Review paper

Association between dermatological diseases and pathological changes in the gastrointestinal tract

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Abstract

A lot of primary dermatologic diseases, such as mastocytosis and *epidermolysis bullosa*, have a tendency to manifest their symptoms in the digestive tract. Malignant melanoma is one of the most common neoplasms that form metastases in the intestines. Almost all patients with systemic scleroderma have symptoms resulting from a pathological process that takes place in the esophagus. On the other hand, the skin is the area of extraintestinal manifestation of various gastrointestinal pathologies. The strongest linkage is observed between *dermatitis herpetiformis*, *pyoderma gangrenosum*, *erythema nodosum* and intestinal inflammation. Bazex syndrome, *acanthosis* nigricans and the sign of Leser-Trélat are paraneoplastic syndromes that suggest existence of gastrointestinal cancers, that is why thorough knowledge of their clinical characteristic is extremely important.

Key words: mastocytosis, systemic scleroderma, *erythema nodosum*, *dermatitis herpetiformis*, paraneoplastic syndromes, Peutz-Jeghers syndrome, Gardner syndrome.

Introduction

All atypical skin changes affecting patients consulted by doctors of various specialties should always generate interest. This statement applies especially to gastroenterologists, surgeons and rheumatologists, for whom the dermatological signs may become an important diagnostic clue.

Primary skin diseases may alter functioning of the gastrointestinal tract. Also, a wide range of dermatological signs may result from pathological processes that take place at each level of the alimentary canal. The aim of this article is to present several syndromes that may manifest on the skin as well as in the gastrointestinal tract.

Gastrointestinal signs that may occur in the course of primary disorders of the skin and mucous membranes

Malignant melanoma (melanoma malignum) is a highly malignant neoplasm that originates from melanocytes [1]. This heterogeneous tumour may have various morphological, histological and biological features. That is why there are several clinical types of malignant melanoma: superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, subungual melanoma and acral lentiginous melanoma [2].

Malignant melanoma may also primarily arise from uvea, meninges, especially the pia mater and arachnoid mater, mucous membranes of the nasal cavity, the oral cavity and the anus. Malignant melanoma is also responsible for 1-3% of cases of primary gastrointestinal malignant tumours, where the primary lesions may grow at each level of the alimentary canal. However, metastases from the cutaneous form of malignant melanoma to the gastrointestinal tract are much more common [3]. Malignant melanoma is one of the most frequent causes of metastases to the alimentary canal. The diagnosis of metastases and dermatological changes may be synchronized, but the metastases are usually found some time after removal of the primary cutaneous lesions. The mean time between the diagnosis of malignant melanoma and finding of the metastases in the gastrointestinal tract is nearly 40 months. The malignant melanoma metastases to the alimentary canal are usually asymptomatic. These tumours are found in only 1.5-4.49% of living patients. Many more metastases are diagnosed in post-mortem examinations. The tumours are found in small intestine (59%), colon (22%), ventricle (20%), rectum (5%) and oesophagus (4%) [4].

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Possible symptoms of the malignant melanoma metastases to the gastrointestinal tract are not specific and include gastrointestinal bleeding, abdominal pain, signs and symptoms of ileus or intussusception, and weight loss.

Mastocytosis is a disorder caused by excessive growth of mastocytes in the skin, bone marrow, the liver, the spleen and lymph nodes. Due to various clinical manifestations the disease is subclassified as follows: cutaneous mastocytosis, that may take the form of *urticaria pigmentosa* or *mastocytoma*; indolent systemic mastocytosis (ISM) – indolent mastocytosis of the bone marrow, systemic mastocytosis with an associated clonal haematological non-mast cell lineage disease (SM-AHNMD), mast cell leukaemia, mast cell sarcoma and extracutaneous mastocytosis [5].

