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Actinomycosis Actinomycosis is uncommon, and most physicians' personal experience with its clinical presentations is limited. Laboratory identification of the etiologic agents from the order Actinomycetales is not routine. Thus, actinomycosis remains a diagnostic challenge, even for a skilled clinician. However, this infection is usually curable with medical therapy alone. Therefore, an awareness of the full spectrum of clinical syndromes can expedite diagnosis and treatment and minimize unnecessary surgical interventions, morbidity, and mortality. Classical actinomycosis is an indolent, slowly progressive infection caused by anaerobic or microaerophilic bacteria, primarily of the genus Actinomyces, that colonize the mouth, colon, and vagina. Mucosal disruption may lead to infection at virtually any site in the body. In vivo growth of actinomycetes usually results in the formation of characteristic clumps called grains or sulfur granules. The clinical presentations of actinomycosis are myriad. Common in the preantibiotic era, actinomycosis has diminished in incidence, as has its timely recognition. Actinomycosis has been called the most misdiagnosed disease, and it has been said that no disease is so often missed by experienced diagnosticians. Three "classic" clinical presentations that should prompt consideration of this unique infection are (1) the combination of chronicity, progression across tissue boundaries, and mass-like features (mimicking malignancy, with which it is often confused); (2) the development of a sinus tract, which may spontaneously resolve and recur; and (3) a refractory or relapsing infection after a short course of therapy, since cure of established actinomycosis requires prolonged treatment. ■ ■ETIOLOGIC AGENTS Actinomycosis is most commonly caused by A. israelii, A. naeslundii, Schaalia (Actinomyces) odontolyticus, A. viscosus, Schaalia (Actinomyces) meyeri, A. graevenitzii, and A. gerencseriae. Infections due to Winkia (Actinomyces) neuii have been increasingly recognized. Most if not all actinomycotic infections are polymicrobial. Aggregatibacter (Actinobacillus) actinomycetemcomitans, Eikenella corrodens, Enterobacteriaceae, and species of Fusobacterium, Bacteroides, Capnocytophaga, Staphylococcus, and Streptococcus are commonly isolated with actinomycetes in various combinations, depending on the site of infection. Their contribution to the pathogenesis of actinomycosis is uncertain. Genome-based analysis and comparative 16S rRNA gene sequencing have led to the identification of an ever-expanding list of Actinomyces species and a reclassification of some species to other genera. In recent years, many prior Actinomyces species have been placed into new genera including Schaalia, Winkia, Gleimia, and Pauljensenia, though most publications have yet to adapt these new taxonomic changes. At present, 33 species remain in the Actinomyces genus with at least 26 species implicated as causes of human disease. Gleimia (Actinomyces) europaeus, A. radingae, Schaalia (Actinomyces) turicensis, Schaalia (Actinomyces) cardiffensis, A. urogenitalis, Pauljensenia (Actinomyces) hongkongensis, Schaalia (Actinomyces) georgiae, Schaalia (Actinomyces) massiliensis, A. timonensis, Schaalia

(Actinomyces) funkei, Trueperella (Arcanobacterium) pyogenes, Trueperella (Arcanobacterium) bernardiae, and Propionibacterium propionicum are additional causes of human actinomycosis, albeit not always with a “classic” presentation. ■ ■EPIDEMIOLOGY Actinomycosis has no geographic boundaries and occurs throughout life, with a peak incidence in the middle decades. Males have a threefold higher incidence than females, possibly because of poorer dental hygiene and/or more frequent trauma. Improved dental hygiene and the initiation of antimicrobial treatment before actinomycosis fully develops have probably contributed to a decrease in incidence since the advent of antibiotics. Individuals who do not seek or have access to health care, those who have an intrauterine contraceptive device (IUD) in place for a prolonged period (see “Pelvic Disease,” below), and those

who receive bisphosphonate treatment (see “Oral–Cervicofacial Disease,” below) are probably at higher risk.

