International Journal of Dermatology, Venereology and Leprosy Sciences

E-ISSN: 2664-942X
P-ISSN: 2664-9411
www.dermatologypaper.com
Derma 2021; 4(2): 09-12
Received: 05-04-2021
Accepted: 07-06-2021

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Study of pigmentary disorders of skin associated with underlying chronic liver disease

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DOI: https://doi.org/10.33545/26649411.2021.v4.i2a.83

Abstract
Background: Chronic liver Disease is associated with a plethora of cutaneous changes which occur early in the course of disease and are significant enough to be noticed by the patient and people around. Hyperpigmentation of skin is one of the most common and important change, which can be a subtle guide to a non-dermatologist towards making an early diagnosis of underlying liver disorder.
Aim: To study the clinical and histopathological profile of hyperpigmentation in patients of chronic liver disease.
Materials and Methods: A prospective, observational study was done on 110 patients with chronic liver disease of varied etiology of duration more than 6 months. A detailed interrogation of the subjects was done. Presenting complaints were recorded onset, progression and duration of complaints was noted. The chronology and pattern of hyperpigmentation with regard to liver disease was noted carefully. The severity of the liver disease was assessed using Child's criteria. Skin biopsy was done in consenting patients.
Results: Pigmentary disorders were present in 49.1% of patients. The common pigmentary disorder being hyperpigmentation present in 41.8% of patients, most of the patients belonged to the category of alcoholic liver disease (40.7%).Face was the most common site affected (39.1%).Histopathological examination of these hyper pigmented skin lesions revealed increased melanin pigment in all layers of the epidermis.
Conclusions: Hyperpigmentation is associated with underlying chronic liver disease. It occurs early in the course of disease and can provide subtle clues regarding the presence of underlying liver disease.

Keywords: Chronic liver disease, cutaneous marker, hyperpigmentation

Introduction

Chronic Liver disease (CLD) is associated with a wide range of cutaneous changes. When skin lesions occur in association with liver disease, they are generally not specific to a particular hepatic pathology, but most florid cutaneous lesions are generally seen in alcoholics. Even early abuse can result in distinctive skin changes or exacerbate existing cutaneous disorders [1].

Niederau *et al*. [2] reported an association of the frequency of several skin changes with the degree of liver fibrosis by using Univariate analysis. They concluded that the discriminative power of skin changes with regard to various grades of liver fibrosis was better than the laboratory values and the aspartate aminotransferase/platelet ratio. Altered skin colour is probably the best recognized cutaneous manifestation of hepatic disease, Jaundice being the most common finding. Both jaundice and skin pigmentation occurs in the disease states that produce extra hepatic biliary obstruction and in primary biliary cirrhosis [3]. Although jaundice is more clearly associated with CLD, the present study aims at clarifying the association of pigmentation with CLD. Both diffuse and circumscribed colour changes may occur in CLD. Blotchy circumscribed areas of dirty brown pigmentation are seen occasionally with accentuation of normal freckling and areola pigmentation.

The association between CLD and hyperpigmentation is an important subject. There is no unanimity in the data related to certain important aspects like frequency, consistency, relevance, diagnostic significance of pigmentary changes, associated with liver disease. No comprehensive studies have been carried out in this regard in Indian context except for a couple of sporadic case reports [4], despite the fact that CLD is a common problem. In view of the above facts, the present study was under taken.

The aim was to study the clinical and histopathological profile of hyperpigmentation in patients of CLD.

Materials and Methods

A prospective, observational study was carried out on 110 patients with CLD of various etiologies, attending a tertiary care hospital over a period of one year duration.

Patients with diagnosed CLD of duration more than 6 months were included in the study. A provisional clinical diagnosis was made on the basis of clinical features. All cases of CLD attending Outpatient Department of Gastroenterology from a tertiary care hospital were included in the study. Confirmation of CLD was done by relevant laboratory tests, including liver biopsy (when indicated) by the gastroenterologist and then the subjects were included in the study.

CLD was defined as a disease process of the liver involving progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis [5].

The severity of the liver disease was assessed using the Childs criteria as listed in Table 1.

Table 1: The severity of the liver disease was assessed using the Child's criteria:

	Category A	Category B	Category C
Bilirubin(mg/ml)	<2	2-3	>3
Albumin(g/dl)	>3.5	3-3.5	<3
Ascites	None	Easily controlled	Poorly controlled
Neurological disorder	None	Minimal	Advanced
Nutrition	Excellent	Good	Wasting

For all the cases. Child Pugh Score was calculated by adding scores of 5 factors. Total score ranges from 5-15.Accordingly, the patients were classified in to Child Pugh class i.e. a score of 5-6 (class A), 7-9 (class B),>10 (class C)

Patients on concomitant drug therapy which might induce pigmentary changes (e.g. antiviral, oral corticosteroids, hormonal contraceptives etc.) were excluded from the study.

