Plasmodium Vivax Malaria and Cardiac Complication

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Abstract. Plasmodium vivax (P. vivax) is known as a benign pattern of malaria. In recent years, Plasmodium vivax can also cause severe malaria infection that contributes to various manifestations in human organs. Cardiac complications associated with P. vivax malaria are rarely seen, but have recently been reported. This review aimed to identify the cardiac complication related to P. vivax malaria. Articles about cardiovascular manifestation in P. vivax malaria were collected from databases, including Google Scholar and PubMed. Relevant articles about P. vivax malaria and other severe malaria were included. Cardiac complication has occurred in malaria due to single P. vivax infection as seen in P. falciparum infection. There are only limited articles of cardiac involvement in P. vivax malaria and most of them are case reports. Myocarditis is the most common cardiovascular complication associated with severe P. vivax malaria. The key symptom that indicates a vivax malaria patient with cardiac complication is chest pain or chest discomfort especially in the substernal area. Some manifestations of cardiac related to P. vivax malaria are ventricle dilatation, decrease left ventricular ejection, hypokinesis of myocardium, change in cardiac enzyme, and ECG alterations. These clinical symptoms are emerging in young children and adult patients. Reported cases are the most typical in vivax endemic regions. The subclinical cardiovascular alteration also presents in patients with non-severe P. vivax malaria. Our review identifies a potential link between P. vivax single-infection and cardiovascular manifestations. It is essential to consider the possibility of cardiac complication in P. vivax malaria with a worsening condition. Further and more extensive studies of cardiac involvement in P. vivax malaria are required, especially in endemic areas.

Keywords: cardiac · complication · myocarditis · vivax malaria

1 Introduction

An estimated 229 million malaria cases occur in endemic countries [1]. Despite the decline in cases from the previous year, malaria remains a global health challenge. Plasmodium falciparum and P. vivax are the most prevalent species causes of human malaria infection. Plasmodium falciparum has received more attention because of its severity. However, P. vivax is the most geographically widespread parasite causing malaria and

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still a significant health problem in 49 endemic countries in 2018 [2]. Historically, P. vivax is called benign tertian malaria. In recent years, P. vivax has appeared as a new severe malaria that causes various complications in many organs [3, 4]. A prospective study in Gujarat, India, showed that severe P. vivax malaria was more common than severe P. falciparum malaria, especially in adult patients presenting with jaundice [5]. It is in accordance with Gujarat as an endemic P. vivax malaria region. The number of severe P. vivax malaria cases has also increased in the Republic of Korea from 2000 to 2016 [6]. Plasmodium vivax infection carries the same risk of causing severe malaria and death as P. falciparum infection [7, 8]. Thrombocytopenia, acute renal failure, severe anemia, shock, coma, severe malnutrition, jaundice, lien rupture, and respiratory distress are common complications of severe P. vivax malaria.

Cardiac involvement due to P. vivax malaria is extremely infrequent, but recently, a few cases have been reported about this. Though uncommon, the health professional should be aware of the possibility of fatal cardiac complications due to P. vivax malaria. Based on the available data, we identified the cardiac involvement in P. vivax malaria.

2 Method

Articles about cardiovascular manifestation in P. vivax malaria were collected from databases, including Google Scholar, and PubMed. We used the keywords vivax, myocarditis, carditis and cardiac with a time limit of 20 years. We obtained 16 articles consisting of 14 case report articles and two prospective research articles. The inclusion criteria were infection by Plasmodium vivax, which caused cardiac complications. Exclusion criteria were co-infections by others plasmodium or non-plasmodium. Based on the inclusion and exclusion criteria, 14 articles were reviewed/.

3 Resut and Discussion

3.1 The Cardiac Manifestation of P. Vivax Malaria

Cardiovascular manifestations are usually associated with severe P. falciparum malaria. Cardiac involvement due to P. vivax malaria has been reported in some endemic countries, but its prevalence is unknown. A prospective study [9] showed cardiac complication in 17% of severe malaria cases (9 P. falciparum, 5 P. vivax and 3 mixed) with a 45.

