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Clinical presentation and diagnosis of toxoplasmic encephalitis in Japan

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ABSTRACT

Distinguishing life-threatening toxoplasmic encephalitis (TE) from brain lymphoma in patients with acquired immunodeficiency syndrome (AIDS) may be difficult. Empiric anti-toxoplasmosis treatment is often initiated because of the reluctance in performing brain biopsies, which may delay the diagnosis and treatment of brain lymphoma in Japan. In this study, we retrospectively examined the clinical characteristics of 13 AIDS patients with TE in Japan, including magnetic resonance imaging and thallium 201 (201Tl) single photon emission computed tomography (SPECT) findings, cerebral spinal fluid analysis, serology, and polymerase chain reaction (PCR) results. All patients improved on anti-toxoplasmosis treatment. Of the 11 patients who underwent serological testing, 6 (55%) had a positive serological result. Of the 7 patients who underwent PCR testing, 3 (42.9%) had a positive PCR result. Nine of 11 patients with TE (81.8%) had multiple lesions. Analysis of the sites of TE lesions did not reveal a difference in site predilection between TE and brain lymphoma. Uptake was negative in all 9 patients who underwent 201Tl SPECT. The study findings suggest that toxoplasma serostatus and PCR may be used to discriminate TE from brain lymphoma. No focal accumulation of 201Tl is strongly suggestive of TE in patients with AIDS in Japan.

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1. Introduction

Toxoplasma gondii is an obligate intracellular protozoan parasite that possesses the unusual capability to infect a variety of warm-blooded animals, including humans [1]. Toxoplasmic encephalitis (TE) is a life-threatening opportunistic infection of the central nervous system (CNS) caused by reactivation of latent *T. gondii*, especially in immunocompromised patients, those with acquired immunodeficiency syndrome (AIDS), and organ transplant recipients [2,3]. In the USA, the incidence of human immunodeficiency virus (HIV)-associated toxoplasmosis dropped markedly after the introduction of highly active antiretroviral therapy in 1995; however, its decline after 2000 started to slow possibly due to delayed HIV diagnosis or failure of antiretroviral therapy [4]. The prevalence of TE is associated with the prevalence of *T. gondii* infection in the general population, which varies depending on the population and geographic location [5]. Data on the incidence and clinical cases of TE in Japan is limited because of the difficulty in establishing the definitive diagnosis of TE and the lack of clinical studies.

In addition, no studies have provided a clinical overview of TE in Japan. In this study, we retrospectively analyzed 13 cases of TE, including their clinical features, the effectiveness of diagnostic procedures, and disease management. A retrospective analysis of TE patients with focal CNS lesions was also conducted. The accuracy of diagnosis based on radiological findings of magnetic resonance imaging (MRI) and thallium 201 (201TI) single photon emission computed tomography (SPECT) was compared with those using polymerase chain reaction (PCR) and cerebral spinal fluid (CSF) examination.

2. Patients and methods

2.1. Patients

A total of 13 Japanese AIDS patients with TE who presented between 2005 and 2011 at the Tokyo Metropolitan Cancer and Infectious Diseases Center of Komagome Hospital or the Tokyo Metropolitan Bokutoh General Hospital were enrolled in this study. All patients had focal intracranial mass lesions detected by MRI. Medications for HIV infection had not been commenced at the time of TE diagnosis. Patients'

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characteristics are summarized in Table 1. The 10 men (76.9%) and 3 women (23.1%) had a median age of 41 years (range, 33–62 years). Definitive diagnosis of TE was made on the basis of the effectiveness of *T. gondii*-specific chemotherapy against acute progressive neurologic symptoms and MRI-proven multiple brain abscesses. All patients responded consistently to anti-toxoplasmosis treatment and were therefore diagnosed as having TE. Although anti-toxoplasmosis treatment initially improved Case 11, as shown by clinical and radiological findings, the patient, who was diagnosed as having TE, relapsed and died of primary CNS lymphoma (PCNSL). Case 12 had multiple lesions, some of which responded to anti-toxoplasmosis treatment, and the patient was therefore diagnosed as having TE. However, the remaining lesions that were non-responsive to this treatment were defined as being due to co-infection with *Cryptococcus neoformans* on brain biopsy and were improved by fluconazole.

2.2. Clinical presentation, laboratory and radiology findings

The following data in the patient records were reviewed: age, sex, HIV status (CD4 cell count and HIV viral load) at the time of TE diagnosis, presenting symptoms, serology, cerebrospinal fluid analysis, and response to anti-toxoplasmosis treatment. The results of *T. gondii* IgG-enzyme-linked immunosorbent assay (ELISA) were available in 11 patients. The results were interpreted according to the manufacturer's instructions as follows: ≪6 IU/mL, negative; 6–8 IU/mL, borderline; ≫9 IU/mL, positive. Lumbar puncture had been performed in all cases. Focal intracranial mass lesions were demonstrated by contrast-enhanced MRI brain scan in all patients. The following neuroimaging features were documented: location, size, gadopentetate dimeglumine (Gd-DTPA) enhancement characteristics, number, and signal intensity on MRI. Brain SPECT and nested PCR of CSF samples using oligonucleotide primers to amplify *T. gondii*-specific 18S-rDNA gene as described previously [6] were also performed to reach a definitive diagnosis of TE in several patients.

