Comparison between solitary and multiple intracranial tuberculoma

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ABSTRACT

الأهداف: مقارنة وتحليل السمات المرضية (الباثولوجيكيه)، السريرية والإشعاعية للتورم السلي المفرد و/أو المتعدد للجهاز العصبي المركزي .

الطريقة: أجريت دراسة في جامعة الجنوب المركزية – مستشفى زنجاي الأول – تشانجتشا – هونان – الصين، خلال الفترة مابين 1998م وحتى 2008م. باستخدام الرنين المغناطيسي (MRI) تمت مقارنة وتحليل 42 مريضاً مصاب بالتورم السلي في الجهاز العصبي المركزي (CNSTs). وتم تأكيد التشخيص النهائي بواسطة تحليل الأنسجة (علم أمراض الأنسجة).

النتائج: لاحظنا أن 42 (64.3%) من المرضى يعانون من التورم السلي المتعدد في الجهاز العصبي المركزي، منهم (55.6%) من الحالات كانت مصحوبة بالتهاب السحايا، و (44.4%) بدون التهاب السحايا. كانت الآفات المفردة موجودة في (35.7%) من المرضى، (80%) كانوا دون التهاب سحايا، (20%) مصحوبة بالتهاب السحايا. أما في التورم السلي المتعدد CNSTs 55.6% كانت عبارة عن أورام حبيبية (حبيبومات) غير متجبنة، (74.1%) أورام حبيبية (حبيبومات) متجبنة ذات مركز صلب، في حين كانت التورم السلي المفرد (CNSTs) عبارة عن أورام حبيبية (حبيبومات) متجبنة ذات مركز صلب (80%). أما بالنسبة للآفات المتعددة فكانت المواقع المفضلة هي الفص الصدغي، الفص الأمامي، المخيخ (cerebella)، في حين إن الآفات المفردة كانت مواقعها المفضلة هي الفص القمي والمخيخ. الجدير بالذكر أن السمات التي تم تشخيصها بواسطة تحليل الأنسجة كانت هي نفسها في جميع المرضى.

خاتمة: التورم السلي المتعدد (CNSTs) عادةً ما يكون مصحوباً بالتهاب السحايا، في حين يحدث التورم السلي المفرد (CNSTs) مصحوباً بدرجة أقل من المظاهر السريرية الغير نمطية. لوحظ الاختلاف في المواقع المفضلة لكلاً من التورم السلي المفرد والمتعدد.

Objective: To compare and analyze the clinical, radiological, and pathological features of solitary or/and multiple CNS tuberculomas (CNSTs).

Methods: The study was conducted at Central South University, First Xiangya Hospital, Changsha, Hunan, China between 1998-2008. Forty-two subjects with diagnosed CNSTs were compared and analyzed by multiple or solitary lesions seen on enhanced MRI. The final diagnosis of tuberculomas was confirmed by histopathology.

Results: From the 42 subjects, 64.3% multiple CNSTs were observed, out of which, 55.6% were with meningitis and 44.4% without meningitis. Of the CNSTs, solitary lesions were present in 35.7%, 80% of which were without meningeal involvement, and 20% with meningeal involvement. In multiple CNSTs, 55.6% were noncaseating granulomas, and 74.1% caseating granulomas with a solid center, while in solitary CNSTs, 80% were caseating granulomas with a solid center. For multiple lesions, temporal lobe, frontal lobe, cerebella, and brain stem were predilection sites. While for solitary lesions, apical lobe, and cerebellum were predilection sites. The histopathological features were the same in all multiple and solitary lesions.

Conclusions: Multiple CNSTs are more often associated with meningitis, while solitary CNSTs particularly occur with less or atypical clinical manifestation. Difference in the predilection sites between multiple and solitary CNSTs were observed.

