

Profile of Cutaneous Manifestations in Chronic Liver Disease in H. Adam Malik General Hospital Medan

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Abstract- Introduction: Chronic liver disease (CLD), caused by occurrence of abnormalities that occur continuously without healing in at least six-months. Among all extrahepatic manifestations of liver disease, skin manifestations are the most common.

Objective: To determine the description of skin disorders in CLD.

Methods: A descriptive study involving subjects with CLD (especially chronic hepatitis-B, chronic hepatitis-C, and liver cirrhosis) that attending to internal department of H.Adam Malik General Hospital Medan during October 2018. Skin disorders were diagnosed through history taking and clinical examination.

Results: Out of 42 subjects, highest proportion was male (71,4%) and highest distribution in age group of 46-55 years (30,95%). The most common causes of CLD were chronic hepatitis-B (45,2%), followed by liver cirrhosis (38,1%), and chronic hepatitis-C (16,7%). The most common cutaneous manifestations were xerosis (95,2%), pruritus (50%), and gutate hypopigmentation (33,3%). Other cutaneous manifestations included spider angioma (30,95%), hyperpigmentation (23,8%), tinea versicolor (21,4%), palpable purpura and folliculitis (16,7%), dilated abdominal veins and paper money skin (14,3%), jaundice (9,5%), prurigo of hebra and miliaria rubra (4,76%), and most rarely were lichen simplex chronicus, vitiligo, and palmar erythema (2,38%). Most subjects in this study had more than one cutaneous manifestations.

Conclusion: CLD can give a wide spectrum of cutaneous manifestations, included xerosis, pruritus, pigmentary changes, vascular changes, jaundice, and infections. This manifestations give a strong correlation between skin and liver disease, that can be a clue to the presence of underlying liver disease.

Index Terms- chronic liver disease, chronic hepatitis B, chronic hepatitis C, cutaneous manifestations, liver cirrhosis

I. INTRODUCTION

Skin is the largest organ of body where it often gives a sign of the underlying systemic diseases.^{1,2,3} Skin can also be seen as a "mirror" that can project on the surface of the body from disease conditions which covers the liver. The liver is the second largest organ, where dysfunction of the liver often causes changes that are generally associated with skin, nails and hair. This change is generally not specific because it does not indicate a specific diagnosis and can arise in diseases that do not affect the

hepatobiliary system. However, sometimes a combination of cutaneous signs and symptoms can provide clues to the underlying disease.⁴

Among all extrahepatic manifestations of liver disease, skin manifestations are the most common manifestations. Khan et al reported 30 patients (60%) of chronic hepatitis C infection, 14 patients (28%) of chronic hepatitis B infections, 2 patients (4%) of primary biliary cirrhosis and 2 patients (4%) of Wilson's disease, found extrahepatic manifestations of pigmentation (82%), Terry's nails (80%), xerosis and excoriation (72%), non-scarring hair loss from the axillary and pubic regions (64%), spider naevi and palmar erythema (36%), lichen planus (4%), vitiligo (2%) and hepatocutaneous syndrome (2%).⁵

Akhter and Said reported manifestations of chronic hepatitis B infection in the form of serum sickness-like syndrome (10-20%), polyarteritis nodosa (30-50%), and Gianotti-Crosti syndrome.⁶ While Kappus and Sterling reported extrahepatic manifestations of skin in chronic hepatitis B in the form of serum sickness-like syndrome (10-20%), glomerulonephritis (0.1-25%), polyarteritis nodosa (30-70%), and dermatologic conditions such as Gianotti-Crosti syndrome, bullous pemphigoid, lichen planus, cryoglobulinemia, and Guillain-Barré syndrome.⁷

