AN OUTBREAK OF ACUTE EOSINOPHILIC MYOSITIS ATTRIBUTED TO HUMAN SARCOCYSTIS PARASITISM

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Abstract. Seven members of a 15-man U.S. military team that had operated in rural Malaysia developed an acute illness consisting of fever, myalgias, bronchospasm, fleeting pruritic rashes, transient lymphadenopathy, and subcutaneous nodules associated with eosinophilia, elevated erythrocyte sedimentation rate, and elevated levels of muscle creatinine kinase. Sarcocysts of an unidentified Sarcocystis species were found in skeletal muscle biopsies of the index case. Albendazole ameliorated symptoms in the index case; however, his symptoms persisted for more than 5 years. Symptoms in 5 other men were mild to moderate and self-limited, and 1 team member with laboratory abnormalities was asymptomatic. Of 8 team members tested for antibody to Sarcocystis, 6 were positive; of 4 with the eosinophilic myositis syndrome who were tested, all were positive. We attribute this outbreak of eosinophilic myositis to accidental tissue parasitism by Sarcocystis.

Human muscular sarcocystosis (syn. sarcosporidiosis) is a rare infection caused by coccidian parasites in the family Sarcocystidae. More than 100 different species of Sarcocystis occur worldwide in a wide range of domestic and wild animal reservoirs, with reported prevalences varying between 10% and 100% in domestic livestock.1,2 Sarcocystis species typically have a two-host predator-prey life cycle. The sexual cycle occurs in enterocytes of the definitive host, resulting in shedding of sporulated, infective oocysts or sporocysts in feces, which in turn can infect an intermediate host upon ingestion. Sporozoites excyst from the ingested sporocysts and initiate an asexual cycle, often multiplying initially in blood vessels to form schizonts. Merozoites released from these schizonts eventually encyst in muscular and/or neural tissues, forming sarcocysts. Inside tissue sarcocysts, the merozoites divide into pairs by endodyogeny to form microcytes, undifferentiated forms that are typically globular. The microcytes eventually give rise to mature, banana-shaped bradyzoites. The sarcocyst becomes infective for the definitive host only when bradyzoites are formed; schizonts and microcytes are not infective. Upon ingestion of infected tissue by the definitive host, the bradyzoites transform directly into male and female gamonts in enterocytes, sporulate, and shed oocysts within 7–14 days, completing the cycle.1

Humans may serve as intermediate or definitive hosts for various Sarcocystis species, but not for the same Sarcocystis species. Sarcocystis hominis and S. suihominis are two species acquired in humans by eating uncooked sarcocysts from beef or pork, respectively. Only the sexual parasite life cycle of these species has been demonstrated in the intestines of humans. Humans also may become accidental intermediate hosts for a number of species of Sarcocystis. Only sarcocyst stages have been demonstrated in human tissues. The life cycle and definitive host are not known for any species of Sarcocystis that forms sarcocysts in humans.1 Most reports of human tissue infection with sarcocysts have been considered to be incidental observations, and most reported cases were acquired in the Far East.1,3

Here we describe an outbreak of an acute illness in U.S. military personnel after a field operation in Malaysia, characterized by fever, eosinophilia, myositis, and evidence of infection with a species of Sarcocystis. This outbreak of eosinophilic myositis in previously healthy combat troops suggests that Sarcocystis infection can cause significant clinical illness in humans.

PATIENTS AND METHODS

Description of the military operation in Malaysia. In May 1993, a 15-man U.S. Air Force Special Tactics Team based in Okinawa, Japan participated in a joint U.S.-Malaysian civic action project. Five men remained at an airfield support camp near Kuala Lumpur, and 10 men deployed for one week to a remote area in central, peninsular Malaysia working closely with the local population in austere field conditions in a jungle village approximately 80 km northeast of Kuala Lumpur. All of the men had previously worked in the Malaysian jungle, but had normal aviation physical examination results within 1 year prior to deployment. The team constructed huts and irrigation sluices in a rural Malaysian village and lived intimately with the local populace, using their hosts’ facilities for sleeping, bathing, and eating. Seasonal monsoon rains were particularly heavy, but the team continued to work, and at times went shirtless and shoeless in the heavy rain, and were given to sport in the ankle deep mud. They later reported extensive physical contact with soil, including exposure to the eyes, nose, and mouth from mud wrestling. They also went swimming in fresh water pools, drank untreated water, and consumed native foods, including lizard meat, soups, and fresh vegetables that were often not well cooked. Compliance with daily doxycycline anti-malarial prophylaxis was irregular at best, and none at all in some cases.

