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REVIEW

Much More than Trousseau Syndrome. The Broad Spectrum of the Pancreatic Paraneoplastic Syndromes

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Abstract When 150 years ago Armand Trousseau proposed that some thrombotic events might be the first sign of concealed visceral malignancies, these findings seemed to be just of anecdotal interest. Since then, however, we have learned that adenocarcinomas, including pancreatic cancers could be associated with a wide spectrum of paraneoplastic syndromes. They may precede the detection of the tumor, may occur simultaneously or may develop during its progression. Due to various hematologic, endocrine, cutaneous, articular, neuromuscular, renal or even psychiatric syndromes, their correct interpretation is intriguing, and because their early signs are not necessarily recognized first by oncologists, the paraneoplastic syndromes pose a diagnostic challenge. Unfortunately, we cannot generalize about their mechanisms, because the molecular backgrounds are far-reaching. In most of the cases, the pancreatic cancer cells release various factors into the bloodstream triggering the coagulation cascade. These patients frequently present with venous thromboembolism, and sometimes they are resistant to anticoagulation. The simultaneous thrombotic and bleeding evens do reflect the abnormal hemostasis. In other instances autoantibodies are formed against cutaneous, renal, neuromuscular or nervous tissues, but the mechanism of some syndromes remains unclear. Clinicians should be aware that pancreatic carcinoma may be associated with not just the Trousseau-syndrome.

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Introduction

Paraneoplastic syndromes are clinical symptoms or signs that are causally related to and governed by the malignant neoplasms themselves, but not resulted from the local extension of the tumors, instead, they represent their far impact. From definition the hormonal effects are also excluded if the given hormone was released by the corresponding endocrine neoplasm. In other words, paraneoplastic syndromes are mediated by either cancer-derived, biologically active substances or by autoimmune mechanisms, but the exact cause of some clinical appearances is still unclear. These syndromes may involve specific tissues or organs, while others are presented by systemic manifestations. Sometimes they are just annoying or irritating for the patients, but in other cases they profoundly determine the quality of life, moreover, some such syndromes may be fatal. They usually follow the already established tumors, but in some other cases, their early presentation may draw the attention to the hidden malignancy. It is important to emphasize that to define the paraneoplastic syndromes the tumors should be treatment-naïve, because certain cytostatic therapies may also induce similar symptoms.

Various paraneoplastic syndromes have been described in many types of cancers, but in this review we just focus on the classical ductal adenocarcinoma, which accounts for the overwhelming majority of the pancreatic malignancies. The cystic mucinous lesions and the islet cell tumors are not discussed.

Most pancreatic cancers produce clinical symptoms mainly by their local effects (compression of the surrounding tissues, infiltration of nerves, vessels or the adjoining organs), so they

behave as space-occupying masses. In a minority of cases, however, this tumor presents variable paraneoplastic syndromes, making the diagnosis more difficult.

Most of the studies reporting the paraneoplastic effects of the pancreatic cancer (PC) emphasize its association with the venous thromboembolic events (VTE), but the palette is more colorful, because the tumor may induce not just hematologic, but also endocrine, cutaneous, articular, neuromuscular, renal or even psychiatric syndromes. In this review we will also discuss these manifestations.

Hematologic Syndromes

Armand Trousseau, a French internist (1801–1867) was the first to propose a non-accidental association between concealed visceral cancers and hypercoagulable state resulting in an increased risk of venous thrombosis [1]. Although he termed "*phlegmasia alba dolens*", referring as to the deep vein thrombosis of extremities, this is not the only manifestation, the syndrome bearing his name is used in a broader sense. Later on, the "*Trousseau syndrome*" has become a popular synonym of migratory thrombophlebitis, but the cancer-induced/related hypercoagulability does involve a much wider spectrum of clinical manifestations, from the deep vein thrombosis, pulmonary thromboembolism, thrombophlebitis, non-bacterial verrucous endocarditis, arterial thromboembolisation to the chronic disseminated intravascular coagulopathy (DIC).

Venous thromboembolism is not a specific complication of the pancreatic cancer. Comprehensive studies have unanimously revealed that it was strongly linked to malignant tumors, these cancer patients had a significantly higher risk [2–4] including ovarian, bronchial, colonic, renal, prostatic, gastric carcinomas [2, 5, 6], but this finding was also observed in some non-carcinomatous malignancies, e.g. brain tumors or malignant lymphomas [2, 4, 7]. The highest risk is seen in mucin-producing adenocarcinomas and metastatic tumors [8, 9].

