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Malaria Diagnosis by Automated Blood Analyzer

ABSTRACT & COMMENTARY

Synopsis: *A 6-year-old boy presented with fever and abdominal pain and a complete blood cell count using an automated blood cell analyzer led to the diagnosis of Plasmodium vivax malaria.*

Source: Jones KN, et al. Diagnosis by automated blood analyzer. *Clin Infect Dis*. 2001;33:1886, 1944-1945.

A previously healthy 6-year-old boy who recently immigrated to the United States from Honduras presented with a history of fever, abdominal pain, and headache. Although initially afebrile, while in the emergency department his axillary temperature reached 41.6°C and he vomited 3 times. His physical exam was remarkable for a palpable spleen tip and a liver that extended 1 cm below the right costal margin. A routine white blood cell (WBC) count was performed by use of the Cell-Dyn 4000 automated blood-cell analyzer (Abbott) giving the scattergram.

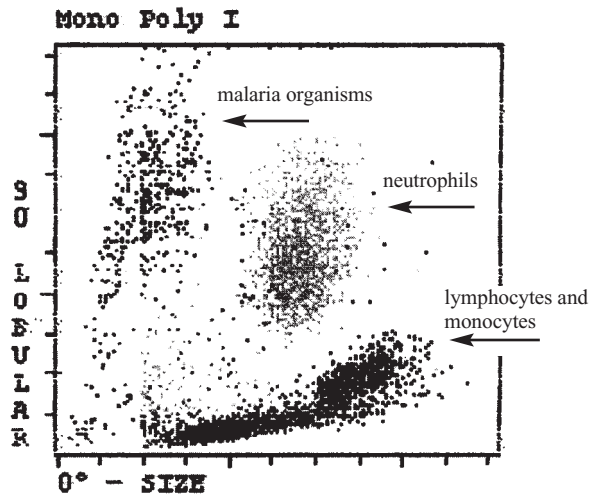
In the process of obtaining a routine WBC count with the Cell-Dyn 4000, red blood cells (RBCs) were lysed and free malarial parasites were then detected as a distinct population on the basis of light-scattering traits, such as cytoplasmic and nuclear optical characteristics (ie, size, granularity, lobularity, and complexity). The malaria organisms in Figure 1 appear as a population that is slightly smaller than lymphocytes with a low angle of scatter (1'- 3') but greater granularity and surface complexity as shown by the pattern of orthogonal scatter (90'). *P vivax* malaria was confirmed in this patient by examination of Wright-Giemsa-stained slides.

COMMENT BY MARY-LOUISE SCULLY, MD

Automated blood cell analyzers can contribute to the detection of malaria especially in the cases when there is no clinical suspicion. The blood-cell analyzer (Abbott, CD 3500) has been reported to detect levels of parasitemia as low as 1500 parasites/µl. However, an experienced pathologist can detect as few as 5-20 parasites/µl of blood using light microscopy of Giemsa-stained blood films. Therefore, it should be emphasized that the automated blood cell analyzer is not an appropriate screening test for malaria, but may play a role in situations where malaria is not suspected.

The careful examination by a trained microscopist of a well-prepared stained blood film remains the "gold standard"of malaria diagnosis having excellent sen-

Figure 1



Scattergram generated by an automated blood-cell analyzer for the patient with *Plasmodium vivax* malaria. Compare with Figure 2 below.

sitivity, the ability to characterize all 4 *Plasmodium* species as well as being used to quantify parasitemia. The disadvantages of the Giemsa-stained thick blood films (G-TBF) are that it is labor-intensive, and its success depends on having well trained microscopists. PCR has even greater sensitivity than the G-TBF as shown by several authors who reviewed PCR positive/G-TBF negatives and confirmed that "false"positives were in fact true positives.[1] Some experts now question if indeed the G-TBF is still the proper yardstick by which to measure all other tests.