Gastrointestinal symptoms in the course of mastocytosis are common; some studies estimate the correlation at nearly 85% [6]. The patients suffer from recurrent abdominal pain (51%), diarrhoea (43%), nausea and vomiting (28%). It is thought that these symptoms are caused by interactions among mediators released in excess by proliferating mastocytes. The pain associated with mastocytosis may be located in the epigastric region, and then is usually a result of gastric or duodenal peptic ulcers caused by overproduction of gastric acid that is stimulated by histamine released from mastocytes. The ulcers are numerous, extensive and resistant to standard treatment. Those features may erroneously indicate Zollinger-Ellison syndrome. The diarrhoea is caused by hypersecretion of gastric acid, malnutrition, oedema and lesions in the intestinal mucous membrane or poor peristalsis altered by infiltration of mastocytes [6]. Gastrointestinal bleeding is a less common symptom of systemic mastocytosis and affects nearly 11% of patients. It may be a result of gastric and duodenal peptic ulcers or oesophageal varices developing in the course of portal hypertension. Hepatomegaly is found in 41-72% of patients with mastocytosis and develops due to massive mastocytes infiltration in the liver, that in 4% of cases is followed by cirrhosis [6]. Endoscopic findings observed at each level of the gastrointestinal tract in the course of mastocytosis are presented in Table 1.

Systemic sclerosis (scleroderma) is a chronic disorder of connective tissue that is characterized by progressive fibrosis of the skin and internal organs, presence of specific autoantibodies and vasculopathy. There are three main subtypes of scleroderma: diffuse systemic sclerosis, limited systemic sclerosis, and systemic sclerosis *sine scleroderma*. Fifty-five-ninety percent of patients with systemic sclerosis suffer from certain gastrointestinal symptoms [7]. These symptoms are usually caused by motor dysfunction and damage to the mucous membranes and affect mainly the oesophagus and distal segments of the alimentary canal, rarely the stomach, the small intestine and the colon. Autoantibodies may play a significant role in the pathogenesis of these changes.

Some of available analyses indicate that patients with severe gastrointestinal complications have significantly higher levels of antibodies against muscarinic acetylcholine receptor 3 [8]. The levels of factors causing fibrosis and progressive damage to the intestinal wall, such as transforming growth factor β (TGF-β) and connective tissue growth factor (CTGF), are also higher [7]. In 10% of patients the gastrointestinal symptoms develop before the dermatological changes. The most common symptoms are regurgitation, eructation, heartburn, retrosternal pain and dysphagia, and they are caused by altered peristalsis in lower parts of the oesophagus. In the stomach, gastroparesis and gastroscopic signs of "watermelon stomach" may be observed. Gastric antral venous ectasia (GAVE) may result in upper gastrointestinal bleeding. The symptoms caused by intestinal dysfunction are diarrhoea and chronic constipation. Bacterial overgrowth and pseudo-obstruction may result in severe abdominal pain, malnutrition and weight loss.

Epidermolysis bullosa is a group of genetically determined bullous skin diseases (genodermatoses) in which multiple bullae occur after various mechanical injuries. There are three main types of epidermolysis bullosa if classified according to the level of skin where the process of epidermolysis takes place: in epidermolysis bullosa simplex (EBS) the bullae are formed within the epidermis, in epidermolysis bullosa junctionalis (EBJ) within the dermo-epidermal junction, and in epidermolysis bullosa epidemolytica within the dermis. Carmi syndrome is one of the subtypes of epidermolysis bullosa junctionalis in which pyloric atresia is one of the features. Epidermolysis bullosa with pyloric atresia is an autosomal recessive disease caused by mutation in genes encoding integrin

Table 1. Changes found at particular levels of the gastrointestinal tract in the course of mastocytosis

Oesophagus	Stomach and duodenum	Small intestine	Colon and rectum
• Oesophagitis • Oesophageal strictures • Oesophageal varices	• Peptic ulcers • Thickening of the ventrical and duodenal folds • Limited hyperaemic and nodular regions in the mucous membranes	• Thickening and oedema of folds in the intestinal wall • Widening of the intestinal lumen	• Nodular lesions • Numerous polyps • Telangiectasia • Hyperaemic regions in the rectal mucous membrane

Table 2. Diseases associated with erythema nodosum [13]

