Jpn. J. Infect. Dis., 58, 387-389, 2005

Short Communication

Tuberculous Meningitis with Multiple Intracranial Tuberculomas Mimicking Neurocysticercosis Clinical and Radiological Findings

Oral Oncul*, Orhan Baylan[1], Hakan Mutlu[2], Saban Cavuslu and Levent Doganci[1]

Department of Infectious Diseases and Clinical Microbiology and [2]Department of Radiology, Gulhane Military Medical Academy, Haydarpasa Training Hospital, Istanbul and [1]Department of Microbiology and Clinical Microbiology, Gulhane Military Medical Academy, Ankara, Turkey

(Received July 21, 2005. Accepted October 12, 2005)

SUMMARY: Central nervous system (CNS) tuberculosis (TB), the most dangerous form of TB, remains a public health problem, particularly in developing countries. In the differential diagnosis of intracranial tuberculomas (ICTs), images on radiological findings should be differentiated from other causes of space-occupying lesions. These lesions include malignant diseases such as glioma or lymphoma, pyogenic abscess, toxoplasmosis, neurocysticercosis (NC), sarcoidosis, hydatidosis and late syphilitic involvement of CNS. We present a case with multiple ICTs mimicking NC with similar clinical and imaging manifestations in a young immunocompetent patient. The diagnosis was based on brain magnetic resonance imaging findings. The definitive diagnosis was confirmed mycobacteriologically in cerebrospinal fluid and sputum specimens. Adequate response to anti-TB chemotherapy was achieved while multiple ICTs in the brain disappeared slowly. In the absence of appropriate therapy, these pathologies might be fatal; the possibilities of differential diagnosis would be of great clinical importance, particularly because of the different treatment protocols required for the NC and ICTs.

Extrapulmonary tuberculosis (EPTB) is observed in approximately 20% of all tuberculosis (TB) cases, and its incidence has increased in recent years (1). Central nervous system (CNS) TB, the most dangerous form of TB, accounts for approximately 5% of EPTB cases (2). Tuberculous meningitis (TBM) is the most common form of CNS-TB; however, solitary or multiple intracranial tuberculomas (ICTs) in particular occur less frequently (2-4). Even though CNS-TB is an uncommon entity; the disease affects 0.5 to 2% of patients with systemic TB. However, ICTs account for a significant portion of intracranial masses in developing countries (5). Mortality is greatest in patients younger than 5 years of age (20%) or older than age 50 (60%), or in whom illness has been present for more than 2 months (80%) (6).

Neurocysticercosis (NC) is one of the pathologies most frequently seen by neurosurgeons from developing countries. Although brain cysticercosis is endemic in Latin America, Asia, and Africa with the exception of Muslim countries, it can be diagnosed throughout the world in patients who have migrated from endemic countries and due to the consumption of unhygienic water and foods (7). Approximately 2.5 million people worldwide carry the *Taenia solium* tapeworm, and not less than 20 million people are infected with *T. solium* cysticerci (8). Conservative estimates describe 50,000 deaths every year due to NC (9). The diagnosis of cerebral cysticercosis is based, primarily, on typical imaging characteristics in computed tomography (CT) or magnetic resonance imaging (MRI), and on clinical features. The presence of subcutaneous cysts as subcutaneous nodules usually confirms the diagnosis (7).

In this report we are presenting a case with multiple ICTs mimicking NC with similar clinical and imaging manifestations in a young patient. A 21-year-old male farmer from Southeast Anatolia was first seen in a local general health-care center with high fever, cough, headache, weakness, pain in the neck, and loss of weight in April 2003. The initial diagnosis of this patient had been bacterial pneumonia, and the patient had superfluously received broad-spectrum antibiotics. Until August 2003, he continued seeking medical aid without any improvement, and he was then admitted to our hospital in August 2003 with a worsening condition.

In the familial history of the patient, it was noted that his father had anti-TB chemotherapy (ATCT) for pulmonary TB 4 years prior. The patient reported seizures in the last days. The patient had been smoking a packet of cigarette daily for the last 6 years. On physical examination, moderate papilledema and neck stiffness were noted on the first day of admission. Other systemic and detailed neurological examinations were normal. His urinalysis, hemogram, serum biochemical parameters and serum electrolytes were normal. The appearance of his cerebrospinal fluid (CSF) was cloudy, and was gray in color with increased opening pressure. The biochemical and cytological examination of the CSF revealed proteins at a concentration of 1,655 mg/dL, glucose at 19 mg/dL (the concordant blood glucose level was 75 mg/dL), lactate dehydrogenize at 128 U/L, and 390 mononuclear cells/mm^3. Aerobic bacteria were not isolated from CSF and urine cultures. Normal nasopharyngeal flora were detected by nasopharyngeal culture.