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Tuberculosis is still a major cause of public health problems in developing and industrialized nations. In developing countries, an indigent economic and social situation is responsible for the spreading of

the disease with the highest rates of morbidity and mortality, while in the developed world, drug abuse and immunosuppressive therapies for certain diseases have contributed to the resurgence of tuberculosis.[1] The most common manifestations of CNS tuberculosis are intracranial tuberculomas (ICTs) and tubercular meningitis (TBM).[2,3] In developing countries, 5-11% of CNS mass lesions are tuberculomas.[4,5] They are relatively unusual in the developed nations, but because of an increase in immigrant populations and the association of tuberculosis with acquired immunodeficiency syndrome, it will be more and more frequently encountered in the future. Clinical manifestations and consequences of accurate and early diagnosis are the key elements in the management of central nervous system tuberculomas (CNSTs). Prompt diagnosis may lead to earlier treatment and better results; therefore, its identification on imaging is crucial for its management. The CNSTs have been differentiated from other causes of intracranial masses such as pyogenic abscess, toxoplasmosis, sarcoidosis, hydatidosis, syphilitic gummas, primary or metastatic malignant disease including glioma and lymphoma.[6] The principal imaging techniques utilized in characterization of these lesions are CT and enhanced MR imaging. The result produced by CNSTs on a CT may be completely impossible to differentiate from those of these other conditions. The use of imaging tools, such as enhanced MRI may be useful in the diagnosis.[6-8] However, neuroimaging studies have failed to reliably diagnose tuberculomas, necessitating histological confirmation.[9,10] The characteristics of solitary and multiple ICTs are extremely diverse. The understanding of their characteristics and difference may contribute to the early diagnosis. To investigate the difference between the solitary and multiple CNSTs, we retrospectively analyzed the clinical, radiological, and pathological features of 42 adult patients who had CNSTs.

Methods. This retrospective study was approved by the Department of Neurology of Xiangya Hospital of Central South University, Changsha, Hunan, China. Forty-two patients with CNSTs were retrospectively included in this study between 1998 and 2008 at the Department of Neurology of Xiangya Hospital of Central South University. There were 24 males,

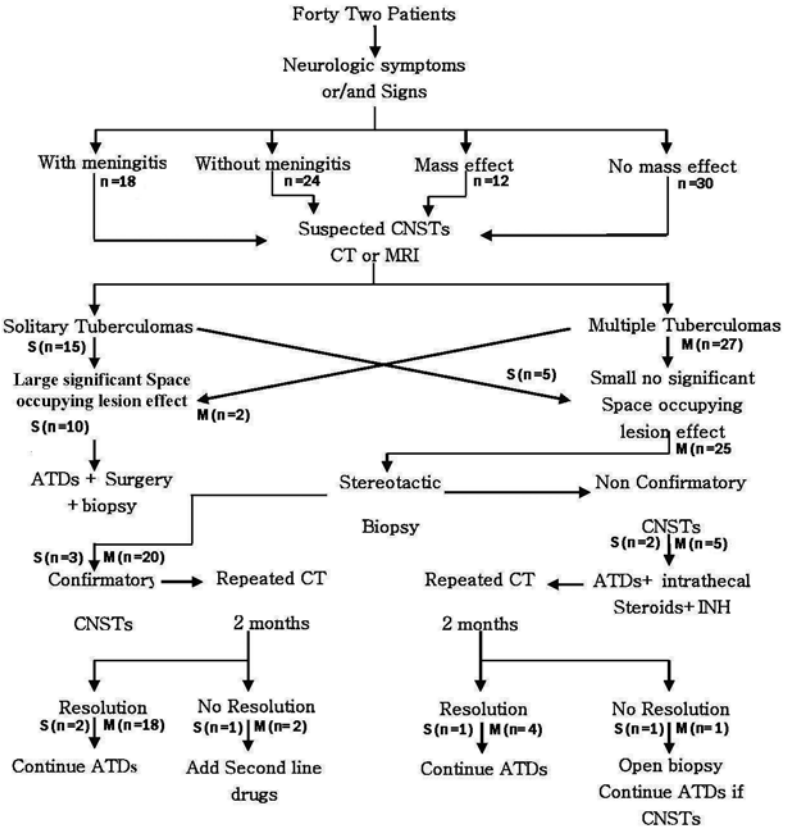

Figure 1 - Management protocol for all patients. n - number of the patients, M - multiple intracranial tuberculomas, S - solitary intracranial tuberculomas, ATDs - antitubercular drugs, CNSTs - central nervous system tuberculomas

