Original Article

A Case Series Report of Unusual Presentations of Clinical Plasmodium Vivax Infection in District Bannu and Adjacent Areas

Clinical Plasmodium Vivax infection

Raza Muhammad Khan and Asmatullah Khan

ABSTRACT

Objective: The objective of this study was a case series report of unusual presentations of clinical Plasmodium Vivax infection in district Bannu and adjacent areas.

Study Design: Descriptive, case series.

Place and Duration of Study: This study was conducted at the Department of Medicine, DHQ Teaching Hospital (DHDTH) Bannu, and Khyber Pakhtunkhwa. Study was carried out for a period of 12 months, from April 2016 to April 2017.

Materials and Methods: Data were collected from 100 patients, who were having clinical vivax malaria but negative thick and thin smear, presented with unusual symptoms, signs and laboratory findings, from April 2016 to April 2017.

Results: Out of 100 patients, 41 patients were males (41%) and 59 (59%) were females. All of these were having negative thick and thin smear for vivax malaria. Out of these, all 100 patients (100%) were having Headache and Splenomegaly (mild <4cm). 45 patients (45%) were having Arthralgia/ Myalgia (nonspecific, where no other obvious cause was found), 28 patients (28%) were having Lower Backache (especially in young patients aged <35yrs, who were non-obese with BMI <23 Kg/M2), 44 patients (44%) having Calf Muscle Pain, 21 patients (21%) having Fever on alternate day (repeated after 48hrs), 17 patients (17%) having Mild jaundice (Bilirubin >1.1mg/dl but <4mg/dl, while G6PD was normal) , 50 patients (50%) having Pallor/Anemia (Hb<10mg/dl), 9 patients (9%) having Pain Abdomen (in school going aged <15yrs), 18 patients (18%) having Sense of bitter taste in mouth, 7 patients (7%) having no fever, 32 patients (32%) having Thrombocytopenia (platelets <150,000/microL) and 39 patients (39%) having Herpes labials.

Conclusion: In our set up, Vivax malaria seems to be chronic and endemic, but undiagnosed on routine smear examination, and it has a diverse unusual clinical presentations. So it demands a high suspicion and vigilance on part of a physician for prompt diagnosis and early treatment, to decrease the disease burden and its complications

Key Words: Vivax Malaria, Unusual Presentations, Bannu.

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INTRODUCTION

Malaria is a potentially life-threatening disease. It is caused by infection with a protozoa plasmodium. It is transmitted by an infective female anopheles mosquito, a vector. Less common routes of plasmodium infection are through blood transfusion and maternal-fetal transmission. It predominantly occurs in tropical areas. It may present with fever and a wide range of symptoms.

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The 5 Plasmodium species known to cause Malaria in humans are: P falciparum, P vivax, P ovale, P malaria, and P knowlesi.[1,2,3]

These Plasmodium species can usually be distinguished by morphology on a blood smear (Thin film). Among patients with malaria, 5-7% is infected with more than a single plasmodium species.[2] Each Plasmodium species has a specific incubation period. P falciparum infection typically develops within one month of exposure, while P vivax and P ovale may emerge weeks to months after the initial infection. Also P vivax and P ovale have a hypnozoite form, so the parasite can linger in the liver for months before emerging and inducing recurrence after the initial infection. Treating the hypnozoite form with a second agent (i.e. primaquine) is necessary to prevent relapse from this latent liver stage. When P vivax and P ovale are transmitted via blood rather than by mosquito, then no latent hypnozoite phase occurs.

Each Plasmodium species has a defined area of endemicity. Those people are at risk that are living in or traveling to areas of Central America, South America,

Hispaniola, sub-Saharan Africa, the Indian subcontinent, Southeast Asia, the Middle East, and Oceania. Individuals traveling to malarial regions must educate regarding prevention strategies and prophylactic antiprotozoal medications.

Timely identification of the infecting species is extremely important, as P falciparum infection can be fatal and is often resistant to standard chloroquine treatment. P falciparum and P vivax are responsible for most new infections.

