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Actinomycosis, Nocardiosis, and Botryomycosis

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Diseases caused by filamentous bacteria (*i.e.*, achnomycosis and nocardiosis) are discussed together with botryomycosis because they produce similar histopathologic changes in the lungs. The filamentous bacteria belong to the order Actinomycetales and include members of the families Actinomycetaceae, Nocardiaceae, and Streptomycetaceae. Members of the order Actinomycetales, which are also of medical interest but are not filamentous, usually produce different symptoms, such as extrinsic allergic alveolitis (see Chap. 65). Some members of the family Nocardiaceae are excluded from this discussion because they produce different types of diseases (*e.g.*, tuberculosis, leprosy, diphtheria) and because they differ morphologically. The agents that produce botryomycosis are a variety of common gram-positive and gram-negative, nonfilamentous bacteria.

ACTINOMYCOSIS

The Actinomycetaceae are gram-positive, non–acid-fast filamentous bacteria that live as commensals in the oral and intestinal tracts of humans and other animals. *Actinomycosis* is a chronic disease characterized by suppurative granulomatous lesions containing grains known as sulfur granules. The genera producing pulmonary disease in humans are *Actinomyces, Bifidobacterium*, and *Arachnia*. All are endogenous oral saprophytes found in periodontal pockets, carious teeth, dental plaque, and tonsillar crypts. Actinomycosis produces several anatomoclinical forms: cervicofacial, thoracic, abdominal, cervical, genitourinary, and dermatologic infections; uncommonly, the localized intrusion becomes a disseminated infection.

Thoracic infection can involve the lungs, pleura, chest wall, or mediastinum. Although these bacteria produce disease as secondary invaders after trauma or surgical injury, most thoracic infections follow aspiration of contaminated oral debris from an infection of the tongue or gingiva. Less commonly, thoracic infection can result from esophageal penetration or from retroperitoneal or transdiaphragmatic spread. Rarely, thoracic infection is the result of spread from a cervicofacial lesion.

Actinomyces israelii, Actinomyces viscosus, Actinomyces naeslundii, Actinomyces odontolyticus, and *Actinomyces meyeri*, all normal inhabitants of the human oral cavity, can produce human disease, but most infections are caused by *A. israelii*.[1–5] *Arachnia propionica*, formerly *Actinomyces propionicus*, and *Bifidobacterium adolescentis* may also be pathogenic.

Actinomycotic lesions characteristically contain other bacteria. *Actinobacillus actinomycetem-comitans, Eikenella corrodens, Capnocytophaga* sp., and other oral bacteria are typically isolated with *Actinomyces*. These bacteria are believed to act synergistically with *Actinomyces* to produce actinomycosis.

A patient with thoracic actinomycosis usually presents with a productive cough and low-grade fever. Hemoptysis as a result of parenchymal destruction may develop. Sputum cultures seldom yield the pathogen. Untreated, the bacteria can penetrate through the pleura and thoracic wall to the skin surface, forming discharging sinus tracts. Patients become progressively more short of breath and anemic; they experience weight loss, night sweats, and increasing fever. Chest x-ray films are usually nonspecific, but they may reveal massive consolidations, usually in the hilar region or in the basal areas. Less often, a chronic bilateral patchy pneumonia, apical cavitary lesions, or an enlarging mass infiltrating the fissures may be seen. Findings of thoracic actinomycosis include periostitis or frank bone destruction of ribs, vertebrae, sternum, or the shoulder girdle adjacent to a pulmonary lesion and extension through an interlobar fissure. Dissemination occurs more often in patients with thoracic actinomycosis than with other forms of the disease, probably because thoracic disease is difficult to diagnose and often

goes unrecognized until empyema or a chest wall fistula develops, enabling the infection to spread. Rarely, the first complaint of a patient whose pulmonary symptoms are minimal may be a cutaneous lesion that arises as a result of hematogenous dissemination.