Epidemiologic investigation. Within 3 weeks after the team returned from field operations, 2 team members had sought care from their flight surgeon with acute fever, bronchospasm, and myositis. They both had elevations of hepatic...
enzyme levels and eosinophilia. We started an outbreak investigation to aid in diagnosis and to screen for clinically inapparent cases. All 15 members of the team were interviewed and examined. Team members were placed in a jungle cohort (10 men) or airfield cohort (5 men) according to their duties in Malaysia. The following laboratory studies were performed on all members of the jungle cohort: white blood cell count and differential count; thick and thin peripheral blood smears; serum levels of lactate dehydrogenase, aspartate aminotransferase, and Wintrobe erythrocyte sedimentation rate. In addition, alanine aminotransferase and creatinine phosphokinase (CK) serum levels were determined on 6 and 5 of the 7 affected team members, respectively. Laboratory findings are shown in Table 1. Blood sera were also drawn and held frozen for serologic studies, detailed in the case reports below. Team members were sorted into symptomatic and asymptomatic groups, based on interview and laboratory abnormalities.

**Outbreak case summary: patient 1.** One week after returning from Malaysia, this 35-year-old member of the jungle cohort noted mild diarrhea of 1-week duration. Ten days after returning, he developed severe generalized myalgias and arthralgias associated with fleeting pruritic rashes, productive cough, headache, generalized fatigue, nocturnal diaphoresis, intermittent fevers up to 38.9°C, shaking chills, malaise, insidious muscle wasting with sporadic fasciculations, and transient right upper quadrant pain. He lost 9 kg of body weight over the ensuing 2-month period, and complained of hollow indentations in the skeletal muscles of his extremities. These could be palpated on clinical examination, and were consistent with loss of muscle mass. He had a history of seasonal rhinitis and allergy to sulfonamides, but he denied any history of L-tryptophan ingestion. There was no lymphadenopathy or hepatosplenomegaly on physical examinations. Erythromycin therapy for presumptive bronchitis had no effect. Over the course of four months, his symptoms waxed and waned, and firm, fixed, non-tender subcutaneous nodules appeared on his elbows, legs, and abdomen. He was also noted to have transient, blanching, erythematous patches scattered over the trunk. His peripheral blood eosinophilia ranged from 9% to 19% during this period. Transient diffuse, generalized, 1–2-cm lymphadenopathy was noted on subsequent examinations, and on one occasion he had bitemporal muscle tenderness to palpation. He remained clinically stable with gradual improvement, and his eosinophilia normalized over the next six months.

**Outbreak case summary: patient 2.** This 37-year-old man was well until approximately two weeks after returning from Malaysia, when he developed fevers between 38.3°C and 39.7°C, night sweats, severe soreness and stiffness of the muscles of his neck, back, and legs, and pronounced fatigue. These symptoms resolved after approximately two weeks. However, six weeks later he noted the onset of a productive cough with yellow sputum and chest tightness. Over the course of three months he experienced diffuse migratory myalgias with muscle wasting, and lost 6 kg of weight. His physical examination results were normal except for generalized, shotty lymphadenopathy and bilateral expiratory wheezes at the lung bases. His white blood cell counts were normal, but total eosinophil counts were elevated up to 1,656/mm³. No biopsy was performed in patient 2.

**Laboratory evaluation of patients 1 and 2.** An extensive diagnostic evaluation of the two men was done. Serology for human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, hepatitis viruses A, B, and C, leptospirosis, amebiasis, toxoplasmosis, trichinosis, strongyloidiasis, filariasis, and schistosomiasis were all negative in both patients. Antinuclear antibody, rheumatoid factor, and serum IgE levels were normal. Stools were negative for ova and parasites, white blood cells, and occult blood. A string test and examination of the sputum for nematode larvae was negative in patient 1. Esophagogastroduodenoscopy with aspirates and duodenal mucosal biopsies were normal and negative for parasites in both men. Patient 1 had Salmonella meleagridis cultured from the stool without persistent diarrhea. Blood cultures were negative in both men. Empiric treatment with courses of doxycycline, diethylcarbamazine (DEC), metronidazole, mebendazole, and thiabendazole were ineffective in both cases. No microfilarias were detected on day- or night-time peripheral blood smears before or after DEC challenge in either patient. Radiographs of the chest, pulmonary function testing, electrocardiograms (ECGs), and computed tomography scans of the abdomen and pelvis were negative in both patients. Patient 1 also had normal nerve conduction and electromyogram test results three months after onset of symptoms; however, fasciculations were not present at the time of examination. Tissue biopsies performed 3 months after his initial presentation were positive for sarcocysts as described below (biopsy specimen photomicrographs are shown in Figures 1–4).

