Although the majority of the cases of malaria diagnosed in the United States occurs in persons who have traveled to or emigrated from malaria-endemic countries, outbreaks of locally acquired malaria occur occasionally in densely populated areas of the nation. The emergence of an autochthonous malarial outbreak depends on the simultaneous occurrence of several factors, namely, the presence of competent and specific mosquito vectors, the particular Plasmodium species, certain favorable environmental conditions, and human hosts carrying parasitic gametocytes.

The diagnosis of malaria relies on the identification of Plasmodium parasites in peripheral blood films of patients with clinically suspected malaria who had recently traveled to or have arrived from an endemic area. However, in the context of a locally acquired malaria outbreak without a known ‘index’ or source case, certain hematological parameters may be used by laboratory personnel to selectively prepare peripheral blood smears (when not ordered by the physician) in search of parasites.

This article describes our recent experience and reviews the pathogenesis of the hematological findings associated with malarial infection.

Although the majority of the cases of malaria diagnosed in the United States occurs in persons who have traveled to or emigrated from malaria-endemic countries, outbreaks of locally acquired malaria occur occasionally in densely populated areas of the nation. The emergence of an autochthonous malarial outbreak depends on the simultaneous occurrence of several factors, namely, the presence of competent and specific mosquito vectors, the particular Plasmodium species, certain favorable environmental conditions, and human hosts carrying parasitic gametocytes.

The diagnosis of malaria relies on the identification of Plasmodium parasites in peripheral blood films of patients with clinically suspected malaria who had recently traveled to or have arrived from an endemic area. However, in the context of a locally acquired malaria outbreak without a known ‘index’ or source case, certain hematological laboratory parameters may prompt a peripheral blood smear examination in search of parasitic forms, especially in cases in which the level of parasitemia is low. Five out of a total of 8 cases detected during the recent autochthonous outbreak of P. vivax malaria reported in Palm Beach County, FL, were diagnosed in our institution. We observed a common pattern of thrombocytopenia and relative monocytosis, by automated count, in the initial 3 cases. This finding resulted in reflexive preparation of peripheral blood smears, especially in those patients presenting with unexplained fever to the emergency department (ED), in order to search for malarial parasites. This article reviews the epidemiologic, clinical, and laboratory aspects of malarial infection, with special emphasis on the hematological parameters that may be valuable in identifying cases, especially in the context of an autochthonous epidemic. The pathogenetic theories involved in the peripheral blood smear findings of individuals infected with malarial parasites are also discussed.

**Background**

Malaria is the most prevalent infection in the world, with an estimated 300 to 500 million cases per year. In the late 1940s, the socioeconomic conditions, vector control efforts, and public health preventive measures resulted in successful eradication of malaria in the United States. Nevertheless, surveillance of cases has been maintained since 1957. Approximately 1,000 to 1,500 cases per year are reported to the Centers for Disease Control and Prevention (CDC). The most commonly affected states are those with densely populated urban areas, particularly those receiving an important international traveling influx (New York, California, New Jersey, and Florida). Most Plasmodial infection
cases reported in the United States are imported by persons who have traveled to countries where malaria is endemic. Eleven outbreaks of locally acquired, mosquito-transmitted malaria have been documented during the past 10 years, all caused by *P. vivax*. The largest outbreaks reported in the country occurred in California in 1952, 1986, and 1988 (35, 28, and 30 cases respectively). More recently, 8 cases of locally-acquired mosquito-transmitted *P. vivax* malaria were reported in Palm Beach County, FL, during the months of July through September 2003. Five out of the 8 cases were seen at our institution, including the 2 initial patients who presented simultaneously to our ED. After observing a particular pattern in the automated hematological scattergram of the first 3 infected patients (therefore in the context of a declared local malaria outbreak), we decided to implement peripheral smear review in search of malarial parasites whenever encountering this particular scattergram pattern in any individual reporting to our ED with unexplained fever. Following these observations, recommendations regarding laboratory malaria screening were communicated to other area hospitals.

