International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 08, Issue 03, March 2023,
https://doi.org/10.23958/ijirms/vol08-i03/1644

Original article

Skin Biopsies in Gastrointestinal Diseases: A Single Centre Experience from North India

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Received 22 February 2023; Accepted 15 March 2023; Published 18 March 2023

Abstract

Skin manifestations have always been alarming to the patient and often warrant complete clinical evaluation. A thorough understanding of relationship between gastrointestinal (GI) disorders and skin diseases can alert the clinician to an underlying occult GI disorder. The aim of the study was to review the cutaneous changes in patients with co-existent, often masked GI diseases and to observe the underlying pathophysiology of such lesions. This was a retrospective, record based observational study. The archived histopathology reports & medical records of patients over a period of 5 years were searched and all patients who underwent skin biopsy with co-existent GI diseases were included. Out of a total of 218 patients of GI diseases who had dermatological manifestations, only 44 were biopsied. Pruritis (n=175), koilonychia (n=52) and erythematous rash (n=35) were the most common clinical features. Psoriasis (n=4), vasculitis (n=4), Dermatitis Herpetiformis (n=3) and pyoderma gangrenosum (n=5) were often seen associated with benign GI diseases like Inflammatory Bowel Diseases, Chronic Liver Disease, Malabsorption syndrome etc. Sweets syndrome (n=2) and cutaneous metastatic nodules (n=3) were associated with underlying malignancy particularly of gall bladder and pancreas.

Keywords: ***skin biopsy, gastrointestinal disorders, cutaneous manifestations, benign, malignant.***

Introduction

Skin is the largest organ of the human body and reflects the state of functioning of our organs [1]. There are numerous disorders in the gastrointestinal tract (Inflammatory Bowel Disease (IBD), celiac disease, gastritis, pancreatitis etc.) as well as chronic liver diseases which can cause cutaneous manifestations [2]. The proposed pathophysiology suggests there is a loss of equilibrium between host defense and tolerance, leading to overactivity of some immune pathways. There may also be an underlying genetic linkage responsible for the cutaneous disease. The immune dysregulation results in a lymphocyte mediated destructive process [3].

Both Dermatologists and Gastroenterologists should be aware of the cutaneous manifestations as these may be the first alarm of underlying liver or gastrointestinal (GI) disease and may even be more debilitating than the underlying disease itself. Dermatological manifestations can increase the risk of developing other extra-intestinal manifestations as well, all of which increase morbidity and mortality in GI disease. Hence early diagnosis and appropriate therapeutic intervention is warranted in such cases [4]. These findings will also help other family members who may need appropriate screening tests and genetic counseling [5]. The present study lays stress on cutaneous manifestations in various gastro-intestinal and hepatobiliary diseases in patients attending a tertiary referral centre of North India.

The aim of this study is to document the spectrum of cutaneous lesions in patients of gastro-intestinal diseases and to observe the clinical presentation and histopathological diagnosis of all patients in the study group.

Material and Methods

This was a retrospective medical record based observational study carried out in the Department of Pathology during January 2016 and January 2021 (5 years). All biopsied patients attending Dermatology OPD who were having a co-existent gastrointestinal disorder (like gastritis, diarrhoea, Jaundice, loose stools etc.) in the study duration were studied whereas patients who had co-existent primary skin disease elsewhere were excluded. The hospital records of all the patients fulfilling the inclusion criteria were analyzed and their clinical features, and demographic details were compiled. Histopathological findings of skin biopsy were tabulated.

Results

A total of 218 patients of various GI disorders attended the Medicine/Gastroenterology/Dermatology OPD with co-existent

skin lesions. The commonest symptom was pruritis (n=175, 80.2%) which was often protracted and disabling in the majority of patients. Muco cutaneous and nail changes were seen in less than a quarter of patients (n=52) with development of koilonychia, splinter hemorrhages and subungual hyperkeratosis. Cheilitis(n=14) and angular stomatitis (n=6) were seen in patients of suspected malabsorbtion syndrome.

Skin biopsies were carried out in 44 patients, out of these 36 were benign while 8 were harbouring an underlying malignancy in gastrointestinal tract. The mean age of patients manifesting cutaneous lesions in an underlying benign GI disease was 35.7 years with a Male: Female ratio of 1:1.2 whereas the mean age for cutaneous manifestations in an underlying GI malignancy was 43.8 years with an equal sex ratio.

