Case Reports and Technical Note

Nocardia Asteroides Meningitis

A Case Successfully Treated with Large Doses of Sulfadiazine and Urea

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Meningitis caused by nocardia asteroides has rarely been reported without a cerebral abscess and secondary spread of the infection.1,2,5,7,8,9 There has been only 1 case reported as a cure.3 The purpose of this case report is to demonstrate the value of large doses of sulfadiazine, plus the adjuvant use of urea, and problems encountered with this regimen during the apparently successful treatment of a patient with diffuse nocardia asteroides meningitis.

Case Report

History. A 50-year-old man was in excellent health until August 31, 1963, when he had an automobile accident in rural Greece. He was thrown from the vehicle to the ground, remained unconscious for about 2 hours and sustained multiple scalp lacerations. Skull films were reported negative. During the next several days, scalp cleansing and toilet were alleged to have been casual. He returned to his home in Bangkok after 8 days, feeling well. One week later he noted retro-orbital headache and decreased mental acuity. These symptoms progressed and on October 13, bilateral carotid angiograms demonstrated bilateral subdural hematomas. An osteoplastic bone flap was reflected on the right and a burr hole was placed on the left to evacuate the subdural fluid collection and membranes. The scalp at that time appeared normal and without signs of infection. Postoperatively he ran a fever to 102°F daily. Local infection was suspected and the bone flap was removed. Repeat angiograms suggested persistence of a hematoma at the right frontal pole. An additional right frontal burr hole was placed on November 1, and a small amount of subdural fluid evacuated. Diffuse meningeal infection by then was apparent in cerebrospinal fluid findings, and in the clinical response to treatment with tetracycline, antimicrobials, chloramphenicol and penicillin, given alone and in a variety of doses and combinations.

Examination. He was transferred by air to the neurosurgical service at the Upstate Medical Center on November 28, 1963. On admission, he complained of retro-orbital pain, photophobia, diffuse headache, backache and stiff neck. Blood pressure, pulse and respirations were normal. Temperature was 102°F. His mental reactions were sluggish but oriented. The scalp incisions were well healed but the skull defect was bulging and not pulsating. Neurological examination showed no evidence of localizing neurological deficit. Visual fields were full and the fundi normal. Cranial nerve function and deep tendon reflexes were normal. The general physical examination was normal. There was no demonstrable motor or sensory deficit. There were no cutaneous lesions. An x-ray of the chest was normal. The white blood cell count was 14,700 with 83% neutrophiles. Hematocrit was 37%. The spinal fluid was cloudy and contained 570 white cells (99% mononucleares) with a protein of 200 mg./100 ml, glucose of less than 25 mg./100 ml and a chloride of 122 mg./100 ml. Fasting blood sugar was 118 mg./100 ml. with a 1 plus sugar in the urine.

Treatment. During the 1st week the patient ran a fever to 101°F daily. Because a diagnosis of an infected subdural hematoma was considered, penicillin (12 million units daily) and streptomycin (1 gm. daily) were administered. On December 5, a pneumoecephalogram showed moderate symmetrical ventricular dilatation without evidence of a mass. Smears of spinal fluid from this examination were negative for organisms.

There was slow progressive deterioration in the patient's health thereafter, with continued fever to 102°F daily. Lassitude and mental deterioration increased. The addition of oxacillin (4 gm. daily) and isoniazid (600 mg. daily) did not alter the course.

On December 22, 1963, spinal fluid cultures, planted on December 2, and December 5, were positive for nocardia asteroides. The organisms were totally resistant in vitro to penicillin, tetracycline and streptomycin. They were resistant to 5 mg./100 ml. of sulfonamide but killed by 10 mg./ml. dosage.

Sulfasoxazole, 5 gm. daily, was started on December 23. It was increased to 5 gm. daily on December 28. On January 14, 1964, spinal fluid glucose was still below 25 mg./100 ml. There were 1100 cells per ml. and sulfasoxazole levels of 5 mg./100 ml. in spinal fluid were measured. His gradual deterioration continued.

On January 27, all drugs, including sulfasoxazole, were stopped and sulfadiazine was started as the sole therapy. It was given orally in 2 gm. doses, 4 times daily, with 1 gm. of sodium bicarbonate for each gram. As this was well tolerated, sulfadiazine was increased to 12 gm. a day on February 3, 1964, with a proportionate increase in bicarbonate. Acidic urine sediment with red blood cells and traces of albumin became apparent soon thereafter, and a mixture of citric acid, sodium citrate and potassium citrate was added. Microscopic hematuria and crystalluria continued with acid urine. Consequently, the daily dose of sulfadiazine was reduced first to 10 gm. (February 17) and then to 9 gm. (February 19).

On February 22, urea, 30 gm. 4 times daily, was added and the dose of sulfadiazine again increased to 12. Urea was decreased to 20 gm. 4 times daily on March 8 and discontinued on April 20. Daily amounts of sodium bicarbonate ranged from 6 to 12 gm. during this period.

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— the variations being dependent upon the degree of edema and urinary output. The patient maintained an oral intake of nearly 5000 to 6000 cc. fluid daily while receiving high doses of sulfadiazine. Spinal fluid cultures taken on February 14 and thereafter remained sterile. All other abnormalities of the spinal fluid slowly improved thereafter.