For the study subjects, relevant personal data including education, salary, addictions- alcohol, smoking etc. was recorded. A history and complete physical examination of all the patients was done. This included presenting complaints regarding their onset, progression and duration. The chronology and pattern of hyperpigmentation with regard to liver disease was noted carefully. A detailed systemic examination – was carried out including – assessment of neurological status and per abdominal examination.s

Laboratory investigations included - Complete hemogram including ESR, Liver function test including S. Bilirubin – Direct and indirect, liver enzymes – SGOT, SGPT and ALP. Total protein and serum albumin, viral markers – HbsAg, HbeAg, HbeAb, IgMAntiHbcIM, HBV DNA, Anti HCV and HCV RNA were done routinely for all patients.

A Skin biopsy from the most representative lesion was done for cases with cutaneous hyperpigmentation who gave their consent for the procedure. The sections were studied under light microscopy and the histopathological changes were assessed. Special stains for melanin (Fontana Masson silver method) and iron (Perl's' Prussian blue) were also carried out.

Observations and Results

Most of the patients belonged to the age group of 41-50 years, (n= 47 or 42.7%) with the 31-40 years age group being the second largest with n= 25 (22.7%). There was a male preponderance with 80 (72.7%) male and 30 (27.3%) females. The body mass index was calculated for all patients, Majority of the patients 77(70%) had low body mass index, the average value being 19.3.Significant history of alcohol intake (i.e. more than 50 grams per day for ten years duration) was present in 62(56.4%).

Pruritus was one of the commonest symptoms in the study cohort. It was present in 38 (34.5%) of patients. Hyperpigmentation was often associated with pruritus in many patients.

Jaundice was present in only 7(6.4%) of patients of CLD On the other hand, hyperpigmentation was present in 46(41.8%) of patients. Oral mucosal pigmentation was present in 5(4.5%) patients.

Nail changes included Terry's white nails, present in 11(10%) of patients out of which 7 patients were of alcoholic liver disease and 4 were of chronic liver disease hepatitis B related(CLD-B). Hypoalbunemia was present in 24.5% of these patients. Longitudinal melanonychia was present in 4(3.6%) cases.

Pigmentary abnormalities associated with various CLD as per the etiology are shown in Table 2. Pigmentation was greater in intensity at the time of episode of acute illness and in majority improved as the acute episode subsided.

Table 2: Pigmentary abnormalities associated with various CLD as per the etiology (N=54)

Etiologic process of CLD		
Hyperpigmentation	No.	%
Alcoholic liver disease(ALD)	22	40.7%
Chronic liver disease-Hepatitis B(CLD-B)	14	25.9%
Chronic Liver Disease –Hepatitis C(CLD-C)	7	12.9%
Autoimmune	0	
Wilsons	3	5.5%
Sarcoidosis	0	

Etiologically, alcoholic liver disease was responsible for most of the cases of CLD with cutaneous hyperpigmentation=22 i.e. 40.7% of the total of 46 patients presenting with hyperpigmentation).On comparing presence of hyperpigmentation between various aetiologies of CLD following results were obtained –Chronic liver disease hepatitis-C (CLD –C) and Alcoholic liver disease (ALD) (P value=0.016-i.e. a significantly higher number of patients of ALD had hyperpigmentation as compared to those of CLD-C.

Chronic liver disease hepatitis-B (CLD –B) and ALD (p value=0.114)

CLD-B and CLD-C (p value=0.517)

According to severity classification of CLD (graded by Child's criteria) it was observed 34.7% of patients of hyperpigmentation belonged to Child's category A, 28.2% to Child's category B and 36.95% to Child's category C. No significant difference was found between these groups.

As is evident from Table 3, the most common site affected by pigmentary anomaly was face 18(39.1%) followed by extremities, which are photo exposed areas.

Table 3: Distribution of pigment site in patients of CLD (N=46)

Site	No.	%
Face	18	39.1
Extremities/Face	9	19.6
Trunk	8	17.4
Generalized	5	10.9
Extremities	3	6.5
Extremities/trunk	3	6.5
Total	46	100%

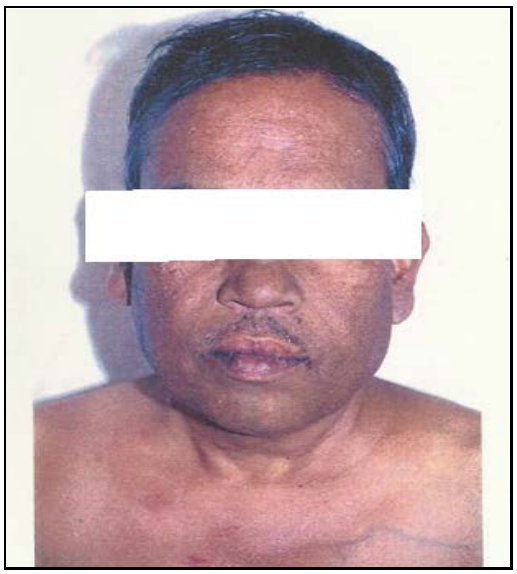

Fig 1: Hyperpigmentation over face, icterus, spider angiomas and collateral blood vessels over upper chest are visible in a case of alcoholic liver disease.

