

Multisystem Inflammatory Syndrome in Adults and Severe Toxoplasmosis: Similar Clinical Presentations, Potentially Severe Outcomes

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We report a case of a 21-year-old previously healthy man who developed severe toxoplasmosis with chorioretinitis and myositis 2 months after receiving corticosteroids for presumed multisystem inflammatory syndrome in adults, in the setting of a recently acquired acute *Toxoplasma* infection, likely during a trip to Latin America.

Keywords. multisystem inflammatory syndrome in adults (MIS-A); COVID-19; severe toxoplasmosis.

In the coronavirus disease 2019 (COVID-19) era, multisystem inflammatory syndrome in adults (MIS-A) and in children (MIS-C) have become potentially life-threatening conditions [1]. Acute toxoplasmosis, particularly in patients infected with atypical more virulent *Toxoplasma gondii* strains, is associated with high morbidity and mortality [2–7]. We report a case of a 21-year-old previously healthy man who developed severe toxoplasmosis after receiving corticosteroids for presumed MIS-A, in the setting of a recently acquired acute *Toxoplasma* infection. MIS-A and severe toxoplasmosis unfolded during 3 hospitalizations over a 3-month period. This case underscores the need to consider toxoplasmosis, among other pathogens, when treating patients for acute COVID-19 or MIS-A/MIS-C, especially with prolonged courses of immunosuppressive medications.

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Appropriate diagnostic evaluation and prompt initiation of anti-*Toxoplasma* treatment can be life-saving.

CLINICAL CASE

A 21-year-old previously healthy, United States-born, nonobese white man presented to an adult emergency department with 7 days of fever, headache, generalized myalgias, arthralgias, and diarrhea beginning 1 day after returning to the United States from a 5-week trip to Ecuador and Costa Rica.

First Hospitalization

On day of illness (DOI) 8, the patient presented in shock, was febrile (39.8°C [103.7°F]) and profoundly hypotensive, and responded to fluid resuscitation. His physical examination was notable for extremity tremors. Laboratory results demonstrated transaminitis, hyponatremia, and elevated lactate, C-reactive protein (CRP), and procalcitonin (Figure 1). Blood and urine cultures were obtained and empirical antimicrobials were started with vancomycin, piperacillin-tazobactam, and azithromycin. Pending results of malaria thick and thin smears and additional zoonotic testing, he was prescribed atovaquone-proguanil and doxycycline, respectively (Figure 1). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nasopharyngeal polymerase chain reaction (PCR) was positive. Within 24 hours, he developed pleuritic chest pain and hypoxemia. Chest radiograph was normal, but chest computed tomography (CT) on DOI 9 revealed diffuse bilateral confluent ground glass opacities, numerous centrilobular nodules, bilateral trace pleural effusions, and mildly enlarged mediastinal and bilateral hilar lymph nodes (Figure 2A). Remdesivir and dexamethasone were started but were discontinued 48 hours later, after resolution of hypoxemia and fever; additional data confirmed a low SARS-CoV-2 viral load (high cycle threshold value of 36) and positive SARS-CoV-2 spike protein immunoglobulin G (IgG) antibodies (after 2 COVID-19 messenger RNA vaccine doses). High-sensitivity troponin was elevated, suggesting myocarditis, whereas B-type natriuretic peptide was normal. Transthoracic echocardiography revealed mild global hypokinesia, and electrocardiography was normal.

Additional epidemiologic history included spending time in the Amazon jungle 14 days prior to symptom onset, consuming local foods including tapir (no raw meat), and drinking from local water sources. Stool PCR was positive for *Giardia*. While awaiting the results of possible zoonotic infections, he completed 10 days of doxycycline (Figure 1). Blood cultures were sterile. Given also rapid clinical improvement, antibiotics (except doxycycline) were discontinued after 48 hours. He was discharged home on DOI 11 with down-trending high-sensitivity troponin.

