

Peculiarities of a malaria case imported from Myanmar to Moscow (Russian Federation)

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Abstract

An imported case of presumably Chesson strain *Plasmodium vivax* from Myanmar to Moscow is presented. In the absence of radical treatment with primaquine the patient experienced a series of 5 subsequent relapses after treatment with Delagil (chloroquine). The period between relapses ranged from 47-61 days. It is concluded that importation of Chesson-like strains with high relapse frequencies, in conjunction with their relative tolerance to primaquine and the absence of adequate treatment with this drug, might result in the re-establishment of local transmission in areas free of malaria but with high receptivity.

1 Introduction

Malaria was eliminated from the Russian Federation by the end of the 1950s. However, considerable parts of its territory still have high 'receptivity' to malaria, defined as the ability of local malaria vectors to support malaria transmission under suitable climate conditions [1]. Proven efficient malaria vectors in various parts of the Russian Federation are *Anopheles maculipennis*, *An. messaea*, *An. superpictus*, *An. sacharovi*, and *An. claviger*. Importation of malaria cases into the Russian Federation takes place continuously from various parts of the World. The majority of imported *P. falciparum* cases originates from the African region, and does not represent a direct epidemiological threat to the Russian population due to incompatibility of these parasites with local malaria vectors [2], while imported cases of *P. vivax* are largely confined to the Central, South and South East Asian region and all of these can easily be transmitted by local malaria vectors [3]. Over the last three years, all imported *P. falciparum* cases responded well to treatment with Lariam (mefloquine), and all *P. vivax* cases to chloroquine and standard treatment with primaquine. In 2010, one case of *P. vivax* imported from Myanmar produced a prolonged series of relapses after treatment with Delagil (chloroquine) only, due to temporary shortage of primaquine in the health treatment facility where the patient was treated. The details of that case are described here.

2 Case presentation

Patient D., male, 55 years of age, was on a business trip to Myanmar from 17 February 2010 through 18 May 2010.

During his stay, he visited various parts of the country, in particular the cities of Yangon and Mandalay, Kachin and Mon states. The two latter states are known to experience high levels of malaria transmission. Personal chemoprophylaxis was not taken.

The first fever attack occurred on the 4th day after returning to Moscow from Myanmar (the last place visited there was Mon state). The patient was hospitalised on the 5th day after the onset of fever (9th day after return). Laboratory diagnosis on admission revealed the presence of a mixed malaria infection – *P. falciparum* (density: 100-890/ml) and *P. vivax* (density: 3-100/ml), which is in line with the high prevalence of mixed infections described from Myanmar [4]. Clinical status was determined to be moderate. The subject was treated with Lariam (mefloquine) at a total dose of 1500 mg in one day (750 mg + 500 mg + 250 mg at 6-8 hr intervals). This was followed by quinine i/v (2.0 g). Asexual forms of *P. vivax* and *P. falciparum* were cleared on the 2nd and 3rd day, respectively. Fever disappeared on the 3rd day after treatment. The patient was discharged following 7 negative laboratory control examinations of blood slides. Treatment with the standard course of primaquine could not be undertaken due to shortage of the drug. This temporary shortage was due to the following reasons. With malaria elimination being achieved in the USSR during 1950s and 1960s, local production of primaquine was stopped. The stock of the drug in the country thereafter relied upon importation from abroad. Since procurement of primaquine is a centralised process it takes time to procure the drug and transport and distribute it to the peripheral health facilities. This absence of primaquine caused a series of five relapses in the patient as described below.

The first laboratory confirmed relapse of *P. vivax* was recorded on 21 July 2010, 50 days after successful treatment of the primary episode. The patient was treated with the standard course of Delagil (chloroquine; 1500 mg/3days). Parasite clearance occurred one day after this treatment. The patient was discharged after 5 negative blood slides.

The second laboratory confirmed relapse occurred 55 days (on 22 September 2010) after successful treatment of the first relapse. Delagil treatment again resulted in complete disappearance of parasites on the 3rd day after treatment. Six subsequent laboratory examinations of blood slides confirmed absence of parasites in the blood of the patient.

