

## CASE REPORT

# Disseminated toxoplasmosis with atypical symptoms which developed with exacerbation of systemic lupus erythematosus

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*Toxoplasma* is a common parasite worldwide that mainly affects the brain, lungs and eyes. Although toxoplasmic encephalitis is a lethal disease without treatment, past case reports show most patients with systemic lupus erythematosus who developed toxoplasmic encephalitis were misdiagnosed and treated as neuropsychiatric systemic lupus erythematosus, which led to unfavorable outcomes. We herein describe a case of disseminated toxoplasmosis affecting all the above organs with atypical symptoms, which developed with exacerbation of systemic lupus erythematosus. She had initially manifested with retinochoroiditis without vitritis, mild cognitive impairment and an isolated lung mass. These are completely different from the classic symptoms of toxoplasmosis that have been reported in patients with HIV infection and/or those after hematopoietic transplantation. Our case, together with previously reported cases, suggests the manifestation of toxoplasmosis that develops in systemic lupus erythematosus patients can be different from that seen in conventional cases and varies between individual patients. Our case highlights both the difficulty in and the importance of diagnosing toxoplasmosis in patients with systemic lupus erythematosus and provides helpful information to identify this rare, devastating, yet treatable disease. *Lupus* (2019) **28**, 133–136.

**Key words:** Systemic lupus erythematosus; neuropsychiatric systemic lupus erythematosus; disseminated toxoplasmosis; pulmonary toxoplasmosis; ocular toxoplasmosis; cerebral toxoplasmosis

## Introduction

Toxoplasmosis is a life-threatening complication in patients with an advanced stage of HIV infection and those after hematopoietic stem cell transplantation, mainly affecting the brain, lungs and eyes.<sup>1</sup> In contrast, toxoplasmosis does not frequently occur in patients with autoimmune diseases receiving immunosuppressive treatment and is not considered as a common opportunistic infection affecting these patients. However, when toxoplasmosis develops in a patient with systemic lupus erythematosus (SLE), it can mimic neuropsychiatric SLE (NPSLE). Because the prognosis and the

clinical outcome of toxoplasmosis depend on early diagnosis and treatment, it is important for rheumatologists to know its clinical features and to consider its possibility.

We herein describe a case of disseminated toxoplasmosis presenting with worsening vision, mild cognitive impairment and a mass lesion in the lung, which developed along with the exacerbation of SLE and posed a diagnostic challenge.

## Case report

A 43-year-old woman with a 2-year history of SLE was admitted to our hospital for a fever and a 2-month history of visual impairment. Her SLE initially manifested with fever, malar rash, arthritis, hypocomplementemia, leukopenia and positive anti-DNA antibody and was successfully treated

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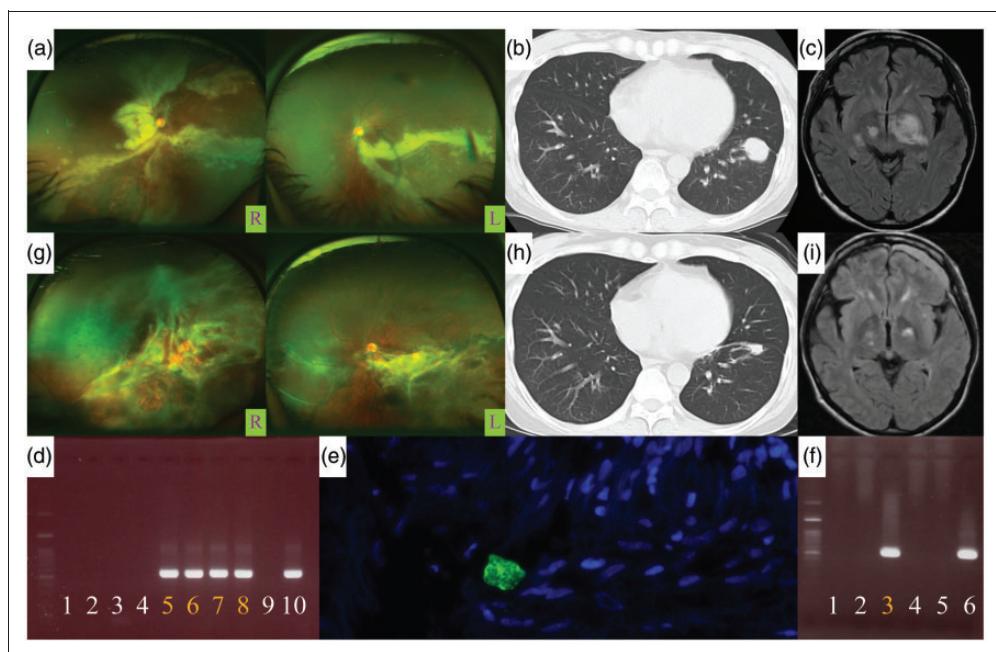
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with prednisolone 20 mg once daily. Then 6 months prior to admission, azathioprine 50 mg once daily was added to her treatment and her daily prednisolone dose was increased from 2 mg to 10 mg due to a worsening malar rash. On admission, she was alert, had a fever (38.6°C), malar rash, bilateral visual acuity loss (0.01 in the right eye and 0.1 in the left eye in decimal visual acuity) and bilateral retinochoroiditis on fundus examination (Figure 1a). Blood tests showed leukopenia (white blood cell count: 1,900/μl), hemolytic anemia (hemoglobin: 7.7 g/dl, reticulocyte: 3.7%, haptoglobin <10 ng/ml), hypocomplementemia (C3: 38 mg/dl, C4: 5 mg/dl, CH50: 14.6 U/ml), which all suggested the exacerbation of SLE. Although she had no respiratory symptoms, a chest radiograph and computed tomography (CT) scan revealed a mass lesion in the left lung, which was not present 2 months before (Figure 1b). The daily prednisolone dose was increased up to 40 mg and azathioprine was switched to tacrolimus, which improved her symptoms except for the lung mass and bilateral visual impairment. Blood tests showed