■ ■PATHOGENESIS AND PATHOLOGY The etiologic agents of actinomycosis are members of the normal oral flora and are often cultured from the bronchi, the gastrointestinal tract, and the female genital tract. The critical step in the development of actinomycosis is disruption of the mucosal barrier. Local infection may ensue. Once established, actinomycosis spreads contiguously in a slow, progressive manner, ignoring tissue planes. Although acute inflammation may initially develop at the infection site, the hallmark of actinomycosis is the characteristic chronic, indolent phase manifested by lesions that usually appear as single or multiple indurations. Central necrosis consisting of neutrophils and sulfur granules develops and is virtually diagnostic. The fibrotic walls of the mass are typically described as “wooden.” The responsible bacterial and/or host factors have not been identified. Over time, sinus tracts to the skin, adjacent organs, or bone may develop. In rare instances, distant hematogenous seeding may occur; lymphatic spread and associated lymphadenopathy are uncommon. As mentioned above, these unique features of actinomycosis mimic malignancy, with which it is often confused. Foreign bodies appear to facilitate infection. This association most frequently involves IUDs. Reports have described an association of actinomycosis with HIV infection; transplantation; common variable immunodeficiency; chronic granulomatous disease; treatment with anti–tumor necrosis factor α agents, glucocorticoids, or bisphosphonates; and radio- or chemotherapy. Actinomycosis after SARS-CoV-2 infection is reported but the association is not well-established. Ulcerative mucosal infections (e.g., by herpes simplex virus or cytomegalovirus) may facilitate disease development. CHAPTER 180 ■ ■CLINICAL MANIFESTATIONS Oral–Cervicofacial Disease Actinomycosis occurs most frequently at an oral, cervical, or facial site, usually as a soft tissue swelling, abscess, mass, or ulcerative lesion that is often mistaken for a neoplasm. Dental diseases or procedures are common precipitating factors. The angle of the jaw is generally involved, but a diagnosis of actinomycosis should be considered with any mass lesion or relapsing infection in the head and neck. Radiation therapy and medicationrelated osteonecrosis of the jaw (MRONJ) due to antiresorptive therapy with bisphosphonates and anti–receptor activator of nuclear factor-κβ ligand (RANKL) such as denosumab, angiogenesis inhibitors, and tyrosine kinase inhibitors have all been recognized as contributing to an increasing incidence of actinomycotic infection of the mandible and maxilla (Fig. 180-1). Canaliculitis (commonly due to P. propionicum), Actinomycosis FIGURE 180-1 Bisphosphonate-associated maxillary osteomyelitis due to Actinomyces viscosus. A sulfur granule is seen within the bone. (Reprinted with permission from NH Naik, TA Russo: Bisphosphonate related osteonecrosis of the jaw: The role of Actinomyces. Clin Infect Dis 49:1729, 2009. © 2009 Oxford

University Press.)

A FIGURE 180-2 Thoracic actinomycosis. A. A chest wall mass from extension of pulmonary infection. B. Pulmonary infection is complicated by empyema (open arrow) and extension to the chest wall (closed arrow). (Courtesy of Dr. C. B. Hsiao, Division of Infectious Diseases, Department of Medicine, State University of New York at Buffalo.) otitis, sinusitis, and laryngeal disease also can develop. Pain, fever, and leukocytosis are variably reported. Contiguous extension to the cra nium, cervical spine, or thorax is a potential sequela. Thoracic Disease Thoracic actinomycosis, which may be facili tated by aspirated foreign material such as animal bones or teeth, usually follows an indolent progressive course, with involvement of the pulmonary parenchyma and/or the pleural space. Chest pain, fever, and weight loss are common. A cough, when present, is vari ably productive. The usual radiographic finding is either a mass lesion or pneumonia. On computed tomography (CT), central areas of low attenuation and ring-like rim enhancement may be seen; cavitary disease may develop. More than 50% of cases include pleural thicken ing, effusion, or empyema (Fig. 180-2). Rarely, pulmonary nodules or endobronchial lesions occur. Lesions suggestive of actinomycosis include those that cross fissures or pleura; extend into the mediasti num, contiguous bone, or chest wall (empyema necessitatis or empyema necessitans); or are associated with a sinus tract. In the absence of these findings, thoracic actinomycosis is usually mistaken for a neoplasm or pneumonia due to more usual causes. PART 5 Infectious Diseases Mediastinal infection is uncommon, usually arising from thoracic extension but rarely from perforation of the esophagus, trauma, or extension of head and neck or abdominal disease. The structures within the mediastinum and the heart can be involved in various com binations; consequently, the possible presentations are diverse. Primary endocarditis (in which W. neuii has been increasingly described), esophageal infection, and isolated disease of the breast occur. A B FIGURE 180-3 Hepatic–splenic actinomycosis. A. Computed tomogram showing multiple hepatic abscesses and a small splenic lesion due to Actinomyces israelii. Arrow indicates extension outside the liver. Inset: Gram stain of abscess fluid demonstrating beaded filamentous gram-positive rods. B. Subsequent formation of a sinus tract. (Reprinted with permission from M Saad: Actinomyces hepatic abscess with cutaneous fistula. N Engl J Med 353:e16, 2005. © 2005 Massachusetts Medical Society. All rights reserved.)

