Late-Onset Cerebral Vasculitis with Tuberculous Meningitis: A Case Report

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Abstract

Tuberculous cerebral vasculitis (TCV) is a catastrophic complication of tuberculous meningitis (TBM). We report herein the case of a 41-year-old woman with TBM who presented with a fever and headache for 2 weeks. Cerebrospinal fluid analysis revealed pleocytosis with lymphocytic predominance. On admission day 4, an anti-tuberculosis regimen and oral prednisolone were initiated; on day 30, she developed TCV during tapering of the prednisolone dosage. After supportive care and an increased dosage of prednisolone, her condition gradually improved to normal. We suggest that TCV should be included in the differential diagnosis of any case of neurological deterioration arising during the course of TBM. (J Intern Med Taiwan 2014; 25: 362-370)

Key Words: Tuberculous meningitis, Cerebral vasculitis, Literature review, Risk factor

Introduction

Cerebral vasculitis represents inflammation of cerebral blood vessel walls[1], and tuberculous cerebral vasculitis (TCV) accounts for 12.5% of secondary cerebral vasculitides[2]. TCV is a catastrophic complication of tuberculous meningitis (TBM)[3], and TBM occurs in 1.5–5% of tuberculosis cases in Taiwan[4].

TCV causes severe neurological sequelae[3] and is rarely a fatal disorder. We report herein a case of a 41-year-old woman with a documented diagnosis of TBM with TCV.

Case

A 41-year-old woman with peptic ulcer history developed a headache for 2 weeks prior to admission. Her body weight was approximately 60 kg. Her headache characteristics were as follows: a visual anesthesia score of 6–7/10, a duration of 1–2 hours, an onset to maximal intensity interval of seconds, a frequency of 2–3 times/day, aggravated by exercise, and relieved by rest. The headache was not related to posture, cough, or exertion. The headache became more severe and frequent (2 times/day) with nausea and vomiting. One day before admission, she experienced flu-like symptoms before the headache. She

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reported no history of blurred vision, double vision, neck pain, or change in consciousness. Subsequently, she was brought to the emergency room for help, where neurological examination revealed neck stiffness and a positive Brudzinski's sign on the left side. An emergency computed tomography (CT) of the brain revealed mild brain swelling. Cerebrospinal fluid (CSF) from a subsequent lumbar puncture revealed a white cell count (WBC) of 433/μL, a lymphocyte count of 97%, a lactate level of 6.9 mmol/L, a protein level of 246 mg/dL, a glucose level of 12 mg/dL, negative results on India ink staining, negative cryptococcal antigen test result, an initial pressure of 120 mm H_2O, and a closing pressure of 100 mm H_2O. Initial laboratory data showed a WBC count of 12,200/μL, a serum glucose level of 130 mg/dL, and normal liver and renal function test results. The initial chest film showed no definite active lung lesion. Under a tentative diagnosis of meningitis, the patient was admitted. The brain magnetic resonance imaging (MRI) scan of the brain is shown in Figure 1. Serology tests for human immunodeficiency virus and cryptococcus was negative. A combination of ceftriaxone, vancomycin, and acyclovir was prescribed as empirical therapy. Three days later, a second CSF study showed persistent pleocytosis with lymphocytic predominance and an increased protein level.

Based on the clinical findings and CSF analysis, TBM was considered. Analysis of CSF was negative for bacterial culture, herpes simplex polymerase chain reaction result, acid-fast staining and *Mycobacterium tuberculosis* complex (MTBC) direct test. On admission day 4, Rina (300 mg/day rifampicin plus 150 mg/day isoniazid), ethambutol (800 mg/day), and pyrazinamide (1200 mg/day)(HERZ), were empirically prescribed, as well as prednisolone 10 mg po every 8 hours. Renal function, liver function, bilirubin and uric acid levels were monitored regularly. Because the patient became comatose on admission day 10, a brain CT was performed which showed persistent brain edema with hydrocephalus. Serial CSF values are shown in Table 1. Increased intracranial pressure (370 mm H2O) was noted by a follow-up lumbar puncture on admission day 11, intravenous glycerol (250 ml every 6 hours) and intravenous dexamethasone (5 mg every 6 hours) was prescribed, and a neurosurgeon was consulted. A lumbar drain was suggested for relief of acute symptoms and a ventriculoperitoneal shunt (VPS) was recommended if symptoms of hydrocephalus persisted. However, the patient's family hesitated to

