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Histopathological evaluation of skin in cirrhotic patients with pruritus

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by

Abstract:

Background: Cirrhosis often is a silent disease Clinical symptoms at presentation may include jaundice of the eyes or skin, pruritus, gastrointestinal bleeding, coagulopathy, increasing abdominal girth, and mental status changes. Pruritus may be the presenting symptom, arising years before any other classic clinical and laboratory markers of hepatic dysfunction. This study examines the clinical, laboratory and histopathological changes in the skins of cirrhotic patients with pruritus in comparison with cirrhotic patients without pruritus and healthy control skins .

Patients and Methods: To evaluate clinical, laboratory and histopathological changes in cirrhotic patients with pruritus, cirrhotic patients without pruritus and corresponding healthy (control). skin biopsies (20 specimens each) using hematoxylin and eosin stain and to study mast cell density using gimesa stain.

Results: In the skin biopsy specimens of the cirrhotic patients with pruritus we found several histological changes including: epidermal hyperplasia (acanthosis) ,vascular ectasia(dilated dermal blood vessels), hypertrophied dermal nerve endings, mixed inflammatory cellular infilterate and lymphocytic vasculopathy (swelling of the endothelial cell lining of the blood vessels without fibrinoid necrosis, leucocytoclasia or extravasation of red blood cells). Evaluation of mast cell count in Gimesa stained skin sections revealed an increased numbers of these cells in the group of cirrhotic patients with pruritus (N=5-10). The cells noted in perivascular, perineural and interstitial distribution (between collagen bundles).

Conclusions: We report, for the first time, some histopathologial changes in the skins of cirrhotic patients with pruritus in comparison with cirrhotic patients without pruritus and healthy control skins .

Introduction:

Cirrhosis refers to a progressive, diffuse, fibrosing and nodular condition that disrupts the entire normal architecture of the liver **(١).** In developed countries, the leading causes of cirrhosis are HCV infection, alcohol misuse, and nonalcoholic fatty liver disease (**2).** Hepatitis B viral infection is the most common cause of cirrhosis in developing countries **(3).** The prognosis of cirrhosis is highly including etiology, severity, presence of complications, and comorbid diseases **(4).** Cirrhosis often is a silent disease Clinical symptoms at presentation may include jaundice of the eyes or skin, pruritus, gastrointestinal bleeding, coagulopathy, increasing abdominal girth, and mental status changes **(5).**

Pruritus is a common symptom in hepatobiliary disorders, particularly in those related to cholestasis. Its prevalence is variable among liver diseases, ranging from 5% in chronic

hepatitis C virus infection to 70% in primary biliary cirrhosis. There is no correlation between severity of liver disorders and cholestasis and pruritus intensity (**6**). pruritus may be the presenting symptom, arising years before any other classic clinical and laboratory markers of hepatic dysfunction **(7).** Pruritus can be localized or generalized, continuous or intermittent, and can sometimes be represented by a complaint of burning, tingling or pricking sensations on the skin**.** Most cases start generally in the palms of the hands and soles of the feet, progressing to the extensor surface of the upper limbs, face and upper region of the trunk. Its severity can also be graded from mild to severe **(8)**. In mild presentations, it rarely means some degree of compromise in individual daily activities, which is more common in severe cases that also compromise sleep patterns and causes depression and low quality of life in some cases. In the most severe and refractory cases, it can sometimes lead to suicide attempts **(9).** Pruritus can vary day by day and be more intense during the evenings and late afternoon **(10)**. Excessive hot and humid weather exacerbates its symptoms as well as dietary changes with meals rich in carbohydrates and the use of tight clothes (**11)**. It is also well-established that acute stress and psycho-emotional situations can trigger or exacerbate its severity (**12)**.