Pyoderma gangrenosum (n=4,11.1%), psoriasis (n=4,11.1%) were the most common dermatological manifestations in benign GI diseases whereas Erythema nodosum was seen in only 1 case of Ulcerative colitis. Chronic lichenoid dermatitis (n=3,8.3%) and small vessel lymphocytic vasculitis (n=3,8.3%) were seen exclusively in chronic liver diseases/cirrhosis (**Table 1**). Cutaneous nodules (n=3) and sweets syndrome (n=2) were the most common presenting manifestations of occult GI malignancies (**Table 2**).

Table 1: Spectrum of cutaneous manifestations in Benign Gastrointestinal diseases (n=36)

Skin lesion	No.of cases	M: F	GI disease
Eruptive xanthoma	1	F	Chronic liver disease (CLD)
Pyoderma gangrenosum	5	3:2	Inflammatory Bowel Disease (IBD) (4) Viral Hepatitis (1)
Pancreatic panniculitis	1	F	Chronic pancreatitis
Lichenoid dermatitis	3	1:2	CLD
Palmo plantar keratoderma	2	M	CLD (2)
Kyrles disease/Acquired perforating collagenosis	2	1:1	Diabetes Mellitus with IBD (1) Gastritis with Chronic Renal Failure (1)
Psoriasis	4	3:1	IBD (3) Chronic hepatitis C (1)
Sweets syndrome	3	2:1	DM with IBD (2) Viral hepatitis (1)
Acquired Acrodermatitis enteropathica/ Zinc deficiency	1	M	Celiac disease (1)
Granuloma annulare	1	F	DM with gastritis
Scleroderma	2	F	H.pylori gastritis (1) Esophageal stricture (1)
Chronic lymphocytic vasculitis	3	1:2	Cirrhosis (3)
Erythema nodosum	1	F	Ulcerative Colitis
Dermatitis herpetiformis	3	2:1	Celiac disease (3)
Fixed drug eruptions	2	F	CLD
Peutz-Jeghers Syndrome	2	1:1	Intestinal polyps

Table 2: Cutaneous manifestations in malignant GI disease (n=8)

Lesion	Number of cases	Sex ratio	Underlying GI malignancy
Sweets syndrome	2	F	CA esophagus (1) CA gall bladder (1)
Prurigo Nodularis	1	M	CA cecum
Seborrheic keratosis	1	M	CA colon
Metastatic cutaneous nodules	3	2:1	CA gall bladder (2) CA pancreas (1)
Atopic dermatitis	1	F	GIST Ileum

Table 3: Distribution of patients according to underlying pathophysiology

a) Specific GI diseases causing particular dermatological manifestations	CLD	Xanthoma
b) Both skin and GIT being simultaneously affected by systemic diseases	IBD Diabetes Mellitus	Psoriasis Kyrles disease
c) Primary skin disorders affecting the GI	H.pylori gastritis	Scleroderma
d) Drug reactions as part of treatment by gastroenterologists	CLD	Fixed Drug Eruptions
e) Malabsorption/GI disease leading to nutritional deficiency	Coeliac disease	Acrodermatitis enteropathica Dermatitis herpetiformis

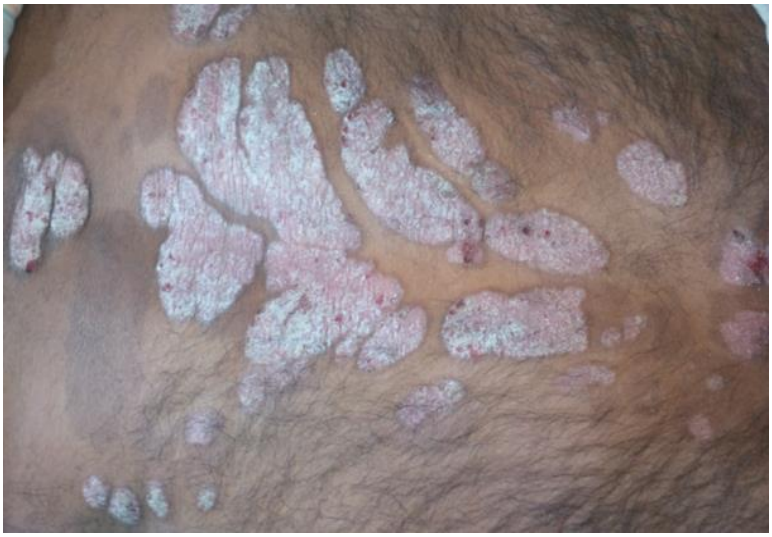


Figure 1: Shiny, silvery plaques of psoriasis in a patient with underlying Ulcerative colitis.