Frequency of thrombotic events in pancreatic carcinomas highly varies in different studies (17–57%) [10], but it is evident that the relative risk for VTE is significantly increased. Meta-analysis data from 40 reports indicated a 6.1-fold elevation, that figure is among the tumors with the highest risk [2]. It seems that the ethnicity should also be taken into consideration, because in a Korean study a low VTE occurrence (5.3%) was reported [11]. In a Hungarian, autopsy-based study covering 60 years we found 33.1% of VTE [12], in a Swedish autopsy material encompassing almost 24,000 cases, pulmonary thromboembolism was detected in 42% of cases [13]. While in some tumors (breast, lung, uterus, brain) the thrombotic complication is usually a terminal sign, in pancreatic and prostatic carcinomas it frequently presents in an early stage [14].

The traditional Trousseau-syndrome – migratory thrombophlebitis – is strongly associated with malignant tumors, mainly (but not exclusively) with adenocarcinomas, however, it is not specific for pancreatic cancer, because it may also occur in lung, urogenital or gastrointestinal malignancies [15, 16]. Although it is also a form of hypercoagulability, it is rarely published in the literature. Moreover, thrombophlebitis migrans may also complicate non-malignant diseases such as acute pancreatitis, Buerger's disease, myelodysplastic syndrome, etc.

Another manifestation of the enhanced coagulation is the "marantic", nonbacterial thrombotic endocarditis, observed in about 5% of patients with malignant diseases, but its diagnosis is not so easy, just the various, embolism-related neurological symptoms may draw attention to the underlying cause [17, 18]. Before death it is rarely diagnosed. In our 60-year autopsy series we have found only 10 cases (2.3% of all pancreatic cancer).

Arterial thrombosis is a very rare complication of pancreatic cancer, just sporadic case reports are available [19–21]. It is not so surprising, because the arterial thrombi are typically resulted from endothelial damage, while the involvement of the coagulative cascade is marginally affected. Various mechanisms of pathogenesis are suspected, such as arterial spasms, cryoglobulin precipitation, direct tumoral invasion of the vessel wall, embolization from marantic thrombi, or de novo thrombus formation.

Disseminated intravascular coagulation (DIC) in pancreatic cancer may occur in subclinical or in acute forms [22, 23], and both complications further aggravate the otherwise poor prognosis of this tumor. Interestingly, *Kus* et al. presented a peculiar case in which DIC and several types of coagulation abnormalities occurred simultaneously, indicating a combined effect of the tumor [23].

Pathogenesis

The pathogenesis of the increased coagulability is a complex phenomenon (Table 1). Some decades ago the paraneoplastic thrombophlebitis was simply believed to be induced by release of thromboplastin-like molecules [15]. This view, however, is just an oversimplification, although the precise mechanism is still vaguely understood. To tell the truth, one cannot generalize about the pathogenesis, because due to tumor heterogeneity the molecular mechanisms may differ from case to case. Even so, there are well established observations and facts that may orientate us and some excellent overviews outline this issue [24–26].

In pancreatic cancer patients a number of coagulation parameters are abnormally expressed. For example, significantly higher levels of fibrinogen, F-VIII, D-dimer were observed, while the protein C or antithrombin III levels have diminished, but their levels could change during tumor progression [27]. There are several reports indicating that the platelets are also of crucial importance. Thrombocytosis is associated with poorer prognosis; the overall survival is lower in these patients [28, 29].

Table 1 Potential mechanisms and pathogenesis of hypercoagulability in pancreatic cancer

Higher levels of
fibrinogen
F-VIII
D-dimer
tissue factor (mainly in microparticle forms)
thrombin-antithrombin III complex
cystein proteinase cancer procoagulant
Decreased levels of
protein C
antithrombin III
Thrombocytosis (spontaneous or induced)
Induced platelet-aggregation
Interaction of secreted mucin with L-selectin and P-selectin
Upregulation of tissue factor by TNF-α, IL-1
Activation of factor XII by tumor-derived, cell-free DNA

Heinmöller et al. have reported results from in vitro study evidencing that pancreatic carcinoma cells were able to induce platelet aggregation at a thrombin-dependent manner [30].

Hematological paraneoplastic syndromes mainly observed in mucin-producing adenocarcinomas, therefore it is logical to suppose that pancreatic mucin takes part in these processes. In an earlier publication a patient with cystadenocarcinoma was presented suffering from a progressive leukocytosis had a very high concentration of granulocyte-colony stimulating factor (G-CSF) [31]. When highly purified mucin was injected into mice, rapid generation of platelet-rich microthrombi has been formed. The authors hypothesized that tumor-derived, secreted mucin in the circulation interacted with leukocyte L-selectin and platelet P-selectin triggering the clot formation in small vessels [32].

Most of the studies aim to clarify the role of tissue factor (TF) in the hypercoagulable state. In pancreatic cancer patients a significant elevation of TF and thrombin-antithrombin III complex was observed [33]. In the same publication the authors have reported results of 8 human pancreatic cancer cell lines; all of them expressed TF on the cell membranes and alternatively spliced TF was also expressed in 6/8 lines. The VTE risk with high TF level is about 26%, in comparison with the 4.5% in subjects with low levels [34]. Immunohistochemically, TF was detected in 89% of PC samples, but none in the normal pancreata [34].

