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Cancer and Itch

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Itch represents a common and significant source of morbidity in the oncological setting. Itch sometimes can be associated with an underlying malignancy, most commonly leukemia or lymphoma. Alternatively, itch may present secondary to malignant invasion causing hepatic or renal dysfunction. Finally, itch may be related to therapeutic regimens for the underlying malignancy. This article seeks to review the clinical scenarios in which itch affects the oncological patient, to briefly present the latest understanding of the molecular and cellular mechanisms of malignancy-related itch, and to review currently available therapeutic options.

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Pruritus, or itch, is a sensation that induces the desire to scratch. Although a rare occurrence in most malignancies, itch can be a significant cause of morbidity in the oncological setting. Itch may be localized or generalized, mild to severe, and can have a significant effect on quality of life. Intractable itch may hinder daily activities and sleep, and vigorous scratching increases the risk of developing cutaneous skin infections. Itch associated with malignancy is often difficult to treat and may be minimally responsive to common treatments for pruritus. However, ongoing research in the pathophysiological basis of itch continues to reveal new targets that may offer additional therapeutic options to clinicians treating these patients. Pruritus in the oncology patient may be divided into three categories: itch preceding or directly associated with malignancy, itch indirectly associated with malignancy, or itch associated with treatment of malignancy.

Pruritus Preceding Malignancy or Paraneoplastic Itch

Pruritus has been observed as a presenting symptom of malignancy. Chronic pruritus, or itch lasting more than six weeks, may be a paraneoplastic sign.[1] In small studies of patients who have pruritus of unknown etiology and are eventually diagnosed with a malignancy, lymphoma and leukemia have been most commonly reported.[1] This observation has been well-described in patients with cutaneous T-cell lymphomas (CTCL; Fig. 1), in which itch may precede formal diagnosis by months to years.[2-4] Cases involving non-Hodgkin's lymphoma (Fig. 2), multiple myeloma, chronic lymphocytic leukemia (CLL), and chronic myelomonocytic leukemia have also been reported.[1,5-7] Pruritus has also been observed in patients before the diagnosis of solid tumors, including lung, gastric, and laryngeal tumors.[1,5,6] Per the experience of one author, itch localizing to the legs, upper trunk, and extensor surfaces of the upper extremities may be suggestive of the presence of a systemic carcinoma.[8]

Another example of paraneoplastic itch is eosinophilic dermatosis of myeloproliferative disease, a persistent, erythematous, pruritic, papulonodular eruption that occurs in a variety of blood dyscrasias.[9] Byrd et al[9] proposed the following criteria for diagnosis: (1) pruritic papules, nodules, and/or vesiculobullous eruption resistant to conservative treatment; (2) eosinophil-rich dermal lymphohistiocytic infiltrate (superficial and deep) on histopathologic examination; (3) exclusion of other causes of tissue eosinophilia, including immunobullous diseases, parasitic infections, known insect bite, or drug reactions; and (4) preexisting diagnosis of a hematologic malignancy or dyscrasia or its subsequent development. These lesions may initially be thought to be an exaggerated delayed hypersensitivity response to insect bites, consistent with observations Weed first described in patients with CLL.[10] Subsequently, however, reported cases included patients with lymphomas and leukemia other than CLL,[11] without a history of insect bites.[11,12] The eruption has preceded the diagnosis of mantle cell lymphoma, acute monocytic leukeumia, and myelodysplastic syndrome.[9,11]

Finally, several primary dermatologic conditions are associated with an increased risk of malignancy and have been reviewed recently.[1] For example, dermatitis herpetiformis is

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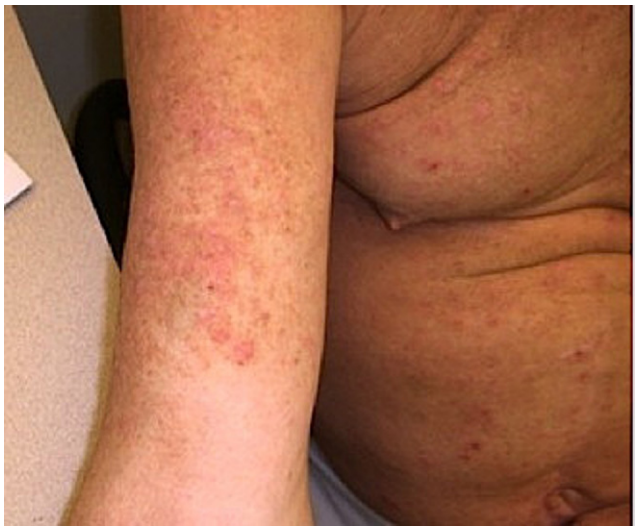

Figure 1 Pruritus associated with CTCL. Patient who presented with intractable pruritus and excoriated erythematous scaling patches and plaques several months before the biopsy-proven diagnosis of CTCL. Patient did not respond to oral antihistamines, UVB, PUVA, opioid agonist/antagonist (butorphanol), and had minimal relief with gabapentin. Patient ultimately developed Sézary syndrome, did not respond to systemic therapies, and died.

typically extremely pruritic and has been associated with a two-fold greater risk of malignant lymphoma and a borderline increased risk of leukemia.[13] Dermatomyositis can also be highly pruritic,[14] and this rash has been associated with a wide variety of solid tumors.