2.3. Analysis of clinical data

Data analysis was conducted by the National Defense Medical College. This study was approved by the Ethics Committees of the National Defense Medical College, Tokyo Metropolitan Cancer and Infectious Diseases Center of Komagome Hospital and Tokyo Metropolitan Bokutoh General Hospital.

3. Results

3.1. Laboratory features at presentation

Of the 13 patients, 12 had a CD4 cell count below 100/μL, and the median count was 14/μL. Of the 11 patients with ELISA results, only 6 (55%) were positive, 1 (9%) was borderline, and 4 (36%) were negative for anti-*T. gondii* IgG at the time of TE diagnosis. The positive ELISA tests did not correlate with the CD4 cell counts at the time of diagnosis of TE. The median CSF cell count was 3/μL (range 0–86/μL) and the median CSF protein concentration was 48.0 mg/dL (range 16.7–134.0 mg/dL). The CSF glucose levels were below the normal limit in all patients (median concentration was 46 mg/dL, range 36–77 mg/dL). Of the 7 patients with CSF samples analyzed by nested PCR, *T. gondii* DNA was detected in only 3 (42.9%).

3.2. MRI imaging of the brain

Of the 11 patients who underwent enhanced MRI with Gd-DTPA, 9 (81.8%) had multiple lesions while 2 (18.2%) had solitary lesions (Table 2). The median number of lesions per patient was 3 (range 1–7).

The location of the lesions was divided into six categories: (a) periphery (cortex and corticomedullary junction), (b) white matter, (c) central (basal ganglia, thalamus), (d) periventricular, (e) brain stem and (f) posterior fossa, based on the findings of a previous report [7]. Of the 37 lesions in the 11 patients, the most common locations were the white matter (n = 21, 56.8%), followed by periphery (cortex and corticomedullary junction; n = 6, 16.2%), and basal ganglia (n = 5, 13.5%), and the least common locations were the posterior fossa (n = 3, 8.1%), thalamus (n = 1, 2.7%), and brain stem (n = 1, 2.7%) (Table 2). The contrast-enhanced CT appearance of TE is described by Dina [7], Ernst et al. [8], and Lorberboym et al. [9] and some of their findings are comparable with our findings in Table 2.

Lesion size was variable. Of the 37 lesions in 11 patients, 15 (40.5%) were <10 mm in diameter and 22 (59.5%) were ≥10 mm (Table 3).

Table 1
Patients' characteristics.

Case	Age (years)	Sex	CD4 (μL)	HIV (copies/mL)	Ab.[a]	PCR	Cerebrospinal fluid			Diagnosis	Treatment	
							Cells (μL)	Protein (mg/dL)	Glucose (mg/dL)		Regimen	Outcome
1	47	F	10	780	ND[b]	ND	22	71.0	37	TE[c]	P[f] + C[g]	Improved[i]
2	36	M	51	670,000	ND	(−)	3	47.0	45	TE	P + C	Improved
3	48	M	68	530,000	(+)	ND	4	134.0	36	TE	P + C	Improved
4	40	M	3	130,000	(−)	ND	1	16.7	47	TE	P + C	Improved
5	40	M	6	97,000	(+)	ND	4	36.4	46	TE	P + C	Improved
6	41	M	55	260,000	(+)	ND	45	130.0	44	TE	P + C	Improved
7	33	M	64	56,000	(−)	ND	12	53.8	46	TE	P + C	Responded[j]
8	39	M	25	130,000	(+)	(−)	2	48.0	47	TE	P + S[h]	Improved
9	42	M	115	59,000	(+)	(+)	86	114.0	77	TE	P + S	Improved
10	43	M	6	170,000	(+)	(−)	0	43.4	50	TE	P + S	Improved
11	62	F	0	200,000	(±)	(+)	0	30.1	53	TE + L[d]	P + S	Responded
12	44	M	14	110,000	(−)	(+)	3	116.0	37	TE + C[e]	P + C	Improved
13	35	F	9	240,000	(−)	(−)	1	33.3	47	TE	P + C	Improved

[a] Antibody.
[b] Not determined.
[c] Toxoplasmic encephalitis.
[d] Lymphoma.
[e] Cryptococcoma.
[f] Pyrimethamine.
[g] Clindamycin.
[h] Sulfadiazine.
[i] TE lesions were improved completely by the anti-toxoplasmosis therapy.
[j] TE lesions were reduced in size by the anti-toxoplasmosis therapy, but the patient died during the TE therapy due to another opportunistic disease.

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