**Outbreak case summaries: patients 3–7.** Four other patients in the jungle cohort developed symptoms including...
bronchospasm, myalgias, fleeting rashes, and diffuse lymphadenopathy within 2 months of returning from Malaysia. Patient 7 was asymptomatic, and had only laboratory abnormalities identified by screening tests. Thus, 7 outbreak cases were identified, and all were members of the 10-man jungle cohort; none of the 5 men in the airfield support team had clinical symptoms or screening laboratory abnormalities. Patient 3 had an enlarged inguinal lymph node, from which a biopsy specimen was obtained; it revealed only reactive, inflammatory lymphadenopathy. Biopsies and additional special serologic tests were not performed in the other team members. Over a 6-month period, signs and symptoms in the affected team members waxed and waned. Patients 1 and 2 presented earlier and were much more symptomatic than the others, complaining bitterly of muscle wasting, myalgias with fasciculations, and weight loss. After 6 months, laboratory abnormalities and symptoms disappeared in all patients except patient 1, as described above. The results of laboratory studies in all the affected team members are summarized in Table 1.

**Case definition.** A team member with fever and/or eosinophilia (> 5% of total white blood cells or > 450 eosinophils/mm³) was defined as an outbreak case. The team member with *Sarcocystis* organisms demonstrated on muscle biopsy was defined as a definite *Sarcocystis* case. Six team members with clinical symptoms and/or eosinophilia, with or without serologic evidence of exposure, were defined as possible *Sarcocystis* cases. Two team members without the clinical syndrome, with positive serologic antibody test results, were defined as exposed to *Sarcocystis*.

**Long-term clinical course of patient 1.** One year after initial presentation, patient 1 developed acute appendicitis with a peri-appendiceal abscess. Surgical pathology of the resected appendix was reported only as an appendix with inflammation, and no sarcocysts were noted; however, the surgery and subsequent pathologic examination were performed as an emergency procedure at another facility, and no special pathologic identification procedures were attempted. The only abnormal laboratory finding in the presurgical evaluation was a mildly elevated erythrocyte sedimentation rate. Within a few months of the surgery, patient 1 again sought treatment from his aviation physician for recurrent myositis. He complained of renewed myalgias, fasciculations, and subcutaneous nodules associated with palpable crepitus and chronic cough. He also noted easy fatigability, extreme exercise intolerance, and dyspnea on exertion. He
had milder eosinophilia and serum enzyme abnormalities at
this follow-up visit. Results of an air-contrast barium enema,
colonoscopy, upper gastrointestinal contrast series with
small-bowel follow-through, and repeat abdomino-pelvic CT
scan were negative. In light of this otherwise negative eval-
uation, his recurrent symptoms were considered to be man-
ifestations of chronic Sarcocystis infection, and the relation-
ship to appendicitis to be coincidental. His symptoms per-
sisted, and 18 months after his initial presentation, he was
treated with albendazole, 400 mg twice a day for 15 days.
This therapy immediately elicited acute intense pruritis, fol-
lowed by gradual waning of chronic symptoms. After dis-
continuation of albendazole treatment, his complaints grad-
ually returned over several weeks, and therapy was repeated
at a higher dose (600 mg twice a day for another 20 days).
Following this extended course of therapy, his symptoms
abated, but during re-evaluation for return to aviation duty
one year later, he was discovered to have borderline left
atrial enlargement on an echocardiogram with associated
nonspecific ECG abnormalities, suggestive of possible Sar-
cocystis myocarditis. Over the course of another year of ob-
ervation, these cardiac abnormalities normalized. Four
years after first seeking medical care for this syndrome, he
was restored to aviation duty after having a normal repeat
echocardiogram. Five years from the first onset of symp-
toms, he reported occasional episodes of mild pruritis
and/or paresthesia, without eosinophilia or other laboratory
evidence of active infection.

Tissue preparation methods. Tissue biopsy specimens of
muscle taken from the right anterior forearm and left anterior
thigh of patient 1 were fixed in formalin and processed rou-
tinely in the laboratory at the Tripler Army Medical Center
(Honolulu, HI) and submitted to the Armed Forces Institute
of Pathology (Washington, DC). Sections were stained by
the following methods: hematoxylin and eosin, Movat, Gi-
emsa, Ziehl-Neelsen, periodic acid–Schiff, Gomori methen-
amine-silver, and Brown-Hopps.