By February 10, after 2 weeks therapy with sulfadiazine, the patient's mental acuity had improved, headaches diminished and the bulging skull defect subsided.

In late February, the patient developed ileus and complained of bilateral flank pain, more in the left. Urinary calculi were first passed on March 14 and there was a succession of small calculi thereafter. An intravenous pyelogram in late April revealed bladder calculi but no significant damage in the renal collecting systems or in kidney function. When the dose of sulfadiazine was reduced to 6 grams daily, no further stones were noted. The microscopic hematuria cleared. The stones were composed of calcium oxalate dihydrate.

In early April, the dose of sulfadiazine, urea and bicarbonate were reduced and the patient was discharged from the hospital on April 10, still taking 6 grams of sulfadiazine and bicarbonate daily. He felt well and had no demonstrable clinical deficit. Fig. 1 summarizes the major sequence of events during his hospitalization.

Following hospital discharge, the patient remained well. He returned to Thailand in May and went to work immediately. Doses of sulfadiazine and bicarbonate were reduced to 4 gm. daily at that time. In July, 1964, they were further reduced to 2 gm. daily. Neurological and physical examinations in November, 1964, were normal. A letter received in the spring of 1965 indicated that good health continued.

### Discussion

Among the reported cases of nocardia meningitis, 21 different therapeutic regimens were prescribed, including antimeningoococcic serum, various sulfonamides, penicillin, streptomycin, tetracycline, chloramphenicol, isoniazid, cortisone, oleandomycin, nystatin, vancomycin, novobiocin, amphetamine and iodides. Jacobson and Cloward's case was the only one reported as a cure; it was treated with sulfadiazine, penicillin and streptomycin (sulfadiazine 6–8 grams daily, and intravenous penicillin 2.5–10 million units daily). The patient was treated for 28 days. A ventricular catheter was used for 12 days to help control increased intracranial pressure. The other cases were often associated with localized abscesses.
in the central nervous system but the final fatal event in each was diffuse meningeval infection.

The distinction between diffuse meningeval involvement and localized nocardial abscess in the central nervous system, generally metastatic from lung, is important since the 2 forms of infection differ with regard to treatment and prognosis. The neurological signs and cerebrospinal fluid studies in this case all pointed to a diffuse subarachnoid infection. As he recovered there were no localizing signs.

We are not certain as to the origin of this man's nocardial infection. Presumably it was implanted in his scalp at the time of the accident and remained as a latent cutaneous infection with introduction into the subarachnoid space during evacuation of the subdural hematomas. No evidence of a primary pulmonary or cutaneous infection could be found.

The management of this patient was complicated by side effects of the therapy. We were convinced that sulfadiazine concentrations in spinal fluid had to exceed 10 mg./100 ml. and that large oral doses would therefore be required.

Urea may have been a useful adjunct to sulfadiazine therapy in this instance. That urea may enhance the bacteriostatic action of sulfonamides in vitro by its antagonism of antisulfonamide agents (methionine and para-aminobenzoic acid) was first reported in 1942. Its clinical efficacy in the management of sulfa resistant gonorrhea was impressive. Ecker reported its use in the management of E. coli meningitis.

However, no instance in which the clinical use of urea and sulfadiazine for extended periods of time and at the doses used in the management of this case has been reported. The prolonged use of these combined agents at high dose levels seemed warranted since we wished to maintain a cerebrospinal fluid sulfa level of more than 10 mg./100 ml. in the face of a usually lethal form of meningitis.

The urea may have contributed to the occurrence of the oxalate renal calculi by increasing the rate of conversion of glycine to oxalate through glyoxylic acid and establishing high levels of serum and urinary oxalate. No serum oxalate determinations were made and we mention this possibility so that a more detailed consideration of this observation may be made in other instances.

We noted that the cerebrospinal fluid sulfa level diminished when urea was administered with sulfadiazine. We cannot establish from our data whether this was secondary to a return of the blood brain barrier to normal with clearing infection or due to a change in the blood brain barrier related to the urea independent of the inflammatory response. It has been suggested that the diuresis associated with the administration of urea may contribute to this observation but the serum sulfadiazine levels showed no clear relation to the urinary output or urea dose in our patient and we doubt that diuresis was a primary factor in this observation.

Prolonged sulfadiazine therapy at low dosage (2 gm. daily) was recommended for this patient since his meningitis was presumably untreated with adequate antibiotics for 3 months and the possibility of a late recurrence from localized pockets of viable organisms in the subarachnoid space seemed plausible.

**Summary**

A 50-year-old man developed diffuse nocardial meningitis following an automobile accident and the evacuation of bilateral subdural hematomas. Treatment with penicillin, streptomycin, oxacillin and sulfasoxazole was unsuccessful. High spinal fluid levels of sulfadiazine were finally achieved with 12 gm. of sulfadiazine and sodium bicarbonate daily and 12-30 gm. of urea 4 times a day in association with an oral intake of from 5000-6000 cc. daily. The patient recovered without neurological deficit and showed no evidence of recurrent infection fifteen months after the initiation of prolonged therapy.

**References**