**Autochthonous Malaria Outbreak in Palm Beach County**

Eight cases of locally acquired, mosquito-transmitted *P. vivax* malaria were reported in Palm Beach County, FL, from mid-July through mid-September 2003. In 7 of the 8 cases, the same strain of *P. vivax* was demonstrated by molecular genotyping (the results of the genotyping for the eighth case of malaria were not available). The cases presented as follows.

**Case 1:** A 37-year-old man presented in the ED of our institution with a 6-day history of fever, chills, headache, vomiting, and anorexia. The requested automated complete blood cell (CBC) count and white blood cell differential showed relative monocytosis and thrombocytopenia.

**Case 2:** On the same date as case 1, a 46-year-old man neighbor to the first patient presented to our ED with a 3-day history of fever, chills, headache, vomiting, anorexia, dehydration, and malaise.

**Case 3:** Three weeks later, a 32-year-old man presented to our ED with a month history of intermittent fever, chills, headache, and vomiting.

**Case 4:** Four days after case 3, a 45-year-old man presented to our ED with a 2-day history of fever, chills, headache, arthralgias, and malaise.

**Case 5:** Five days after case 4, a 23-year-old man presented to our ED with a 12-day history of fever, chills, arthralgias, diarrhea, and vomiting.

**Case 6:** A day after case 5, a 17-year-old boy was admitted to a second community hospital with an 8-day history of fever, chills, and headache.

**Case 7:** A day after case 6, a 48-year-old man was admitted to the second community hospital with a 2-day history of fever, chills, vomiting, and anorexia.

**Case 8:** About 3 weeks later, a 26-year-old man was admitted to a third community hospital with a 7-day history of fever and chills.

A peripheral blood cell scattergram representative of the patients admitted at our institution (cases 1 through 5) is depicted in [F1].

All the patients’ Wright-Giemsa-stained peripheral blood smears showed malarial parasites, mainly trophozoites (‘ring’ forms) and schizonts, morphologically compatible with *P. vivax* species [I1] and [I2], confirmed by RNA polymerase chain reaction (PCR) analysis. Demonstration that all individuals were infected by the same strain of *P. vivax* was accomplished by multilocus genotyping. The local Department of Health
conducted targeted mosquito trapping expeditions within 2 miles of the patients’ homes, resulting in isolation of the mosquito species *Anopheles quadrimaculatus* (n=33) and *Anopheles crucians* (n=425), identified at the CDC; however, malarial parasites could not be demonstrated in the mosquitoes tested.

The epidemiological data of the 8 cases of locally acquired mosquito-transmitted *P. vivax* malaria that occurred in Palm Beach County, FL, 2003 are listed in **T1**. The most relevant automated hematological laboratory data obtained on the day of the patients’ admission to the ED is compiled in table [**T2**].

### Public Health Aspects

None of the patients had a previous history of malaria, recent travel to malaria-endemic regions, blood transfusions, organ transplantation, intravenous drug abuse, or immunodeficiency. All the individuals resided within a radius of 4 miles and approximately a maximum of 10 miles away from the airport. They all had exposure to mosquitoes, either by working or spending leisure time outdoors.

The County Public Health Department immediately developed and implemented a program of surveillance, which included communications to local hospitals, physician offices, infectious disease specialists, county health department clinics, and schools, via telephone call, letter, and/or e-mail. Performing blood smears for malaria screening in all cases of unexplained fever was advised. Press conferences, multilingual radio and television advertisements, posters, informative brochures, and automated calls with a pre-recorded message to more than 500,000 homes in a radius of 5 miles of the residence of the first 2 patients were additional tools that the local public health department used to educate the population about the infectious outbreak. Preventive measures included: distribution of mosquito repellent (DEET: N-diethyl-m-toluamide) to high-risk populations, recommendations regarding use of protective clothing outdoors, and draining stagnant water reservoirs, which are considered mosquito breeding sites. In addition, environmental measures were also adopted, such as placement of mosquito traps and aerial/ground insecticide spraying in a targeted area.

A putative ‘index’ case (the original *P. vivax*-infected individual functioning as a source for the local mosquito-transmitted cases) could not be identified.