Tissue factor is a 47 kDa transmembrane glycoprotein that is upregulated in the cancer cells and together with its soluble form it may contribute to activation of the coagulation pathways as it was demonstrated by several studies. In the circulation it can be coupled with factor VIIa that complex further activates the factor IX, X [8]. The TF-expressing tumor cells spontaneously release this molecule and in form of microparticles they are highly procoagulant [35]. This finding was also reinforced in mouse model [36]. Moreover, these microparticles may bind to the sites of vascular injury enhancing the thrombogenic effect [35]. They can be detected by flow cytometry in 2/3 of PC patients [37], reflecting the aggressiveness of the tumor [38]. When the TF activity was measured by one-stage kinetic chromogenic method, higher VTE incidence was observed in pancreatic carcinomata than in other cancer types [39]. Thus, the TF-positive microparticles seem to be useful biomarkers in cancer patients who are at high risk for thrombotic complication.

Another molecule expressed by the pancreatic tumor cells is the cysteine proteinase cancer procoagulant (CP) that directly activates factor X, but indirect mechanisms are also implicated. Among them, tumor necrosis factor alpha (TNF-α), interlukin-1 (IL-1) are able to upregulate TF [8], but the interrelationships are much more complex, because inflammatory cytokines, vascular endothelial growth factor (VEGF), cell adhesion molecules, lymphoid cells and monocytes, altered microvessel density, etc. all interact in the enhanced paraneoplastic thrombogenesis [8, 24, 26].

The treatment of these hematological complications is difficult, because sometimes the thrombotic events are resistant to the standard therapies, moreover, hypercoagulability and bleeding tendencies not infrequently occur simultaneously. This fact underlines that in Trousseau syndrome the coagulation/anticoagulation system is profoundly altered.

Another problem is, that pancreatic cancer patients receiving chemotherapy are more likely to develop VTE [6, 40, 41]. Sometimes unexpected thrombocytosis is induced [42], or major bleeding complications occur [41]. In these cases it is not so easy the discriminate between the effect of the tumor itself and the side effect of the drugs, but is also conceivable that the cytostatic agent alter the molecular pattern of the cancer cells. Some chemotherapeutic drugs hit the liver, resulting in an aberrant synthesis of coagulative or anticoagulative factors. Although this is a reversible effect, the endothelial damage may remain persistent, and it favors the thrombus formation [43]. On the other side, chemotherapy results in a release of cell-free DNA from the destroyed cancer cells which may activate factor XII and the clotting cascade [9].

These complex relationships are summarized in Fig. 1.

Endocrine Syndromes

Here we just discuss the syndromes related to ductal carcinoma (Table 2); the islet cell tumors are out of our focus.

The relationship between diabetes mellitus and pancreatic cancer has been complicated by the existence of bidirectional association between these entities. Epidemiologic evidence suggest that patients with long-standing diabetes are about at two-fold risk for pancreatic cancer, but this risk increases to 4–

