

Skin manifestations of pancreatic diseases

Lumir Kunovsky^{a,b,c,d,e}, Petr Dite^{f,g}, Eva Brezinova^{b,h}, Libuse Sedlakovaⁱ, Jan Trna^{b,e}, Petr Jabandziev^{b,j,k}

Although symptoms of pancreatic diseases such as pancreatitis, acute and chronic and, carcinoma of the pancreas are mainly gastrointestinal in nature, the extra-pancreatic symptoms are also important. These include skin symptoms, such as pancreatic panniculitis, acanthosis nigricans, livedo reticularis, necrolytic migratory erythema, cutaneous signs of hemorrhage, as in persons with severe acute pancreatitis, or the finding of cutaneous metastases of pancreatic carcinoma, which may be a sign of advanced disease. The pancreas is therefore one of those organs for which diagnosis and therapy are often multidisciplinary. In this review article, we summarize current knowledge of the possible skin manifestations of pancreatic disorders.

Key words: acute pancreatitis, chronic pancreatitis, pancreatic cancer, skin lesions, pancreatic panniculitis, livedo reticularis, acanthosis nigricans, necrolytic migratory erythema

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^aDepartment of Surgery, University Hospital Brno, Czech Republic

^bFaculty of Medicine, Masaryk University, Brno, Czech Republic

^c2nd Department of Internal Medicine – Gastroenterology and Geriatrics, University Hospital Olomouc, Czech Republic

^dFaculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic

^eDepartment of Gastroenterology and Digestive Endoscopy, Masaryk Memorial Cancer Institute, Brno, Czech Republic

^fDepartment of Gastroenterology and Internal Medicine, University Hospital Brno, Czech Republic

^gFaculty of Medicine, University of Ostrava, Czech Republic

^h1st Department of Dermatovenerology, St. Anne's University Hospital, Brno, Czech Republic

ⁱDepartment of Dermatology, Military Hospital Brno, Czech Republic

^jDepartment of Pediatrics, University Hospital Brno, Czech Republic

^kCentral European Institute of Technology, Masaryk University, Brno, Czech Republic

Corresponding author: Petr Jabandziev, e-mail: jabandziev.petr@fnbrno.cz

INTRODUCTION

Acute pancreatitis, chronic pancreatitis, and pancreatic cancer are among the most common pancreatic disorders. The global incidence of acute pancreatitis is 34/100 000 inhabitants/year¹. Worldwide, the incidence of chronic pancreatitis is 5–14/100 000. The incidence in the Czech Republic is 7.9/100 000 inhabitants/year². There has been an alarming increase in the incidence of pancreatic cancer in the Czech Republic (22/100 000 in 2018) to a level that is among the highest in the world³. In addition to obvious gastrointestinal symptoms, pancreatic diseases may present less frequently with various skin symptoms⁴.

In this review article we discuss the skin symptoms of diseases of the pancreas. We systematically searched the literature from databases MEDLINE, PubMed and Google Scholar.

Table 1 provides an overview of cutaneous manifestations and pancreatic diseases². After icterus, which is the skin manifestation most commonly presenting in cases of bile duct obstruction in acute biliary pancreatitis, chronic pancreatitis and pancreatic cancer, additional, less frequently co-occurring symptoms and skin diseases are listed in the table.

Table 1. Skin changes in pancreatic diseases.

Icterus (jaundice)
Pancreatic panniculitis
Hemorrhagic manifestations (Cullen's, Grey Turner's, Fox's signs)
Cutaneous metastases (Sister Mary Joseph nodules)
Livedo reticularis (Walzel's sign)
Acanthosis nigricans
Necrolytic migratory erythema
Cutaneous wheal

(modified from Miulescu et al.⁴)

PANCREATIC PANNICULITIS

Sometimes known as pancreatic fat necrosis, this disease affects about 2–3% of all patients with pancreatic disease⁵. Panniculitis was first described in 1883 by Hans Chiari. Subsequently, this skin disease was identified in the acute form of pancreatitis as well as in chronic pancreatitis and in pancreatic cancer⁶. Panniculitis predominantly affects men. It occurs with particular frequency in individuals with the alcoholic form of the disease⁷. A mechanism that would explain the relationship between

pancreatic disease and the finding of panniculitis is not precisely known. One theory suggests the release of pancreatic enzymes into the bloodstream that causes an increase in vascular permeability with subsequent hydrolysis of neutral lipids to fatty acids and glycerol, thereby generating necrosis and, in general, inflammatory processes⁸. Another hypothesis is that degradation of pancreatic enzymes is impaired and thus this increase not only in the blood but also in skin lesions⁹. Alpha-1 antitrypsin deficiency also has been considered to have an effect in cases of so-called metabolic panniculitis¹⁰.

Other possible mechanisms include the action of inflammatory cytokines (particularly adipocytokines) or a role of immunocomplexes involving phospholipase 2 as a mediator¹¹.