### Epidemiologic and Clinical Aspects of Malarial Infection

Malaria is a mosquito-transmitted infectious parasitic disease caused by

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### Palm Beach County Recent Autochthonous Malaria Outbreak: Epidemiological Data

<table>
<thead>
<tr>
<th>Date of DX</th>
<th>Sex</th>
<th>Age</th>
<th>Occupation</th>
<th>Travelling History</th>
<th>Body Temperature</th>
<th>Signs &amp; Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>male</td>
<td>46</td>
<td>construction worker</td>
<td>No</td>
<td>99.1°F</td>
<td>fever, headache, myalgias, chills vomiting, anorexia</td>
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<td>Case 2</td>
<td>male</td>
<td>37</td>
<td>plumber</td>
<td>Bahamas 6/03</td>
<td>100.1°F</td>
<td>fever, headache, myalgias, chills vomiting, anorexia, diarrhea</td>
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<tr>
<td>Case 3</td>
<td>male</td>
<td>32</td>
<td>bank clerk</td>
<td>Bahamas 5/03, California 7/03</td>
<td>102.5°F</td>
<td>fever, chills, vomiting, headache, sweating</td>
</tr>
<tr>
<td>Case 4</td>
<td>male</td>
<td>45</td>
<td>homeless</td>
<td>No</td>
<td>103.4°F</td>
<td>fever, chills, vomiting, diarrhea</td>
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<tr>
<td>Case 5</td>
<td>male</td>
<td>23</td>
<td>blood bank dispatcher</td>
<td>Massachusetts 6/03</td>
<td>103.1°F</td>
<td>fever, headache, myalgias, vomiting, loose stools</td>
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<tr>
<td>Case 6</td>
<td>male</td>
<td>17</td>
<td>student dispatcher</td>
<td>Unknown</td>
<td>101.1°F</td>
<td>fever, chills, headache, myalgias</td>
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<tr>
<td>Case 7</td>
<td>male</td>
<td>48</td>
<td>carpenter</td>
<td>Unknown</td>
<td>100.0°F</td>
<td>fever, chills, vomiting, anorexia</td>
</tr>
<tr>
<td>Case 8</td>
<td>male</td>
<td>26</td>
<td>carpenter</td>
<td>Unknown</td>
<td>103.0°F</td>
<td>fever, chills, vomiting, anorexia</td>
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### Palm Beach County Recent Autochthonous Malaria Outbreak

<table>
<thead>
<tr>
<th>WBC</th>
<th>Segmented</th>
<th>Neutrophils</th>
<th>Lymphocytes</th>
<th>Monocytes</th>
<th>Platelets</th>
<th>RBC</th>
<th>Hb</th>
<th>Htc</th>
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<tr>
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<td>50.1</td>
<td>33.7</td>
<td>13.9</td>
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<td>37.6</td>
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<td>4.33</td>
<td>36.8</td>
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<td>82.0</td>
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<td>3.81</td>
<td>69.3</td>
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<td>10.8</td>
<td>63.3</td>
<td>4.62</td>
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<tr>
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<td>51.7</td>
<td>21.0</td>
<td>26.2</td>
<td>71.3</td>
<td>4.32</td>
<td>13.4</td>
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<td>10.3</td>
<td>30.4</td>
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<td>10.6</td>
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<td>92.0</td>
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<td>11.9</td>
<td>35.4</td>
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<tr>
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<td>52.5</td>
<td>28.0</td>
<td>17.4</td>
<td>129.0</td>
<td>3.67</td>
<td>11.6</td>
<td>33.6</td>
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<tr>
<td>Case 8</td>
<td>4.50</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>60.0</td>
<td>4.43</td>
<td>14.1</td>
<td>40.7</td>
</tr>
</tbody>
</table>