The lungs may develop multiple abscesses, bronchiectasis, pleural and pulmonary adhesions, and pleural thickening (Color Fig. 40-1). Bronchial fistulas, emphysematous blebs, dense fibrosis, empyema, and extensions to the pericardium also occur. The spread of the infection to regional bones can produce destructive lesions. The pulmonary lesions are indurated, yellow-white masses with hard, fibrous tracts and soft, pus-filled centers. The initial acute inflammatory response evolves into suppurative granulomas surrounded by inflamed granulation tissue. Foamy macrophages account for the yellow color seen, and the characteristic sulfur granules are found in the midst of neutrophils (Color Fig. 40-2). The granules or grains are dense, 30- to 400-μm rosettes of branching filaments, with club-shaped bodies at the periphery and filaments in a fairly radial distribution (Color Fig. 40-3). Actinomycetes usually stain best with the Giemsa and with the Brown-Hopps (Color Fig. 40-4) and Brown and Brenn tissue Gram stains. The filaments are best visualized with Gomori methenamine silver (GMS) stain. The agents of eumycetomas and botryomycosis also produce conglomerated masses of organisms in a matrix, but they can be differentiated from actinomycosis by the lack of the characteristic clubbed peripheral fringe of the actinomycotic granule and by the nature of the organism within it. The granule represents a mineralized mycelial mass cemented by host calcium phosphate produced by the phosphatase activity of tissue inflammation. The surface clubs are filaments encased in polysaccharide-protein complexes. A tentative diagnosis of actinomycosis can be made by finding the granules within a purulent exudate. A Gram stain of the granule reveals the delicate, intertwined, gram-positive filaments. *Actinomyces* organisms can be cultured from sputum, biopsy specimens, and autopsy material.

NOCARDIOSIS

Among the Nocardiaceae, there are several genera of medical importance: *Nocardia, Mycobacterium*, and *Corynebacterium*. In this chapter, the focus is on *Nocardia*, the organisms that cause nocardiosis.

Nocardiosis occurs mainly in immunocompromised patients. Most commonly, the acute form of the infection occurs in patients with lymphoreticular malignancy, systemic lupus erythematosus, nephrotic syndrome, or pulmonary alveolar proteinosis and in those receiving corticosteroids.[6–8] Less often, it is a chronic pulmonary infection of apparently immunocompetent persons.[9]

Nocardiosis is produced by the soil-inhabiting actinomycetes, *Nocardia asteroides, Nocardia brasiliensis*, or *Nocardia caviae (Nocardia otitidis-caviarum)* and rarely by *Nocardia transvalensis*.[10] Three clinical syndromes are associated with these agents: primary cutaneous, primary subcutaneous, and primary pulmonary and systemic infection. In all syndromes, the *Nocardia* organisms are usually introduced through the respiratory tract; traumatic introduction occurs rarely. The genus *Nocardia* includes 20 species, and most are soil or water organisms with a worldwide distribution. *N. asteroides* is by far the most common cause of pulmonary and systemic nocardiosis.

The presenting symptoms in nocardiosis may include fever, anorexia, malaise, weight loss, pleurisy, productive cough, and hemoptysis. Some patients manifest tracheitis, bronchitis, pleuropulmonary fistulas, or a disseminated miliary disease with diffuse organ involvement. The brain is affected in about one third of all patients, and neurologic symptoms can dominate the clinical picture. Less common presentations mimic tuberculosis, carcinoma, or lung abscess. The chest x-ray findings are nonspecific; they may consist of fluffy infiltrates or irregular densities, subpleural plaques, single or miliary nodules, single or multiple abscesses, cavitation, or alveolar or interstitial reticulonodular infiltrates.[11]

Natural immunity to *Nocardia* species is high, and aspiration of *N. asteroides*, a common soil organism, is frequent. There is a low-level reactivity in the general population to skin test antigens. Transient colonization of bronchi without clinical symptoms is well documented. The alveolar macrophages of persons with normal, healthy immune systems readily eliminate the organism.

Grossly, pulmonary nocardiosis consists of a single or multiple scattered abscesses. The lungs may have a combination of pneumonic consolidation and cavities. Pleural involvement manifests as fibrinous pleurisy, empyema, multiple abscesses, or effusions with fibrosis. Infarction and atelectasis are rare. Hilar adenopathy is common. The abscesses are typically soft and friable, and on cut section, they usually contain granular, gray-white material resembling liquefactive necrosis or tumor tissue (Fig. 40-1).

