Acute Muscular Sarcocystosis: An International Investigation Among Ill Travelers Returning From Tioman Island, Malaysia, 2011–2012

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Background. Through 2 international traveler-focused surveillance networks (GeoSentinel and TropNet), we identified and investigated a large outbreak of acute muscular sarcocystosis (AMS), a rarely reported zoonosis caused by a protozoan parasite of the genus Sarcocystis, associated with travel to Tioman Island, Malaysia, during 2011–2012.

Methods. Clinicians reporting patients with suspected AMS to GeoSentinel submitted demographic, clinical, itinerary, and exposure data. We defined a probable case as travel to Tioman Island after 1 March 2011, eosinophilia (>5%), clinical or laboratory-supported myositis, and negative trichinellosis serology. Case confirmation required histologic observation of sarcocysts or isolation of Sarcocystis species DNA from muscle biopsy.

Results. Sixty-eight patients met the case definition (62 probable and 6 confirmed). All but 2 resided in Europe; all were tourists and traveled mostly during the summer months. The most frequent symptoms reported were myalgia (100%), fatigue (91%), fever (82%), headache (59%), and arthralgia (29%); onset clustered during 2 distinct periods: “early” during the second and “late” during the sixth week after departure from the island. Blood eosinophilia and elevated serum creatinine phosphokinase (CPK) levels were observed beginning during the fifth week after departure. Sarcocystis nesbitti DNA was recovered from 1 muscle biopsy.

Conclusions. Clinicians evaluating travelers returning ill from Malaysia with myalgia, with or without fever, should consider AMS, noting the apparent biphasic aspect of the disease, the later onset of elevated CPK and eosinophilia, and...
On 25 October 2011, GeoSentinel, the surveillance program of the International Society of Travel Medicine (ISTM) and the US Centers for Disease Control and Prevention (CDC) [1], was notified of a cluster of ill German patients recently returned from Tioman Island, off the eastern coast of peninsular Malaysia (Figure 1) [2, 3]. These patients had an unusual clinical presentation: All of them reported fever and significant muscle pain, had blood eosinophilia and elevated serum creatinine phosphokinase (CPK) levels, and tested seronegative for trichinellosis and toxoplasmosis. A muscle biopsy from one of these patients was diagnostic for acute muscular sarcocystosis (AMS), a rarely reported zoonotic infection. The GeoSentinel...
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Sarcocystosis Outbreak on Tioman Island

METHODS

Epidemiologic Investigation
GeoSentinel is a global provider-based, traveler-focused sentinel surveillance network established collaboratively by ISTM and the CDC [1]. The 57 GeoSentinel sites in 24 countries consist of travel and tropical medicine clinics that actively monitor travel-related morbidity. TropNet is a European travel and tropical medicine research and surveillance network [15]. Together, these networks encompass >110 travel and tropical medicine sites and >225 participating affiliated sites worldwide.

After the first patients were reported, members of these networks were notified of the outbreak through e-mail alerts and other informal channels. In addition, the networks communicated to the larger infectious diseases community through ProMED Mail postings [16–19] and published outbreak alerts [2, 4]. Relevant global public health authorities were also notified. All were encouraged to report patients suspected of having AMS to GeoSentinel. Clinicians were asked to complete 2 structured questionnaires: one for demographic and clinical data and one for travel and exposures. They were also asked to document the date of onset for a list of symptoms that were based on our experience with the first reported patients, as well as a literature review. This outbreak investigation was determined to be public health response, and thus institutional review board review was not required. All patients gave informed consent.

We report only those patients meeting an intentionally specific outbreak case definition of probable or confirmed AMS. A probable case required travel to Tioman Island after 1 March 2011, with myositis, eosinophilia >500 cells/μL, and negative trichinellosis serology. Myositis required at least 1 of the following: a complaint of muscle pain and a CPK level >200 IU/L; muscle tenderness documented on physical examination; or histologic evidence of myositis in a muscle biopsy. Case confirmation required histologic observation of intramuscular cysts compatible with sarcocysts or the isolation of Sarcocystis species DNA from a muscle biopsy.

Laboratory Analysis
Diagnostic testing was at the discretion of the clinician but could include complete blood counts and differentials, serum biochemical testing, electrocardiography, echocardiography, imaging studies, and electromyography. Some patients were tested for specific diseases such as malaria, intestinal parasites, toxocariasis, filariasis, and dengue, chikungunya, and Epstein-Barr virus infection. Serum samples were requested, and testing at the CDC Parasitic Diseases Reference Laboratory for trichinellosis, toxoplasmosis, and strongyloidiasis was performed on available samples not previously tested as part of the initial clinical evaluation. Sera were also used by the CDC for developing a serological assay for human sarcocystosis using both whole digested merozoites and recombinant surface peptides of Sarcocystis neurona.