Individuals acquire this infection in an endemic area after a mosquito bite. They may develop immunity to malaria, but when they leave the endemic area may lose this protection. When return to an endemic area, they are at increased risk of developing severe malaria, if reinfected. Human immunodeficiency virus (HIV) and malaria co-infection is a significant problem across Asia and sub-Saharan Africa, where both diseases are relatively common. Malaria during the first trimester of pregnancy increases the risk for miscarriage[4]. The plasmodia cause lysis of infected and uninfected RBCs, suppression of hematopoiesis, and increased clearance of RBCs by the spleen, which leads to anemia as well as splenomegaly. Over time, malaria infection may also cause thrombocytopenia. Splenic rupture may be associated with P vivax infection secondary to splenomegaly resulting from RBC sequestration. P vivax infects only immature RBCs, leading to limited parasitemia. The sickle cell trait (hemoglobin S), thalassemia's, hemoglobin C, and glucose-6-phosphate dehydrogenase (G-6-PD) deficiency are protective against death from P falciparum malaria. The sickle cell trait is more protective than the other 3. Individuals with hemoglobin E may be protected against P vivax infection.[5]

Worldwide, an estimated 300-500 million cases occurring annually[6]. In 2010, there were 1691 cases, representing a 14% increase from 2009 and a 30% increase from 2008[7]. Internationally, malaria is responsible for approximately 1-3 million deaths per year, and 80-90% of the deaths each year are in rural sub-Saharan Africa[6]. Malaria is the world's fourth leading cause of death in children younger than age 5 years.

Like in other parts of the world, malaria is a leading cause of morbidity and mortality in Pakistan. It is one of the 6 priority communicable diseases posing threat to the health of millions. With one million estimated and 300,000 confirmed reported cases each year, Pakistan has been grouped with Afghanistan, Somalia, Sudan and Yemen accounting for more than 95% of the total regional malaria burden. Pakistan is among seven countries of the WHO Eastern Mediterranean Region, sharing 98% of the total regional malaria burden[8]. An estimated 98% of Pakistan population (205 million) is at varying risk, while around 60% (123 million) population at high risk for malaria. In this country, Malaria with Plasmodium vivax is more common (88%), while malaria with Plasmodium falciparum is seen only during rainy seasons or post rain, accounting for 12% of the malaria burden[9]. According to Pakistan Annual Malaria Report 2019, during 2018, highest number of cases was reported from Sindh, 34.5% (129,085), Khyber Pakhtunkhwa, 31.0% (115,995), followed by Tribal Districts, 17.6% (65,853)[11]. Highest numbers of the reported cases were P. Vivax (PV) 84.0% (314,574).

No local data is available regarding clinical vivax malaria with unusual presentations, in out set up. This is a randomized study at smaller scale which can later be applied at larger scale. Persons living in areas of malaria endemicity may develop partial immunity to infection with time and repeated exposure. This limited immunity reduces the frequency of symptomatic malaria and also reduces the severity of infection. They also have unusual presentations. Malaria is preventable and treatable. However, the lack of prevention and treatment due to poverty, terrorism, military operations, and other economic and social instabilities in these endemic areas results in a large number of undiagnosed cases. So the early diagnosis and prompt treatment of malaria is not satisfactory in Khyber Pakhtunkhwa, in our setup and adjacent FATA areas.

Keeping this in mind, the following study was designed to report the unusual presentations of clinical vivax malaria in our community**.**

MATERIALS AND METHODS

Descriptive, case series study, Department of Medicine, DHQ Teaching Hospital Bannu KPK, and 12 months from April 2016 to April 2017.

100 patients, all having headache and mild splenomegaly <4cm, but no obvious cause, and smear for MP was negative. Consecutive, Non-probability Sampling. All those patients complaining of Headache, having mild splenomegaly <4cm below left costal margin, with negative MP smear, of Either gender, aged above 12 and under 60 years, also having 2 or more of the following unusual presentations of Vivax Malaria: 1)-Arthralgia/ Myalgia (nonspecific, where no other obvious cause was found), 2)-Lower Backache (esp. in young patients aged <35yrs, who were non-obese with BMI <23 Kg/M2), 3)- Calf Muscle Pain,4)-Fever on alternate day (repeated after 48hrs), 5)-Mild Jaundice (Bil >1.1mg/dl but <4md/dl, while G6PD was normal), 6)-Pallor/Anemia (Hb<10mg/dl), 7)-Pain Abdomen (in school going aged <15yrs), 8)-Sense of bitter taste in mouth, 9)-No fever,10)-Herpes Labials is, 11)-Thrombocytopenia Platelets (<150,000/microL) Those patients who were not filling the inclusion criteria, have taken standard dose of antimalarial, G6PD deficient, patients terminally ill, and patients who were not willing to be included in study, and patients mentally retarded were not included because, as they were either already treated, would not benefit from future planned treatment or would give recall bias. If