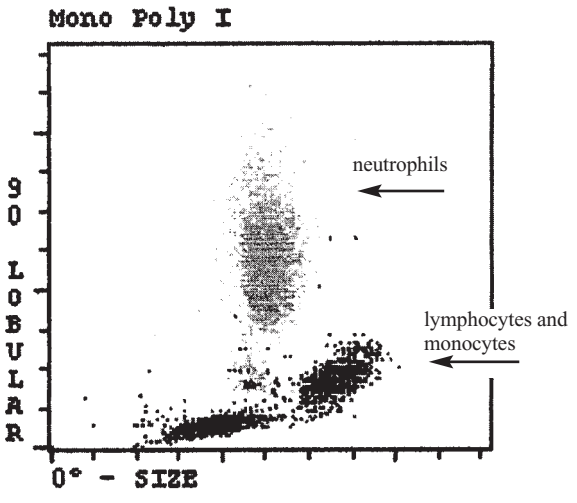
In a recent review, Moody defines a rapid diagnostic test for malaria as a method that requires 1 hour or less.[2] Fluorescent dyes such as acridine orange (AO) and benzothiocarboxypurine (BCP) are dyes that have affinity for the nucleic acid in the parasites' nucleus. The nucleus will exhibit an apple green or yellow fluorescence when excited by UV light at a wavelength of 490 nm. The centrifugal quantitative buffy coat or QBC II (QBC, Becton Dickinson) combines an AO-coated capillary tube and an internal float to separate layers of granulocytes and platelets using centrifugation. Parasites usually concentrate in the granulocyte-erythrocyte interface and can be viewed using a long-focal-length objective (paralens) with a fluorescent microscope. Results of experimental and field studies to assess sensitivity of QBC have varied, but the majority show sensitivities of more than 90%. The largest study of 18,845 blood samples showed a positivity rate of 25% for QBC (100% sensitivity) and 18% for G-TBF.[3]

The major advantage of the QBC is its speed and relative ease of interpretation. The disadvantages would be the need for electricity, the cost of capillary tubes and equipment, and the difficulty in species identification and quantification. An added benefit of the QBC may lie in its ability to diagnose other diseases in the febrile patient such as relapsing fever, African trypanosomiasis, and filariasis.[4-6] The QBC also gives the clinician in the field a simultaneous hematocrit and platelet count. These are extremely useful data since anemia and thrombocytopenia are important indicators of severe illness.

Another fluorescent microscopy technique is the Kawamoto technique in which a fluorescent microscope is fitted with an interference filter and AO is used to stain thin blood films. Expertise is needed to distinguish parasites from the Howell-Jolly bodies since they will stain with AO as well. Another fluorochrome technique using a solution of benzothiocarboxypurine (BCP) applied to an unfixed, dry, thick blood film has a reported sensitivity and specificity of greater than 95% for *P falciparum*. This method overcomes the necessity for rapid examination that is often needed in other fluorescence techniques.

PCR, although strictly not a rapid method, is certainly going to play an important future role in malaria diagnosis, perhaps even modifying our "gold standard." The value of PCR lies in its excellent sensitivity (able to detect ≤ 5 parasites/µl of blood) and its ability to detect all species of *Plasmodium* in nested or multiplex assays. PCR-based methods are useful for malaria studies on strain variations, mutations, and the study of parasite genes involved in drug resistance. As PCR technology improves, this technique may be able to be performed fast enough to be more useful to the clinician.

Figure 2



Scattergram generated by an automated blood-cell analyzer for a person without malaria. Adapted from: *Clin Infect Dis*. 2001;33:1944-1945.

Table

Immunochromatographic Malaria Tests

Test	Target Antigen	Species detected
Parasite F	HRP-II	*P falciparum*
ICT Pf	HRP-II	*P falciparum*
Path Falciparum Malaria IC	HRP-II	*P falciparum*
Optimal	pLDH	*P falciparum* and *P vivax*
ICT Pf/Pv	Aldolase/HRP-II	*P falciparum* and *P vivax*

A recent congress of the World Health Organization produced a document entitled *New Perspectives in Malaria Diagnosis*. In this document, the term rapid diagnostic tests (RDTs) was restricted to immunochromatographic methods to detect *Plasmodium*-specific antigens in a fingerprick blood sample.[7] These tests can be performed in about 15 minutes by persons with minimal training and require no electricity or special equipment. These tests often have a test strip or dipstick bearing monoclonal antibodies directed against the target parasite antigen (*see Table*).

