WŁODYKA, Jagienka Agata, ZELIK, Urszula, PRZYGODA, Maria, DOMINO, Wiktoria, TRESTKA, Gabriela, ADAMCZYK, Sabina, STĘPIEŃ, Kamila, ŚNIEŻNA, Joanna, FLORCZAK, Wojciech, DZWONNIK, Karol and DZIEWIC, Jakub. Pathophysiological mechanisms, multidimensional diagnostics and modern therapies of pruritus in pancreatic cancer: review and perspectives. Quality in Sport. 2025;37:57137. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.37.57137
https://apcz.umk.pl/QS/article/view/57137

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 26.12.2024. Revised: 14.01.2025. Accepted: 20.01.2025 Published: 21.01.2025.

Pathophysiological mechanisms, multidimensional diagnostics and modern therapies of pruritus in pancreatic cancer: review and perspectives

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Abstract

Introduction and purpose: Pruritus is a subjective, unpleasant sensation that leads to scratching and significantly impacts the quality of life of patients. In pancreatic cancer, its etiology is multifactorial. It can result from various mechanisms, with a particular emphasis on cholestasis, which represents the most important and frequent cause of this symptom, as well as paraneoplastic processes, neuropathic mechanisms, or side effects of therapy. The aim of this study is to analyze the mechanisms responsible for pruritus in pancreatic cancer, discuss diagnostic challenges, and review the available therapeutic methods and challenges, including bile duct decompression, the use of autotaxin inhibitors, opioid receptor antagonists, and SSRI drugs. The article is based on an analysis of the available scientific literature and cited sources.

Description of the state knowledge: Topics discussed include pathomechanisms of pruritus in pancreatic cancer include cholestatic, opioid-induced, paraneoplastic, neuropathic and pruritus caused by antineoplastic therapies. Another key topic is the diagnostic process for pruritus in pancreatic cancer patients, which involves laboratory and imaging studies, clinical dermatological assessment, and differential diagnosis. Lastly, a comprehensive therapeutic approach is addressed, consisting of causal treatment, pharmacological interventions, and supportive care.

Keywords: pruritus, pancreatic cancer, cholestasis, autotaxin, LPA, SSRI

Introduction

Pruritus is one of the oldest symptoms known to humanity. It was first described in 1660 by Haffenreffer as an unpleasant sensation leading to scratching [1]. In cancer, pruritus often manifests as a persistent and challenging symptom to treat, significantly impairing patients' quality of life. It has a chronic nature and is independent of histamine, unlike allergic pruritus, which is accompanied by characteristic skin changes such as redness and hives [2].

In malignancies, patients' skin may appear clinically unchanged, without primary dermatological lesions. Nevertheless, they may experience severe itching, leading to intense scratching, resulting in secondary skin changes such as excoriations, dermatitis, and skin damage, often causing significant pain [2,10]. This phenomenon necessitates a detailed analysis, particularly of the pathophysiological mechanisms underlying it.

In pancreatic cancer, pruritus is most commonly associated with cholestasis but may also result from paraneoplastic mechanisms, neuropathy, or side effects of therapy [2,3]. Among patients diagnosed with pancreatic neuroendocrine tumors (PNET)—rare tumors constituting about 2% of all pancreatic cancers—severe pruritus has been reported as a primary symptom in

approximately 1-8% of cases [4]. Numerous reports suggest that pruritus may accompany almost every malignancy, often attributed to the release of toxins and immune system alterations [4]. Due to the distinct mechanisms driving cancer-associated pruritus, standard treatment with antihistamines is usually ineffective [2]. This highlights the need for developing alternative therapeutic strategies. This article aims to analyze the pathomechanisms of pruritus in pancreatic cancer and review the available diagnostic methods and therapeutic challenges.