B Abdominal Disease Abdominal actinomycosis poses a great diag nostic challenge. Months or years usually pass from the inciting event (e.g., appendicitis, diverticulitis, peptic ulcer disease, spillage of gall stones or bile during cholecystectomy, foreign-body perforation, bowel surgery, or ascension from IUD-associated pelvic disease) to clinical recognition. Because of the flow of peritoneal fluid and/or the direct extension of primary disease, virtually any abdominal organ, region, or space can be involved. The disease usually presents as an abscess, a mass, or a mixed lesion that is often fixed to underlying tissue and mistaken for a tumor. On CT, enhancement is most often heterogeneous and adjacent bowel is thickened. Sinus tracts to the abdominal wall, to the perianal region, or between the bowel and other organs may develop and mimic inflammatory bowel disease (Chap. 337). Recurrent disease or a wound or fistula that fails to heal suggests actinomycosis. Hepatic infection usually presents as one or more abscesses or masses (Fig. 180-3). Isolated disease presumably develops via hema togenous seeding from cryptic foci. Imaging and percutaneous tech niques have resulted in improved diagnosis and treatment. All levels of the urogenital tract can be infected. Renal disease usu ally presents as pyelonephritis and/or renal and perinephric abscess. Bladder involvement, usually due to extension of pelvic disease, may result in

ureteral obstruction or fistulas to bowel, skin, or uterus. Acti nomyces can be detected in urine with appropriate stains and cultures. Pelvic Disease Actinomycotic involvement of the pelvis occurs most commonly in association with an IUD but can also be associated with other foreign bodies, such as surgical mesh. When an IUD is in place or

FIGURE 180-4 Computed tomogram showing pelvic actinomycosis associated with an intrauterine contraceptive device. The device is encased by endometrial fibrosis (solid arrow); also visible are paraendometrial fibrosis (open triangular arrowhead) and an area of suppuration (open arrow). has been used but removed, pelvic symptoms should prompt consider ation of actinomycosis. The risk, although not quantified, appears small. The disease rarely develops when the IUD has been in place for <1 year, but the risk increases with time. Symptoms are typically indolent; fever, weight loss, abdominal pain, and abnormal vaginal bleeding or discharge are the most common. The earliest stage of disease—often endometritis— commonly progresses to pelvic masses or a tuboovarian abscess (Fig. 180-4). Unfortunately, because the diagnosis is often delayed, a “frozen pelvis” mimicking malignancy or endometriosis can develop by the time of recognition, which may lead to unnecessary surgery. Cancer antigen 125 levels may be elevated, further contributing to misdiagnosis. In contrast to malignancy and tuberculosis, pelvic actinomycosis only uncommonly includes ascites and lymphadenopathy. An endometrial biopsy may enable diagnosis in a minimally invasive fashion. Actinomyces-like organisms (ALOs), which are identified in Papa nicolaou-stained specimens in (on average) 7% of women using an IUD, have a low positive predictive value for diagnosis. The detection of ALOs in an asymptomatic patient warrants education and close follow-up but not removal of the IUD unless a suitable contraceptive alternative is agreed on. In the presence of symptoms that cannot be accounted for, it seems prudent to remove the IUD and—if advanced disease is excluded—to initiate a 14-day course of empirical treatment for possible early endometritis. Central Nervous System Disease Actinomycosis of the central nervous system (CNS) is rare. Single or multiple brain abscesses are most common. Individuals with hereditary hemorrhagic telangiectasia are at increased risk for brain abscess with Actinomyces as the potential etiologic agent. An abscess usually appears on CT as a ring-enhancing lesion with a thick wall that may be irregular or nodular. Magnetic res onance perfusion and spectroscopy findings have also been described, as have primary meningitis, epidural or subdural space infection, and cavernous sinus syndrome. Musculoskeletal and Soft Tissue Infection Actinomycotic infection of bones and joints is usually due to adjacent soft tissue infec tion but may be associated with trauma, injections, surgery (e.g., pros theses), osteoradionecrosis and bisphosphonate osteonecrosis (limited to mandibular and maxillary bones), or hematogenous spread. Because of slow disease progression, new bone formation and bone destruction can be seen concomitantly. Infection of soft tissue is uncommon and is usually a result of trauma. Actinomycetoma is a slowly progressive infection of the skin and subcutaneous tissue that is usually seen in warm climates. Despite the name being suggestive of Actinomyces as a causative agent, it is most commonly caused by Nocardia or Actino madura species (Chap. 179).