Serologic test methods. Sera obtained early in the investi-
gation were lost in shipment. Seven team members were
transferred out of the unit and were unavailable for repeat
blood testing. The 8 remaining members of the team had
blood drawn 18 months after initial presentation for detec-
tion of antibodies to Sarcocystis using Western blot analysis
as previously described. Briefly, cell culture–derived mer-
ozoites of S. neurona were solubilized and proteins were
separated by sodium dodecyl sulfate–polyacrylamide gel
electrophoresis. Proteins were electroblotted onto nitrocel-
lulose paper and exposed to diluted patient sera. Antibodies
to Sarcocystis were detected by Western blot analysis. This
test has been evaluated for cross-reactivity to related para-
sites and is non-reactive with Toxoplasma and related spe-
cies (Granstrom DE and others, unpublished data).

RESULTS

Patient 1 tissue biopsy. The pathologic biopsy specimens
from patient 1 were positive for focal, microscopic, cystic
collections of organisms identified as Sarcocystis species,
with associated tissue eosinophilia and inflammation, con-
firming the diagnosis of Sarcocystis myositis. The histopath-
ologic changes were essentially identical in both biopsy
specimens. Several intramuscular sarcocysts were identified
in both specimens. The sarcocysts appeared to be viable
(Figures 1–3). The sarcocyst wall was thin (< 0.5 μm) and
enclosed densely packed zoites that were difficult to mea-
sure. Both metrocytes and bradyzoites were observed within
the sarcocysts (Figure 3). Most sarcocysts seen were in
cross-section; one sarcocyst was cut longitudinally and mea-
sured 620 μm by 50 μm (Figure 1). There was no tissue
reaction immediately adjacent to the sarcocysts; however,
mild diffuse tissue eosinophilia was present, and focal areas
of necrosis and acute inflammation with neutrophils were
seen within the muscle tissue of non-adjacent areas (Figure
4).

Serology of antibody to Sarcocystis. Results of serology
testing in the jungle team members are shown in Table 1.
Five of the team members from the jungle detachment were
tested and found to be seropositive, 1 of whom was asymp-
tomatic and without laboratory evidence of infection. One
of 3 asymptomatic men from the airfield support detachment
who were tested was also positive. Thus, of 8 team members
tested for antibodies to Sarcocystis, 6 were positive; of 4
with the eosinophilic myositis syndrome who were tested,
all were positive, and 2 of 4 without evidence of the clinical
syndrome were also positive.

DISCUSSION

Humans can be an accidental intermediate host for Sar-
cocystis species that normally infect an unidentified carn-
vore. In Malaysia, the definitive host is putatively a python,
which preys upon various species of monkey. This is sup-
ported by ultrastructural studies of sarcocysts in human tis-
sue, which are morphologically similar to those found in
Macaca fascicularis.6,7

In an extensive review in 1979, only 40 cases were re-
ported worldwide in which Sarcocystis was confirmed in hu-
mans.7 Seven cases were associated with muscle pain
or weakness, although the investigators in that series consid-
ered most of the infections to be incidental findings. Two of
these cases were acquired in Malaysia, and were associated
with an eosinophilic myositis syndrome.8 Since then, 12 oth-
er cases of skeletal sarcocystosis have been reported. Six
were identified in a subsequent review.1 An Australian man
with a history of travel to Thailand in 1990 provided a bi-
opsy specimen for a painful muscle attributed to sarcocys-
tosis.9 A case in an Egyptian patient was reported in 1990
with cytopathologic features of myositis characterized as
highly pathogenic, and associated myocyte distortion attrib-
uted to the sarcocyst wall.10 Three new cases were reported
in Malaysians in 1992, which were also considered to be
incidental findings by the investigators.11 Finally, a 1995
Belgian case report of clinical eosinophilic myositis syn-
drome following extensive travel to the tropics was attribut-
ed to Sarcocystis infection.12 In all, there have been a total
of 52 confirmed cases of human muscular sarcocystosis, in-
cluding reports of 41 skeletal and 11 myocardial muscle in-
fecions. Of these, 10 were associated with myalgias and/or
myositis, and 13 (25%) were acquired in Malaysia. Peripheral blood eosinophilia has been reported in two previous cases of Sarcocystis myositis.8,12

