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Case Report

Disseminated Toxoplasmosis associated with Haemophagocytic Lymphohistiocytosis in a Patient with the Human Immunodeficiency Virus: A Case Report and Literature Review

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ABSTRACT

Disseminated toxoplasmosis associated with haemophagocytic lymphohistiocytosis (DT-HLH) is rare and difficult to diagnose compared to disseminated toxoplasmosis or HLH presenting alone. Because of the limited number of reported cases, the clinical characteristics and outcomes of DT-HLH are unknown. We report a case of DT-HLH in a human immunodeficiency virus (HIV)-infected patient who was successfully treated with early anti-toxoplasmic therapy and performed a comprehensive literature review. A 33-year-old Cameroonian woman was transferred to our hospital owing to HIV infection and encephalitis. Although she developed HLH, bone marrow biopsy did not reveal the cause. She was diagnosed as having DT-HLH via polymerase chain reaction testing of bone marrow biopsy tissue, blood, and cerebrospinal fluid. DT-HLH improved within the initial two weeks of treatment for toxoplasmosis (sulfamethoxazole-trimethoprim, trimethoprim 10 mg/kg/day and clindamycin 1,800 mg/day) before the introduction of antiretroviral therapy. To our knowledge, only eight cases of DT-HLH have been previously reported in the literature. Most patients died within three weeks of hospitalisation and were diagnosed by autopsy. Conversely, patients diagnosed antemortem were all treated and survived, including the currently reported patient. DT-HLH can lead to poor prognosis without early and proper treatment. Clinicians should consider toxoplasmosis in the differential diagnosis of HLH.

Introduction

Toxoplasma gondii causes encephalitis mainly in immunocompromised patients (e.g. human immunodeficiency virus [HIV]-infected patients) (Montoya and Liesenfeld, 2004). Disseminated toxoplasmosis (DT), defined by the presence of *T. gondii* cysts or tachyzoites in more than one organ or in the blood, is a rare and life-threatening infection. Antemortem diagnoses are difficult to perform because DT is less likely to be suspected as a differential diagnosis and the serological test is not necessarily reliable in immunocompromised hosts.

Haemophagocytic lymphohistiocytosis (HLH), which is difficult to diagnose, is an often fatal hyperinflammatory syndrome defined according to HLH-2004 criteria and HScore (Yildiz et al., 2021). Infection-associated HLH caused by diverse microbes is classified as secondary compared to familial HLH, which is driven by genetic mutation. Since uncontrolled infection can lead to HLH, it is critical to identify and treat the causative microorganism.

Epstein-Barr virus and cytomegalovirus are the most common viruses associated with HLH, while *Mycobacterium tuberculosis* is the most common bacteria associated with HLH (Yildiz et al., 2022). DT associated with HLH (DT-HLH) occurs rarely and is even more difficult to diagnose than DT or HLH presenting in isolation. Few cases have been reported since the first case report in 1994 (Blanche et al., 1994), and the clinical characteristics and outcomes of DT-HLH are unknown. Here, we describe

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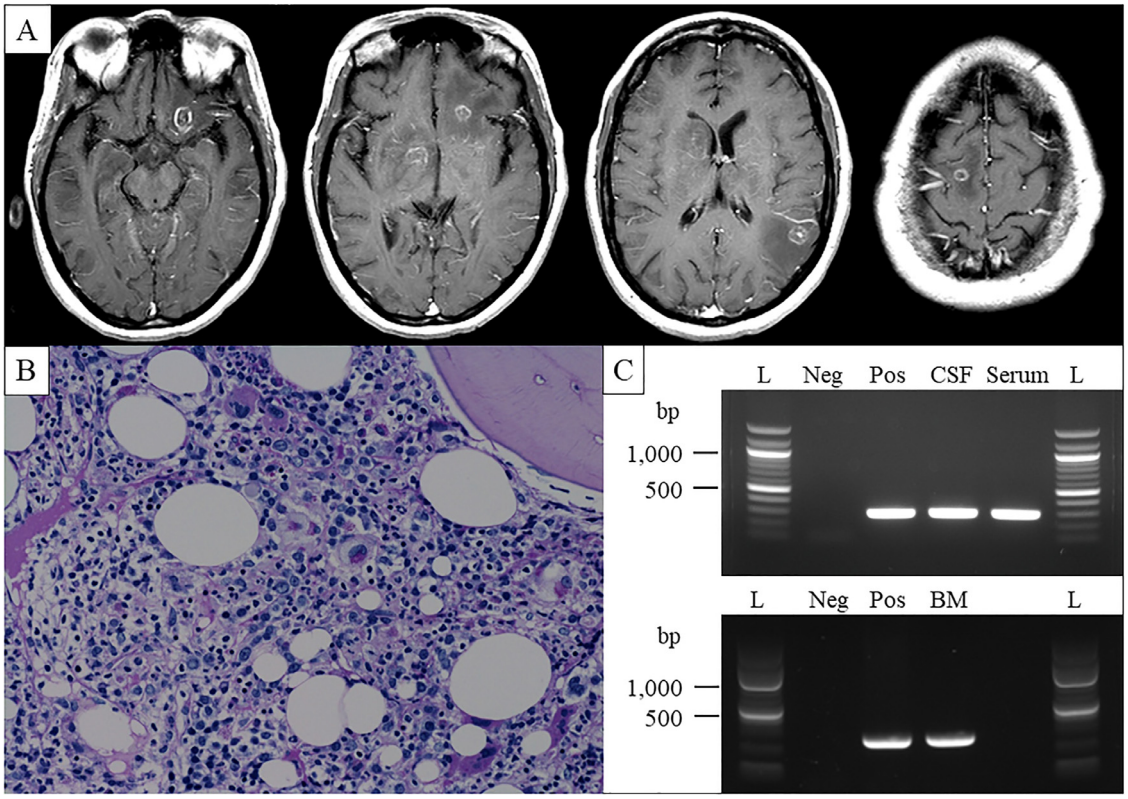