Clinical manifestations	Fever & hypotension											Fever & hypotension											Chorioretinitis		Splenomegaly									
	Headache			Tremors			Hypotension			Myocarditis																								
Laboratory results	Hospitalization 1											Hospitalization 2											Neuro		Cards		Hospitalization 3							
	Days since illness onset	8	9	10	11	20	21	22	23	24	25	26	27	28	29	30	31	46	47	68	82	83	84	85	86	87	88							
WBC (10 ⁹ /L)	9.28	6.07	9.18	13.18	11.65	9.42	9.31	10.1	7.77	10.25	7.8	6.4	9	7.8	9.7	9	6.6	7.3																
Hemoglobin (g/dL)	14.6	11.7	11.2	11.1	13.2	12.4	11	11.4	11.4	11.3	10.8	10.4	10.6	11.8	11.5	11.4		11								6.9								
Hematocrit (%)	42.4	33.4	32.2	31.8	39.5	37.1	33.1	33.7	34.4	34.1	31.6	31.2	31.5	35.1	33.9	34.8		33.5								30								
Platelets (K/L)	211	180	176	247	399	339	374	395	365	377	346	375	410	445	468	327	395	366								354								
ESR (mm/h)	9																35	25	18	42	25													
CRP (mg/dL)	3.65		6.94		1.41									<0.5	<0.5	<0.5	<0.5	1.1								<0.5								
PCT (ng/mL)	2.26																									<0.5								
d-dimer (ng/mL)									0.95	0.85	1.04	1.14			1.13	1.24	0.87	0.66																
LDH (U/L)									516	1227	1054							1616																
Ferritin (ng/mL)					1379										1445	769																		
ALT (U/L)	249	148	129	154	83	61	53	48	73	74	71			66	61	74	203	137							77	67								
AST (U/L)	173	109	109	143	57	45	46	48	77	82	65			41	44	59	277	168							86	89								
Albumin (g/dL)	3.7	2.6	2.6	2.8	3.4	2.9	2.8		3.4	3.3						3.3	4								3.2	3								
Lactate (mmol/L)	2.9	2.3	1.8																															
Sodium (mmol/L)	128	128	130	135	133	134	134	132																		134	134							
CPK (U/L)					159				346								3666	2147	2147	1357						505								
Aldolase (U/L)																	47.3	22.8				22.8												
hs troponin (ng/L)		242	136				187											22.8																
Troponin I (ng/mL)										0.192	0.152	0.131	0.088	0.068	0.044	0.142	0.393	0.121																
BNP (pg/mL)		53					21							102.6	151.6	188.2	96.6																	
SARS-CoV-2 PCR (NP)	detected															negative				negative														
SARS-CoV-2 Antibodies	positive															negative																		
Toxoplasmosis testing																							Toxo Ab, PCR (U, V)		Ab panel		Toxo seq							
Therapies	vancomycin											SoluCortef (2 mg/kg)											Prednisone (60 mg/day)		30 mg									
	piperacillin/tazobactam											IVIG 1											IVIG 2		IVIG 3									
	azithromycin																								pyrimethamine									
	doxycycline x 10 days																								sulfadiazine									
	malarone																								leucovorin									
	remdesivir																																	
	dexamethasone																																	
Imaging & other diagnostics	CXR		CT chest		MRI brain		cMRI		ECHO		ECHO		ECHO		ECHO		Vitreous tap		MRI brain															
			ECG		MRI spine		Holter		ECG		cMRI		MRI orbits		MRI spine				Lumbar puncture															
			ECHO		Lumbar puncture																													