mild cytomegalovirus (CMV) antigenemia (CMV C10/11: 0 and two positive cells per slide) and an elevated serum level of β-D glucan (86 pg/ml). HIV antibody was negative. Treatment with ganciclovir and voriconazole was given for the possibility of CMV and/or fungal infections, which only improved the CMV antigenemia and serum β-D glucan levels but made no improvement in clinical symptoms. She lost her right visual acuity and her left visual acuity was worsened to 0.04 two weeks after admission.

Although the patient had no difficulty in making conversation and had no abnormality on the brain CT and MRI scans, she showed an apathetic reaction against her worsening visual acuity. Then 4 weeks after admission, she developed involuntary movement in her left face and neck. Cerebrospinal fluid (CSF) examination showed mild elevation in cell count (seven cells per μl), an elevated protein level (77 mg/dl) and a decreased glucose level (59 mg/dl), and the brain MRI at this time showed cerebritis in the bilateral basal ganglia (Figure 1c).



**Figure 1** Funduscopy, brain MRI, lung computed tomography (CT), PCR, and immunostaining. (a) Funduscopy shows sub-retinal exudate and wide areas of retinochoroidal atrophy without vitritis bilaterally. (b) Chest CT scan shows a mass lesion in the left lower lung. (c) Fluid attenuated inversion recovery (FLAIR) image of brain MRI shows high intensity areas in the bilateral basal ganglia. (d) Toxoplasmic PCR on cerebrospinal fluid (CSF) fluid shows positive result (lanes 1–4, serum; lanes 5–8, CSF fluid; lane 9, negative control; lane 10, positive control). (e) Toxoplasmic immunostaining on transbronchial lung biopsy (TBLB) specimen identifies *Toxoplasma gondii* (*T. gondii*). (f) Toxoplasmic PCR on TBLB specimen (lane 3) shows positive result (lanes 1–4, TBLB specimen; lane 5, negative control; lane 6, positive control). (g) Funduscopy after 6 months of toxoplasmosis treatment shows improved subretinal exudate. (h) Chest CT scan after 4 weeks of toxoplasmosis treatment shows marked improvement. (i) FLAIR image of brain MRI after 4 weeks of toxoplasmosis treatment shows marked improvement of encephalitis with epidural edema due to lumbar puncture.

Although the lung mass lesion and the fundus findings were not typical and the patient had no exposure to wild or pet animals or a raw diet, the cerebritis in the bilateral basal ganglia raised the possibility of toxoplasmosis. Additional investigations revealed elevated anti-*Toxoplasma gondii* (*T. gondii*) IgG and IgM titers in serum and CSF, positive *T. gondii* polymerase chain reaction (PCR) in CSF (Figure 1d), and positive *T. gondii* immunostaining and PCR on the transbronchial lung biopsy specimen (Figures 1e and 1f). The patient was diagnosed with disseminated toxoplasmosis. The avidity of anti-*T. gondii* IgG was low (0.24%), indicating an acute rather than latent infection.