and 18 females with age ranged from 18-63 years. In uncooperative patients, sedation was given in appropriate doses. The biopsy of the lesion was performed either under ultrasound guidance (stereotactic) or by open craniotomy. The diagnosis was based on typical CSF features, history of contact with an active tuberculosis patient, enzyme linked immunosorbent assay (ELISA) for tubercular antigen, response to specific therapy, typical radiological features and positive CSF, and confirmed by histopathology. Grocott, GMS, and PAS were negative in all patients' tissue. The management protocol for all patients is shown in **Figure 1**. The treatments used in our patients were quadruple antituberculosis chemotherapy (isoniazid, rifampicin, pyrazinamide, and ethambutol), second-generation chemotherapeutic agents (ofloxacillin, kanamycin, streptomycin, ciprofloxacillin) and INR and steroids.

Results. The duration of illness ranged from 16-140 days. All patients were from low social and economic condition families; none had HIV infection. Of the CNSTs, immuno-compromise was present in 13 patients (31%), 9 were treated with glucocorticosteroids, 3 had hepatitis B, and one was treated with anti-tubercular therapy because of his pulmonary tuberculosis. In 18 (42.9%) patients who underwent chest radiograph or CT, 10 patients (23.8%) had active pulmonary tuberculosis and 8 patients (19.1%) had inactive tuberculosis. Twelve patients with CNSTs underwent surgical excisions. The clinical manifestations of the multiple or solitary lesions of tuberculomas are summarized **Table 1**. Among the total of 42 patients, 27 patients could be evaluated as having multiple tuberculomas with meningitis (55.6%) or without meningitis (44.4%). They were classified as noncaseating granuloma (55.6%) or caseating granuloma with solid center (74.1%) (**Figure 2**). Tuberculomas with solitary lesions were observed in 15 (35.7%) patients, out of which there were 3 patients (20%) with meningitis, and 12 (80%) without meningitis. In these 15 patients, 12 patients (80%) (**Figure 3**) had caseating granuloma with solid center and the remainder (20%) had caseating granuloma with liquid center. Furthermore, tuberculomas were seen in various locations. For multiple lesions, temporal lobe (33.3%), frontal lobe (50%), cerebella (45.2%), and brain stem (47.6%) were predilection sites, and lesions were usually dissymmetry distributed. While for solitary lesions, the apical lobe (6/15, 40%), and cerebellum (5/15, 33.3%) were predilection sites. Of the 15 patients with solitary lesions, 2/15 (20%) were located in the boundary of the frontal and temporal lobe, 1/15 (6.7%) were in the brain stem, and 1/15 (6.7%) were in the occipital lobe.

Table 1 - Demographic data and clinical manifestations of the solitary or multiple intracranial tuberculomas (N=42).