45% mortality rate. In this study, the most common cardiac manifestation was circulatory failure followed by congestive heart failure and pulmonary edema.

Reports on cardiovascular manifestations in single P. vivax infection are very few and most of them are case reports. From the case reports, myocarditis was the most common cardiac manifestation due to severe single P. vivax infection, which occurs in children and adults (Table 1). Moreover, the other cardiac manifestations that can occur in P. vivax malaria are hypotension, conductive abnormalities, myopericarditis, heart failure, acute myocardial infarction and pulmonary edema [9]. The common symptoms indicating these cardiac complications are chest pain in the substernal area, tachycardia and shortness of breath. Most cases that have any abnormality result in ECG and

Table 1. Case reports of cardiac complication due to single P. vivax malaria

No	Reference	Location	Patient characteristic	Cardiac manifestation	Electrocardiogram and Echocardiogram Results	Elevated cardiac enzymes	Severe thrombocytopenia
1.	[21]	South Korea	27 y.o, women	myocarditis	nonspecific ST-T change in the II, III, and AVF leads, LVEF[a] 61%,,hypokinesia motion of the inferior wall.	yes	yes
2.	[22]	India	17 y.o, man	myocarditis	Tachycardia and AV block; hypokinesis of myocardium with compromised LV systolic function, LVEF[a] 44%	yes	-
3.	[23]	India	19 y.o, women	myocarditis	global left ventricular hypokinesis with LVEF 40%.	no	yes
4.	[24]	India	20 y.o, man	Myocarditis,	ST-T changes in leads II, III, aVF and V4-V6; LVEF 25%	no	
5.	[25]	Brazil	35 y.o, man	Myocarditis, pulmonary edema	left ventricular dilatation during systole, diffuse hypokinesis and mild mitral regurgitation, LVEF[a] 47%	no	yes
6.	[26]	India	20 y.o, women	Myocarditis, heart failure	sinus tachycardia; severe global hypokinesis, LVEF 30%		yes
7.	[27]	India	27 y.o, pregnant women	Myopericarditis	Sinus tachycardia, ST depression andT inversion in V2-V6; LVEF[a] 45%	no	yes
8.	[28]	India	22 y.o, man	Myocarditis and heart failure	Sinus tachycardia, T inversion in inferior lead; LVEF 25–30%	no	no
9.	[29]	India	55 y.o, man	AMI2	ST segment elevation in leads V2 -V6; LVEF[a] 64%	no	yes
10.	[30]	India	22 y.o, man	myocarditis,	Sinus exit block; suggestive of LVEF 25%	no	yes
11.	[31]	Emigrant Pakistan	56 y.o, man	myocarditis	sinus tachycardia, nonspecific ST and T-wave changes; diffuse hypokinesis with LVEF[a] 22%.	-	no

[a] LVEF = left ventricle ejection fraction; [2] = acute myocardial infarction

echocardiogram examination. A few cases have elevated cardiac serum enzymes. Similarly, Gunther et al. assessed only 0.6% elevated Troponin T as a sign of myocardial damage in P. falciparum malaria [10].

Myocarditis refers to an inflammation disease in myocardium. Acute myocarditis has a variety of clinical manifestations, ranging from asymptomatic to congestive heart failure and sudden death. Myalgia, palpitation, fever and dyspnea are nonspecific symptoms of myocarditis. The histological examination from myocardium specimen or an autopsy required to confirm myocarditis, but it is rarely performed. However, clinically suspected myocarditis can be determined if it meets at least one clinical presentation and one diagnostic criterion without a previous history of cardiovascular disease [11]. Clinical presentation of suspected myocarditis: acute chest pain or pericarditis, new-onset (< 3 months), chronic onset (> 3 months), worsening dyspnea, palpitation, unexplained arrhythmia, syncope, and unexplained cardiogenic shock. The diagnostic criteria for suspected myocarditis are new abnormal EKG or Holter stress testing, elevated cardiac enzyme (Troponin I and Troponin T), structural and functional abnormalities of echocardiogram, and tissue characterization by cardiac imaging.

