Chronic Coccidioidal Meningitis

Report of Two Cases

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Since Posadas' cases\textsuperscript{16,17,23} of coccidioidal granuloma reported from Argentina in 1892, interesting and valuable information has accumulated from studies made of infections occurring largely in the San Joaquin Valley of California.\textsuperscript{2,6,8,9,11-14,16,18-20,22} The central nervous system has been affected in some 25\% of the fatalities of the disseminated granulomatous variety.

Instances of so-called primary coccidioidal meningitis happen infrequently, seldom are diagnosed prior to autopsy, and often such patients are operated upon for suspected intracranial tumors.\textsuperscript{1,2,17,21,24,25}

Since the introduction of the antifungal antibiotic, amphotericin B, the importance of establishing an early diagnosis in instances of this elusive disease is readily apparent.\textsuperscript{7,9,25-27} The differential diagnostic problems involved in cases of chronic coccidioidal meningitis are again apparent in the following two cases.

Case Reports

Case 1. A 38-year-old woman was seen in consultation August 14, 1952, at the Foster Memorial Hospital in Ventura. Severe right-sided headaches associated with vomiting and blurred vision were noted about June 20. She found the onset much like influenza with generalized aching and some stiffness of the neck. Her family and past history was not remarkable. She was admitted to the hospital on July 19.

Examination. The patient appeared ill and kept the right eye closed because of blurred vision. Both optic discs were blurred. There was no neck stiffness. There was a non-purulent inflammatory swelling of the mucous membranes of the frontal sinuses. A radiograph of the chest on July 20 disclosed an inflammatory process in the right upper lobe. The white blood cells count was 11,000, 96\% of which were lymphocytes.

It was believed the patient was suffering from a virus type of encephalomyelitis. The possibility of chronic coccidioidal meningitis was considered, but a negative skin test was believed to have eliminated this possibility. A spinal fluid culture was sterile, and virus studies of the blood were non-contributory. No yeast cells were found in the spinal fluid.

Ventriculography on September 30 showed that both ventricles were about twice normal size; the lateral films outlined the fourth ventricle. It was felt these findings eliminated the possibility of an expanding lesion and were consistent with a virus encephalomyelitis. Radiographs of the chest on July 28 demonstrated incomplete resolution of the inflammatory process of the right upper lobe.

Gradually the patient became afebrile, the headaches diminished, and she was discharged on October 8. Her husband reported that she lost consciousness on one occasion 3 weeks after discharge but otherwise continued to improve until 5 weeks after discharge when the right leg became so weak that she was unable to stand.

The patient was admitted to the Ventura General Hospital November 21, 1952, where she died May 3, 1953.

Autopsy. An autopsy disclosed coccidioidomycosis of the brain, spinal cord, and meninges with communicating hydrocephalus, chronic suppurative pyelocystitis, and pulmonary atelectasis.

Comment. The negative coccidioidin skin test led to erroneous exclusion of the diagnosis ultimately established by necropsy. Quite often patients with disseminated coccidioidomycosis do not react to the skin test,\textsuperscript{20} while the complement fixation test is invariably positive, its titer generally reflecting the severity of the infection. Blood sent for virus studies was not diagnostic. As is often the case in chronic coccidioidal meningitis, the spinal fluid culture was negative. Since the introduction of amphotericin B, the significance of the complement fixation test has new importance. At the time this patient was...
seen, there was no therapeutic agent which would have altered her prognosis.

**Case 2.** This 15-year-old boy had an illness diagnosed as measles in September, 1956. After apparent recovery, he became lethargic, with occasional frontal headaches, vomiting, and a low-grade fever.

**Examination.** Examination on June 18, 1957, disclosed an ill, gaunt boy who nonetheless was mentally clear and cheerful. The general physical and neurological examination failed to reveal anything noteworthy. The referring record included a normal urinalysis, a moderate leucocytosis with an elevated sedimentation rate, a negative radiograph of the chest, a negative coccidioidin skin test, a negative purified protein derivative (PPD) test, and a normal electrocardiogram. Febrile antigens in January and again in May, 1957, were negative as was the serology. The spinal fluid cell count was 13 lymphocytes, the protein 236 mg%, and the colloidal gold and serology were negative. Large, irregular, slow waves with a phase reversal in the left frontal region were described in the electroencephalographic report. It was believed this was a case of measles encephalitis and not an expanding lesion, and that the elevated protein in the spinal fluid was consistent with that seen in a Guillan Barré syndrome from an infectious neuronitis due to virus encephalitis.

When seen in July, 1957, the patient felt much better; there had been no change in the general physical or neurological examination. Radiographs of the chest were still normal. However, in December, 1957, although the patient was able to remain up longer, his hands were becoming weak, and he was bothered with blurred vision. At this time there was papilledema bilaterally, Hoffmann and Babinski signs were present on the left side, and there was ataxia of the upper and lower extremities. The dynometric reading was minimal in the right hand and unattainable in the left.

Because of this change, he was admitted to the Santa Barbara Cottage Hospital on December 16, 1957. An arteriogram and ventriculogram were completed on December 18. Although the anterior cerebral artery was in its normal midline position, the vascular pattern suggested symmetrical ventricular enlargement. This was verified by a ventriculogram, and was felt to be consistent with an expanding lesion in the posterior fossa.