Clinical manifestations	Multiple lesions, n=27 (64.3%)		Solitary lesions, n=15 (35.7%)	
	With meningitis	Without meningitis	With meningitis	Without meningitis
Patient number: n (%)	15 (55.6)	12 (44.4)	3 (20)	12 (80)
Age, year (mean)	19-63 (42.3)	20-36 (28)	28-61 (46.3)	18-30 (22.5)
Gender (M/F)	1:4	1:3	1:2	1:1
Duration of illness (days)	16-60 (32.8)	20-90 (44.6)	31-75 (53.9)	25-140 (68.8)
Onset of disease: n (%)				
Acute	6 (40)	3 (25)	0	3 (25)
Subacute	9 (60)	6 (50)	3 (100)	6 (50)
Chronic	0	3 (25)	0	3 (25)
Headache: n (%)	15 (100)	12 (100)	3 (100)	12 (100)
Fever: n (%)	13 (86.7)	9 (75)	0	6 (50)
Weakness of limbs: n (%)	10 (66.7)	7 (58.3)	1 (33.3)	6 (50)
Cranial nerve palsy: n (%)	15 (100)	10 (83.3)	0	0
Seizure: n (%)	0	0	2 (66.7)	5 (41.7)
Conscious disturbance: n, (%)	11 (73.3)	4 (33.3)	1 (33.3)	4 (33.3)
Behavioral changes: n (%)	6 (40)	5 (41.7)	0	3 (25)
Extra CNS TB: n (%)	14 (93.3)	8 (66.7)	0	0
Neck stiffness: n (%)	15 (100)	9 (75)	0	7 (58.3)
Romberg sign (+): n (%)	6 (40)	5 (41.7)	2 (66.7)	4 (30)
Hydrocephaly: n (%)	13 (86.7)	3 (25)	1 (33.3)	2 (16.7)
Prognosis: n (%)				
Curing	0	2 (16.7)	2 (66.7)	4 (33.3)
Amelioration	7 (46.7)	7 (58.3)	1 (33.3)	4 (33.3)
Severe sequelae	4 (26.6)	1 (8.9)		1 (8.9)
Death	4 (26.6)	3 (25)		1 (8.9)

CNS - central nervous system, TB - tuberculosis

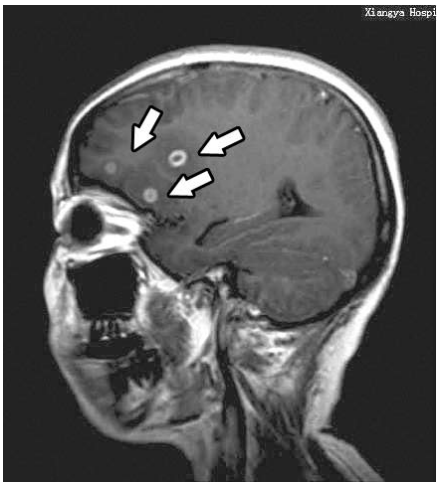

Figure 2 - A T1-weighted sagittal plane MRI showing left multiple frontal lobe tuberculomas with contrast enhancement giving to it a ring-enhancement appearance and perifocal edema.

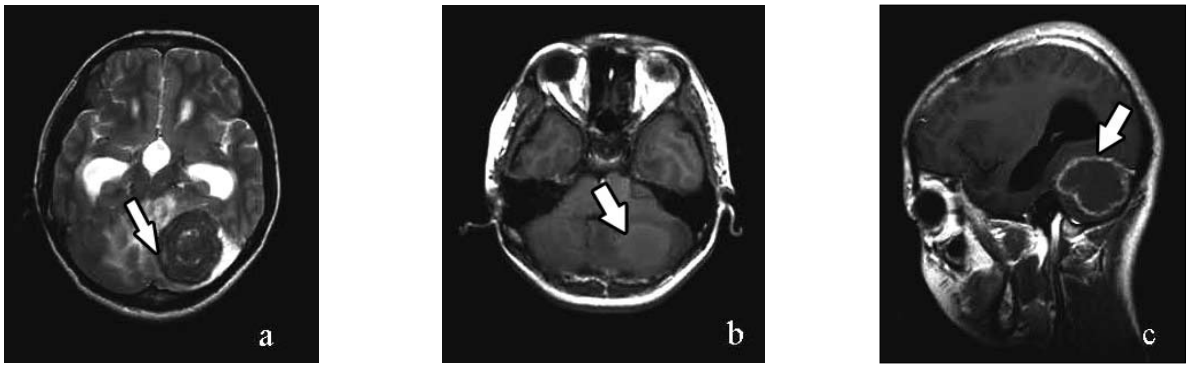

Figure 3 - Solitary tuberculoma with hydrocephaly **a)** T2 and **b)** pre-contrast T1-weighted axial images show presence of solitary tuberculomas at left cerebellum with iso-intense on T1 weighted image and hypo-intense on T2-weighted image with perifocal edema. **c)** Post-contrast T1-weighted sagittal plane images demonstrate thick ring-enhancement with lateral cerebral ventricle pressed.

