Neurophysiologic approach to pruritus and pain in cancer patients

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Summary

Itch and pain, like other sensations, serve as physiological self-protective mechanisms. However, in many clinical conditions, unrelieved itch and pain have potentially devastating effects on body functions. Thus, these two sensations present maladaptive phenomena. In this review, we present the neurophysiologic mechanisms of pruritus and pain, including their mutual interactions, but the accent is on causes, consequences and assessment of pruritus and pain in cancer patients. Understanding the mechanisms of pain and itch may optimize pain control in cancer patients and enhance their quality of life.

Key words: cancer, neurophysiology of itch, neurophysiology of pain, pain, pruritus

Introduction

It is estimated that more than 7 million deaths per year worldwide are caused by cancer, and only in the United States each year more than half million die from the disease. Thus cancer pain that occurs in approximately one third of patients at the time of diagnosis and about three fourths of patients with advanced disease [1-3], confronts many physicians. Pruritus is not commonly associated with cancer, except in some types of lymphoreticular type of malignancy, superficial spreading melanoma, and various cutaneous metastases [4-7]. However, morphine and other opioids, especially when used for neuraxial analgesia and some other systemically or topically applied medications, can cause severe localized or widespread pruritus [8]. These unpleasant sensations are intensified by the interaction with other cancer symptoms that are regularly present in advanced disease stages (weakness, nausea, dyspnea, constipation, and impaired cognition). Fortunately, cancer pain can be effectively treated in approximately 90% of patients with non-invasive pain management [9]. Appropriate use of invasive procedures may help most of the remaining patients [10]. Pruritus in cancer patients, including patients with intractable itch, may be effectively controlled in most of the cases [11]. Thus, a patient with cancer should not live with unrelieved pain or pruritus.

In order to properly control pain and pruritus, it is necessary to modify the source of these sensations, alter their central perception, and block their pathways to the central nervous system. To individualize management of these symptoms, a thorough assessment of each patient’s disturbing sensation, cancer, concurrent medical problems, and psychological status is required. This paper reviews the neurophysiology of pain and pruritus in cancer patients. To get information on integrative anticancer therapies, physical and psychosocial therapies, and procedural interventions aimed at both comfort and function of cancer patients, readers should consult extensive or specific articles [12,13] and textbooks [14-17].

Pruritus and pain

Pruritus and pain are two types of sensations that
in animals and humans have phylogenetically evolved in order to detect harmful stimuli that may serve for preventing excessive stimulation and minimizing tissue damage. The other sensations, such as, touch, vibration, cold, heat, vision, and hearing may also serve for avoiding noxious stimuli and dangerous situations—as a physiological self-protective mechanism. Certain defense strategy is present even in unicellular organisms which can move away from threatening environments, but the emergence of a specialized nervous system in multicellular organisms coordinated escape responses. The presence of sensory neurons in animals enabled the stimulus to activate the brain, where such stimuli produce specific sensations and adequate responses.

The patients sometimes cannot precisely differentiate sensations of itch and pain, and it has been suggested that itch and pain are caused by different levels of sensory receptors activity. However, because electric stimulation of itch spots produces itch at low stimulation and a higher level of stimulation does not produce pain, this theory seems doubtful [18]. Pain (L. from poena - fine, punishment, or penalty) may be defined as an unpleasant sensation that can range from mild and localized discomfort to agony as a consequence of injury, disease, or emotional disorder. Pruritus (L. from prurire - to itch) or itch (from the old English giccan) is sensation that the patient instinctively attempts to relieve by scratching or rubbing. Some clinicians distinguish itch (“an uneasy sensation of the skin that inclines the person to scratch the part affected”) and pruritus (“generalized itching in the absence of primary skin disease”) [19]. However, it is often difficult to differentiate these sensations, and separation of the two terms could become misleading. In this text, we use these two terms interchangeably.