**Operation.** Exposure of the cerebellum through a suboccipital craniotomy disclosed whitish granulomas over both cerebellar hemispheres and along the spinal cord visualized beneath the cerebellar hemispheres. Although similar to tubercular granulomas, because of the long period of survival, it was believed this was a manifestation of chronic coccidioidal meningitis. Arachnoid strips, obtained for pathological examination, revealed active and inactive lesions containing numerous characteristic spores of *Coccidioides immitis*.

**Postoperative Course.** In view of the patient's debilitation, his postoperative course was gratifying. The admission coccidioidin skin test had again been negative. During a period of 2 months, he received a total of 1500 mg of amphotericin B intravenously. Complement fixation tests sent to the California State Laboratory confirmed the diagnosis of disseminated coccidioidal infection. The patient improved and was returned home for further convalescence. He gained weight, but was again troubled with headache, nausea, and vomiting.

The patient was readmitted July 29, 1958, and received a total of 150 mg of amphotericin B intravenously in injections of 25 mg each. At this time the spinal fluid protein was 7.6 gm, and the sugar 12 mg%; there were 64 lymphocytes and the gold curve was paretic. Again the complement fixation tests were strongly positive. After being discharged August 5, he was readmitted for additional treatment five times, the last being from October 26 to December 17, 1959. During these admissions, he received a total of 1525 mg of amphotericin B intravenously and 4 mg intrathecally. The high titer of complement fixation of serum and spinal fluid remained unimproved. While there was some variation in his condition, he failed to show any significant improvement.

The patient was last seen at home February 27, 1960. At this time he was quite ill and had the appearance of a severe case of progressive muscular atrophy. He was unable to move his arms and legs. There seemed no indication for further medication, not only because of his intolerance to the drug, but because any
thought of recovery even with significant disability seemed out of the question. He died March 13, 1960.

Autopsy. The salient features of the autopsy were the findings of widespread coccidioidal mycosis associated with nearly complete destruction of both adrenals by coccidioidal granulomas. There were many abscesses and granulomas involving the meninges, and one involving the pineal. Coccidioidal granulomas were scattered throughout both lung fields. There was also a marked hydrocephalus with occlusion of the fourth ventricle by a coccidioidal granuloma.

Comment. When seen in consultation there was little to suggest chronic coccidioidal meningitis. The history of measles followed by his lethargy seemed compatible with the diagnosis of measles encephalitis. The rash believed due to measles without doubt was the result of coccidioidomycosis; this occurs in only about 4% of male patients with primary coccidioidomycosis. The two negative skin tests were deceptive; with the development of papilledema it was believed the patient had an expanding lesion. As in many other cases the diagnosis was established following the suboccipital craniotomy. Had the diagnosis been established early and adequate treatment instituted promptly, recovery might have been anticipated.

Discussion

The endemic area for coccidioidomycosis extends through western Texas, the southern part of New Mexico, Arizona, Nevada, and into the San Joaquin Valley of California. Due to dust inhalation containing the fungus in the form of arthrospores, infection occurs in the majority of persons within 4 years of residence in these regions. Interestingly, some 60% of those infected are entirely unaware of the infection, and yet acquire a complete and permanent specific immunity.

In the nondisseminated cases, the skin test becomes positive first, the precipitin later, the proportion of positive tests reaching a maximum in the third week. The complement fixation antibodies appear more slowly than the precipitins and persist longer. In the disseminated cases, the complement fixation test is positive in some 99% of the cases, and its titer generally reflects the severity of the infection. With regression of the titer, the prognosis improves. As is becoming more appreciated, most patients with disseminated coccidioidomycosis do not react to the skin test.

As in many other cases the diagnosis was established following the suboccipital craniotomy. The importance of a more frequent use of the complement fixation test is apparent; certainly if a skin test is employed, the precipitin and complement fixation tests should naturally follow. Facilities for such tests should not be limited, but made available in the majority of laboratory facilities. Regardless of the progress of the disease, no precipitin reaction occurs after 3 or 4 months.

Because of similarities in the clinical picture, the differential diagnosis between the fungi comprising the blastomycetes is important. In this group cryptococcosis or torula infection, blastomycosis or oidomyco- cosis, and coccidioidal granuloma are most apt to be confused. Tuberculosis, moreover, may be strikingly similar in its manifestations. Diagnosis is dependent upon laboratory findings.

Chest radiographs may lead to the impression of coccidioidomycosis, as should an elevated eosinophile count. Active infection is indicated by an increased sedimentation rate. A pleocytosis, associated with increased protein and reduced glucose in the spinal fluid, should call for exclusion of coccidioidomycosis. Coccidioidal meningitis, notoriously insidious in onset, usually occurs as a single manifestation of dissemination from the initial pulmonary focus. When untreated, the mortality approaches 100% within a year after the onset.

That some two-thirds of infected individuals recover with lasting immunity indicates a variation in the resistance of the host as well as a difference in the virulence of the fungus.

Additionally, coccidioidal infection is more resistant and less responsive to the antifungal effect of amphotericin B than the other pathogenic fungi, so that more intensive and prolonged therapy is required for its control. Because injections at the lumbar and cisternal regions are not without side effects and technical problems, the use of intraventricular administration, as outlined by Ommaya, may be required.
Summary

We have reported two cases of chronic coccidioidal meningitis and have emphasized the deceptive nature of the skin test and the reliability of complement fixation tests diagnostically. Since amphotericin B has specific therapeutic value it is important to utilize all laboratory means to make the diagnosis early and to avoid erroneous exploration for a suspected brain tumor or abscess.

References