The third relapse took place on 27 November 2010, following successful treatment of the second relapse (after 61 days). Again, the case was treated with Delagil only, and parasites were cleared on the 3rd day after treatment and confirmed by 6 subsequent negative blood slides.

The fourth relapse was recorded on 21 January 2011, 53 days after treatment of the third relapse. Treatment with Delagil was again successful, and parasites disappeared on the third day after treatment. Five subsequent laboratory examinations of blood slides revealed no parasites.

The fifth relapse occurred 47 days thereafter (14 March 2011) following successful treatment of the previous relapse. Standard treatment with Delagil was again successful, as confirmed by laboratory examinations. As soon as primaquine was made available to the treatment facility, the patient was immediately contacted and was treated with the standard course of primaquine (15 mg during 14 days). Monthly follow up of the patient revealed that since then he did not experience a relapse.

3 Discussion

In the course of epidemiological interpretation of the case, the first major consideration was to exclude the presence of parasites of *P. vivax* resistant to chloroquine. The appearance of malaria parasites well after 28 days following the use of Delagil (chloroquine) indicates the absence of resistance to the drug. Moreover, during the period between the 1st, 2nd, 4th and the 5th relapse the patient was examined for the presence of parasites in the blood using PCR, the results of which were all negative. The use of PCR was exclusively to further confirm the absence of chloroquine resistance in this imported case. In doing so, we strictly followed the PCR procedures described by Snounou *et al.* [5].

Due to non-availability of facilities to undertake genetic genotyping at that time the second consideration was to establish the phenotype of this case based on epidemiological characteristics. *P. vivax* in Myanmar is considered to constitute a large group of so called 'tropical strains of *P. vivax* malaria'. Various authors include in this group para-

sites of *P. vivax* from the South Pacific (Papua New Guinea, Solomon Islands, Vanuatu, the Philippines, and Indonesia) and Southeast Asian regions (Vietnam, Cambodia, Thailand, Myanmar, North-Eastern states of India [6-9]. Inside this group, there are two distinct sub-populations of *P. vivax* – the Chesson strain and strains with short incubation and short latency periods [10,11]. These strains can relapse more frequently in a given period of time as compared with strains acquired elsewhere and they do so within the short latent period after the initial attack [7]. The most remarkable among these strains is the Chesson strain, characterised by frequent relapses (at 3-week intervals) with high relapse rates (70-80%) [9,12] and relative tolerance to standard dose treatment with primaquine [7,13]. Strains with short incubation and short latent periods differ from the Chesson strain in that short-term relapses generally occur during the period of about 2-3 months and the relapse rate rarely exceeds 50% [10].

This imported case from Myanmar undoubtedly falls into the category of 'tropical vivax malaria', demonstrating high frequency of relapses in the absence of radical treatment with primaquine. However, it does not fully correspond to the typical Chesson strain due to the fact that the frequency of relapses varied in the range of 47-61 days, which is rather closer to the strains with short-term incubation and short-term latency. It differs, however, from the latter in that five relapses occurred over a period of 266 days.

Efforts to find a possible explanation in the literature for the peculiarities of this imported strain revealed that cases similar to the above have been described in several publications. Charoenlarp and Harinasuta [14] report the results of the treatment of two 'tropical vivax malaria' cases in Thailand with various antimalarials. One case was treated with quinine only, but after 1 month it produced the first relapse with 3 subsequent relapses with the same frequency; it was cured only with an increased dose of primaquine. Thus, the case appeared to be the Chesson strain due to its patent frequency of relapses, high relapse rate and relative tolerance to standard (15mg x 14 days) primaquine treatment. The second case was treated with chloroquine only and resulted in a series of 3 subsequent relapses at 2-month intervals; it was also cured with an increased dose of primaquine. Again, a well-defined frequency of relapses during the period beyond 3 months put this case in the category of the Chesson strain. In Thailand, Looareesuwan *et al.* [15] treated 35 *P. vivax* cases with a combination of atovaquone and proguanil plus primaquine at a dose of 30 mg during 14 days. In spite of the increased dose of primaquine, relapses occurred by day 55 in 5.7% of those treated. In studies on the efficacy of pyronaridine in vivax malaria in Sichuan Province, China, Kang *et al.* [16] reported occurrence of relapses in 8.1% of treated persons by day 30 after treatment. Srivastava *et al.* [17], in Gujarat state, India, reported a high relapse rate (27.7%)