Cutaneous lesions have been also observed in around 20-40% of patients with chronic hepatitis C infection, where skin manifestations most often include pruritus (50%), urticaria (20.8%), lichen planus (20.8%), prurigo (8.3%), palpable purpura (8.3%), cryoglobulinemia (62.5%), and porphyria cutanea tarda (20%).⁸ Garcovich et al classified cutaneous extrahepatic manifestations of chronic hepatitis C infection divided into cutaneous conditions with fixed epidemiological and pathogenetic relationship (such as mixed cryoglobulinemia, lichen planus, and porphyria cutanea tarda), cutaneous conditions with possible relationship (pruritus, nodular prurigo/lichen simplex chronicus, and necrolytic acral erythema), and cutaneous conditions with anecdotal connection (psoriasis, chronic urticaria, vitiligo, erythema multiforme, erythema nodosum, and pyoderma gangrenosum).⁹

In patients with liver cirrhosis, palmar erythema has been reported to appear in 23% of cases, spider angiomas at 33% and triads of palmar erythema, spider angiomas and white nails appear in 21% of patients. Vascular changes/lesions (palmar erythema, spider angioma, caput medusa), pruritus, coagulation defects, jaundice and pigmentation abnormalities, nail changes (nail clubbing, Terry's nail, and flat nail), and axillary and pubic hair loss.¹⁰

Some studies that assessed skin manifestations in chronic liver disease, such as liver cirrhosis, hepatitis B, and hepatitis C, are still not consistent and varying. Most studies originated from western literatures, and no one has reported the incidence of cutaneous manifestations in chronic liver disease abnormalities in Indonesia. The present study was aimed to determine the description of skin disorders in chronic liver disease.

II. METHODS

The present study was a cross-section based observational study which included 42 patients of chronic liver disease with diagnose of chronic hepatitis B, chronic hepatitis C, and liver cirrhosis during October 2018, presenting in the Department of Internal Medicine, H. Adam Malik General Hospital Medan, were enrolled in the study. All diagnoses of chronic hepatitis B, chronic hepatitis C, and liver cirrhosis had been established by internal medicine specialists. Detailed history taking and complete clinical examination was done and the clinical data was recorded as per the proforma. Skin disorders are diagnosed through history taking and clinical examination by dermatologists. This study has been approved by the Health Research Ethics Commission of the Faculty of Medicine, Universitas Sumatra Utara/H. Adam Malik General Hospital Medan.

III. RESULTS

Total 42 subjects, with the highest proportion was male (71,4%) and female (28,6%), the highest distribution in the age group of 46-55 years (30,95%) and the lowest in the age group of 26-35 years (9,52 %). The most common etiology of chronic liver disease in this study were chronic hepatitis B infections (45,2%

cases), followed by liver cirrhosis (38,1% cases) as the second most common cause, and chronic hepatitis C infections (16,7% cases).

TABLE 1. ETIOLOGY AND TYPE OF DISORDER / DISEASE (N=42)			
No..	Etiology of liver disease	Number of cases	Percentage of Cases
1.	Chronic Hepatitis B	19	45,2%
2.	Liver Cirrhosis	16	38,1%
3.	Chronic Hepatitis C	7	16,7%
Total		42	100%

The most common cutaneous manifestations observed in our study was xerosis, which was seen in 95,2% cases. The second common manifestation observed was pruritus seen in 50% cases. The third common manifestation observed was gutate hypopigmentation seen in 33,3% cases. Other cutaneous manifestations included spider angioma seen in 30,95% cases, hyperpigmentation seen in 23,8% cases, tinea versicolor seen in 21,4% cases, palpable purpura and folliculitis (16,7% cases, respectively), dilated abdominal veins and paper money skin (14,3% cases, respectively), jaundice seen in 9,5% cases, prurigo of hebra and miliaria rubra (4,76% cases, respectively), and most rarely are lichen simplex chronicus, vitiligo, and palmar erythema (2,38% cases, respectively). Most of the subjects in this study had more than one cutaneous manifestation.