*Automated hematological laboratory data obtained on the day of presentation to the emergency department. Reference values: white blood cell count (WBC): 3.6-11.0 x 10^3/mm^3; differential: % segmented neutrophils: 36.0-66.0%; % lymphocytes: 23.0-43.0%; % monocytes: 0.0-10.0%; platelet count: 150-450 x10^3/mm^3; red blood cell count (RBC): 5.5-5.9 x10^6/mm^3; hemoglobin (Hb): 13.0-18.0 g/dL; hematocrit (Htc): 40.0-52.0%. (-) unknown.
Plasmodium protozoa. Although a number of Plasmodium species have been identified, only 4 are considered pathogenic for humans (vivax, ovale, falciparum, and malariae). Malaria is the most commonly occurring infectious disease in the world, estimated to affect 300 to 500 million individuals annually worldwide. It was introduced in North America during the 16th and 17th centuries, coinciding with the influx of European colonizers and African slaves respectively, and eventually became endemic through the continental United States with the exception of certain areas (New England, mountainous, and desert regions). As the socioeconomic conditions improved and mosquito control measures were implemented, the frequency of malarial infection declined progressively since the 1800s. Eradication of malaria in the United States was declared successfully accomplished in the late 1940s. The continuous surveillance implemented since 1957 has made possible the detection of imported and locally acquired mosquito-transmitted malarial outbreaks nationwide.

Continuous surveillance of malarial infection in the United States requires mandatory case reporting to the CDC. The latest data indicates a decrease of 1.4% in cases reported in 2002 compared with year 2001. Most of the cases are imported by travelers returning from endemic areas, but occasionally small outbreaks of locally acquired malaria occur. In fact, 11 outbreaks of autochthonous malaria, involving 20 cases have been reported to the CDC since 1992.

Several factors (parasite-, vector-, host-, and environmental-related) are required for the effective transmission and spread of malarial organisms.

1. **Parasite-dependent factors**: Understanding the life cycle of this parasite is paramount to implement effective epidemiological control measures. The Plasmodium life cycle includes sexual and asexual phases that occur in the mosquito vector and in the human host, respectively. Only the female Anopheles mosquito, but not the male, is capable of harboring the development of infective Plasmodial sporozoites after fertilization of ingested gametocytes obtained from an infected person via a mosquito bite. When the female anopheline mosquito takes a blood meal, the sporozoites are introduced into the host’s blood stream where they reach the liver (exoerythrocytic phase). Within the hepatocytes, they evolve into hypnozoites (latent forms of P. vivax and ovale only) and merozoites. The latter are then released into the circulation where they enter erythrocytes via specific receptor-ligand interactions. Once inside the red blood cell, the merozoite matures into a trophozoite (‘ring’ and ameboid forms), which is usually the parasitic form recognized during examination of Wright-Giemsa stained peripheral blood smear preparations. The trophozoite then undergoes division several times within the host red blood cell, giving rise to a schizont. Schizonts contain multiple nuclei, each one constituting a new merozoite. Eventually, the parasitized red cell lyses releasing the merozoites, which in turn infect other circulating erythrocytes, contributing to the host parasitemia. Male and female gametocytes are formed synchronously to merozoites. These circulating parasite sexual forms may be ingested by female anopheline mosquitoes while taking a blood meal. The gametocytes undergo fertilization and maturation within the mosquito’s gut until they become infective sporozoites, which migrate to the insect’s salivary gland, completing the life cycle of the parasite.

The incubation period varies depending on the Plasmodium species (P. falciparum: 7 to 14 days; P. vivax and ovale: 8 to 14 days; and P. malariae: 7 to 30 days); all the species with the
exception of *P. falciparum* may cause infection relapses if not treated adequately, due to hepatic dormant forms of the parasite (hypnozoites).

Besides infection via mosquito vectors, malaria may be transmitted through the use of contaminated needles, by blood transfusion from infected donors, or congenitally from mother to fetus.

2. **Vector-dependent factors**: The most commonly involved malaria-transmitting anopheline species reported in the United States are *An. quadrimaculatus*, *An. freeborni*, and occasionally *An. hermsi*. Anopheline mosquitoes may be found in all 48 contiguous states of the United States. Once the mosquito acquires *Plasmodium* organisms, it remains infective for its life span (usually 2 to 6 weeks). Only the female of *Anopheles* mosquito genus is infective.