Figure 1. (A) Contrast-enhanced brain magnetic resonance imaging (CE-MRI).
CE-MRI demonstrated multiple nodules with ring enhancement surrounding oedema.
(B) Haematoxylin and eosin staining of bone marrow biopsy tissue.
Bone marrow biopsy findings showed foamy macrophage accumulation and haemophagocytosis. The cause was not identified.
(C) A polymerase chain reaction (PCR) test specific to *T. gondii*.
T. gondii-specific 18S ribosomal DNA was detected in cerebrospinal fluid, serum, and bone marrow biopsy samples using the nested PCR technique.
Abbreviations: L, ladder; Pos, positive control; Neg, negative control; CSF, cerebrospinal fluid; BM, bone marrow sample; bp, base pair.

a case of DT-HLH that occurs in an HIV-infected patient. We also present a comprehensive literature review informing this case discussion.

Case report

A 33-year-old Cameroonian woman was transferred to our hospital because of fever, impaired consciousness, and positive HIV screening test. On arrival, her vital signs were as follows: blood pressure, 120/62 mmHg; pulse, 170 beats/min; respiratory rate, 40 breaths/min; and temperature, 40.1°C. Her physical examination revealed a Glasgow coma scale score of 5 (E2V2M1) but no signs of meningeal irritation. Laboratory results at admission were as follows: white blood cell count, 5,900/μL; haemoglobin level, 9.5 g/dL; platelet count, 123,000/μL; aspartate aminotransferase level, 223 U/L; lactate dehydrogenase level, 2,885 U/L; triglyceride level, 245 mg/dL; ferritin level, 20,577 ng/mL; and soluble interleukin-2 receptor level, 1,023 U/mL. Her $CD4^+$ T cell count was 4/μL. The HIV viral load was 470,000 copies/mL; a serological test for *T. gondii* was positive for immunoglobin G (IgG).

Computed tomography revealed splenomegaly but no peripheral lymphadenopathy, hepatomegaly, or major abnormalities in the lung and other intra-abdominal organs. Contrast-enhanced brain magnetic resonance imaging (CE-MRI) demonstrated multiple nodules 9–15 mm in diameter in both cerebral hemispheres, right pallidum, and right cerebellum with ring enhancement and surrounding oedema (Fig. 1A). Cerebral spinal fluid (CSF) examination revealed a normal cell count (lymphocyte, 2/μL; neutrophil, 1/μL) and mildly elevated protein level (201 mg/dL). *T. gondii*-specific 18S ribosomal DNA (rDNA) was detected in CSF and serum samples by nested polymerase chain reaction (PCR).

Following the diagnosis of toxoplasmic encephalitis on the day of admission, we started treatment with sulfamethoxazole-trimethoprim (TMP-SMX, trimethoprim 10 mg/kg/day) and clindamycin (CLDM, 1,800 mg/day). Bone marrow biopsy was performed on the sixth day of hospitalisation, as bicytopenia progressed despite treatment (haemoglobin, 6.2 g/dL; platelets, 67,000/μL). Haematoxylin and eosin (HE) staining on bone marrow biopsy showed haemophagocytosis but no findings of infections or malignancies (Fig. 1B). Five of the eight HLH-2004 criteria were met (fever, splenomegaly, hyperferritinemia, bicytopenia, and haemophagocytosis), and the probability of HLH was more than 99% based on the HScore (262 points). Nested PCR was reconducted using the paraffin-embedded bone marrow sample, and *T. gondii*-specific 18S rDNA was detected (Fig. 1C). Hence, the patient was diagnosed as having DT-HLH. Anti-toxoplasmic therapy was continued, after which her HLH improved to an HScore of 163 points on the 13th hospital day. Her TMP-SMX and CLDM treatment regimen was changed to atovaquone (3,000 mg/day) on the 20th hospital day due to leukopenia. Antiretroviral therapy (ART, emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg and raltegravir 800 mg) was started on the 32nd hospital day. She completed six weeks of treatment for *T. gondii* and was discharged on the 62nd hospital day without any complications. One year of secondary prevention was followed by no recurrence during three years of follow-up.