**Neurophysiology of itch**

Pruritus can be evoked only from the superficial layers of skin, mucous membranes, and conjunctiva directly by mechanical, chemical, thermal or electrical stimulation, or indirectly through release of chemical mediators. It may be also generated independently of peripheral nervous stimulation by damage of spinal ganglia, nerve root impingement, injury of spinal cord and cerebral damage. Itch receptors (prurceptors, itch nociceptors) probably belong to the class of polymodal receptors that respond to multiple stimulatory modalities [20]. A remarkable progress has been made in the past few years on the signaling mechanisms that nociceptors use to detect noxious stimuli [17]. Thus, nociceptors may express the vanilloid receptors (RV1) to detect heat (above 42°C) and protons (pH below 5.9), mechanically gated channels (“stretch receptors”) to detect mechanical stimuli, and a complex array of receptors to detect inflammation-associated factors released from damaged tissue (such as, protons, bradykinin, endothelins, and prostaglandins). The mechanisms of noxious signaling mechanism were mainly studied in pain, but similar signaling takes place in itch sensation, as well [21].

Thus, it seems that there is no specialized prurceptor on peripheral nerve endings; only itch-conducting neurons seem to be specific kind of C-fibers that transmit itch sensation from the prurceptor to the itch portion of the spinal pathway. From the itch nociceptors, mainly concentrated in the dermo-epidermal junction and sometimes in the epidermis as free nerve endings, pruritic information is transmitted through itch-mediating non-myelinated, very slow-conducting C-fibers via the dorsal root ganglion to the spinal cord. At the spinal level, they synapse with secondary neurons that belong to the spinothalamic tract which crosses over to the contralateral side and ascend to the ventral medial and dorsal medial thalamic nuclei. Nuclear projections from the former thalamic nucleus terminate in the sensorymotor cortex, while projections from the latter nucleus terminate in the anterior cingulated cortex. Activation of the motor and cingulated cortex explains why the perception of itch provokes scratch and why there is an affective component of itch [19]. The role of the thalamus in the modulation of pruritus is not clear.

Itch is a symptom that may accompany a primary skin disease or skin affection (e.g., scabies, pediculosis, insect bites, urticaria, atopic dermatitis, contact dermatitis, and dermatitis herpetiformis), systemic disease (e.g., obstructive biliary disease, uremia, lymphomas, leukemia, polycythemia rubra vera), present as side effect of drugs (e.g., opiates, barbiturates, salicylates, allopurinol, gold salts, nicotinic acid, cisplatin, etoposide, procarbazine), or it may occur during the later months of pregnancy [22-24]. Experimentally, itch can be produced by intradermal injection of pruritic substances, such as histamine, compound 48/80, substance P, vasoactive intestinal peptide (VIP), neurotensin, prostaglandins (PGs), neurokinin A, calcitonin gene-related peptide (CGRP), and capsaicin, or by electrical stimulation.

Intradermal injection of histamine causes a characteristic “triple-response” or “wheal-and-flare response.” The effect involves 3 cell types: smooth muscle, endothelium of small blood vessels, and sensory nerve endings. A reddening at the site of injection is caused by dilatation of small vessels, followed soon
by an edematous wheal at the injection site and a red irregular flare surrounding the wheal. The sensation of itch accompanies the appearance of these skin changes. In surrounding skin areas, local application of a pruritic stimulus can elicit enhanced pain (hyperalgesia), itch to pricking (hyperkinesis) and itch in response to innocuous stroking (allokinesis). Most of these local skin changes, including itch, produced by histamine or histamine liberators (such as compound 48/80 and morphine), can be blocked by prior administration of a H1 receptor blocking agent, and only partially by a H2 receptor antagonist [25]. These observations proved that histamine is the main itch-inducing substance released from the mast cells in many skin diseases and they explain why H1 receptor antagonists often effectively suppress itch. Lidocaine also reduces histamine-induced itch and flare reactions demonstrating that mast cells are in close relationship with “itch receptors.” Mast cell activation stimulates the synthesis of several arachidonic acid metabolites and the platelet-activating factor (PAF). Intracutaneously injected, PAF induces a dose-dependent flare-and-itch which is also inhibited by H1 antagonists [26]. However, there are many types of itch that do not respond to antihistamines, for example itch produced by PGD2 that is released in urticaria, erythema of the skin caused by PGE2, and flare response to substance P or bradykinin, and interleukins (ILs). IL-2 that is used in the treatment of some malignant diseases regularly causes itching [27,28], while cyclosporine, a potent inhibitor of IL-2 production by lymphocytes, is effective in treating itch in atopic dermatitis and other forms of severe pruritus [29].