Infections	Miscellaneous disorders
Bacterial:	Autoimmune disorders:
• Streptococcus A	• Ulcerative colitis
• Bartonella henselae – cat scratch disease	• Crohn's disease
	• Behçet's disease
• Yersinia	• Sarcoidosis
• Salmonella	• Spondyloarthropathies
• Shigella	Malignant neoplasms:
• Campylobacter	• Lymphoma
• Mycoplasma	• Leukaemia
Viral:	Side effects of drug intake:
• HIV	• Sulphonamides
• HSV	• Phenytoin
• HBV	• Oral contraceptives
• HCV	• Minocycline
• EBV	• Salicylates
Fungal:	• Idiopathic *erythema nodosum*
• Histoplasmosis	
• Coccidioidomycosis	
Parasitic:	
• Toxoplasmosis	
• Amoebiasis	
• Giardiasis	
• Ascariasis	

α6 and β4. Generalized bullae are associated with inborn pyloric, oesophageal or duodenal atresia, nail dystrophy and enamel hypoplasia [1, 2]. Pyloric atresia was also described in several cases of epidermolysis bullosa simplex: in the Dowling-Meara syndrome. Strictures in the oesophagus, constipation, tongue strictures, ankyloglossia and microstomia are common in the dystrophic type of epidermolysis bullosa [9].

Ehlers-Danlos syndrome is a group of genetically determined disorders caused by various defects in collagen synthesis. This results in cutaneous hyperelasticity and fragility, joint hypermobility, and vascular diathesis. Various gastrointestinal complications are characteristic for the Ehlers-Danlos syndrome type IV, the vascular type, in which multiple, enormous diverticula, rectal prolapse, hernias, gastrointestinal bleeding and spontaneous intestinal perforation may occur. The perforation usually affects younger patients and is situated in the sigmoid colon [10].

Dermatological manifestations of gastrointestinal disorders

Inflammatory bowel disease is an idiopathic disorder in which dermatological manifestations are frequently observed. Nearly 30% of patients with inflammatory bowel disease present with various skin changes [11]. *Pyoderma gangrenosum*, *erythema nodosum*, perianal changes, aphthous stomatitis, urticaria and purpura are the most common dermatological signs. There have been several cases of leukocytoclastic vasculitis described in the course of ulcerative colitis. Moreover, the connection between inflammatory bowel disease and psoriasis is also currently taken into consideration. Skin changes in the course of inflammatory bowel disease usually progress during relapses of the disorder.

Erythema nodosum is the most common form of panniculitis observed in clinical practice. The acute type is characteristic for young women and is preceded by severe headaches, fatigue and malaise. Cutaneous and subcutaneous, limited, painful tumours without signs of necrosis are found on lower legs, thighs and forearms and disappear after 3-6 weeks without scarring. *Erythema migrans* is the chronic form of *erythema nodosum*.

Erythema nodosum may develop in the course of infections, autoimmune disorders and other diseases that are summarized in Table 2.

Erythema nodosum in the course of inflammatory bowel disease is 3 to 6 times more frequently observed in women. There is a correlation between exacerbations of the bowel disease and manifestation of the dermatological symptoms of *erythema nodosum*. *Erythema nodosum* is also more common in patients with spondyloarthropathies associated with inflammatory bowel disease [12].

Pyoderma gangrenosum (PG) is a rare skin disorder with an unknown aetiology. It is characterized by painful, destructive, spreading ulcers, covered with necrotic tissue with elevated borders [2]. Immunological dysfunction regarding cell-mediated reactions, circulating immune complexes, cytokines and altered functioning of neutrophils, monocytes and lymphocytes play a significant role in the pathogenesis of PG. Pathergy, which is a reaction characteristic for the disorder, involves formation of rapidly spreading ulcerating lesions after minor injuries such as subcutaneous injections. *Pyoderma gangrenosum* is associated with systemic diseases in 50% of patients. This skin disorder may occur in the course of malignant neoplasms, especially leukaemias, vascular disorders, diabetes, spondyloarthropathies, systemic lupus erythematosus, psoriatic arthritis, and liver diseases [14]. It is observed in 1-2% of patients with inflammatory bowel disease [15]. *Pyoderma gangrenosum* is more frequent in patients with ulcerative colitis than with Crohn's disease. There are several clinical types of the disorder: ulcerative – with rapidly suppurating ulcers; pustular – discrete self-limited pustules are usually observed in patients with inflammatory bowel disease; bullous – superficial blisters that may progress to ulcers.