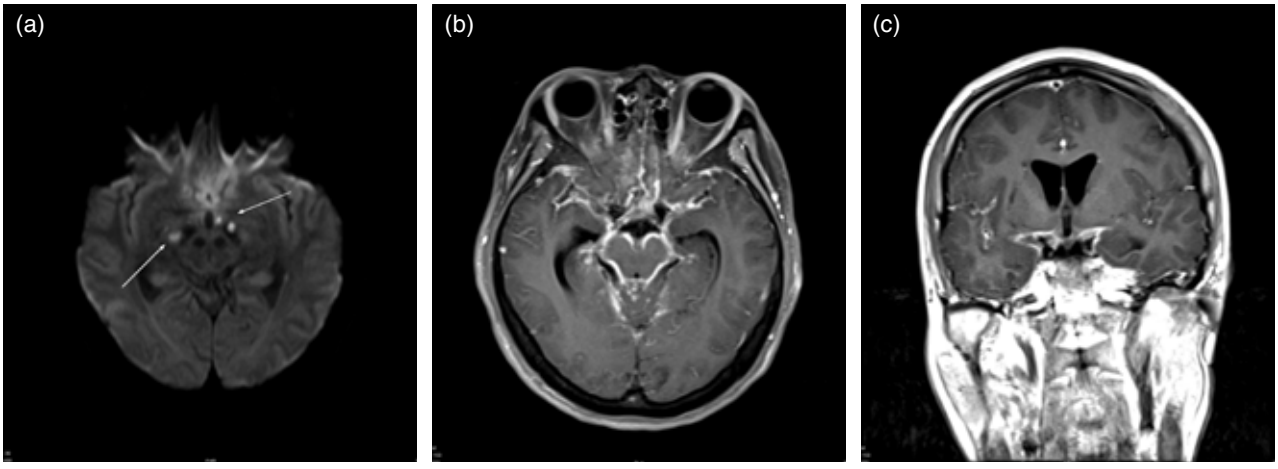

Figure 1. Axial diffusion-weighted image (a) reveals acute infarctions in the hypothalami and midbrain on both sides of the brain. Gadolinium-enhanced T1 axial and coronal MRI images (b and c) shows marked, diffuse leptomeningeal enhancement over the basilar cistern and right sylvian fissure and hydrocephalus.

give consent to the operation, because of concern with the high rate of VPS occlusion associated with a high CSF pleocytosis and protein level. On admission day 15, abdominal distension with abdominal pain was noticed, and an abdominal sonography showed bilateral hydronephrosis with severe urinary retention in the urinary bladder. A Foley catheter inserted was draining 2,300 ml of urine, and an atonic bladder was suspected. On admission day 20, a brain CT revealed persistent hydrocephalus, and the VPS was performed smoothly after her family gave consent to this procedure on admission day 23. However, on post-operation day 1, polyuria (8000 c.c./day) was observed. Diabetes insipidus was diagnosed, and desmopressin was administered. On admission day 21, mycobacterial culture of a CSF specimen collected on admission day 1 showed positivity for MTBC, confirming the diagnosis of TBM. The patient's condition stabilized, and the HERZ regimen was continued. Oral prednisolone was tapered gradually. However, on admission day 30, she became drowsy, and an emergency MRI was arranged (Figure 2). The findings were compatible with cerebral vasculitis, resulting in a diagnosis of TCV. We increased the corticosteroid dosage from 10mg/day into 30mg/day and re-added