In addition to the activation of peripheral nerve endings, itch can be induced by nerve inflammation or compression. It is well known that stimulation of sensory neurons at the level of dorsal root ganglia causes activation of peripheral terminals and release of bioactive substances [30,31]. These substances act on target cells in the periphery (mast cells, immune cells, and smooth muscle) producing “neurogenic inflammation”, a phenomenon characterized by redness and warmth, swelling, and hypersensitivity. The small diameter sensory neurons which are sensitive to capsaicin, the vaniloid found in hot peppers, are important for the generation of neurogenic inflammation. Thus, if the capsaicin-sensitive fibers are destroyed, neurogenic inflammation produced by antidromic stimulation of sensory fibers (Adelta and C-fibers) will be attenuated. These fibers originate from the small dorsal root ganglion cells, and if they are stimulated, substance P and CGRP is released peripherally and in the dorsal spinal cord. Release of these peptides produces symptoms of neurogenic inflammation by acting on the mentioned target cells (endothelial cells, mast cells, immune cells, and arterioles). Thus, a lesion that causes pruritus can also be localized in the spinal ganglia (e.g., herpes zoster infection and postherpetic neuralgia), in spinal cord (e.g., burning itch caused by treatment with thalidomide and pruritus associated with spinal administration of morphine), or at the cerebral level (e.g., stroke, inflammation, and brain tumor localized in the region of the middle cerebral artery, capsula interna or thalamus that may cause unilateral pruritus on the contralateral side) [27,32]. For developing proper strategies for the treatment of itch, it is important to recognize the type of itching that may be classified as cutaneous (pruritoceptive), neurogenic/neuropathic, and psychogenic, or their combination.

**Neurophysiology of pain**

Exposure of skin and other organs to dangerous stimuli causes the sensation of pain which is a protective response to tissue injury, and it may be critical for survival. Pain can also occur without external provocation, or it may be generated by innocuous stimuli. Acute pain is ultimately integrated in corticofugal centers of the brain, and it fulfills a warning role. On the contrary, chronic pain may persist long after the injury is healed, and it may spread to adjacent or distant body parts. Chronic pain is a maladaptive phenomenon that frequently leads to morphologic changes both in the peripheral and central nervous system (CNS) that may deteriorate body functions. Clinical pain is a complex process; it often involves the interplay of various underlying mechanisms, including acute and chronic inflammation that may cause nociceptive sensation.

In the visceral organs, pain stimuli are usually associated with pathological processes, such as inflammation, ischemia or mesenteric stretch. These organs do not respond to many other stimuli, as cutting, burning or clamping. Hence, the visceral organs are not, like the skin or mucous membranes, equipped with receptors capable of detecting noxious stimuli that are present in the environment. Following tissue injury, sensory neurons may be sensitized and become highly responsive to noxious stimuli. So, the pain signals from visceral organs that come to the brain promote immobility to minimize organ damage and increase survival.

**nociceptive pain**

Pain may be either nociceptive (normal functioning of pain fibers) or neuropathic (misfiring from the
Peripheral nerves, spinal cord, or brain). Nociceptive pain process can participate in both acute and chronic pain. It is usually elicited by the activation of specific nociceptors (L. nocere to injure; nociceptor – a receptor which is stimulated by injury). Pain nociceptors (Adelta- and C-fibers) are activated only by intense, damaging, or noxious stimuli, and they should be distinguished from the primary sensory receptors (Abeta-fibers) which are activated by low-intensity or innocuous stimuli. To activate cutaneous nociceptors, the stimulus has to reach noxious range. For example, at temperatures above 43°C their firing rates increase and such stimulus produces nociceptive pain.

We experience nociceptive pain in almost daily contact with the objects that are too hot or cold, too hard, or contain irritable chemicals. Rare individuals have congenital insensitivity and indifference to pain stimuli and this defect may cause horrible deformities and early death (mainly in childhood) because such persons fail to notice injuries and illnesses [33]. More often, deficits of pain perception are acquired due to certain brain lesions.

A pain message is progressively transmitted to and processed in the higher nervous centers via the spinothalamic tract and several other pathways (e.g., dorsal column pathway). The conscious perception of pain is an extremely complex process that includes series of mechanisms that occur in the periphery, in the dorsal horn of the spinal cord (primary processing), supraspinal relay centers, such as the thalamus (secondary processing), and in the corticolimbic structures. In addition to afferent pathways for pain transmission, a variety of local and long-loop connections exist at every neuraxial level. They modulate (augment or diminish) the evoked afferent inputs.