Pathophysiology of Pruritus in Pancreatic Cancer

Pruritus likely represents an adaptive mechanism that triggers the scratching reflex, aimed at protecting the body from potentially harmful stimuli. This mechanism may be initiated by stimuli activating polymodal nociceptors—sensory fibers responsive to multiple types of stimuli—which react to noxious inputs. The transmission of itch-inducing impulses occurs via unmyelinated C-fibers, which are also involved in pain signaling. [5,20] However, research suggests the existence of neurons that exclusively respond to histamine, identified as specialized itch-conducting units. [5]

Cholestatic Pruritus

Cholestasis is the primary mechanism responsible for the development of pruritus in patients with pancreatic cancer. During cholestasis, bilirubin, cholesterol, and bile acids accumulate in the plasma due to impaired bile flow. This phenomenon is currently attributed to the presence of the enzyme autotaxin, a pathological metabolite that catalyzes the release of lysophosphatidic acid (LPA) from lysophosphatidylcholine. LPA is a potential mediator with pruritogenic properties. [8] LPA concentrations in cholestatic patients increase only in the presence of pruritus, and autotaxin activity correlates with itch intensity in the skin. [8] Unmyelinated C-fibers are responsible for itch transmission in cholestasis. These fibers are activated by LPA and other mediators, such as histamine or substance P. The increased sensitivity of these fibers leads to an intensified itch sensation. [3,8,10]

Opioid Mechanisms

Enhanced opioid signaling in the central nervous system plays a significant role in the pathogenesis of cancer-related and cholestatic pruritus. [9] In cholestasis, there is an increased activity of μ-opioid receptors (MOR) and reduced activity of κ-opioid receptors (KOR). The diminished function of KOR, which naturally suppresses pruritus, contributes to its amplification. [9,10] Activation of MOR on C-fibers further increases their sensitivity to

pruritogenic stimuli. This phenomenon is exacerbated in cholestasis by the accumulation of bile acid metabolites, which can stimulate itch transmission. [9,10] These mechanisms explain the efficacy of opioid antagonists such as naloxone and naltrexone, which effectively alleviate pruritus by rapidly reducing its intensity. [18] Unfortunately, in cancer patients, opioid antagonist therapy is limited due to the potential for triggering the recurrence of pain. [18]

Paraneoplastic Pruritus

The pathophysiology of paraneoplastic pruritus involves complex interactions among inflammatory, neurogenic, and immunological processes. Paraneoplastic pruritus is autoimmune in nature and is often associated with hematological malignancies such as Hodgkin's lymphoma, as well as skin cancers like mycosis fungoides. [17] Major hypotheses suggest that excessive release of cytokines and inflammatory mediators, such as interleukins and TNF-α, caused by the presence of cancer can activate nerve endings, leading to the sensation of itch. [7,17] An example is IL-31, which plays a role in the pathogenesis of pruritus in both atopic diseases and paraneoplastic pruritus. [7,17] Additionally, tumors can affect the regulation of neuropeptides, such as substance P, as well as the expression of NK-1 receptors, rendering the nerves involved in itch transmission more sensitive. [6,16]

Neuropathic Pruritus

Neuropathic pruritus arises from damage to neurons involved in itch signal transmission. [12] It can manifest as a symptom of tumors developing within the nervous system or result from direct tumor invasion of neural pathways. [7]

Pruritus Induced by Cancer Therapy

Pruritus is a common side effect of anti-cancer drugs. The potential mechanism involves nerve endings in the skin, unmyelinated C-fibers, neurotransmitters, or regulation of various receptors, such as serotonin, neurokinin-1 (NK-1), opioid, and gamma-aminobutyric acid (GABA) receptors. [19] Another possible mechanism for targeted therapy-induced pruritus is dryness and skin inflammation, such as papulopustular eruptions, caused by impaired skin barrier function and increased mast cell numbers in the dermis. [19] A 2018 study found that the prevalence of this side effect ranged from 2.2% to 47% across different categories of targeted cancer therapies. [19] This adverse reaction may also occur following the administration of opioid medications to patients. [6]

Diagnostics

The diagnosis of pruritus in pancreatic cancer patients requires a multifaceted approach, incorporating clinical evaluation, laboratory testing, and imaging studies. Identifying the specific causes and underlying mechanisms is crucial for accurate diagnosis and implementation of appropriate treatment strategies.