Coeliac disease is no longer considered an isolated disorder of the gastrointestinal tract, and is regarded as a systemic disease. Gluten hypersensitivity may develop as gluten enteropathy, dermopathy, gluten ataxia, or

Table 3. Strength of evidence for association between gluten intolerance and skin diseases [16]

	Proven association between gluten hypersensitivity and the dermatological disorder	Improvement after gluten-free diet and/or serological markers of coeliac disease	Coexistence of gluten intolerance and skin changes in case studies
Autoimmune disorders	*Dermatitis herpetiformis*	*Alopecia areata* Dermatomyositis Cutaneous vasculitis	Linear IgA bullous dermatosis Vitiligo Systemic lupus erythematosus Lichen sclerosus
Allergic diseases		Urticaria Atopic dermatitis Prurigo nodularis	
Inflammatory diseases		Psoriasis	*Pustulosis palmaris et plantaris* Erythroderma *Pityriasis rubra pilaris*
Miscellaneous disorders		Chronic ulcerative stomatitis	Annular erythema *Cutis laxa* Skin amyloidosis Ichthyosis *Leukonychia transversa*

encephalopathy. There are numerous reports connecting gluten intolerance with various skin disorders, which are summarized in Table 3 [16].

Duhring's disease (*dermatitis herpetiformis*) is an autoimmune bullous disease associated with intolerance toward alcohol insoluble fractions of gluten: gliadin, the protein found in wheat; secalin, isolated from rye; avenin, found in oats; and hordein, in barley. Duhring's disease is caused by IgA deposits in the papillary dermis, where they trigger an immunological cascade reaction, sequestration of neutrophils, and activation of complement in response to chronic stimulation of intestinal mucous membrane by gluten proteins.

Coeliac disease and *dermatitis herpetiformis* have been observed in genetically predisposed individuals with specific human leukocyte histocompatibility antigens: HLA A1, HLA B8, HLA DQ2. Autoimmunization takes place due to antigen similarity between gluten proteins and proteins of predisposed people [1]. Transglutaminase 3, which is a cytosolic enzyme engaged in building of cell membranes during keratinocyte differentiation, is the main autoantigen. Epidermal transglutaminase is highly homologous with tissue transglutaminase TG2 that is found in the intestines [17].

Duhring's disease manifests clinically as blisters, pustules, plaques and excoriation on the extensor surface of elbows, knees, the gluteal region and the trunk. They are associated with severe pruritus. Most patients with *dermatitis herpetiformis* present intestinal lesions characteristic for coeliac disease; however, they do not always have symptoms, and that often leads to misdiagnosis and delay in proper treatment.

Cronkhite-Canada syndrome is an uncommon systemic disorder described first in 1955 by Leonard W. Cronkhite Jr and Wilma J. Canada [18]. Less than 400 cases of this disorder have been described, so far. Cronkhite-Canada syndrome is not a genetic disease, but its aetiology has not yet been discovered. A link to autoimmune disorders has been suggested as the disease often coexists with systemic lupus erythematosus, rheumatoid arthritis and systemic sclerosis. The syndrome is characterized by gastrointestinal polyposis, dystrophic nails, alopecia, regions of hyperpigmentation with diameter ranging to 10 cm, and xerostomia. Nails may undergo such processes as onychodystrophy, when they become thinner, stratify and change in colour; onycholysis, that is detachment of the nail plate from the nail bed; or onychomadesis, that is a general loss of fingernails and toenails that usually occurs several weeks before other symptoms of the disease. Alopecia may develop instantly, leading, in a few days, to total loss of hair from the scalp, the face, eyebrows, axillary and genital regions and limbs. Changes that occur in the gastrointestinal tract involve thickening of the gastric mucosa imitating Ménétrier disease, atrophic lesions and polyps. The polyps are small, "strawberry-like". They are hamartomas covered with pathological mucosa. This changed mucous membrane may lead to water-electrolyte imbalance and malabsorption that cause diarrhoea, weight loss, malnutrition and cachexia. Chvostek and Trousseau signs, glossitis, and oedema may also be observed secondary to dietary deficiencies rather than as primary symptoms. Cronkhite-Canada syndrome is associated, in 15% of cases, with

malignant neoplasms of the stomach and the large intestine. The sigmoid colon and the rectum are the most common regions affected by neoplasms [19].

