CASE REPORTS AND TECHNICAL NOTE

NOCARDIOSIS WITH MULTILOCULAR CEREBELLAR ABSCESS
REPORT OF A CURED CASE
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Nocardia is an aerobic, partially acid-fast actinomycete, pathogenic to man and animals. The name "Nocardia" was given in memory of Nocard who in 1888 discovered this organism as the cause of bovine farcy. There are various subspecies of Nocardia, the most common being Nocardia asteroides—also known under the synonyms Cladothrix asteroides, Streptothrix eppingeri, Oospora asteroides, and Actinomyces asteroides.

Even though this organism is a ubiquitous inhabitant of the soil, human nocardiosis appears to be a remarkably rare disease and records of only 54 such cases were found in the literature. The primary lesion is usually found in the lungs and bronchopulmonary lymph nodes, occasionally in the subcutaneous tissues (as the result of accidental penetrating injury), or in the gastrointestinal tract. The infection then spreads by the hematogenous route and frequently produces metastatic intracranial lesions, notably brain abscesses. Among the 54 recorded cases there was proven intracranial involvement in at least 17 cases. The mortality rate of human nocardiosis is high; so far only one instance is known of cured intracranial Nocardia infection. In this case, described by Jacobson and Cloward, a 28-year-old psychotic Japanese woman was proved to have meningitis caused by Nocardia asteroides. The patient recovered after being treated with large doses of sulfadiazine and intramuscular and intrathecal injections of penicillin and streptomycin, combined with ventricular drainage.

Facing the almost hopeless prognosis of intracranial nocardiosis, additional experiences must be gathered and it therefore appears worth while to record any further case of successful treatment. In the following we wish to describe in detail a case of nocardiosis with multilocular cerebellar abscess, terminating in recovery.

851-446. W. van S., a 48-year-old bread salesman, was admitted to Blodgett Memorial Hospital, Grand Rapids, Michigan, on Jan. 20, 1951. Approximately 10 weeks previously, he had begun to complain of general lassitude, and pain in the left shoulder and epigastrium. The condition of his shoulder was diagnosed as calcifying bursitis and was treated by roentgen irradiation and aspiration. The epigastric pain, which occurred chiefly on fasting, was relieved by ingestion of food and antispasmodic drugs. Eight weeks prior to admission, a persistent hacking cough developed, productive of scanty, nonhemorrhagic, nonpurulent sputum.

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† Since this paper was submitted for publication another case of successful treatment of cerebral nocardial infection has been reported (Krueger, E. G., Norsa, L., Kenney, M., and Price, P. A. Nocardiosis of the central nervous system. J. Neurosurg., 1954, 11: 226–233).
There was no fever. Roentgenograms of the chest revealed infiltrative lesions in both lower lung fields, supposedly virus pneumonia. After unsuccessful treatment with penicillin and aureomycin for 16 days, bronchoscopy was performed but this procedure yielded no further information. Thereafter, his general condition deteriorated; he complained of nucho-occipital and frontotemporal headaches, nausea and, finally, of failing vision.

Examination. The patient appeared chronically ill, irritable and anxious. Temperature was 98.6°, pulse rate 84, respiratory rate 18, and B.P. 136/80. Physical examination of the chest revealed no abnormal findings. There was slight epigastric tenderness. The prostate gland was moderately enlarged without signs of malignancy. The left shoulder was "frozen" because of previous bursitis. Neurologic findings were not remarkable.

Urine was normal. RBC 4,380,000, WBC 6,650, Hb. 13.3 gm.—86 per cent, eosinoph. 1, stabs 2, segment 85, lymphs 12. Blood Kahn negative. Serum albumin 3.76; globulin 2.74. Blood N.P.N. 27; fasting blood sugar 129.

Roentgenograms of the chest showed an infiltration in the left lung at the level of the 5th rib near the heart. The left hilar shadow was enlarged. The right lung was normal.