One antigen used is the histidine-rich protein II (HRP-II), a water-soluble protein produced by trophozoites and young (not mature) gametocytes of *P falciparum*. Three commercially available HRP-II antigen dipstick tests with significant published data are the **Parasite F, ICT *Pf***, and the **Path Falciparum Malaria IC** tests. Sensitivities of these kits are generally more than 90% at parasite densities greater than 100 parasites/µl of blood. Below this level, sensitivities fall. False negatives may be due to a gene deletion for the production of HRP-II. Therefore, a strong positive with a test such as ICT *Pf* is highly predictive of *P falciparum* parasitemia, but a negative test should not exclude the diagnosis of malaria.[8]

These 3 RDTs using HRP-II will not detect nonfalciparum malaria. False positives with rheumatoid factor may occur, though less frequently with the monoclonal IgM antibodies used in the **ICT *Pf*** and **Path Falciparum Malaria** tests. A major disadvantage of RDTs using HRP-II antigens is that in many patients the tests remain positive for 7-14 days following treatment—results that may be confused with drug resistance or treatment failure.

Parasite lactate dehydrogenase (pLDH) is a soluble glycolytic enzyme produced by asexual and sexual stages (gametocytes) of all 4 species of malaria parasites. The OptiMAL tests for *P vivax* and *P falciparum* uses 3 monoclonal antibodies that can bind to active pLDH. Two of the antibodies are panspecific recognizing all 4 malaria species and the other is only for *P falciparum*. These monoclonal antibodies do not seem to cross-react with LDH from other organisms such as pathogenic bacteria, fungi, *Leishmania*, or *Babesia* spp. In one series, the sensitivity of the OptiMAL for *P falciparum* was 88% and for *P vivax* 94%.[9] Lower sensitivities are found at levels of parasitemia less than 100 parasites/µl or for *P ovale* and *P malariae*. In the future, a more sensitive monoclonal antibody may help improve detection of *P ovale* and *P malariae*.

Clearance of parasites from the blood during therapy for malaria correlates with a fall in pLDH levels that can be detected with the OptiMAL test. Therefore, tests to detect or measure pLDH might play a future role in monitoring response to therapy, especially in areas where blood films are not easily available.

Aldolase is another enzyme in the glycolytic cycle of the malaria parasite. In the **ICT *Pf/Pv*** test, panspecific monoclonal antibodies against *Plasmodium* aldolase are combined in a test with HRP-II to detect *P vivax* and *P falciparum*. Results for *P vivax* have been disappointing at lower levels of parasitemia. The **ICT *Pf/Pv*** had 96% sensitivity for *P vivax* if there were more than 500 parasites/µl of blood but had only 29% sensitivity for parasite levels less than 500 parasites/µl.[10]

According to the WHO document, an ideal RDT for malaria should 1) detect all 4 species of malaria at least as accurately as microscopy; 2) have a sensitivity of 100% for levels of 100 parasites/µl (0.002% parasitemia); 3) have a specificity of at least 90% for all species; and 4) provide quantitative information on parasite density. Also these test kits should not require refrigeration, be reliable in extreme heat, and have a shelf life of 1-2 years. Further testing in the field and technical improvements are still needed, but someday these test kits may even play a role in the self-diagnosis of malaria in travelers to remote areas. ■

References

1. Seesod N, et al. An integrated system using immunomagnetic separation, polymerase-chain reaction and colorimetric detection for the diagnosis of *P falciparum*. *Am J Trop Med Hyg*. 1997;56:322-328.
2. Moody A. Rapid diagnostic tests for malaria parasites. *Clin Microbiol Rev*. 2002;15(1):66-78.

