 37.7 Leptotrichia buccalis 160 8.0 Propionibacterium spp.a 549 27.5 Other anaerobic bacteria 72 3.6 Total number of cases examined 1997 100.0 a Other than P. propionicum. Modified from Pulverer G, Schütt-Gerowitt H, Schaal KP (2003). Human cervicofacial actinomycoses: microbiological data of 1997 cases. Clin Infect Dis, 37, 490–7. Fig. 8.6.30.1 Actinomycotic sulphur granule. Particle embedded in 1% methylene blue solution, after gently pressing on the coverslip (original diameter 0.8 mm). Note the spherical segment-like structures which represent actinomycete colonies formed in vivo and which are coloured brown because the blue dye has been reduced to its leuco base in the anaerobic centre of the particle. The blue-coloured structures surrounding the colonies are polymorphonuclear granulocytes. Magnification × 60. Fig. 8.6.30.2 Gram-stained smear prepared from a crushed sulphur granule. The causative actinomycetes appear as Gram-positive irregularly curved branching filaments which are partially arranged in nest-like structures. In addition, various other bacteria, particularly Gram-negative rods and Gram-positive cocci, can be seen representing the concomitant flora. Magnification ×1200.

8.6.30 Actinomycoses 1173 macroscopically similar particles of various other microbial and nonmicrobial origins. Clinical manifestations The primary actinomycotic lesion usually develops in tissue adjacent to a mucous membrane at sites such as the cervicofacial, thoracic, and abdominal areas. The infection tends to progress slowly and to penetrate without regard to natural organ borders, or to spread haematogenously even to distant sites. Remission and exacerbation of symptoms with and without antimicrobial treatment is charac- teristic. As in other endogenous microbial diseases, the incubation period of actinomycoses is not defined. Cervicofacial actinomycoses In the most cases, actinomycotic lesions primarily involve the face or neck.

Conditions predisposing to these cervicofacial infections include tooth extractions, fractures of the jaw, periodontal ab- scesses, foreign bodies penetrating the mucosal barrier (bone splin- ters, fish bones, awns of cereals), or suppurating tonsillar crypts. Initially, the cervicofacial actinomycoses present either as an acute, usually odontogenic, abscess or cellulitis of the floor of the mouth, or as a slowly developing chronic hard painless reddish or livid swelling. Small acute actinomycotic abscesses may heal after surgical drainage alone. More often, however, the acute initial stage is followed by a subacute to chronic course if no specific antimicro- bial treatment is given, thereby imitating the primarily chronic form, which is characterized by regression and cicatrization of cen- tral suppurative foci while the infection progresses peripherally pro- ducing hard painless livid infiltrations. These may lead to multiple new areas of liquefaction, fistulae (Fig. 8.6.30.3), which often dis- charge pus containing sulphur granules, and multilocular cavities with poor healing and a tendency to recur after temporary regres- sions of the inflammatory symptoms. With inappropriate or no treatment, cervicofacial actinomycoses extend slowly, even across organ borders, and may become life-threatening by invasion of the cranial cavity, the medias- tinum, or the bloodstream. In contrast, the so-called (peri)apical actinomycosis which is clinically indistinguishable from common apical periodontitis and which has been accused of being respon- sible for lack of healing after endodontic treatment or tooth implant surgery, essentially always remains localized, responds to usual peri- odontitis treatment, and represents no serious threat to the patient’s health or life. This condition should, therefore, not be termed ‘actinomycosis’, but possibly ‘actinomycete periodontitis’. Thoracic actinomycoses Thoracic manifestations, which are much less common than the cervicofacial form (Table 8.6.30.3), usually develop after aspiration or inhalation of material from the mouth (dental plaque or calculus, tonsillar crypt contents) or a foreign body that contains or is con- taminated with the causative agents. Occasionally, this form of dis- ease may result from extension of an actinomycotic process of the neck, from an abdominal infection perforating the diaphragm, or from a distant focus by haematogenous spread. Primary pulmonary actinomycoses present as bronchopneumonic infiltrations that may imitate tuberculosis or bronchial carcinoma radiographically, appearing as single dense or multiple spotted shadows in which cavitations may develop (Fig. 8.6.30.4). If not diagnosed and treated properly, pulmonary infections may extend through to the pleural cavity producing empyema, to the pericar- dium, or to the chest wall; they may even appear as a paravertebral (psoas) abscess tracking down to the groin. Detailed aetiology, patho- genesis, and clinical relevance of a condition termed ‘endobronchial actinomycosis’ remain to be definitely clarified. Abdominal actinomycoses Actinomycoses of the abdomen and pelvis are rare (Table 8.6.30.3). They originate either from acute perforating gastrointestinal dis- eases (appendicitis, diverticulitis, various ulcerative diseases), from surgical or accidental trauma including injuries caused by ingested bone splinters or fish bones, or from inflammations of the female internal genital organs. Women with have intrauterine contraceptive devices or vaginal pessaries for long periods often show a characteristic colonization of the cervical canal and the uterine cavity, but particularly of the thread of the intrauterine contraceptive device, by various fermen- tative actinomycetes and other anaerobes resembling the synergistic

