Clinical Case Report

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Primary central nervous system ALK-positive anaplastic large cell lymphoma in an adult

A rare case report

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Abstract

Rationale: Anaplastic large cell lymphoma (ALCL) is an aggressive non-Hodgkin lymphoma. It mostly invades lymph nodes with extranodal involvement observed in the soft tissue, bone, and skin.

Patient concerns: We report a 34-year-old Chinese male patient who presented with headache, diplopia, and vomit. Cerebrospinal fluid (CSF) analysis via lumbar puncture showed elevated CSF pressure, elevated CSF protein concentrations, decreased CSF glucose and chloride concentration significantly, and pleocytosis of 68 to 350×10^6/L, in which lymphocytes and monocytes were predominant. These changes could be suggestive of tuberculous (TB) meningitis. Enhanced magnetic resonance imaging of spinal cord delineated multiple enhancing nodules in spinal cord, cauda equina, and cristae membrane, and multiple abnormal enhancing lesions in bilateral lumbar intervertebral foramen.

Diagnoses: Spinal dura mater biopsy and paraffin pathology examination revealed anaplastic lymphoma kinase positive ALCL.

Interventions: High-dose methotrexate, cytosine arabinoside craniospinal, and radiotherapy.

Outcomes: Last follow-up on September 22, 2015 showed no evidence of tumor recurrence and the lower extremity muscle strength recovered to 4/5.

Lessons: ALCL of primary central nervous system is an exceedingly rare tumor, which is usually misdiagnosed as meningitis (especially TB meningitis) according to clinical manifestation and laboratory examination. Thus closely monitoring patient's conditions and timely adjusting therapeutic regimen during treatment are necessary.

Abbreviations: ALCL = anaplastic large cell lymphoma, ALK = anaplastic lymphoma kinase, Ara-C = arabinoside, CNS = central nervous system, CSF = cerebrospinal fluid, CT = computed tomography, HD MTX = high-dose methotrexate, MRI = magnetic resonance imaging, PET-CT = positron emission tomography-computed tomography, TB = tuberculosis.

Keywords: anaplastic large-cell lymphoma, anaplastic lymphoma kinase-positive, case report, central nervous system, meningitis, primary

1. Introduction

Anaplastic large cell lymphoma (ALCL) was described by Stein in 1985[1] as a group of CD30 (Ki-1) positive pleomorphic large cells. Immune phenotype and gene rearrangement display ALCLs originating from T-cell or null-cell phenotype,[2] in which the former accounts for 80%, and the latter 20%. About 40% to 60% ALCLs with the t (2; 5) (p23; q35) translocation[2] express the nucleophosmin-anaplastic lymphoma kinase (ALK), a chimeric protein exerting significant oncogenic potential due to sustained activation of tyrosine kinases. Based on ALK, the immune marker, expressing or not, ALCLs are divided into ALK-positive and ALK-negative[3] phenotypes. ALK-positive ALCLs are commonly seen in patients at the age below 30, often involving the lymph nodes and extranodal sites. In addition to skin, bone, and soft tissue, it can also occur in the lung, stomach, brain, gums, nasopharynx, tonsils, and other rare locations. Compared with ALK-positive ALCLs, ALK-negative ALCLs are commonly present at a middle-aged and elder groups, with a more unfavorable prognosis.[2,4]

ALCLs involving primary central nervous system (CNS) are extremely rare,[5] which may occur at all ages, with most patients below 50 years old and predominantly male. The clinical symptoms are various, and the main manifestations are increased intracranial pressure and headache that are triggered by tumor oppression, nausea, seizures, and movement disorders. Lesions mainly locate on the tentorium cerebelli, primarily on the parietal lobe, frontal lobe, temporal lobe, and occipital lobe, often accompanied by violating local pia mater.[6,7]

2. Patient information

A 34-year-old male was admitted to hospital on October 31, 2013 because of headache after catching cold, diplopia, and vomit for