Table 1. Serial CSF data

	Unit	Day 1	Day 3	Day 11
Initial pressure	mm H_2O	120	120	370
Appearance		clear	clear	clear
RBC count	/μL	5	4	566
Nucleated cell count	/μL	433	600	288
Neutrophil	%	3	6	1
Lymphocyte	%	97	91	98
Cell no. counted		100	100	100
initial pressure	mm H_2O	120	110	370
Cryptococcal Ag		negative		
Streptococcus B Ag		negative		
Haemophilus influenzae type b Ag		negative		
Streptococcus pneumoniae Ag		negative		
Neisseria meningitidis A, C, Y, W135 Ag		negative		
N. meningitidis serotype B/*Escherichia coli* K1 Ag		negative		
India ink		negative		
Direct Gram stain		negative		
Protein	mg/dL	246	264	442
Glucose	mg/dL	12	12	16
Glucose (serum)	mg/dL	130	115	126
Lactate	mmol/L	6.9		
Lactate (serum)	mmol/L	1.5		
LDH	U/L	60	73	103

aspirin. On admission 41, serial liver enzyme test showed hepatitis, then we hold anti-TB medication and re-evaluate her liver enzyme test according to the guidelines for TB treatment[5]. Right hand tremor, persisting for more than 1 hour, was noted at night; associated with a decreased level of consciousness and a lack of upward gaze for both eyes; serum electrolytes were normal. A subsequent electroencephalography revealed diffuse cortical dysfunction.

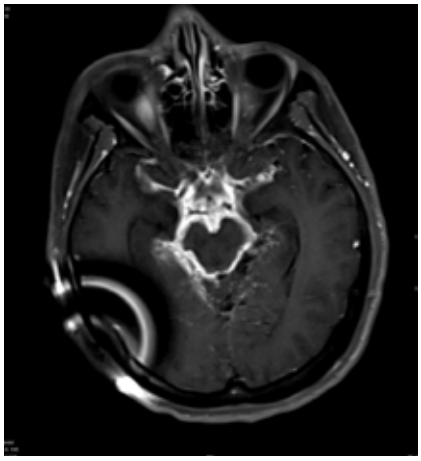

Figure 2. One-month follow-up gadolinium-enhanced T1 axial image (2) shows progressive basilar meningitis. Because a perforator infarct occurred around Willis' circle and because of debris located at the base of the skull, there was no evidence of narrowing of an artery inside the brain; the findings were compatible with tuberculous cerebral vasculitis.

Levetiracetam solution was given for control of focal seizure, probably resulting from TBM. On admission day 53, susceptibility testing for MTBC displayed susceptibility to all tested drugs. A follow-up liver enzyme test showed improvement; therefore, on admission day 55, anti-TB medication was re-started, and ethambutol, isoniazid, and pyrazinamide were rechallenged serially according to the guidelines for TB treatment[5]. At the same time, we opted to administer 300 mg oral rifabutin daily instead of rifampicin. The patient's right hand tremor improved considerably under clonazepam and levetiracetam. The sequelae of TCV included focal neurological deficit (left limb weakness), a confused state, and seizures. She received isoniazid 300 mg/day, rifabutin 300 mg/day, ethambutol 800 mg/day, and pyrazinamide 1200 mg/day for 2 months, then switched to isoniazid 300 mg/day, rifabutin 300 mg/day , and ethambutol 800 mg/day. There were no further episodes of fever or seizure attacks, and her condition gradually stabilized. On admission day 90, she was discharged, and she was followed up at the outpatient clinic. A follow-up MRI of brain is shown in Figure 3. The total duration of anti-TB therapy was 14 months. Her condition gradually improved to normal without significant neurological sequela.