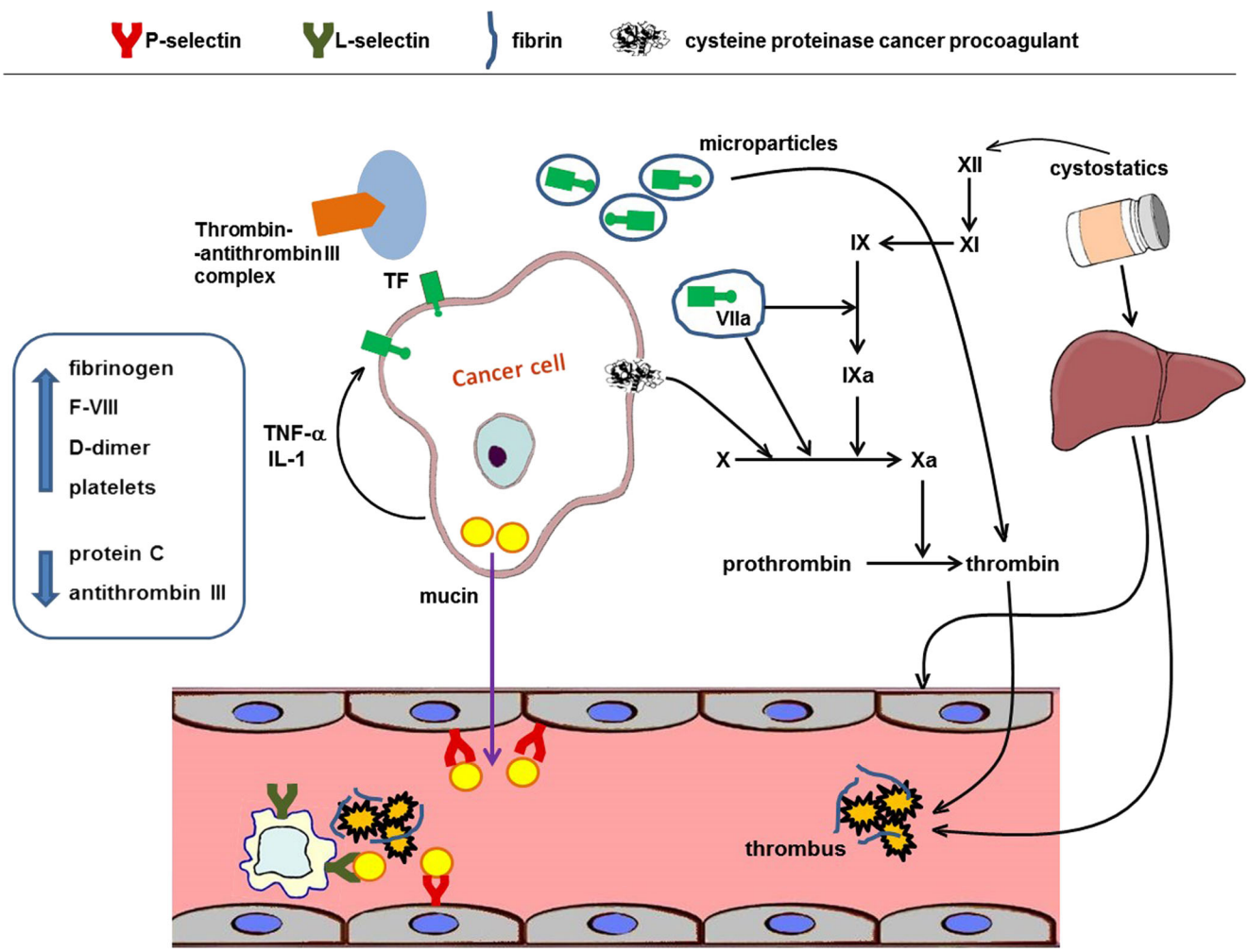

Fig. 1 Potential mechanisms behind the Trousseau syndrome. The hypercoagulability in pancreatic cancer patients is a very complex and just partially elucidated phenomenon, but is mainly governed by the altered pancreatic cells. The well-regulated coagulative balance is frequently shifted towards the procoagulants, the thrombin-antithrombin III complex level is elevated. Carcinoma-derived molecules, such as TF, cysteine proteinase cancer procoagulant (alone, coupled with some coagulative factors or in microparticles) can activate various components of the coagulation cascade, resulting in a thrombogenic effect. Moreover, TF is upregulated by the TNF-α, or IL-1. The secreted mucin may also interact with endothelial or white blood cell selectins, leading again to clot formation. Sometimes, the cytostatic treatments will show an undesirable effect by altering the synthetic machinery of the liver, or the destroyed tumor-DNA may directly activate some coagulative factors. TF = tissue factor; TNF-α = tumor necrosis factor-α; IL-1 = interleukin-1

7-fold in those with diabetes duration >3 years [44]. However, the higher risk of pancreatic cancer in people with a new-onset diabetes when compared with long-standing diabetes indicates that pancreatic cancer itself can also cause diabetes. This type of diabetes called de novo or *type 3c diabetes* (T3cDM).

Table 2 Endocrine syndromes associated with pancreatic cancer

Paraneoplastic syndrome	Remark
Diabetes mellitus	bidirectional association
De novo (T3cDM) diabetes mellitus	
Non-islet cell tumor hypoglycemia (NICTH)	extreme rare
Hypercalcemia	extreme rare

Approximately 50–80% of pancreatic ductal adenocarcinoma patients have some forms of DM or impaired glucose tolerance. Studies found that diabetes was new-onset (beginning up to 1 year preceding the diagnosis of cancer) in 74–88% of pancreatic cancer [45]. It suggests the hypothesis that pancreatic cancer-induced diabetes could be a paraneoplastic phenomenon. Compelling clinical and laboratory evidence support this theory: diabetes is prevalent in small pancreatic cancers and diabetes occurs before the cancer is radiologically detectable; in contrast to type II diabetes mellitus, in T3cDM weight loss often manifests before the development of diabetes; it improves after surgical resection of tumor. A study of 41 diabetic pancreatic cancer patients, who underwent pancreaticoduodenectomy, confirms this last statement. Diabetes mellitus resolved postoperatively in 57% of those

with new-onset diabetes ($n = 30$), and none of the patients with long-standing diabetes ($n = 11$) experienced any improvement in glycemic status [45].