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one-and-a-half months. Two to three months ago, the patient felt fatigue, with poor state of mind, then appeared runny nose, sustained headache coupled with paroxysmal deterioration, and mild diplopia after running through the rain a half months ago. Self-administration of some cold medicines relieved runny nose partially. The patient then received antibiotic (specifically unknown) treatment in a local hospital, obtaining remission of headache and diplopia in the short term. Thirty-one days ago, headache and diplopia symptoms were aggravated obviously, the patient appeared projectile vomiting. On a clinical basis, tuberculous (TB) meningitis was diagnosed in the local hospital, and the patient was given treatment measures such as anti-TB, reducing the intracranial pressure and oral dexamethasone. Twenty-six days ago, he presented with low-grade fever from noon to night in the next 7 days and the maximum temperature was 38°C. Seventeen days ago, the doctors stopped using anti-TB medicines on account of discovering suspicious neoplasm cells in cerebrospinal fluid (CSF). The patient was in good nutritional and conscious condition, and had been healthy prior to the illness onset, but lost 6 kg after his illness. Details of relevant past and present medical history and interventions are shown in Table 1 (Fig. 1).

3. Physical examination

Physical examination on admission: His vital signs included blood pressure—120/80 mm Hg, heart rate—59 per min, respiratory rate—18 per min, and body temperature—36.5°C. The patient was in good conscious condition. A neurological examination disclosed binocular diplopia of peripheral vision. In addition to neck stiffness was suspicious positive, other signs of meningeal irritation, Kerning sign, and Brudzinski sign were negative. Babinski reflex was negative bilaterally. Direct and consensual light reflex were absent in the right eye on Day 5 postadmission. The next day, strength was 3/5 in muscles of the right lower extremity followed by progressive weakness till it performing pathological character. At the same time, a sensory examination showed numbness of both lower extremities. On Day 19 postadmission, the patient presented with paraplegia of both lower extremities, and his sensation was partially absent to the level of the xiphoid.

4. Diagnostic assessment

Lumbar punctures performed during the full-blown episode repeatedly showed an increased protein, low glucose and chloride levels, and elevated white blood cell (WBC) counts with elevated CSF pressure, but no clear neoplastic lymphoid cells. Likewise, magnetic resonance imaging (MRI), magnetic resonance angiography, and positron emission tomography-computed tomography (PET-CT) examination did not prompt the central lesions. The outcomes of CSF analysis could be suggestive of TB meningitis; however, CNS tumors could not be excluded. With the progress of the disease, enhanced MRI examination of spinal cord revealed that multiple enhancing nodules in spinal cord, cauda equina, and cristae membrane, and multiple abnormal enhancements in bilateral lumbar intervertebral foramen (Fig. 2). The patient underwent a spinal dura mater biopsy, and paraffin pathology examination which revealed fibrofatty tissue infiltrated by a large number of atypical neoplastic cells, with irregular ovoid, twisted nuclear, visible small nucleoli, and nuclear division easily being seen (Fig. 3). Immunohistochemical stains showed immunopositivity for CD30, ALK, tumor cells Vimentin, LCA, TIA1, GranzymeB, and CD56, but negative immunoreactivity for AE1/AE3, CD20, CD3, CD68 (KP1), CD68 (PGM1), CD4, and CD8 (Fig. 4). In situ hybridization was undertaken, and demonstrated Epstein–Barr virus was negative. In order to minimize the damage to the patient, no further biopsy of the brain has proceeded. On the seventh postbiopsy day, PET-CT examination documented (Fig. 5): increased glucose metabolism in the right mesial temporal lobe, considering trigeminal neuropathy; multiple equal density lesions in spinal, with increased glucose metabolism in different degrees; multiple increased glucose metabolism lesions in cauda equina; multiple lumbar nerve root and the first sacral nerve of right sides got thickening, with significantly increased glucose metabolism widened bilateral lateral ventricles and third ventricle. Combined with the dynamic changes of the patient's symptoms and signs, clinical examination results on hospital, we took meninges as the primary lesion with secondary spinal cord and spinal dural involvement. The final diagnosis was finally revised as primary CNS ALK-positive ALCL.

In consideration of CSF changes, particularly chloride decreasing significantly, it was inclined to diagnose this patient as TB meningitis at the onset of the disease. But the effect of diagnosis therapy was not as well as expected. As the disease progresses, patients had new symptoms, which promoted the correct diagnosis as a valuable clinical guideline.

The patient achieved good prognosis with complete remission following 6 cycles high-dose Methotrexate with Leucovorin rescue, 1 cycle high-dose Cytosine arabinoside, a simultaneous 6 cycles of intrathecal chemotherapy, and twice craniospinal radiotherapy. Related examinations showed no evidence of neoplasm recurrence, and the lower extremity muscle strength was recovered to 4/5.