The sputum contained no acid-fast organisms but on culture there was heavy growth of Streptococcus viridans and scanty growth of Staphylococcus aureus and nonpathogenic yeasts.

Roentgenograms of the upper gastrointestinal tract disclosed a peculiar rugal pattern compatible with the diagnosis of gastritis or duodenitis. The duodenal bulb was deformed suggesting ulcer (or prolapsed gastric mucosa?). On the cholecystogram there were areas of decreased density, suggestive of gallstones.

Course. At this state of the investigation no definite diagnosis could be made. It was felt that the gastrointestinal findings were probably unrelated to the pulmonary lesion, the anatomic nature of which remained obscure; the possibility of a primary bronchogenic carcinoma was considered. In the 10 days following admission, new and progressive symptoms appeared pointing to a lesion of the central nervous system. He became increasingly lethargic, depressed and refused to eat. Urinary retention occurred on several occasions. Nucho-occipital headaches and nausea were frequent and at times associated with vomiting. Finally, his pulse rate dropped to 50–60 per min.

Lumbar puncture revealed an initial pressure of 150 mm. of H₂O. The fluid was clear, colorless, and contained 1 lymphocyte; total protein 114 mg., sugar 76.9, gold curve and Kahn negative.

Neurosurgical consultation was then obtained. The emaciated patient was conscious but lethargic, indifferent and without psychomotor initiative. The right suboccipital region was tender to pressure and the neck was moderately rigid. There was mild paresis of the left 6th nerve with marked horizontal nystagmus to the left, less to right, and slight vertical nystagmus upwards. Pupils, fundi and fields were normal. A slight left lower facial weakness was noted. There was generalized hypotonicity, especially in the left arm and leg. The left extremities exhibited mild paresis, kinetic ataxia, dysmetria and slowing of diadochokinesis. When attempting to sit he fell asymmetrically to the right and backwards. There was bilateral positive Babinski sign. All other reflexes were normal. Sensory changes could not be demonstrated.

Detailed EEG study revealed numerous bursts of high voltage 1 to 2 per sec. delta waves occurring bilaterally, especially in the frontal, parietal and temporal areas, and with greater emphasis on the right side. These findings indicated either a diffuse degenerative process or a deep cerebral focal lesion. It was suggested that if the lesion was in the posterior fossa it would more likely be on the left side. Roentgenograms of the skull showed slight displacement of the calcified pineal shadow to the left.

Reviewing the case in the light of the neurologic findings, it was now assumed that the patient had multiple expanding intracranial lesions, with a large mass in the left cerebellum and possibly additional lesions in the cerebral hemispheres. Intracranial metastases from bronchogenic carcinoma appeared to be the most likely diagnosis, yet metastatic intracranial granuloma could not be ruled out. Intracranial abscess was considered improbable because of the absence of fever and of inflammatory reaction in blood and spinal fluid.
Operation, Feb. 3, 1951. Ventriculography demonstrated considerable symmetrical enlarge ment of the lateral ventricles and 3rd ventricle. The aqueduct and proximal portion of the 4th ventricle were angulated forward and displaced to the right. The ventricular fluid contained no cells and only 5 mg. per cent protein. The presence of an expanding mass in the left cerebellar hemisphere was thus confirmed but any sizeable supratentorial mass was ruled out.

Immediate left suboccipital craniectomy was done under local anesthesia. On exploratory tap of the left cerebellar hemisphere, firm resistance was encountered at a depth of 2 cm., and a little deeper, an abscess cavity was entered, yielding yellow pus. After uncapping the overlying cerebellum, the thin friable capsule of the abscess was exposed; it broke during dissection, spilling 25 cc. of pus. No sooner had the wall of the abscess been removed than another smaller abscess was brought into view and then excised. A cluster of four additional smaller abscesses embedded in thick avascular fibrous granulation tissue was removed—the deepest of these was the size of a hazelnut and had the thickest capsule. Thus all pathologic tissue was resected except a few indurated areas at the dorsal surface of the cerebellum. The multilocular abscess had occupied the entire dorsolateral part of the left cerebellar hemisphere and extended almost to the incisura tentorii. The wound was tightly closed after instilling an aqueous solution of 100,000 u penicillin into the operative cavity and another 25,000 u into the lateral ventricle.