A special form of panniculitis in chronic pancreatitis is the so-called PPP syndrome, referring to panniculitis + pancreatitis + polyarthritides¹². This syndrome is characterized by a presence of intraosseous fat necrosis. Panniculitis and polyarthritides may not always be associated with pancreatitis; pancreatic carcinoma may also be present¹³. Panniculitis is the first symptom of pancreatic disease to occur in 30–40% of cases, but in cases of pancreatic carcinoma this may be as high as 68% (ref.¹⁴). Clinically, panniculitis is manifested by erythematous and painful subcutaneous nodules that may ulcerate, with brown-colored, viscous to oily fluid exiting the ulcer as a sign of colliquative fat necrosis¹⁵. Panniculitis is most commonly localized in the distal parts of the lower limbs (Fig. 1), especially around the knee joints, but it can be localized elsewhere, for example in the axilla.

Fernandez-Sartorio et al. published their observations in an 88-year-old patient with panniculitis and ampullary adenocarcinoma⁸. After insertion of a biliary stent, pancreatic enzyme levels in serum decreased. Above all, however, skin manifestations were significantly and favorably affected.

NECROLYTIC MIGRATORY ERYTHEMA

This finding is a manifestation of a type of neuroendocrine tumor – a glucagonoma. Clinically, the condition is accompanied by overproduction of glucagon as a part of so-called glucagonoma syndrome. Glucagonoma syndrome is characterized by a presence of diabetes mellitus, stomatitis or glossitis, anemia, weight loss, and the skin condition necrolytic migratory erythema¹⁶. The disease was first described in a diabetic patient with a pancreatic tumor in 1942 (ref.¹⁷). Since then, more than 600 cases involving this disease have been reported¹⁶. The characteristics of glucagonoma include frequent formation of metastases. Approximately 20% of all cases comprise part of the multiple endocrine neoplastic syndrome type 1 (MEN 1) (ref.¹⁸). An open question is whether glucagon *per se* initiates the skin changes or, as seems more likely, whether amino acid or essential fatty acid deficiency causes epidermal protein depletion and necrosis. Also, significantly lower serum zinc levels in those patients with glucagonoma have been reported in the literature¹⁹.



Fig. 1. Panniculitis – indurated nodules in the crural region. From archive of the 1st Department of Dermatovenereology, St. Anne's University Hospital and Faculty of Medicine, Masaryk University, Brno.

Clinically, necrolytic migratory erythema is manifested by the formation of plaques having so-called central lucency or the formation of induced lesions with crusts on the periphery²⁰. Development is quite rapid. Within days, erythematous foci change into necrolytic foci with crusts and subsequent hyperpigmentation. This occurs predominantly on the feet, shins, gluteal region, and forearms.

ACANTHOSIS NIGRICANS

This disease is characterized by hyperpigmented circles of thickened skin, with epidermal acanthosis, the lesions being localized symmetrically most often in the axillae and groin area²¹. In the affected areas, we find skin resembling tree bark or a plowed field (Fig. 2). Acanthosis is a manifestation of insulin-resistant diabetes or obesity²². In patients with acanthosis who lose weight under unclear circumstances, a malignant form of the disease should always be suspected. Hypothetically, acanthosis is associated with metabolic syndrome, which is an etiologic factor in both benign and malignant pancreatic diseases. Metabolic syndrome is associated with secretion of a number of factors, such as insulin-like growth factor (IGF), epidermal growth factor (EGF), and fibroblast growth factor (FGF), leading to fibroblast proliferation and keratinocyte formation²³⁻²⁵. In patients with pancreatic carcinoma and acanthosis nigricans, a clinical symptom is pruritus, accompanied by cutaneous or even mucosal papillomatosis²⁶.



Fig. 2. Acanthosis nigricans on perineum.
From archive of the 1st Department of Dermatovenerology, St. Anne's University Hospital and Faculty of Medicine, Masaryk University, Brno.



Fig. 3. Livedo racemosa.
From archive of the 1st Department of Dermatovenerology, St. Anne's University Hospital and Faculty of Medicine, Masaryk University, Brno.

CUTANEOUS HEMORRHAGIC MANIFESTATIONS IN PERSONS WITH ACUTE PANCREATITIS

Acute pancreatitis has presenting symptoms that include skin changes in the periumbilical area (Cullen's sign) or on the flanks (Grey Turner's sign). These changes also predict severity of the disease and the possibility for complications. They occur in about 3% of people with acute pancreatitis²⁷. Fox's sign is caused by retroperitoneal leakage of hemorrhagic ascites along the fascia of the psoas muscle and iliacus muscle into the ligamentum inguinale and from there into the submucosal space of the upper thigh. The finding is described as ecchymosis of the proximal thigh²⁸.

Cullen's sign, like Grey Turner's sign, is a marker as to the severity of acute pancreatitis, and, according to an earlier publication by Dickson and Imrie²⁹, the mortality rate of acute pancreatitis with findings of these skin changes is up to 37%. A study by Fujiwara et al. of 277 subjects with acute pancreatitis found Cullen's sign in 1.8% of all subjects enrolled³⁰. Cullen's sign is not specific to acute pancreatitis. It has been described, for example, in extrauterine pregnancy, perforated duodenal ulcer, splenic rupture, and hepatocellular carcinoma³¹.

