Paradoxical progression of tuberculous lesions during chemotherapy of central nervous system tuberculosis

Report of four cases


Department of Neurosurgery, Osmania Medical College and Osmania General Hospital, Hyderabad, Andhra Pradesh, India

The peculiar phenomenon of paradoxical progression during the treatment of central nervous system tuberculosis is discussed. A few cases with this phenomenon were reported in the past, and the authors have treated four such cases. During the treatment for tuberculous meningitis, the four patients developed new lesions, mainly in the form of tuberculomas, which progressed for some time and later regressed. In all these cases the initial drug regimen was not changed, except for the addition of steroids for a short period at the time of deterioration. All four patients underwent ventriculoperitoneal shunt insertion during the course of treatment. The authors discuss the significance of the changes in the lesions and management of such cases, and review the literature.

KEY WORDS • paradoxical expansion of tuberculoma • tuberculoma

Tuberculous infection of the brain is a condition commonly encountered by neurosurgeons in developing countries. Computerized tomography (CT) has changed the outlook in managing these cases. It is concluded that in geographical regions where tuberculosis is prevalent, lesions suggestive of a tuberculous origin should be treated with a trial of antituberculous drugs, and only explored if the patient deteriorates clinically, or if the lesions fail to respond to the drug regimens as evidenced by serial scans. In contrast, there are certain cases in which the patient improves clinically although the lesions progress radiologically. After this initial progression, on continuation of the same antituberculous drugs the lesions regress and disappear. Hence it is very important to know about this phenomenon so as to avoid unnecessary surgery. These are the lesions that create management problems.

Case Reports

Case 1

This 18-year-old man was admitted to the hospital in May 1989 with altered sensorium and signs of meningitis, diagnosed as tuberculous meningitis. He was given streptomycin, isonicotinyl hydrazine (INH), rifampicin, and pyrazinamide (PZA). Because the patient developed jaundice, rifampicin was discontinued and ethambutol was added. No brain parenchymal lesions were observed on CT scan. Streptomycin was stopped after 90 days and the other three drugs were continued. The patient was readmitted to the hospital after 8 months of outpatient treatment. At the time of readmission he was unconscious with left hemiplegia. Computerized tomography scanning revealed communicating hydrocephalus with tuberculoma in the right internal capsule region. A ventriculoperitoneal (VP) shunt was placed and a course of dexamethasone was started. His recovery was rapid, with improvement of hemiplegia in 1 month. Dexamethasone was stopped after 4 weeks, and since then he has been asymptomatic. A repeat CT scan obtained 11 months later revealed further progression of the tuberculoma (Fig. 1 left), but because the patient was asymptomatic, the same antituberculous drugs were continued. A repeat scan done 1 year later revealed regression of tuberculoma (Fig. 1 right). He was given antituberculous drugs for a period of 30 months. At present the patient is asymptomatic and leads a normal life.

Case 2

This 4-year-old girl was admitted with signs of meningitis, which was confirmed as tuberculous meningitis on cerebrospinal fluid (CSF) analysis. She had persistent vomiting and headache. She was given streptomycin, INH, rifampicin, and PZA. On CT scanning, communi-
cating hydrocephalus was detected. A VP shunt was placed and the patient was discharged from the hospital because she was asymptomatic. Streptomycin was discontinued after 3 months. One month later she was readmitted in an unconscious state with left hemiparesis. At this time, CT scans revealed tuberculoma in the midbrain region, with perilesional edema (Fig. 2 left). Dexamethasone was added to her drug regimen. She had gradual improvement, and repeat CT scans obtained 6 weeks later revealed new tuberculomas with enlargement of old ones (Fig. 2 right). Because the child was improving clinically, no change in her drug regimen was contemplated. Dexamethasone was withdrawn at 8 weeks. Antituberculous drugs were given for a period of 2 years. Presently she is asymptomatic except for mild weakness in her left lower limb.

Case 3

This 3-year-old boy was admitted with signs and symptoms of meningitis confirmed as tuberculous meningitis on CSF analysis. He was given a four-drug regimen of streptomycin, INH, rifampicin, and PZA. By the end of 1 month he was asymptomatic and was discharged from the hospital. Streptomycin was discontinued after 3 months. Four months later he was readmitted to the hospital with neurological deterioration. At the time of hospitalization, he was unconscious with bilateral papilledema and fixed and dilated pupils. Computerized tomography revealed communicating hydrocephalus and basal exudates, with tuberculoma in the posterior third ventricular region and midbrain (Fig. 3 left). A VP shunt was placed, and a course of dexamethasone was started. The child made a rapid recovery. A follow-up CT scan revealed a decrease in basal exudates, but new tuberculomas had developed in the frontal and parietal lobes and also in the vermis, with expansion of existing lesions (Fig. 3 right). In view of his improving clinical status, no change in drug regimen was made. At the end of treatment, the child was asymptomatic.

Case 4

This 14-year-old girl was admitted to the hospital with fever and altered sensorium, and CSF analysis was consistent with tuberculous meningitis. She was given a four-drug regimen of streptomycin, INH, PZA, and rifampicin. Her level of consciousness improved, but headache was persistent. A CT scan was obtained and was suggestive of communicating hydrocephalus. A VP shunt was placed. Ten weeks later, a repeat scan revealed thick basal exudates that were not present in the earlier scan (Fig. 4 left). Dexamethasone was added to her regimen, and in 1 week she became asymptomatic. Streptomycin was stopped after the full course had been given and dexamethasone was withdrawn after 4 weeks. She remained asymptomatic for the next 2 months and then developed suppurative cervical lymphadenopathy. The histopathological appearance of the excised tissue was consistent with tuberculosis. A repeat CT scan at this time revealed resolution of basal exudates (Fig. 4 right). She has been asymptomatic since the last scan.