Detailed History and Therapy Analysis

Conducting a comprehensive medical history is vital, including detailed information about the duration, localization, presence of associated skin symptoms, and severity of the pruritus. Inquiry into the patient's current medications is essential, especially regarding the use of opioids, which may induce pruritus through their mechanisms of action on opioid receptors. [9,18] It is also important to assess the use of anti-cancer therapies, particularly targeted therapies such as epidermal growth factor receptor (EGFR) inhibitors. These can lead to pruritus through neurogenic or dermatological mechanisms, including epidermal barrier dysfunction and increased activity and density of mast cells in the skin. [19,20] Such mechanisms can cause symptoms like xerosis (dry skin) or inflammatory papulopustular eruptions, which are characteristic side effects of this drug class. [9,19,20]

Laboratory Testing

Laboratory evaluation plays a significant role in diagnosis, including blood counts and liver function tests such as alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT). Increased activity of these enzymes may suggest mechanical cholestasis, which is common in pancreatic cancer due to bile duct compression. Bilirubin levels should also be measured to assess the degree of bile stasis, with elevated conjugated bilirubin levels serving as a hallmark of impaired bile flow. Additionally, autotaxin (ATX) testing can be considered as a biomarker for cholestatic pruritus. [8,10]

Imaging Studies

Performing contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis is essential for evaluating tumor-induced bile duct compression and the presence of metastatic disease. [8,10] These imaging techniques also aid in assessing the feasibility of stent placement for cases of biliary obstruction. Endoscopic retrograde cholangiopancreatography (ERCP) may complement imaging by enabling visualization of the bile ducts and facilitating therapeutic interventions, such as bile duct

decompression via stent placement. This procedure can effectively alleviate cholestatic symptoms, including persistent pruritus. [8,10]

Clinical Dermatological Evaluation

Skin assessment is crucial for detecting changes indicative of pruritus with dermatological origins, especially in patients undergoing anti-cancer therapies. Such changes may include xerotic eruptions, erythema, and other inflammatory skin lesions resulting from epidermal barrier dysfunction due to targeted therapies. Additional findings may include exfoliation (xerosis effect), hyperpigmentation or depigmentation due to melanocyte damage caused by anti-cancer drugs, as well as excoriations, skin fissures, and erosions caused by chronic scratching.[11,19]

Neuropeptides and NK-1 Receptors as Diagnostic Targets

The role of neuropeptide mechanisms, including the activity of substance P and the regulation of neurokinin-1 (NK-1) receptors, should be considered in diagnosing pruritus in pancreatic cancer patients. These mechanisms support the potential use of NK-1 receptor antagonists in symptomatic therapy. [6,16]

Differential Diagnosis of Pruritus Etiology

Differentiating the causes of pruritus in pancreatic cancer patients is critical and requires detailed evaluation. If laboratory and imaging studies do not indicate cholestasis, other potential mechanisms should be considered, such as dermatological conditions or adverse effects of cancer therapies. Neuropathy, resulting from tumor invasion into the celiac plexus, is another possibility. This plexus, as a key nerve center for abdominal innervation, can be directly irritated or damaged by the growing tumor, potentially leading to neuropathic pruritus. [6,20] Addressing various etiologies, including bile stasis, epidermal barrier disruption, or excessive neuropeptide receptor activation, allows for more targeted diagnostics and treatment strategies. [9,16,19]

Therapy of Pruritus in Pancreatic Cancer: Multidirectional Therapeutic Strategies

Causal Treatment

The primary approach to managing cholestatic pruritus in pancreatic cancer patients involves restoring bile flow to alleviate symptoms. This can include surgical or endoscopic procedures,

such as the placement of a stent in the common bile duct. This intervention facilitates the drainage of bile from the liver, thereby reducing bile acid levels in the body and relieving pruritus. [19] Clinical studies have confirmed that stent placement can significantly improve the quality of life for pancreatic cancer patients by decreasing the severity of pruritic symptoms. [8] In cases where stent placement is not feasible, biliary drainage is performed, which also enhances bile flow. This approach is particularly useful for patients with advanced pancreatic cancer, where traditional surgical options are limited. [19]

