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☐ **Brief Communication** ☐

A relapsed case of imported tertian malaria after a standard course of hydroxychloroquine and primaquine therapy

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Abstract: Resistance of *Plasmodium* species to antimalarial agents has become increasingly challenging to the management and prevention of malaria. We experienced an imported case of tertian malaria due to *Plasmodum vivax* relapsed after a seemingly successful treatment with conventional course of hydroxychloroquine and primaquine. A 35-year-old man developed fever three days after return from India and mainland China. After his illness was diagnosed as tertian malaria, he was managed with hydroxychloroquine and then primaquine (primaquine base 15 mg/day for 14 days). Thereafter peripheral blood smears showed no malarial parasites, and there was no relapse of symptom until the 55th post-treatment day, however, six months after the above treatment tertian malaria relapsed. He was managed with the same medications again and malaria did not relapse for 10 months.

Key words: *Plasmodium vivax*, primaquine, relapse

Tertian malaria is seldom a fatal illness, but the infection has a high morbidity and the rate of relapse can be rather high. It is a usual practice to administer the combination therapy of chloroquine and primaquine; chloroquine is effective against parasites in asexual phase while primaquine is the only drug working on hypnozoites, thereby preventing relapse.

But since Moore and Lanier (1961) had discovered chloroquine resistant falciparum malaria in Colombia for the first time, chloroquine-resistance has been observed in most regions excluding some countries in Central America and the Middle East. This resistance against chloroquine was also observed in tertian malaria in Southeast Asia and Papua New Guinea (Baird *et al.*, 1991).

Recently there have been increasing reports on the relapse of tertian malaria after administration of not only chloroquine, but also primaquine (Krotoski, 1980). Chesson strain, a well-known tropical strain, revealed only 70% of radical cure rate (Coatney and Getz, 1962). While this primaquine tolerant strain has existed mainly in the South Pacific and Southeast Asia (Bunnag *et al.*, 1994), it is possible that this strain will spread to the entire world in line with the mobility of human beings. In this context it is important to identify and confirm primaquine-resistant vivax malaria in a timely manner, but the accurate assessment of the therapeutic effect of primaquine may be difficult at times.

It had been claimed that tertian malaria had been completely extinguished in the latter part of the 1970s in Korea (Soh *et al.*, 1985). But since 1993, this tertian malaria has reemerged to infect soldiers and civilians living near the

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armistice line (Yim *et al*, 1996), resulting in 1,724 cases in 1997 (Anonymous, 1998). Also imported malaria from an overseas trip has become a medical problems to the extent of calling social attention (Lee *et al*, 1988). Despite increase of patients with malaria, there has been only one report on the relapse of tertian malaria after being treated with primaquine in the Korean medical literature (Kim *et al*., 1997). We hereby present a case of tertian malaria relapsed after a seemingly successful treatment with hydroxychloroquine and primaquine and a review of literature.

A 35-year-old man visited the hospital with complaint of high fever of eight days' duration. The patient made a business trip to Bombay in India and Sichuan in China for 15 days without any antimalarial prophylaxis. On the third day after return from his trip, he developed fever rising up to 40°C and was admitted to another general hospital to receive some antibiotics for five days, which reduced the fever. But on the next day after discharge from the hospital, he developed again the symptom of high fever, fatigue, general weakness, anorexia, and therefore was transferred to our hospital.

At the time of admission, a physical examination showed 130/90 mmHg of blood pressure, 76/min of pulse rate, 20/min of respiratory rate and 38.7°C of body temperature. There was a slight hepatosplenomegaly on palpation. Laboratory examination showed hemoglobin 12 gm/dL, white blood cell count 5,000/mm^3 with 56% lymphocyte, platelet count 65,000/mm^3, alkaline phosphatase 405 IU/L, lactate dehydrogenase 713 IU/L, alanine aminotransferase 163 IU/L, aspartate aminotransferase 87 IU/L, and prothrombin time 73%. Urinalysis showed more than 25 red blood cells per high power field. Hepatosplenomegaly was observed in abdominal sonography. Peripheral blood smears showed schizonts having more than 14 merozoites and numerous trophozoites with an irregular form of the cytoplasm in enlarged erythrocytes, which were diagnostic for tertian malaria. Administration of hydroxychloroquine sulfate, 800 mg as a loading dose and then 400 mg each 6, 24, and 48 hr later, reduced the fever to normal. Primaquine base of 15 mg/day was administered for two weeks to prevent relapse and then the patient was discharged from the hospital.

On the 13th, 40th, and 55th day after administration of hydroxychloroquine, peripheral blood smears did not show any malarial parasite; and alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase became normal. There was no relapse of symptoms.

Six months after discharge from the hospital, however, the patient visited the hospital again with the chief complaint of high fever; peripheral blood examination showed ring forms of *P. vivax* with reduced platelet count (91,000/mm^3) and elevation of lactate dehydrogenase (626 IU/L). After administration of hydroxychloroquine and primaquine in the same manner as the first hospitalization, malarial parasites were not found in peripheral blood smears; lactate dehydrogenase was also reduced to normal of 340 IU/L. Symptoms have not relapsed during 10 months of observation.