From the day of surgery the patient was given 2,400,000 u aqueous penicillin and 2 gm. dihydrostreptomycin daily, but on the 2nd postoperative day the dose of penicillin was increased to 4,800,000 u.

Bacteriological Studies. Direct smear of the pus revealed no organisms. Culture on blood agar and Sabouraud’s media revealed a large chalky white, aerobic colony after 10 days’ incubation. It was composed of gram-positive, nonacid-fast mycelia and was classified tentatively as Nocardia asteroides. Guinea pig innoculation on two occasions failed to produce lesions. The organism was submitted to three other mycological laboratories; two reported it was typical of Nocardia asteroides and one felt it probably was Nocardia asteroides. This organism was inhibited in vitro by no less than 10 u of penicillin. Chloromycetin also was slightly inhibitory but terramycin, aureomycin and bacitracin were ineffective.

Histologic examination of the tissue removed at operation revealed multiple foci of suppuration in the parenchyma of the brain. Some were recent and other larger foci had a peripheral zone of fibroblastic proliferation forming a definite wall and replacing parenchyma of the brain. Polymorphonuclear leucocytes predominated but were mixed with lymphocytes, and a few plasma cells and eosinophiles. Granules were not seen but a McManus stain (PAS) revealed groups of gram-positive hyphae and mycelia interlacing between groups of leucocytes. Other organisms were neither seen nor cultured from the material.

Course. The patient had not only tolerated the operation well but showed immediate and progressive improvement. His sensorium cleared, temperature remained normal and signs of meningeal irritation did not develop. In an effort to achieve an optimal blood level, the dose of penicillin was doubled (9,600,000 u daily) and sulfadiazine was added in doses of 6 gm. daily; dihydrostreptomycin was discontinued after 1 week. Actually the minimum blood level of penicillin was maintained at 10 u/cc. and that of sulfadiazine was 15 mg. per cent. Under this management the patient continued to improve. He became alert and accessible, yet relapsed occasionally into a confused state. The cerebellar syndrome receded, especially in the lower extremity. The incision healed well.

He was discharged to a local hospital in Grand Haven, Michigan, on the 15th postoperative day, where the same doses of penicillin and sulfadiazine were administered for 8 additional weeks. In total he had been given 643.2 million u of penicillin and 414 gm. of sulfadiazine in 72 days; furthermore, he had received 15 gm. of dihydrostreptomycin in 8 days.

When last seen in November 1953, 2 years and 9 months postoperatively, he had no complaints referable to his nervous system and led a normal life. He had gained 20 lbs. in weight. He appeared to be mentally normal. There were still mild residual cerebellar signs in the left upper extremity and some periarthritic stiffening of the left shoulder. Chest x-rays were normal. Complete blood count, urinalysis and sedimentation rate were normal.
NOCARDIOSIS WITH CEREBELLAR ABSCESS

COMMENT

Even though the exact nature of the pulmonary lesion was not verified in our observation, it is reasonable to assume that it was a pneumonitis caused by Nocardia and probably represented the primary focus of infection. From reports of the literature one gains the impression that the pulmonary lesions, unless too far advanced, respond more readily to treatment than the cerebral lesions.

The intracranial manifestations of nocardiosis tend to be multiple because of their metastatic origin. In the early stage, purulent metastatic encephalitis develops, followed by encapsulated brain abscesses. In some of the recorded cases, including our own, the inflammatory meningeal reaction was surprisingly slight or even absent. In others, such as in the observation of Jacobson and Cloward, frank meningitis dominated the picture. The fact that the ventriculogram of their patient was normal in the presence of meningitis, may suggest associated brain swelling caused by encephalitic involvement. In more chronic lesions there is tissue necrosis, and abscess formation with surrounding nonspecific granulomatous inflammation (without epithelioid or giant cells). Multiplicity and dissemination of the abscesses account for some of the therapeutic failures, and conversely, the favorable outcome in our own case may be attributed to the circumscribed character of the lesions.