Fig. 8.6.30.3 Primary chronic cervicofacial actinomycosis with several draining sinus tracts in a 42-year-old man. Table 8.6.30.3 Localization of human actinomycotic infections Body site involved Number Percentage of cases Cervicofacial area 3197 97.9 Thoracic organs 41 1.3 Abdominal organs including small pelvis 20 0.6 Extremities 4 0.1 Central nervous system 4 0.1 Total number of cases 3266 100.0 Modified from Schaal KP, Pulverer G (1984). Epidemiologic, etiologic, diagnostic,

and therapeutic aspects of endogenous actinomycete infections. In: Ortiz-Ortiz L,

Bojalil LF, Yakoleff V (eds) Biological, biochemical, and biomedical aspects of actinomycetes, pp. 13–32. Academic Press, Orlando.

section 8 Infectious diseases 1174 actinomycotic flora. However, this colonization only rarely results in an invasive actinomycotic process. Most abdominal actinomycoses present as slowly growing tu- mours, which, in the absence of sinus tracts discharging pus with sulphur granules, are difficult to differentiate from malignant neo- plasms such as colonic, rectal, ovarian, or cervical carcinomas. By direct extension, any abdominal tissue or organ may be involved including muscle, liver, spleen, kidney, fallopian tubes, ovaries, testes, bladder, or rectum. This can present as a ‘frozen’ pelvis. Haematogenous liver abscesses have been seen, especially associated with genital actinomycoses. Actinomycotic infections of the central nervous system Actinomycoses of the brain and the spinal cord are very rare. They may arise from direct extension of cervicofacial infections. Haematogenous spread is also possible, particularly from primary lesions in the lungs or abdomen. The spinal canal may be directly involved from these sites. Brain abscess is much more common than meningitis. Actinomycoses of the bone In contrast to bovine actinomycosis which usually affects the skel- eton, bone involvement in humans is very rare. It usually develops by direct extension from soft tissue infection resulting in a peri- ostitis with new bone formation visible by radiography. If the bone itself is invaded, localized areas of bone destruction surrounded by increased bone density usually develop. Mandible, ribs, and spine are most frequently involved. Osteonecrosis of the jaw, seen with bisphosphonates, and radionecrosis may predispose to actinomycoses. Actinomycotic endocarditis Endocarditis due to fermentative actinomycetes has occasionally been described. However, detailed bacteriological information on this condition is not yet available so that it remains to be seen whether it may rightly be termed actinomycosis or has merely to be considered an aetiological variant of the common form of endo- carditis caused by indigenous oral microbes. Cutaneous actinomycoses Actinomycotic lesions of the skin are extremely rare. Usually, they originate from wounds that were contaminated with saliva or dental plaque following human bites or fist fights, but they may also re- sult from haematogenous spread. Symptoms are similar to those of cervicofacial actinomycoses. Diagnosis Clinical symptoms are often misleading, especially in the early stages of the disease, histopathological appearances are unreliable, and diagnosis chiefly rests on bacteriological methods. Radiography In cervicofacial cases, radiography is useful only for detecting bone involvement. A pulmonary infiltrate associated with a pro- liferative lesion or destruction of ribs is highly suggestive of either actinomycosis or a tumour. Radiography may also help to locate the abdominal processes and to identify the involvement of organs such as liver, kidney, urinary bladder, or ureter. In general, however, radiographic changes are not diagnostic. Laboratory diagnosis Clinical chemistry and haematology Small, localized actinomycotic lesions are not usually associated with abnormalities. In advanced cases, however, especially those in the thoracic or the abdominal area, a raised erythrocyte sedimen- tation rate and pronounced leucocytosis may be seen. When the central nervous system is involved, a polymorphonuclear or mono- nuclear pleocytosis is commonly found. The protein content of the cerebrospinal fluid is frequently elevated and the sugar content moderately depressed. Bacteriology Pus specimens containing sulphur granules and occasionally looking like semolina should prompt the clinician to ask, and the bacteriologist to look specifically for, actinomycetes using suitable cultural techniques and other methods. Pus, sinus discharge, bronchial secretions, granulation tissue, or biopsy materials are suitable specimens. Precautions must be taken to prevent contamination of the specimen by the indigenous mucosal flora. In cases of cervicofacial actinomycoses, pus should therefore be obtained only by transcutaneous puncture

