Review article

Skin as a mirror of gastrointestinal diseases

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ABSTRACT

The closely related origins of the skin and the gastrointestinal system make for a fascinating grouping of diseases with concomitant involvement of these two important organ systems. The dermatologic manifestations may precede clinically evident gastrointestinal disease and help in early diagnosis, saving unnecessary wastage of time and resources. In this overview, we review the cutaneous manifestations of various hereditary, neoplastic and inflammatory gastrointestinal diseases including the various polyposis syndromes, hereditary colorectal cancers, inflammatory bowel diseases, etc. Dermatologic manifestations of acute and chronic hepatic and pancreatic diseases have also been discussed. This review underscores the importance of collaboration between dermatologists and gastroenterologists for better and efficient management of the affected patients.

Keywords: Gastrointestinal diseases, Genodermatoses, Hepatitis, Inflammatory bowel disease, Pancreatic diseases, Polyposis syndromes

INTRODUCTION

Skin is the largest organ of the body. With a wide surface area and being the outermost covering of the human body, skin has proven to be of good diagnostic help or atleast raise the index of suspicion that something inside the covering is wrong. Like many other systemic diseases, ,gastrointestinal tract (GIT) diseases may present with cutaneous symptoms, either primarily or secondarily as a sequalae to gut pathology, embryologic development being responsible for such clinically important associations. The cutaneous manifestations frequently occur before or concomitantly with the gastrointestinal pathology. Dermatologists and gastroenterologists should therefore, be vigilant enough to note the various cutaneous signs and diagnose or keep a high index of suspicion of a particular GI pathology so that an unnecessary work up or wastage of resources is avoided and the diagnosis is made at the earliest.

This review focuses on the various cutaneous manifestations of GIT diseases and includes the following:

I. Cutaneous manifestations of gastrointestinal diseases including inflammatory bowel disease, autoimmune diseases with skin and GIT involvement, genodermatoses, and the various hereditary gastrointestinal cancers.

II. Cutaneous manifestations of liver diseases

III. Cutaneous manifestations of pancreatic diseases.

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I. CUTANEOUS MANIFESTATIONS OF GASTROINTESTINAL DISEASES

Inflammatory Bowel Disease and Skin

Ulcerative colitis (UC) and Crohn's disease (CD) together comprise the vast majority of the cases that are considered inflammatory bowel disease (IBD). In a recent study, the prevalence of CD and UC in children younger than 20 years was 43 and 28 per 100,000, respectively. In adults, the prevalence of CD and UC was 201 and 238, per 100,000 respectively.[1] UC usually starts in the rectum and spreads in a retrograde fashion whereas CD can occur anywhere in the GIT, predominantly affecting the small intestine, leaving behind skip areas.[2] CD can involve the anal and oral mucosa as well and therefore can be more evident to a dermatologist.

The cutaneous manifestations of IBD can be classified as follows:

A) Specific lesions - Occuring as a result of direct extension of IBD to the contiguous areas, and cutaneous lesions of Crohn's disease at an anatomically unrelated site, that is, metastatic CD.

Oral apthous ulcers

Oral aphthae are seen in IBD both as a part of the reactive disease process and nutritional deficiencies because of malabsorption.[19]

Epidermolysis Bullosa Acquisita (EBA)

EBA is a chronic autoimmune disease that is characterized by subepidermal blister formation that often progresses to scarring in anatomic areas prone to trauma, such as the hands and feet. The association is hypothesized to be the result of the NC1 domain of type VII collagen which is present at the dermo-epidermal junction of both the skin and intestinal epithelium.[20]

Vasculitis

Vasculitis like Cutaneous polyarteritis nodosa (CPN) and necrotising vasculitis (NV) have also been reported as reactive lesions of IBD. While CPN manifests as panarteritis with perivascular infilterate on skin biopsy,[21] NV is characterized by the presence of neutrophilc infiltration and nuclear debris around post capillary venules.[22]

Autoimmune Diseases with Skin and GIT Involvement

A. Bowel Associated Dermatosis Arthritis Syndrome (BADAS)

It is a recurrent and episodic syndrome consisting of a combination of flu like symptoms, polyarthralgia, and a cutaneous eruption of papules and pustules. It is associated with blind loops of bowel or other causes of stasis of bowel content. Peptidoglycans from gastrointestinal flora may be the antigenic trigger for immune complex-mediated vessel damage and thus, development of cuatneous lesions.[23]

The cutaneous manifestations of BADAS consist of crops of small macular lesions that progress into papules and later pustules on a purpuric base, most often on the arms and other areas of the upper body.[23,24] BADAS is also associated with GIT diseases like UC, CD, etc.

B. Henoch Scoenlein Purpura (HSP)

It is an IgA mediated leucocytoclastic vasculitis that presents with a combination of cutaneous lesions of palpable purpura, arthritis, abdominal pain, nephritis. Infection with group A beta hemolytic streptococci have found a role in the pathogenesis of HSP.[25]

Palpable Purpura on dependent sites of the body like buttocks and legs is a sine qua non in the diagnosis of HSP.[26] Histopathology reveals leucocytoclastic vasculitis with perivascular IgA deposits visible on DIF.