The relapse of tertian malaria after administration of chloroquine and primaquine is attributed to the resistance against chloroquine or recrudescence, low susceptibility (tolerance) or resistance against primaquine, inadequate dose, or the possibility of reinfection (Collins and Jeffry, 1996). Although it is not easy to distinguish which one of these is the cause of the relapse of this patient, the timing of relapse after treatment is one clue to differentiate recurrence due to primaquine tolerance/resistance from recrudescence. If the relapse takes place later than 2-3 months from the last day of infection, it is considered to be due to primaquine tolerance/resistance rather than chloroquine resistance (Pukrittayakamee, 1994; Collins and Jeffrey, 1996). Peripheral blood smears of our patient were normal up to 55 days after the treatment and relapse took place after 6 months; there has been no relapse for 10 months after a re-treatment with chloroquine and primaquine; and he has never been to an area north of Kyonggi-do, Republic of Korea, where indigenous tertian malaria occurs (Yim *et al*., 1996). These facts highly suggest that the relapse of malaria in this patient is due to

recurrence rather than reinfection or recrudescence. Completion of a course of hydroxychloroquine and primaquine therapy during hospitalization removed the possibility of relapse due to a low drug compliance.

If one has developed malaria after a long trip to many areas, it is difficult to pinpoint the area where the infection occurred. But it is learned that 0.1 person per 1,000 population is infected by malaria in China and residents in regions of high incidence of malaria represents below 1% of the total population (WHO, 1997). Sichuan is not a region of high incidence of malaria. Compared to this, 2.6 persons per 1,000 population contracted malaria in India, which means the possibility of more than 90% of population being infected by malaria. Bombay, India is one of 15 regions with high frequency of malaria infection (WHO, 1996). Therefore, it is highly probable that the patient acquired the infection in Bombay.

There is still no established protocol for the treatment of primaquine-resistant tertian malaria. Generally, a larger dose of primaquine is effective, but it may cause drug toxicity; a recommended dose varies according to the geographical location and types of the strain. The experience of using 15 mg/day in the past showed that the second relapse rate after retreatment with the same dose is similar to the first relapse rate. So it is generally recommended to administer 15 mg/day for 14 days in regions like India, Colombo, and Korea where the relapse rate is about 3%. If such dose is administered to patients relapsed after a conventional course of primaquine therapy, the possibility of the second relapse is only 3%, thereby reducing the relapse rate as a whole to a low rate of about 0.09%. On the contrary, if the same dose is administered for a patient infected in the tropical zone such as Southeast Asia and Papua New Guinea where the relapse rate is 6-30% (Pukrittayakamee *et al.*, 1993; Bunnag *et al.*, 1994), the second relapse rate is likely to rise up to 30%. So the relapse rate is nearly 10% as a whole. For this reason, it is prudent to administer a conventional dose repeatedly in the temperate zones whereas doubling the dose (treatment total dose of 6 mg/kg) is recommended in the tropical areas. Accordingly, when this patient developed the relapse, we administered a usual dose again and, though the passage of 10 months may not be sufficiently long, no symptom of relapse has yet developed. In clinical practices, what is needed to clinician is knowing the countries or areas with a high relapse rate. There are several reports on the rates of relapse of tertian malaria from endemic areas after treatment with primaquine, but these reports have a possibility to overestimate the relapse rates because reinfection can not be ruled out. Thus relapse rates among infected travelers from developed countries may be more reliable. Thus, the rates are low in Sri Lanka (0%), Vietnam (0%), Philippines (0%), and India (4.5%); intermediate in Thailand (8.7%), Indonesia (9.3%), and Pakistan (10%); high in Malaysia (20%), Solomon Islands (20%), Papua New Guinea (24.1%), and Brazil (50%) (Kimura *et al.*, 1996). Also the rate among American soldiers returning from the Operation Desert Storm is high (43% and 35%) (Smoak *et al.*, 1997).

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=초록=

Hydroxychloroquine과 primaquine 통상 용량으로 치료한 후 재발한 유입 삼일열 말라리아 1예

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최근 primaquine으로 완치 (radical cure)된 후에도 재발하는 삼일열 말라리아 보고가 많아지면서 primaquine에 대한 내성 가능성이 언급되고 있다. 저자들은 해외여행 중에 감염된 삼일열 말라리아를 hydroxychloroquine과 primaquine으로 치료한 후 재발한 예를 경험하였기에 문헌고찰과 함께 보고한다. 35세 남자 환자가 내원 34일 전부터 15일간 인도 뭄바이와 중국 쉬천에 출장 다녀왔고 귀국 3일 후부터 고열이 발생하여 발열 17일째 본원에 입원하였다. 말초혈액 도말검사에서 분열체 내의 분열소체의 수가 14개 이상 되고 세포질 형태가 불규칙적인 영양형이 보여 삼일열 말라리아로 진단한 후 hydroxychloroquine를 투여하고 열이 떨어진 후 primaquine (15 mg/일, 14일간)을 투여하였다. 치료 후 55일째까지 말라리아 재발의 증상이 없었고 말초혈액 도말에서도 말라리아 원충이 없음을 확인하였다. 6개월 후 다시 발열이 생기고 말초혈액 도말검사에서 분열소체와 영양형이 보여 재발로 진단하였다. 처음 입원 때와 같은 방법으로 치료하였고 현재까지 10개월간 경과 관찰 중이며 증상의 재발은 없었다.

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