of the ab- scesses or by transcutaneous needle biopsy after thorough skin disinfection. When abscesses have already been incised, a suffi- cient amount of pus should be collected instead of using only a swab. Because sputum always contains oral actinomycetes, bron- chial secretions should be obtained by transtracheal aspiration, or Fig. 8.6.30.4 Chest radiograph of pulmonary actinomycosis of the right upper lobe in a 62-year-old man. Initially, the disease was mistaken for bronchial carcinoma. It was diagnosed only after a huge subcutaneous abscess had developed covering the whole right shoulder blade.

8.6.30 Actinomycoses 1175 material should be collected by transthoracic percutaneous needle biopsy. Percutaneous puncture of suspected abscesses, possibly under radiological control, is often the only way of obtaining suit- able specimens for diagnosing abdominal actinomycoses. The transport of specimens to the bacteriological laboratory should be as fast as possible, preferably by messenger. Alternatively, a reducing transport medium such as one of the modifications of Stuart's medium should be used. The specimen should arrive in the laboratory within 24 h, although it has occasionally proved possible to isolate actinomycetes from samples that took 7 days or more to get to the diagnostic laboratory by post. A quick and comparatively reliable tentative diagnosis is possible microscopically when sulphur granules are present (Fig. 8.6.30.1). The demonstration of concomitant bacteria in Gram-stained smears prepared from crushed granule material (Fig. 8.6.30.2) allows the differentiation of actinomycotic granules from similar particles produced by Nocardia spp., Actinomadura spp., or Streptomyces spp. Use of transparent culture media and careful microscopic exam- ination of the cultures, preferably on Fortner plates, after at least 2, 7, and 14 days of incubation enables a specialized laboratory to detect possible actinomycete colonies and to subculture them for identification. Isolation and definite identification to the spe- cies level may require a further 1 to 2 weeks. Techniques such as the application of gene probes or the polymerase chain reaction for detecting and identifying fermentative actinomycetes directly in clinical samples are not yet widely used; however, sequencing of the 16S rRNA gene often helps to identify actinomycete cultures to spe- cies level although this technique is intrinsically a phylogenetic and taxonomic rather than a diagnostic tool. The use of MALDI-TOF (matrix-assisted laser desorption ionization time-of-flight) mass spectrometry to identify actinomycetes is promising and might allow identification of branching bacteria that have been misiden- tified previously. Serological diagnosis None of the routine serological methods has yet provided satis- factory results because sensitivity and specificity have been found to be too low. Treatment As the aetiology of human actinomycoses is always polymicrobial, the antibacterial drugs used for treatment should in principle cover both the causative actinomycetes and all of the concomi- tant bacteria. This usually requires the administration of drug combinations in which aminopenicillins currently represent the therapeutic basis because they are slightly more active against the pathogenic actinomycetes than is penicillin G and because they are able to inhibit Aggregatibacter (Actinobacillus) actinomycetem- comitans which is usually resistant to narrow-spectrum penicil- lins. However, the presence of concomitant β-lactamase producers such as Bacteroides fragilis, B. thetaiotaomicron, or Staphylococcus aureus (β-lactamase producing) may impair the therapeutic effi- cacy of aminopenicillins and that of many other β-lactams so that the combination with a β-lactamase inhibitor is advisable or even necessary. For cervicofacial actinomycoses, amoxicillin plus clavulanic acid has proved to be the treatment of choice. Three doses of 2.0 g amoxi- cillin plus 0.2 g clavulanic acid every day for 1 week and three doses of 1.1 g of the combination for an additional 7 days usually result in complete cure. Thoracic actinomycoses mostly respond to the same regimen. However, it is advisable to maintain doses of 2.2 g 3 times a day for 2 weeks, and to continue treatment for 3 to 4 weeks. Advanced pulmonary cases may require the addition of 2 g