**Neuropathic pain**

Neuropathic pain is caused by nerve injury, tissue damage, or inflammation. The response to noxious stimuli is exaggerated (hyperalgesia) and the sensation of pain can be produced by innocuous stimuli (alldynia). Thus, neuropathic pain can occur without provocation or it can be evoked in response to noxious or non-noxious (innocuous) stimuli. The receptors and primary sensory neurons involved in generating innocuous sensation, nociceptive and neuropathic pains are presented in Table 1.

**Table 1.** Role of primary afferent sensory neurons in innocuous sensation, nociceptive and neuropathic pain. Hyperalgesia and allodynia represent the post-injury pain hypersensitivity or nociceptive sensitization. Following tissue injury, inflammation or nerve injury, endogenous stimuli, such as protons (pH changes), bradykinin, histamine, substance P, serotonin, prostaglandins, and other mediators sensitize nociceptors. Central sensitization may also occur. The letters A and C are used to classify axons according to propagation velocity. Abeta- and Adelta-fibers are myelinated with propagated velocity 35-75 m/sec and 5-30 m/sec, respectively. C-fibers are non-myelinated with propagated velocity of 0.5-2 m/sec. Roman numerals are used to classify axons according to size. Class I has axon diameter 12-20 mm (Alpha-fibers), class II 6-12 mm (Beta-fibers), class III 1-6 mm (Adelta-fibers), and class IV <1 mm (C-fibers). The information propagated by the larger, more rapidly conducting fibers is more precise than that provided by the smaller, more slowly conducting fibers. The cell bodies of these sensory fibers that innervate the head and body are located in the trigeminal and dorsal root ganglia, respectively.

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Receptors</th>
<th>Sensation</th>
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<tbody>
<tr>
<td>Low-intensity (mechanical)</td>
<td>Low-threshold mechano-receptors</td>
<td>Innocuous sensation (light touch, mild</td>
</tr>
<tr>
<td></td>
<td>(Abeta-fibers)</td>
<td>pressure, vibration, brush, joint sensations)</td>
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<tr>
<td>Low-intensity (thermal)</td>
<td>Low-threshold thermo-receptors</td>
<td>Innocuous thermal sensation</td>
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<td></td>
<td>(Adelta-fibers for cold; C-fibers for heat)</td>
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<tr>
<td>High-intensity (mechanical, thermal, chemical)</td>
<td>High-threshold mechano-heat</td>
<td>Acute nociceptive pain</td>
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<td></td>
<td>nociceptors (Adelta- and C-fibers)</td>
<td></td>
</tr>
<tr>
<td>High-intensity (mechanical, thermal, chemical) + tissue damage</td>
<td>High-threshold or mechano-heat nociceptors (Adelta- and C-fibers)</td>
<td>Hyperalgesia (sensitivity is also spread from the site of injury to non-injured areas)</td>
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<tr>
<td>Low-intensity (mechanical, thermal) + tissue damage</td>
<td>Abeta-fibers</td>
<td>Allodynia (pain is produced by previously innocuous stimuli)</td>
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Some mechanisms essential to induction of chronic neuropathic, especially cancer pain, have been gradually revealed [17]. Thus, due to the damage of a peripheral tissue, sensory neurons may change their phenotype and the activation threshold of nociceptors becomes lower, and previously “silent” nociceptors may be activated. These high “plastic” properties of sensory neurons explain peripheral sensitization that is manifested as alldynia and hyperalgesia. Various inflammatory mediators, such as PGs, bradykinin, ATP, cytokines, neurotrophins, nitric oxide, and protons (pH changes) may have an important role in the induction of chronic, neuropathic pain [34]. Non-neural glial and immunocompetent cells have also been shown to play a modular role in the response to inflammation and injury, and thus they may modify nociception.

Peripheral neuropathy originates due to a cascade of events that up-regulate the expression of membrane channels both at the site of peripheral nerve damage and nociceptive neurons of the dorsal root ganglion. Sprouting axons, that take place around the cell bodies at the dorsal root ganglion, release various substances that exaggerate pain. In the spinal cord, N-methyl-D-aspartate (NMDA) receptors are activated by glutamate released from afferent nerves that conduct nociceptive information. Their activation induces neuronal sensitization that is the basis for prolonged painful state. Further enhancement of nociception is produced when peripheral nerve injury induces reduction of inhibitory interneuron influences in the dorsal horn.

