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## ACTINOMYCOSIS - CEREBRAL INFECTION PRESENTING AS A BRAIN TUMOR

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#### INTRODUCTION

Actinomycosis is an uncommon disease in any age group. It is particularly unusual in children, being accorded only brief discussion in a current textbook of pediatrics<sup>1</sup> and is not discussed in recent pediatric literature. Ordinarily, the disease appears in any of several well-defined forms; the cervicofacial type, as a chronic pulmonary infection or as an indolent bone infection. In most patients only one of these types usually occurs. The present case is reported because of the peculiar presenting symptomatology and also because of the co-existence of pulmonary and cerebral lesions due to Actinomyces bovis (Israeli).

The patient was a 13 year old white male with the chief complaint of anorexia, weight loss for three months and vomiting the past two days. He was well until approximately two months prior to admission at which time he had several attacks of abdominal pain associated with vomiting and headache and leg pains. He was admitted to another hospital where an appendectomy was performed, and the patient was discharged being told that he had rheumatic fever. After discharge the patient continued to complain of headache, nausea and vomiting with pain in varying joints. He had had a progressive weight loss, losing a total of approximately 20 pounds. He had had no chorea, no subcutaneous nodules, no particular tachycardia. Two days prior to admission the patient began to have marked nausea and projectile vomiting associated with a fever. The day of admission his temperature was 101 degrees, and he had had a drenching sweat the night before.

The past history was that at the age of  $2\frac{1}{2}$  years the patient had a blow on the head after falling out of a truck with no known unconsciousness. He had had routine immunizations and had had the usual childhood diseases. There was a maternal aunt who died of tuberculosis with whom the child had no contact. There was no family history of allergy, thyroid disease or convulsions. There are four siblings, all in good health. One year prior to this admission the child had a severe respiratory infection said to be "almost pneumonia". Child lived with his father in a rural area. The parents have been divorced for several years.

Physical examination on admission revealed a well developed, poorly nourished white male who appeared chronically ill. He was slightly pale. His temperature was 101, pulse 141, respirations were 28 and a blood pressure of 92/70 was obtained. Examination of the head revealed a normal shape and contour with closed fontanels. The ears revealed intact tympanic membrane with clear canals. There was no gross defect in hearing. The eyes revealed round and equal pupils which reacted to light

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and accomodation, the sclerae were clear and extra ocular movements seemed normal. There was a question of some blurring of the disc margins. The nose was negative. The mouth revealed normal teeth in good repair, normal tonsils and a clear pharynx. The neck revealed some pain in the back on slow flexion but there was no rigidity. The chest was clear to auscultation and percussion. The heart revealed questionable enlargement to the left. There was an irregularity in rhythm with a pulse rate of 140. There was a harsh systolic murmur heard over the entire pre-cordium but heard best in the third innerspace at the left mid-clavicular line. Femoral pulses were palpable. Examination of the abdomen revealed no masses. There was a right lower quadrant recent scar, and there was no tenderness. The back revealed definite costo-vertebral angle tenderness on the right. Neurological examination revealed very active, but bilaterally equal, deep tendon reflexes. There were no pathological reflexes and sensorium was clear. The initial impression was that of rheumatic heart disease with possible auricular fibrillation, and brain tumor was to be considered.

Laboratory studies obtained on the day of admission revealed a sedimentation rate of 34, a normal urine, 10.2 grams of hemoglobin, 9,600 white cells with 77% polymorphonuclears and 23% lymphocytes. There were a negative Kline and a negative blood culture. Blood agglutinations were negative for typhoid. The initial chest x-ray revealed an aorta of normal size with moderate hilar enlargement. Bronchial vascular markings were reported to show a fairly normal distribution. There were several somewhat rounded areas of infiltration in the lower portion of the right lung field. There were areas of lessened density in the center of these nodules suggesting the possibility of cavitation (Fig. I). No bony destruction was seen, and the lateral revealed a normal spine. X-ray of the skull revealed no evidence of fracture or increased intra-cranial pressure. There were no abnormal densities or areas of erosion. Cautious lumbar puncture was done without difficulty and colorless fluid obtained. The laboratory examination of the spinal fluid revealed sugar of 47 milligrams percent, a protein of 150 milligrams percent and a chloride of 762 milligrams percent. There were 222 white blood cells, mostly mononuclears in the spinal fluid. Spinal fluid culture failed to yield any growth of organisms.

