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# Co-infection with Plasmodium Falciparum and Plasmodium Vivax ： A Case Report

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## Abstract

Taiwan has had no cases of autochthonous malaria reported since 1974. All cases since then have been imported. We report a Taiwanese man with no history of travel outside Taiwan who was co-infected with of Plasmodium falciparum and Plasmodium vivax. The only possible source we could discover was a nephew who had contracted both parasites in the Solomon Islands. He had recurrent fever and parasitemia after returning to Taiwan. Our patient might have been infected by disease introduced by his nephew. The clinical course was characterized by an irregular fever pattern, hepatosplenomegaly, jaundice, pulmonary edema, and there was apparent multi-drug resistance, but his parasitemia finally resolved with the use of artesunate. This case is particularly important because of a negative travel history, raising the possibility of further autochthonous cases occurring in that area. Also, a co-infection with both P. falciparum and P. vivax raises certain challenges during treatment, as resistance to antimalarial drugs may differ between the two organisms. ( J Intern Med Taiwan 2005; 16: 195-200 )

**Key Words ： Plasmodium vivax, Plasmodium falciparum, Co-infection**

## Introduction

Malaria is the most common parasitic infection. All continents are at risk, but it is particularly a problem in tropical countries. Taiwan has had no autochthonous malaria since 1974. All reported cases since then have been imported, a problem that is enhanced by increasing international travel. We report the case of a patient in Taitung county with malaria but who had no travel history.

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## Case report

A 57-year-old man was admitted to MacKay Memorial Hospital in Taitung on September 5, 2003. He was previously healthy and denied use of alcohol, tobacco, or illegal drugs. He was an employee of the sanitation department in the Taimali District, Taitung County. Three days prior to admission, he suddenly developed a fever with chills, upper abdominal pain, diarrhea, and headache. His temperature was 39 ℃ to 40 ℃. The fever subsided several hours later, associated with diaphoresis, but recurred over the next few days without following a clear temporal pattern. The upper abdominal pain was dull and did not radiate. His appetite was poor. He had episodic diarrhea beginning on the second day after the onset of fever. The stool was watery and dark brown, but there were no melena or blood.

He denied having traveled out of Taitung County, had eaten no unusual food, and had no recent animal bites. He occasionally had insect bites to which he paid little attention. None of his relatives, friends, or co-workers had similar symptoms. However, his nephew had been in the Solomon Islands on business from January to June of 2003. He contracted malaria there and was partially treated. However, he had recurrent fever after returning to Taiwan. In September, a blood smear was done which was positive for Plasmodium falciparum and P. vivax.

On admission, the patient's temperature 37.2 ℃, heart rate 90, respiratory rate 20, and blood pressure 120/90. The only remarkable physical finding was mild upper abdominal tenderness. His hemoglobin was 12.9 gm/dL, hematocrit 38.2%, WBC 4400/ul, and platelets 28000/ul. On examination of a blood smear, ring forms were seen within erythrocytes.( Fig. 1). The diagnosis of malaria was subsequently confirmed by the Center for Disease Control (CDC).

Therapy was begun with minocycline, 200 mg immediately, followed by 100 mg every 12 hours and

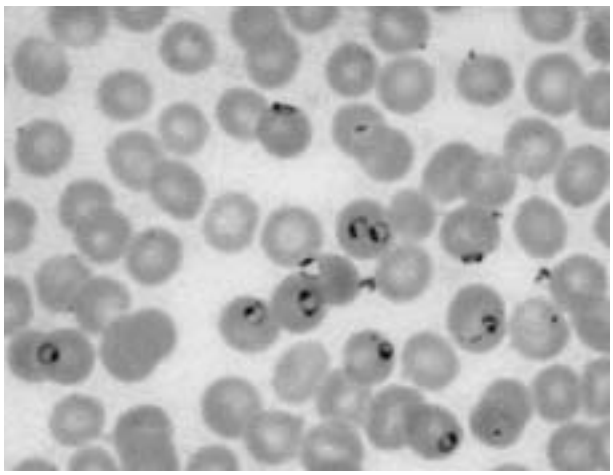

Fig.1.Liu's stain. 1000x. Thin film. P. falciparum. Trophozoites characterized by delicate ring, chromatin in two fine dots.

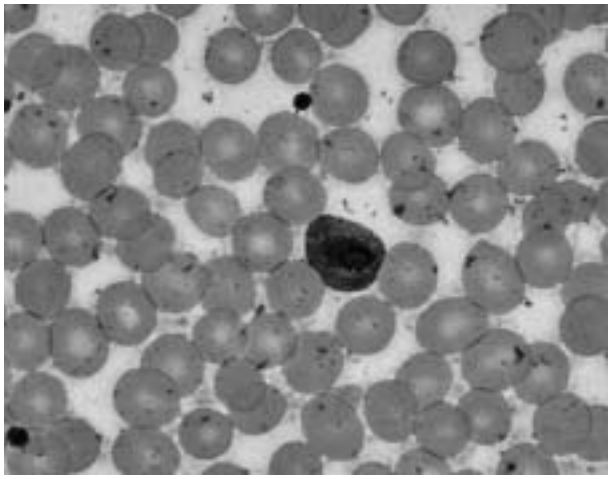

Fig.2.Liu's stain. 1000x. Developing trophozoites of P. vivax, characterized by large, irregular shape, prominent vacuole and fine pigments.

hydroxychloroquine 800 mg immediately while we awaited delivery of chloroquine from the CDC. When that became available, we gave oral chloroquine 1000 mg immediately, 500 mg six hours later, and another 500 mg 24 hours later.