Central sensitization is manifested by hyper-responsiveness to peripheral pain stimulus that is triggered by nociceptive afferents, and which outlasts the initiating input. Although the detailed cellular and molecular mechanisms still remain obscure, central sensitization appears to be the consequence of slow synaptic potentials (lasting about 1 min) generated by high-threshold afferents, Adelta- or C-fibers [35]. The slow synaptic potentials are produced by the neurotransmitters glutamate, substance P, and neurokinin A. They diffuse across the synaptic cleft and activate NMDA, non-NMDA, or neurokinin receptors in the postsynaptic membrane generating a slow postsynaptic potential. Depolarization of the postsynaptic neuron leads to an influx of Na⁺ and Ca²⁺ which leads to further depolarization. Ca²⁺ entering the postsynaptic neuron induces central sensitization, which is manifested as an increase in excitability. Repetitive stimulation of the afferents maintains central sensitization via Ca²⁺-mediated second messengers (e.g., phosphatases, phospholipases and protein kinases) and by immediate early gene expression, e.g., c-fos and c-jun [35].

**Sensory and affective pain perception**

It is widely accepted that the perception of pain can be separated into sensory and affective dimensions. The studies that combine brain imaging with psycho-physiological methods have led to better understanding of the complex mechanisms by which sensory and affective of pain perceptions are inter-related and how these aspects can be modulated by cognitive factors [36]. Spinal ascending pathways (e.g., spinal pathways to medial thalamic nuclei, amygdala, hypothalamus, reticular formation, and limbic structures) provide direct inputs to the brain areas involved in affective behavior. Another pathway to the same structures comes from spinal pathway to somatosensory thalamic (ventroposterior lateral and ventroposterior medial) and cortical areas (S1, S2, and the posterior parietal cortex). This indirect pathway provides an input of information to cortical limbic structures (insula cortex, anterior cingulated cortex) that are related to the overall status of the body to provide pain affect. Thus, anterior cingulated cortical and subcortical structures establish the emotional response on the basis of inputs that come via both direct and cortico-limbic pathways.

When a lesion occurs in the area of the brain that participates in the processing of pain stimuli, deficits in one or more of the components of pain perception may occur [37]. Lesions of the medial pain system (anterior cingulated cortex or insular cortex) may cause a loss of the affective-motivational component of the pain. The deficit of the affective-motivational component of the pain, with preserved sensory discrimination is called “asymbolia for pain” [38]. Such patients perceive painful stimuli but do not have emotional responses and withdrawal movements. Pain asymbolia may be present in a congenital defect of the anterior cingulated cortex [33]. The lesions of the lateral pain system affect the primary and secondary somatosensory cortex, and they cause loss of the sensory-discriminative components of pain.

**Interactions of pruritus and pain**

Itch and pain are not usually present together at the same cutaneous area, and – as it is well known – mild itch sensation can be even abolished by the painful sensations caused by scratching (Figure 1). This common experience of itch inhibition by pain stimuli in normal conditions has been experimentally proved. In one of such experiments, histamine-induced itch was successfully inhibited by electrical cutaneous field stimulation. The large area of itch inhibition around
an electrically stimulated site indicates a central mode of action [38]. Quite opposite phenomenon, pruritus enhanced by pain inhibition, may be relevant in some clinical conditions. For example, this mechanism might induce segmental itch when an opioid receptor agonist is spinally administered to induce segmental analgesia. The antipruritic effect of opioid antagonists, observed in experimental itch and in patients with cholestatic itch, is also based on central interaction between pain and itch [39]. Cooling and warming the skin have opposite effect on itch. Cooling inhibits itch by both central and peripheral mechanisms, while warming of the skin enhances itch. But, when heating of the skin becomes painful, central inhibition of pruritus offsets this effect [40].