Microscopically, the lesions contain central liquefactive and suppurative necrosis (Fig. 40-2), lymphocytes, plasma cells, numerous histiocytes, and giant cells in a loose granulomatous arrangement. Norcardiosis elicits less of a host response than actinomycosis, producing less fibrosis and scarring. Unlike actinomycosis, *N. asteroides* does not usually produce granules, nor is there a tendency to form sinus tracts. *N. brasiliensis* and *N. caviae* do have some propensity to form granules and sinus tracts. The grains formed by *N. brasiliensis* are white to yellow, soft to firm, and lobed. The grains of *N. caviae* are white, soft, and amorphous. Only rarely does nocardiosis produce distinct granulomas with central necrosis. Caseating granulomas usually indicate coinfection with *Mycobacterium tuberculosis*.

Nocardia organisms are easily missed in routine microscopic examination, because they do not stain well with hematoxylin and eosin. Like *Actinomyces* organisms, *Nocardia* organisms are gram-positive, filamentous bacteria (Color Fig. 40-5). *N. asteroides* and *N. brasiliensis* are acid-fast; most other *Nocardia* species are not.

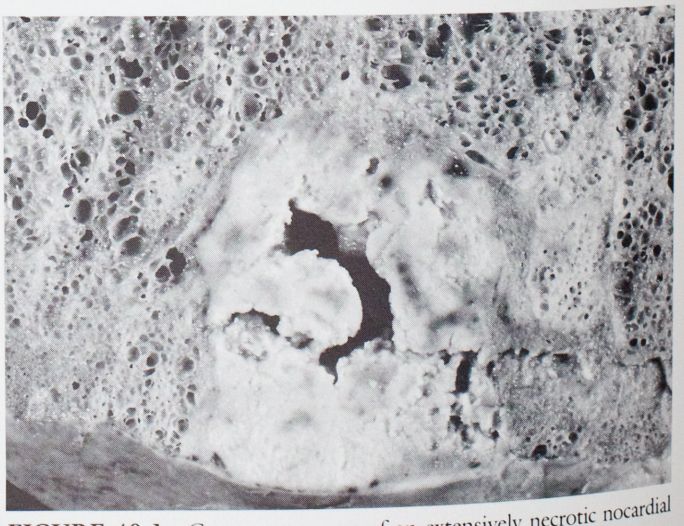

FIGURE 40-1. Gross appearance of an extensively necrotic nocardial abscess in lung tissue and pleura. (Contributed by the editor.)

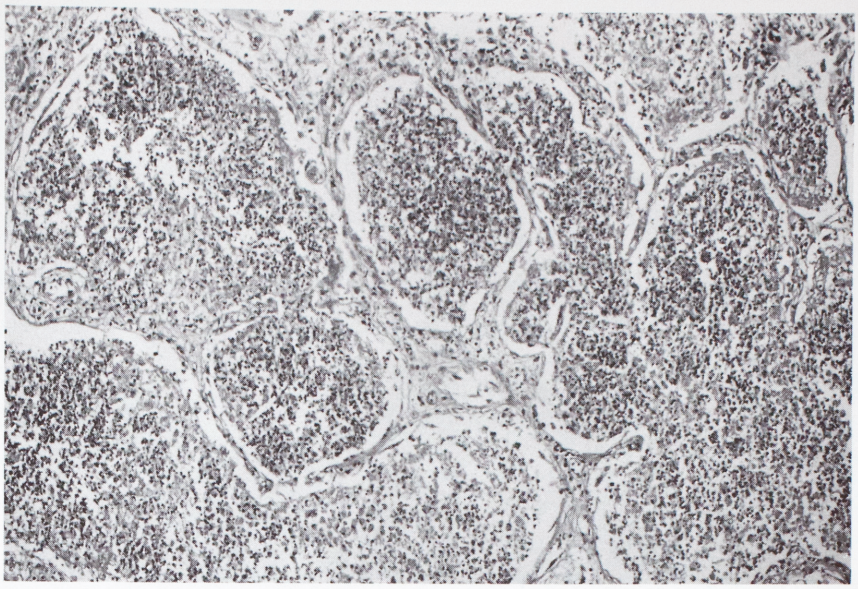

FIGURE 40-2. A microscopic view of nocardiosis shows intense suppuration of the alveolar tissue. (H & E stain; low magnification; contributed by the editor.)

