Abstract. Plasmodium vivax malaria reemerged in the Republic of Korea in 1993 near the Demilitarized Zone (DMZ). We reviewed clinical features of 101 symptomatic patients with vivax malaria. Of the patients, 77 patients (76.3%) were veterans who had served near the DMZ; their median age was 23 years. The duration of the minimum latent period was $>6$ months in 66.2% (51 of 77) of the patients (median, 278 days). Tertiary fever developed in 69 patients (68.3%). Severe thrombocytopenia with platelet counts $<60,000/\mu L$ was common (29.6% of patients). The parasite densities ranged 32–52,127 parasites per microliter of blood (geometric mean, 1,287). The only complication was a splenic rupture in one patient. All patients responded promptly to chloroquine therapy. Our data suggest that the clinical features of reemerging vivax malaria may be similar to those of Korean vivax malaria reported in the past.

INTRODUCTION

Indigenous malaria due to Plasmodium vivax had been prevalent in Korea for many centuries. The prevalence of vivax malaria among febrile patients was approximately 15% in the 1950s and was as high as 41.5% in highly endemic areas in the 1960s. During the Korean War (1950–1953), 11% (152 of 1,350) of Canadian veterans who fought in Korea developed malaria after returning home. Because of improved socioeconomic conditions and malaria-control activities, the incidence of vivax malaria had been decreasing since the early 1970s, and indigenous malaria had virtually disappeared from the Republic of Korea (ROK) by the late 1970s. Not until 1993 did the first case of reemerging malaria appear in the ROK (population 45 million). Since that time, the annual incidence of vivax malaria has been increasing every year, and $>9,000$ cases were reported by the end of 1999. Almost all of the reemerging malaria cases have been confined to the northwestern part of Kyounggi-do Province near the Demilitarized Zone (DMZ) that divides the ROK and North Korea. Because of these epidemiological characteristics, 80% of the reemerging malaria cases have occurred among soldiers serving near the DMZ. In addition, recently discharged veterans have accounted for 47% of the malaria cases among civilians. This unique situation gave us an opportunity to study the latent period and clinical features of vivax malaria in nonimmune patients.

PATIENTS AND METHODS

Three university-affiliated hospitals, Seoul National University Hospital, Chungbuk National University Hospital, and Chonnam National University Hospital, participated in this study. Patients with P. vivax malaria diagnosed between January 1, 1996, and December 31, 1999, were reviewed. Those patients who had traveled outside the ROK to malarious areas were excluded. The diagnosis was made when the characteristic parasites of P. vivax were identified on peripheral blood smears. The patients were treated with the standard regimen, 1.5 g of chloroquine followed by 15 mg of primaquine daily for 2 weeks.

The minimum latent period was defined as the period from the last day of exposure to mosquitoes in the endemic area to the first day of malarial attack. We defined the endemic areas of reemerging vivax malaria in the ROK as the malaria-endemic areas as determined by Lee and others. It is freezing cold during winter season in the ROK, and May to October is the only season when environmental conditions permit transmission of P. vivax. Therefore, the last day of military service was assumed to be the last day of exposure if a veteran had been discharged (and left the endemic areas) between May 1 and October 31. The last October 31 was assumed to be the last day of exposure if the veteran had left the endemic areas between November 1 and April 30. Because the mandatory duration of military duty is 26 months in the ROK, most of the veterans had spent at least 2 consecutive summers in the endemic areas. All the peripheral blood films were examined by an expert under the microscope at $\times1,000$ magnification for the presence of malaria parasites. The number of parasites per 100 white blood cells (WBC) were counted, and the parasite densities were calculated on the basis of the number of parasitized red blood cells per WBC and actual total WBC.

RESULTS

Patient characteristics. A total of 101 patients with symptomatic vivax malaria were included in the study. None had a known history of previous malaria attack. Of the 101 patients, 77 (76.3%) patients were veterans who had served near the DMZ. 9 (8.9%) patients were travelers to the endemic areas, and 8 (7.9%) patients were residents of the endemic areas. Seven (6.9%) patients had no history of travel to the endemic areas, and 5 of them lived in the northern part of Seoul, which is located $\sim50$ km south of the DMZ. The median age of the patients was 23 years (range, 17–77 years), and the male to female ratio was 93:8.