3. Damodar SU. Evaluation of acridine-orange staining of centrifuged parasites in malarial infection. *Indian J Med Sci*. 1996;50(7):228-230.
4. Cobey FC, et al. Short report: Detection of *Borrelia* (relapsing fever) in rural Ethiopia by means of the quantitative buffy coat technique. *Am J Trop Med Hyg*. 2001;65(2):164-165.
5. Baily JW, et al. The use of acridine orange QBC technique in the diagnosis of African trypanosomiasis. *Trans R Soc Trop Med Hyg*. 1992;86(6):630.
6. Freedman DO, et al. Rapid diagnosis of Bancroftian filariasis by acridine orange staining of centrifuged parasites. *Am J Trop Med Hyg*. 1992;47(6):787-793.
7. World Health Organization. 2000. WHO/MAL/2000.1091. New Perspectives in Malaria Diagnosis. World Health Organization, Geneva, Switzerland.
8. Wongsrichanalai C, et al. Comparison of a rapid field immunochromatographic test to expert microscopy for the detection of *Plasmodium falciparum* asexual parasitemia in Thailand. *Acta Trop*. 1999;73:263-273.
9. Palmer CJ, et al. Evaluation of the OptiMAL test for rapid diagnosis of *Plasmodium vivax* and *Plasmodium falciparum* malaria. *J Clin Microbiol*. 1998;36:203-206.
10. Tjitra E, et al. Field evaluation of the ICT malaria *Pf*/*Pv* immunochromatographic test for detection of *Plasmodium falciparum* and *Plasmodium vivax* in patients with presumptive clinical diagnosis of malaria in eastern Indonesia. *J Clin Microbiol*. 1999;37: 2412-2417.

Eosinophilia in Travelers

ABSTRACT & COMMENTARY

Synopsis: *Eosinophilia in returning travelers has limited predictive value for travel-related infections. Helminthic infections are the most common diagnoses made in travelers with eosinophilia, especially when it is moderate to marked.*

Source: Schulte C, et al. Diagnostic significance of blood eosinophilia in returning travelers. *Clin Infect Dis*. 2002;34:407-411.

A RETROSPECTIVE ANALYSIS WAS CONDUCTED ON 14,298 returned travelers seen in the Department of Infectious Diseases and Tropical Medicine at the University of Munich, Germany, from January 1995 through December 1999. The majority of patients (96.8%) had traveled to developing countries. Eosinophilia in this study was defined as at least 8% of the white blood cell count. The evaluation of patients with eosinophilia included: microscopic examination of stool, urine, blood, wounds, skin; rectal mucosal snips; 24-hour terminal urinalysis for *Schistosoma* ova; skin snips for *Onchocerca volvulus*; serology for fascioliasis, filariasis, hydatid disease, amebiasis, schistosomiasis, toxocariasis, trichinosis; antigen-capture ELISAs for *Giardia lamblia* and *Entamoeba histolytica*.

A total of 689 patients (4.8%) were found to have eosinophilia, with more males affected (male-to-female ratio = 1.77). Mean age of patients was 34.3 years, and the majority were Europeans. Duration of travel ranged from 3 days to 32 years, with a median stay of 35 days. A comparison of the risks of developing eosinophilia showed the highest risk for those who had traveled to west Africa (RR = 2.95), whereas travels to Latin America, Southeast Asia, and the Indian subcontinent had lower risks of developing eosinophilia (RR = 0.39-0.91).

Although some patients did present with fatigue (24.4%), diarrhea (21.3%), and skin lesions (17.1%), 33% of the patients with eosinophilia were asymptomatic. Definite diagnoses were made in only 36% of patients, and only 18.9% were found to have a specific helminthic infection. The positive predictive value of eosinophilia for helminthic infections was 18.9%, whereas the negative predictive value was 98.7%. The probability of obtaining a definite diagnosis increased as the degree of eosinophilia increased, reaching more than 60% when eosinophils were greater than 16%. In patients with more pronounced levels of eosinophilia, the positive predictive value for helminthic infection reached 46.6%.

Highest percent eosinophil counts occurred among patients diagnosed with helminthic infections. A total of 52.4% of all definite diagnoses made were helminthic infections. On the other hand, only 41.5% of patients found to have helminthic infections actually showed eosinophilia at presentation, consistent with the concept that certain parasites cause eosinophilia only during their migration through tissues.