Disseminated Disease Hematogenous dissemination of disease from any location rarely results in multiple-organ involvement. S. meyeri is most commonly involved. The lungs and liver are most often affected, with the presentation of multiple nodules mimicking disseminated malignancy. The clinical presentation may be surprisingly indolent given the extent of disease.

■ ■DIAGNOSIS The diagnosis of actinomycosis is rarely considered. All too often, actinomycosis is first mentioned by the pathologist after extensive surgery. Since medical therapy alone is frequently sufficient for cure, the challenge for the clinician is to consider the possibility of acti nomycosis, to diagnose it in the least invasive fashion, and to avoid unnecessary surgery. The clinical and radiographic presentations that suggest actinomycosis are discussed above. Of note, hypermetabolism has been demonstrated by 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) in actinomycotic disease. Aspirations and biopsies (with or without CT or ultrasound guidance) are being used successfully to obtain clinical material for diagnosis, although surgery may be required. The microscopic identification of sulfur granules (an in vivo matrix of bacteria, calcium phosphate, and host material) in pus or tissues, which increases with the examination of additional histo pathologic sections and the use of positively charged slides to optimize adhesion, is the most common means of diagnosis. Occasionally, these granules are identified grossly from draining sinus tracts or pus. Peri odic acid–Schiff (PAS), Grocott methenamine silver (GMS), and Gram stains may be helpful to identify actinomycotic aggregates in surgical specimens. On hematoxylin-eosin stain, the granules may be eosino philic or variably surrounded by a radiating fringe of eosinophilic clubs called the Splendore-Hoeppli phenomenon (Fig. 180-5). Although sulfur granules are a defining characteristic of actinomycosis, granules also are found in mycetoma (Chaps. 179 and 225) and botryomycosis (a chronic suppurative bacterial infection of soft tissue or, in rare cases, visceral tissue that produces clumps of bacteria resembling granules). These entities can easily be differentiated from actinomycosis with appropriate histopathologic and microbiologic studies. Microbiologic identification of actinomycetes is often precluded by prior antimicro bial therapy or failure to perform appropriate microbiologic cultures. For optimal yield, the avoidance of even a single dose of antibiotics is mandatory. Although some species can grow aerobically, isolation is maximized under anaerobic conditions, usually requiring 5–7 days but potentially up to 2–4 weeks. The use of 16S rRNA gene amplification and sequencing by clinical microbiology laboratories is increasing and is enhancing diagnostic sensitivity and specificity. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) holds similar promise, but databases are still being optimized. Because actinomycetes are components of the normal oral and genitaltract flora, their identification in the absence of sulfur granules in sputum, bronchial washings, and cervicovaginal secretions may reflect colonization rather than infection. CHAPTER 180 Actinomycosis TREATMENT Actinomycosis Decisions about treatment are based on the collective clinical experience of the past 75 years. Actinomycosis requires prolonged treatment with high doses of antimicrobial agents; suitable antimi crobial agents and those deemed unreliable are listed in Table 180-1. The need for intensive treatment is presumably due to the drugs’ poor penetration of the thick-walled masses common in this infec tion and/or the sulfur granules themselves, which may represent a biofilm. Although therapy must be individualized, the IV adminis tration of 18–24 million units of penicillin daily for 2–6 weeks, fol lowed by oral therapy with penicillin or amoxicillin (total duration, 6–12 months), is a reasonable guideline for serious infections and bulky disease. For penicillin-allergic patients, tetracyclines, ceftri axone, or carbapenems are reasonable alternatives. Less extensive disease, particularly that involving the oral–cervicofacial region or