3. **Environmental-dependent factors**: Environmental temperatures below 16°C or above 33°C impede completion of the parasite life cycle within mosquitoes for *P. vivax* and *falciparum*. Humidity and other weather conditions, as well as the presence of adequate mosquito breeding sites, are also intervening factors that affect survival of mosquitoes, essential for completion of the *Plasmodia* life cycle.

4. **Human host-dependent factors**: Human reservoirs for the parasite (undiagnosed, untreated individuals) must exist as a source of *Plasmodium* gametocytes for the *Anopheles* female mosquito to become infected and complete the parasite life cycle. Risk areas are those with high influx of visitors and immigrants from malaria-endemic countries, with the possibility of providing ‘index’ cases for the secondary development of locally acquired infection of the inhabitants of the area.

The typical clinical manifestations of malarial infection include fever accompanied by some or all of these signs and symptoms: chills, sweating, malaise, headache, nausea, vomiting, abdominal pain, and myalgias. The fever is paroxysmal, occurring at regular intervals, coinciding with the rupture of schizonts (tertian malaria: every 48 hours due to *P. vivax*, *ovale*, and *falciparum*; quartan malaria: every 72 hours, caused by *P. malariae*). Pulpable hepatosplenomegaly and lymphadenopathy are not uncommon. In severe cases, usually due to *P. falciparum* infection, neurological manifestations ensue (‘cerebral malaria’), such as seizures, meningismus, and altered mental status among others.

**Diagnosis**

The diagnosis of malarial infection relies on the detection of parasitic forms in peripheral blood smears. Both thick and thin smears are prepared. The former to facilitate the detection of parasitic forms, especially when the level of parasitemia is low; the latter for species identification based on morphological characteristics. Collection of a blood sample in EDTA preservative for PCR analysis (usually performed in the state laboratory) is strongly advised in order to confirm the species, as well as for genotyping and strain identification (detailed information is available at the CDC Web site: www.dpd.cdc.gov/dpdx/).

**Prophylaxis and Treatment**

The laboratory plays a decisive role in determining the most adequate treatment for malarial infection. The distinction of *P. falciparum* versus non-*falciparum* species is paramount since infection with the former may rapidly cause life-threatening complications. The treatment of *P. falciparum* infestation depends on the geographic location where it was acquired. For adult infections acquired in countries where chloroquine-resistant *P. falciparum* is reported, treatment with oral quinine sulfate is indicated (650 mg q8h for 7 days) along with doxycycline (100 mg q12h for 7 days); otherwise, the use of oral chloroquine (600 mg base followed by 300 mg base in 6 hours, and then 300 mg base/day for 2 days) is indicated for all *Plasmodium* species. Since *P. ovale* and *vivax* cause relapses, patients infected with these species should receive oral primaquine (15 mg base/day for 2 weeks). All the patients of our locally transmitted malarial outbreak were treated accordingly.

Prophylaxis with oral chloroquine (300 mg/week, for 2 weeks before traveling and 4 weeks after returning) is advised when traveling to endemic areas of all *Plasmodium* species, naturally with the exception of chloroquine-resistant *P. falciparum*, which should receive oral mefloquine (250 mg/week, for 2 weeks before traveling and 4 weeks after returning), or the recently approved combination of atovaquone-proguanil (250 mg and 100 mg respectively, taken once daily beginning 1 or 2 days prior to travel through 7 days post-travel).

Additional treatment and prophylactic regimens may be found elsewhere.

**Hematological Laboratory Findings and Pathogenetic Theories**

Anemia and thrombocytopenia are common findings among individuals with malarial infection. Most studies regarding the hematological manifestations of malarial infection have been conducted in endemic countries where overlapping hemoglobinopathies, nutritional deficiencies, and altered immunological status may obscure the changes directly related to the parasitic infestation. A retrospective study conducted in the United Kingdom based on cases of imported *P. falciparum* malarial infection in returning travelers without known immunodeficiencies, concurrent viral infection, and inflammatory conditions or hemoglobinopathy revealed that the most common hematological findings were thrombocytopenia (67%) and relative lymphopenia (63%). Interestingly, only 15% of the patients were anemic (Hb <12.0 g/dL for men and <10.0 g/dL for women) at the time of presentation.

