Fulminating Pulmonary Nocardiosis*

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Nocardiosis is a chronic suppura-
tive infection which usually mani-
ifests itself by involvement of the lungs, skin
or brain, and which in man is almost always
due to Nocardia asteroides.

The concept of this disease goes back to
the late 19th century when Nocard de-
scribed a fungus in connection with cases
of bovine farcy, a disease of cattle charac-
terized by multiple cutaneous abscesses,
draining sinuses, emaciation and pulmo-
nary involvement. Subsequent writings on
nocardiosis have taken the form of case
reports or excellent reviews such as those
of Henrici and Gardner,† Benbow et al.,
Hager et al.,† Tucker and Hirsch, and
Ballenger and Goldring.

The relative rarity of the disease together
with its treatable nature emphasize the
importance of calling it to the attention of
the practicing physician periodically. As
Glover and associates have stated, the dis-
ease is not new, but it is highly likely to go
unrecognized. This is amply attested by the
proportion of fatalities among the reported
cases, most of which have been diagnosed
either in the immediate antemortem period
or not until post-mortem examination.

These several facts plus the review of
some important practical considerations
concerning the disease and the responsible
organism will serve as apologia for yet an-
other case report.

CASE REPORT

A 40-year-old Negro man entered the hospital
with a two-day history of left pleuritic chest
pain accompanied, on the day prior to admi-
mission, by fever, shaking chills and cough produc-

dive of moderate amounts of yellow sputum. His
past history indicated only a background of alco-
holism and an episode of bronchopneumonia
treated with good results at this hospital some
seven months prior to his present admission. No
specific organism was recovered from either
blood or sputum cultures at that time.

Physical examination: Blood pressure 130/90,
pulse 120 and regular, respirations 24 and shal-
low, temperature 102°F. rectally. His skin was
hot and moist. The chest demonstrated an in-
spiratory lag on the left. The lungs revealed
dullness with increased tactile fremitus, bronchial
breath sounds, coarse rales, and a pleural friction
sound over the left lower lateral chest. The
remainder of the physical examination was not
remarkable.

Laboratory: The white blood cell count was
12,000 per mm³ with 76 per cent segmented
forms and 10 per cent band forms. The hemato-
crit was 38. Urinalysis was normal, and the BUN
which was 32 on admission fell to normal levels
after hydration. A total protein with A/G ratio
and a fasting blood sugar were normal. A BSP
revealed 15 per cent retention in 45 minutes. His
admission chest x-ray film (Fig. 1) showed an
area of consolidation in the left lower lung field.
The smear of the sputum revealed mainly Gram-
positive diplococci, but the culture of that speci-
men subsequently grew out only three plus colon
intermedius in addition to normal flora.

Hospital Course: Several features of the hos-
pital course are graphically presented in Fig. 2.
He was initially treated for a period of 36 hours
with an investigative intramuscular tetracycline
derivative, but on the night of the second day,
his temperature rose acutely and the medical
officer-of-the-day discontinued this antibiotic and
started penicillin which he then received for a
period of two weeks. Chloramphenicol was added
on the sixth day at the time of another tempe-
rature rise. His chest x-ray film showed almost
complete consolidation of the left lower lobe on
the fourth day, but by the eighth day this
showed definite evidence of clearing though there
now appeared a right basal infiltrate (Fig. 3).
Four days later this area revealed clearing, but
a new infiltrate was seen just above the right
hilum. By the 18th day, a repeat chest x-ray film,
following four or five days of a hectic tempera-
ture course, showed marked right upper and
mid-lung field infiltrates (Fig. 4). Repeat sputum
and blood cultures were not helpful.
On the evening of the 19th day, he was very toxic, with marked tachypnea, ineffective cough, and high fever. A tracheostomy was done and large quantities of greenish-yellow sputum were obtained. Considerable improvement in his respiratory pattern occurred. In the absence of cultural direction for selection of antibiotic therapy, he was empirically placed on polyvalent coverage, and parenteral hydrocortisone was added with the thought that this drug might help to tide him over until the new antibiotic regimen could take effect.