Figure 1. Clinical course: Hospitalizations and laboratory and imaging evaluations. Additional laboratory results: Day of illness (DOI) 23: cerebrospinal fluid (CSF) white blood cell count (WBC), 37 cells/ μ L (73% lymphocytes); red blood cell count (RBC), <3 cells/ μ L; protein, 103 mg/dL; glucose, 53 mg/dL; CSF cultures, negative; CSF meningitis/encephalitis multiplex polymerase chain reaction (PCR) panel, negative; CSF Venereal Disease Research Laboratory test, negative. DOI 84: CSF WBC, 13 cells/ μ L (95% lymphocytes); RBC, 1 cell/ μ L; protein, 62 mg/dL; glucose, 95 mg/dL; CSF meningitis/encephalitis multiplex PCR panel, negative; CSF *Toxoplasma* DNA PCR, negative. DOI 82: *Toxoplasma* immunoglobulin M (IgM), >160 IU/mL (reference value, <7.2 IU/mL); *Toxoplasma* immunoglobulin G (IgG), >400 IU/mL (reference value, <7.2 IU/mL). Confirmation at the Remington Laboratory for Specialty Diagnostics: *Toxoplasma* IgG dye test, 1:32 000 (reference value, <1:16); *Toxoplasma* IgM enzyme-linked immunosorbent assay (ELISA), 11.5 (reference positive value, \geq 2.0), *Toxoplasma* immunoglobulin A ELISA, >21.8 (reference positive value, \geq 2.1), and *Toxoplasma* IgE ELISA >18.8 (reference positive value, \geq 1.9); *Toxoplasma* IgG avidity, 6 (low; reference value for low IgG avidity, <20). Metagenomics next-generation sequencing (mNGS) in plasma: positive for *T. gondii* (5491.6 molecules per plasma microliter). mNGS also detected Epstein-Barr virus and cytomegalovirus, which were not considered to be of clinical significance. Reference ranges and units: albumin, 3.4–5.2 g/dL; aldolase, 1.5–8.1 U/L; alanine aminotransferase, <36 IU/L; aspartate aminotransferase, 15–50 IU/L; B-type natriuretic peptide, <100 pg/mL; creatinine phosphokinase, <289 U/L; C-reactive protein, <1 mg/dL; d-dimer, <0.5 μ g/mL; erythrocyte sedimentation rate, <15 mm/hour; ferritin, 31–294 ng/mL; hemoglobin, 13.5–18 g/dL; hematocrit, 41%–53%; high-sensitivity troponin, <53 ng/L; lactate, 0.5–1.6 mmol/L; lactate dehydrogenase, 325–650 U/L; procalcitonin, <0.5 ng/mL; platelets, 142–508 K/ μ L; sodium, 135–145 mmol/L; WBC, 4.5–11 10^3 / μ L. Abbreviations: Ab, antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; Cards, cardiology outpatient evaluation; cMRI, cardiac magnetic resonance imaging; CPK, creatine phosphokinase; CRP, C-reactive protein; CT, computed tomography; CXR, chest radiograph; ECG, electrocardiogram; ECHO, echocardiogram; ESR, erythrocyte sedimentation rate; hs troponin, high-sensitivity troponin; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NP, nasopharyngeal; Neuro, neurology outpatient evaluation; PCR, polymerase chain reaction; PCT, procalcitonin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; seq, sequences (by mNGS); Toxo, *Toxoplasma*; U, urine; V, vitreous fluid; WBC, white blood cell.

Second Hospitalization

He was readmitted 9 days after discharge (DOI 20), with recurrence of fever (38.9°C [102°F]), generalized weakness, fatigue, shortness of breath with exertion, headache, neck pain, orthostatic symptoms, worsening fine tremor in extremities, myoclonic jerks, and unstable gait, but no meningismus or encephalopathy. He was again in shock, poorly responsive to fluids, and required fludrocortisone and midodrine. Laboratories revealed hyponatremia, ongoing troponin leak, and elevated ferritin, though down-trending CRP and liver enzymes. Head and neck CT and brain and spine magnetic resonance imaging (MRI) were normal. Cerebrospinal fluid (CSF) examination showed normal opening pressure but elevated protein and a lymphocytic pleocytosis. CSF cultures and infectious diseases diagnostics were negative (Figure 1). Cardiac

MRI (cMRI) on DOI 24 confirmed myocarditis according to Lake Louise criteria [8], with mild left ventricular systolic dysfunction, diffuse myocardial inflammation/edema, nonischemic fibrosis, and interstitial expansion (Figure 2B) despite normal Holter monitor. Concern for post SARS-CoV-2 MIS-A prompted initiation of intravenous immunoglobulin and solumedrol on DOI 25 (Figure 1). Fevers resolved and was discharged after 11 days on a prolonged prednisone taper, lisinopril, low-dose aspirin, exercise restriction, and outpatient follow-up with cardiology and neurology.

After discharge, he continued to have generalized fatigue, myalgias, muscle weakness, and worsening myositis, including a 10-fold increase in creatine kinase, new splenomegaly, and ongoing tremors, partially responsive to clonazepam. Repeat cMRI on DOI 68 showed mildly decreased left ventricular