TABLE 2. TYPE OF CUTANEOUS MANIFESTATIONS IN CHRONIC LIVER DISEASES			
No.	Tippe Manifestasi Kutaneus	Number of cases	Percentage of Cases
1.	Xerosis	40	95,2
2.	Pruritus	21	50
3.	Gutate hypopigmentation	14	33,3
4.	Spider angioma	13	30,95
5.	Hyperpigmentation	10	23,8
6.	Tinea versicolor	9	21,4
7.	Palpable purpura	7	16,7
8.	Folliculitis	7	16,7
9.	Dilated abdominal veins	6	14,3
10.	Paper money skin	6	14,3
11.	Jaundice	4	9,5
12.	Prurigo of hebra	2	4,76
13.	Miliaria rubra	2	4,76
14.	Lichen simplex chronicus	1	2,38
15.	Vitiligo	1	2,38
16.	Palmar erythema	1	2,38

IV. DISCUSSION

Out of 42 subjects of chronic liver disease in this study, the highest proportion was male, 30 subjects (71.4%), and 12 were women (28.6%), with the highest distribution in the age group of

46-55 years (30.95%) and the lowest in the age group of 26-35 years (9.52%). A similar study by Khan et al in Pakistan also showed that out of 50 patients, 64% were male and 36% were female.⁵ Study by Choudhury et al in India also reported that out of 100 cases, 84% were male and 16% were female, with male to

female ratio of 5.25:1.¹¹ The high prevalence of male patients was attributed to greater access to health services centers.¹²

The most common etiology of chronic liver disease in our study was chronic hepatitis B infections (45.2%), followed by liver cirrhosis (38.1%), and chronic hepatitis C infections (16.7%). A similar study by Gavli et al in India reported the most common etiology was hepatitis B (32%), followed by alcoholic liver disease (26%), hepatitis C (14%), cholestatic liver disease (8%), hepatocellular carcinoma (6%), Wilson disease (4%), and autoimmune disease (2%).¹² Study by Khan et al reported different things in Pakistan, where out of 50 patients, most common etiology was chronic hepatitis C infections (60%), followed by chronic hepatitis B infections (28%), cirrhosis primary biliary and Wilson's disease (4%).⁵ While study by Godara et al in India, reported most common etiology was malignancies (18.4%), followed by non-alcoholic steatohepatitis (18.2%), cholelithiasis (15.8%), and cirrhosis (13.9%).¹ The high incidence of hepatitis B and C is associated with the increased availability of serological examinations, screening for viral markers in liver involvements, blood transfusions, and surgical procedures.¹² In Indonesia, the proportion of patients with liver cirrhosis is most often caused by hepatitis B virus infections, alcoholic liver disease, and hepatitis C virus infections so that these etiologies of chronic liver disease were the most common.¹³

Among the various types of cutaneous manifestations in our study, xerosis was the most frequent skin lesion (95.2%), where this finding was higher than other similar studies. Similar studies by Gavli et al and Choudhury et al reported xerosis was 78% and 62%, respectively.^{11,12} Xerosis is the most common manifestation of liver dysfunction caused by prolonged nature of disease and decompensation, with malnutrition. This condition is also caused by an increase in transepidermal water loss and a decrease in skin hydration associated with ceramide and type I collagen degradation. These manifestation occurred in all types of liver diseases, the most common being cholestatic (100%), followed by hepatitis B infections (87.5%), Wilson's disease (75%), hepatocellular carcinoma (75%), hepatitis C infections (71.43%), alcoholic liver disease (50%).¹²

Pruritus was the second most common manifestation in our study, which was 50% of cases. Similar studies by Gavli et al reported pruritus in 45% cases, Choudhury et al reported pruritus in 27% cases, and Kochhar et al reported pruritus in 92% cases as the most common symptom.^{11,12,14} Pruritus in chronic liver diseases is caused by an accumulation of toxins and bile salts in the body and deposition in the skin, causing irritation and itch. Pruritus was observed in 100% cases of cholestatic disease, 50% cases of hepatitis B infection, 42.3% cases of alcoholic liver disease, 37.5% cases of hepatitis C infection, 33.33% cases of hepatocellular carcinoma, and 25% cases with unknown etiology.¹²