5. Therapeutic interventions

The patient was started with anti-TB therapy (Rifampicin, Pyrazinamide, Ethambutol, and Isoniazid quadruple therapy), and reduced intracranial pressure treatment with Mannitol and 5 mg Dexamethasone after he hospitalized. On the 5th hospital day, he complained of decreased vision in his right eye. MRI of his brain failed to show any lesion, suggested it was more likely to diagnosis as TB meningitis. Considering anti-TB drugs could induce retrobulbar neuritis, Ethambutol and Isoniazid were stopped taking, added Moxifloxacin and increasing the dose of Dexamethasone to 10 mg at the same time. On the 6th hospital day, the patient presented with progressive weakness of the right lower extremity, numbness of both lower extremities, which could not be explained by TB meningitis. The following MRI of spinal cord revealed that multiple enhancing nodules in spinal cord, cauda equina, and cristae membrane. On the 12th hospital day, he underwent a spinal dura mater biopsy and was diagnosed as ALK-positive ALCL. On the 19th hospital day, he was found double-leg paralyzed, sensation partially absent to the level of the xiphoid and was turned over to an hematologist for active treatment. The patient then achieved the following treatment, 6 cycles of systemic high-dose methotrexate (HD MTX, 10 mg) and 1 cycle of high-dose cytosine arabinoside (Ara-C, 8 g) along with 6 cycles of intrathecal chemotherapy, and twice craniospinal radiotherapy.

6. Follow-up and outcomes

The patient had no further discomfort after chemotherapy. The last follow-up on September 22, 2015 showed no evidence of tumor recurrence and the lower extremity muscle strength recovered to 4/5.

Table 1

Timeline.

Dates	Relevant past medical history and interventions								
	Chief complaint	Signs	Diagnostic testing				Interventions		
Preadmission									
45th d	Headache and runny nose	/	/	/	/	/	Self-administration of cold medicines and received antibiotic (specifically unknown) treatment		
31st d	Headache, diplopia, and vomiting	/	CT: lateral ventricles, third ventricle enlargement	Blood RT: WBC counts increased, the proportion of neutrophil and monocytes increased	Blood biochemistry: slightly elevated liver enzymes, low sodium chlorine	/	/	/	/
29th d		/	/			CSF: elevated pressure (350 mmH_2O), 390 WBC/mm^3 with 70% of neutrophil, a higher protein levels, and lower glucose and chloride (115 mmol/L)	TB meningitis, and start with quadruple anti-TB treatment	Dehydration treatment	5 mg/d dexamethasone
26th d		Low-grade fever from noon to night in the next 7 d and the maximum temperature was 38°C	CT: third ventricle enlargement			/			
23rd d			/			CSF: elevated pressure (230 mmH_2O), 210 WBC/mm^3 with 62.5% of lymphocytes, a higher protein levels, and lower glucose and chloride (111 mmol/L)			
17th d	Aggravating headache, diplopia		PET-CT: no clear neoplastic lymphoid cells			CSF: elevated pressure (230 mmH_2O), 68 WBC/mm^3 with 62% of lymphocytes, a higher protein levels, and lower glucose and chloride (118 mmol/L)	CNS Neoplasms? Stop anti-TB therapy		
3rd d		/	/					Stop	Stop
	History of present illness and interventions								
	Chief complaint	Signs	Diagnostic testing				Interventions		
On admission									
1st d	Headache and vision abnormalities	Normal body temperature, binocular diplopia of peripheral vision, neck stiffness, pathological negative		Blood RT: WBC counts increased, the proportion of neutral and monocytes increased	Blood biochemistry: slightly elevated liver enzymes, low sodium chlorine	CSF: normal pressure (180 mmH_2O), 11 WBC/mm^3, a higher protein levels, and lower glucose and chloride (112 mmol/L)		Dehydration treatment	
2nd d			Consultation for local hospital CT/MRI/PET-CT: the left ventricle enlargement			/	Anti-TB therapy		5 mg/d dexamethasone
5th d	Episodic exacerbation of headache, eye remaining small amount of light perception	Only a small amount of light and direct light reflex disappearing in the right eye, indirect light reflex disappearing in the left eye	Enhanced MRI of head: bilateral cerebral and cerebellar hemispheres abnormal meningeal enhancement, the right optic nerve is much more enlarged comparing with the contralateral (Fig. 1)			CSF: elevated pressure (310 mmH_2O), 41 WBC/mm^3, a higher protein levels, lower glucose and chloride (108.4 mmol/L), a few scattered atypical lymphoid cells	Stop taking Ethambutol and Isoniazid		10 mg/d dexamethasone

(*continued*)

Table 1

(continued).