COMMENT BY LIN H. CHEN, MD

Eosinophilia is usually defined as > 450 eosinophils/mm^3, and can be associated with a wide variety of diseases including infectious, allergic, neoplastic, and idiopathic causes. Eosinophils are leukocytes produced in the bone marrow, and the development of eosinophils is controlled by cytokines, especially IL-5.[1] Eosinophil levels show a diurnal pattern, being highest in the early morning, and the levels also decrease with an increase in endogenous and exogenous steroids.[1] Following exposure to helminths, the eosinophil response tends

to be greater in travelers than in those with chronic exposure.[2] Additionally, eosinophilia can precede patent infections.[1] Moreover, eosinophils can increase after treatment of parasitic infections such as schistosomiasis,[3] lymphatic filariasis,[3] and onchocerciasis.[4] Eosinophilia can also last for 3-6 months after treating infection such as loiasis.[5]

Numerous helminth infections are associated with eosinophilia, but most protozoa are not usually associated with eosinophilia. Two exceptions are *Isospora belli* and *Dientamoeba fragilis*. When other protozoa are identified in patients with eosinophilia, one should suspect and look for helminth infections. The helminth infections commonly associated with eosinophilia include:[1,8] *Angiostrongylus cantonensis*, ascariasis, clonorchiasis, fascioliasis, fasciolopsiasis, filaria (*Wuchereria bancrofti*, *Brugia malayi*, *Brugia timori*, *Loa loa*, *Onchocerca volvulus*), gnathostomiasis, hookworm (*Necator americanus*, *Ancylostoma duodenale*), flukes (*Nanophyetus salmincola*, *Heterophyes heterophyes*, *Metagonimus yokogawai*, *Paragonimus westermani*, schistosomiasis), strongyloidiasis, trichinellosis, and toxocariasis. Other causes of eosinophilia that may be encountered by travelers include scabies, myiasis, coccidioidomycosis, chronic indolent tuberculosis, HIV, and drug reactions, especially to antibiotics.[1,8]

Any search for parasites should depend on the specific risks encountered by the traveler. Therefore, a detailed exposure history is crucial in the evaluation of eosinophilia in a traveler. Especially important are preexisting allergies, medications, travel itinerary, specific areas visited, duration of travel, food, and water sanitation, accommodations, exposures to fresh water, animals, insects, and sexual contacts. Physical signs and symptoms such as skin lesions, pruritus, wheeze, cough, hepatomegaly, abdominal pain, and neurologic findings may suggest more specific investigations.

The laboratory evaluation of eosinophilia should be guided by the suspicion of specific pathogens. The initial tests usually include a complete blood count with differential, an absolute eosinophil count in order to characterize the degree of eosinophilia, chemistries, urinalysis, a PPD skin test, 3 stool samples for ova and parasites, and chest x-ray. IgE may not be helpful because of its lack of specificity. If the history indicates possible exposure, serologies for strongyloidiasis, schistosomiasis, toxocariasis, and filariases would be useful. Further evaluation can be sought with additional serology, skin snips, biopsy of tissue (skin, rectum, bladder, liver, muscle, cyst), and examination of tissues and fluids for ova and parasites. For those patients identified with strongyloidiasis, treatment is recommended to avoid possible hyperinfection syndrome at a later time. When no definite diagnosis is reached, common practice is to reevaluate in 3-6 months. If eosinophilia persists, repeat blood, stool, and urine studies should be done, and empiric treatment of strongyloidiasis or hookworm with ivermectin or albendazole can be considered.[1]

It is often challenging to make a definite diagnosis in returned travelers presenting with eosinophilia, and this study confirms the low yield in establishing one. A previous study by Libman and colleagues[9] concluded that eosinophil counts had a limited role in screening asymptomatic expatriates for schistosomiasis, filariasis, and strongyloidiasis. The sensitivity of eosinophil count as a screening test for these parasites in the Libman study was 38%, and the positive predictive value of eosinophilia for these parasites was 9%. The Schulte study observed that travelers who visited West Africa had the highest risk for developing eosinophilia. Although eosinophilia only had a positive predictive value of 18.9% for all helminth infections, more than half of the definite diagnoses made were helminth infections. Finally, helminth infections were more likely to be identified when the eosinophil count reached a higher level (>16%). Given the difficulty in establishing definite diagnoses in travelers presenting with eosinophilia, further study on the etiology and epidemiology of eosinophilia in travelers would be valuable for those who provide post-travel evaluations. ■