Dermatological paraneoplastic syndromes in malignancies of the gastrointestinal tract

Skin symptoms are observed in a lot of patients with malignant neoplasms of internal organs. Some gastrointestinal tumours are capable of overproduction of proteins that have certain regulatory functions such as epidermal growth factor (EGF) and TGF that stimulate keratinocyte proliferation.

Acanthosis nigricans is a disorder in which focal, hyperkeratotic, usually symmetrical lesions and verrucas occur on the face, axillae, elbows, knees, in the intermammary region and around the umbilicus and the anus [20]. There are several types of *acanthosis nigricans* according to the aetiology of the syndrome. These types are summarized in Table 4.

Insulin and insulin-like growth factors are responsible for dermatological lesions in the benign form of *acanthosis nigricans*, while TGF-α and EGF cause the symptoms in the malignant form [21].

Fifty to ninety percent of cases of *acanthosis nigricans maligna* are associated with adenocarcinoma located in the abdominal cavity, and 55-61% are found in the stomach [22, 23]. Nearly 61% of cases of *acanthosis nigricans maligna* are diagnosed simultaneously with an associated neoplasm. However, in 17.6% of patients the skin changes are signs of an underlying condition [20]. The oral mucous membrane undergoes pathological transformation in 25-50% of cases. The filiform papillae of the tongue elongate, and verrucous lesions appear on the oral commissures. These pathological findings are usually skin-coloured. Sudden manifestation of *acanthosis nigricans* in patients older than 40 years without earlier signs of endocrine pathologies or genetic disorder should always suggest thorough investigation to exclude malignancies [20].

Acanthosis nigricans maligna may be associated with the tripe palms syndrome, which involves thickening of dermatoglyphs due to connective tissue hyperplasia that makes the skin papillae more prominent, similar to bovine intestinal mucous membrane with villi. This sign increases the risk of malignant neoplasm development. Tripe palms syndrome is associated with adenocarcinoma in 53% of cases and in 35% of patients the gastric cancer is the underlying condition [24].

Leser-Trélat sign is a rare paraneoplastic syndrome for which sudden manifestation of numerous verrucae senilis is characteristic. These lesions are usually flat or slightly raised above the skin surface, well defined, with pigmentation matching the overlying skin. Occasionally, they are prominent, verrucous, hyperkeratotic, brown, rarely pedicled [25]. They cover the trunk irregularly, sometimes forming a Christmas-tree pattern. These lesions do not undergo malignant transformation; however, they coexist with gastrointestinal tumours. They may herald colon cancer, gastric cancer or tumours of other parts of the alimentary canal. In 1993 Ellis and Yates suggested that sudden manifestation of numerous warts is caused by TGF that exceeds the threshold level and triggers proliferation of keratinocytes in predisposed individuals [26].

Florid cutaneous papillomatosis (*papillomatosis florida cutis verruciformis*) is another paraneoplastic syndrome characterized by verrucous eruptions with brown pigmentation and smooth, velvety surface. The lesions are