Because *Nocardia* organisms retain fuchsin less tenaciously than *Mycobacterium* organisms, a modified acid-fast stain (*i.e.*, Fite-Faraco, Coates-modified Fite) that uses peanut oil and substitutes 1% sulfuric acid for acid alcohol is used (Color Fig. 40-6*A*).[12,13] *Nocardia* organisms also stain with GMS if the staining time is extended (Color Fig. 40-6*B*), but the organisms do not stain with periodic acid-Schiff or Gridley fungus stains. *Nocardia* organisms characteristically appear as delicate, multibranched filaments with beaded chains of bacillary bodies. The branching tends to be at right angles to the main axis. *N. asteroides* sometimes aggregates into pseudogranules, but these are loosely organized compared with the grains of actinomycosis.

In high-risk patients, nocardiosis should be suspected if soft tissue swellings or neurologic symptoms develop in conjunction with a chronic or recurrent pulmonary infection. Other agents, such as *Aspergillus* species, *Cryptococcus* species, *Toxoplasma* species, and *M. tuberculosis* can produce combined neurologic and pulmonary symptoms in immunocompromised patients and must be excluded.[14]

A Gram stain with a modified acid-fast stain of pus or sputum can establish the diagnosis. *N. asteroides* is not fastidious; it grows readily at 37°C on ordinary laboratory media without antibiotics. It grows equally well under aerobic and anaerobic conditions.[15]

Humoral antibody tests are not clinically useful, because there are many cross reactions with species of *Mycobacterium* and *Streptomyces*. Testing for a specific *Nocardia* antigen appears useful, but there is no available skin test.[16]

Before sulfonamide therapy for nocardiosis was implemented, the disease was universally fatal. *Nocardia* organisms are sensitive to several antibiotics, but the prognosis is still poor, especially if metastasis has occurred. The most common sites to which *Nocardia* organisms disseminate are the skin and central nervous system.

STREPTOMYCETACEAE

Streptomyces bacteria are aerobic actinomycetes that are primarily agents of subcutaneous infection. They can produce a clinical and pathologic entity that may be difficult to differentiate from the actinomycetoma caused by Actinomycetaceae. *Streptomyces* organisms are extremely common members of the soil flora. Nonpathogenic species of *Streptomyces* are frequently isolated from sputum and other respiratory specimens and must be differentiated from pathogenic bacteria. *Streptomyces somaliensis* is a well-known agent of actinomycetoma. It is most prevalent in parts of East Africa and the Middle East. This bacterium is rarely documented in North or South America, except in Mexico, where it accounts for about 3% of patients with actinomycetoma.

Although this agent belongs to a different family of bacteria, the clinical disease is essentially the same as that caused by members of the Actinomycetaceae, but the infections caused by *Streptomyces* species are slightly less aggressive. The openings of the sinus tracts are not raised or indurated, and bone is not destroyed extensively, although muscle can be heavily invaded.[17]

The gross and microscopic lesions are similar to those caused by members of the Actinomycetaceae. The grains of *Streptomyces* organisms tend to be large (*e.g.*, 2 mm) and yellow. The granules are found in the center of suppurative granulomas, and they display an amorphous center that is light purple with pink patches and dark filaments at the edge (Fig. 40-3). Sharp clubs are not seen at the edge of the granules. The filaments of *Streptomyces* species are shorter and broader than those of *Actinomyces* organisms (Color Fig. 40-7). Because pulmonary cases are not well documented and I have no pulmonary cases in my files, the figures depicted are from a patient with subcutaneous infection caused by *Streptomyces* organisms.

The diagnosis of *S. somaliensis* infection is made by culturing the organism. It is differentiated from *Nocardia* organisms by inoculating plates of casein, xanthine, and tyrosine agars; incubating them for as long as 2 weeks at 30°C; and observing for hydrolysis.

In addition to the Actinomycetales, Nocardiaceae, and Streptomycetaceae families, members from other families of the order Actinomycetales can produce actinomycetoma of the skin, mucous membranes, and subcutaneous tissues. These include species of *Actinomadura*, *Nocardiopsis*, and *Dermatophilus*. They are not known to produce significant pulmonary disease.