ampi- cillin three times a day in order to increase the tissue concentration of aminopenicillin and, depending on the composition of the con- comitant flora, the use of an antimicrobial specifically active against resistant Enterobacteriaceae; the application of drugs such as metro- nidazole or clindamycin against strict anaerobes is only necessary as an adjunct to the aminopenicillins in chronic cases with reduced blood supply. Since in abdominal actinomycoses Enterobacteriaceae and β- lactamase producing Bacteroides spp. are usually present and the correct diagnosis is mostly established late, suitable antimicrobial combinations for these cases are amoxicillin plus clavulanic acid plus metronidazole plus tobramycin (gentamicin) or ampicillin plus clindamycin plus an aminoglycoside. Meropenem might also be a good choice, but this drug has not yet been widely used for treating actinomycotic infections. Neither clindamycin nor metronidazole should be used alone. Clindamycin is almost completely ineffective against Aggregatibacter (Actinobacillus) actinomycetemcomitans and metronidazole shows no activity at all against pathogenic actinomycetes. The use of fur- ther combinations, including additional aminoglycosides, ceph- alosporins, or β-lactamase-stable penicillins, may be necessary depending on the presence of unusual aerobic organisms. In pa- tients allergic to penicillin, tetracyclines or possibly cephalosporins may be tried instead of aminopenicillins. Incision of abscesses and drainage of pus might still be necessary as an adjunct to the anti- microbial chemotherapy and may help to accelerate recovery and to decrease the risk of relapses. Prognosis The prognosis of cervicofacial and cutaneous actinomycotic infec- tions is good provided that the diagnosis is established early and antimicrobial treatment is adequate. However, thoracic, abdominal, and systemic manifestations remain serious conditions that require all possible diagnostic and therapeutic efforts. Without proper treat- ment, the prognosis is grave. Other diseases caused by fermentative actinomycetes Fermentative actinomycetes play some part in dental caries and periodontal disease, but are clearly not the most important mi- crobes contributing to these important health problems. Lacrimal canaliculitis with and without conjunctivitis is commonly caused by fermentative actinomycetes, in particular P. propionicum, but less frequently also by Actinomyces israelii, A. gerencseriae, A. naeslundii, A. oris, or A. odontolyticus. The concomitant flora, when present, is usually less complex than that of typical actinomycoses. Removal of

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