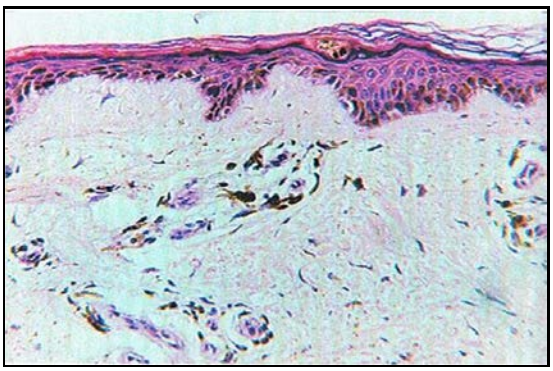

Fig 2: Hematoxylin and eosin stain showing increased melanin pigment in epidermis and dermis.

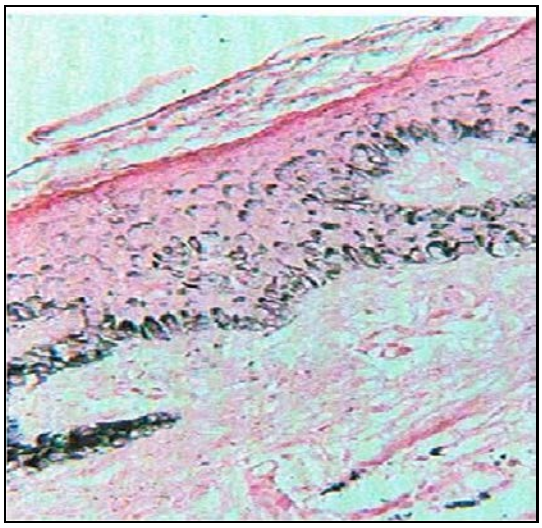

Fig 3: Masson Fontana stain for melanin showing increased melanin in all layers of epidermis and dermis.

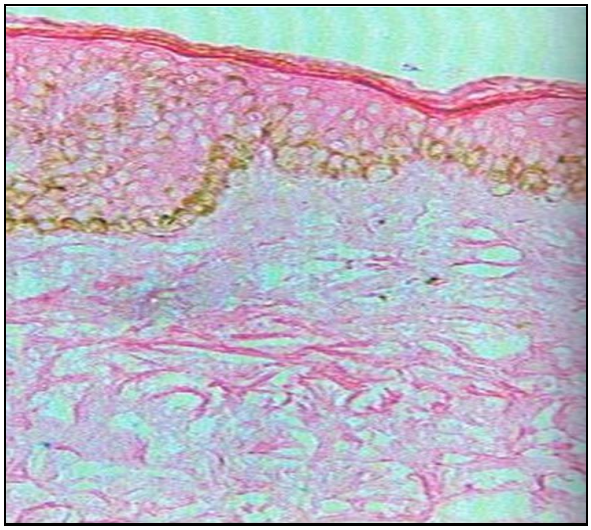

Fig 4: Perls' Prussian blue stain for iron revealed absence of iron deposits.

The Pigmentation presented as a diffuse, muddy brownish hue, most commonly involving the face (Figure 1). In advanced cases, it extended onto extremities. Many patients showed hyperpigmentation of skin around the eyes. Pigmented macules were occasionally seen over palms and soles.

Table 4: Histopathological profile of pigmentary anomalies in patients of CLD (who gave their consent for the procedure).(N=19)

Pigmentary abnormality		Histopathological features		
Increased melanin in epidermis and dermis		Increased melanin in stratum basale	No increase in melanin	Absent melanin in Stratum Basale
Hyper pigmented skin lesion	12(63.3%)	3(15.7%)	2(10.5%)	0

Among the histopathological specimens evaluated, (Table 4) there was increased melanin pigment identified in all layers of the epidermis on Haematoxylin and Eosin-stained sections (Figure 2). This was seen in12 out of 19 cases. Special stains for melanin (Fontana Masson as shown in figure 3) supported the findings. Special stains for iron (Prussian blue) revealed no iron deposits (figure 4).

