Peripheral Blood Count Abnormalities and Skin Manifestations Among Patients with Hepatitis in Gestation

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Abstract

Introduction: Pakistan is the 6th most populist country in approximately 108 million. Prevalence of HCV infection reported in various studies by the Pakistani authors ranges from 2-14%. From the pathogenetic point of view in hepatitis, it is believed that disorders of primarily immunocomplex genesis generate skin vasculitis, Raynaud's syndrome, nodular periarteritis, and mixed cryoglobulinemia. Pregnancy is a period in which more than 90% women have significant and complex skin changes that may have great impact on the woman's life. These changes are mainly due to a number of complexes endocrinological, immunological, metabolic, and vascular changes occurring in pregnancy that may influence the skin in various ways.

Objective: To evaluate the burden of thrombocytopenia along with skin manifestations and hepatitis in gestation.

Methods: This was cross sectional study conducted over a period of 2 years. Study was conducted at hepatitis OPD of tertiary care hospitals of Karachi. Pregnant women of age ranging between 29-35 years and gestational age between 28-38 weeks were selected. Linear regression analysis was performed to determine the independent relationship between the dependent variable of platelets, p value <0.05 was considered statistically significant. The study protocol was approved by ethical review committee.

Results: Frequency of thrombocytopenia was 68.8%. Majority of patients (36.2%) were mild thrombocytopenic. The regression coefficient, b (Unstandardized Coefficients), of AST indicates if AST increases by 1 SD (standard deviation) platelets level will decrease by 105.88 SD units. The variable of 'AST' is the predictor of platelets level, with a Beta

(Standardized Coefficients) of 0.65, a moderate effect size which was statistically significant.
Conclusion: High frequency of association between thrombocytopenia and hepatitis-C. Disorders of primarily immunocomplex genesis generate skin vasculitis, and mixed cryoglobulinemia. Changes with pigmentation are among the most pronounced skin changes during pregnancy.

Keywords: Thrombocytopenia, Cutaneous infection, Hepatitis

Introduction

Pakistan is the 6th most populist country in approximately 108 million. Prevalence of HCV infection reported in various studies by the Pakistani authors ranges from 2-14%.[1] Approximately 10 million people in Pakistan are infected with HCV with prevalence rate varies between the four provinces; prevalence rate reported in Punjab is 6.7%, in Sindh 5%, in Baluchistan 1.5%, and in Khyber Pakhtunkhwa1.1%.[2,3]

The World Health Organization (WHO) had estimated that 180 million people are infected with Hepatitis C virus in 2009.[4] HCV principally replicates in the liver and its replication has been reported in peripheral blood cells, causing thrombocytopenia which has been noted in patients with HCV infection.[5-7] Thrombocytopenia in patients with hepatitis C may be the result of several factors: bone marrow inhibition, decrease liver thrombopoietin production, hypersplenismsecondary to portal hypertension, autoimmune mechanism and bone marrow suppression due to HCV.[8,9]

From the pathogenetic point of view in hepatitis, it is believed that disorders of primarily immunocomplex genesis generate skin vasculitis, Raynaud's syndrome, nodular periarteritis, and mixed cryoglobulinemia.[10] Cutaneous lesions associated with liver disease may result from immune-complex-mediated vascular injury, proven histologically by vascular deposits of immunoglobulin's, complement, and fibrin in the skin, as well as hypocomplementemia, circulating immune complexes, and mixed cryoglobulinemia.[11] Regarding bullous pemphigoid, hepatitis B surface antigen (HBsAg) seems to have a trigger function for inducing nonspecific immune reactivation or by stimulating specific antibody production that may cross-react with BP antigens.[12] Pregnancy is a period in which more than 90% women have significant and complex skin changes that may have great impact on the woman's life.[13] These changes are mainly due to a number of complex endocrinological, immunological, metabolic, and vascular changes occurring in pregnancy that may influence the skin in various ways.