Table 4. Clinical forms of acanthosis nigricans

Type of acanthosis nigricans	Characteristic features
Type 1 – *Acanthosis nigricans benigna hereditaria*	Unilateral lesions caused by sporadic autosomal dominant mutations and familial autosomal dominant forms
Type 2 – *Acanthosis nigricans benigna*	Associated with endocrine disorders such as diabetes, Addison's disease, acromegaly, Cushing's syndrome. There are two subtypes of *acanthosis nigricans benigna*: subtype A: HAIR-AN syndrome – hyperandrogenaemia, insulin resistance, *acanthosis nigricans*. This subtype is associated with polycystic ovarian syndrome. Subtype B: related to diabetes, ovarian hyperandrogenaemia, and such autoimmune disorders as systemic lupus erythematosus, systemic sclerosis, Sjögren syndrome, Hashimoto thyroiditis
Type 3 – Pseudo-*acanthosis nigricans*	Associated with obesity and insulin resistance
Type 4 – Drug-induced *acanthosis nigricans*	Substances that may induce skin lesions characteristic for *acanthosis nigricans* are nicotinic acid, diethylstilbestrol, growth hormone
Type 5 – *Acanthosis nigricans maligna*	This is a paraneoplastic syndrome usually associated with adenocarcinoma of the gastrointestinal tract, most frequently of the stomach, genitourinary tract, breast cancer and lymphomas

situated on proximal parts of lower limbs, hands, lips, oral mucosa and the nose. Epidermal deposits may imitate cactus spines. This syndrome is associated with malignancies in 100% of cases, especially with adenocarcinoma of the stomach and intestines [27].

Hypertrichosis lanuginosa acquisita manifests by rapid growth of long, thin, fair hair similar to *lanugo* on the face and auricles, but sparing the hands, feet and genital region. *Hypertrichosis lanuginosa acquisita* may be caused by metabolic and endocrine dysfunctions, such as hyperthyroidism, *anorexia nervosa* or porphyria. This may also be a drug-induced syndrome (*Ciclosporinum*, *Minoxidilum*, interferon, *Phenytoinum*, glucocorticosteroids).

Nearly 50 cases of *hypertrichosis lanuginosa acquisita* as a paraneoplastic syndrome have been described so far, sometimes coexisting with *acanthosis nigricans maligna* or tripe palms syndrome. Signs of *hypertrichosis lanuginosa acquisita* in women suggest existence of colon cancer, while in men they suggest lung cancer or colon cancer [28].

Bazex syndrome is an obligatory paraneoplastic syndrome. It is characterized by psoriatic-like lesions. The syndrome is nine times more common in men. Primarily, the hyperkeratotic lesions occur in acral regions, on fingers, toes and auricles. Hyperkeratotic plaques spread, affecting palms, soles, knees, elbows and even the trunk. Bazex syndrome is always associated with malignant neoplasms; they are tumours of the upper respiratory tract and the beginning of the alimentary tract in 80% of cases, and the histopathological investigation is positive for squamous cell carcinoma in 64%. Fifty percent of newly diagnosed patients already have positive regional lymph nodes [29].

Genetically determined syndromes with predisposition to neoplastic transformation in the gastrointestinal tract and with characteristic dermatological signs

Hamartomatous polyposis syndromes

Peutz-Jeghers syndrome is an autosomal dominant disorder characterized by hyperpigmentation of the skin and mucous membranes with gastrointestinal polyposis. The diagnosis may be made in patients with hamartomatous polyps, accumulation of melanin in vermilion, and positive family history for the Peutz-Jeghers syndrome. The lesions in the skin and mucous membranes in the course of Peutz-Jeghers syndrome usually occur in infancy and disappear in adolescence. The macules are dark brown or blue-brown, with diameter 1-5 mm, located on the vermilion in 94% of patients, on buccal mucous membranes in 66%, on hands in 74% and on feet in 62% of cases [30, 31]. They may also occur in the genital region, around the eyes and the anus. The macules are caused in 95% of cases by macrophages loaded with melanin found in the dermis. Peutz-Jeghers polyps are typical hamartomatous lesions. They affect nearly 88% of patients. The hamartomas occur in the small intestine (64%), large intestine (64%), stomach (49%), and rectum (32%) [30, 31]. Occasionally they are found in the renal pelvis, the urinary bladder, lungs, and the nasal passage [32]. They usually begin growing in the first decade of life, causing symptoms after 10 to 20 years, leading to ileus in 43% of patients, abdominal pain (23%), and blood in the stool (14%). Intussusception is the most common complication of the disease [30, 31]. Peutz-Jeghers syndrome is caused by mutation in the STK11/LKB 11 gene situated on chromosome 19p13.3 and has incomplete penetrance and variable expressivity. The gene encodes a serine-threonine kinase that is a tumour-suppressor protein [32, 33]. The mutation increases the risk for carcinogenesis to 93% throughout life [34]. Malignant tumours develop in the oesophagus, stomach, small intestine, colon, pancreas and breast in women. That is why patients with Peutz-Jeghers syndrome should be thoroughly monitored with regular endoscopic investigations. It is recommended to remove polyps larger than 1 cm or rapidly growing [30].