At present, the diagnosis of nocardiosis cannot be made by clinical or roentgenologic means, yet it should be suspected if a chronic infectious state is associated with lymphadenopathy, and pulmonary and cerebral lesions. If, however, as in our case, the signs of general systemic infection are minimal, the differential diagnosis against bronchogenic carcinoma with cerebral metastases must be considered.

Laboratory identification of the Nocardia species is relatively simple although proof of pathogenicity is sometimes difficult. The branching filamentous organisms are aerobic, gram-positive, partially acid-fast or nonacid-fast. They require 2–3 weeks to develop a typical colony, but grow readily at 37°C. or room temperature on a variety of simple media, including Sabouraud’s glucose agar and beef infusion glucose agar. The colonies are usually glabrous, wrinkled or granular and tough. Occasional strains produce aerial mycelia giving a powdery or chalky appearance to the colony. Most species of Nocardia are mere saprophytes, but Nocardia asteroides is pathogenic to laboratory animals and man, yet the degree of pathogenicity is variable. Intravenous injections in rabbits usually produce miliary abscesses in many organs whereas intramuscular or subcutaneous injections produce only local abscesses.

Successful treatment of cerebral Nocardia infection requires surgical removal of the focus (or foci) and extremely vigorous and prolonged chemotherapeutic and antibiotic treatment. Surgical management of a nocardial abscess differs little from that of other brain abscesses. The lesion should be radically excised; simple drainage is ineffective because of the multilocular character of the abscesses and the prolific growth of the organisms. Total excision may be admittedly impossible in the presence of multiple abscesses. At the time of operation the diagnosis of Nocardia is, as a rule, not yet made. It is therefore advisable to instill a suitable antibiotic solution into the operative site and into the ventricle in order to control other bacterial invaders.

Effective medical treatment requires determination of the drug sensitivity of the organisms. Sensitivity studies in vitro are valuable but do not necessarily permit one to predict the therapeutic effect in vivo. Runyon, Strauss, Kligman and Pillsbury investigated experimentally pathogenicity and drug sensitivity of Nocardia asteroides. These authors found that the organism is inhibited in vitro by sulfa-
diazone, aureomycin and myvizon, and to a lesser extent by chloromycetin and streptomycin. Penicillin, on the other hand, had only minimal inhibitory effect or none at all, unless given in extremely high doses.

In vivo (by means of animal protection tests), sulfadiazine again proved to be the most effective drug, whereas aureomycin and myvizon gave only limited protection. Clinical experiences with the treatment of nocardiosis have been so far too limited in number for conclusive evaluation; moreover, in most cases, several drugs have been used in combination. All authors agree, however, that sulfadiazine is effective and should be given in large doses over a long period. The opinions about penicillin are divided; most investigators consider it ineffective, yet in some of the recorded cases Nocardia was quite susceptible to this drug (e.g. in the case of Hager, Migliaccio and Young6). In our own observation the sensitivity ratio was low, i.e. no less than 10 μ of penicillin/cc. were needed to inhibit the growth of the organism. The different strains of Nocardia probably vary in their penicillin sensitivity. A similar situation obtains for aureomycin and streptomycin.

From these observations one can draw only one practical conclusion, viz. sulfadiazine must be given in combination with appropriate antibiotics in high doses over a long time. If penicillin is used, it should be administered in sufficiently large amounts to attain an effective blood level, i.e. a drug concentration that inhibits the organism in vitro. This was accomplished in our case by a daily dose of 9,600,000 μ of penicillin. Although Nocardia may be sensitive to streptomycin, prolonged use of this drug is undesirable because of its adverse side effects (on the 8th nerve).

REFERENCES