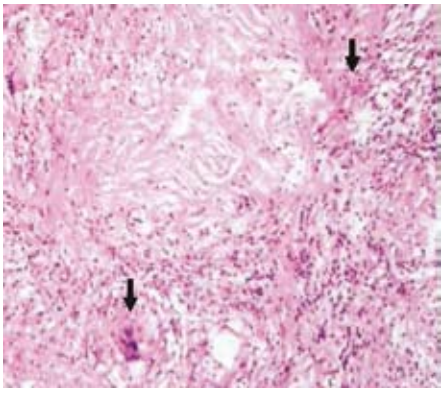

Figure 4 - Granulomatous inflammation with caseous necrosis forming a tuberculoma (Hematoxylin & Eosin x 125).

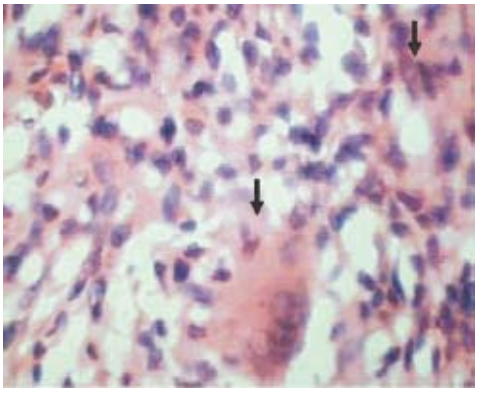

Figure 5 - Epithelioid cells, multinucleated giant cells, and lymphoplasmacytic cells (imprint-smear, Hematoxylin & Eosin x 500).

Meningeal enhancements were seen in the basal cistern (83.3%), suprasellar cistern (55.6%), lateral cleft cistern (27.8%), and cisterna ambiens (38.9%). Nineteen patients (45.2%) had associated hydrocephalus, and 35.7% of patients (15/42) had ischemic changes. The ischemic changes were mostly located in the basal ganglia bilaterally. In 4 patients, the hydrocephalus resulted from compression of the basal subarachnoid cisterns by narrowing of the aqueduct and third ventricle by tuberculomas. Epithelioid cell granulomas with multinucleated giant cells, inflammatory cells, and caseous necrosis were observed in all patients (**Figures 4 & 5**).

Discussion. Tuberculoma of the brain is the most common feature of CNSTs, accounting for 1% of tuberculosis patients.[11] The conditions such as emergence of AIDS,[12] intravenous drug use, alcoholism, transplantation, aggressive chemotherapy, and so forth[13] are mainly considered to be responsible for the annual increase of the disease. In this paper, the annual increase between years 1998 and 2008 was not observed. We demonstrated that low social and economic conditions, exposure to active tuberculous patients, and positive family history are associated with the prevalence of the disease.[14]