Cowden syndrome is one of the diseases composing the PHTS-PTEN group (phosphatase and tensin homologue hamartoma tumour syndrome) with Bannayan-Riley-Ruvalcaba syndrome and Proteus syndrome [35]. The skin lesions characteristic for Cowden syndrome are trichilemmoma (that is a skin-coloured nodule attached to the hair follicle, found around lips, nose and ears), acral keratosis and verrucous pustules. Lipomas, neuromas, haemangiomas and fissured tongue may also be found. Hamartomatous polyps develop in the gastrointestinal tract: in the stomach (75%), the colon (66%) and the duodenum (37%). The disease is associated with higher risk of breast cancer, endometrial cancer and non-medullary thyroid cancer [36].

Adenomatous polyposis syndromes

Gardner syndrome is a rare autosomal dominant disorder with high penetrance, that is characterized by intestinal polyposis and tumours of bones and soft tissue. The disease is one of the forms of familial polyposis described by Gardner et al. in the mid 20th century. The syndrome is associated with mutation in the APC gene

Table 5. The Amsterdam criteria II

- Three or more family members with HNPCC-related cancers, one of whom is a first degree relative of the other two
- Two successive affected generations
- One or more of the HNPCC-related cancers diagnosed under age 50 years
- Familial adenomatous polyposis (FAP) has been excluded
- The tumours have been histopathologically verified

found on chromosome 5q21-q22. The mutation characteristic for Gardner syndrome causes extra-intestinal manifestations and malignant transformation of intestinal polyps. Mutation of the MYH (1p 34.3-p32.1) gene and such environmental factors as diet and cigarette smoking have an additional effect. Most cases of Gardner syndrome have been described among members of certain families. Nearly one third of cases were caused by sporadic mutations [37]. Epidermal cysts are the most common dermatological lesions observed in Gardner syndrome. These changes are benign, develop from sebaceous glands, and are filled with sebum and deposits of keratinocytes. They are elastic, movable nodules covered with normal skin. Epidermal cysts in Gardner syndrome manifest in early infancy in atypical locations: on the face, limbs and scalp. They are usually numerous. Apart from those lesions, skin fibromas, lymphomas, leiomyomas, neurofibromas and regions of hyperpigmentation may be observed.

Colon polyps in Gardner syndrome are numerous and have a nearly 100% probability of malignant transformation. Other neoplasms associated with Gardner syndrome are carcinoma of the ampulla of Vater, hepatoblastoma, medulloblastoma, glioblastoma, craniopharyngioma, thyroid cancers, osteosarcoma, chondrosarcoma and liposarcoma [2, 38].

Hereditary non-polyposis colon carcinoma and dermatological manifestations

Muir-Torre syndrome is a variant of hereditary non-polyposis colon carcinoma (HNPCC), caused by mutations in the hMLH1 and hMLH2 genes. The disease is autosomal dominant. Patients with Muir-Torre syndrome fulfil the Amsterdam criteria II for HNPCC (Table 5) and have characteristic skin changes: numerous sebaceous cysts on the face and keratoacanthomas. The Muir-Torre syndrome is associated with higher risk of cancer of the stomach, intestines, the endometrium, kidneys and ovaries [39].

To summarize, a lot of gastrointestinal disorders may lead to specific dermatological manifestations. Correct diagnosis of the skin signs may help in the differential diagnosis of such underlying conditions as cancers that may be serious in prognosis. On the other hand, all physicians should be aware that patients suffering from chronic dermatological conditions may have severe gastrointestinal symptoms, which the doctors should alleviate and thus prevent serious complications.

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