The etiopathogenesis of the thrombocytopenia is unclear and remains controversial. Several theories have been proposed, including nonimmunologically mediated mechanisms, such as direct interaction of the parasite with circulating platelets and/or phagocytosis of platelets, and immune-mediated destruction of platelets. A study conducted by Kelton and colleagues demonstrated an increase in the serum
levels of platelet-associated IgG (PAIgG) antibody, parallel to a decrease in circulating platelets, and conversely, a decrease in PAIgG levels and platelet count returning to normal as the parasites were cleared from the circulation. These observations suggested a putative role of PAIgG in the pathogenesis of malaria-associated thrombocytopenia. According to the investigators, the aforementioned increment in serum PAIgG levels may be a consequence of the release of IgG from the alpha granules or from the surface of the platelets as they are destroyed.

Other pathogenetic theories involve expression of malarial antigen on the platelet surface, a phenomenon that presumably occurs through a passive mechanism of absorption of soluble antigen onto the platelet. The development of anti-malarial antibodies directed against malarial antigen expressed on platelets has been proposed as a causal factor involved in thrombocytopenia. Interestingly, these antibodies are not detected in the serum of infected patients until several days after the parasites appear in the circulation. It has been suggested that the reason for the lack of early detection of serum antimalarial antibody is due to its binding to platelets in the first days of blood parasitemia. According to several authors, the platelet malarial antigen is coated by circulating antimalarial antibodies, subsequently promoting platelet clearing from the circulation by the spleen. However, this theory has been challenged by the study of Looareesuwan and colleagues, who failed to demonstrate a relationship between platelet count and serum levels of free and bound platelet-directed antibodies. These investigators speculated that an increase in the platelet clearance capacity of the spleen during malarial infection may be an important factor involved in pathogenesis of the thrombocytopenia; however, they were not able to exclude an immune-mediated mechanism.

In vitro studies during acute malarial infection have shown an increased platelet aggregation response to ADP, adrenaline, collagen, and ristocetin, as well as increased serum levels of platelet specific proteins (beta-thromboglobulin and platelet factor 4). Ultrastructural studies performed on the platelets of Plasmodium-infected patients have shown alterations in platelet morphology including centralization of dense granules, glycogen depletions, and pseudopod formation, likely indicating in vivo platelet activation. Looaresswan and colleagues theorized that in vivo platelet activation and aggregation may play a role in the increased removal activity of the spleen during acute Plasmodium infection. In addition, an increase in pooled platelets within the vasculature of the enlarged spleen and liver of these patients (platelet sequestration) may explain both the thrombocytopenia during the parasitemia phase and the rapid recovery of normal platelet counts after treatment.

Murine animal models have also been used to elucidate the pathogenesis of thrombocytopenia during acute malarial infection. Using mice infected with Plasmodium berghei, the observations indicated increased peripheral platelet destruction rather than decreased marrow production. According to these studies, the thrombocytopenia appears to be modulated by CD4+ T-lymphocytes. T-helper lymphocyte depletion prevented thrombocytopenia and conversely, T-helper cell reconstitution resulted in decreased platelet counts. The bridge between a T-cell dependent immune response and a humoral immune-mediated mechanism in the development of thrombocytopenia may be explained by the modulatory effects that T-lymphocytes have on the production of anti-platelet antibodies by B-cells, by releasing certain cytokines such as tumor necrosis factor alpha (TNF-α), gamma interferon (γ-interferon), and neopterin. These and other monocyte-derived cytokines (interleukin-6, interleukin-10) may participate in the development of malaria-related thrombocytopenia, but their specific roles remain obscure. The complexity and intricacy of these immune interactions await additional studies to further elucidate these mechanisms.