At the discretion of the clinician, some patients underwent muscle biopsy. All biopsies were examined histologically by a pathologist at the institution where collected. When possible, tissue blocks, frozen tissue, and extracted DNA cryoprecipitate were sent to the CDC Infectious Diseases Pathology Branch for additional examination, including histopathology, polymerase chain reaction (PCR) detection, and DNA sequencing analysis of Sarcocystis species 18S ribosomal RNA (rRNA) amplicons.

Human muscular sarcocystosis is caused by an intracellular protozoan parasite of the genus Sarcocystis (available at: http://www.istm.org/geosentinel and http://www.istm.org/eurotravnet and TropNet (available at: http://www.tropnet.net) networks contacted their members and alerted relevant public health authorities to conduct additional case finding. Within days of the network alerts, additional patients were identified, prompting further investigation [2, 4].

GeoSentinel (available at: http://www.cdc.gov/dpdx/sarcocystosis/index.html). First described in 1843, approximately 130 species of Sarcocystis have been identified from a variety of wild and domestic mammals, birds, and reptiles [5]. These organisms have an obligatory 2-host life cycle, alternating between predator and prey (the definitive–intermediate hosts). Humans are the definitive host for Sarcocystis hominis and Sarcocystis suihominis, acquired by eating undercooked sarcocyst-containing beef or pork, respectively. Definitive host infection is limited to the intestine and may cause acute gastroenteritis, although most infections are probably asymptomatic [6]. Humans can also become the accidental dead-end intermediate host for an unknown number of other Sarcocystis species, presumably acquired by ingesting sporocyst-containing food or water contaminated with feces from infected carnivores. In the intermediate host, generations of reproduction occur in the vasculature, ultimately leading to the formation of characteristic cysts (sarcocysts) within myocytes of skeletal, cardiac, and, infrequently, smooth muscle.

Until recently, <100 cases of human muscular sarcocystosis were reported in the literature, particularly from Malaysia [7–9]. The majority of these cases were diagnosed incidentally in asymptomatic persons or in patients whose symptoms were not clearly related to their Sarcocystis infection. At most, 10 of these cases had symptomatic AMS [10–13]; an additional recent report describes an outbreak involving 89 patients with AMS acquired on Pangkor Island, off the west coast of peninsular Malaysia [14]. Effective treatment for this disease has not been determined.

The principal objectives of this investigation were to describe the clinical, laboratory, and epidemiologic characteristics of this outbreak of AMS. We also sought to identify possible sources of infection among the ill travelers, and to alert clinicians to consider AMS when evaluating ill returned travelers.
For histopathologic examination, 3-µm sections were cut from formalin-fixed, paraffin-embedded muscle biopsy specimens and stained with hematoxylin and eosin. For electron microscopy (EM), a paraffin section was embedded in Epon-Araldite epoxy resin, removed from the slide and glued to a blank EM block, sectioned and stained, and examined in an FEI Tecnai Spirit microscope. PCR amplification was performed with a primer pair designed to amplify a fragment of approximately 800 base pairs from the 18S rRNA gene of different species of Sarcocystis [20]. Amplicons were sequenced by using BigDye version 3.1 chemistry (Applied Biosystems), and sequence data were analyzed as previously described [21].

Statistical Analysis
Descriptive statistics were estimated using SAS software, version 9.2 (SAS Institute).

RESULTS

Epidemiologic Characteristics of Case Patients
Demographic and Travel Characteristics
From October 2011 through April 2013, 99 ill persons who returned home after travel to Tioman Island were reported to GeoSentinel as having suspected AMS. Overall, 68 (69%) patients met the case definition and were included in the analysis; 62 were probable and 6 were confirmed cases. The median age of these patients was 34 years (range, 4–72 years); 39 (57%) were female. Of the 31 who did not meet the case definition, 24 did not satisfy criteria for myositis and 5 did not have eosinophilia, trichinellosis testing, or both.

More than three-quarters of the case patients resided in either Germany (43%) or France (34%). Fourteen (21%) lived elsewhere in Europe (6 in the Netherlands, 3 in Switzerland, 2 each in Belgium and Spain, and 1 in Italy); the 2 non-Europeans resided in Canada and Singapore. Most traveled to Tioman Island during the European summer months (Figure 2); all were tourists. The median stay was 5 days (range, 3–16 days), with 49 (72%) of the travelers staying <7 days.