Electroencephalogram (EEG) showed intermittent delta activity in the parieto-occipital region on the bilateral side and in the thalamus region on the right side. Routine X-rays of the skull, thigh and forearm were normal. Cranial MRI revealed multiple small nodules at the gray-white junction of both the cerebral and cerebellar hemispheres, the brainstem, the right thalamus, the anterior limb of the left internal capsule and the body of the corpus callosum (Figure 1).

Antibody-ELISA (Dynatech Laboratories, Inc., Alexandria,

*Corresponding author: Mailing address: Department of Infectious Diseases and Clinical Microbiology, Gulhane Military Medical Academy, Haydarpasa Training Hospital, 34670, Uskudar-Istanbul, Turkey. Tel: +90 216 542 24 58, Fax: +90 216 348 78 80, E-mail: robertcool@graffiti.net

Va., USA) for cysticercosis was negative in both serum and CSF. A purified protein derivative (PPD) skin test was non-reactive. However, adenosine deaminase levels in CSF (16 U/L) and serum (42 U/L) were above the normal limits (<10 U/L and <30 U/L, respectively). Ehrlich-Ziehl-Neelsen (EZN) staining of the CSF and sputum samples was positive for acid-fast bacilli (AFB). The chest X-ray showed signs of pulmonary TB with a triangular consolidation of the left upper lobe with blurred limits and small cavitary lesions. The mycobacterial cultures of CSF and sputum samples were found to be positive for the *Mycobacterium tuberculosis* complex (MTC) by conventional (Löwenstein Jensen medium; Diomed Inc., Istanbul, Turkey) and radiometric (BACTEC 460 TB culture system, Becton Dickinson Diagnostic Instruments, Sparks, Md., USA) methods. The CSF was also tested with a polymerase chain reaction (PCR) assay for MTC. A standard protocol for the extraction of MTC-DNA was used. The result of MTC-PCR was positive. The urine was also tested with a microscopic examination with EZN and radiometric and conventional cultures; however, the results were found negative for mycobacteria. The immune status of the patient was normal. Anti-HIV antibody and Venereal Disease Research Laboratory (VDRL) tests were negative.

The susceptibility testing of the MTC isolate to four first-line anti-TB drugs (isoniazid [INH], rifampicin [RIF], streptomycin [SM], ethambutol [EMB]) was evaluated by the BACTEC 460 TB radiometric system. The agent was found susceptible to four first-line anti-TB drugs. The ATCT was planned for 12 months. First, the patient was treated orally with INH (300 mg/day), RIF (600 mg/day), SM (1 g/day) and morfazinamid (3 g/day) for 2 months, and then was treated with INH and RIF for the following 10 months. A high dose of pyridoxine (PDX) was given to prevent possible INH-related neuropathy. Carbamazepine (400 mg/day) and famotidine (80 mg/day) were added to the therapy. Mannitol (20%) (100 mL/day) was given for 6 days. Prednisolone (40 mg/day) was used for the first 28 days with a decreasing dose. A repeat MRI after 4 months showed complete resolution of all the lesions (Figure 2). During this period the patient remained asymptomatic.

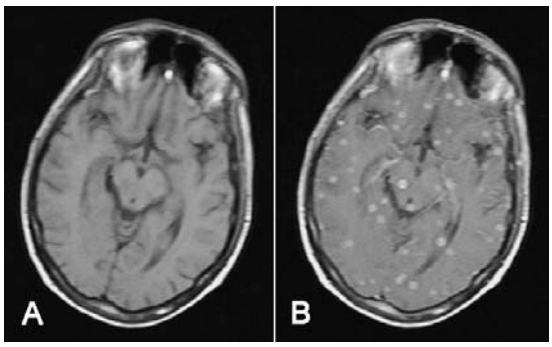

Fig. 1. Axial magnetic resonance images of a 21-year-old male patient with miliary tuberculosis on admission. (A) T_1-weighted magnetic resonance image (640/14) shows nothing remarkable at the level of the midbrain. (B) Contrast-enhanced T_1-weighted magnetic resonance image (640/14) shows multiple small nodular areas of enhancement that are predominantly located at the gray-white junction.