included in the study, these would act as confounders to introduce bias in the study results. The study was conducted after approval from hospitals ethical and research committee/ board. All the patients who were meeting the inclusion criteria, as per operational definitions, presented to the Department of Medicine, DHQ Teaching Hospital Bannu, through emergency or OPD, were included in the study. All patients were first counseled for interview. The purpose and benefits of the study were explained to all patients, and a written informed consent was obtained from all who agreed to participate in the study. A detailed medical history was taken from all the patients, regarding duration and pattern of disease and its various unusual symptoms. Then these patients (study population) were examined for Temperature, Anemia, Jaundice, Herpes labials and splenomegaly, these patients were investigated for Hb%, platelets count, and Bilirubin level (and if >1.1mg/dl then G6PD estimation) from hospital lab, and their status noted on flow sheet as data collection tool having all variables of interest.

All the patients were categorized in various groups based on cluster of unusual presentations. All the information including name, age, gender, address, disease pattern, various symptoms, signs and lab values were recorded in that pre- designed Performa. Only a complete Performa was subjected to analysis. Strict exclusion criteria were applied to control confounders and bias in the study results. Data obtained was entered into SPSS version 23 and analyzed in descriptive statistics. Mean ± SD were calculated for numerical/ quantitative variables like age. Frequencies and percentages (%) were calculated for categorical/ qualitative variables such as gender, disease pattern and various unusual presentations. These were stratified among age and gender to see the effect modifiers. All results were presented in the form of tables, charts**.**

RESULTS

A total of 100 patients with clinical vivax malaria were included in the study. Out of these 100 patients, 41 patients were males (41%) and 59 (59%) were females, with M/F ratio of 1.0: 1.44.

Table No.1: Age distribution of Study population (N=100)

	Total patients (N)	Range	Min. (yrs)	Max.	Mean (years)	Std. Deviation
Age in Yrs	100	46	13	59	32.78	12.695

Table No. 2: Gender Distribution of study Population (N=100)

		Frequency	Percent
Gender	Male	41	41.0
	Female	59	59.0
	Total	100	100.0

Table No. 3 Percentages of Various Unusual Presentations of Vivax Malaria (N=100):

Sign& symtopms		Arthra Liga / Myalgia (%)	Lower Backache (%)	Calf Muscle pain (%)	Fever On Alternate Day (%)	Mild Jaundice (%)	Pallor Anemia (%)	Pain Abdoen (%)	Sense of Bitter Taste in Mouth (%)	No Fever (%)	Thrombo-cytopenia (%)	Herpes labials (%)
	Yes	45	28	44	21	17	50	9	18	7	32	39
	No	55	72	56	79	83	50	91	82	93	68	61
	Total	100	100	100	100	100	100	100	100	100	100	100

Table No. 4: Age (in Years) and Pain Abdomen/Lower Back Ache association (n=100)

		Pain Abdomen		Lower Back Ache	
		Yes	No	Yes	No
Age (in years)	<15	9	3	3	9
	16-34	0	48	22	26
	>35	0	40	3	37
Total		9	91	28	72

Their age ranged between 13 and 59 years, and the mean age was 32.78±12.695 years. All of these were having negative thick and thin smear for vivax malaria. Out of these, all 100 patients (100%) were having Headache and Splenomegaly (mild <4cm). 45 patients (45%) were having Arthralgia/ Myalgia (nonspecific, where no other obvious cause was found), 28 patients (28%) were having Lower Backache (especially in young patients aged <35yrs, who were non-obese with BMI <23 Kg/M2), 44 patients (44%) having Calf Muscle Pain, 21 patients (21%) having Fever on alternate day (repeated after 48hrs), 17 patients (17%) having Mild jaundice (Bilirubin >1.1mg/dl but <4mg/dl, while G6PD was normal), 50 patients (50%) having Pallor/Anemia (Hb<10mg/dl), 9 patients (9%) having Pain Abdomen (in school going aged <15yrs), 18 patients (18%) having Sense of bitter taste in mouth, 7 patients (7%) having no fever, 32 patients (32%) having Thrombocytopenia (Platelets <150,000/micro L) and 39 patients (39%) having Herpes Labials. So all of these patients were having headache, mild splenomegaly and 2 or more of above unusual clinical presentations of vivax malaria, having negative thick and thin smear for vivax malaria, and they all responded to antimalarial drugs. (Tables 1-4).