Here is an ill-defined heterogeneous group of dermatoses that are specific to pregnancy and seen only in pregnancy and/or the postpartum period referred to as specific dermatoses of pregnancy. Hyperpigmentation is most common presentation of pregnancy due to elevated serum levels of MSH, estrogen or progesterone. Chloasma or melasma is also known as mask of pregnancy, seen in 45-75% of women in pregnancy presented with irregular sharply demarcated brownish pigmentation of the face mainly over Centro facial or malar region.[14] Striae distensae (striae gravidarum) develop in up to 90% of women during the sixth and seventh month of pregnancy and are partial tears in the structures of the skin, which appear as reddish or bluish depressed streaks, usually on the abdomen but also on the breasts and thighs.[15] Capillary hemangioma is seen in about 5% of women during pregnancy especially in the head and neck region. Atopic eruption of Pregnancy is evident by dermatoses in pregnancy, accounting for 50% of patients, starts

early in 75% before the third trimester, and tends to recur in subsequent pregnancies. Obstetric cholestasis is manifested by pruritus in pregnancy with or without laboratory evidence of cholestasis. Incidence is 1 in 50 to 5,000 pregnancies.[16] The aim of this study was to evaluate the burden of thrombocytopenia along with skin manifestations and hepatitis in gestation.

Objective of the Study

The objective of this study was to evaluate the burden of thrombocytopenia along with skin manifestations and hepatitis in gestation. Thrombocytopenia can interfere with diagnostic procedures such as liver biopsy and minor procedures such as tooth extraction etc. because of risk of bleeding. It can also prevent patients from successful antiviral treatment. This study will be helpful in planning further treatment strategies in patients with hepatitis and skin manifestations in gestation to prevent bleeding complications.

Materials and methods

Study design and study cases

This was cross sectional study conducted over a period of 2 years. Study was conducted at hepatitis OPD of tertiary care hospitals of Karachi. Individuals were enrolled as patients from the Clinical Bacteriology and Communicable Disease Clinics, Abbasi Shaheed Hospital, Civil Hospital and Jinnah Postgraduate Medical Center following their informed consent. The study conformed to the Helsinki Declaration and was approved by the ethical review board. Total numbers of eighty pregnant patients with diagnosed thrombocytopenia, hepatitis C or B and skin manifestations were enrolled in this study.

Sample Size: The sample size calculation was done by using the World Health Organization (W.H.O.) software for “Sample Size Calculation” edited by L. Lemeshow and S. K. Lwanga. The results of this study are valid as confirmed by sample size calculation, where α=5%, 1-β=90, P1=0.05, P2=0.10, n (sample size)=80. Pregnant women of age ranging between 29-35 years and gestational age between 28-38 weeks were selected. All the subjects were briefed about the nature of the study and an informed consent was taken.

Exclusion Criteria was patients not willing to participate in the study, diagnosed chronic liver disease patients with incomplete laboratory findings, patients attending OPD for follow up. Patient’s serum reports containing platelet count were collected. Platelet count of <150,000/μL was labeled as thrombocytopenia.10Depending on the severity of platelet reduction (normal range: 150,000 to 450,000 platelets/μL), the patients were divided into 3 groups: with severe thrombocytopenia: <50,000/μL; moderate thrombocytopenia :> 50,000/μL - <75,000 /μL and mild thrombocytopenia: >75,000 - <150,000/μL.[11,12]

Statistical analysis

Demographic profiles including name, age, gender, socioeconomic status were also noted. Data were analyzed using the software package used for statistical analysis (SPSS) for Windows (version 20; SPSS, Chicago, IL, USA). Continuous variables were presented as mean ± SD and categorical variables were presented as frequency or percentage. Linear regression analysis was performed to determine the independent relationship between the dependent variable of platelets and independent variables of AST, ALT and alkaline phosphatase and neutrophils. The relationships among the

variables were analyzed by means of Spearman's correlation. Differences were considered significant at $p<0.05$.

Results

A total of 500 patients of hepatitis were included in study and demographic profile is shown in table in Table I. Descriptive statistics of hepatic enzymes, thrombocytes and neutrophils are shown in table II. Frequency of thrombocytopenia was 55 (68.8%). According to severity, the frequency of mild thrombocytopenia was 29 (36.2%), moderate 12 (15%) and severe thrombocytopenia was 14 (17.5 %) as shown in Table II. Regression analysis and Pearson correlation between the enzymes is shown in Table III. Cutaneous manifestations in hepatitis and gestation are shown in Table IV.

Linear regression analysis

Model 1(table III)

R is 0.65 which is the multiple correlation coefficient shows a moderate correlation between the dependent variable of platelets(Vitamin B12) and independent variables of AST, ALT and Alkaline phosphatase.

R2 value represents the proportion of variance in the dependent variable of platelets that can be explained by Aspartate aminotransferase, Alanine aminotransferase and alkaline phosphatase.