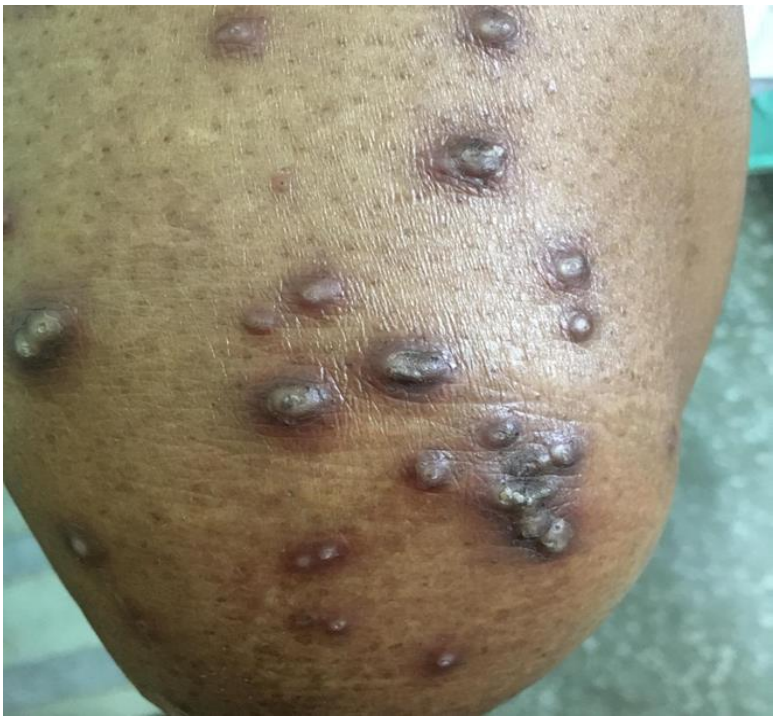


Figure 2: Keratotic follicular papules of Kyrle's disease in patient of IBD with Diabetes Mellitus.

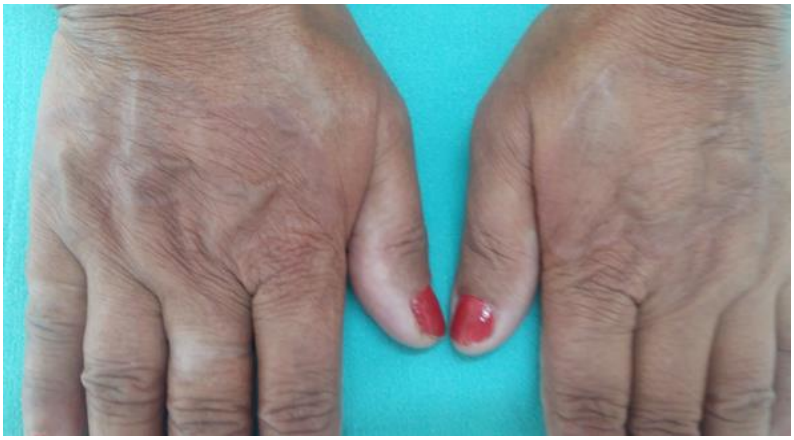


Figure 3: Granuloma annulare in a patient of chronic superficial gastritis

Discussion

Skin disorders & Gastrointestinal diseases and are often inter-related. These can be either a) Specific GI diseases causing particular dermatological manifestations, b) Both skin and GIT being simultaneously affected by systemic diseases, c) Primary skin disorders affecting the GI, d) Drug reactions as part of treatment by gastroenterologists, e) Malabsorption/GI disease leading to nutritional deficiency [3].

Idiopathic urticaria, acne rosacea, lichen planus, Behcet's disease, scleroderma, Henoch schonlein pupura are some of the

manifestations of H.pylori gastritis induced skin changes. These lesions may be due to immune mediated reaction following cross-reactivity between Helicobacter pylori and human host [6]. In our study gastritis was associated with scleroderma and granuloma annulare in one case each while one patient on regular dialysis for 8 years with co-existent Diabetes and H. pylori gastritis presented with acquired perforating collagenosis (Kyrles disease).