The pathogenesis of pancreatic cancer-associated diabetes is still need to be elucidated. The substantial risk factors for type 2 diabetes (older age, obesity, family history of diabetes) also predispose for T3c diabetes. Supernatants from pancreatic cell lines have been shown to induce both insulin resistance and beta-cell dysfunction. Patients with pancreatic cancer-induced diabetes have also high insulin levels like in type 2 diabetes.

Beta-cell dysfunction is unlikely to be simply caused by the destruction of the gland by the tumor, the onset of the diabetes years before the cancer diagnosis and the high prevalence of diabetes in small tumors suggest a humoral process rather than a local effect. There is a presumption that beta-cell dysfunction is mediated by exosomes carrying β-cell toxic cargo [46]. These exosomes are secreted by the tumor and shed into the blood circulation. The main mediator, a 52 amino acid peptide, adrenomedullin is the product which is mainly responsible for this type of diabetes. Adrenomedullin binds to its receptor on the surface of β-cells (ADMR) in order to inhibit insulin secretion together with CRLR and RAMP 2 or 3 co-receptor activation. Exosomes enter β-cells through caveolin-dependent endocytosis and macropinocytosis. Adrenomedullin increases cAMP concentration in pancreatic islets, which normally would cause an increase in insulin secretion. Despite the increase in the cAMP level, there is a paradoxical inhibition of insulin secretion caused by an unresolved ER stress due to a failure of unfolded protein response (UPR). Adrenomedullin upregulates ER stress genes, Bip (ER chaperon protein) and Chop (inducer of apoptosis) and overwhelming ER stress leads to increased reactive oxygen/nitrogen species (ROS/RNS) production. Another characteristic of impaired UPR in β-cells is the increased coupling of proinsulin to Bip in the ER. ADMR blockade dissolves these effects [46].

Taken together, adrenomedullin causes a failure of the UPR and this leads to β-cell death. However, further research will be required to understand and specify the molecular mechanism of the failed UPR in response to adrenomedullin. Moreover, it is possible that other mediators of β-cell dysfunction might also exist.

Insulin resistance in pancreatic cancer is presumed to occur at the postreceptor level. In the search for the mechanism, islet amyloid polypeptide (IAPP) as a putative mediator was proposed. The level of IAPP was higher in pancreatic cancer patients than in diabetic or healthy controls [47]. IAPP is also known to cause insulin resistance in skeletal muscles. IAPP is normally secreted along with insulin by beta-cells. In contrast to the normal state, pancreatic cancer induces beta-cells to selectively secrete IAPP. Unfortunately, IAPP is not a good diagnostic tool in patients with pancreatic cancer. Other probable mediators have been identified, such as vanin-1/matrix metalloproteinase-9 and S-100A8 N-terminal peptide, which cause insulin resistance in vitro, but further research is needed to explore their role in the cancer. Hyperinsulinemia caused by the peripheral resistance stimulates proliferation of pancreatic cancer through insulin-like growth factor receptor and G-protein coupled receptors. Hyperglycemia also has proliferative effects and has been shown to enhance local invasiveness and metastatic potential of the cancer.

Adipose tissue inflammation has not been directly investigated in pancreatic carcinomas. However, there is a hypothesis that panniculitis does happen in pancreatic cancer and causes adipokine (such as adiponectin and leptin), cytokine and NEFA (non-esterified fatty acids) release. NEFA has a direct toxicity to pancreatic β-cells, it is a substantial mediator in peripheral insulin resistance, consequently it leads to β-cell dysfunction and β-cell loss [cit.44]. Adiponectin, leptin and cytokines, such as tumor necrosis factor (TNF), monocyte chemoattractant protein 1 and IL-6 are also believed to be crucial factors in peripheral insulin resistance. Further research will be needed to discover how pancreatic cancer interacts with adipose tissue, but there are potential mechanisms explaining the connection: the tumor itself releases factors exerting direct effects on adipose tissue; sensitization of the circulating naive macrophages, which are likely to reach the adipose tissue; or activation of the pancreatic macrophages.

Patients with new-onset diabetes have a higher probability of early diagnosis with pancreatic cancer. This type of diabetes offers an opportunity to detect the tumor in asymptomatic stage. If a marker that can distinguish pancreatic cancer-associated diabetes from type 2 diabetes would be identified, new onset diabetes could be a promising screening target [48].

Hypoglycemia is an extremely rare paraneoplastic syndrome in patients suffering PC [49, 50]. This phenomenon was named as a non-islet cell tumor hypoglycemia (NICTH), and has been associated with various malignant tumors (carcinomas, sarcomas or even hemopoetic malignancies). Concerning pancreatic cancer just case reports are found in the literature. The most probable explanation is that the tumors produce a prohormone form of IGF-II ("big IGF-II") inhibiting the GH and the insulin secretion, so there is a shift to smaller circulating complexes in the bloodstream, accompanied by a low concentration of IGF-I. The hypoglycemia is the net result of decreased glucose production in the liver and the increased glucose uptake in muscles and in the adipose tissue.