Twelve hours after his tracheostomy, he showed marked improvement with a slower respiratory rate, decrease in fever (? due to corticosteroids), and some clearing of his lungs clinically, though bilateral physical findings persisted. At this time, the culture of the sputum obtained the previous evening by tracheostomy showed small, 2-3 mm. dull white colonies sitting on the blood agar like puff balls. These were subsequently shown to be fungus colonies. An x-ray film taken at this time showed even further involvement of the lungs and in spite of all therapeutic measures the patient died.

At necropsy, the patient was found to have confluent abscess formation in all lobes with the process being most marked in the right upper lobe. Sections of this area revealed tissue invasion by a fungus (Fig. 5). There was no evidence of involvement of the central nervous system.

The organism responsible for this infection was identified as a probable Nocardia by the hospital laboratory. Further identification was obtained through the assistance of Miss Charlotte Campbell of the Walter Reed Army Institute of Research (Walter Reed Army Medical Center), Drs. Chester Emmons and H. F. Hasenclaver of the National Institutes of Health and Dr. Ruth E. Gordon of the Rutgers University Institute of Microbiology. It was noted that the organism formed aerial hyphae and failed to hydrolyze casein and did not utilize tyrosine. Consequently the culture was identified as representing a strain of Nocardia asteroides.

**Mycology**

In the past there has been considerable taxonomic confusion with respect to the Nocardia. As mentioned above, Nocard described an organism of this genus in association with bovine farcy, but Eppinger was the first to describe a human infection due to this agent and the organism he recovered from the brain abscess of his patient was called Cladothrix asteroides.

The place of the Nocardia in the biologic scheme is sometimes confused and it is well to give a broad outline such as has been done by Hiddlestone. Accordingly, a schema such as the following should prove helpful in orientation:

I. Thallophyta
   A. Algae
   B. Fungi
      1. Eumycetes
         2. Pseudomyces
            a. Myxomycetes
            b. Schizomycetes
               1. Eubacteriales
               2. Actinomycetales
                  a. Streptomycetaceae
                  b. Mycobacteraceae
                  c. Actinomycetaceae
                     (i.) Actinomycetes
                     (ii.) Nocardia

Though Bergey's Manual lists 33 species of Nocardia, only seven have been found in association with human disease, and of these only two have been responsible for systemic infections. In systemic infection, *N. asteroides* is so overwhelmingly predominant as the etiologic agent that any discussion of human systemic nocardiosis can legitimately be limited to it.

The organism is aerobic and easily but slowly cultured on all the common laboratory media. It will occasionally form pigmented waxy colonies which have been likened to piled up candle drippings, while at other times, and with other strains (as in the case reported above), the production of

**FIGURE 1:** Admission chest x-ray film.
aerial chalky white mycelia is more characteristic. The case reported also demonstrates that on occasion the organism may grow with surprising rapidity. Zinsser’s Bacteriology describes the Nocardia in cell cultures as consisting of delicate branching hyphae, but emphasizes the important point that in routine culture they tend to fragment into bacillary and coccoid forms leading to easily understood confusion with non-fungal organisms.

On staining, the organism is usually acid-fast and the suggestion is frequently made that dilute sulfuric acid should be used instead of the usual acid-alcohol in order to bring out the acid-fastness of the organism. Drake and Henrici, however, emphasize that smears made directly from sputum tend to be acid-fast even to acid-alcohol, so that variations in the acid-fast staining technique can be reserved for smears made from cultures. It is apparent that the cultural characteristics and staining properties of this organism, when found in a clinical setting of pulmonary infection, make for frequent confusion with tuberculosis. The confusion is ordinarily further compounded since after the initial sputum smear shows acid-fast organisms, daily sputum collections are then sent to the laboratory for tubercle bacillus culture. The absence of tubercle bacilli in the patient means that these cultures will be reported negative for tuberculosis and additionally the concentration methods used in tuberculosis cultures may destroy the Nocardia and consequently these organisms will not be reported from the laboratory either. Bernstein and colleagues, however, have reported three cases in two of which there was growth of Nocardia even after tubercle bacillus concentration methods (3 to 4 per cent NaOH and incubation for 30 minutes) had been used.