The treatment with ganciclovir and voriconazole was switched to pyrimethamine 200 mg on the first day, followed by 50 mg once daily, and sulfadiazine 1 g four times per day, the first-line regimen for toxoplasmosis. The patient's vision in her left eye did not further deteriorate and her funduscopic findings (Figure 1g) and cognitive impairment gradually improved. Brain MRI and chest CT scan 4 weeks after the treatment showed marked improvement of the pulmonary mass lesion and the cerebritis, respectively (Figures 1h and 1i). The treatment against toxoplasmosis was continued for 1 year, and the patient has shown no signs of relapse after an additional 6 months of follow up.

## Discussion

Our case demonstrates that disseminated toxoplasmosis can develop in patients with SLE and manifest with atypical presentation. In fact, our case presented with three unusual manifestations.

Firstly, the pulmonary toxoplasmosis in our case accompanied no respiratory symptoms and manifested as an isolated mass lesion on a chest CT. In a past study of pulmonary toxoplasmosis involving 64 HIV-positive patients, 92% of patients had respiratory symptoms including cough and dyspnea.<sup>2</sup> Typical radiological findings were bilateral interstitial infiltrates, predominantly in the bases of the lung.<sup>2</sup> To the best of our knowledge, there have been no past reports of pulmonary toxoplasmosis that manifested as a mass lesion.

Secondly, the ocular toxoplasmosis in our case showed retinochoroiditis without vitritis on funduscopy. In a past study of 109 patients with ocular toxoplasmosis, all patients had vitritis as the main fundus finding,<sup>3</sup> and only a few cases of ocular toxoplasmosis lacking vitritis have been reported in the literature.

Thirdly, the initial presentation of cerebral toxoplasmosis in our case was mild apathy alone. The common symptoms of cerebral toxoplasmosis have been reported to be headache (55%), confusion (52%), focal neurologic deficits (69%), psychomotor retardation (38%) and disturbed consciousness (42%).<sup>4</sup>

Table 1 summarizes the previously reported and current cases of SLE complicated with toxoplasmosis.<sup>5-10</sup> All but one case had cerebral toxoplasmosis and only two cases including ours manifested as disseminated toxoplasmosis involving the lungs. Our case is the first to report disseminated toxoplasmosis involving the three most commonly affected organs. Our case, together with previous reports, suggests the manifestation/severity of toxoplasmosis can vary among lupus patients, possibly depending on pathogen factors (e.g. genotype), the phase of infection (i.e. acute vs latent), lupus disease activity, treatment regimen/dose/length and the consequent level/type of immunosuppression.

Nine out of 13 previously reported SLE cases of toxoplasmosis were not diagnosed until autopsy (Table 1). Of note, all but one received treatment for NPSLE. This clearly illustrates the difficulty in differentiating cerebral toxoplasmosis from NPSLE by routine investigations for encephalitis. In addition, the current case indicates that atypical ocular and pulmonary manifestations of toxoplasmosis can also mimic other opportunistic infections such as cytomegalovirus infection, fungal infection and nocardiosis, further complicating the process of differential diagnosis.

In contrast, all five patients who were diagnosed with toxoplasmosis improved after receiving specific treatment and survived. Two cases were diagnosed by brain biopsy, one by serology and retinal PCR, and another by serology and diagnostic treatment. In our case, the serum and CSF PCR and the immunostaining of the lung biopsy specimen provided definitive diagnostic information. Because these diagnostic tests or procedures are not usually performed unless we suspect toxoplasmosis, it is important for rheumatologists to consider the possibility of toxoplasmosis when a patient with SLE shows atypical features or an unfavorable response to treatment for SLE.