Some lung tumors are well known to secrete ectopic hormones, but the exocrine pancreatic cancer is hormonally inactive. As an exception, a peculiar case was reported from Parma University: an undiagnosed pancreatic cancer revealed at autopsy was secreting parathyroid hormone related protein plus the patient had hyponatremia due to inappropriate ADH secretion [51]. In another case hypercalcemia was the initial manifestation of a metastatic carcinoma due to parathormon-related peptide (PTHrH) secretion, and it was successfully palliated with bisphosphonate and diuretics [52]. The

production of the given peptide in the tumor can be evidenced by immunohistochemistry and a reverse-transcription polymerase chain (RTPCR) method [53].

Cutaneous and Melanocytic Paraneoplastic Syndromes

Acanthosis nigricans (AN) manifests as a hyperpigmented thickening of the skin usually in the intertriginous zones, however, 30% of the affected people also have lesion of the oral mucosa or in the scalp, areolae or eyelids. Malignant acanthosis nigricans can occur simultaneously, but it can also precede or follow the onset of internal malignancy, most commonly gastric adenocarcinoma and less commonly liver, pancreatic, lung, ovary, uterus, breast, kidney and prostate carcinomas. The diagnosis is based on the clinical findings. Features suggestive of paraneoplastic AN are: rapid extensive progression of florid skin lesions in unusual locations, such as the mucosal membranes, palms and soles of the feet in non-obese, elderly persons.

Malignant acanthosis on the palms is referred to as tripe palms. It is characterized by the appearance of hypertrophic papillation, exaggerated dermatoglyphics and hyperkeratosis of the palms and soles. 23% of tripe palms lesions occur after diagnosing malignancy and 17% coincide with it.

The pathomechanism is poorly understood. Activation of signaling pathways by binding of growth factors to specific skin receptors that stimulate cellular proliferation and thickening of the skin has been proposed. However, complete remission has been reported with tumor regression and as many as 30% of lesions resolve with cancer-directed therapy.

In acquired diffuse palmoplantar keratoderma the skin changes are characterized by uniform, yellow, hyperkeratotic thickening of the palms and soles leading to an irregular, cobblestone appearance. It often occurs along with other paraneoplastic syndromes, such as AN, hypertrophic osteoarthropathy or paraneoplastic acrokeratosis. Apart from pancreatic cancer, the lesion has been linked with a variety of other tumors, such as breast, lung, gastric carcinomas and, or even to leukemias and lymphomas. The skin lesion usually coincides with the presence of the associated tumor, and often improves or regresses with effective cancer therapy. *Ulla* et al. in 2008 presented a case with plantar keratoderma associated with pancreatic adenocarcinoma. A 76-year-old woman presented a sudden onset of the lesion and the detailed checkup revealed. After distal pancreatectomy, her cutaneous lesions disappeared [54].

The pathogenesis is unknown. Tumor induced growth factor production is believed to stimulate hyperkeratosis, but more study is needed.

Pancreatogenic panniculitis is a rare disease involving fat necrosis in the fat tissue. The lesion affects 2–3% of patients with pancreatic disease. In 2009, *Chee* reported an 84-year-old man with multiple tender, red, brownish nodules on his lower limbs and discharging lesions on his hands associated with fever, cachexia and pain in the left knee. CT has revealed a tumorous mass in the head of the pancreas. In the skin biopsy extensive areas of necrotic subcutaneous fat were found surrounded by florid acute and chronic inflammation consistent with pancreatic panniculitis [55].

Pancreatic panniculitis has a high mortality rate unless the underlying pancreatic abnormality is reversed. Several case studies have shown its resolution after surgical intervention or medical management of the underlying pancreatic disease. *Meier* et al. described a 68-year-old woman suffering from painful, subcutaneous nodules on her lower extremities. The clinical examinations revealed a solitary liver metastasis of a pancreatic carcinoma removed seven years before. After embolization and surgical resection of the metastasis the serum lipase level has become low and the painful nodular panniculitis disappeared completely [56].

Cox et al. reported an elderly woman with rapidly progressive painless, woody induration of the hands in association with pancreatic cancer. Together with skin biopsy it was classified as an example of cancer-associated fasciitis-panniculitis syndrome [57].

The sign of Leser-Trelaut is defined as the rapid increase in the number and size of seborrhoic keratoses in patients with an internal malignancy. Lesions can develop anywhere, but mainly on the chest and the back and it occurs with high frequency in association with other paraneoplastic syndromes, such as AN and tripe palms. It has been linked to solid tumors, especially adenocarcinomas (pancreas, stomach, lung, colon, etc.). The lesions do not require specific therapy, and they may resolve with the cancer therapy.