The patient's hospital course did not change over the next three days. There was a presistence of the frontal headache with vomiting, and careful neurological three days after admission revealed a cerebellar type ataxia of the right arm and leg with questionable deviation of the tongue to the left and no definite papilledema. There were no pathological reflexes. Repeat blood count revealed 10.5 grams of hemoglobin, 4,200 white blood cells, 90% polymorphonuclears, 10% lymphocytes. The N. P. N. was 32 milligrams percent and fasting blood sugar was 92 milligrams percent. A smear seen in special hematology revealed normal cell morphology. An OT of 1 milligram was also negative. He was started on chloromycetin and sulfadiazine. He died suddenly on the tenth hospital day, the day prior to scheduled ventriculograms. An EEG was not obtained.

Discussion: This seriously ill boy was admitted to the hospital with a combination of symptoms and findings suggestive of chronic infection over at least a two or three



Figure 1

"There is a cavity in the right lower lung with some parenchymal infiltration laterally."

month period with localization in the lung fields and in the central nervous system. The findings in the spinal fluid coupled with the physical findings on neurological examination suggested an infection of the meninges and/or localized infection of the brain itself, that is abscess or encephalitis. The nature of the spinal fluid, that is mononuclear cells and a markedly elevated protein coupled with a normal cerebral spinal fluid sugar suggest a tuberculous infection. If this were a more acute bacterial abscess or chronic meningitis we would expect the spinal fluid protein to be much lower and the cell count itself to be higher. The infection would have presented with polymorphonuclears earlier, but it could concievably have shifted to a more chronic inflammatory cell picture at this time. The fact that the culture was negative on routine laboratory methods is, of course, against the more common bacteria and again suggestive of an acid fast organism. To reach a decision as to organism when one looks at the chest x-ray it becomes again very difficult. The lung picture could be compatible with tuberculosis and cavitation, but it does not rule out a bacterial abscess and chronic pneumonia. It is certainly conceivable with the laboratory and physical findings that the sequence of events was that of a pulmonary infection perhaps starting with the "almost pneumonia" one year ago and manifesting iteslf in acute fashion. When examining more closely the peripheral blood smear, a white count of 9,600 with 77% polymorphonuclears is definitely not suggestive of a bacterial

pulmonary abscess. It is, however, not very significant nor suggestive of tuberculosis. The OT being negative is at least a definite point against tuberculosis, but if this child is as acutely ill as the picture seems to be he could be relatively anergic and unable to respond to the skin tests. The heart, which can not be ignored, presented patholigical findings as indicated here, and it is possible that the child has had rheumatic fever and contracted this other chronic illness. It is possible, however, that this heart is one presenting subacute bacterial endocarditis, the multiple bacterial emboli accounting for the many abscesses in the lungs and brain. The blood cultures being negative are not helpful in this diagnosis nor are they against it. The peripheral blood count should be somewhat more elevated than it is, however, in subacute bacterial endocarditis. The spleen was not enlarged, and if this child were putting out multiple emboli you would certainly expect to find a spleen filled with emboli. It is possible, however, in trying to explain the heart findings that this represents only a functional murmur and that there is no significant pathology in the heart.

In summary we have a young boy with negative tuberculin skin tests, a nondescript peripheral blood picture and a definite abnormal chemistry to the spinal fluid, who presents himself with marked generalized disease symptoms, pulmonary abscesses and central nervous system symptoms. The most likely thing would appear to be a primary pulmonary abscess with secondary spread to the central nervous system, either in the form of encephalitis, meningitis or most likely abscesses. In spite of the negative tuberculin test and because of the non-inflammatory type blood picture, I would believe that tuberculosis would be the most likely cause and the over-whelming nature of it accounting for the ultimate demise.

#### DISCUSSION OF PATHOLOGIC FINDINGS

At autopsy this boy showed bilateral pulmonary abscesses, the largest of which measured 4 cm. in diameter. The brain showed numerous abscesses, up to 3 cm. in diameter scattered through the cerebellum. The purulent material was greenish-yellow. No definitive granules were seen. There was some generalized cerebellar edema with some flattening of the convolutions of the brain.