Peabody and Seabury point out several reasons why the organism is frequently missed: (1) it breaks into the bacteria-like fragments mentioned previously which are seen on smear, but the organism is ordinarily so slow growing that cultures are not saved until they would have become positive since they have usually been submitted as routine bacterial cultures rather than fungal cultures, (2) it is acid-fast, and this in combination with a pulmonary lesion will satisfy those who do not require cul-

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**Figure 2:** Graphic summary of hospital course.
tural identification, that tuberculosis is present, and (3) if the sputum has been submitted for tubercle bacillus culture, the Nocardia (if it is not destroyed by the concentration methods used) grows too rapidly and is too pigmented to be considered a *Mycobacterium tuberculosis*, and consequently it is discarded as a saprophytic Mycobacterium.

Wichelhausen and co-workers, in a case reported from this institution eight years ago, made the important point that when actinomycosis and nocardiosis are being considered in the differential diagnosis, it is important to do fungus cultures early since these fungi may well be affected by the antibiotic therapy which is started after the initial routine cultures have been taken. This is in marked contrast to most other fungi, which are so resistant to antibacterial antibiotics that cultures can be done at any time with a good percentage yield of organism recovery.

A further point of importance is that, as emphasized by Peabody and Seabury, and Katz, the mere recovery of this organism, especially in patients with chronic bronchopulmonary disease, is most difficult to interpret. It is undoubtedly much more commonly a simple saprophyte rather than a pathogenically significant organism, and demonstration of tissue invasion is the most positive indication of its etiologic significance in a given infection.

**The Disease in Man**

Nocardiosis in man usually presents as a pulmonary infection with a tendency to chronicity though acute varieties are known, and indeed our patient progressed to a fatal termination in less than one month. We feel that the pulmonary infiltrates which were present early in our patient's course were not caused by Nocardia since they responded so rapidly to therapy, in a fashion which is not at all typical of fungal diseases.

In the lung, the radiologic features are variable and non-specific and may resemble tuberculosis, pneumonia, or lung abscess. It has also been reported that the incidence of empyema may be as high as 25 per cent and may be seen, as with emphyema of other etiologies, in association with bronchopleural fistula. Probably the most common pulmonary picture is that of a confluent bronchopneumonic process which may progress to frank consolidation frequently with subsequent pleural involvement.

![Figure 3](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21407/)

**Figure 3**: Chest x-ray film one week after admission showing clearing of original infiltrate and development of right basal infiltrate.

**Figure 4**: Chest x-ray film showing spread of involvement to right upper lobe.
The picture in the central nervous system is that of brain abscess and indeed is a frequent enough occurrence so that it should be suspected as the etiologic agent in every case of brain abscess. Rivera and Perez\(^{18}\) state that cerebral involvement results in 100 per cent fatality, but Krueger and associates,\(^{19}\) in an earlier article, reported a successfully treated patient who had pulmonary nocardiosis complicated by a metastatic cerebral abscess.

Bobbitt and colleagues\(^{20}\) have listed the known clinical presentations as follows: tracheitis, bronchitis, pleuropulmonary fistula, pneumonia, peritonitis, meningitis, ischiorectal abscess, perirectal abscess, keratoconjunctivitis, endocarditis, miliary abscesses in the thyroid, liver, spleen, lymph nodes, kidneys, adrenals, intestines and skeletal muscles.

The clinical syndrome is highly variable and, as with all infectious processes, is modified by host resistance, pathogenicity of the organism in question, and duration of the disease.

The pathologic process evoked by the Nocardia has been studied by McCarthy\(^{21}\) who reported that in experimental infection of the eye in animals, microabscesses were formed. Cruz and Clancy\(^{22}\) report caseation necrosis without giant cells, a marked surrounding cellular reaction, but no fibroblastic reaction. The necrotizing nature of the pathologic process, without local containment by fibrotic reaction, explains the widespread crossing of fascial planes referred to by Wichelhausen and her group.\(^{18}\)

**TREATMENT**

The treatment of nocardiosis is both surgical and medical. The surgical aspect is directed essentially toward the treatment of abscesses and empyema cavities according to the well-established surgical principles of incision and drainage, with the realization that the abscesses may often cross fascial planes as mentioned earlier.

The history of the medical treatment of this infection is substantially that of the history of antimicrobial agents in general. In the early part of this century, iodides and thymol were used without great success. With the advent of the antibiotic era, practically all the known antibiotics have been tested for activity against the Nocardia. These extensive clinical and bacteriologic investigations have left little doubt that sulfadiazine is the agent of choice.