In these case reports (Table 1), the cardiac manifestations were reversible with a variety of recovery periods. However, early detection and appropriate treatment in these cardiac complications are needed to prevent worsening conditions. The severity of cardiovascular complication in P. vivax malaria also leads to a more extended hospital stay. The severe P. vivax malaria could be life-threatening and requires Intensive Care Unit (ICU) facilities [12]. A prospective study showed asymptomatic cardiac involvement in 26 non-severe P. vivax malaria patients compared to the control group. These cardiovascular changes are reversible after seven days of illness [13]. Although other studies are not yet available, this limited result provides evidence of a possible cardiac involvement in the pathophysiology of P. vivax infection. Currently, there is no available data about the associated cardiac complication in P. vivax malaria with other factors such as age, previous history of malaria, the severity of disease, and presence of comorbid. There is an excellent opportunity for further research about the cardiac involvement of P. vivax malaria, especially in endemic countries. More epidemiological studies are also needed to estimate the prevalence of severe P. vivax malaria [14].

3.2 Pathogenesis of Cardiac Involvement in P. Vivax Malaria

The pathogenesis of cardiac involvement in malaria is poorly understood. There are several hypotheses associated with the mechanism of cardiac involvement in severe malaria. The possible cause of cardiac involvement in P. vivax malaria is microvascular obstruction due to cytoadherence, rosette formation, cytokine inflammatory, and metabolic impairment.

Microcirculation impairment occurs due to the cytoadherence process which obstructs capillaries by infected RBCs. The blockade of capillaries results in ischemic cardiomyopathy. Previously, this capability of the cytoadherence mechanism was only known by P. falciparum. However, few autopsy studies have reported vivax-infected RBCs microcirculation accumulation of vivax-infected RBCs [15]. The ex vivo studies demonstrated the cytoadherence phenomena of vivax-infected RBCs on placental tissue and human lung endothelial cells although this cytoadherence was lower than falciparum-infected RBCs [16]. The affinity of cytoadherence of vivax-infected RBCs is as strong as falciparum-infected RBCs after the adhesion process [17].

Rosettes are proliferation of erythrocytes that result from the binding of other non-infected RBC with infected-RBCs. Rosettes are known as a mechanism of P. vivax to avoid the phagocytosis process [18] and are closely associated with increased rigidity of vivax-infected RBCs [19]. It possibly contributes to microvascular obstruction [15].

Production of cytokines inflammatory in P. vivax infection is more significant than P. falciparum infection. Cytokines mediated endothelial activation has been suggested to contribute to microvascular obstruction and end-organ pathology [15]. This mechanism might be associated with possible cardiac ischemia in P. vivax malaria [20]. Severe P. vivax malaria with thrombocytopenia and microvascular thrombosis is also possible to contribute to microvascular obstruction [15].

Although this pathogenesis is unclear, P. vivax has been shown to contribute to severe malaria. Future research is needed to identify the clarity of this pathogenesis.

4 Conclusion

This present review identifies severe P. vivax malaria as having the same risk of cardiac complication as P. falciparum malaria. The substernal chest pain and shortness of breath became a crucial key to consider a possibility of cardiac complication in severe P. vivax malaria. Further and more extensive studies of cardiac involvement in P. vivax malaria are required, especially in endemic areas.