	History of present illness and interventions				
	Chief complaint	**Signs**	**Diagnostic testing**	**Interventions**	
6th d	Episodic exacerbation of headache, right eye; blindness (in the morning), urinary retention (at night)	Myodynamia of the right lower extremity reduced to grade III	/		
7th d	Episodic exacerbation of headache, vision recover gradually, urinary retention	The left lower limb paresthesia, the myodynamia of right lower extremity muscle abnormalities, with pathological signs, lower extremity numbness	/		
8th d			/		
9th d			Enhanced MRI of spinal cord delineated multiple enhancement nodules in spinal cord, cauda equina, and cristae membrane, and multiple abnormal enhancement lesions in bilateral lumbar intervertebral foramen	Stop anti-TB therapy	20 mg/d dexamethasone
12th d	Episodic exacerbation of headache, vision recover gradually, urinary retention	Right lower extremity flaccid paralysis, with pathological symptoms	Spinal cord biopsy: gray-red lesions with tough quality, clear border and epidural adhesions in the lumbar intervertebral 3 and 4. Pathologically diagnosed as "CD30 positive, ALK-positive anaplastic large cell lymphoma"		10 mg/d dexamethasone
17th d	Episodic exacerbation of headache, lower limbs paraplegia, urinary retention, constipation	Temperature is normal, paresthesia plane gradually increased to the xiphoid; visual acuity gradually recovered			
19th d			PET-CT: pathological changes in spinal cord, temporal lobe, and nerve root	Turn to department of hematology for further treatment	

CNS = central nervous system, CSF = cerebrospinal fluid, CT = computed tomography, MRI = magnetic resonance imaging, PET-CT = positron emission tomography-computed tomography, RT = routine examination, TB = tuberculosis, WBC = white blood cell.

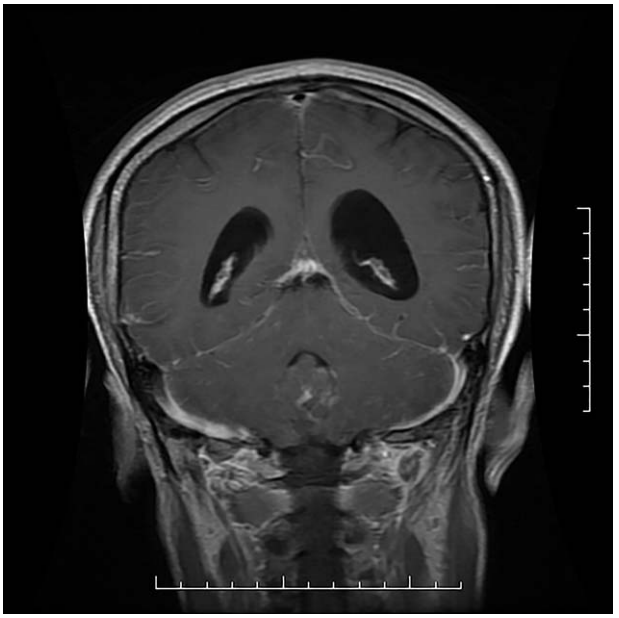

Figure 1. Enhanced magnetic resonance imaging of head revealed bilateral cerebral and cerebellar hemispheres abnormal meningeal enhancement.

