Nocardial infections tend to relapse (particularly in patients with chronic granulomatous disease), and long courses of antimicrobial therapy are necessary (Table 199-2). If disease is unusually extensive or if the response to therapy is slow, the recommendations in Table 199-2 should be exceeded.

With appropriate treatment, the mortality rate for pulmonary or disseminated nocardiosis outside the CNS should be <5%. CNS disease carries a higher mortality rate. Patients should be followed carefully for at least 6 months after therapy has ended.

200 Actinomycosis and Whipple's Disease

Thomas A. Russo

Actinomycosis and Whipple's disease share characteristics that confound even the skilled diagnostician. Because both diseases are uncommon, the physician's personal experience with their clinical presentations is limited. The laboratory identification of the etiologic agents from the order Actinomycetales is not routine. Thus they remain a diagnostic challenge. However, both of these chronic infections are curable, usually with medical therapy alone. Therefore, an awareness of the full spectrum of these diseases, prompting clinical suspicion, can expedite their diagnosis and treatment and minimize unnecessary surgical interventions (especially with actinomycosis), morbidity, and mortality risk.

ACTINOMYCOSIS

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 clinicians.

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, A. odontolyticus, A. viscosus, A. meyeri, and A. gerencseriae*. 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.

Comparative 16S rRNA gene sequencing has led to the identification of an ever-expanding list of *Actinomyces* species and a reclassification of some species to other genera. At present, 46 species and 2 subspecies have been recognized (*www.bacterio.cict.fr/a/actinomyces.html*). *A. europaeus, A. neuii, A. radingae, A. graevenitzii, A. turicensis, A. cardiffensis, A. houstonensis, A. hongkongensis, A. lingnae, A. massiliensis, A. timonensis*, and *A. funkei* as well as two former *Actinomyces* species—*Arcanobacterium pyogenes* and *Arcanobacterium bernardiae*—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 (IUCD) 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. 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 IUCDs. Reports have described an association of actinomycosis with HIV infection; transplantation; common variable immunodeficiency; chronic granulomatous disease; treatment with infliximab, glucocorticoids, or bisphosphonates; and radio- or chemotherapy. Ulcerative mucosal infections (e.g., by herpes simplex virus or cytomegalovirus) may facilitate disease development.

CLINICAL MANIFESTATIONS

Oral-Cervicofacial Disease Actinomycosis occurs most frequently at an oral, cervical, or facial site, usually as a soft tissue swelling, abscess, or mass lesion that is often mistaken for a neoplasm. 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 (Chap. 44). Radiation therapy and especially bisphosphonate treatment have been recognized as contributing to an increasing incidence of actinomycotic infection of the mandible and maxilla (Fig. 200-1). Canaliculitis (also commonly due to *Propionibacterium propionicum*), otitis, and sinusitis also can develop. Pain, fever, and leukocytosis are variably reported. Contiguous extension to the cranium, cervical spine, or thorax is a potential sequela.

Thoracic Disease Thoracic actinomycosis, which may be facilitated by foreign material, 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 variably productive. The usual radiographic finding is either a mass lesion or pneumonia. On CT, central areas of low attenuation and ring-like rim enhancement may be seen. Cavitary disease or mediastinal or hilar adenopathy may develop. More than 50% of cases include pleural thickening, effusion, or empyema (Fig. 200-2). Rarely, pulmonary nodules or endobronchial lesions occur. Lesions suggestive of actinomycosis include those that cross fissures or pleura; extend into the mediastinum, contiguous bone, or chest wall; 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.