Duration of the minimum latent period. We were able to estimate the duration of the minimum latent period in 77 patients. Of these 77 patients, 73 patients were veterans and 4 patients were civilians. The duration of the minimum latent period was $<4$ months in 26 patients (33.8%), with a median duration of 32 days. The duration of the minimum latent
period was > 6 months in 51 patients (66.2%), with a median duration of 278 days.

Of these 77 patients, 31 had received chloroquine prophylaxis and 12 had not. The history of prophylaxis was uncertain in 34 patients (open bars). The ratio of patients with shorter minimum latent periods to those with longer minimum latent periods was 12:19 in those who had received prophylaxis, 3:9 in those who had not received prophylaxis, and 11:23 in the uncertain group. The difference in these ratios was not statistically significant. In the 4 civilians who had traveled to the endemic area and who had not received prophylaxis, the durations of the minimum latent periods were 22, 32, 45, and 317 days (Figure 1).

Monthly distribution of the onset of malaria. The onset of malaria was concentrated in the summer season (July–September). Of the 101 patients, 30 patients (29.7%) developed malaria in July, 26 patients (25.7%) in August, and 21 patients (20.8%) in September. These 77 patients comprised 76.2% of the total number of patients. None of the patients, including those 36 patients who had been exposed to malaria-bearing mosquitoes in previous years, developed malaria during the winter season (Figure 2).

Symptoms and physical findings. Fever and chill developed in all of the patients. Tertian fever, a characteristic fever pattern of \( P. \) vivax malaria, developed in 68.3% (69 of 101) of the patients. Of these 69 patients, 64 (92.8%) developed tertian fever during the first week of illness, 4 during the second week, 0 during the third week, and 1 during the fourth week. Other major symptoms included headache in 84 (83.2%) patients, myalgia in 43 (42.6%), nausea in 24 (23.8%), diarrhea in 24 (23.8%), vomiting in 17 (16.8%), and cough in 15 (14.9%).

The spleen was palpable in 43 (42%) patients, and the liver was palpable in 16 (15.8%) patients. Tenderness in the right upper quadrant of the abdomen was found in 9 (8.9%) patients, conjunctival injection in 4 (4.0%) patients, petechiae in 3 (3.0%) patients, rash in 2 (2.0%) patients, and herpes labialis in 1 (1.0%) patient.

Laboratory abnormalities. Laboratory abnormalities are common; anemia (hemoglobin < 12 g/dL) in 52 (51.5%) patients, leukopenia (WBC < 4,000/μL) in 20 (19.9%), and thrombocytopenia (< 150,000/μL) in 86 (85.1%). Platelet counts were < 60,000 per microliter of blood in 30.0% (30 of 101) of the patients. However, clinical bleeding was not observed in these patients. Of the patients who were tested, platelet-associated antibody was positive in 66.7% (20 of 30), and anti-platelet antibody was positive in 10.7% (3 of 28).

The levels of transaminases were elevated (> 2 times normal shown in Table 1. Hematological abnormalities were very common; anemia (hemoglobin < 12 g/dL) in 52 (51.5%) patients, leukopenia (WBC < 4,000/μL) in 20 (19.9%), and thrombocytopenia (< 150,000/μL) in 86 (85.1%). Platelet counts were < 60,000 per microliter of blood in 30.0% (30 of 101) of the patients. However, clinical bleeding was not observed in these patients. Of the patients who were tested, platelet-associated antibody was positive in 66.7% (20 of 30), and anti-platelet antibody was positive in 10.7% (3 of 28).

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Figure 1. The distribution of the minimum latent period of reemerging vivax malaria in 77 patients in the Republic of Korea. Of the 77 patients, 31 patients (solid bars) received chloroquine prophylaxis, and 12 patients (hatched bars) did not receive prophylaxis. The history of prophylaxis was uncertain in 34 patients (open bars). It is of note that the distribution curve showed a bimodal pattern. Of the 77 patients, the minimum latent periods were < 121 days in 26 patients and > 180 days in 51 patients. The median duration of the minimum latent periods was 1 month in the former and 10 months in the latter. There were no patients with minimum latent periods of > 2 years.

Figure 2. The monthly distribution of reemerging vivax malaria in 101 patients in the Republic of Korea. The last possible season of exposure to \( P. \) vivax was unknown in 60 patients (open bars). Five patients (hatched bars) developed symptoms in the same calendar year in which they had been exposed to \( P. \) vivax. The exposure season was > 1 year before the symptoms developed in 36 patients (solid bars). It is of note that all these 36 patients also developed symptoms during the summer season (July–September).