Opposed relationship between pain and pruritus that is observed under normal conditions, disappears in patients with chronic pruritus. However, central sensitization for itch causes that stimulation of $\Delta$- and $C$-nociceptors can induce itch. (Thus, a pin-prick, that in normal condition inhibits itch, in the presence of central sensitization for itch may be perceived as itching). Similar phenomenon is observed in patients with atopic dermatitis who perceive painful electrical stimuli as itching [39]. The mechanism of this sensitization includes inflammatory mediators (e.g., bradykinin, serotonin, prostanoids, and low pH) and increased production of trophic factors which initiate sprouting of epidermal nerve fibers. Therefore, increased nerve fiber density is observed in patients with chronic pru-
ritus [41]. In addition to sprouting, increased levels of local nerve growth factor and neurotrophin-4 can sensitize both “pruriceptors” and nociceptors [42]. Anti-inflammatory therapy, affecting the peripheral mechanisms, reduces both sensitizations for pain and for itch. Perhaps a common central mechanism for these two sensations could implicate similar therapeutic approaches for centrally mediated itch [43].

Causes, consequences and assessment of pruritus and pain in cancer patients

It is well known that unrelieved pain or excessive pruritus is incapacitating and has devastating effect on quality of life. These highly disturbing sensations interfere with physical functioning and social life and have negative psychological impact. Thus control of pain and pruritus is both therapeutic and ethical obligations.

Cancer pain afflicts one third of patients with newly diagnosed cancer, more than half of patients that receive anticancer therapy, and three fourths of patients with advanced disease [1-3]. Some malignant diseases, especially those that affect lymphoreticular tissue, are associated with itch, but itch is a frequent side effect of some medications that are used in cancer patients. To avoid undertreatment of pain and severe itch in cancer patients, it is necessary to identify and evaluate these symptoms and make plans for an effective therapeutic strategy that includes both symptomatic and causal approach. In this section, we briefly present causes, consequences and assessment of pruritus and pain in cancer patients.

Pruritus in cancer patients

Pruritus could be the first symptom or it may be associated with extended course of the disease. However, it may be, as it is frequently the case, unrelated to the patient’s malignant disease (e.g., dry skin which is often observed in elderly patients). Generalized pruritus may appear without skin lesions, for example in biliary obstruction, lymphomas (Hodgkin’s disease, non-Hodgkin’s lymphoma), leukemia, and polychthemia vera. Pruritic rush that appears with skin lesions (e.g., mastocytosis, mycosis fungoides and its leukemic phase called Cezary syndrome) is often difficult to diagnose. Cutaneous metastases of some cancers may also cause itch [4-7,44,45]. Pruritus linked with cancer is frequently termed “pruritus paraneoplasticus.” The intensity of itch could be mild, moderate, or severe. Persistent scratching, especially due to the itch caused by neuraxial opioids, in patients with coexisting skin diseases, may cause new skin lesions known as the isomorphic Koebner phenomenon [46,47]. Koebner phenomenon caused by radiation therapy may, eventually, cause linear basal cell carcinoma [48]. Untreated itch may cause discomfort, sleep disturbances, derange in daily activities, loss of weight, increased irritability, stress, and psychic responses.

In men, the cancers that most commonly metastasize to the skin include carcinoma of the lung and colon, followed by melanoma of the oral cavity, kidney and stomach. In women, breast carcinoma that metastasizes to the ipsilateral chest wall is the most common cutaneous metastasis. Less often, the skin metastases come from carcinoma of the colon, lung and ovary, and melanoma [49,50]. These metastases may cause pruritus. Primary tumors or metastases localized in the CNS might also be associated with itch. For example, brain tumors frequently cause pruritus that is localized in the nasal region [51]. Extrahepatic biliary obstruction by tumors causes cholestasis that is regularly associated with severe generalized pruritus which is especially intense on hands, feet and around tight-fitting clothes. The patients with unrevealed jaundice due to pancreatic cancer regularly complain that the itching is the worst symptom [11]. It seems that the bile acids in plasma or skin are not the major cause of itching because there is a poor correlation between the skin concentration of bile salts and intensity of itch. Elevation of endogenous opioids in the blood of patients [52], and some benefits obtained with opioid antagonists [53], indicates that a central mechanism may participate in cholestatic pruritus, as well.

Drug-induced pruritus in cancer patients is as prevalent as pruritus caused by the cancer itself. In addition to various chemotherapeutic drugs (e.g., plant alkaloids, alkylating agents, antimetabolites, and thalidomide), pruritus may be induced by opioids, analgesics, diagnostic contrast media, skin medications, and radiotherapy [44,54,55].