DISCUSSION

A total of 100 patients with clinical vivax malaria were included in this study. Out of these 100 patients, 41 patients were males (41%) and 59 (59%) were females. All of these were having negative thick (quantitative) and thin (qualitative) smear for vivax malaria on routine examination. Out of these, all 100 patients (100%) were

having Headache, Splenomegaly (mild <4cm), and 2 or more of the unusual clinical presentations of vivax malaria, so they were treated as clinical vivax malaria, and they all responded to antimalarial drugs. The following unusual clinical presentations noted, were present in different percentages and overlap pattern:
1**)**-Arthralgia/ Myalgia (nonspecific, where no other obvious cause was found), 2**)**-Lower Backache (especially in young patients aged <35yrs, who were non-obese with BMI <23 Kg/M2), 3**)**-Calf Muscle Pain, 4**)**-Fever on alternate day (repeated after 48hrs), 5**)**-Mild Jaundice (Bil >1.1mg/dl but <4md/dl, where G6PD was normal), 6**) -** Pallor/Anemia (Hb<10mg/dl), 7**)**-Pain Abdomen (especially in school going, aged <15yrs), 8)-Sense of bitter taste in mouth, 9**)**-No fever, 10**)**-Herpes Labialis,11**)**-Thrombocytopenia (Platelets <150,000/ microL). Their percentages are shown in table No: 3. The Pain Abdomen in 9 patients (9%), was more in school going young patients (all 9 patients), while Lower Backache in 28 patients (28%) ,was noted especially in young patients aged <35yrs, who were non-obese with BMI <23 Kg/M2 (in 25 patients out of 28). This is shown in table no: 5.
It showed that vivax malaria seems more common, chronic and endemic here, but undiagnosed on routine smear examination and having diverse unusual clinical presentations. So they are left untreated and they have chronic and vague symptoms. The possible reasons of this high prevalence in our setup are low quality smear examination in labs, partial and incomplete antimalarial doses, and low level of suspicion on part of a treating physician. All these patients were started on standard doses of antimalarial and they responded well.
This study was a preliminary randomized study in this area and on small scale which can later be applied at larger scale. It presents 100 clinical vivax malaria patients, both out patients and in-door patients, who were aged 13 and 59 years, and the mean age was 32.78±12.695 years. All of them were smear negative, but having headache and mild splenomegaly, plus 2 or more of unusual clinical presentations of vivax malaria, and all of them responded to standard dose of antimalarial. It showed than vivax malaria seems here endemic, chronic but undiagnosed, though it can be easily early diagnosed and promptly treated to decrease disease burden and prevent complications. This was because of lack of awareness/ education on part of the patients, lack of good quality smear examination in labs, partial and incomplete antimalarial doses and low level of suspicion on part of a treating physician**.**

CONCLUSION

This study has demonstrated that patients with clinical vivax malaria were undiagnosed on smear, but having other unusual presentations in our set up, where it seems endemic and chronic. It was because of low quality smear examination in labs, partial and incomplete antimalarial doses and low level of suspicion on part of a treating physician. Therefore, all health care providers should counsel and educate the patients, regarding preventive measures against malaria infections, screen these patients for malaria, and if suspected to be infected with Plasmodium vivax, then promptly treat them with standard antimalarial with proper doses, to prevent its complications and decrease disease burden. It is essential for physicians caring these patients to be aware and alert for unusual presentations of vivax malaria for early diagnosis and prompt treatment**.**

Author's Contribution:

Concept & Design of Study:	Raza Muhammad Khan
Drafting:	Asmatullah Khan
Data Analysis:	Raza Muhammad Khan
Revisiting Critically:	Raza Muhammad Khan Asmatullah Khan
Final Approval of version:	Raza Muhammad Khan

Conflict of Interest: The study has no conflict of interest to declare by any author.

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