References

1. Moore TA, Nutman TB. Eosinophilia in the returning traveler. *Infect Dis Clin North Am*. 1998;12:503-521.
2. Nutman TB, et al. *Loa loa* infection in temporary residents of endemic regions: Recognition of a hyperresponsive syndrome with characteristic clinical manifestations. *J Infect Dis*. 1986;154:10.
3. Ottesen EA, Weller PF. Eosinophilia following treatment of patients with schistosomiasis mansoni and Bancroft's filariasis. *J Infect Dis*. 1979;139:343.
4. Limaye AP, et al. Interleukin-5 and the post-treatment eosinophilia in patients with onchocerciasis. *J Clin Invest*. 1991;88:1418.
5. Klion AD, Ottesen EA, Nutman TB. Effectiveness of diethylcarbamazine in treating loiasis acquired by expatriate visitors to endemic regions: Long-term follow-up. *J Infect Dis*. 1994;169:604.
6. DeHovitz JA, et al. Clinical manifestations and therapy of *Isospora belli* infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1986; 315:87.
7. Cuffari C, Oligny L, Seidman EG. *Dientamoeba fragilis* masquerading as allergic colitis. *J Pediatr Gastroenterol Nutr*. 1998;26:16.
8. Wilson, ME, Weller PF. Eosinophilia. In: Guerrant RL, Walker DH, Weller PF, eds. *Tropical Infectious Dis-*

eases. Philadelphia, PA: Churchill Livingstone; 1999:1400-1419.
9. Libman MD, MacLean JD, Gyorkos TW. Screening for schistosomiasis, filariasis, and strongyloidiasis among expatriates returning from the tropics. *Clin Infect Dis*. 1993;17:353-359.

Fluconazole Therapy for Cutaneous Leishmaniasis

ABSTRACT & COMMENTARY

Synopsis: *The azole drug group has shown demonstrable activity against leishmanial organisms. However, most cutaneous leishmaniasis will generally heal spontaneously after several months without therapy. Is there any benefit to therapy with these agents as an alternative to either not treating or using potentially more toxic antimony-based agents?*

Source: Alrajhi A, et al. Fluconazole for the treatment of cutaneous leishmaniasis caused by *Leishmania major*. *N Engl J Med*. 2002;346:891-895.

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONtrolled trial assessed the efficacy of oral fluconazole at an oral dose of 200 mg daily for 6 weeks. A total of 106 patients from Riyadh, Saudi Arabia, where *Leishmania major* is endemic, were recruited to receive fluconazole as treatment and 103 patients were assigned to receive placebo. Criteria for exclusion were pregnancy or potential for pregnancy, breast-feeding, the presence of face or ear lesions, the presence of more than 10 lesions, liver, or kidney disease. Most of the patients were foreign construction workers from countries were cutaneous leishmaniasis is not endemic. One of 5 patients was a local national. A 3-month follow-up of 80 drug-treated and 65 placebo-treated patients showed healing was complete in 63 of 80 fluconazole-treated patients (79%) and only 22 of the 65 placebo patients (34%). Using an intention-to-treat analysis, the rates of healing were 59% and 22% for drug and placebo groups, respectively, with a relative risk of complete healing using fluconazole therapy of 2.76 (CI, 1.84-4.12). Adverse effects were similar in both the treatment and placebo groups.

COMMENT BY MICHELE BARRY, MD, FACP

Cutaneous leishmaniasis of the Old World is endemic on the Arabian Peninsula, within the Middle East, and parts of East Africa. Fluconazole had been used in a trial performed in India against visceral leishmaniasis, but therapy failed with all patients eventually relapsing.[1] Other azoles derivatives such as ketoconazole and itraconazole have been studied for the treatment of visceral and cutaneous leishmaniasis, but without achieving statistically significant differences between treatment and placebo groups.[2,3] Of interest in the current study was a significantly quicker time to healing (8.5 weeks as compared to 11.2 weeks) in fluconazole-treated patients. Since all *L major* lesions eventually heal without treatment, the cost of fluconazole and ability of a patient to adhere to 6 weeks of daily medication should be factored into any decision to use this agent. Of note, only 1 woman was included in this study due to exclusionary criteria and the population studied. ■

References

1. Sundar S, et al. Treatment of kala-azar with oral fluconazole. *Lancet*. 1996;348:614.
2. Momeni A, et al. Treatment of cutaneous leishmaniasis with itraconazole: Randomized double-blind study. *Arch Dermatol*. 1996;132:784-786.
3. Saenz R, Paz H, Berman J. Efficacy of ketoconazole against *Leishmania braziliensis* panamensis cutaneous leishmaniasis. *Am J Med*. 1990;89:147-155.