Human muscle sarcocystosis is highly prevalent in Southeast Asia. Muscle tissue examinations in Malaysia were positive in 21% of 100 consecutive routine autopsy samples,13 and 19.8% of a Malaysian population sample had serologic evidence of sarcocystosis exposure.14 Although these infections have been considered to be incidental findings, some investigators have suggested that sarcocystosis may be emerging as a significant food-borne zoonosis in Southeast Asia.15 Clinically significant intestinal Sarcocystis infections in humans have rarely been reported, and include 6 cases of segmental enteritis, which is also associated with tissue eosinophilia.16

Of the 52 reported cases, most were asymptomatic; however, 10 had symptoms, including fasciculations, myalgias, muscular weakness and wasting, subcutaneous nodules, and intermittent bronchospasm. In one patient, symptoms persisted for 7 years after diagnosis.9 Symptoms of infection have been attributed to disintegration of skeletal muscle cysts, but may also be an immune-mediated response to the presence of immature forms of Sarcocystis in early infections.10 A number of veterinary drugs have proven effective in control of acute sarcocystosis in livestock, but no effective treatment for human sarcocystosis has been described, although the disease is generally self-limited.13,16

In the muscle biopsies of patient 1, we demonstrated metacyclics, which are characteristic of the acute infectious phase, and differentiated bradyzoite forms. The pathologic findings in patient 1 were morphologically similar to the four previously reported human cases from Malaysia with myositis and eosinophilia, having the same characteristic disseminated foci of sarcocysts, cyst morphology, and pericystic inflammation.8,9,12 In our cohort, we identified 1 case of biopsy-proven acute Sarcocystis eosinophilic myositis and 6 cases of eosinophilic myositis syndrome. The elevated levels of CK (skeletal muscle fraction) and aldolase indicate that myositis was present in at least 5 cases. The epidemic nature of this outbreak in previously healthy soldiers implies that they were infected by a common point source exposure during their sojourn in the jungle. The 75% positive serologic test results for antibody to Sarcocystis in the 8 men available for testing, while nonspecific, strongly suggests exposure to Sarcocystis. Further supporting this inference was the additional history that each of the seropositive support base team members had been field team members on at least one previous mission to Malaysia, suggesting prior exposure to Sarcocystis. Previous studies have shown a very low (0–3.6%) prevalence of antibody to Sarcocystis in Occidentals.2,17 The six clinical cases that did not provide biopsy samples had the same clinical syndrome of muscular, pulmonary, and generalized systemic symptoms, associated with a constellation of similar laboratory abnormalities. For all these reasons, these 6 cases likely represent self-limited Sarcocystis eosinophilic myositis as well. This clustering of illnesses makes it extremely unlikely that their symptoms were caused by one of the rare, noninfectious causes of eosinophilia and myositis such as hypereosinophilic syndrome, relapsing eosinophilic perimyositis, periarteritis nodosa, or eosinophilic fasciitis (Shulman’s Syndrome).18 Our cases resemble the eosinophilia-myalgia syndrome due to L-tryptophan ingestion, but our patients denied taking this agent.19

A growing body of evidence suggests that Sarcocystis muscle infection can be associated with significant disease.1–3,5,8–16 The high prevalence of muscle infection in indigenous Malaysian populations suggests that sarcocystosis is a common, seldom recognized infection in Malaysia.11,15 As described above, other investigators have reported a spectrum of manifestations ranging from asymptomatic or acute, self-limited complaints to moderately severe, chronic illness. We conclude that Sarcocystis was the etiologic agent of the eosinophilic myositis syndrome in patient 1, and was the likely cause of the syndrome in the other affected men, based on the common exposure, simultaneous onset of symptoms and/or laboratory abnormalities, and identical clinical features in all of the affected team members. Although patient 1 had serious, chronic sequelae, the other team members had milder, self-limited illnesses. This outbreak suggests that Sarcocystis may be an overlooked cause of unexplained eosinophilia. Our experience with albendazole therapy in patient 1 suggests that it may be useful in suppressing chronic symptoms of Sarcocystis infection. It is uncertain whether this treatment cures systemic infection with Sarcocystis, but it did appear to have some clinical benefit on the mild cardiomyopathy in our patient, although this may have been coincidental. The lack of tissue diagnoses in all members of the team is a limitation of this case series. Biopsies of the other affected patients could have provided conclusive diagnostic evidence of the parasite in all 7 cases, but the logistics of transporting patients and/or tissue samples from their remote duty station made this prohibitively difficult.

Sarcocystis was identified as the etiologic agent of eosinophilic myositis in this outbreak, and may also have the potential to become an opportunistic infection in immunocompromised patients, such as those with toxoplasmosis. Sarcocystis eosinophilic myositis is a potential threat to indigenous populations as well as to military personnel and other travelers in regions with poor sanitation.

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