Gastrointestinal manifestations are seen in 50% -75% cases of HSP and consist of colicky abdominal pain arising as a consequence of GIT vasculitis. Rarely it can be associated with bowel infarction, perforation and intussusception involving the small bowel most commonly. It preceeds purpura in 20% cases.[27]

Arthritis in HSP involves lower extremity joints and is seen in 80% of cases of HSP. The arthritis in HSP is self limiting and non destrucutive.[27]

The most serious complication of HSP is nephritis progressing to end stage renal disease (ESRD). About 40% patients with HSP develop nephritis out of which only a small fraction progress to develop ESRD.[27]

C. Dermatits Herpetiformis (DH)

DH is an autoimmune inflammatory subepidermal bullous disorder which is extremely pruritic skin condition and is currently considered to be a cutaneous manifestation of celiac disease with an incidence of 25%.[28] Both conditions are associated with HLA DQ2 (95% cases) and HLA -DQ8 in majority of the remaining cases.[29] In these patients, ingested gluten elicits an IgA mediated immune response, directed at gliadin and tissue transglutaminase in the gut and also epidermal transglutaminase.[30]

Cutaneous lesions consist of extremely pruritic vesicles on an erythematous urticarial background usually arranged symmetrically on the extensor surfaces such as the elbows, knees, shoulders and buttocks. Most of the lesions are excoriated at the time of presentation due to intense pruritus and it is usually not possible to find out an intact vesicle.[28,31]

Celiac disease is characterized by maldigestion and malabsorption of nutrients due to inflammation of gut due to gliadin indigestion. In the GIT celiac disease can be diagnosed by the presence of villous atrophy with elevated intraepithelial lymphocytes. Cases of DH have milder degree of villous atrophy than that seen with frank celiac disease.[32] Gluten free diet results in miraculous recovery of GIT symptoms whereas cutaneous symptoms take about 2 years to disappear.[33,34] Dapsone helps to tide over this 2 year long lag period. For patients intolerant to

lesions' in the retina are considered pathognomonic for PXE.49 Gastrointestinal bleeding occurs in 15% of cases, with patients presenting with symptoms of melena and hemetemesis.[48]

F. Kaposi Sarcoma (KS)

There are multiple subtypes of KS. KS is a tumor tied to infections with human herpesvirus 8, with staining for D2-40 and LYVE-1 indicating a lymphatic endothelial cell origin.[50] Cutaneous lesions are seen in almost every patient with KS. These lesions generally arise on the lower extremities or head and neck as macules of a pink, red, brown, or violaceous hue that evolve frequently into papules, nodules, or plaques.[51]

As per autopsy findings in HIV patients with KS, the GIT is involved in 50-80% cases of KS in the presence of skin lesions.[52] Gastrointestinal lesions may occur anywhere along the GIT. The oropharynx is the most common site of involvement, where a violaceous stain on the hard palate is often seen. KS of the GIT can have significant morbidity when leading to obstruction, acute appendicitis, severe GI bleed, malabsorption, weight loss, or diarrhea.[52]

Cutaneous Manifestations of Heredietary Gastrointestinal Cancers

About one third of the colorectal cancers are familial and some of them have a genetic basis. Heredietary malignancies include nonpolyposis and polyposis colorectal cancer, hamartomatous polyposis, and Cronkhite-Canada syndrome. The early diagnosis of these syndromes is imperative, so that appropriate surveillance and prevention can be initiated. These syndromes are briefly described below.

A. Hereditary nonpolyposis colon cancer or Lynch syndrome (LS)

LS is an autosomal dominant disorder that is caused by germline mutations in the mismatch repair genes MLH1,MSH2, MSH6, and PMS2.[53] It is associated with colon cancer along with an increased risk of developing endometrial, urologic, small bowel, ovarian, hepatobiliary, and brain cancers. MuireTorre syndrome (MTS) is a variant of LS characterized by all of the typical LS tumors along with cutaneous involvement. Skin manifestations include sebaceous adenomas, epitheliomas, carcinomas, or multiple keratoacanthomas.[54]

B. Familial adenomatous polyposis (FAP) and Gardner syndrome (GS)

FAP and GS result from a germline mutation in the APC gene, a tumor suppressor gene located on the long arm of chromosome 5 (5q21-q22).[55] Patients with FAP and GS are predisposed to malignancies, including duodenal, thyroid, brain (most often medulloblastomas), adrenal, and liver cancers in addition to CRC.[54] Gardner's syndrome in addition has various cutaneous features which include epidermoid cysts, lipomas, desmoid tumors, and dental abnormalities.[54]

C. Hamartomatous Polyposis Syndromes

Peutz-Jeghers syndrome [PJS]