Exposures
Complete travel and exposure data were submitted from 61 (90%) case patients. Most lodging, eating, and recreational activities were concentrated on the northwest coast of Tioman Island; no single village or attraction was visited by >40 (68%, data missing for 2) case patients (Figure 1). All travelers reported eating at restaurants and lodging at resorts, hotels, huts, or bungalows; no single eating or lodging establishment was visited by >22 (36%, Table 1). All case patients visited a beach, and...
Clinical and Laboratory Findings
Case patients first became ill a median of 11 days (range, 0–40 days) after departing from Tioman Island. The most frequent symptoms reported among the 68 case patients were myalgia (100%), fatigue (91%), fever (82%), headache (59%), and arthralgia (29%); other symptoms were less frequently reported (Figure 3). Patients were first evaluated by the reporting clinician at different points during the course of their illness; physical examination data were collected only on that first visit, which was a median of 44 days (range, 12–79 days) after departing from the island. Twenty-nine of 55 (53%) case patients were febrile (temperature ≥38°C); 19 of these had a temperature ≥39°C. Muscle tenderness was present among 47 of 64 (73%) and was described as moderate or severe in 32 (68%). Thirty-eight of 64 (88%) had tenderness involving their extremities; 1 reported tenderness of the masseter muscle of the face and another of the tongue. Skin rash, lung findings, and lymphadenopathy were each found in ≤3 patients. One patient reported subcutaneous nodules on the chin and neck that resolved prior to presentation, and another had muscle fasciculations involving all 4 extremities. One patient had a thrombosis of the left sigmoidal and transverse sinuses followed by pulmonary emboli; no clotting abnormality was found, and a sarcocystosis-related vasculitis could not be ruled out. One patient was pregnant at the time of infection; she experienced no complications. No patient was known to have an underlying medical condition (such as immunosuppression) that would have been expected to have affected the infection. At least 7 case patients (10%) were hospitalized; none required intensive care.

Onset of the 5 most frequent symptoms appeared to cluster during 2 distinct periods: early during the second and late during the sixth week after departure (Figure 4A). No other symptom showed this pattern. To account for persons presenting at different times during the course of their illness, we also restricted the analysis to those who sought care after the fourth postdeparture week; the biphasic symptom-onset pattern persisted. For 25 (37%) patients, the illness was described as phasic, intermittent, or waxing–waning in character, with periods of symptoms separated by a period of relative improvement.

Although few absolute eosinophil counts or serum CPK levels were performed during the first 4 postdeparture weeks, elevations in both were noted most frequently during the late period, after the fourth week postdeparture (Figure 4B and 4C). Of 10 case patients with a mildly elevated CPK-myocardial band (MB) fraction, 8 had a normal electrocardiogram (ECG), echocardiogram, or troponin, and none were thought to have cardiac pathology. One patient with a normal CPK-MB fraction, troponin, and ECG on presentation had an echocardiogram showing mild dilation of right ventricular outflow and was thought clinically to have developed mild myocarditis. Eighteen (26%) case patients had positive Toxoplasma immunoglobulin G, but all those tested were immunoglobulin M negative (6 unknown). Strongyloides serology was positive in 4 (6%, 2 unknown). Attempts to develop and validate a serologic assay for human sarcocystosis species infection were unsuccessful due to inconsistent reactivity of sera from patients with confirmed sarcocystosis and cross-reactivity of sera from patients with known toxoplasmosis.

Patients were treated with a range of antiparasitic agents, including albendazole, as well as oral steroids. Some clinicians...
reported symptom improvement on oral steroids, although we could not determine whether improvement was due to the medication or the natural course of the illness. The patient with mild myocarditis was treated with oral steroids and improved, although causality could not be established.

**Histopathology and Species Identification**
Fifteen patients had a muscle biopsy performed a median of 60 days postdeparture (range, 39–92 days). All tissue samples were examined histologically by a pathologist where collected. The CDC received tissue from a total of 14 (93%) biopsied patients, as tissue blocks, extracted DNA cryoprecipitate, frozen tissue, and/or prepared slides. Photographs of representative histopathology were received from 8 patients, 1 from the patient from whom tissue was not available. In all samples and photographs examined, histopathology showed inflammation that was predominantly perivascular within the endomysium and perimysium with a wide range of severity, from rare foci of predominantly lymphohistiocytic inflammation to more frequent foci of mixed inflammation (Figure 5A). Sarcocysts were observed histologically in the muscle of only 6 patients (40%), despite intensive searches including examination of >60 sections from a single muscle biopsy sample in which a lone sarcocyst was observed by a pathologist at the point where collected. When present, intramyocytic sarcocysts were characterized by single, large (up to 100 µm in width and several hundred micrometers in length), thin-walled, septated cysts containing innumerable, crescent-shaped bradyzoites that were approximately 4 × 8 µm (Figure 5B); no inflammation was observed immediately adjacent to any sarcocyst. By EM, large cysts were found embedded in skeletal muscle; they contained numerous, approximately 3.5 µm bradyzoites (Figure 5C). The cyst wall demonstrated short, undulating type 1 protrusions (Figure 5D) [5].