Pigmentary changes manifested in two forms, namely gutate hypopigmentation (33.3%) and hyperpigmentation (23.8%). Gutate hypopigmentation was most commonly found in both the upper and lower extremities, while hyperpigmentation was more common in the body, back and lower extremities. Similar studies by Gavli et al reported hyperpigmentation (40%) and guttate hypopigmentation (48%), while Choudhury et al reported hyperpigmentation (40%) and guttate hypopigmentation (24%).^{11,12} Gutate hypopigmentation had been reported in 100%

cases of hepatocellular carcinoma and autoimmune liver diseases, 75% cases with unknown etiologies, and 50% cases of alcoholic liver diseases and hepatitis B infections. Hyperpigmentation was seen in 100% cases of Wilson's disease and liver diseases with unknown etiologies, 75% cases of hepatocellular carcinoma, 42.86% cases of hepatitis C infections, 25% cases of hepatitis B infections and 25% cases of alcoholic liver diseases.¹²

In our study, manifestation of spider angiomas was found in 30.95% cases. Similar studies conducted by Khan et al and Niaz et al reported spider angiomas in 36% and 31.1% of cases, respectively.^{5,15} While study by Gavli et al reported spider angiomas only in 3% cases.¹² These vascular lesions occurred due to increased of estrogen levels, such as in cirrhosis, estrogen therapy, severe malnutrition, or during pregnancy.^{4,12}

Tinea versicolor occurred in 21.4% cases in our study. Study by Choudhury et al reported tinea versicolor in 2% cases, Rao et al reported in 14% cases, and Gavli et al reported in 29% cases.^{11,12,16} Tinea versicolor is more common in patients with decompensation, and usually associated with low socioeconomic status and poor personal hygiene.¹² Folliculitis occurred in 16.7% cases in our study. Study by Choudhury et al reported only in 2% of cases.¹¹

Palpable purpura was found in 16.7% of cases in our study. Similar study by Gavli et al reported petechiae, ecchymosis, hematoma and purpura seen in 19% cases, as a result of liver dysfunction that caused by conditions of deficiency of blood clotting factors, hypersplenism and thrombocytopenia.¹² Similar finding was also reported by Choudhury et al, where petechiae, purpura and ecchymosis appear in 22% cases.¹¹

Dilated abdominal veins and paper money skin occurred in 14.3% cases in our study, respectively. Whereas palmar erythema occurs in 2.38% cases. These three manifestations were especially found in subjects with liver cirrhosis. Studies by Niaz et al reported 6% cases of dilated abdominal veins, Choudhury et al reported 15% cases, and Gavli et al reported 36% cases of dilated abdominal veins.^{11,12,15} Dilated abdominal veins was seen in decompensated liver diseases with ascites and caused by hormonal imbalances and increased of estrogen levels.¹² Study by Godara et al reported paper money skin especially in adult patients (11.8% cases).¹ Patients with cirrhosis have many thin superficial capillaries that spread randomly to the part of upper body.^{4,17} Study by Choudhury et al reported palmar erythema in only 3% of cases.¹¹ Khan et al reported 36% cases of palmar erythema.¹⁸ And there were no cases of palmar erythema seen in the study which was conducted by Gavli et al.¹²

Jaundice occurred in 9.5% cases in our study. Jaundice was reported to be the most common manifestation (79.5%) in the study conducted by Godara et al.¹ Studies by Gavli et al reported jaundice in 33% cases, Niaz et al reported 35.4% cases of jaundice, and Choudhury et al reported 40% cases of jaundice.^{11,12,15} Jaundice is caused by an accumulation of bilirubin under the skin and clinically arises when the bilirubin levels is above 2.5 mg/dL. Jaundice was seen in 100% cases of cholestasis and autoimmune diseases.¹²

Other cutaneous manifestations in our study were prurigo of hebra (4.76%), miliaria rubra (4.76%), and most rarely were lichen simplex chronicus and vitiligo (2.38%, respectively). Study by Gavli et al reported vitiligo in only 3% cases and dermatitis in 7% cases.¹² Whereas Choudhury et al reported vitiligo in only 1%

cases and dermatitis in 10% cases.¹¹ There were no studies that reported the presence of prurigo of hebra or miliaria rubra.

V. CONCLUSION

CLD can give a wide spectrum of cutaneous manifestations, included xerosis, pruritus, pigmentary changes, vascular changes, jaundice, and infections. This manifestations give a strong correlation between skin and liver disease, that can be a clue to the presence of underlying liver disease

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