It is caused by germline mutations in the STK11 gene present on chromosome 19p13.3,[56] is characterized by hamartomatous polyposis, mucocutaneous pigmentation, and an increased risk of visceral malignancy. Mucocutaneous pigmented lesions are found in 95% of patients of PJS, usually develop in childhood and often precede GI symptoms. The small melanotic macules not only cluster around the mouth, nostrils, eyes, digits, dorsal or volar aspects of the hands and feet, and the perianal region but also have been reported on the vermillion borders of the lip, labial mucosa, palate, and tongue.[54]

Cowden syndrome

It is the most common phosphatase and tensin homolog hamartomatous tumor syndrome,[57] with mucocutaneous lesions like trichilemmomas, oral papillomatosis, facial papules, and acral keratoses along with increased risk for breast, colon, and thyroid cancers.[54]

Bannayan-Riley Ruvalcaba syndrome

It is characterized by hamartomatous gastrointestinal polyps, hyperpigmentation of glans penis or vulva, macrocephaly, hemangiomas, and developmental delay.[58]

Cronkhite-Canada syndrome

It is characterized by diffuse gastrointestinal polyposis and ectodermic cutaneous findings including nail dystrophy (present in 98% of affected individuals), alopecia, and diffuse hyperpigmentation.[59]

II. CUTANEOUS MANIFESTATIONS OF LIVER DISEASE

Liver diseases can be broadly classified into-acute & chronic liver diseases.

infection.[69] Cutaneous findings are secondary to immune complex deposition & include palpable purpura, livedo reticularis, acrocyanosis, haemorrhagic bullae,urticaria and ulceration.[70] Preceeding HCV infection has been reported in upto 30% of patients with the cutaneous variant of PAN.[71] A clear association has been found between HCV infection and Porphyria cutanea tarda (PCT), with anti-HCV antibodies found in upto two-thirds of these patients.[72] Overall PCT appears to be uncommon as a manifestation of HCV positivity. A distinctive dermatosis termed Necrolytic Acral Erythema appears to occur almost exclusively in individuals with HCV infection.[73]

HCV infection has been very variably (0.1%-35%) associated with lichen planus, especially in mucosal erosive or long standing disease.[70]

Cutaneous Manifestations of Primary Biliary Cirrhosis (PBC) and Biliary Tract Disease

From the dermatological standpoint, primary biliary cirrhosis (PBC) is the most important biliary tract disease. The cutaneous features of significance are marked itch, excoriation, hyperpigmentation and various xanthomatous lesions due to secondary hyperlipidaemia.[74] Xanthelasma, palmar crease, tuberous and tendinous xanthomas may all occur.

III. CUTANEOUS MANIFESTATIONS OF PANCREATIC DISEASE

Apart from jaundice and panniculitis, skin changes in pancreatic disease are uncommon.

Acute pancreatitis

Acute pancreatitis can lead to retroperitoneal bleeding & bluish discolouration of the flank (Grey turner's sign), periumblical area (Cullen's sign), upper thigh (Fox's sign) or scrotum (Bryant's sign).[75]

Chronic pancreatitis

Chronic pancreatitis may be accompanied by skin signs of nutritional deficiencies owing to malabsorption like widespred scaling, hair loss and pigmentation. Livedo reticularis has been described in both acute and chronic pancreatitis as 'Walzel's sign'.[76]

Systemic nodular fat necrosis is a rare condition that affects 2-3% of patients with pancreatic disease, out of which, pancreatitis (both acute & chronic) accounts for about two-thirds and carcinoma one-third of the cases.[77] Clinically patient presents with fever, abdominal pain,blood eosinophilia, synovitis of small joints and nodular tender lesions, usually 1-3 cm in diameter with predilection for trunk and lower extremities. Lesions persist for 2-3 weeks and usually heal without scar formation.

Necrolytic migratory erythema is a cutaneous reaction that occurs in context of hyperglucagonaemia, usually due to glucagonoma, The typical patient with glucagonoma is a woman 45-65 years of age, presenting with the usual features like weight loss (67%), anaemia (33%), glucose intolerance (56%) and necrolytic migratory erythema (72%).[78] The rash is itchy or burning and particularly affects flexural sites on the lower abdomen, groin, buttocks and thighs. It is initially macular, extending to form superficially eroding areas of erythema that progress to fragile vesicle and bullae formation. Irregular centrifugal extension of the annular lesions causes a marginated, often crusted, polycyclic or geographical pattern.

CONCLUSION

The closely related origins of the skin and the gastrointestinal system make for a fascinating grouping of diseases with concomitant involvement of these two important organ systems. The cutaneous signs sometimes provide a clue for the underlying systemic condition and vice versa. Thus, skin at times acts a mirror to underlying gastrointestinal diseases. This calls for a collaboration among the dermatologists and gastroenterologists so that early diagnosis of diseases involving both the systems is possible, avoiding undue wastage of resources and time, thus, providing major benefit to the affected patient.

CONFLICTS OF INTEREST: None

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