Pruritus and Existing Malignancy

Itch in relationship to a known malignancy is most commonly observed in patients with lymphoma. Pruritus is a common symptom of Hodgkin's and non-Hodgkin's lymphoma, affecting up to 25% of patients with Hodgkin's disease.[7,15,16] Approximately 5% of Hodgkin's disease patients rate their itch as severe, a classification that has been associated with poor prognosis.[16] Almost all patients with CTCL have significant complaint of itch.[17] As mentioned previously, itch of normal-appearing skin may be the only manifestation of early CTCL. Patients with advanced CTCL or Sézary syndrome are often extremely itchy,[18,19] and severe pruritus has been reported in up to 68% of patients with the folliculotropic form.[20] Eosinophilic dermatosis of myeloproliferative diseases has been reported in patients with CLL, acute lymphocytic leukemia, and large-cell lymphoma.[9,11]

Itch is also a frequent symptom of skin cancers, and its presence is an important factor to consider when deciding to biopsy a concerning skin lesion. Alterations in cutaneous sensation may suggest a more aggressive, invasive process. Itch was reported in 22% of lesions identified as primary melanoma[21] and may be a significant presenting sign. Nonmelanoma skin cancers, including squamous (SCC) and basal (BCC) cell carcinomas, may also present with pruritus. Oncologists should have a low threshold for dermatologic consultation when presented with suspicious skin lesions, especially in patients who are on long-term immunosuppression. The risk for developing BCC increases linearly with increased duration of immunosuppression, whereas the risk for developing SCC increases exponentially.[22] It has also been reported that at least 50% of white transplantation recipients will eventually develop a BCC or SCC.[22]

Pruritus Indirectly Related to Malignancy

Itch may also be indirectly related to cancer, usually the result of tumor growth affecting internal organs. The most common manifestation occurs with invasive tumors of the liver. The itch of cholestasis has been attributed to increased opioidergic tone[23] with some contribution from the accumulation of bile salts, bile acids, bilirubin, and other cholephiles.[24] Ursodeoxycholic acid, bile sequestrants, such as cholestyramine, and surgical intervention may reduce pruritus. Sertraline and rifampicin have been used with some success as well.[24] Opioid antagonists are often of limited utility because pain management often takes priority in these patients. However, some reports have found naloxone, naltrexone, and nalmefene to be effective at reducing itch.[25]

In rare instances, tumor invasion of the kidney or ureteric obstruction may cause renal failure with uremic itch. Although not completely understood, pruritus in this context may be caused by the accumulation of pruritogenic metabolites[26] or the development of a proinflammatory state, associated with an imbalance of TH1 cytokines.[24] Treatment with topical agents, low-dose neuroleptics, phototherapy, tacrolimus, thalidomide, mu-opioid antagonists, and kappa-opioid agonists have been used with varying success.[24,25]

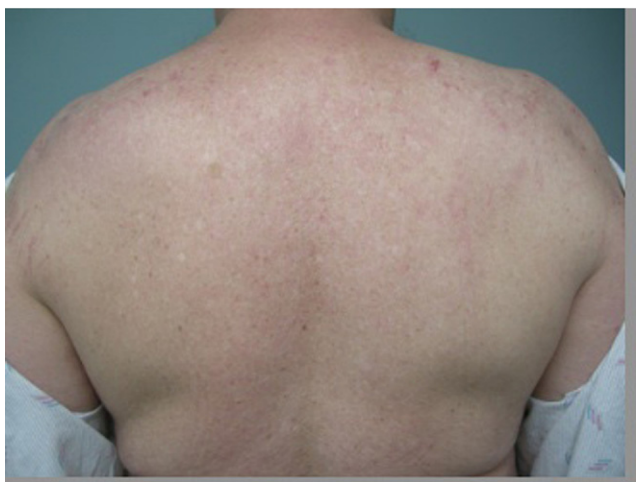

Figure 2 Pruritus associated with non-Hodgkin's lymphoma. Patient presented with generalized pruritus and no primary cutaneous lesions. Note excoriations of the upper back and posterior shoulder (Photo courtesy of Dr Milan Anadkat, Washington University School of Medicine, St. Louis, MO).