Pharmacological Treatment

When mechanical interventions are not fully effective, pharmacological treatments can be employed, such as: autotaxin inhibitors, selective serotonin reuptake inhibitors (SSRIs) and opioid receptor antagonists. Clinical studies suggest that autotaxin inhibitors may represent a promising option for managing pruritus in pancreatic cancer patients. By inhibiting autotaxin, an enzyme responsible for producing lysophosphatidylcholine (LPA), these treatments reduce LPA levels, a key mediator associated with pruritus in cholestatic conditions. Consequently, this results in decreased itch intensity. [8] SSRIs, including sertraline, paroxetine, and fluvoxamine, have proven effective for the symptomatic treatment of pruritus. These drugs modulate the activity of serotonin, a neurotransmitter implicated in pruritus mechanisms. Clinical trials involving 21 patients with liver disease-related pruritus demonstrated that sertraline was effective and well-tolerated at doses of 75-100 mg/day. [14] Paroxetine has been shown to specifically reduce pruritus in cancer patients. [15] A broader study with 72 patients (45 women, 27 men, aged 28-88 years) highlighted the efficacy of paroxetine and fluvoxamine, with 49 patients achieving significant relief from pruritus. [16] However, SSRIs are not without adverse effects, with nausea and vomiting reported in 70.8% of patients during the aforementioned study. [16] Sertraline is preferred for pancreatic cancer patients due to its lower incidence of side effects. Therapy should begin with low doses (e.g., 25 mg once daily), increasing every two days. Results can often be observed within days. [16] Agents like naloxone and naltrexone, which act as opioid receptor antagonists, may help alleviate pruritus associated with opioid-mediated signaling. However, their use can potentially exacerbate pain by counteracting the effects of opioids, commonly used for pain management in pancreatic cancer patients. This duality presents a therapeutic challenge, necessitating careful risk-benefit assessment and close clinical monitoring to minimize the risk of increased pain symptoms during treatment. [9,13]

Supportive Therapies

Supportive therapies focus on improving patient comfort through skin care, reducing pruritus-aggravating factors, and employing topical pharmacological interventions. Regular use of emollients—external preparations with moisturizing, lubricating, and skin-softening properties—helps maintain the integrity of the skin barrier, which is crucial in preventing skin dryness (xerosis) that can exacerbate pruritus. [11,21] It is recommended to use products rich in lipids and ceramides, which support the reconstruction of the epidermal barrier [11,21].

Additional measures include brief baths in lukewarm water using unscented products containing natural mineral substances, as well as wearing loose, breathable clothing free of irritating elements. To prevent skin damage, patients should also keep their nails short and well-filed, an important aspect for minimizing irritation and the risk of skin infection. [12]

In cases where pruritus has an inflammatory component, topical corticosteroids may be applied; however, their effectiveness in cholestatic pruritus is limited. [12,21]

Equally important is psychological support, given the significant decline in quality of life experienced by patients due to both the cancer itself and the persistent pruritus it causes. [21]

Summary

Pruritus in pancreatic cancer requires a multifaceted diagnostic and therapeutic approach and remains a challenging symptom to manage. It arises from various mechanisms, including paraneoplastic and neuropathic processes. However, it most commonly occurs due to cholestasis and can be alleviated through mechanical decompression of the bile ducts, such as by placing a stent in the common bile duct. Modern treatments, such as autotaxin inhibitors, SSRIs, and opioid antagonists, provide effective therapeutic options. Nonetheless, further research is needed to develop optimal treatments that minimize side effects while effectively addressing pruritus. A comprehensive understanding of pathophysiological mechanisms, thorough diagnostic evaluation, and the application of advanced therapeutic techniques enable effective symptom control and improvement in patients' quality of life.

Author's contribution:

Conceptualization: J.W.; methodology: U.Z., M.P,; software: W.D., G.T.; formal analysis: S.A., K.S., J.Ś., W.F., K.D., J.D.; investigation; J.W., U.Z., M.P., W.D., G.T., S.A., K.S., J.Ś., W.F., K.D., J.D.; resources: J.W., U.Z., M.P., W.D., G.T., S.A., K.S., J.Ś., W.F., K.D., J.D.; data curation: J.W., U.Z., M.P., W.D., G.T., S.A., K.S., J.Ś., W.F., K.D., J.D.; writing-rough

preparation: J.W., U.Z., M.P., W.D., G.T., S.A., K.S., J.Ś., W.F., K.D., J.D.; writing–review and editing: J.W., U.Z., M.P., W.D., G.T., S.A., K.S., J.Ś., W.F., K.D., J.D.; visualization: J.W., U.Z., M.P.,; supervision: W.D., G.T., S.A., K.S.,; project administration: J. Ś., W.F., K.D., J.D.

Supplementary Materials: They have not been provided.

Funding statement: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest. All authors have read and agreed to the published version of the manuscript.

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