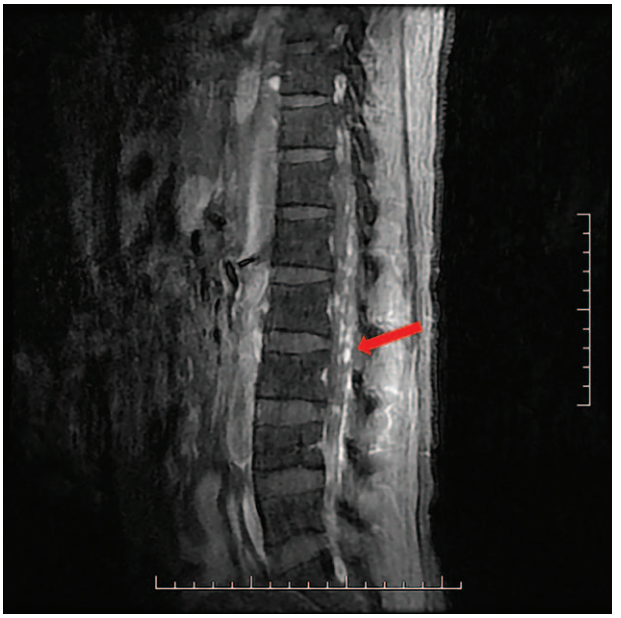

Figure 2. Enhanced magnetic resonance imaging of spinal cord delineated multiple enhancement nodules in spinal cord, cauda equina, and cristae membrane (arrow).

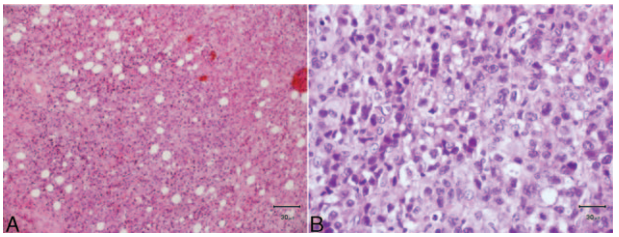

Figure 3. The histologic section of spinal cord showed fibrofatty tissue infiltrated by a large number of atypical cells (A, HE ×100), with irregular ovoid, twisted nuclei, visible small nucleoli, and nuclear fission easily to see (B, HE ×400). HE = hematoxylin–eosin.

7. Discussion

ALCLs of primary CNS occur at all ages, and most patients are below 50 years old and predominantly male. The overall survival estimates are notably various from the shortest only 1 month,[8] to longest up to more than 8 years.[6] The etiology of ALCL of primary CNS is still unknown and exact diagnosis depends on pathological examination and immunological phenotypes identification. Although the spinal dura mater biopsy prompted us the final diagnosis and the treatment based on ALK-positive ALCL was effective, our limitation is that future biopsy of the patient's meninx was not performed since this would do a great harm on the patient himself.

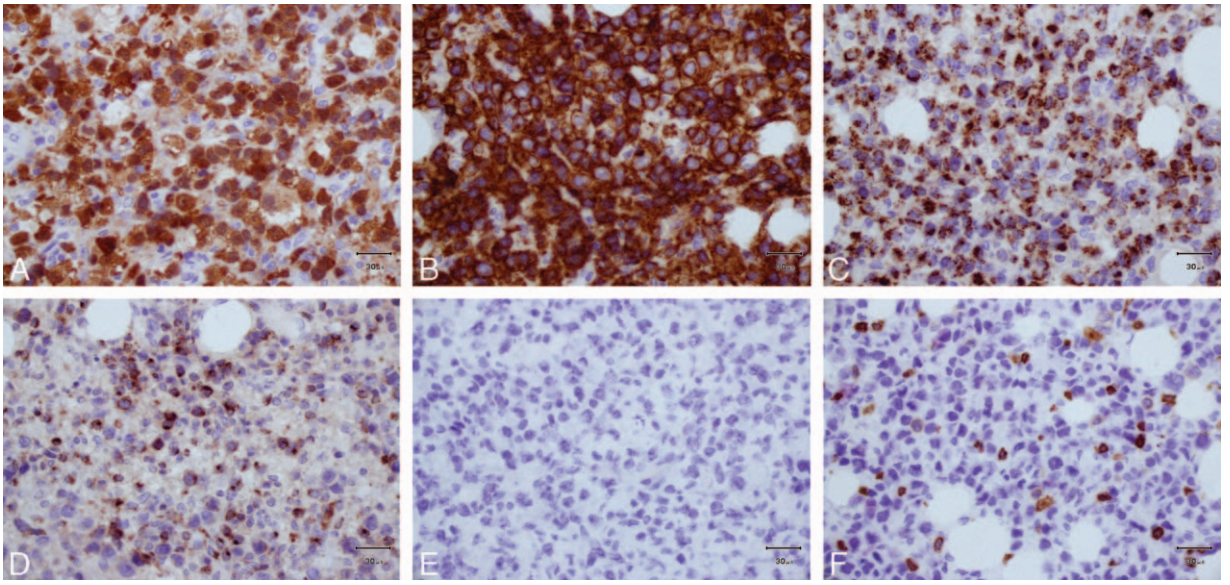

Figure 4. Immunohistochemical stains showed immunopositivity for ALK (A), CD30 (B), TIA-1 (C), and GranzymeB (D), but negative immunoreactivity for CD20 (E) and CD3 (F).