For the current case, if we had known that disseminated toxoplasmosis can occur in lupus patients and present with atypical manifestations, we could have reached the correct diagnosis earlier and could have saved the vision in her right eye. Our case highlights both the difficulty in and the importance of diagnosing toxoplasmosis in patients

**Table 1** Previously reported and current cases of toxoplasmosis with SLE

Authors	Journal	Sex	Age (years)	Treatment at toxoplasmosis onset	Affected organ	Diagnostic method	Outcome
Dubin <i>et al.</i>	Arch Dermatol, 1971	M	33	Prednisolone 10 mg/d Hydroxychloroquine 200 mg/d	Cerebrum	Autopsy	Died
Gleason <i>et al.</i>	Arch Intern Med, 1974	M	22	Not described	Cerebrum Lung	Autopsy	Died
Townsend <i>et al.</i>	Arch Neurol, 1975	M	49	Prednisolone 10 mg/d	Cerebrum	Autopsy	Died
Wilson <i>et al.</i>	Am J Ophthalmol, 1980	F	50	Prednisolone 10-60 mg/d	Cerebrum	Autopsy	Died
Mazer <i>et al.</i>	AJNR Am J Neuroradiol, 1983	M	22	Not described	Cerebrum	Autopsy	Died
Deleze <i>et al.</i>	J Rheumatol, 1985	F	27	Prednisolone 10 mg/d Chlorambucil 6 mg/d	Cerebrum	Autopsy	Died
Zamir <i>et al.</i>	Mayo Clin Proc, 1999	F	48	Methylprednisolone 60 mg/d	Cerebrum	Autopsy	Died
Seta <i>et al.</i> <sup>5</sup>	Rheumatology (Oxford), 2002	F	24	Prednisolone 12.5 mg/d	Cerebrum	Brain biopsy	Improved
Yamamoto <i>et al.</i> <sup>6</sup>	Br J Ophthalmol, 2003	F	47	Prednisolone 0.5 mg/kg/d	Eyes	Serology PCR	Improved
Pagalavan <i>et al.</i> <sup>7</sup>	Med J Malaysia, 2011	M	18	Prednisolone 30 mg/d	Cerebrum	Serology Treatment response	Improved
Lummus <i>et al.</i> <sup>8</sup>	Clin Neuropathol, 2014	F	44	Prednisolone 60 mg/d	Cerebrum	Autopsy	Died
Huang <i>et al.</i> <sup>9</sup>	Int J Adv Med, 2015	M	47	Prednisolone 5 mg/d Hydroxychloroquine 400 mg/d Cyclophosphamide of unknown dose	Cerebrum	Brain biopsy	Improved
Murro <i>et al.</i> <sup>10</sup>	J Clin Neurosci, 2016	F	36	Not described	Cerebrum	Autopsy	Died
Furuya <i>et al.</i>	Current report	F	43	Prednisolone 2 mg/d	Eyes Lung Cerebrum	Serology PCR Lung biopsy	Improved

with SLE and provides helpful information to identify this rare, devastating, yet treatable disease.

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### References

- Montoya JG, Liesenfeld O. Toxoplasmosis. *Lancet* 2004; 363: 1965–1976.
- Rabaud C, May T, Lucet JC, Leport C, Ambroise-Thomas P, Canton P. Pulmonary toxoplasmosis in patients infected with human immunodeficiency virus: A French National Survey. *Clin Infect Dis* 1996; 23: 1249–1254.
- Tugal-Tutkun I, Corum I, Otuk B, Urgancioglu M. Active ocular toxoplasmosis in Turkish patients: A report on 109 cases. *Int Ophthalmol* 2005; 26: 221–228.
- Porter SB, Sande MA. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. *N Engl J Med* 1992; 327: 1643–1648.
- Deleze M, Mintz G, del Carmen Mejia M. Toxoplasma gondii encephalitis in systemic lupus erythematosus: A neglected cause of treatable nervous system infection. *J Rheumatol* 1985; 12: 994–996.
- Zamir D, Amar M, Grosman G, Weiner P. Toxoplasma infection in systemic lupus erythematosus mimicking lupus cerebritis. *Mayo Clin Proc* 1999; 74: 575–578.
- Seta N, Shimizu T, Nawata M, *et al.* A possible novel mechanism of opportunistic infection in systemic lupus erythematosus, based on a case of toxoplasmic encephalopathy. *Rheumatology (Oxford)* 2002; 41: 1072–1073.
- Pagalavan L, Kan FK. Cerebral toxoplasmosis in systemic lupus erythematosus following intravenous methylprednisolone. *Med J Malaysia* 2011; 66: 68–70.
- Lummus S, Kleinschmidt-DeMasters BK. Predominantly periventricular necrotizing encephalitis due to toxoplasmosis: Two unusual cases and review of literature. *Clin Neuropathol* 2014; 33: 29–37.
- Murro D, Novo J, Arvanitis L. Asymptomatic diffuse “encephalitic” cerebral toxoplasmosis in a woman with systemic lupus erythematosus. *J Clin Neurosci* 2016; 29: 194–196.