LIVEDO RETICULARIS

Livedo reticularis is a cutaneous lesion characterized by livid reticular skin striations³². Livedo reticularis is a sign of alterations in cutaneous blood circulation associated with a variety of both physiological and pathological conditions. In 1907, Ehrmann described two distinct types of the condition, namely, so-called physiological livedo reticularis and pathological livedo, termed livedo racemosa³³. Today, livedo reticularis is primarily categorized as a benign disease affecting young to middle-aged persons, preponderantly occurring in females. The reticular discoloration is symmetric and mostly reversible. In contrast, pathologic livedo racemosa is an irreversible development and is primarily a secondary change (Fig. 3). Although clinically it resembles livedo reticularis, the reticular striations of the skin distinctively resemble patches of forked lightning. Upon palpation, an induction of streaks is evident that is histologically suggestive of vasculitis (Fig. 4). The most frequently reported association is with antiphospholipid antibody positivity³⁴.

Livedo reticularis has been described as a sign of pancreatic involvement, but this is highly controversial. Acute pancreatitis with livedo reticularis was described in 1927 by Walzel, who found cyanotic marbling of the skin of the abdomen, chest, and flanks in patients with a necrotizing form of acute pancreatitis^{35,36}. It has been suggested that the possible cause of this finding in the acute necrotizing form of pancreatitis may be the toxic effect of trypsin, leading to inadequate blood supply to the skin area.

Chronic pancreatitis is described on rare occasions as a disease linked to livedo reticularis³⁷. A case report of a patient with chronic pancreatitis described relapsing



Fig. 4. Necrotic tissue breakdown due to vasculitis.
From archive of the 1st Department of Dermatovenereology, St. Anne's University Hospital and Faculty of Medicine, Masaryk University, Brno.



Fig. 5. Cutaneous metastases of pancreatic adenocarcinoma.
From archive of the 1st Department of Dermatovenereology, St. Anne's University Hospital and Faculty of Medicine, Masaryk University, Brno.

livedo reticularis with a possible immune component as a mediating cause of the skin lesions, where histology using immunofluorescence revealed immunoglobulin and complement deposits. What was surprising, however, was that the expected vasculitis was not found.

CUTANEOUS METASTASES AND PANCREATIC CARCINOMA

Cutaneous metastases of pancreatic cancer are very rare (Fig. 5). Similarly, publications on this topic are rather scarce^{38,39}. Cutaneous metastases of pancreatic cancer are historically referred to as Sister Mary Joseph nodule (or node) formations and are most commonly localized umbilically⁴. Publications regarding cutaneous metastases in persons with pancreatic endocrine tumors are slightly more numerous⁴⁰. Particularly noteworthy is that discovery of cutaneous metastases may be the first finding in

patients with pancreatic neuroendocrine tumors, even before definitive diagnosis⁴¹.

A case report and literature review by Zhou et al.⁴², published in 2014, reviewed a total of 54 publications on the topic of skin metastases in people with pancreatic cancer. It showed a higher incidence of skin metastases in men (who made up 61.9% of the cases reported) compared to women, with the age of these people most commonly ranging between 60 and 80 years. Localization of metastases only around the umbilicus occurred in 28.6% of cases. Extra-umbilical localization was present in up to 68.3%. In the remaining 3.1%, metastases occurred around the umbilicus and also in the area outside the umbilicus. In this cohort of 63 patients, cutaneous metastases were first detected in 55.6% and only subsequently was a diagnosis of pancreatic cancer made. The finding of tumor metastases in the skin was associated with shorter survival time, and 53.2% of persons did not survive the 6-month period following the detection of skin metastases⁴².

CONCLUSION

These most common cutaneous changes in pancreatic disease that we report here are important for developing a deeper understanding of the processes outside the abdominal cavity to which pancreatic disease leads and which may be of diagnostic and prognostic value in cases of pancreatic disease.

Clearly, pancreatic panniculitis, necrolytic migratory erythema, skin lesions in acute pancreatitis, acanthosis nigricans, and, of course, the finding of skin metastases, which may precede actual pancreatic diagnosis, are of value in diagnosing pancreatic disease. The finding of livedo reticularis in pancreatic disease is of questionable diagnostic significance, however. The finding of such skin changes as Cullen's, Grey Turner's, or Fox's signs may be of prognostic value. As is well understood, the finding of skin metastases is associated with advanced pancreatic cancer.

The diagnosis and therapy of pancreatic diseases are indisputably multidisciplinary, and therefore knowledge of possible skin changes and the significance of such findings, including their correct clinical interpretation, must be part of any such approach.

Search strategy and selection criteria

Our aim was to provide a review of current data about pancreatic diseases and their possible skin manifestation. Scientific articles were searched using the MEDLINE, PubMed and Google Scholar databases. The search terms used included "pancreas diseases or disorders", "skin lesions", "pancreatic panniculitis", "livedo reticularis", "acanthosis nigricans", "necrolytic migratory erythema", "cutaneous hemorrhagic manifestations" and "cutaneous metastases".

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