Ten patients had PCR testing for *Sarcocystis* species DNA; 1 biopsy sample, also with sarcocysts visible on histopathology, was positive. The sequencing analysis of the amplified fragment showed 100% similarity with the 18S rRNA gene from *Sarcocystis nesbitti* (GenBank accession number HF544323).

**DISCUSSION**
We report 68 travelers with AMS acquired while vacationing on Tioman Island, Malaysia. The spectrum of AMS in humans is broad: from asymptomatic, which may characterize most infected patients [7–9], to severe and relapsing illness lasting years [11]. Comparable with other reports, the majority of the Tioman Island patients experienced muscle pain, fatigue, fever, and headache. In contrast, we did not find cough, rash, lymphadenopathy, swelling, facial tenderness, subcutaneous nodules,
or cardiac abnormalities to be prominent, although patients were not examined at standardized intervals [10–14].

Onset of symptoms occurred in 2 distinct phases: early (beginning within the second week postdeparture) and late (beginning within the sixth week postdeparture). As others have reported, more than one-third of our patients experienced waxing and waning of symptoms [11, 14]. We found that the late phase corresponded with a rise in the serum CPK level and blood eosinophil count, possibly reflecting the onset of an immune-mediated myositis. All 15 muscle biopsies showed histologic evidence of varying degrees of diffuse multifocal myositis; all were done on or after the 39th day after departure from the island, and none had evidence of inflammation immediately adjacent to any observed sarcocyst. As few CPK determinations and no biopsies were done within 5 weeks of departure from the island, earlier development of myositis cannot be ruled out. The lack of clinical suspicion, reflected by the paucity of serum CPK and biopsy data in the early weeks, however, suggests that this is unlikely.

The phasic nature of AMS in humans reported here is well characterized in animals with experimentally induced intermediate-host infections [5]. Signs and symptoms of disease in animals reflect the stages of development and the migratory trajectories of the parasite as it passes from the intestine via the vascular endothelium to its final destination within the myocyte. The exact time course, however, depends on the specific species of infecting Sarcocystis and the specific host species that is infected [5]. Given the patterns observed among the Tioman Island patients, we hypothesize that disease in humans parallels that seen in animals. More work is needed to characterize the pathophysiology of disease in humans infected by Sarcocystis species as the intermediate host.

Despite the presence of swimming beaches and lodging across the island, the ill travelers concentrated most of their activities on the northwest portion; however, no obvious source of infection could be identified through epidemiologic analyses, although nearly all case patients reported potential exposure to untreated water. Cats were ubiquitous and were frequently observed in tourist areas, with nearly three-quarters of the case patients reporting having either touched or fed a cat. Although long-tailed macaques [22] and numerous reptile species, including water monitors and a variety of snakes [23], inhabit Tioman Island, few patients reported contacts. Interestingly, an environmental evaluation on the island conducted by the Malaysia

![Image](https://example.com/image.png)

Figure 4. Timing of specific elements of acute muscular sarcocystosis. A, Onset of the 5 most frequently reported symptoms of acute muscular sarcocystosis relative to the number of weeks since departing from Tioman Island; onset clustered during the second (early) and the sixth (late) postdeparture weeks. More than 1 onset date for at least 1 of these symptoms was reported by 15 patients (myalgia [n = 10], fever [n = 7], headache [n = 2], fatigue [n = 1]; none for arthralgia). For 25 (37%) patients, the illness was described as phasic, intermittent, or waxing–waning in character, with periods of symptoms separated by a period of relative improvement. B and C, All blood absolute eosinophil counts and serum creatinine phosphokinase (CPK) levels, respectively, for all patients relative to the number of weeks since departing Tioman Island. Each case patient may have had >1 of each laboratory determination. One absolute eosinophil count of 6200 cells/µL and 1 CPK level of 3900 U/L, each from a different patient, is not included in B and C, respectively. *Based on the case definition, >500 cells/µL is considered elevated. †Based on the case definition, >200 U/L is considered elevated.
Ministry of Health (MMoH) in response to this outbreak isolated *Escherichia coli* from almost all, and parasites from several, sampled water sources, although no *Sarcocystis* species were recovered [24]. In addition, no *Sarcocystis* species sporocysts were observed in the animal feces that were sampled, including from cats. Although the MMoH isolated *Toxoplasma gondii* from sampled cats, none of the case patients identified during this outbreak had evidence of acute toxoplasmosis, as might be expected if cats were the source of this outbreak. Notably, the MMoH did not sample any local rodent, bird, or reptile species during their survey of the island, and their investigation was limited in scope and conducted during the monsoon season, at a time when no infections among travelers were being reported [22–25]. Travelers to Tioman Island should be advised to practice proper precautions, including avoiding contact with animals, eating and drinking safe food and water, and washing hands frequently.