To assess the intensity of itch, a patient-reported visual analogue scale or numerical rating (0-none and 10-worst experience) is often used. In addition to intensity, for global evaluations of itch, it is necessary to determine its distribution (focal, multifocal, or generalized), skin changes (primary that are caused by a disease or secondary due to scratching or rubbing), temporal and other relationships.

Pain in cancer patients

Pain in cancer patients may be caused by the disease itself, by cancer treatments (e.g., chemotherapy,
surgery, radiation therapy), and by causes unrelated to the cancer or cancer treatment (e.g., arthritis, herniated disc, and pain that originates from muscles or connective tissue). Acute cancer pain has recent onset and short duration; it is often associated with anxiety, moaning and grimacing, and signs of generalized sympathetic activity. Chronic pain persists over a long period of time; it often gradually increases in parallel to neoplastic growth, or regresses with neoplastic reduction. A transitory exacerbation of severe pain in the cancer population with chronic pain managed with opioid drugs is termed “breakthrough pain” [56]. Acute pain syndromes are, in the majority of cases, caused by diagnostic or therapeutic interventions, while chronic pain syndromes are usually caused by the neoplastic processes. Cancer pain is most often caused by tumors invading bone, such as metastases of the prostate, breast, lung, kidney or thyroid cancer, and due to the skeletal complications in advanced disease, e.g., pathological fractures and spinal cord compression. The vertebrae are the most common sites of bone metastases, where they may cause vertebral collapse, radiculopathy, and epidural spinal cord compression. The latter complication represents a medical emergency due to the possibility of permanent neurological damage [57]. Pain frequently comes from infiltration or compression of somatic nerves, while muscle weakness and atrophy follows involvement of motor nerve or mixed nerve involvement. Frequent localization of nerve damage most commonly occurs at the paravertebral, retroperitoneal or chest wall lesions. Cancer pain syndromes are less frequently caused by tumors invading skin, blood vessels, or by obstructing the hollow viscera. Acute pain in cancer patients mainly belongs to the category of nociceptive somatic or visceral pain; it rarely has characteristics of neuropathic pain. In contrast, chronic cancer pain frequently belongs to the category of neuropathic pain. Painful neuropathy is also frequently observed after surgery, chemotherapy, or radiation therapy. Thoracotomy, mastectomy, neck dissection, and nephrectomy are major source of postsurgical neuropathy. Such pain develops several weeks or months postoperatively, as a continuous dull pain with intermittent lancinating pain episodes [58].

Cancer pain may damage various body functions and amplify depression and fatigue. Accurate diagnosis of the cancer process is necessary because specific surgical, chemotherapeutic or radiation therapy can radically help in pain management. However, before exact diagnosis is made and specific treatment is performed, pain should be adequately tested.

For optimal treatment of cancer pain, it is necessary to assess each patient’s pain (e.g., intensity, acute or chronic, specific site, relationship to tumor progression or unrelated to malignancy, mechanism of pain, type and stage of malignant disease, other medical problems, and psychosocial status) [59]. In unidimensional assessment of pain intensity, visual analogue scale or numerical rating (0-none and 10-the worst pain) is most often used. Most often, pain ratings of 1 to 4 correspond to mild pain, ratings of 5-6 represent moderate pain, and 7-10 severe pain [60]. Other unidimensional assessments include verbal rating scale (i.e., “none”, “mild”, “moderate”, “severe”), and a pictorial scale. The choice of a type of pain assessment may depend on the patient’s age, ability to communicate, or other specific conditions.

More accurate pain assessment that is especially needed with chronic pain identifies its quality (somatic, visceral, nociceptive, or neuropathic), distribution (focal, multifocal, generalized pain), temporal property, and association features (presence or absence of sympathetic activity, daily function, sleep). However, some of these signs may be difficult to distinguish from other cancer-related effects, especially when an extensive multidimensional effect and pain survey is performed [61]. Proper assessment of pain characteristics by using multidimensional assessment may help in selecting the best therapeutic approach, such as selection of proper analgesic drug, route of administration, rate of dose titration, nerve blocks, radiotherapy, or surgical treatment.

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References

for myelofibrosis with myeloid metaplasia. Cancer 2006; (Epub ahead of print).