Celiac disease (CD) is a type of malabsorption syndrome characterized total or subtotal villous atrophy,the disease tends to improve with a gluten free diet. CD is associated with various skin diseases. The pathophysiology implicated behind the immune response in CD is considered an abnormal small intestinal permeability which may allow the crossing of endogenous or exogenous antigens and thereby cause skin lesions [7]. In our study 3 patients of CD had bullous lesions of Dermatitis Herpetiformis while 1 patient had nutritional (Zinc) deficiency associated Acrodermatitis Enteropathica. This patient had chief complains of persistent diarrhea with perioral rashes. Dermatitis herpetiformis (DH) is a chronic, gluten sensitive disease which presents with bullous skin lesions. The skin lesions are usually symmetrically distributed on the extensor surfaces. There is a slight male predominance which was also observed in our study. Biopsy reveals microabscess rich in neutrophils and eosinophils in the papillary dermis. Direct Immunofluorescence shows IgA deposition [8]. Antibodies implicated in DH are Antigluten, antiendomysium, antigliadin and tissue transglutaminase antibodies. Treatment involves gluten free diet and dapsone [9].

Inflammatory bowel diseases which constitute Ulcerative colitis (UC) and Crohns disease often presents with lower GI bleeding. Dermatological changes described in these patients are palpable purpura, leukocytoclastic vasculitis, edema and hemorrhage [10]. Fissuring in the perianal area leading to ulcers and abscesses are commonly seen in Crohn's disease. The changes in gut can be seen in the oral cavity as well. These changes include ulceration, cobblestone mucosa and nodules. Finding of painful, necrotic skin ulcers with undermined borders were seen in 4 cases of IBD in our study. The lesions were non-scarring and sterile. Skin biopsy revealed dense neutrophilic aggregates and these cases were diagnosed as pyoderma gangrenosum. Almost half of the patients with pyoderma gangrenosum had underlying ulcerative colitis. Our study showed a female predominance similar to a study by Trost et al [11]. Erythema Nodosum presents as tender red nodules particularly on the anterior aspect of the leg. It may occur at any point in the course of inflammatory bowel disease or may be associated with relapse of Ulcerative Colitis [12]. In our study 2 women already taking treatment for UC presented with painful red nodules on legs and arms. Both these showed septal panniculitis on skin biopsy and were diagnosed Erythema Nodosum. Psoriasis was seen in 2 patients of Ulcerative colitis. Psoriasis is seen in approximately 7-10% of patients with IBD. This has been linked to certain gene loci on chromosomes 3, 4, 6, and 16 [13].

Chronic liver diseases (auto immune hepatitis, viral hepatitis, alcoholic hepatitis, and cirrhosis) constituted 1/3rd cases of benign GI lesions with dermatological manifestations in our study. The commonest cutaneous symptom in patients with liver disease is pruritus followed by spider angiomatous spider nevi, palmar erythema, papery skin, xanthelasmas, hyperpigmentation, and nutritional deficiencies [14]. Besides pruritis and skin rashes, palpable purpura was seen in all our patients particularly in lower limbs. One case showed eyelid xanthelasma (**Photomicrograph 1**). One case showed medium vessel vasculitis and a diagnosis of Polyarteritis Nodosa was made. The association between HBV and PAN has been documented earlier also [15]. Frequency of cutaneous manifestation in CLD in a prospective study by Cacoub et al in France was upto 17% which may be postulated to (i) Direct infection of Hepatitis Virus in the skin, (ii) Immune mediated Leukocytoclastic vasculitis, (iii) Malfunctioning of another organ affected by HCV leading to skin manifestations (iv) Drug induced reactions in the course of treatment [16]. However, these cutaneous manifestations seen in patients with liver disease are nonspecific and generally do not point towards a specific hepatic disorder. These findings should always be interpreted in the context of clinical features and liver function tests.

Pancreatic panniculitis is associated with a wide variety of pancreatic disorders such as acute or chronic pancreatitis,post-traumatic pancreatitis, pancreatic pseudocysts etc. Periumblical ecchymosis (Turner's sign) and ecchymosis of flank (Cullen's sign) are few of the classic dermatological changes seen in acute pancreatitis. These may be explained by extravasation of hemorrhagic peritoneal fluid into the skin leading to localized hematoma formation [17]. In our study, a middle-aged woman presented with tender, erythematous, painless subcutaneous nodules occurring on abdomen, back and extremities. On biopsy lobular panniculitis was seen along with basophilic degeneration of adipocytes and dystrophic calcification. These degenerated adipocytes resembled ghost cells. (**Photomicrograph 2**). Other biochemical investigations revealed raised amylase and lipase enzymes thus leading to a diagnosis of chronic pancreatitis.