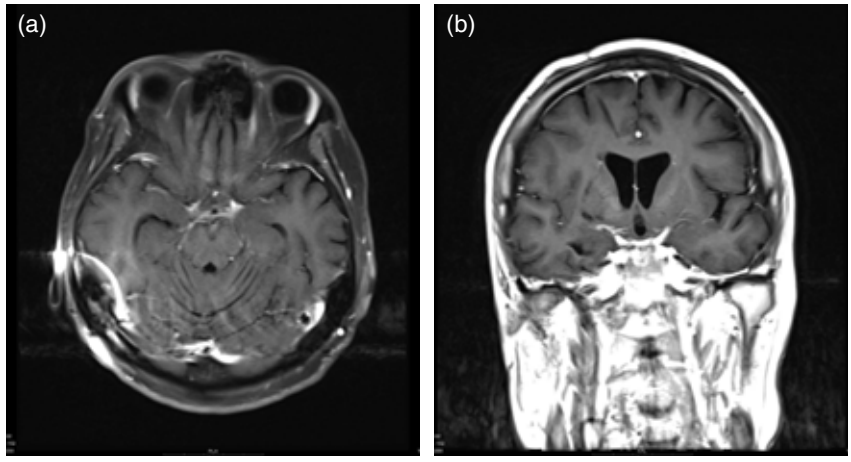

Figure 3. Seven-month follow-up gadolinium-enhanced T1 axial image (a) and coronal MRI scan (b) show significant shrinkage of the basilar meningitis, but hydrocephalus persisted.

Discussion

This is the first case report in central Taiwan to describe a patient with TBM who developed TCV, despite with the use of corticosteroid prior to the onset of the TCV. TCV is a catastrophic complication of TBM, and its occurrence ranges from 6% to 47%[6-9]. Prednisolone is an important component of the treatment regimen for TBM, starting with a high dose (60 mg) that is gradually reduced over 6 weeks. The treatment is then stopped or continued as a low dose (5 mg), depending on the patient's condition[10,11]. The advantages of adjunctive corticosteroid therapy over standard therapy for MTBC infection are increased survival and less frequent sequelae[10,11]. Some studies with shorter corticosteroid treatment durations (2–4 weeks)[12,13] yielded disappointing results, and studies with longer durations demonstrated significant benefits[10,14,15,16]. We recommend that the corticosteroid dosage should be tapered slowly over more than 4 weeks with carefully monitoring of the clinical condition.

In Chan's study[17], only 16.7% of patients had cerebral infarcts at the time of diagnosis of TBM, but cerebral infarcts developed in 10 additional patients (10/12). In addition, Chan also reports that the occurrence of cerebral infarcts is around 41.7% (5/12) at 40 days after onset in patients who were given corticosteroids[17]. This is in accordance with the presentation of our patient. In fact, TCV can develop despite treatment with antituberculous drugs, corticosteroids, and aspirin. In the case reported here, the patient received antituberculous therapy and corticosteroid therapy starting on admission day 4, yet TCV developed on admission day 30.

Previously reported risk factors for TBM and TCV reported include female gender [18], hypertension[19], the presence of human immunodeficiency virus infection[20], prolonged duration of pre-existing symptoms[21-23], hydrocephalus[19,23], high CSF neutrophil counts[9,19], meningeal enhancement on initial brain imaging[9], advanced stage of meningitis[19], and tuberculoma[21] (Table 2). On the basis of our experience with this case, we suggest that TCV be included in the differential diagnosis of neurological deterioration arising during the course of TBM. However, these signs are not specific to cerebral vasculitis[17]. Moreover, the occurrence of asymptomatic vasculitis-associated strokes ranges from 22.2% to 25%[17,24].

With regard to imaging modalities, both cerebral CT and cerebral MRI can contribute to diagnosing TCV, but cerebral vasculitis is not directly visible on CT or MRI. The effectiveness of CT scans in detecting cerebral ischemia ranges from 20.5% to 38%[25]. Brain MRI is sensitive but lacks specificity for detecting vasculitis-associated parenchymatous anomalies in a published series[3,26]. A study by Hajj-Ali[26] showed that MRI was superior to CT in diagnosing TBM and its complications such as stroke, and the present report supports these findings.