after treating *P. vivax* cases with chloroquine (1500 mg) and primaquine (15 mg x 5 days) with a lag period of two months. Miller *et al.* [18], in trials on the sensitivity of four Central-American strains of *P. vivax* to primaquine, described that out of 57 volunteers treated with a standard combination of chloroquine and primaquine, 2 persons relapsed, 46 and 160 days after the treatment. Hanf *et al.* [12] in Camopi, French Guiana, determined the *P. vivax* relapse pattern after treating cases with chloroquine only. It was reported that 42% of these relapsed one month after the primary attack, 59% within 2 months and 63% within 3 months. It was concluded that the relapse pattern was compatible with the pattern of the Chesson strain.

Our case data is in agreement with the results derived from these earlier studies. Thus, mepacrine (quinacrine, atebine) were known to delay early relapses of *P. vivax* by approximately 30 days compared with quinine treatment (from 3-7 weeks)[19]. Slowly eliminated anti-malarials delayed the onset of *P. vivax* relapse, and consequently reduced their frequency, but did not appear to reduce the overall number of relapses experienced [9,20]. For example, chloroquine was found to delay early relapse appearance by 2-6 weeks [21]. The presented case from Myanmar does not differ much from the above-cited data, the only difference being that the frequency of relapses was not well defined, ranging from 47 to 61 days. Nevertheless, the case may be attributed to the Chesson strain of *P. vivax*.

Importation of ‘tropical vivax malaria’, including the *P. vivax* Chesson strain, to areas freed of malaria potentially has an advantage of re-establishment of local transmission over temperate zone vivax strains because they produce more relapses and demonstrate varying levels of tolerance towards primaquine treatment. The ability of local malaria vectors to transmit imported strains of *P. vivax* might facilitate the establishment of local malaria transmission [22] as was demonstrated in Moscow city and the adjacent Moscow oblast (province) between 2000-2008. At that time, importation of *P. vivax* by migrant labourers took place from malaria-endemic areas of the ex-Soviet republics Azerbaijan, Kirgizstan, Tajikistan, Uzbekistan where two types of *P. vivax* prevail. Presence of efficient malaria vectors in Moscow – *Anopheles messeae* and *An. maculipennis*, the breeding sites of which are temporary collections of water, ponds, etc., facilitated local transmission of malaria from these imported sources of infection. A sufficiently long malaria transmission season (from July to September) and appreciable vector densities (average density of anopheles larvae was 8.4/m²) further facilitated local transmission, which resulted in the occurrence of 207 indigenous cases of *P. vivax* between 2000-2008 [23]. A similar situation was observed in the territory of the Moscow oblast, where during the same period 174 indigenous cases of *P. vivax* were reported. The density of local malaria vectors (both *An. messeae* and *An. maculipennis*) was

even higher than in Moscow city (maximum density reported in in July – up to 235 adults per resting site, and larval densities up to 73/m²) [24]. Since 2009, following dramatic reduction of malaria transmission in Kirgizstan, Uzbekistan, Tajikistan and Azerbaijan, only a few sporadic cases of *P. vivax* (secondary from imported) have been registered in the Russian Federation.

4 Conclusion

This is the first officially registered case of presumably the Chesson strain of *P. vivax* imported in the Russian Federation. Potential implications of the importation of cases of ‘tropical vivax malaria’ in regions free of local malaria transmission but with high ‘receptivity’ are as follows: in the absence of adequate radical treatment with primaquine, there is a high probability of the occurrence of short-term relapses, which under favourable conditions might result in the re-establishment of local malaria transmission in areas freed of malaria. Moreover, laboratory personnel engaged in malaria diagnosis should be aware that imported cases of *P. falciparum* malaria from Southeast Asia can suppress parasites of *P. vivax* in mixed infections; detection of falciparum malaria should therefore not mean to arrest further examination of blood slides. Finally, a ready stock of primaquine should be available at all health facilities engaged in the diagnosis and treatment of malaria cases and be regularly replenished.

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