Discussion

Cutaneous manifestations are one of the most common extra hepatic manifestations of CLD. They can often provide the first clue to the possibility of underlying liver disease. An early recognition by the clinician can prompt the search for a cause and enable initiation of appropriate care in a timely manner. Various cutaneous manifestations conventionally associated with CLD include pruritus, jaundice, and lichen planus etc. Pigmentation is a not so well reported and evaluated cutaneous manifestation which if duly recognized, can be helpful in early diagnosis.

Patients of chronic liver disease have a muddy gray colored hyperpigmentation predominantly over sun exposed areas.it can be predominantly over perioral, periocular areas and palmar crease [6, 7].

Earlier studies conducted by Ghent *et al*. [8] and Chevrant *et*

al. [9] have reported that some patients with hepatic disease demonstrate hyperpigmentation instead of or in addition to jaundice. They associated such pigmentation with hemochromatosis and cirrhosis.

In our study, majority of the patients or their relatives noticed a progressive darkening of the skin over the face and extremities, few months prior to the onset of the manifestation of liver disease. This is an important finding as it can provide a subtle early clue to a non-dermatologist regarding the underlying disease process. Pigmentation was greater in intensity at the time of episode of acute illness and in majority improved as the acute episode subsided.

Hyperpigmentation was seen to be most common in patients of CLD induced by ALD. Smith *et al*. reported that pigmentary changes are most impressive with primary biliary cirrhosis (PBC) but can also be seen in other types of CLD especially ALD. We did not come across any patient with PBC in our series.

The pigmentation noticed was typically a brownish grey colour, signifying the depth of pigment deposits. It was reported to start mainly from face and gradually involved the extremities. Many patients revealed especially noticeable hyperpigmentation of the skin around the eyes.

Chevrant *et al*. had reported a generalized pattern of pigmentation with accentuation over sun exposed areas and flexures. This is in sync with our findings. The most common site affected by pigmentary anomaly in our series was the face followed by extremities. This is concordant with the findings of Berman *et al*. [10]. India is a tropical country with a good amount of sun exposure. Fitzpatrick Skin type V is the predominant skin type in our country and this skin type is more prone to photo- induced pigmentation. Hyperpigmentation was often associated with pruritus in many patients. This may be related to the nutritional status of the patient. Majority of the patients of CLD especially alcoholics suffer from malnutrition-leading to dry skin- which in turn leads to itching. Moreover dry skin per se is present in elderly age group in our series maximum patients were found in the age group of 51-60 years of age. Malabsorbtion with malnutrition may cause symmetrical melanin hyperpigmentation of the skin [11].

For the reasons mentioned above, both itching and melanosis can be concomitantly present in a case of CLD. The other concept proposed by Burton *et al*. [12] supports the correlation of pruritus with melanosis that the bile salts produced a cytotoxic effect on cells resulting in the release of proteolytic enzyme which produce pruritus. These enzymes activate epidermal tyrosinase by cleaving a peptide from the inactive precursor protyrosinase, releasing active enzyme. Further this concept can explain the relation of itching and hyperpigmentation also. Secondly; pruritus per se can lead to hyperpigmentation as a result of friction and excoriations induced by scratching which result in post inflammatory hyperpigmentation. This type of hyperpigmentation induced by pruritus was common over back and extremities which are accessible areas.

Histopathological examination of hyperpigmented areas in our patients revealed increased melanin in all the layers of epidermis with dermal incontinence. Special stains for melanin was positive and those for iron were negative. This is in accordance with findings of Mills *et al*. [13] who reported extensively dispersed melanin pigment throughout all layers of epidermis and dermis. Chevrant *et al*. Reported extensive melanin but confined to the basal layer apart from melanophages in the dermis in cases with hemochromatosis. this is discordant with our finding of melanin being present throughout the epidermal thickness The probable explanation for this finding might be that majority of patients included in the study were of Fitzpatrick skin type v, which is a darker skin type hence the dispersion of melanin throughout the epidermis.

Terry's white nails were present in 10% of patients out of which majority were of alcoholic liver disease. Hypoalbunemia was present in 24.5% of these patients. Terry [14] has incriminated hypoalbuminemia in the pathogenesis of terry's white nails. As majority of our patients with this nail change were of ALD, hypoalbunemia is also feature of ALD, so it may explain the terry's nail finding in ALD. Longitudinal melanonychia was present in 4(3.6%) cases. Thus pigmentary anomaly of nail was not found to be a significant finding.

Conclusions: To conclude, the present series shows that hyperpigmentation is associated with underlying liver disease. It occurs early in the course of disease and can provide subtle clues to the dermatologist regarding the presence of underlying liver disease. Further case control studies are required to make a conclusive statement.

Conflicts of interests- None
Source of Funding- None

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