PART 5 Infectious Diseases TABLE 180-1 Appropriate and Inappropriate Antibiotic Therapy for Actinomycosisa CATEGORY AGENT Extensive successful clinical experienceb Penicillin: 3–4 million units IV q4hc,d Amoxicillin: 500 mg PO q6h Erythromycin: 500–1000 mg IV q6h or 500 mg PO q6hc Tetracycline: 500 mg PO q6h Doxycycline: 100 mg IV or PO q12h Minocycline: 100 mg IV or PO q12h Clindamycin: 900 mg IV q8h or 300–450 mg PO q6hc Anecdotal successful clinical experience

Ceftriaxoned Imipenem-cilastatin Piperacillin-tazobactam Agents predicted to be efficacious on the basis of in vitro activity Vancomycin Dalbavancin Linezolid Rifampin Ertapenemd Meropenem Tigecyclined Eravacycline Azithromycind Agents that should be avoided Metronidazole Aminoglycosides Oxacillin, dicloxacillin Cephalexin Ceftazidime Daptomycin Fluoroquinolones aAdditional coverage for concomitant “companion” bacteria may be required. bControlled evaluations have not been performed. Dose and duration require individualization depending on the host, site, and extent of infection. As a general rule, a maximal parenteral antimicrobial dose for 2–6 weeks followed by oral therapy, for a total duration of 6–12 months, is required for serious infections and bulky disease, whereas a shorter course may suffice for less extensive disease, particularly in the oral–cervicofacial region. Monitoring the impact of therapy with computed tomography or magnetic resonance imaging is advisable when appropriate. cRecent in vitro data have demonstrated resistance in up to 33% of isolates. dThis agent can be considered for at-home parenteral therapy; penicillin requires a continuous infusion pump. A B FIGURE 180-5 Microscopic evaluation of actinomycotic sulfur granules. A. Actinomycotic sulfur granule with gram-positive Actinomyces organisms surrounded by eosinophilic, proteinaceous coating called the Splendore-Hoeppli phenomenon. B. Actinomycotic granule appearance with Grocott methenamine silver stain. (Courtesy of Ayesha Arshad, MD, VA Western New York Healthcare System.) the isolation of Actinomyces in the absence of tissue changes associ ated with actinomycosis, may be cured with a shorter course. For home IV therapy, the ease of once-a-day dosing makes ceftriaxone appealing in certain circumstances; however, a greater body of lit erature supporting its efficacy would be desirable. The availability of portable infusion pumps for home therapy allows for both the appropriate dosing and practical administration of IV penicillin. For infections in critical sites (e.g., CNS), this approach remains the safest until more information is available on other agents. The phar macokinetic properties, availability of oral and parenteral formula tions, and potential efficacy of azithromycin also make this agent appealing. Unfortunately, few in vitro and no clinical data exist on its use to treat actinomycosis. If therapy is extended beyond the resolution of measurable disease, the risk of relapse—a clinical hall mark of this infection—will be minimized; CT and magnetic reso nance imaging (MRI) are generally the most sensitive and objective techniques by which to accomplish this goal. A similar approach is reasonable for immunocompromised patients, although refractory disease has been described in HIV-infected individuals. While the role played by “companion” microbes in actinomycosis is unclear, many isolates are pathogens in their own right, and a regimen cov ering these organisms during the initial treatment course is reason able. Isolation of Actinomyces from blood cultures in the absence of defined infection may represent contamination or transient bacte remia from a mucosal site of colonization, in which case treatment may not be necessary. Combined medical–surgical therapy is still advocated in some reports. However, an increasing body of literature now supports an initial attempt at cure with medical therapy alone, even in extensive disease. CT and MRI should be used to monitor the response to therapy. In most cases, either surgery can be avoided or a less exten sive procedure can be used. This approach is particularly valuable in sparing critical organs, such as the bladder or the reproductive organs in women of childbearing age. For a well-defined abscess, percutaneous drainage in combination with medical therapy is a reasonable approach. When a critical location is involved (e.g., the epidural space, the CNS), when there is significant hemoptysis, or when suitable medical therapy fails, surgical intervention may be appropriate. In the absence of optimal data, the combination of a prolonged course of antimicrobial therapy and resection—at least of necrotic bone for radiation- and medication-related osteonecrosis of the jaw—is a reasonable approach.

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