A number of studies considered CNSTs as a consequence of TBM; however, tuberculomas may present with meningitis, may lead to meningitis, or may develop during the treatment of TBM. Also, it can occur in otherwise healthy individuals.[15] According to our results, half of CNSTs presented without meningitis and extra CNS TB, especially those with solitary lesions.[16] The diagnosis of CNSTs is difficult; whatever resources are available to the therapist. This is because it does not come on suddenly with classic meningitis symptoms. Furthermore, untreated ICTs are always fatal so that the clinical diagnostic aids or laboratory assay must be highly sensitive. The high mortality associated with CNSTs can be due to multiple factors, including the lack of specific signs and symptoms that allow early diagnosis of TBM. In our patients, multiple and solitary tuberculomas usually presented with acute or subacute headache, fever, and weakness of limbs. Most clinical findings are not consistent with TBM, and patients with TBM usually present with a longer prodromal stage, as TBM is a chronic disease. The lack of specific signs and symptoms suggests a set of potentially discriminative features between multiple and solitary ICTs. In suggesting these features, we would like to stress the following points: 1) Multiple tuberculomas are more common than solitary ones. 2) Solitary CNSTs present a subtler clinical picture than multiple CNSTs. The typical presentations for multiple CNSTs are headache, meningeal irritation, cranial nerve palsy, neurologic deficits, and mental status changes, while solitary CNSTs may manifest themselves with seizures. 3) Most multiple CNSTs patients do have extra-CNS tuberculosis that results from the hematogenous spread of a distant focus of Mycobacterium tuberculosis infection, while a small number of solitary CNSTs patients have extra CNS TB because of extension of the CSF infection into the adjacent parenchyma via cortical veins or small penetrating arteries.[17] We presume that this phenomenon is due to the different route of infection of the 2 types; the multiple ones are mostly second to hematogenous spread, while the others evolve from CSF infection into the adjacent parenchyma. Surgical intervention may be necessary in situations with solitary CNSTs tuberculosis or multiple CNSTs with mass effect. In the CNS, tuberculous solitary lesions (or micro tuberculomas) grow slowly and become encapsulated after a latent period, resulting in paradoxical progression of existing lesions. This may be supported by an accompanying immunological phenomenon, namely, the local perilesional secondary granulomatous vasculitis associated with intimal proliferation and degeneration of the vessel wall with occlusion of the vessel lumen, which worsens the penetration of the tuberculostatic drugs into the lesions. However, multiple tuberculomas are usually small, disperse, and deep, and prompt anti-tuberculosis drugs treatment usually can achieve good therapeutic effect. The prognosis in solitary CNSTs patients is better than those with multiple tuberculomas, most of the patients will improve.

In this study, the multiple CNSTs were mainly located in the temporal lobe, frontal lobe, cerebella and brain stem, while solitary CNSTs were located in the apical lobe and cerebellum. The frontal lobe (50%) is the most involved region in our series. A number of studies analyzed the efficacy of radiological investigations in the diagnosis of CNSTs. Contrast enhanced MRI had an opportunity to diagnose the localized lesions, meningeal enhancement, and brain stem involvement.[6,18] The MRI features of the tuberculoma depend on whether the granuloma is caseating with a solid center, or caseating with a liquid center or noncaseating. Noncaseating granuloma is hypointense on T1-weighted images and hyperintense on T2-weighted images; and usually shows homogeneous enhancement on contrast-enhanced MRI.[17,19] In the solid caseating granuloma, the central portion enhances heterogenously, whereas the capsule presents a ring-enhancing pattern, which tends to be unbroken and is usually of uniform thickness. This kind of lesion appears relatively hypo- or isointense on T1-weighted images and iso- or hypointense on T2-weighted images.[17] The granulomas with central

liquefaction appear centrally hypointense on T1- and hyperintense on T2-weighted images with a peripheral hypointense rim on T2-weighted images. After injection of Gd-DTPA, the 2 types of caseating granuloma demonstrate intense rim enhancement of the lesion on T1-weighted image. The hypointense rim represents the tuberculoma capsule.[17] The images acquired after intravenous gadolinium administration in these cases also show rim enhancement. In the liquefaction stage, lesions may be indistinguishable on MR imaging from true tuberculous or pyogenic abscess formation.[17] Those studies demonstrated that neuroimaging might be helpful in the diagnosis of tuberculosis, however, histopathological examination is the golden standard in the setting of exact diagnosis as seen in our study. Some tuberculomas cannot be identified by the stereotactic biopsy method. It may be the one explanation why open biopsy was performed.

We conclude that most patients presented with headache, weakness of limbs, and ataxia. Solitary CNSTs present a subtler clinical picture than multiple CNSTs. The typical presentation for multiple CNSTs was slow progressive fever, signs of meningeal irritation, followed by cranial nerve involvement. However, seizures were a typical presentation for solitary CNSTs. The prognosis of most patients with solitary tuberculoma was good, and better than those with multiple tuberculomas. Temporal lobe, frontal lobe, cerebella, and brain stem were preferable locations for multiple tuberculomas, while the apical lobe and cerebellum were preferable locations for solitary tuberculomas. Histopathological features were the same in both multiple and solitary tuberculomas. The patients' age (18-63 years) seems to be the only limitation in our study, and further research is warranted to provide a new diagnostic basis for ICTs.