The role of macrophage colony stimulating factor (M-CSF) and P-selectin has also been studied in the context of malaria-associated thrombocytopenia. P-selectin is a protein expressed on the surface of activated platelets and endothelial cells and also secreted into the plasma in situations in which there is endothelial cell and platelet damage. Although some studies may suggest that there is a role for this molecule in the pathogenesis of malaria-induced thrombocytopenia, the absence of elevated P-selectin plasma levels in uncomplicated Plasmodium infection may signify that platelet and/or endothelial activation might not play a significant role in the development of thrombocytopenia in these patients.

It is known that treatment with recombinant human M-CSF induces reversible, dose-dependent thrombocytopenia. In fact, increased serum levels of endogenous M-CSF have been demonstrated in patients with immune-mediated thrombocytopenic conditions, such as idiopathic thrombocytopenic purpura (ITP). In ITP, antibody-coated platelets are cleared from the circulation by macrophages via Fc receptor-mediated phagocytosis. In acute malarial infection, there is proliferation of spleen, liver, and bone marrow macrophages in order to effectively remove damaged erythrocytes. The study by Lee and colleagues showed a strong association of high serum levels of M-CSF and thrombocytopenia in patients infected with Plasmodium falciparum and P. vivax (up to a 7-fold increase for severe parasitemia and a 4-fold increase for uncomplicated malaria). The proliferation of macrophages promoted by M-CSF appears mostly confined to the reticuloendothelial system (bone marrow, spleen, and liver). According to this study correlation with peripheral blood monocyte counts was not observed.

During our local malarial outbreak, we observed the combination of relative monocytosis with thrombocytopenia by automated counts. Since this pattern was noted in the first 3 patients with P. vivax malaria admitted to our ED, peripheral blood smear review...
was implemented whenever encountering such a pattern in the hematologic scattergram. Therefore, in the context of an autochthonous malarial outbreak, peripheral blood smear evaluation may be of value in detecting patients infected with malaria when low platelet count and relative monocytosis are detected by automated methods.

Although not all the individuals affected during the locally acquired malaria outbreak in our county presented with lymphopenia or neutropenia, *Plasmodium* infection is reported to be frequently associated with decreased neutrophilic and lymphocytic cell counts.\(^{10,20}\) One of the proposed explanations for the neutropenia is the sequestration of neutrophils that presumably occurs in the spleens of malaria-infected patients.\(^{21}\) On the other hand, although lymphopenia is not an uncommon finding, some investigators have described a polyclonal B-lymphocyte proliferation instead, presumably the result of secretion of chemotactic lymphokines and lymphocyte mitogens by activated monocytes in response to phagocytosis and presentation of parasite antigens.\(^{22,23}\) The disparity of these observations remains unexplained, further reinforcing the complex nature of the immune responses occurring in the context of malarial infection.

**Conclusion**

Locally acquired mosquito-transmitted malarial infection is a phenomenon that occasionally occurs in the United States, particularly in densely populated urban areas. The laboratory plays a fundamental and decisive role by providing initial diagnosis and identification of *Plasmodium* species, which is not only necessary to adequately select antimalarial therapy for the affected individuals, but also to alert public health authorities, in order to develop and implement rapid and efficient epidemiological measures. Individuals presenting to our ED with unexplained fever and a combination of relative monocytosis with thrombocytopenia in the automated hematologic scattergram resulted in the preparation of a peripheral blood smear to exclude malarial infection. Early laboratory diagnosis of malaria is necessary to provide adequate treatment to reduce morbidity and mortality, prevention of relapses (depending on the species), and rapid implementation of public health preventive measures in the community. Doing so facilitates containment and eradication of the infectious outbreak. Recommendations to community hospital laboratories located within the affected area were issued based on these observations.

**Acknowledgements:** We would like to thank the laboratory technologists and technicians at JFK Medical Center, Bethesda Memorial Hospital, and the Wellington Regional Medical Center; all the physicians involved in the care of the infected patients (especially the emergency department at JFK Medical Center, Drs. C. Rumball and K. Scheppke); the Palm Beach County Public Health Department (particularly, Drs. J. Malecki and S. Kumar); and finally to Mrs. Carolyn Moss and Mrs. Sharon Reuben for their involvement, collaboration, and technical assistance in the preparation of this article.