Over the next several days, the patient's abdominal pain increased and localized in the right upper quadrant. Laboratory data showed direct bilirubin 0.6 mg/dl, total bilirubin 1.4 mg/dl, GOT 59 u/L, and GPT 31 u/L. An abdominal echo on day 2 showed an edematous gall bladder wall, minimal ascites, and a space-occupying lesion in the liver consistent with a hemangioma. On day 3, hepatosplenomegaly became

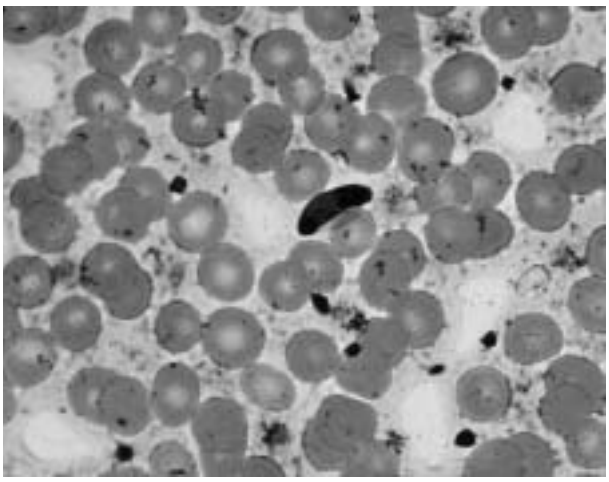

Fig.3.Liu's stain. 1000x. Thin film. P. falciparum. Microgametocytes: kidney shaped, chromatin in fine granules, dark pigments.

evident on physical examination and was confirmed by echography. The same day, the patient complained of dyspnea and orthopnea. Arterial blood gas testing on room air showed a pH of 7.5, $PCO_2$ 21.6 mmHg, $PO_2$ 61.7 mmHg, $HCO_3$ 16.4 mmol/L, BE -6.8 mmol, and $O_2$ saturation 94%. A chest x-ray was interpreted as showing mild pulmonary edema. This was treated with furosemide and oxygen, the symptoms gradually resolved over several days, and improvement was seen on chest x-ray.

The patient's fever persisted and his blood smear continued to be positive for parasites, so oral quinine was begun on day 3,650 mg immediately, followed by 650 mg three times a day, and was given until day 7. After one week of treatment, his fever began to subside, as did the abdominal tenderness and hepatosplenomegaly. There was thrombocytopenia on admission (28000/ul), and the platelet count fell further to 6000/ul on day 2, at which time he was given a transfusion of 12 units of platelets. As the fever and hepatosplenomegaly subsided, the platelet count improved, reaching 75000/ul by day 6.

A blood smear was examined daily by both our laboratory and the CDC. On day 7, the CDC reported co-infection with both P. falciparum and P. vivax. (Fig. 2, Fig. 3) We therefore discontinued quinine and for the treatment against P. vivax we gave primaquine, 30 mg daily beginning on day 8 and this medication was continued until day 22 of hospitalization, completing course of fourteen days. Beside , as local health authority provided us oral mefloquine on day 8, we begun this medication 750 mg immediately followed by 500 mg twelve hours later, in expectation to eliminate P. falciparum. The blood smear was negative on day 12 but parasitemia was seen again on day 13. At that point, the infectious disease consultant suspected that the P. falciparum was resistant to quinine as well mefloquine, so we began artesunate, 200 mg immediately and then 100 mg daily for 3 days. The blood smear became negative again on day 14, and the patient was discharged on day 22 after 4 days with negative blood smears and after completing 14 days of treatment with primaquine.

## Discussion

Several interesting issues are raised by this case. The source of the patient's infection is not clear, since he had not traveled to any areas where malaria is endemic. Co-infection with two different plasmodium species is reported in 5% to 7% of all cases of malaria [1,2]. Co-infection may be more common than suspected. P. falciparum co-infection with either P. vivax or P. malariae seems to be the commonest co-infection. A low level of parasitemia of either species may be undetectable initially and lead to the false impression of single infection [3].

There are few longitudinal studies of this type of co-infection. The interaction of the parasites with the host's immune system is complex and incompletely understood. Clinical studies have suggested some interesting phenomena. For example, P. vivax infection may be protective when coexisting with P. falciparum, with less severe disease and a lower level of parasitemia than seen in an infection with P. falciparum alone. The response to therapy also may be different when co-infection exists. If either of the infecting species is resistant to therapy, the other may survive to a greater degree, leading to greater para-

sitemia. If co-infection is not recognized early and the patient is treated for falciparum infection alone, P. vivax may became a hazard because liver hypnozoites will cause persistent parasitemia, with a high risk of relapse [3,4].