Corticosteroids are the cornerstone of therapy for TBM with TCV and should be prescribed in combination with anti-tuberculous regimens to treat TBM. This regimen lowers the risk of death and neurological sequelae in survivors[27].Treatment for TCV is based on corticosteroids[17,26-28]. The pathophysiological mechanisms and non-infectious immunological mechanisms can play an important role in infectious vasculitides[29]. A study by Javaud[24] reported that the median time to the onset of TCV after starting anti-tuberculous therapy was 51 days for the duration of corticosteroid administration. Treatment should include the combination of 4 agents as the initial regimen, including isoniazid, rifampicin, ethambutol, and pyrazinamide. According to current guidelines, the median treatment duration is 9–12 months[25]. Although the duration of anti-tuberculous therapy for TBM is controversial, the evidence for short-course therapy for TBM is still weak[30]. One option is adding an

Table 2. Evidence-based literature review of risk factors for tuberculous meningitis and tuberculous cerebral vasculitis

Risk factors	Study design	Enrolled cases	Results	Reference
Female gender				
Female gender	Retrospective	42 patients	Prolonged duration of pre-existing symptoms and female gender were found as significant risk factors in those who developed neurological sequelae ($p < 0.01$ and $p < 0.05$, respectively).	Cagatay AA, et al. 2004
Hypertension				
Hypertension	Observational	122 patients	Hypertension ($p = 0.007$), stage of meningitis ($p = 0.001$), and presence of hydrocephalus ($p = 0.002$) and exudate ($p = 0.007$) were significantly related to stroke in TBM	Kalita J, et al. 2009
Presence of HIV infection				
Presence of HIV infection	Retrospective	30 patients	Twenty-six were evaluated for stroke, and 6 (23%) had a stroke. The latter 6 had advanced stages of meningitis, 2 tested positive for HIV, 3 tested negative for HIV, and HIV testing was not performed in 1. Of 7 patients without stroke who were tested for HIV, only 1 tested positive.	Pasticci MB, et al. 2013
Advanced stage of disease at clinical presentation				
Advanced stage of disease at clinical presentation	Retrospective	65 patients	Of the 25 patients with ischemic infarction, 23 (92%) had hydrocephalus, 19 (76%) had basal exudates, and 2 (8%) had tuberculomas. The outcome was poor since no patient with infarction recovered completely	Leiguarda R, et al. 1988
Prolonged duration of pre-existing symptoms				
Prolonged duration of pre-existing symptoms	Retrospective	42 patients	Prolonged duration of pre-existing symptoms and female gender were found as significant risk factors in those who developed neurological sequelae ($p < 0.01$ and $p < 0.05$, respectively).	Cagatay AA, et al. 2004
Prolonged doctor delays of antituberculosis and steroid therapies	Retrospective	91 patients	When compared with the non-CI group, patients with CI were associated with a prolonged doctor-initiated delay of antituberculosis therapy and steroid therapy, neurosurgical intervention for hydrocephalus, focal weakness and dementia as sequelae, and a poor outcome.	Sheu JJ, et al. 2012
Hydrocephalus				
Hydrocephalus	Observational	31 patients	Hydrocephalus at presentation was associated with a longer duration of presenting symptoms ($p = 0.01$), ataxia ($p = 0.001$), advanced stages of TBM ($p = 0.045$), a longer delay before commencement of anti-tuberculous chemotherapy ($p = 0.001$), stroke ($p = 0.012$), and a poor outcome at 1 year ($p = 0.001$).	Chan KH, et al. 2003
Presence of hydrocephalus	Observational	122 patients	Hypertension ($p = 0.007$), stage of meningitis ($p = 0.001$), and presence of hydrocephalus ($p = 0.002$) and exudate ($p = 0.007$) were significantly related to stroke in patients with TBM.	Kalita J, et al. 2009
High CSF neutrophil counts				
High CSF neutrophil counts	Prospective	38 patients	The percentage of cerebrospinal fluid leukocytes that were neutrophils was significantly higher in patients with stroke (68%) than in patients without stroke (31%; $p = 0.0001$).	Koh SB, et al. 2006