Biliary Cyclospora Infection in Compromised Hosts

ABSTRACT & COMMENTARY

Synopsis: *Immunocompromised individuals are at increased risk for severe complications from infectious causes of traveler's diarrhea. For example, greater risk of dehydration and sepsis has been reported in immunocompromised hosts who acquire Campylobacter jejuni. Several opportunistic pathogens have been implicated as the cause of biliary disease in patients with HIV infection and immunosuppression, such as cytomegalovirus, Cryptosporidium, and Microsporidium. A recent report indicates that biliary complications due to cyclosporiasis can also occur in this group.*

Source: Zar FA, El-Bayoumi E, Yungbluth MM. Histologic proof of acalculous cholecystitis due to *Cyclospora cayetanensis*. *Clin Infect Dis*. 2001;33:E140-141.

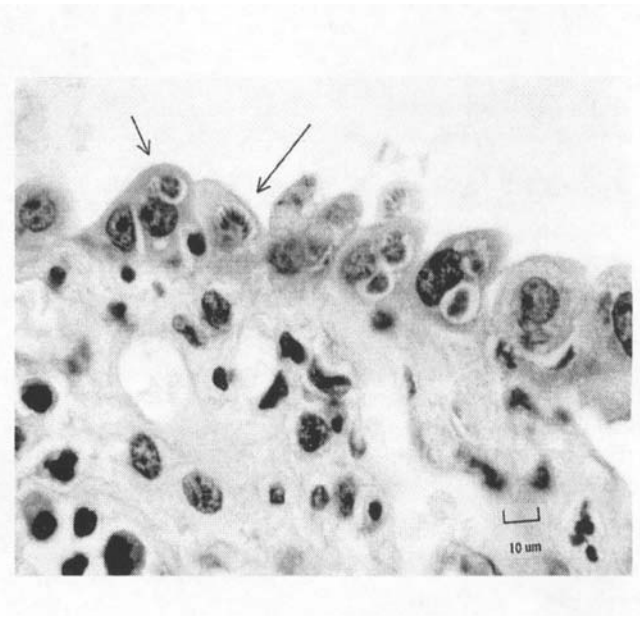
THIS REPORT IS THE FIRST HISTOLOGICALLY DOCUmented case of *Cyclospora cayetanensis* associat-

ed with acalculous cholecystitis. The most common clinical manifestation of the coccidian parasite *C cayetanensis* is profuse watery diarrhea, which can occur in either immunocompetent or immunosuppressed persons. In this case, Zar and associates report a 35-year-old man with AIDS, whose CD4 count was 11 cells/mm^3 2 months prior to this admission. He presented with a 10-day history of sudden onset watery diarrhea. There was no evidence of fecal blood or white cells and no documented travel history. In addition to having 6 stools per day, he developed fever on day 5 of his illness associated with right upper quadrant pain, which worsened while eating and radiated to the right subscapular region. He was not receiving antiretroviral therapy or trimethoprim-sulfamethoxazole, and had a history of Stevens-Johnson syndrome associated with taking this combination agent 3 years earlier. His examination was significant for pain on deep palpation of the right upper quadrant, but without evidence of guarding or rebound tenderness.

His WBC was 4100 cells/mm^3; hemoglobin 10.3 g/dL; hematocrit 31.4%, and platelets 129,000/mm^3. Serum electrolytes, creatinine, and liver function tests were all within normal limits. A right upper quadrant ultrasound showed thickening of the anterior portion of the gallbladder wall with no stones, pericholecystic fluid, or dilation of the bile ducts. Acid-fast oocysts measuring 8-10 µm in diameter, typical of *C cayetanensis*, were seen on Kinyoun stain performed on a concentrated stool specimen.