Chronic pruritus and vigorous scratching can lead to skin complications such as abrasions, folliculitis, prurigo nodularis and lichenification (**9)**. It is of difficult relief leading the patient to rub the affected area or even leading to the use of sharp tools, like brushes, forks, knives and screwdrivers to promote abrasions to obtain some degree of improvement (**13)**. It generally regresses when liver failure begins and does not have a linear correlation with alkaline phosphatase serum levels, gamma-glutamyl transferase, bilirubin or serum concentrations of bile salts **(14)**. Among individuals with pruritus, 11% present with refractory sensation with no relief of symptoms, and in cases with cholestasis its severity and refractoriness represent a formal indication of liver transplantion even in the absence of liver failure **(15).**

Patients and methods: This Case – control hospital based study was carried out at the Department of Dermatology, Venereology and Andrology jointly with Department of Gastroenterology and Tropical Medicine at Sohag University Hospitals, Egypt. The study was approved by the institutional Ethics and Research Committee of Faculty of Medicine, Sohag University, Egypt.

Patients: The study included 40 patients (20 were cirrhotic with pruritus and 20 were cirrhotic without pruritus) as well as from 20 age and sex matched healthy volunteers who attended the outpatient clinic of Dermatology, Venereology and Andrology Department or Department of Gastroenterology and Tropical Medicine Sohag University Hospital bet January 2015 to June 2016. An informed consent was obtained from all participants after full explanation of the procedure. Patients with history of associated endocrinal disordes e.g; diabetes mellitus, thyroid disease or chronic renal illness and Patients presented with other itchy or non-itchy dermatoses were excluded from the study.

Clinical evaluation:

All the patients were subjected to full history taking and complete dermatological examination.

Histopathological evaluation:

Punch skin biopsies (4 mm) each were obtained from all participants. The formalin fixed- paraffin embedded tissues were processed for routine histology (Hematoxylin and eosin stains) and special (Giemsa stain) at the Department of Pathology, Faculty of Medicine, Assuit University Hospitals under the supervision of Prof, Dr. Mahmoud Rezk Abd El Wahed Hussein.The sections were histologically evaluated for histological changes and the number and distribution of mast cells were examined (Giemsa stain) and the mean counts of cells were reported. The histological evaluation were blindly performed by two independent pathologists (Prof. Mahmoud Rezk Abd elwahed Hussein and Dr. Asmaa Mahmoud Ahmed).

Results:

The study included 40 patients were divided into two groups ; cirrhotic patients with pruritus (N=20), cirrhotic patients without pruritus (N=20) as well as 20 age and sex matched healthy volunteers as a control group. The ages of cirrhotic patients with pruritus group ranged from (35- 67 years) with mean ± SD (52.7 ± 9.1), in cirrhotic patients with pruritus ranged from (47- 67 years) with mean ± SD (55 ± 5.3) and in the control group ranged from (37- 60 years) with mean ± SD (51 ± 7.3). There was no statistical significant difference between the studied groups as regard age.The total number of males in the studied groups is 31(9 cirrhotic patients with pruritus, 11 cirrhotic patients without pruritus and 11 control group).Total number of females in the studied groups is 29 (11 cirrhotic patients with pruritus, 9 cirrhotic patients without pruritus and 9 control group). There was no statistical significant difference between the studied groups as regard sex. There was no statistical significant difference between the studied groups as regard other sociodemographic data including: residence, marital status and special habits.

Histopathological findings:

Evaluation of histopathological using hematoxylin and eosin stained sections (H&E) was done and compared among the studied three groups. In the skin biopsy specimens of the cirrhotic patients with pruritus we found several histological changes including: epidermal hyperplasia (acanthosis) ,vascular ectasia(dilated dermal blood vessels), hypertrophied dermal nerve endings, leucocytoclasia (swelling of the endothelial cell lining of the blood vessels without fibrinoid necrosis, or extravasation of red blood cells). Mixed inflammatory cellular infilterate and lymphocytic vasculopathy. Evaluation of mast cell count in Gimesa stained skin sections revealed an increased numbers of these cells in the group of cirrhotic patients with pruritus (N=5-10). The cells noted in perivascular, perineural and interstitial distribution (between collagen bundles) table(1) Figure (1,2).