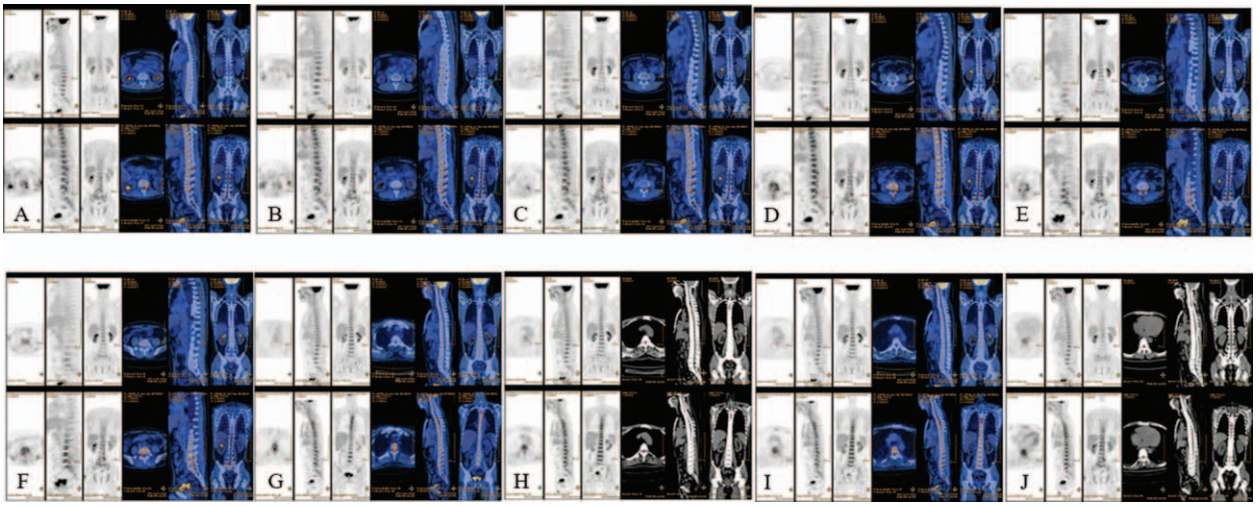

Figure 5. Compared results of twice positron emission tomography-computed tomography (A–J): (A) left L1–2, (B) left L2–3, (C) left L3–4, (D) right L4–5, (E) left L4–5, (F) left L5–S1, (G) T3, (H) T4, (I) T5, and (J) T8.

In this case, the male presented with intermittent fever, persistent headache, vomiting, and diplopia, with suspicious positive meningeal irritation and negative results of CSF etiology examination. CSF analysis showed an increased protein level, low glucose and chloride, high WBC counts with elevated CSF pressure, but no clear neoplastic lymphoid cells, which were in line with the manifestations of TB meningitis. However, the effect of regular anti-TB therapy unsatisfied, prompting a possible misdiagnosis.

CSF biochemical test, such as protein, sugar, and chloride concentration, provides a pivotal reference[9] in diagnosis and treatment of CNS infection. The ratio of chloride concentrations between CSF and blood is about 1:2[9] to maintain normal osmotic balance between blood and CSF. The decreased chloride concentration in CSF is common in TB and cryptococcal meningitis,[10] but also appears in other diseases such as infection, cancer, autoimmune diseases, trauma of CNS, and so on. Thus, the change of chloride concentration in CSF has limited diagnostic value in differential diagnosis of CNS diseases.

When considering meningitis or TB meningitis in the light of clinical manifestations and CSF examination, the patient could undergo diagnostic treatment, and real-time observation to monitor the effect of related therapy. Adjusting therapy timely is important to misdiagnosis. Brain biopsy can be performed when conditions permit, which would help to avoid misdiagnosis and delayed treatment.

8. Patient consent

The patient provided written permission for publication of this case report.

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