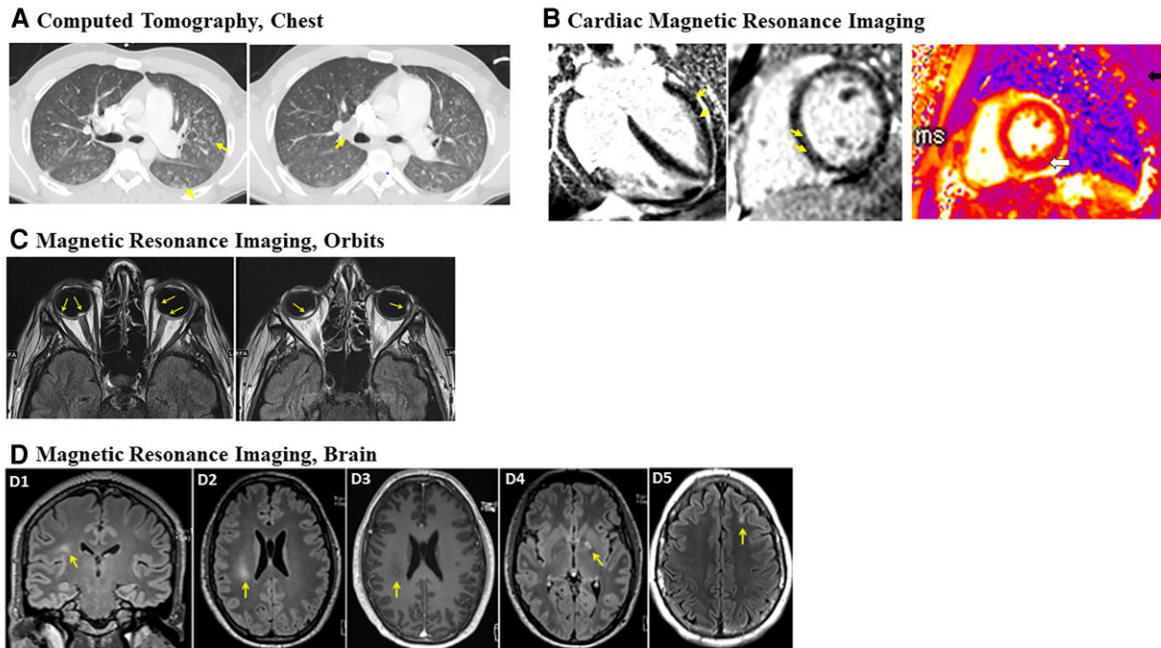


Figure 2. A, Chest computed tomography (CT) (day of illness [DOI] 9): diffuse confluent ground glass opacities of both lungs (yellow arrows, first panel), bilateral trace pleural effusions, and enlarged hilar lymph nodes (yellow arrows, second panel). B, Cardiac magnetic resonance imaging (MRI) (DOI 24): patchy areas of diffuse myocardial enhancement on T1 imaging (yellow arrows, first two panels) and an elevated calculated myocardial extracellular volume (35%; reference value, <25%), suggesting diffuse interstitial expansion. T2 mapping also showed diffuse myocardial edema (white arrow, third panel) when compared with normal skeletal muscle (black arrow, third panel). C, MRI orbits (DOI 82): mild elevation of both optic nerve heads and several hyperintense fluid-attenuated inversion recovery (FLAIR) plaques along the inner margins of both globe walls; largest on right is just below the optic nerve head (7 mm × 2 mm × 10 mm) and on left along the lateral aspect of the globe wall (6 mm × 4 mm × 2 mm), suggesting chorioretinitis (yellow arrows, both panel). D, Brain MRI (with and without contrast) (DOI 83): suggestive of demyelination with patchy increased T2 FLAIR signals in the right posterior frontoparietal centrum semiovale, internal restricted diffusion, minimal enhancement, and increased FLAIR signal of globus pallidus (yellow arrow, D1), axial images associated with mild restricted diffusion (yellow arrow, D2), and minimal internal enhancement on T1 postcontrast (yellow arrow, D3). Several tiny foci of increased FLAIR signal in the left globus pallidus (yellow arrow, D4) and increased T2 FLAIR signal involving the cortex at the depth of the left superior frontal sulcus without restricted diffusion (yellow arrow, D5).

systolic function, but myocardial edema and delayed enhancement had resolved.

On DOI 70, he complained of blurry vision and eye floaters. Fundoscopic examination revealed bilateral focal areas of chorioretinitis, papillitis, vitritis, intraretinal hemorrhage, bilateral optic nerve disc edema, and retinal whitening. Thereafter, he was hospitalized for further evaluation.