Discussion

We report a successfully treated case of DT-HLH that occurred in an HIV-infected patient. The presence of haemophagocytosis was confirmed based on the HLH-2004 criteria and HScore. However, the causative microorganism could not be pathologically identified. Since the patient had been diagnosed with toxoplasmic encephalitis, DT-HLH was suspected and eventually diagnosed by PCR of bone marrow biopsy tissue. This led us to continue standard treatment for *T. gondii* without using corticosteroid for HLH. This treatment regimen dramatically improved the patient's HLH symptomology before ART was introduced for HIV.

To our knowledge, only eight cases of DT-HLH have been reported in the literature so far (Supplementary Table 1) (Blanche et al., 1994; Guillaume et al., 2006; Segall et al., 2006; Duband et al., 2008; Yang et al., 2013; Gay et al., 2019; Kator et al., 2020; Sanchez-Petitto et al., 2020). The mean age of the previously reported patients was 39 years (range, 25–59 years); 88% were male. Seven patients were immunocompromised. The immunosuppression background in the reported cases was as follows: HIV (two cases), organ transplantation (four cases), and diffuse large B-cell lymphoma (one case). The infection sites were in the lung (100%), central nervous system (CNS; 38%), and heart and liver (25%). Approximately half of the previously reported patients presented anti-*Toxoplasma* IgG antibodies. Five patients (63%) died within three weeks of hospitalisation and were diagnosed at autopsy. However, all three patients with antemortem diagnoses of DT-HLH who received anti-toxoplasmic therapy survived. In contrast, all patients who were not treated for toxoplasmosis died, even if they received corticosteroid therapy for HLH. In the currently reported case, DT-HLH was diagnosed by antemortem PCR testing and therefore the patient was treated effectively and timely.

To better describe DT characteristics, we conducted a PubMed database search from 1956 to present using the keyword 'disseminated toxoplasmosis'. We limited our search to manuscripts published in English. Reports with unclear diagnostic methods were excluded. We ultimately identified 89 articles that evaluated DT. Six articles describing five or more cases were included in this review (Supplementary Table 2; 58 immunocompromised patients, 11 immunocompetent patients) (Gleason and Hamlin, 1974; Hofman et al., 1993; Lucet et al., 1993; Albrecht et al., 1996; Small et al., 2000; Demar et al., 2012). The immunosuppression background was as follows: HIV (43 cases), bone marrow transplantation (10 cases), and renal transplantation (one case). Common sites of infection were the CNS (78%), lung (76%), and heart (71%) in immunocompromised patients and blood (45%) and lung (36%) in immunocompetent patients. Even in immunocompromised cases, 79% of the patients had anti-*Toxoplasma* IgG antibodies. In the case reported here, the patient had HIV, CNS infection, and anti-*Toxoplasma* IgG antibodies; these are all considered common characteristics of DT.

DT-HLH is difficult to diagnose because, even with biopsies, it is often impossible to detect *T. gondii* only by HE staining. The combined use of HE staining and the PCR method is useful in such cases. However, most DT-HLH cases are diagnosed by autopsy. In this review, we found that all patients who could be diagnosed antemortem survived. Thus, early diagnosis is extremely important to improve the prognoses in DT-HLH.

In cases of secondary HLH with an unknown cause, DT may be suspected depending on the site of the infection and the presence of anti-*Toxoplasma* antibodies. In DT, the lungs, CNS, and heart were each common sites of infection. If there is inflammation in these organs (in addition to HLH), DT-HLH should be suspected. In the case series reported here, anti-*Toxoplasma* IgG antibodies were positive in more than half of immunocompromised patients. Thus, we conclude that DT should be suspected if the antibodies are positive.

Conclusion

We report a case of DT-HLH that occurred in an HIV-infected patient and was effectively diagnosed and treated without additional recurrence. DT-HLH is difficult to diagnose and can lead to poor prognosis without early and aggressive treatment. Clinicians should suspect and investigate toxoplasmosis according to the sites of infection and/or the presence of anti-*Toxoplasma* antibodies in the differential diagnosis of HLH.

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Ethical statement

Informed consent was obtained for the publication of this article.

Authors' contributions

TW, KM and FN revised the manuscript. TW, AK, NS and SI treated the patient. TW drafted the first version of the manuscript. All authors contributed to the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.08.023.

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