Table 1. Hematological abnormalities were very common; anemia (hemoglobin < 12 g/dL) in 52 (51.5%) patients, leukopenia (WBC < 4,000/μL) in 20 (19.9%), and thrombocytopenia (< 150,000/μL) in 86 (85.1%). Platelet counts were < 60,000 per microliter of blood in 30.0% (30 of 101) of the patients. However, clinical bleeding was not observed in these patients. Of the patients who were tested, platelet-associated antibody was positive in 66.7% (20 of 30), and anti-platelet antibody was positive in 10.7% (3 of 28).
mal) in 15 (14.9%) patients. The level of total bilirubin was elevated (> 2.0 mg/dL) in 11 (10.9%) patients. Of the 25 patients who underwent ultrasonography of the abdomen, the median size of the longest diameter of the spleen was 13.9 cm (range, 11 to 20 cm).

**Parasite densities.** The peripheral blood films were available for parasite count in 81 patients. The parasite densities ranged 32–52,127 parasites per microliter of blood, and the geometric mean parasite density was 1,287. Of the 81 patients, 4 (4.9%) patients had the parasite density < 100 parasites per microliter of blood.

**Initial clinical diagnosis.** The time from the onset of symptoms to diagnosis ranged 2–65 days (median, 12 days). The first clinical diagnosis was malaria only in 63 (62.5%) patients. Among the other patients, 6 were originally diagnosed as typhoid fever, 6 as fever of unknown origin, 3 as hemorrhagic fever with renal syndrome, 3 as acute viral infection, 2 as hepatitis, 2 as acute gastroenteritis, 2 as immune thrombocytopenia, 2 as upper respiratory tract infection, 2 as aplastic anemia, and 1 as viral meningitis.

**Treatment response and complications.** In all patients, fever resolved promptly after a standard course of chloroquine treatment. One patient developed recurrent malaria 299 days after the first attack. At the first attack, this patient had been treated with the standard regimen of chloroquine and primaquine and had no history of visiting the endemic areas after the first treatment. He was treated again with the same standard regimen, and quickly recovered thereafter, without relapse.

Another patient experienced spontaneous rupture of the spleen. This patient underwent an emergency splenectomy on the 15th day of his illness and survived.7

**DISCUSSION**

Vivax malaria had been endemic in Korea for a long time. *Anopheles sinensis* and *Anopheles yatsushiroensis* were known to be the vector hosts capable of transmitting *P. vivax* in Korea.1 The incidence of indigenous malaria decreased rapidly during the 1970s; the number of cases per 100,000 population dropped from 3.6 in 1975, and 0.0 in 1980.2 In the 1960s, the Korean government, in collaboration with the World Health Organization, introduced a malaria eradication project that involved active and passive case detection combined with chloroquine-primaquine treatment of identified patients with malaria. The ecology has also changed since the 1970s, with extensive use of pesticide and herbicides in agriculture. At the same time, the socioeconomic status of Koreans improved. These factors might contribute the rapid disappearance of vivax malaria in the ROK.4

Since the first case of indigenous malaria reappeared in 1993, most of the reemerging malaria had occurred in the regions adjacent to the DMZ (Gimpo, Paju, Yeoncheon, and Cheolwon County) until 1995. Because of this geographical distribution of the cases, it was suggested that the reemergence of vivax malaria might be due to infected mosquitoes that flew in from the northern part of the DMZ (i.e., North Korea). However, data on the malarial situation in the Northern Korea are limited. Other possible explanations may include relapse or long-term latent infection of indigenous malaria in the Paju area (where malaria had been highly endemic in the past), and introduced malaria transmitted by imported cases. However, no case of imported vivax malaria was reported between 1990 and 1993.