Third Hospitalization

Toxoplasma immunoglobulin M (IgM) and IgG serologies were sent and were both highly positive. Confirmatory testing at the Remington Laboratory for Specialty Diagnostics (Palo Alto, California; www.sutterhealth.org/RemingtonLab) showed high-positive *Toxoplasma* IgG dye test, IgM, IgA, and IgE titers and low IgG avidity suggesting of a very recent acute *Toxoplasma* infection, likely acquired during his trip to Latin America. *Toxoplasma gondii* was detected by PCR from vitreous fluid and urine, and plasma metagenomics next-generation sequencing (mNGS) cell-free DNA (Karius, Inc, Redwood City, California) [9, 10] also detected *T gondii* (Figure 1). MRI of the orbits confirmed bilateral posterior uveitis (Figure 2C). A

second lumbar puncture on DOI 84 showed down-trending CSF pleocytosis and CSF protein. Brain MRI on DOI 85 showed findings consistent with postinfectious demyelination (Figure 2D), while the spinal MRI was normal. MRI of the lower extremities showed myositis. On DOI 86, anti-*Toxoplasma* therapy with pyrimethamine, sulfadiazine, and leucovorin was started. At 4-week follow-up there was improvement in visual and retinal findings, resolution of fatigue and myalgias, improvement of tremors and splenomegaly, and normalization of troponin, liver function tests, and creatine kinase.

DISCUSSION

Acute COVID-19 and MIS-A/MIS-C pose a diagnostic and management challenge for clinicians globally. Despite case definitions for MIS-A/MIS-C, there is a significant overlap in symptoms, clinical manifestations, and laboratory evidence of inflammation with other syndromes and infections. Given that COVID-19 and MIS-A/MIS-C may require management with immunosuppressive or immunomodulatory therapies, healthcare providers should prudently consider serologic

screening for toxoplasmosis, among other infectious agents, prior to initiating immunosuppressive therapies. Although our patient had risk factors for toxoplasmosis (travel to the Amazon, consuming local food and drinking from local water sources), absence of conventional risk factors should not exclude the diagnosis of acute toxoplasmosis if clinical presentation is compatible [11, 12]. A common error is the failure to consider toxoplasmosis in the differential diagnosis of such patients in the absence of conventional risk factors for toxoplasmosis (eg, changing cat litter or eating raw meat). *Toxoplasma gondii* is a ubiquitous parasite and the source of the *T gondii* infection (eg, through ingestion of soil-contaminated food) can easily remain unnoticed. Almost 50% of patients with acute toxoplasmosis fail to report classic risk factors for toxoplasmosis [11, 12].

Without histopathologic examination of myocardial, lung, or muscle tissue biopsy and *Toxoplasma* molecular studies during the first 2 hospitalizations, it is difficult to confirm the exact etiology of this patient's initial presentation (MIS-A vs acute severe toxoplasmosis [2–4] vs combination of the above). It is possible that initially the patient had MIS-A, with some response to 2 days of dexamethasone. However, after stopping corticosteroids (after the first hospitalization), his MIS-A symptomatology rapidly worsened, with development of myocarditis, CSF abnormalities, and hyperferritinemia; these only partially improved with subsequent immunosuppressive and immunomodulatory treatment. This patient's initial clinical presentation could have been considered consistent with MIS-A, meeting the Centers for Disease Control and Prevention (CDC) case definition [13], including fever $\geq 38^{\circ}\text{C}$ for ≥ 24 hours, at least 3 MIS-A clinical criteria, with at least 1 being a primary criterion (primary criterion: severe cardiac illness with myocarditis/ventricular dysfunction, and 3 of 4 secondary criteria: new onset of neurologic symptoms with CSF pleocytosis, shock/hypotension and abdominal pain [that persisted despite treatment for giardiasis]), laboratory evidence of inflammation (elevated CRP, procalcitonin, ferritin), and evidence of SARS-CoV-2 infection (positive SARS-CoV-2 PCR and positive SARS-CoV-2 IgG antibodies). The CDC case definition for MIS-A/MIS-C includes as a criterion the absence of alternative plausible diagnoses [13]. However, in this patient, the toxoplasmosis diagnosis was not initially considered and therefore the patient was not initially tested for *T gondii*.