Table 2. Continued

Risk factors	Study design	Enrolled cases	Results	Reference
Presence of exudate in CSF	Observational	122 patients	Hypertension (p = 0.007), stage of meningitis (p = 0.001), and presence of hydrocephalus (p = 0.002) and exudate (p = 0.007) were significantly related to stroke in patients with TBM.	Kalita J, et al. 2009
Meningeal enhancement on initial brain imaging				
Meningeal enhancement on initial brain imaging	Prospective	38 patients	Upon initial CT imaging, meningeal enhancement was found in 11 patients; of these patients, 6 (54.5%) experienced stroke.	Koh SB, et al. 2006
Stage of meningitis				
Tuberculomas	Retrospective	65 patients	Of the 25 ischemic infarction cases, 23 (92%) had hydrocephalus, 19 (76%) had basal exudates, and 2 (8%) had tuberculomas. The outcome was poor since no patient with infarction recovered completely	Leiguarda R, et al. 1988
Stage of meningitis	Observational	122 patients	Hypertension (p = 0.007), stage of meningitis (p = 0.001), and presence of hydrocephalus (p = 0.002) and exudate (p = 0.007) were significantly related to stroke in patients with TBM	Kalita J, et al. 2009

antiplatelet-aggregating agent, in light of their efficacy during the acute phase of ischemic strokes[31]. The regimen lowers the risk of death and neurological sequelae of TBM with TCV[27,31].

In conclusion, we described a case of TBM complicated with TCV. She developed TCV despite using the anti-tuberculosis regimen with a corticosteroid and aspirin, and required slow and careful tapering of the dosage of corticosteroid because of the risks of developing TCV. We suggest that TCV should be included in the differential diagnosis of any of neurological deterioration arising during the course of TBM.

References

1. Sarwar M, Falkoff G, Naseem M. Radiologic techniques in the diagnosis of CNS infections. Neurol Clin 1986; 4: 41-61.
2. Siva A.Vasculitis of the nervous system.Journal of Neurology 2001; 248: 451-68 .
3. Appenzeller S, Faria A, Zanardi VA, Fernandes SR, Costallat LT, Cendes F.Vascular involvement of the central nervous system and systemic diseases: etiologies and MRI findings. Rheumatol Int 2008; 28: 1229-37.
4. Hsueh PR, Liu YC, Sod J, Liu CY, Yang PC, Luh KT.Mycobacterium tuberculosis in Taiwan. J Infect 2006; 52: 77-85.
5. CDC-Taiwan: Taiwan guideline on TB diagnosis and treatment. In: CDC-Taiwan (eds): 4nd ed. Taiwan Centers for Disease Control, Taipei 2012.
6. Dastur DK, Lalitha V., Udani PM, Parekh U. The brain and meninges in tuberculous meningitis. Gross pathology in 100 cases and pathogenesis. Neurology 1970; 18: 86-100.
7. Lan SH, Chang WN, Lu CH, Lui CC, Chang HW. Cerebral infarction in chronic meningitis: a comparison of tuberculous meningitis and cryptococcal meningitis.Q J Med 2001; 94: 247-53.
8. Berenguer J, Moreno S, Laguna F, et al. Tuberculous meningitis in patients infected with the human immunodeficiency virus.N Engl J Med 1992; 326: 668-72.
9. Koh SB, Kim BJ, Park MH, Yu SW, Park KW, Lee DH. Clinical and laboratory characteristics of cerebral infarction in tuberculous meningitis: a comparative study. J Clin Neurosci 2007; 14: 1073-7.
10. Kalita J, Misra UK. Outcome in tuberculous meningitis at 6 and 12 months: a multiple regression analysis. Int J Tuberc Lung Dis 1999; 3: 261-5.
11. Dooley DP, Carpenter JL, Rademacher S. Adjunctive Corticosteroid Therapy for Tuberculosis: A Critical Reappraisal of the Literature. Clin Infect Dis 1997; 25: 872-87.
12. Lepper MH, Spies HW. The present status of the treatment of tuberculosis of the central nervous system. Ann NY Acad Aci 1963; 106: 106-23.
13. O'Toole RD, Thornton GF, Mukherjee MK, Nath RL. Dexamethasone in tuberculous meningitis: relationship of cerebrospinal fluid effects to therapeutic efficacy. Ann Intern Med 1969; 70: 39-48.
14. Ashby M, Grant H. Tuberculous meningitis treated with cortisone. Lancet 1955; 1: 65-6.
15. Voljavec BF, Corpe RF. The influence of corticosteroid hormones in thetreatment of tuberculous meningitis in