It is well known that vivax malaria exhibits 2 different patterns of clinical features, depending on the geographical origin of the parasite. In tropical areas, clinical attacks occur throughout the year. In temperate regions such as the ROK, the parasite has a long-term latency, with no clinical attacks occurring during the colder seasons of the year.3 Previous clinical studies performed in the early 1950s (during the Korean War) and an experimental study have demonstrated that Korean vivax malaria has a long-term latency of 10 months, which is characteristic of vivax malaria in temperate regions.3,10

In our study, two-thirds of the patients experienced long-term latency, with a median duration of 10 months. It was also reported that the mean duration of the latent period was 279 days (range, 153–452 days) in 107 veterans with reemerging vivax malaria in the ROK.4 However, it should be emphasized that most of the patients we studied were veterans. Soldiers who develop malaria during their military service (short-term latency) are treated at military hospitals, and only those who develop malaria after the completion of their military service (long-term latency) are treated at a civilian hospital. Because of this selection bias, those with long-term latency may have been overrepresented in our study. The use of chloroquine prophylaxis in soldiers also might suppress initial attacks. Moreover, we could not know the exact time of exposure in the veterans because they had served for 26 months in the malaria-endemic areas. Therefore, our estimation is a minimum latent period, one based on a season or duration of service in an endemic area instead of a discrete exposure event.

It is interesting to note that the distribution of the latent periods showed a bimodal curve: a small peak at 1–2 months, a large peak at 8–10 months, and no cases at 3–6 months (Figure 1). Given that two thirds of our patients had been exposed to malaria-carrying mosquitoes in previous years, this bimodal distribution suggests that many infections acquired in the summer did not become evident until the following spring or summer. Indeed, the monthly distribution of malaria attacks showed a single peak in a year, with no cases appearing during the winter season. Also of interest is that no patient had a latent period of > 2 years. This finding is consistent with the report by Hankey and others,10 who showed that naturally acquired Korean vivax malaria terminated spontaneously within 2 years after sporozoite inoculation.

Of the 101 patients in this study, 7 patients had not traveled to the endemic areas. It could be that the patients had traveled, but they did not remember; or they may have been exposed outside the known endemic areas. Of the 7 patients, 5 patients lived in Seoul, and 2 of them lived in the most northern part of Seoul (Sooyou-Ri), which is located near the endemic areas. Therefore, they might have been exposed to malaria mosquitoes in Seoul. Indeed, cases of indigenous malaria have been reported in children who lived in Itaewon, a satellite city near to the northern part of Seoul. These cases might indicate that malarious areas have already expanded to the northern border of the metropolitan city of Seoul.11,12

The diagnosis of malaria can be made without difficulty
if it is suspected. Because of the epidemiological characteristics of the reemerging malaria in the ROK (i.e., it occurs in confined areas along the DMZ and most patients are soldiers and veterans who are serving or served near the DMZ), malaria could have been suspected in our patients. In one third of the patients we studied, however, malaria had not been included among the initial differential diagnoses on their first hospital visit. Many patients did not mention that they had been in the endemic areas because they did not realize that they could develop malaria as long as 1 year after exposure to mosquitoes in endemic areas. The lack of tertian fever, an important clue for the diagnosis of vivax malaria, also precluded early suspicion of vivax malaria.

Thrombocytopenia was the most frequent laboratory abnormality found in our patients, presenting in 85.1%. Severe thrombocytopenia of platelet count < 60,000/μL was also seen in 29.6% of the patients. Despite severe thrombocytopenia, coagulation profiles were usually normal in our patients, and clinical bleeding did not occur. Lim and others also reported that thrombocytopenia was present in 72.4% (63 of 87) of patients they studied with Korean vivax malaria. The mechanisms of thrombocytopenia in vivax malaria are poorly understood, but recent studies have suggested that elevated levels of platelet-associated immunoglobulin G and macrophage colony-stimulating factor were associated with thrombocytopenia.

Parasite densities ranged 32–52,000 parasites per microliter of blood in our patients. Of note is that only 4.9% of our patients had parasite densities < 100 per microliter of blood. A recent study showed that OptiMAL test, a dipstick test for the rapid diagnosis of malaria, did not identify blood samples containing parasites at concentration of < 100 per microliter of blood.

In our study, the clinical course of reemerging vivax malaria was usually benign. The only serious complication was the spontaneous rupture of the spleen in one patient. The incidence of this complication has been reported to be 0–2% and was 1% (1 of 101) in this study. Three cases of retinal hemorrhage, which had not been previously reported in vivax malaria, have been also reported in patients with reemerging Korean vivax malaria by other clinicians.

They reported that the retinal hemorrhages in these patients resolved without any sequelae. It should be emphasized again that the ROK had been free of vivax malaria for more than a decade. Therefore, the incidence of complications among nonimmune Korean patients with reemerging malaria might be higher than that among immune patients living in an endemic area.

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