It is still unclear if people became infected by one species first, followed by the second, or if they are simultaneously co-infected with a single mosquito bite.

The most likely source of infection in our case would appear to be the patient's nephew, who was co-infected with both falciparum and vivax malaria in the Solomon Islands but did not have adequate treatment before returning to Taiwan. Presumably, he was bitten by a mosquito which at some later time bit his uncle. This raises the worrying question as to whether the malaria will persist in the mosquito and human population in this part of Taiwan.

The patient had some of the typical manifestations of malaria, including a flu-like prodrome, abdominal discomfort associated with diarrhea, headache, and recurrent fever and chills. His fever, however, did not follow any particular pattern. He also had several of the complications seen in severe malaria, including hepatosplenomegaly, thrombocytopenia, and non-cardiac pulmonary edema. Splenomegaly is a frequent complication of malarial infection [5,6] and may lead to splenic rupture [6]. In areas where chronic infection is frequent, a syndrome called hyperreactive malaria splenomegaly is often seen [7-9], which may be linked to malignant lymphoma, especially in west Africa. Some reports suggest that splenomegaly is particularly common in vivax malaria, especially when prior immunity is lacking. Co-infection with falciparum is thought to further increase the risk of splenomegaly [6-8]. About 5% of patients with severe falciparum malaria have severe thrombocytopenia and bleeding. Milder decreases in platelet counts are much more common and are attributed to splenomegaly [5,10,11]. Our patient had severe thrombocytopenia which improved when the infection came under control and the splenomegaly began to resolve.

Hepatomegaly is also a frequent finding in falciparum malaria [5,12]. The suggested mechanism is invasion by sporozoites, but the true pathogenesis had not been completely elucidated. While jaundice is often present, it is usually due to destruction of erythrocytes rather than hepatic dysfunction.

Non-cardiogenic pulmonary edema is a well-known complication of severe falciparum malaria [1,13,14]. Our patient appears to have had this complication, which responded to diuretics. The pathophysiologic mechanism is thought to be cytoadherence of red cells deformed by intracellular parasites to small vessel endothelium. In addition, the distorted erythrocytes may form intravascular rosettes, further altering the microcirculation. These phenomena are fairly specific to infection with P. falciparum infection, as neither vivax nor ovale produce knobs on the surface of infected erythrocytes [6,16]. Given this propensity of falciparum malaria to precipitate pulmonary edema, it is wise in these patients to avoid other factors that could contribute to this complication, including fluid overload and hypoalbuminemia.

The parasites involved in our patient's infection appeared to be resistant to multiple drugs. Chloroquine, with which we started, is the drug of choice for susceptible plasmodia. However, the patient did not respond to this agent, nor was there a good response to quinine, mefloquine appeared to be only partially effective in this patient. Ultimately, artesunate was required for the treatment. Resistance is a major problem in the treatment of malarial infection [2,17]. For multi-drug resistant P. falciparum, the treatment of choice is mefloquine or quinine combined tetracycline. The latter combination, however, was ineffective for our patient. Since 2001, as response to increasing level of antimalarial resistance, WHO recommended the artemisinin based combination therapy ( ACT ), which includes several advantages: rapid reduction of parasites biomas, rapid resolution of symptoms, it is particularly effective

against multidrug resistant P. falciparum, reduces the carriage of gametocyte, and no paracite resistance has been documented. ACT has been demonstrated to delay the development of resistance, specially in South East Asia, where Thailand has been adopted artesunate plus mefloquine combination as a first line treatment, and this combination has been recommended in South East Asia [17-19].

In conclusion, this patient was infected in Taiwan, suggesting a threat of further autochthonous infections unless action is taken to control the transmission through mosquito [20]. The treatment was more complex because of the co-infection and the presence of drug resistance. Effort should be made to prevent a large outbreak of such a co-infection, which would lead to significant strains on the health care system and economy.

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# 惡性瘧原蟲及間日瘧原蟲合併感染：一病例報告

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## 摘　要

自1974年起台灣已無本土型瘧疾病例報告，所有個案均爲境外移入。一位未曾出國旅行的原住民被診斷爲合併感染惡性瘧原蟲與間日瘧原蟲。我們發現病人的侄兒曾在所羅門群島接觸到上述兩種原蟲，返國後即已產生發燒與原蟲血症。分析病人爲一介入型感染個案，臨床表現有不規則熱、肝脾腫大、黃疸、肺水腫與明顯之多重抗藥性現象。所幸後經青蒿琥酯治癒。這位病人未曾出國而致瘧意味著居住區域蟲媒感染的可能性。合併感染惡性瘧原蟲與間日瘧原蟲對於治療當中產生抗藥性時藥物的考量也有所差異。