**Figure 5:** Photomicrograph of necropsy specimen of lung tissue showing bacillary forms of fungus.
Rivera and Perez's patient responded to chloramphenicol even though in vitro studies indicated that the organism was resistant to this drug. It is worth noting that our patient probably developed his nocardial infection while on a combination of penicillin and chloramphenicol since we are disinclined to believe that his initial pneumonia was due to the fungus, though, as noted in the protocol, no specific organism was isolated on admission.

The excellent study of Strauss and coworkers showed the dichotomy which may exist between in vitro and in vivo studies. His results indicated that the tetracyclines and myvizone (a third line antituberculosis drug) showed excellent inhibition, whereas sulfadiazine provided only partial inhibition against some strains of Nocardia tested in vitro. However, in vivo experiments showed that sulfadiazine provided almost perfect protection against intraperitoneal mouse inoculation while under these circumstances tetracyclines and myvizone afforded only partial protection.

The same type of experience is reported by Runyon who found complete inhibition in vitro by chlortetracycline and by streptomycin and sulfadiazine whereas in vivo tests demonstrated sulfadiazine to be the only drug of value.

Because of the many features of the disease which resemble tuberculosis, isonicotinic acid hydrizide has been studied for activity against Nocardia. However, Dobek states that in his experience 1200 to 1500 mcg./ml. were necessary to inhibit growth under his experimental conditions.

He also reports that this drug has no influence on the course of experimentally induced nocardiosis in vivo.

Sanford also reports extensive investigations with several drugs. He tested 18 strains of Nocardia with erythromycin, novobiocin, cycloserine, polymyxin B, penicillin, neomycin, streptomycin and tetracycline in vitro. Erythromycin and novobiocin were most effective in his studies, but he sums up the current attitude with regard to the treatment of nocardiosis by advising caution in interpreting in vitro tests since there is ample clinical evidence that sulfadiazine is the effective drug.

Peabody and Seabury recommend 4 to 6 gm. of sulfadiazine combined with 2 gm. of a broad-spectrum antibiotic. This regimen should provide a sulfonamide concentration of 10 mgm per cent which should be adequate. He also recommends that treatment be continued for several months after clinical manifestations have cleared before the patient is considered cured.

**Summary**

1. Nocardiosis is a chronic infection of skin, lung, and brain caused in almost all cases by *Nocardia asteroides*.
2. A fatal case of pulmonary nocardiosis which probably developed while on antibiotic therapy is reported.
3. The mycology, pathology and clinical picture are reviewed.
4. Sulfadiazine in a dose of 4 to 6 gm. daily is the drug of choice and should probably be combined with a broad-spectrum antibiotic.
5. Surgical drainage is a necessary concomitant in the presence of abscesses and empyema.

**Resumen**

1. La nocardiosis es una enfermedad crónica de la piel, pulmones y del cerebro, causada en casi todos los casos por *Nocardia asteroides*.
2. Se relata un caso de nocardiosis fulminante del pulmón que se desarrolló mientras se hacía tratamiento con antibióticos.
3. Se presentan los datos de micología, patología y cuadro clínico.
4. La sulfadiazina a la dosis de 4 a 6 gms. por día es el tratamiento de elección y probablemente debe combinarse con el uso de antibióticos de amplio espectro.
5. La canalización quirúrgica se necesita cuando hay absceso y empiema.

**Resumé**

1. La nocardiose est une infection chronique de la peau, du poumon ou du cerveau, provoquée dans presque tous les cas par *Nocardia asteroides*.
2. L’auteur rapporte un cas de décès par nocardiose pulmonaire que s’est probablement développé malgré le traitement antibiotique.
Zusammenfassung

1. Die Nocardiosis stellt eine chronische Infektion von Haut, Lungen und Gehirn dar und wird in fast allen Fällen durch Nocardia asteroides hervorgerufen.


3. Bericht über die Mykologie, Pathologie und das klinische Erscheinungsbild.

4. Sulfadiazin in einer Dosierung von 4-6 g täglich ist das Mittel der Wahl und muß aber wahrscheinlich kombiniert werden mit einem Breitband-Antibioticum.

5. Chirurgische Drainage ist eine notwendige zusätzliche Maßnahme bei Bestehen eines Abszesses oder Empyems.

References