(1) Histopathological findings among the studied groups:

Aspects	Pruritus group (n=20)	Non-pruritus group (n=20)	Healthy skin (N=20)
Epidermis			
Epidermal hyperplasia (irregular acanthosis)	Present	Absent	Absent
Dermis			
Perivascular lymphocytic infiltrate	Mild to moderate density of perivascular lymphocytes and histiocytes (range: 5-8 cells)	Subtle (range: 2-4 cells)	Sutbtle
Dermal vascular ectasia	Present	Absent	Absent
Lymphocytic vasculopathy	Present	Absent	Absent
Hypertrophied nerves	Present	Absent	Absent
Mast cells Giemsa stain)	Present (5-10 cells) in perivascular, about nerves (nerve-mast cell contact) and in interstitial distribution	Rare (range: 1-2 cells, in perivascular location)	rare(range: 1-2 cells, in perivascular location)
Subcutis			
	No significant pathologic changes	No significant pathologic changes	No significant pathologic changes

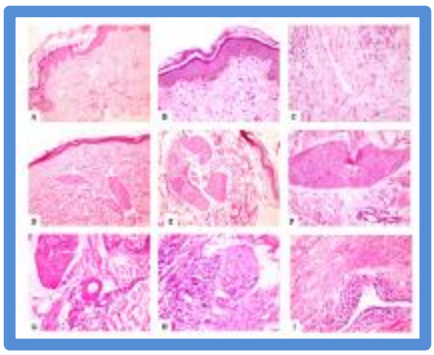

Figure (1): H&E stained tissue sections showing histological differences between cirrhotic patients with and without pruritus. **A-B:** Non-pruritus skin (A 100x) (B 200x) , **C-D-E-F-G-H-I:** Pruritus skin with: vascular ectasia **(C)** (400x), hypertrophied Nerves **(D-E-F)** (D 100x, E 200x, F400x), inflammatory cells around the nerves (**H** 400x) and lymphocytic vasculopathy (**I** 400x)

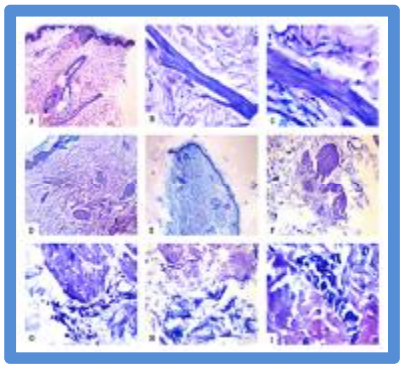

Figure (2): Mast cells (Geimsa stain)
A-I: Hypertrophied nerves in pruritus group with some Mast cells around them as well as in perivascular distribution.(A 100x, B 200x, C 400x, D 100x, E,F 200x, G, H, I 400x)

Discussion:

In the present study the ages of cirrhotic patients with pruritus ranged (35-67) with mean ± SD (52±9.1). liver cirrhosis is more prevalent among malnourished patients over age 50 years of age (**16**). In this study, we found several histological changes in the skin of cirrhotic patients with pruritus including: epidermal hyperplasia, vascular ectasia, hypertrophied dermal nerve endings, mixed inflammatory cellular infilterate and lymphocytic vasculopathy. **O'Keeffe C et al. (2004)** reported mild histological abnormalities in patients with chronic liver disease with and without pruritus including minimal or mild perivenular inflammation with mononuclear cell infiltration (**17**). several cutaneous complications secondary to chronic hepatic pruritus may develop, such as folliculitis, excoriations, prurigo nodularis, and lichenification, can result from long-standing, vigorous scratching activity **(13).** These changes are reminiscent to those of prurigo nodularis and lichen simplex chronicus which represent a cutaneous reaction pattern to repeated rubbing or scratching following pruritus of different origin. They are Histologically characterized by irregular acanthosis, hyperkeratosis, dermal inflammatory cell infilterate and a massive neural hyperplasia .

We found also increased numbers of mast cells which have perivascular, perineural and interstitial distribution. It is unclear whether mast cells can contribute to hepatic pruritus or not. With regard to cholestatic liver disease, plasma histamine levels are higher in patients with pruritus than without pruritus **(17).** Subsequently, bile acids are known to be potent activators of mast cells. As a result, the degranulation of mast cells induced by bile acids and histamine's excretion in consequence might also constitute the reason for itch (**Michalak et al, 2011)**.

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