Laboratory examination of the pus revealed an organism with the cultural and morphological characteristics of Actinomyces bovis (Israeli). Microscopic examinations confirmed these gross findings, and numerous actinomycotic granules were found in the abscesses of the cerebellum and the lungs. While there was some perivascular cuffing in other portions of the brain, these were of a chronic and secondary nature. The meningitis appeared to be of a subacute variety. No granules were found in the meninges.

Figure II shows the presence of the actinomycotic granule in the upper right hand corner of the figure. It is surrounded by numerous polymorphonuclear leukocytes and a few eosinophils. In the lower left hand portion of the microphotograph, the normal folia of the cerebellum can be seen.

Figure III is a close up of a Gram stain of one of the actinomycotic granules found in one of the abscesses. (H. & E. 250x)



Figure 3 Actinomycotic Granule from the Abscess.

#### DISCUSSION OF THE BACTERIOLOGICAL FINDINGS

The actinomycetes are a varied group of filamentous microorganisms with some characteristics common to bacteria and fungi. The organisms range from the strict parasitic anaerobic actinomyces to aerobic non-pathogenic types. The members of this group which have medical interest are the anaerobic *Actinomyces bovis* and *Actinomyces israeli*. The former is responsible for actinomycosis in bovine species and the latter produces the disease in man. Although there are differences among strains of anaerobic *actinomyces* isolated from man and cattle, the single species *Actinomyces bovis* is considered by many investigators to be the etiologic agent of actinomycosis.

Since *actinomyces* are found in the tartar of teeth, in the crypts of tonsils as well as on various mucous membranes, a postive smear or culture from these sites does not necessarily indicate actinomycosis. Therefore, it is of paramount importance that the pus or exudate be collected aseptically, preferably from closed lesions by aspiration with a sterile needle and syringe after adequate disinfection of the skin.

Fresh preparations should be examined for gram-positive, branching, filamentous organisms. These structures are not acid-fast, do not form spores and are nonmotile. The filaments are usually slender (1 micron or less in width) nad have a marked tendency to fragment into bacillory forms.

Since gram-strained smears do not differentiate *Nocardia* from *Actinomyces bovis* the specimen should be cultured both aerobically and anarobically on suitable media, and the cultures identified by various criteria. Growth of *Actinomyces* appears at 37·C in from three to six days. Colonies can be picked from the agar or broth cultures and examined under a coverslip. The organisms are seen as tangled masses of delicate branching hyphae, or small fragments. Smears stained by Gram's method show the fungus to be gram-positive and small fragments frequently give the appearance of diphtheroids.

Inoculations of actinomyces into guinea pigs, rabbits or other animals by any of the common routes frequently produce no effect. Several investigators have reported that the suspension of pure cultures in 5 per cent hog gastric mucin induced progressive disease in white mice when inoculated intraperitonelaly. Others were able to produce actinomycosis in hamsters by intraperitoneal injection of pure culture.

#### TREATMENT

While the cerebeller lesions of this patient seem to have precluded survival, and indeed evaded ante-mortem etiological diagnosis, astinomycosis of more usual lacalization is responsive to combined therapy. This treatment should include intensive multiple antibiotic therapy, adequate surgical extirpation, or incision and drainage where anatomically possible, and radiation therapy of moderate dosage. Procaine penicillin is recommended in doses of 600,000 I. U. daily for a period of ten days. Sulfadiazene has been shown to be especially effective and should be given concurrently in divided doses of 4.0-6.0 gms. daily until improvement occurs and then should be continued for several months in doses of 2.0 gms. daily. Such dosage levels are suitable for all but the smallest of children. More recently broad spectrum antibiotics such as the tetracyclenes have been reported to give very favorable results<sup>2</sup>. The current

edition of Topley and Wilson<sup>3</sup> states the in-vitro sensitivity of the organism has been found to be, in descending order of sensitivity; penicillin, terramycin, choloromycetin, aueromycin and streptomycin. Inorganic iodides, formerly thought to have specific antimycotic action, are no longer regarded as being of value in the management of the disease. Finally, surgical excision or incision and drainage is essential where feasable. Sinus tracts, a common problem in the more usual forms of the disease, should be irrigated with 1% gentian violet solution. Lugol's solution has been used for this purpose but is likely to produce toxic side effects due to absorption of large amounts of iodine by the patient. This combined approach to treatment may be expected to result in a substantial recovery rate.

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