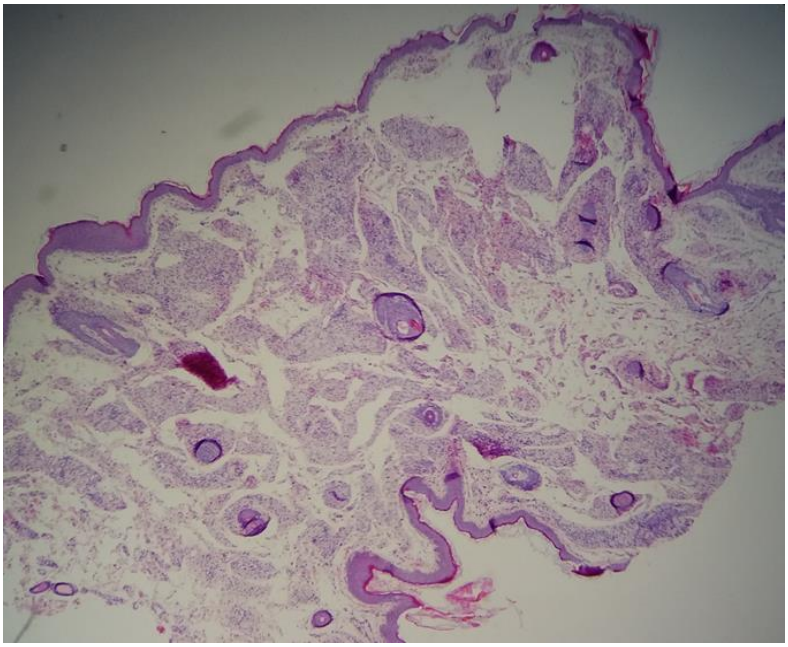
Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder with an underlying STK11/LKB1mutation.Hyperpigmented macules, upto 1-5 mm in size are seen in skin and mucosa, These macules are irregularly distributed over the entire oral cavity including buccal mucosa, gums, hard palate and lower lips. GI tract manifestations include numerous intestinal polyps in the small bowel specially in jejunum, however less frequently colon, rectum, stomach and duodenum are also involved. These polyps are typically hamartomas [18]. Two children in our study with perioral pigmentation had multiple intestinal polyps with presence of smooth muscle fibres within the lamina (hamartomatous polyps).

Malignancies of GIT particularly in advanced stages are often associated with some cutaneous manifestations which are often the first sign of an underlying malignancy. The pathophysiology may be attributed to direct infiltration of skin by metastatic cancer cells (Sister Mary Joseph nodule). Alternatively, the dermatological lesions are because of certain hormones/ chemicals released from underlying malignancy and are called "paraneoplastic syndromes". Metastatic dermal/ subcutaneous nodules are found usually on scalp or abdominal skin. Stomach is the most common primary site. In our study 2 cases of gall bladder and one case of pancreatic adenocarcinoma presented with cutaneous metastasis. (**Photomicrograph 3**).