Adjusted R2 shows a moderate (68%) estimate of effect size. ANOVA table shows the regression model results in a statistically significantly (p value=0.0001) better prediction of dependent variable of platelets.

The regression coefficient, b (Unstandardized Coefficients), of AST indicates if AST increases by 1 SD (standard deviation) platelets level will decrease by -105.88 SD units indicating thrombocytopenia of 105.88 SD units. The variable of 'AST' is the predictor of platelets level, with a Beta (Standardized Coefficients) of 0.65, a moderate effect size which was statistically significant.

The regression coefficient, b (Unstandardized Coefficients), of ALT indicates if ALT increases by 1 SD (standard deviation) platelets level will decrease by -8.57 SD units indicating thrombocytopenia of -8.75 SD units. The variable of 'ALT' is the predictor of platelets level, with a Beta (Standardized Coefficients) of 0.68, a moderate effect size which was statistically significant.

The regression coefficient, b (Unstandardized Coefficients), of ALP (alkaline phosphatase) indicates if ALP (alkaline phosphatase) increases by 1 SD (standard deviation) platelets level will decrease by -44.63 SD units indicating thrombocytopenia of 44.63 SD units. The variable of 'ALP' is the predictor of platelets level, with a Beta (Standardized Coefficients) of 0.25, a low effect size which was statistically significant.

Pearson's correlation matrix

A Pearson's product-moment correlation was run to assess the relationship between liver enzymes, platelets and neutrophils. Preliminary analyses showed the relationship to be linear with both variables normally distributed, as assessed by Shapiro-Wilk test ($p>0.05$), and there were no outliers. There was a strong negative correlation between AST and platelets, $r=0.73$,

$p<0.0005$ with platelets explaining 53% of the variation in platelet concentration.

There was a strong negative correlation between ALT and platelets, r=0.64, p<0.005, with platelets explaining 40% of the variation in platelet concentration (Table IV).

Study Limitation

Although the research has reached its aims, there was a limitation that needs to be mentioned. Due to time limit this research was conducted only on a small size of population who attended the department. As there was no control group this limits the strength of paper.

Ethical Considerations

The study protocol was approved by ethical review committee. Written informed consent was taken from the participants before their enrolment in this study. The participants' involvement in this study was voluntary and no financial incentives were provided to any study participant.

Discussion

In this study, results shows high frequency of association between thrombocytopenia and hepatitis-C. In this study we compared relationship between liver enzymes, platelets and neutrophils in patients with hepatitis-C, that shows linear relationship between liver enzymes and platelets' which is strong negative relationship between liver enzymes and platelets predominantly ALT and AST).

Several reports from different countries (Iran, U.S.A, Turkey, Egypt) confirmed high prevalence of thrombocytopenia in hepatitis C patients. In our study proportion of thrombocytopenia was 68.8% whereas study conducted in civil hospital, Karachi Pakistan showed 53% thrombocytopenia while study of Noor-ul-Iman, Rawalpindi showed 33% thrombocytopenia. This indicates HCV infection is associated with thrombocytopenia and this can interfere with diagnostic procedures such as liver biopsy because of risk of bleeding. In meantime, practioners should consider patients for HCV infection screening with unexplained thrombocytopenia.

Often, changes with pigmentation are among the most pronounced skin changes during pregnancy. The area around your nipples might darken. The same thing can happen with the skin on your inner thighs and genitals. Patient might notice a dark line from your navel to your pubic bone. Dark patches might develop on your face, particularly along the cheek bone and upper lip. This is known as chloasma or mask of pregnancy. Although these skin changes aren't preventable, chloasma can get worse with sun exposure. Silver SG found hyperpigmentation in 75% of cases in our study it was only 34%.[17]

Stretch marks (striae) are pink, red or purple indented streaks that often appear on the abdomen, breasts, upper arms, buttocks and thighs and eventually fade to white or gray. Kroumpouzos G. found striae in 90% of cases and in our study we found in 70% of cases.[18]

Capillary hemangioma or pyogenic granuloma are small, red bumps often appear on the hands, face, and arms. Because they contain so many blood vessels, they bleed easily-often with just mild contact. This type of hemangioma is also sometimes referred to as a "pregnancy tumor" because they often appear during pregnancy, typically in the nose and mouth. Martin AG found capillary hemangioma in 5% of his study and in our study it was only 3% of cases.[19]