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References

1. World malaria report 2020. World Malaria Report 2020, vol. 73, no. 1. 1997.
2. World malaria report 2019, World malaria report 2019. 2019.
3. M. Matlani, L. P. Kojom, N. Mishra, V. Dogra, and V. Singh, "Severe vivax malaria trends in the last two years: a study from a tertiary care centre, Delhi, India," Ann. Clin. Microbiol. Antimicrob., vol. 19, no. 1, pp. 1–11, 2020, doi: https://doi.org/10.1186/s12941-020-00393-9.
4. K. Saravu, K. Rishikesh, A. Kamath, and A. B. Shastry, "Severity in Plasmodium vivax malaria claiming global vigilance and exploration - A tertiary care centre-based cohort study," Malar. J., vol. 13, no. 1, 2014, doi: https://doi.org/10.1186/1475-2875-13-304.
5. A. R. Anvikar et al., "Clinical and epidemiological characterization of severe Plasmodium vivax malaria in Gujarat, India," Virulence, vol. 11, no. 1, pp. 730–738, 2020, doi: https://doi.org/10.1080/21505594.2020.1773107.
6. S. Y. Park et al., "Severe vivax malaria in the Republic of Korea during the period 2000 to 2016," Travel Med. Infect. Dis., vol. 30, no. March, pp. 108–113, 2019, doi: https://doi.org/10.1016/j.tmaid.2019.04.013.

7. J. Kevin Baird, "Evidence and implications of mortality associated with acute plasmodium vivax malaria," Clin. Microbiol. Rev., vol. 26, no. 1, pp. 36–57, 2013, doi: https://doi.org/10.1128/CMR.00074-12.
8. C. Naing, M. A. Whittaker, V. Nyunt Wai, and J. W. Mak, "Is Plasmodium vivax Malaria a Severe Malaria?: A Systematic Review and Meta-Analysis," PLoS Negl. Trop. Dis., vol. 8, no. 8, 2014, doi: https://doi.org/10.1371/journal.pntd.0003071.
9. K. C. Nayak, S. L. Meena, B. K. Gupta, S. Kumar, and V. Pareek, "Cardiovascular involvement in severe vivax and falciparum malaria," J. Vector Borne Dis., vol. 50, no. 4, pp. 285–291, 2013.
10. A. Günther, M. P. Grobusch, H. Slevogt, W. Abel, and G. D. Burchard, "Short communication: Myocardial damage in falciparum malaria detectable by cardiac troponin T is rare," Trop. Med. Int. Heal., vol. 8, no. 1, pp. 30–32, 2003, doi: https://doi.org/10.1046/j.1365-3156.2003.00978.x.
11. B. Bozkurt et al., Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies: A Scientific Statement from the American Heart Association, vol. 134, no. 23. 2016.
12. A. M. Quispe et al., "Plasmodium vivax hospitalizations in a monoendemic malaria region: Severe vivax malaria?," Am. J. Trop. Med. Hyg., vol. 91, no. 1, pp. 11–17, 2014, doi: https://doi.org/10.4269/ajtmh.12-0610.
13. A. C. Alencar-Filho et al., "Cardiovascular changes in patients with non-severe Plasmodium vivax malaria," IJC Hear. Vasc., vol. 11, pp. 12–16, 2016, doi: https://doi.org/10.1016/j.ijcha.2016.03.004.
14. B. A. Rahimi, A. Thakkinstian, N. J. White, C. Sirivichayakul, A. M. Dondorp, and W. Chokejindachai, "Severe vivax malaria: A systematic review and meta-analysis of clinical studies since 1900," Malar. J., vol. 13, no. 1, pp. 1–10, 2014, doi: https://doi.org/10.1186/1475-2875-13-481.
15. N. M. Anstey, B. Russell, T. W. Yeo, and R. N. Price, "The pathophysiology of vivax malaria," Trends Parasitol., vol. 25, no. 5, pp. 220–227, 2009, doi: https://doi.org/10.1016/j.pt.2009.02.003.
16. B. O. Carvalho et al., "On the cytoadhesion of plasmodium vivax-infected erythrocytes," J. Infect. Dis., vol. 202, no. 4, pp. 638–647, 2010, doi: https://doi.org/10.1086/654815.
17. A. C. de Alencar Filho, M. V. G. de Lacerda, K. Okoshi, and M. P. Okoshi, "Malaria and vascular endothelium," Arq. Bras. Cardiol., no. 2, pp. 165–169, 2014, doi: https://doi.org/10.5935/abc.20140088.
18. L. Albrecht et al., "Rosettes integrity protects Plasmodium vivax of being phagocytized," Sci. Rep., vol. 10, no. 1, pp. 1–11, 2020, doi: https://doi.org/10.1038/s41598-020-73713-w.
19. R. Zhang et al., "Rheopathologic Consequence of Plasmodium vivax Rosette Formation," PLoS Negl. Trop. Dis., vol. 10, no. 8, pp. 1–10, 2016, doi: https://doi.org/10.1371/journal.pntd.0004912.
20. A. Dinkar, J. Singh, and S. Singh, "Acute myocardial infarction associated with severe Plasmodium vivax malaria," J. Vector Borne Dis., vol. 57, no. 2, pp. 193–196, 2020, doi: https://doi.org/10.4103/0972-9062.310872.
21. S. A. Kim, E. S. Kim, M. Y. Rhee, S. Il Choi, H. J. Huh, and S. L. Chae, "A case of myocarditis associated with plasmodium vivax malaria," J. Travel Med., vol. 16, no. 2, pp. 138–140, 2009, doi: https://doi.org/10.1111/j.1708-8305.2008.00292.x.
22. K. Gantait and I. Gantait Nayak, "Vivax malaria complicated by myocarditis," J. Assoc. Physicians India, vol. 61, no. DEC, pp. 944–945, 2013.
23. S. Ahmad, M. Dhar, S. Bishnoi, N. Shirazi, and N. K. Bhat, "Acute myocarditis in vivax malaria: An extremely rare complication," Trop. Doct., vol. 43, no. 1, pp. 35–36, 2013, doi: https://doi.org/10.1177/0049475512473601.