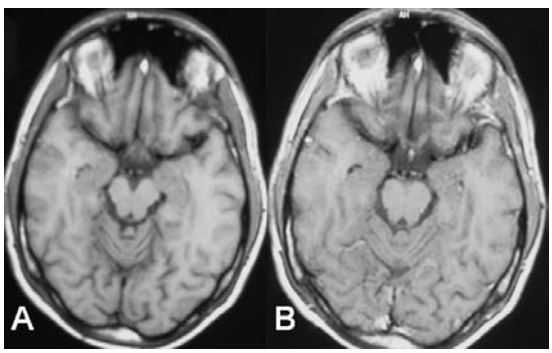

Fig. 2. Axial magnetic resonance images of a 21-year-old male patient with miliary tuberculosis 4 months after antituberculosis chemotherapy. (A) T_1-weighted magnetic resonance image (640/14) shows nothing remarkable at the level of the midbrain. (B) Contrast-enhanced T_1-weighted magnetic resonance image (640/14) shows nothing remarkable at the level of the midbrain.

Multiple ICTs and parenchymal CNS involvements are not frequent TB presentations. The ICTs present a subtler clinical picture than TBM, namely as space-occupying lesions that may manifest themselves with seizures. The presentation is typical for ICTs-slowly progressive headache and signs of meningeal irritation, followed by cranial nerve involvement, other neurologic deficits and progressive mental status changes over a period of weeks. These signs usually follow a subacute or chronic course leading to difficulty in differentiating the lesions, on clinical grounds, from basal carcinomatous meningitis, chemical meningitis and NC, especially in endemic countries (2-4).

Clinical manifestations of NC are varied and non-specific because of the stage, number, size, and locations of the cysticercal cysts within the CNS and the severity of the host immune response to the parasite (10). Seizures and focal neurologic signs have been described in patients with NC, particularly when the parasitic cysts are located in the parenchyma and arachnoid spaces (11). On the other hand, meningoencephalitis may result from an intense immune response to the parasite in several patients. These patients present clinically with confusion, seizures, headaches, nausea and vomiting (12). For this reason, NC and TBM must always be considered to be a part of the differential diagnosis for a new-onset of these signs in endemic areas. As in NC and ICTs, seizures were the most common symptom in our case. The physical examination findings showed signs of space-occupying lesions and edema.

Other evidence of TB (e.g., pulmonary TB) or cysticercosis (e.g., subcutaneous nodule) elsewhere is a great help in making a definite diagnosis. Some of the TBM patients and NC patients do not have pulmonary findings and subcutaneous nodules. Intracranial multiple lesions might be the only radiological findings. In our case, multiple small nodular areas of enhancement that were predominantly located at the gray-white junction were the only lesions shown definitively on MRI. In these situations, it is essential to perform differential diagnosis by conducting the Mantoux test, CSF and serological tests.

ICTs have also been differentiated from other causes of space-occupying lesions such as pyogenic abscess, toxoplasmosis, sarcoidosis, hydatidosis, syphilitic gummas and primary or metastatic malignant diseases including glioma and lymphoma. The findings produced by ICTs on a CT scan may be completely indistinguishable from those of these other conditions. The use of more recent imaging tools such as MRI may be helpful in determining the correct diagnosis (2-4).

The problem of differentiating between cysticercus granuloma and tuberculoma becomes even more complicated in patients having multiple enhancing CT/MRI lesions. The char-

acteristic CT and MRI scan findings include enhancing (ring or nodular) lesions, ranging from 5 to 20 mm in diameter, which may be seen in any part of the cerebral hemisphere. A punctate eccentric high-density structure suggestive of scolex (which is pathognomonic of NC) is seen in 44% of such patients (13). Another characteristic appearance of NC is rounded hypointense non-enhancing lesions. Non-enhancing cystic lesions on CT or MRI showing scolex constitute a small fraction of patients with NC. According to reports, the majority of the patients with NC have single enhancing lesions, though multiple enhancing CT/MRI lesions are also not uncommon (14). In an epileptic patient, the characteristic CT findings along with subcutaneous nodules are virtually diagnostic of NC and usually do not require any further workup (15). These single or multiple lesions pose a challenge both to radiologists and clinicians. The imaging and clinical features of our case were exceedingly similar to those of NC, and it was difficult to differantiate between these two conditions.

The serological tests are extensively used in the diagnosis of cysticercosis. However, recent studies on serum have demonstrated a large number of false positive and false negative results. The sensitivity of these tests decreases considerably when viable parenchymal cysts are not in contact with the CSF or are calcified (16). In contrast, ELISA using CSF was 87% sensitive and 95% spesific (17). On the other hand, the lumbar puncture in TBM usually shows increased opening pressure, and the CSF usually contains between 100 and 1,000 cells per mL. In approximately 65 to 75% of patients, lymphocytes predominate, whereas polymorphonuclear leukocytes predominate in the remainder of patients, generally early in the course of the CNS-TB. The protein concentration is elevated, and the glucose concentration in CSF is usually low in nearly all patients (2). In our case, all the clinic and radiological features were consistent with the diagnosis of NC; however, serological tests and CSF examination established a tuberculous etiology. The patient responded very well to anti-TB drugs, and all intracranial lesions disappeared in the second month of ATCT.