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References

1. Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. ***Am Fam Physician*** 2005; 72: 1761-1768.
2. Kaminogo M, Ishimaru H, Morikawa M, Suzuki Y, Shibata S. Proton MR spectroscopy and diffusion-weighted MR imaging for the diagnosis of intracranial tuberculomas. Report of two cases. ***Neurol Res*** 2002; 24: 537-543.
3. Thwaites GE, Chau TT, Stepniewska K, Phu NH, Chuong LV, Sinh DX, et al. Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. ***Lancet*** 2002; 360: 1287-1292.
4. Bouchama A, al-Kawi MZ, Kanaan I, Coates R, Jallu A, Rahm B, et al. Brain biopsy in tuberculoma: the risks and benefits. ***Neurosurgery*** 1991; 28: 405-409.
5. Mohanty A, Santosh V, Anandh B, Kolluri VR, Vasudev MK, Hegde T, et al. Diagnostic efficacy of stereotactic biopsies in intracranial tuberculomas. ***Surg Neurol*** 1999; 52: 252-257.
6. Jinkins JR, Gupta R, Chang KH, Rodriguez-Carbajal J. MR imaging of central nervous system tuberculosis. ***Radiol Clin North Am*** 1995; 33: 771-786.
7. Gupta RK, Jena A, Sharma A, Guha DK, Khushu S, Gupta AK. MR imaging of intracranial tuberculomas. ***J Comput Assist Tomogr*** 1988; 12: 280-285.
8. Jinkins JR. Computed tomography of intracranial tuberculosis. ***Neuroradiology*** 1991; 33: 126-135.
9. Rahman NU. Intracranial tuberculomas: diagnosis and management. ***Acta Neurochir*** 1987; 88: 109-115.
10. Selvapandian S, Rajshekhar V, Chandy MJ, Idikula J. Predictive value of computed tomography-based diagnosis of intracranial tuberculomas. ***Neurosurgery*** 1994; 35: 845-850.
11. Hejazi N, Hassler W. Multiple intracranial tuberculomas with atypical response to tuberculostatic chemotherapy: literature review and a case report. ***Acta Neurochir (Wien)*** 1997; 139: 194-202.
12. Bishburg E, Sunderam G, Reichman LB, Kapila R. Central nervous system tuberculosis with the acquired immunodeficiency syndrome and its related complex. ***Ann Intern Med*** 1986; 105: 210-213.
13. Prabhakar S, Thussu A. CNS tuberculosis. ***Neurol India*** 1997; 45: 132-140.
14. Bayindir C, Mete O, Bilgic B. Retrospective study of 23 pathologically proven cases of central nervous system tuberculomas. ***Clin Neurol Neurosurg*** 2006; 108: 353-357.
15. Adeolu AA, Shokunbi MT, Malomo AO, Akang EA, Obajimi MO, Komolafe EO. Solitary intracranial tuberculoma in patients without immuno-suppression: a report of three cases. ***Niger Postgrad Med J*** 2006; 13: 69-72.
16. Unal A, Sutlas PN. Clinical and radiological features of symptomatic central nervous system tuberculomas. ***Eur J Neurol*** 2005; 12: 797-804.
17. Bernaerts A, Vanhoenacker FM, Parizel PM, Van Goethem JW, Van Altena R, Laridon A, et al. Tuberculosis of the central nervous system: overview of neuroradiological findings. ***Eur Radiol*** 2003; 13: 1876-1890.
18. Katti MK. Pathogenesis, diagnosis, treatment, and outcome aspects of cerebral tuberculosis. ***Med Sci Monit*** 2004; 10: 215-229.
19. Morgado C, Ruivo N. Imaging meningo-encephalic tuberculosis. ***Eur J Radiol*** 2005; 55: 188-192.