Atopic eruption of pregnancy the term pruritic urticarial papules and plaques of pregnancy (PUPPP) refers to a benign dermatosis that usually arises late in the third trimester of a first pregnancy. The entity previously had been reported as toxemic rash of pregnancy. Ambros-Rudolph CM found in 75% of cases and in our study it was only 37% of cases.[20]

Cholestasis of pregnancy occurs in late pregnancy and triggers intense itching, usually on the hands and feet but often on many other parts of the body. According to Cohen LM the incidence is 1 in 50 to 5,000 pregnancies. In our study it was 35% of cases.[21] Future studies should consider the possibility of incorporating a patient empowerment model which considers the patient as the most important member of the health team and care managers as key health care collaborators able to enhance and support services to patients provided by physicians in the primary health care system.[22]

Conclusion

The results of the our study shows that there is high frequency of association between thrombocytopenia and Hepatitis C. HCV infection is quite a common disease in our setup with a high morbidity. Thrombocytopenia is associated with bleeding tendency and is a common laboratory finding which can complicate various diagnostic and therapeutic procedures. In addition there are cutaneous manifestations in hepatitis in pregnant patients. Further studies are recommended to establish the relative frequency of thrombocytopenia in Hepatitis C patients in Pakistan.

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Table I: Demographic variables.

Age (years)	**Percentage (%)**
29-31	43.8
32-35	50.0
Education	
Illiterate	1.2
Primary	23.8

Secondary	28.8
Intermediate	38.8
Graduate	7.5
Monthly income	
10,000	36.2
10,000 to 20,000	53.8
more than 20,000	10.0

Table II: Descriptive statistics.

Clinical parameters	**Mean ± SD or %**
AST (micro/litre)	72.70 ± 1.70
ALT (micro/litre)	162.95 ± 1.56
ALP (micro/litre)	355.95 ± 1.87
Platelets (micro/litre)	107034.10 ± 1.65
Neutrophils (per mm^3)	1560 ± 1.7
Platelets	**%**
>75,000- <150000	36.2
50,000-74,999	15.0
<50000	17.5
150000-450000	31.2

Table III: Regression analysis. (Dependent variable: Platelets)

Model	**R**	**R Square**	**Adjusted R Square**
1	0.65	0.75	0.68
ANOVA			
Model	**Df**	**F**	**Sig.**
1	3	0.966	0.0001

Coefficients			
Model	**Unstandardized Coefficients**	**Standardized Coefficients**	**Sig.**
	b	Beta	
AST	-105.88	0.65	0.007
ALT	-8.57	0.68	0.0001
Alkaline Phosphatase	-44.63	0.258	0.002

Table IV: Pearson's correlation.

	Platelets	**AST**	**ALT**	**ALP**	**Neutrophils**
Platelets					
Pearson Correlation	1	-0.73	-0.64	-0.26	-0.015
Sig. (2-tailed)		0.0001	0.0001	0.58	0.41
N	80	80	80	80	80
AST					
Pearson Correlation	-0.73	1	0.061	0.08	-0.03
Sig. (2-tailed)	0.0001		0.78	0.62	0.83
N	80	80	80	80	80
ALT					
Pearson Correlation	0.073	0.061	1	0.105	0.0500
Sig. (2-tailed)	0.656	0.710		0.520	0.804
N	80	80	80	80	80
ALP					
Pearson Correlation	0.266	0.080	0.105	1	0.234

Sig. (2-tailed)	0.097	0.624	0.520		0.146
N	80	80	80	80	80
Neutrophils					
Pearson Correlation	-0.015	-0.33	0.040	0.234	1
Sig. (2-tailed)	0.928	0.839	0.804	0.146	
N	80	80	80	80	80

Table V: Cutaneous manifestations in hepatitis and gestation.

Henoch-Schonlein purpura	0.5%
Epidermodysplasia verruciformis, skin carcinoma	0.5%
Erythematous maculopapular and purpuric rashes	0.5%
Hypersensitivity vasculitis	3%
Essential mixed cryglobulinemia	8%
Vasculitic polyneuropathy	0.5%
Urticaria	0.5%
Lichen planus	9%
Sialadenitis	2%
Mooren Coreneal ulceration	4%
Hyperpigmentation	34%
Melasma	23%
Striae gravidarum	70%
Capillary hemangioma	3%