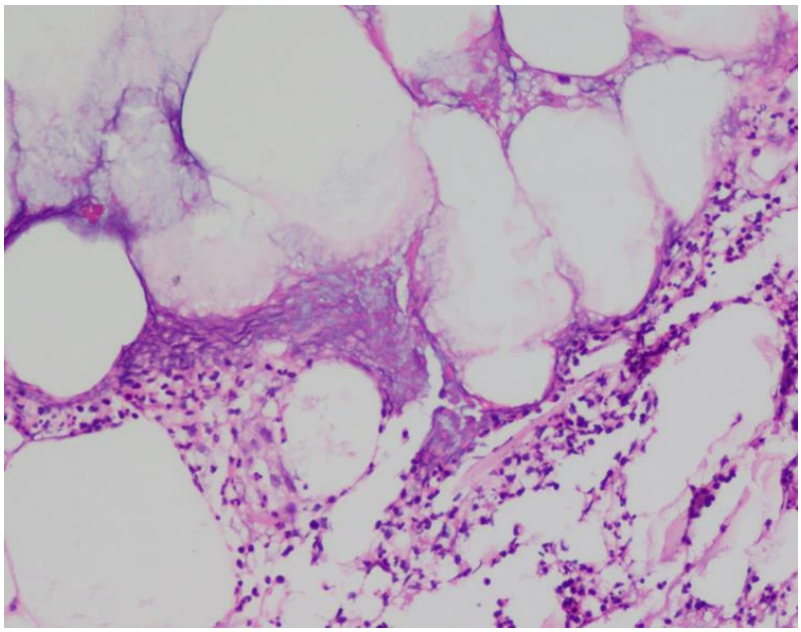
Acute febrile neutrophilic dermatosis or sweet syndrome is characterized by tender and erythematous skin nodules and usually signal an underlying systemic pathology [19]. One case each of carcinoma gall bladder and esophagus presented with febrile neutrophilic dermatosis (Sweets syndrome) in our study.

Multiple seborrheic keratosis when exhibit an increase in size or number are termed Leser-Trélat syndrome (LTS) and point towards an internal malignancy particularlystomach or colon adenocarcinoma, and less frequently carcinomas of esophagus, duodenum or liver [20]. Multiple seborrheic keratosis were seen in a case of descending colon adenocarcinoma in our study.

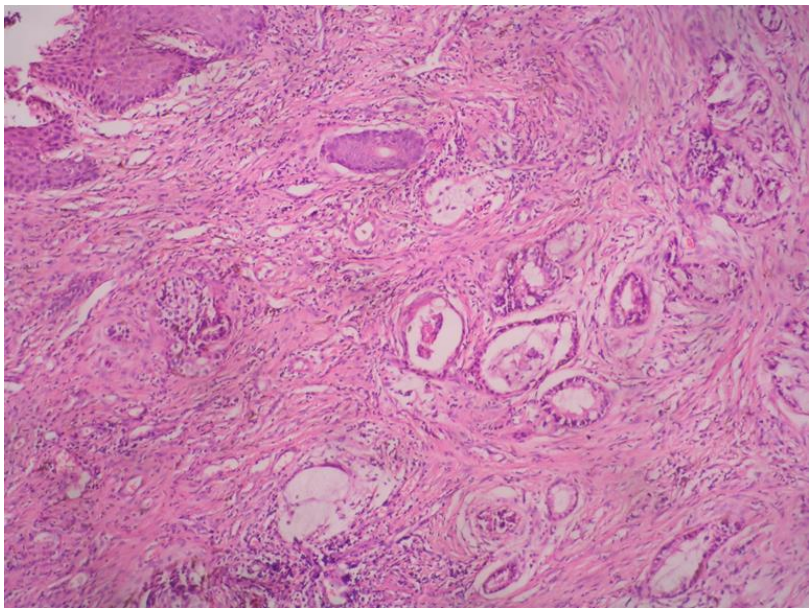
To conclude, thorough clinical history, laboratory investigations and physical examination are needed to diagnose a case of GI disorder. Skin manifestations may be the first sign of an underlying systemic disorder. The clinician should be aware of these changes and initiate timely therapy. This article discusses hepato-gastrointestinal diseases that have associated dermatologic manifestations.



Photomicrograph 1: Xanthoma in chronic liver disease with dermis showing collections of foamy macrophages (H&E:4x10X)



Photomicrograph 2: Septal and lobular panniculitis with ghost cells and necrosis in a case of chronic pancreatitis (H&E:10x10X)



Photomicrograph 3: Metastatic deposits of gall bladder adenocarcinoma in skin (H&E:10x10X)

Limitations of the study

Ours was single centre study in a tertiary referral centre and indicates hospital based prevalence. The observation period was 5 years with limited follow up. A longer duration study with greater number of patients in study group is needed to see whether a strong association exists between GI diseases and cutaneous manifestations.

Ethics committee approval

Ethics committee approval for this study was taken from the institutional ethics.

Author contribution

NS: Conception and design of the work; the acquisition, analysis and interpretation of data for the work; drafting the work; critical revision of the work; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

RJ: Design of the work; contribution in the acquisition and analysis of data for the work; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

SA: Contribution to the conception and design of the work; critical revision of the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Informed Consent

Taken

Conflict of Interest of all authors

None

Financial Support

Nil

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