24. N. Gupta and S. Sahoo, "Plasmodium vivax induced myocarditis: A rare case report," Indian J. Med. Microbiol., vol. 31, no. 2, pp. 180–181, 2013, doi: https://doi.org/10.4103/0255-0857.115224.
25. A. Ventura et al., "Case Report Myocarditis associated with Plasmodium vivax malaria : a case report," Rev. Soc. Bras. Med. Trop., vol. 47, no. 6, pp. 810–813, 2014.
26. N. Nasir, S. Lalani, Z. A. Samani, and A. Almas, "Myocarditis complicating Plasmodium vivax malaria," J. Coll. Physicians Surg. Pakistan, vol. 24, no. November 2018, pp. S96–S98, 2014.
27. A. Sonambekar, N. Gupta, M. Agarwal, S. Rajpal, and A. Aggarwal, "Plasmodium Vivax Associated Myocarditis," Eur. J. Case Reports Intern. Med., vol. 1, no. 1, 2014, doi: https://doi.org/10.12890/2014_000039.
28. N. Dev, A. K. Gadpayle, J. Sankar, and M. Choudhary, "An unusual case of heart failure due to Plasmodium vivax infection with a favorable outcome," Rev. Soc. Bras. Med. Trop., vol. 47, no. 5, pp. 663–665, 2014, doi: https://doi.org/10.1590/0037-8682-0087-2014.
29. I. Dasgupta, J. Das, G. D. Reddy, and I. Mitra, "Unusual presentation of Plasmodium vivax malaria mimicking acute myocardial infarction – a case report," vol. 3, no. 1, pp. 589–592, 2015.
30. S. Kumar, S. Behera, and A. A. Khan, "Malarial Myocarditis: A Rare Complication of Plasmodium vivax: Case Report," J. Clin. Case Reports, vol. 07, no. 03, pp. 8–9, 2017, doi: https://doi.org/10.4172/2165-7920.1000945.
31. F. Y. Khan, "Imported Plasmodium vivax malaria complicated by reversible myocarditis," J. Fam. Community Med., vol. 26, no. 3, pp. 232–234, 2019, doi: https://doi.org/10.4103/jfcm.JFCM_78_19.