Alternatively, it is possible that patient initially had acute severe toxoplasmosis, likely acquired during his trip to Latin America (with or without MIS-A) that initially partially responded to empirical antibiotic treatment. Doxycycline has some anti-*Toxoplasma* activity [14]; however, it is not a conventional anti-*Toxoplasma* treatment. The patient had also received azithromycin and atovaquone as part of his initial antibiotic management; both of these medications have anti-*Toxoplasma* activity. Severe toxoplasmosis presenting

with a septic shock–like picture, pneumonia with ground glass opacities, myocarditis, hepatitis, myositis, and systemic inflammation have been reported even in immunocompetent individuals, particularly if more virulent *T gondii* strains are implicated, such as those found in Latin America [2–7]. This case also illustrates that, in the COVID-19 era, clinicians should beware of anchoring bias in their clinical reasoning and maintain a broad differential when indicated. In several parts of the world (eg, in Latin America and North America from wild-game *T gondii* strains), a number of patients present with severe toxoplasmosis caused by virulent/atypical strains [15]. The clinical manifestations of toxoplasmosis in such settings can be atypical. Patients presenting with systemic inflammation following travel to regions where more virulent *T gondii* strains are circulating should be screened for toxoplasmosis.

Independent of the exact etiology of the patient's presentation, the prolonged corticosteroid course contributed to the development of severe toxoplasmosis. The diagnosis was established only during his third hospitalization, concomitant with the development of acute chorioretinitis, worsening myositis, transaminitis, and new splenomegaly. Regarding his myocarditis, this could have been due to MIS-A, acute toxoplasmosis, or a combination of the above. The clinical and laboratory findings of myocarditis (detected at presentation) did not follow the usual course and response to treatment of MIS-A–associated myocarditis. Troponin, creatine phosphokinase, and symptomatology resolved only after 2–4 weeks of anti-*Toxoplasma* therapy. Regarding his neurologic findings, these could be due to MIS-A, central nervous system (CNS) toxoplasmosis, postinfectious sequelae (post-COVID-19 or post-toxoplasmosis), or a combination of the above. The patient had tremors, headaches, myoclonic jerks, and unsteady gait along with CSF pleocytosis and elevated CSF protein early in the course, but abnormal brain MRI findings, suggestive of postinfectious demyelination, were found on DOI 85. Acute disseminated encephalomyelitis has been reported both with CNS toxoplasmosis [16, 17] and MIS-A/MIS-C [18]. The fact that CSF *T gondii* PCR was negative on DOI 84 does not exclude the possibility of CNS toxoplasmosis earlier in the patient's course.

Severe toxoplasmosis [2–7] can mimic the clinical manifestations of severe COVID-19 or MIS-A/MIS-C, can present concomitantly with COVID-19 or MIS-A/MIS-C, or can develop as sequelae of prolonged immunosuppressive treatment for COVID-19 or MIS-A/MIS-C. A high index of suspicion for toxoplasmosis should be considered in COVID-19 and/or MIS-A/MIS-C patients who do not respond or who clinically worsen with immunosuppressive therapy. Testing should be performed by both serologic and molecular methods, including *T gondii* PCR from blood, bronchoalveolar lavage, urine, CSF, other body fluids or tissue biopsies, and by mNGS from plasma, with the latter having also the possibility to explore infections in diverse

body sites and infections from other pathogens. Treatment should be considered accordingly with oral pyrimethamine/sulfadiazine/folinic acid (first line anti-*Toxoplasma* therapy) or intravenous trimethoprim-sulfamethoxazole (alternative therapy). Factors contributing to severe immunosuppression in COVID-19 include profound lymphopenia and/or treatment with immunosuppressive medications (eg, corticosteroids) and/or immunomodulatory agents [19, 20]. Implementation of routine screening for toxoplasmosis should be considered before initiating immunosuppressive treatment for COVID-19 [21, 22]. Moreover, chemoprophylaxis with trimethoprim-sulfamethoxazole should be considered in selected *T gondii*-seropositive patients with COVID-19 or MIS-A/MIS-C, particularly if high-dose immunosuppressive treatment will be used for prolonged periods (eg, >2 weeks).

Notes

Patient consent. The patient's written consent was obtained. The Institutional Review Board (IRB) of the Nationwide Children's Hospital, Columbus, Ohio, USA reviewed this case report and this study was not deemed to be human research; thus, no additional IRB approval was needed.