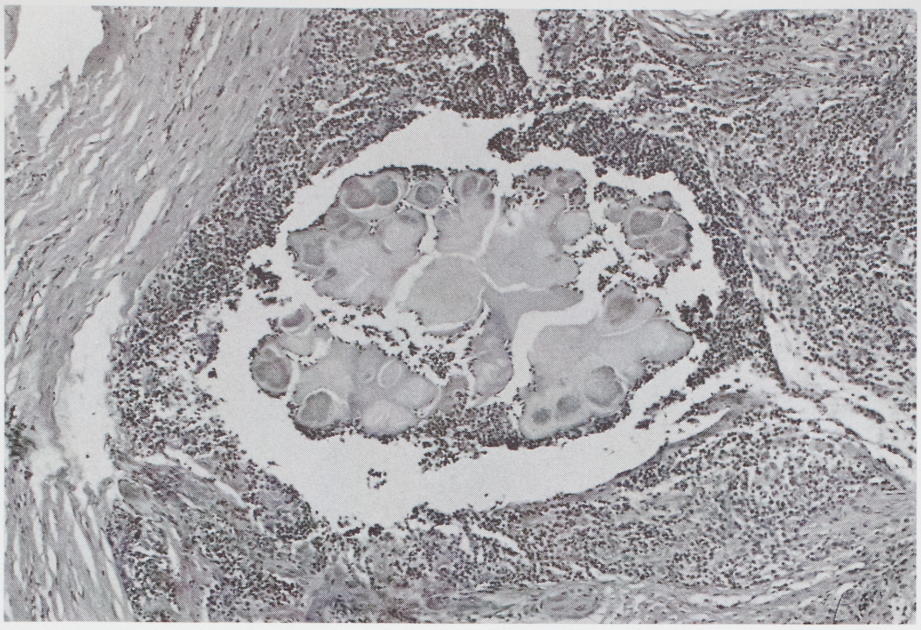

FIGURE 40-3. There is a grain of *Streptomyces* in the center of a suppurative granuloma in the subcutis. Notice the amorphous center and the darker patches at the blunted edges. (H & E stain; low magnification.)

BOTRYOMYCOSIS

Botryomycosis is a chronic, purulent, and granulomatous bacterial infection that usually involves the skin and subcutaneous tissue. The bacteria are commonly introduced through trauma. Ulcers and draining sinuses contain granules in a purulent exudate. The granules contain nonfilamentous bacteria.

Botryomycosis can present as a primary infection of the tongue, nasal septum, or lung, and it can be a disseminated infection.[18] In debilitated patients, dissemination to the liver, lung, kidney, brain, prostate, lymph nodes, and bone occurs.[19] Botryomycosis is more common in patients with obesity compounding diabetes, alcoholism, poor hygiene, general debility, or acquired immunodeficiency syndrome.[20]

The most frequent causative bacterium of botryomycosis is *Staphylococcus aureus*. Other bacteria known to cause botryomycosis include *Staphylococcus epidermidis, Streptococcus* species, *Pseudomonas aeruginosa*, *Escherichia coli, Proteus vulgaris, Neisseria mucosa*, *Actinobacillus lignieresii, Bacteroides* species, and *Propionibacterium acnes*.[21–24] The specific identification requires culturing of the organism.

Botryomycosis affects patients between 9 months and 80 years of age, and three males are affected for every two females.[25] Pulmonary botryomycosis is associated with a chronic pneumonia syndrome. The clinical manifestations are nonspecific, variable, and generally mild. Fever and pleuritic chest pain are common; some patients manifest only recurrent hemoptysis. There is no specific x-ray finding; the x-ray films can show a discrete mass, cavitary lesion, areas of consolidation, or a diffuse infiltrative process. Primary pulmonary botryomycosis is more common in the upper lobes and usually occurs unilaterally. Botryomycosis must be differentiated from actinomycosis, nocardiosis, and Kaposi sarcoma.