The pathomechanism is unknown, alterations in serum levels of human growth factors could play a role, but this is just an unproven hypothesis.

The necrolytic migratory erythema (NME) is almost always associated with alpha-cell tumor of the pancreas, but it might rarely occur in patients with pancreatic ductal adenocarcinoma. The lesions first appear as erythematous papules, later on they merge into painful, polycyclic plaques with crusted vesicles. Especially the intertriginous areas, the lower extremities and the abdomen are involved. Lesions are often cross-infected with *Staphylococcus aureus* or *Candida albicans*. NME is commonly presented with glucose intolerance and hyperglucagonemia. The tumor diagnosis is usually difficult and it often happens years after the appearance of the first skin lesions. Diagnosis is based on the clinical manifestations and the characteristic biopsy appearance.

The pathogenesis is connected with the hypoaminoacidemia induced by glucagon. Glucagon is believed to cause directly skin necrosis and it stimulates the uptake of amino acids in the liver which leads to hypoaminoacidemia. Eradication of the pancreatic cancer or effective chemotherapy usually solves the dermatitis.

Paraneoplastic pemphigus is usually associated with B-cell lymphoproliferative disorders and though its connection with solid tumors is rare, case reports have shown an association also with pancreatic carcinoma [58].

The pathomechanism is still obscure, but humoral and cellular immune mechanisms are likely to play an important role. Paraneoplastic pemphigus is often resistant to treatment, surgical resection of the tumor may not be enough to achieve a remission; combined immunosuppressive therapy is usually needed.

Dermatomyositis is an inflammatory myopathic disease characterized by symmetric proximal myopathy with typical cutaneous changes. It is often associated with an occult neoplasm, therefore, in these patients search for cancer is necessary. In addition to pancreatic carcinomas it is usually associated with ovarian, cervical, lung, gastric cancers and non-Hodgkin lymphomas. In the serum several autoantibodies can be detected: anti-histidyl-tRNA s-synthetase, anti-signal recognition particle, anti-Mi-2 or myositis specific antibody reacting with a 155 kd serum protein. In addition to the classical manifestations, there are also atypical forms that are therapy-resistant.

In the pathogenesis the cell-mediated immunity is supposed to play the main role based on the observation that helper T-cell level is increased. Tumor antigens stimulating immune system are likely to cross-react with self-antigens leading to autoimmune response.

Some other rare cutaneous paraneoplastic syndromes have been published. Erythema nodosum is presented with numerous painful, tender, erythematous to violaceous, subcutaneous nodules on the extremities. It was associated with pancreatic cancer in a case report, where a 59-year-old man presented painful subcutaneous nodules on the anterior surfaces of his legs while he was presumed to have metastatic pancreatic carcinoma [59]. Palmar fasciitis is an uncommon syndrome associated with several malignancies, most often with ovarian cancer but pancreatic, breast, colon and lung carcinomas have also been reported. It is sometimes associated with polyarthritis. Clinical manifestation includes a progression flexion deformity of the fingers on both hands and thickened palmar fascia [60, 61].

Bilateral diffuse uveal melanocytic proliferation is a rare paraneoplastic syndrome in association with pancreatic cancer. The underlying neoplasm produces uveal thickening, retinal detachment and rapid cataract formation which lead to bilateral blindness [62].

The cutaneous and melanocytic paraneoplastic syndromes are summarized in Table 3.

Syndromes Related to Joints

Some of the rheumatologic diseases may also be of paraneoplastic nature and they mimic the genuine arthritis or arthropathies. Such manifestations rarely accompany cancer of pancreas, but they pose a diagnostic challenge. In the background abnormal immune mechanisms are suspected directed against the synovium. In the reported cases the tumors were in advanced, metastatic stage, and the clinical manifestations included atypical, rapid-onset rheumatoid arthritis, palmar swelling or contractures of the hands; in one patient a rheumatoid factor or anticyclic citrullinated peptide (CCP) antibodies could be identified in the serum [63, 64]. These syndromes are rarely isolated, usually several areas with collagen-rich extracellular matrix are involved [61, 64].

Neuromuscular Syndromes

Dermatomyositis (as it was mentioned above) or polymyositis are frequently associated with various adenocarcinomas, and they usually precede the identification of the tumor. These syndromes are rarely associated with pancreatic cancer, but they seem to be reversible after treatments with corticosteroids, cytostatic drugs or after surgical resection [65, 66]. In these patients various antibodies can be identified, such as anti-p155 [67], or KL-6 (a complex sialo-carbohydrate glycoprotein that is present in the MUC1 mucin) [68].