Negroes. Am Rev Respir Dis 1960; 81: 539-45.
16. Escobar JA, Belsey MA, Duenas A, Medina P. Mortality from tuberculous meningitis reduced by steroid therapy. Pediatrics 1975; 56: 1050-5.
17. Chan KH, Cheung RT, Lee R, Mak W, Ho SL. Cerebral infarcts complicating tuberculous meningitis. Cerebrovasc Dis 2005; 19: 391-5.
18. Cagatay AA, Ozsut H, Gulec L, et al. Tuberculous meningitis in adults--experience from Turkey. Int J Clin Pract 2004; 58: 469-73.
19. Kalita J, Misra UK, Nair PP. Predictors of stroke and its significance in the outcome of tuberculous meningitis. J Stroke Cerebrovasc Dis 2009; 18: 251-8.
20. Pasticci MB, Paciaroni M, Floridi P, Malincarne L, Scavizzi M, Baldelli F. Stroke in patients with tuberculous meningitis in a low TB endemic country: an increasing medical emergency? New Microbiol 2013; 36: 193-8.
21. Leiguarda R, Berthier M, Starkstein S, Nogues M, Lylyk P. Ischemic infarction in 25 children with tuberculous meningitis. Stroke 1988; 19: 200-4.
22. Sheu JJ, Hsu CY, Yuan RY, Yang CC. Clinical characteristics and treatment delay of cerebral infarction in tuberculous meningitis. Intern Med J 2012; 42: 294-300.
23. Chan KH, Cheung RT, Fong CY, Tsang KL, Mak W, Ho SL. Clinical relevance of hydrocephalus as a presenting feature of tuberculous meningitis. QJM 2003; 96: 643-8.
24. Javaud N, Certal Rda S, Stirnemann J, et al. Tuberculous cerebral vasculitis: retrospective study of 10 cases. Eur J Intern Med 2011; 22: e99-104.
25. Katti MK. Pathogenesis, diagnosis, treatment and outcome aspects of cerebral tuberculosis. Med Sci Monit 2004; 10: 215-29.
26. Hajj-Ali RA, Calabrese LH. Central nervous system vasculitis.Curr Opin Rheumatol 2009; 21: 10-8.
27. Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev 2008; 23: CD002244.
28. Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J. British Infection Society. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect 2009; 59: 167-87.
29. Donald PR, Schoeman JF. Tuberculous meningitis. N Engl J Med 2004; 351: 1719-20.
30. Prasad KS, Kumar LS, Prasad M, Revanasiddappa HD. Duration of anti-tubercular treatment in tuberculous meningitis: challenges and opportunity. Neurol India 2010; 58: 723-26.
31. van der Worp HB, van Gijn J. Acute ischemic stroke. N Engl J Med 2007; 357: 572-79.

結核性腦膜炎難以避免的結核性腦血管炎：個案報告與文獻回顧

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摘 要

結核性腦血管炎是結核性腦膜炎嚴重的併發症之一。我們報導一名41歲的女子，一開始出現發燒和頭痛兩個星期後，疑似腦膜炎住院，檢驗腦脊髓液，發現細胞增多，以淋巴細胞為主。於住院第4日開始服用抗結核藥物和皮質類固醇，然後病情穩定，逐漸減少皮質類固醇劑量。在住院第30日發生結核性腦血管炎。給予增加皮質類固醇劑量與積極照護後，她的病情逐漸恢復。我們進行相關文獻回顧。在我們的案例中，即使使用皮質類固醇，我們依然要仔細注意那些會發生結核性腦血管炎的高風險患者。結核性腦膜炎患者，應採取適當的照顧，在照顧期間應注意結核性腦血管炎的出現。