Potential conflicts of interest. L. D. is a medical director of Karius Inc. All other authors report no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med* **2020**; 383:334–46.
- De Salvador-Guillouet F, Ajzenberg D, Chaillou-Opitz S, et al. Severe pneumonia during primary infection with an atypical strain of *Toxoplasma gondii* in an immunocompetent young man. *J Infect* **2006**; 53:e47–50.
- Carne B, Bissuel F, Ajzenberg D, et al. Severe acquired toxoplasmosis in immunocompetent adult patients in French Guiana. *J Clin Microbiol* **2002**; 40:4037–44.
- Bossi P, Paris L, Caumes E, Katlama C, Danis M, Bricaire F. Severe acute disseminated toxoplasmosis acquired by an immunocompetent patient in French Guiana. *Scand J Infect Dis* **2002**; 34:311–4.
- Mustafa K, Hillyard J, Nowak E, Slowikowski J, Okogbue I, Garner D. *Toxoplasma* myocarditis: an atypical case in an immunocompetent patient. *IDCases* **2021**; 26:e01273.
- Filipowicz A, Coca MN, Blair BM, Chang PY. Acute myocarditis with cardiogenic shock and multiple organ failure, followed by bilateral panuveitis masquerading as endogenous endophthalmitis, due to *Toxoplasma gondii* in an immunocompetent patient. *Retin Cases Brief Rep* **2021**; 15:575–80.
- Bousquet A, Bigaillon C, Dumitrescu N, et al. Acute myocarditis in an immunocompetent young man: don't forget *Toxoplasma gondii*. *Int J Cardiol* **2016**; 214:358–9.
- Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC white paper. *J Am Coll Cardiol* **2009**; 53:1475–87.
- Wilke J, Ramchandrar N, Cannavino C, et al. Clinical application of cell-free next-generation sequencing for infectious diseases at a tertiary children's hospital. *BMC Infect Dis* **2021**; 21:552.
- Kitsios GD, Bain W, Al-Yousif N, et al. Plasma microbial cell-free DNA load is associated with mortality in patients with COVID-19. *Respir Res* **2021**; 22:24.
- Boyer K, Hill D, Mui E, et al. Unrecognized ingestion of *Toxoplasma gondii* oocysts leads to congenital toxoplasmosis and causes epidemics in North America. *Clin Infect Dis* **2011**; 53:1081–9.
- Boyer KM, Holfels E, Roizen N, et al. Risk factors for *Toxoplasma gondii* infection in mothers of infants with congenital toxoplasmosis: implications for prenatal management and screening. *Am J Obstet Gynecol* **2005**; 192:564–71.
- Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in adults (MIS-A): case definition information for healthcare providers. **2021**. <https://www.cdc.gov/mis/mis-a/hcp.html>. Accessed 1 March 2022.
- Chang HR, Comte R, Pechere JC. In vitro and in vivo effects of doxycycline on *Toxoplasma gondii*. *Antimicrob Agents Chemother* **1990**; 34:775–80.
- Schumacher AC, Elbadawi LI, DeSalvo T, et al. Toxoplasmosis outbreak associated with *Toxoplasma gondii*-contaminated venison—high attack rate, unusual clinical presentation, and atypical genotype. *Clin Infect Dis* **2021**; 72:1557–65.
- Bannoura S, El Hajj R, Khalifeh I, El Hajj H. Acute disseminated encephalomyelitis and reactivation of cerebral toxoplasmosis in a child: case report. *IDCases* **2018**; 13:e00434.
- Aksoy A, Tanir G, Ozkan M, Oguz M, Yildiz YT. Acute disseminated encephalomyelitis associated with acute *Toxoplasma gondii* infection. *Pediatr Neurol* **2013**; 48:236–9.
- Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain* **2020**; 143:3104–20.
- Remy KE, Mazer M, Striker DA, et al. Severe immunosuppression and not a cytokine storm characterizes COVID-19 infections. *JCI Insight* **2020**; 5:e140329.
- National Institutes of Health. COVID-19 treatment guidelines: immunomodulators. **2021**. <https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/>. Accessed 1 November 2021.
- Mewara A, Sahni N, Jain A. Considering opportunistic parasitic infections in COVID-19 policies and recommendations. *Trans R Soc Trop Med Hyg* **2021**; 115:1345–7.
- Abdoli A, Falahi S, Kenarkoobi A. COVID-19-associated opportunistic infections: a snapshot on the current reports [manuscript published online ahead of print 23 August 2021]. *Clin Exp Med* **2021**. doi:10.1007/s10238-021-00751-7.