Discussion

The cases described here have a common feature of progression of pathological lesions during the apparently successful treatment. There was deterioration in neurological status because of new lesions such as tuberculomas or communicating hydrocephalus. All four cases were diag-
Paradoxical progression of tuberculous lesions

Fig. 4. **Left:** Second computerized tomography (CT) scan in Case 4 showing increase in basal exudates. **Right:** Subsequent CT scan in Case 4 showing clearing of basal exudates.

nosed and receiving treatment for tuberculous meningitis. All of them received four drugs for the first 3 months, and three drugs for the remaining period of 15 months or more. All received regular follow-up evaluation and each patient showed good compliance with the treatment regimen. In Case 1, in which resolution of tuberculoma was delayed, antituberculous drugs were given for a prolonged period. These patients received dexamethasone for a short period at the time of clinical deterioration associated with development of tuberculomas. Antiseizure medications were used in all these patients. The interval between the initial illness and detection of progression was variable: 8 months in Case 1, 4 months in Cases 2 and 3, and 6 weeks in Case 4. In previous case reports this interval varied from 10 days to 5 months. The longest latency observed was 18 months. All patients developed new lesions following the asymptomatic period.

In Case 4, the girl improved both systemically and radiologically, but developed cervical lymph node involvement, which subsided on continuation of the same drug regimen. Because no new drugs were used, it is improbable that drug-resistant bacilli were responsible for the development of new lesions. A repeat CT scan showed no fresh lesions. It was thought that cervical lymph node enlargement in patients undergoing treatment for tuberculous meningitis was associated with the development of new intracranial tuberculomas. As seen in Case 4, this presentation may not always develop. All these patients improved rapidly with medical management, and no surgical intervention was planned; therefore, no histopathological confirmation was possible.

In disseminated tuberculosis, tuberculous meningitis is caused by bacilli released from small subpial tuberculomas. Small asymptomatic intracranial tuberculomas are often noted in meningitis. However, in our series all the patients had tuberculomas in deeper parts of the brain, and in one case tuberculoma was seen in the vermis. There have been three more cases reported of infratentorial tuberculomas that developed during treatment. Tuberculoma heals on treatment, but when the BBB is restored, it interferes with drug penetration and in some cases may be responsible for expansion of the lesions.

Conclusions

It is very difficult to explain simultaneous regression of supratentorial tuberculoma and suppuration of tuberculoma in posterior fossa in the same patient with any of the aforementioned theories. Drug resistance as a cause cannot explain the progression, because these patients later responded to the original drug regimens. In one case in which emergency decompression of tuberculoma was performed, the bacilli were cultured and were found to be sensitive to all the antituberculous drugs the patient was using. Later he responded to the same drugs. In all cases, culture sensitivity studies showed that organisms were sensitive to the drugs used, despite which progression of the lesions was observed. It is difficult to reach a conclusion regarding pathogenesis with these varied findings. It may be that some local pathology is responsible for this phenomenon.

Any progression of symptoms in tuberculous meningitis should be investigated, but if new lesions are found there is no need to change drugs immediately. This should not concern the treating surgeon, because these are the

served in certain cases. There have been approximately 30 cases reported with this phenomenon in the past. The largest series was 10 cases reported by Teoh, et al., and the next largest was four cases reported by Chambers, et al.

The pathoetiology of the phenomenon is not well understood. The disease pathology in these cases may be somewhat similar to lymph node enlargement in adequately treated glandular tuberculosis. This was believed to occur because of trapping of antigen-reactive lymphocytes within lymph nodes. Chemotherapy of tuberculosis lesions causes destruction of bacilli and release of tuberculous proteins, which mediate immune reaction, resulting in expansion of the existing lesions. In a country like India in which most of the people are Mantoux-positive, this reaction should be seen more often, and also much earlier. It should also be at a more or less fixed interval after beginning a course of drugs, and might mimic one of the standard immune reactions; however, in these cases it occurred at random.

Poor penetration of the drugs into the lesions may explain enlargement after the latent period. It is possible that the diffusion of drugs into CSF diminishes as meningeal inflammation subsides, thus allowing latent cerebral foci of infection to reactivate and enlarge. However, INH and PZA are supposed to have good penetration even with normal blood–brain barrier (BBB). Dexamethasone, which is supposed to restore the BBB, rapidly improved the patient’s condition in all of these cases.

Steroid usage in tuberculous meningitis is controversial. It is believed to restore the BBB to normal, thereby decreasing drug availability. However, in tuberculomas the use of steroids is advantageous. It decreases perivascular edema and intracranial pressure, and improves patient symptoms, which helps in the critical period. In all reported cases, steroid usage helped significantly. Tuberculoma heals on treatment, but when the BBB is restored, it interferes with drug penetration and in some cases may be responsible for expansion of the lesions.
cases in which prolonged treatment with antituberculous drugs is required.13 The role of dexamethasone in treating these cases is enormous.

References