The mechanism of granule formation is not well understood, but it has been experimentally produced.[26] It probably correlates with an immune defect or an unusual tissue response for handling bacteria. Decreased T- and B-lymphocyte function has been observed in some patients.[27] Some investigators believe that foreign bodies can play a role in the production of botryomycosis, and I have seen cases that support this concept.[28,29] A combination of factors, including the virulence of the microorganisms, their numbers, and the host resistance, is likely.[30]

The botryomycotic lung displays scarring and abscess formation (Color Fig. 40-8), and a cut section reveals loculated, fibrous, pus-filled masses containing sandlike particles (*i.e.*, botryomycotic granules). Microscopic sections contain granules that are virtually indistinguishable in hematoxylin-and-eosin–stained sections from those of actinomycosis or eumycetoma. Clumps of bacteria are surrounded by an amorphous eosinophilic coating, a condition called the Splendore-Hoeppli phenomenon (Color Fig. 40-9; Fig. 40-4). These granules occur within microabscesses that are surrounded by desmoplasia.

The granules of botryomycosis are differentiated from those of actinomycetoma and eumycetoma with special stains. The Brown-Hopps and Brown and Brenn tissue Gram stains and the GMS stain demonstrate nonfilamentous bacteria in patients with botryomycosis. Granules of eumycetomas contain true fungi that belong to the class Eumycetes. There are at least 16 species of fungi that can cause eumycetoma. The fungi in eumycetomas commonly have septate hyphae that are at least 2 μm wide. The hyphae frequently are distorted, bizarre in form and size, and usually contain chlamydospores at the periphery of the granule. Eumycetes stain readily with fungal stains including GMS, periodic acid-Schiff, and Gridley fungus. There are no descriptions of eumycetomas in human lungs.

There are three ways to establish the diagnosis of botryomycosis:

1. Identify granules in pus from draining sinuses.
2. Culture the bacterium from ulcers or exudates of patients with the clinical findings of botryomycosis.
3. Recognize granules in fine needle aspirates, biopsies, or autopsy specimens.

The diagnosis can be crucial to proper treatment. The matrix in the granules is thought to be a barrier that offers some degree of protection to the bacterium. Ideally, culture and sensitivity studies

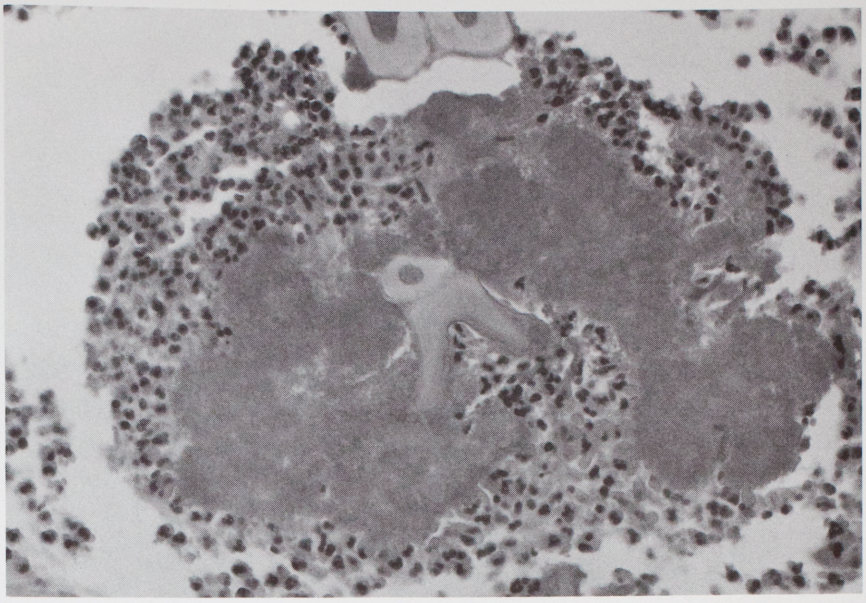

FIGURE 40-4. A lesion of botryomycosis contains plant material in its center. The material may have contributed to the production of the lesion. (H & E stain; intermediate magnification.)

should be done, and antibiotic treatment should be based on the sensitivity studies. In practice, several weeks may be needed to heal because of the inability of the antibiotic to penetrate to the organisms sequestered in the grains. Surgical excision of resectable lesions (*i.e.*, lobectomy) with prolonged antibiotic therapy usually results in a complete recovery.

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