Despite treatment with oral levofloxacin, 500 mg once daily, his pain worsened over the next 2 days and a repeat ultrasound showed thickening of the entire gallbladder wall, but no stones or dilatation of the common bile duct. Adequate filling of the gallbladder and duodenum was demonstrated by hepatic iminodiacetic acid (HIDA) scan. Laparoscopic cholecystectomy was performed on day 3 when the severe pain persisted. The gallbladder was not distended and the mucosal surface was intact. There were no calculi. Routine histologic sections demonstrated acute and chronic cholecystitis. There were numerous intracytoplasmic vacuoles in the gallbladder epithelium that contained *Cyclospora* trophozoites, merozoites, and schizonts (*see Figure 1*). These were also observed in intestinal epithelium, and oocysts were demonstrated on auramine-rhodamine fluorochrome staining. Symptoms resolved and treatment was continued with a 3-week course of oral levoquine followed by indefinite prophylaxis with 500 mg, taken 3 times per week. Stool examination for ova and parasites, obtained 2 weeks after surgery, were negative.

Figure 1



Gallbladder mucosa showing marked inflammation and edema. Surface columnar epithelial cells are infected with *Cyclospora* species at different developmental stages in the coccidian life cycle. Several epithelial cells contain large ovoid unicellular trophozoites in parasitophorous vacuoles. Two cells (arrows) contain meront-stage organisms with multiple crescent-shaped merozoites with pointed ends. Bar, 10 um (hematoxylin and eosin stain; magnification, ×1000).

COMMENT BY MARIA D. MILENO, MD

Although earlier reports had implicated cyclosporiasis as a cause of acalculous cholecystitis, histologic proof had been lacking. Based upon the findings reported for this case, *Cyclospora cayetanensis* might be considered as a potential cause for acalculous cholecystitis in HIV-infected immunosuppressed persons. Travelers with HIV disease may develop biliary complications as well as diarrhea from this agent. Due to a history of severe sulfa allergy this particular patient had not been using trimethoprim-sulfamethoxazole for prophylaxis against *Pneumocystis carinii* pneumonia (PCP), a standard preventive measure for HIV-infected persons whose CD4 counts remain below 200 cell/mm^3. Trimethoprim-sulfamethoxazole is also an effective therapy for *Cyclospora*-associated diarrhea. This case report demonstrates yet another reason to advise HIV-infected individuals to remain consistent with taking both their antiretroviral and prophylactic regimens while traveling abroad. ■

CME Questions

6. All HIV-infected persons may be at increased risk for which of the following during travel?

a. Stevens-Johnson syndrome due to sulfonamides.
b. PCP pneumonia, if the their CD4 count is less than 200 cells/mm^3.
c. Biliary complications if infected and symptomatic from *Cyclospora*-associated diarrhea.
d. b and c
e. a and c

7. All of the following are true regarding diagnostic malaria tests *except*:

a. Detection of HRP-II can persist up to 7-14 days into treatment of malaria.
b. Automated blood cell analyzer is not an appropriate screening test for malaria.
c. If the ICT Pf test is negative, the patient does not have malaria.
d. In tests detecting HRP-II, false positives with rheumatoid factor may occur.
e. A decline in pLDH levels occurs during successful treatment and clearance of malaria parasites from the blood.

8. Which statements regarding eosinophilia are true? More than one may apply. Eosinophilia in travelers:

a. cannot be associated with *Isospora belli* and *Dientamoeba fragilis* because they are protozoa.
b. is always due to helminth infections.
c. should lead to a careful review of exposure to medication, unsanitary food and water, insect bites, contact with fresh water, animals, and sexual contact.
d. is felt to be present when eosinophil counts exceed 450/mm^3.
e. both c and d are correct.

9. Which of the following statements is true?

a. Despite being a self-limited lesion, cutaneous leishmaniasis of the Old World (*L major*) heals faster with all azole compounds.
b. Visceral leishmaniasis in India responds to therapy with azoles such as fluconazole without demonstrable relapses.
c. Fluconazole therapy of *L major* infections results in a more rapid healing time than in placebo-treated controls.
d. Itraconazole eliminates kala-azar after single dose therapy, as demonstrated among nonpregnant Sudanese women.

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