We identified *S. nesbitti* from the formalin-fixed muscle tissue of a patient with acute myositis and multiple sarcocysts observed on microscopic examination of histologic sections. This finding corroborates recent data showing that *S. nesbitti* was recovered from the muscle of 2 of 89 acutely ill patients [14]. *Sarcocystis nesbitti* has been considered to be a potential cause of human infections because it infects Southeast Asian species of nonhuman primates, including the long-tailed macaque, and because it resembles morphologically sarcocysts seen in humans [26–28]. Although the natural life cycle of this organism has not yet been definitively determined, evidence is mounting that *S. nesbitti* has a snake species as its natural definitive host [29–31]. An understanding of the natural life cycle of this zoonotic parasite would aid the development of preventive measures and messaging.

AMS among travelers is largely a clinical diagnosis that requires an understanding of symptoms and symptom progression and the geographic risk distribution of the disease. Early diagnosis is made difficult by the nonspecific nature of the early phase of the disease and the absence of a simple and accurate diagnostic test, such as serology. Diagnosis in the later phase may be easier because relatively few infectious diseases are characterized by clinical myositis and eosinophilia, the most notable exception being trichinellosis. In addition, the biphasic nature of the illness may offer a hint to the clinician. Currently, definitive diagnosis requires histologic observation of sarcocysts in or amplification of *Sarcocystis* species DNA by PCR from a muscle biopsy sample. However, we found that sarcocysts are likely distributed diffusely and difficult to find.

**Figure 5.** Histopathology and electron microscopy. A, Skeletal muscle (SM) with inflammation (arrows) adjacent to a small vessel (v). Inflammation composed of lymphocytes and macrophages with small numbers of plasma cells, eosinophils, and rarely neutrophils. Original magnification ×400, hematoxylin and eosin staining. B, SM with intramyocytic sarcocyst. Note the absence of inflammation surrounding the sarcocyst-containing myocyte. Original magnification 400×, hematoxylin and eosin staining. C, Portion of a cyst within SM, containing abundant bradyzoites (arrow). D, Higher magnification of the cyst wall, showing short protrusions (arrow) and a fairly thin granular layer (GL). Bars = 2 µm (C) and 500 nm (D). Abbreviations: GL, granular layer; SM, skeletal muscle; v, small vessel.
Although there is currently no treatment regimen that has been shown to be effective, anti-inflammatory agents may be helpful in the management of pain. The value of specific antiparasitic agents is an area for further exploration.

These data have several limitations. At the outset of this investigation, AMS in humans was not well characterized and relevant data may have gone unrecorded. Data were gathered retrospectively and at different stages of disease, potentially affecting the accuracy of patient recall. Many clinicians from a variety of countries and practice settings participated in data collection, which may have introduced variability in data consistency. Finally, our methods likely identified more severely affected patients. Our data may not reflect disease among all patients infected with *S. nesbitti*, some of whom may have been asymptomatic.

Our data largely corroborate previous descriptions of human sarcocystosis and offer important new details on this emerging disease. Foremost among these is the suggestion of a 2-phase clinical presentation, commencing about 2 and 6 weeks after infection. Unfortunately, the outbreak investigation did not lend itself to determining what proportion of those infected remain asymptomatic, assessing the various therapeutic measures, or determining the typical duration of illness. Clinicians who see posttravel illness should add AMS to their differential diagnosis of the ill patient returning from Malaysia with myalgia, with or without fever, noting the apparent biphasic aspect of the disease. The later onset of elevated CPK and eosinophilia, and the possibility for relapses. Although only 1 biopsy was positive by PCR, our work and the work of others suggest *S. nesbitti* as a cause of human AMS. Further studies should focus on confirming the natural life cycle of this organism to develop preventive recommendations, following patients along the full course of their illnesses, and studying treatment options. To prevent future illnesses among travelers to Tioman Island, the exact source of the outbreak needs to be determined and transmission interrupted.

**Notes**

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**APPENDIX**

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