Although nearly non-existent in Western and Muslim countries, pathologies such as NC and tuberculoma are on the increase in these countries due to the increase in the immigrant population from areas in which these pathologies are endemic and due to the increase in immunosuppressed HIV patients (5). In the absence of appropriate therapy, these pathologies might be fatal; the possibilities for differential diagnosis would be of great clinical importance, particularly because of the different treatment protocols required for NC and ICT.

ACKNOWLEDGMENTS

This case report has been presented as a poster for the 23th World Congress of Pathology and Laboratory Medicine, Istanbul, Turkey, May 26 - 30, 2005.

REFERENCES

1. Gavazzi, G., Bouchard, O., Bosseray, A., Leclerq, P. and Micoud, M. (1998): Cerebral and pulmonary miliary tuberculosis in an immunocompetent patient: aggravation in an adequately treated patient. Presse. Med., 27, 958-962.
2. Hopewell, P. C. (1994): Overview of clinical tuberculosis. p. 25-46. *In* B. R. Bloom (ed.), Tuberculosis. ASM Press, Washington, D.C.
3. Kilani, B., Ammari, L., Tiouiri, H., Goubontini, A., Kanoun, F., Zouiten, F. and Chaabene, T. B. (2003): Neuroradiologic manifestations of central nervous system tuberculosis in 122 adults. Rev. Med. Interne, 24, 86-96.
4. Ravenscroft, A., Schoeman, J. F. and Donald, P. R. (2001): Tuberculous granulomas in childhood tuberculous meningitis: radiological features and course. J. Trop. Pediatr., 47, 5-12.
5. Kioumehr, F., Dadsetan, M. R., Rooholamini, S. A. and Au, A. (1994): Central nervous system tuberculosis: MRI. Neuroradiology, 36, 93-96.
6. Kennedy, D. H. and Fallon, R. J. (1979): Tuberculous meningitis. JAMA, 241, 264-268.
7. Garg, R. K. (2001): Medical management of neurocysticercosis. Neurol. India, 49, 329-337.
8. Bern, C., Garcia, H. H., Evans, C., Gonzalez, A. E., Verastegui, M., Tsang, V. C. and Gilman, R. H. (1999): Magnitude of the disease burden from neurocysticercosis in a developing country. Clin. Infect. Dis., 29, 1203-1209.
9. Mafojane, N. A., Appleton, C. C., Krecek, R. C., Michael, L. M. and Willingham, A. L. (2003): The current status of neurocysticercosis in Eastern and Southern Africa. Acta Trop., 87, 25-33.
10. Aditya, G. S., Mahadevan, A., Santosh, V., Chickabasaviah, Y. T., Ashwathnarayanarao, C. B. and Krishna, S. S. (2004): Cysticercal chronic basal arachnoiditis with infarcts, mimicking tuberculous pathology in endemic areas. Neuropathology, 24, 320-325.
11. Del Brutto, O. H. and Noboa, C. A. (1991): Late-onset epilepsy in Ecuador; aetiology and clinical features in 225 patients. J. Trop. Geogr. Neurol., 1, 31-34.
12. Garg, R. K., Kar, A. M. and Kumar, T. (2000): Neurocysticercosis like presentation in a case of CNS tuberculosis. Neurol. India, 48, 260-262.
13. Mitchell, W. G. and Crawford, T. O. (1988): Intraparenchymal cerebral cysticercosis in children: diagnosis and treatment. Pediatrics, 82, 76-82.
14. Garcia, H. H., Pretell, E. J., Gilman, R. H., Martinez, S. M., Moulton, L. H., Del Brutto, O. H., Herrera, G., Evans, C. A., Gonzalez, A. E. and Cysticercosis Working Group in Peru (2004): A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. New Engl. J. Med., 350, 249-258.
15. Venkataraman, S. and Vijayan, G. P. (1979): Neurocysticercosis: clinical manifestations and problems in diagnosis. J. Assoc. Physicians India, 27, 543-549.
16. Garcia, H. H. and Del Brutto, O. H. (2000): *Taenia solium* cysticercosis. Infect. Dis. Clin. North Am., 14, 97-119.
17. Corona, T., Pascoe, D., Gonzalez-Barranco, D., Abad, P., Landa, L. and Estanol, B. (1986): Anticysticercous antibodies in serum and cerebrospinal fluid in patients with cerebral cysticercosis. J. Neurol. Neurosurg. Psychiatry, 49, 1044-1049.