Rarely, the central or peripheral nerves may also be attacked by various antibodies produced by pancreatic cancer cells leading to abnormal neuronal functions. It was reported a paraneoplastic gastroparesis, resulting in a delayed emptying of the stomach unrelated to obstruction [69], or a brainstem/cerebellar damage [70]. In the latter case, with abnormalities of eye movement, antibodies have been demonstrated against surface neuronal antigens, including channels and receptors. Opsoclonus, as an involuntary, rapid, disorganized eye movement has also been associated with some malignancies, but pancreatic cancer was just exceptionally found among them. *Aggarwal and Williams* have reported such a case, when an undisclosed, metastatic large ductal adenocarcinoma was associated with opsoclonus. Histological changes of the brain were consistent with a paraneoplastic meningoencephalitis [71]. An autoimmune mechanism is suggested, but the convincing evidence is still missing.

Renal Syndromes

Behind the membranous glomerulopathy/glomerulonephritis malignant neoplasms are frequently identified, but the adult-onset minimal change is an exceptional finding. *Whelan and Hirsel* have reported a single case of minimal change nephropathy with nephrotic syndrome and rheumatic polymyalgia 3 month prior to discovery of a metastatic adenocarcinoma [72]. These symptoms responded well to prednisolone therapy, but the tumor has progressed even after resolution of renal and rheumatic alterations, suggesting that the pancreatic cancer was not likely to produce any factor(s) directly damaging

Table 3 Cutaneous and melanocytic paraneoplastic syndromes associated with pancreatic carcinoma

Disease	Clinical manifestation	Possible Patophysiology
Acanthosis nigricans	hyperpigmented papillomatosis and hyperkeratosis of the skin and mucosal membranes with rapid extensive progression	unknown (activation of signaling pathways)
Tripe palms	acanthosis on the palms	unknown
Acquired diffuse palmoplantar keratoderma	uniform, yellow, hyperkeratotic thickening of the skin	unknown (tumor induced growth factor production stimulates hyperkeratosis)
Pancreatogenic panniculitis	tender, red, brownish subcutaneous nodules	unknown
Sign of Leser- Trelaut	rapid progression of seborrheic keratoses	unknown (tumor induced growth factors)
Necrolytic migratory erythema	erythematous papules, painful, polycyclic plaques, spfc. Vesicles, pustules or flaccid bullae, erosions, crusts	glucagon induced hypoaminoacidaemia
Paraneoplastic pemphigus	painful, ulcerative mucosal erosions, erythema of the skin	unknown (humoral and cellular immune mechanisms)
Dermatomyositis	symmetric proximal myopathy with periorbital edema, heliotrop rash, red, macular rash, V sign Gottron papules erythematous to violaceous plaques subcutaneous calcifications photosensibility	unknown (cell mediated immunity: tumor antigens cross-react witn self-antigens)
Erythema nodosum	painful, tender, erytematous to violaceous, subcutaneous nodules	unknown
Palmar fasciitis	flexion deformity of the fingers, thickened palmar fascia	unknown
Bilateral diffuse uveal melanocytic proliferation	uveal thickening cataract formation bilateral blindness	unknown

the kidney. The authors hypothesized that the carcinoma has led to general derangement of humoral and cellular immunity.

Psychiatric Syndromes

It is obvious that cancer patients, who are aware of their serious illness, develop emotional distress. However, several studies did show that depression may not just accompany but also precede the diagnosis of pancreatic carcinoma [73]. In a recent paper 21 studies have been analyzed and concluded, that affective psychiatric diseases do occur in patients with malignant tumors. Depression was the most frequent and consistent prodromal affective syndrome in pancreatic and lung cancer [74], however, the obvious explanation is still lacking.

These rare paraneoplastic syndromes are summarized in Table 4.

Conclusion

Pancreatic cancer is one of the deadliest malignancies, usually recognized in an advanced stage, therefore, early diagnosis would be of great importance. This tumor is associated with various paraneoplastic syndromes, not just hematological but also endocrine, cutaneous, neuromuscular, renal or even psychiatric ones. These syndromes may precede the appearance of the carcinoma, may occur simultaneously or in late stage of the malignant process. Because the pancreatic cancer should be diagnosed when it is still operable, the knowledge of these

Table 4 Other, less frequent paraneoplastic syndromes associated with pancreatic cancer

Paraneoplastic syndrome	Remark(s)
Atypical, rapid onset rheumatoid arthritis	rare event
Dermatomyositis, polymyositis	rare association can be reversible usually precede the tumor detection
Paraneoplastic gastoparesis	
Opsoclonus	
Nephrotic syndromes	respond well to steroid therapy
Affective psychotic disorders (mainly depression)	

symptoms – although they are nonspecific - may draw attention to this hidden carcinoma.

Author Contributions The authors contributed equally to this work.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

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