Pruritus Associated with Treatment

Itch may also present as a side effect of cancer treatment. Common medications, such as opioids, aspirin, amphetamines, granulocyte colony-stimulating factor, and cholestasis-causing medications, including erythromycin, hormonal treatments, and phenothiazines, are often iatrogenic causes of pruritus.[26,27] Pruritus is also a common side effect of using biological response modifiers, such as interferons and interleukin (IL), including IL-2, which has been used to treat metastatic renal cell carcinoma and malignant melanoma.[28]

Oncology patients also commonly develop hypersensitivity reactions to the medications they take, and these rashes are often pruritic. Antineoplastic agents have also been noted to cause pruritic hypersensitivity reactions via both immunologic and nonimmunologic mechanisms. Platinum-based compounds and l-asparaginase are associated with type I hypersensitivity reactions that can be life-threatening.[29,30] Taxanes are associated with urticaria and pruritus thought to be associated with degranulation of basophils.[31,32] Anthracyclines, such as doxorubicin and daunorubicin, are also associated with pruritus.[4] Itch can also be a component of epidermal growth factor receptor (EGFR) inhibitor-related acneiform skin rashes.[33] EGFR inhibitors, such as gefintib, erlotinib, cetuximab, panitumumab, and matuzumab, have been used to treat a variety of cancers, including tumors of the lung and colon.

Some chemotherapeutic agents can cause an erythematous rash that affects the intertriginous zones, hands and feet, which has been named toxic erythema of chemotherapy. Insult to the eccrine duct, acrosyringium and epidermis via eccrine excretion of chemotherapeutic agents is thought to be the mechanism of damage.[34] The rash occurs most commonly with cytarabine, anthracyclines, 5-fluorouracil, capecitabine, taxanes, and methotrexate, and itch may accompany affected areas.[34] Finally, radiation therapy and many chemotherapeutic agents, including the EGFR inhibitors, may cause xerosis, which can predispose oncology patients to itch.

Pathophysiology

During the past 20 years, much work has been devoted to elucidating the cellular and molecular pathways by which the sensation of itch is transmitted. Although this is an active area of research, the translation of these findings into treatment options is in its earliest stages into treatment options for itch remains challenging.[18] Moreover, there remains controversy regarding relationship of itch and nociception as they are transmitted through the spinal cord to the central nervous system. A complete review of the research concerning itch is beyond the scope of this article, but a more comprehensive summary has been recently published.[35] We will briefly highlight some of the most recent developments in understanding the peripheral mediators of malignancy-associated itch. In addition, we review data that support a common central pathway for itch which represents a promising new target for the development of future therapeutics.

Although the pathophysiology of itch related to malignancy remains unclear, several observations point to inflammation as being a key mediator. Hematologic malignancies classically associated with pruritus are characterized by a T helper 2 (TH2) phenotype.[36,37] Recent studies of patients with chronic atopic dermatitis, another TH2-driven condition, support the contention that dysregulation of the immune system results in pruritus. Evaluation of cytokine expression profiles in patients with chronic atopic dermatitis reveal an increased level of IL-31, a TH2-driven cytokine, compared with nonpruritic psoriatic patients.[38] Indeed, the greatest levels of IL-31 were detected in prurigo nodules. Moreover, in animal models of atopic dermatitis, the administration of monoclonal IL-31 antibodies reduced scratching behavior while not affecting the underlying dermatitis.[39] The identification of this potent mediator of itch represents a promising target for future therapeutics.

Another exciting line of investigation supports the existence of an independent neural circuit in the central nervous system through which pruritogenic stimuli are processed, the so-called "labeled line theory." The first evidence for a labeled line was reported in 2001 when a population of spinal thalamic tract neurons was identified that were responsive to histamine, but not to mechanical, thermal, or mustard oil induced pain.[40] In 2007, Sun and Chen[41] reported the characterization of gastrin-releasing peptide receptor (GRPR) bearing neurons in the lamina I of the dorsal spinal cord. GRPR mutant mice were found to exhibit modestly decreased itching after the injection of compound 48/80a mast cell degranulator that simulates histamine release. Itching behavior was more drastically reduced with injection of SLIGRL-NH2, a PAR2 agonist that mediates histamine independent proteinase induced itch.[42] In addition, GRPR mutant mice had significantly reduced scratching in response to chloroquine administration. Mutation of GRPR did not affect responses to thermal, mechanical, inflammatory, or neuropathic pain. These data suggest that GRPR is a marker for a common downstream circuit for histamine-dependent and independent pruritogenic stimuli that is independent of nociception. In contrast, ablation of neurons bearing neurokinin-1, a spinal thalamic tract marker, compromised both itch and pain sensations.[43] Thus, GRPR positive neurons appear to represent a circuit independent of the spinal thalamic tract.

Assessment

The workup for suspected paraneoplastic pruritus has been discussed by other authors[1] and begins with a comprehensive history and physical examination, including attention to lymph nodes. Complete blood count with differential, lactate dehydrogenase, and liver function tests should also be assessed. In some cases, computed tomography scans of the chest and abdomen should be considered to rule out lymphoma or solid tumors. In patients with known malignancies, a complete history and physical should be performed,

and the physician should pay close attention to medication and treatment histories. Blood tests may include complete blood counts, complete metabolic panel, and erythrocyte sedimentation rate, and biopsies should be taken of any concerning lesions.[26]

Treatment

Often, treating the malignancy itself can help resolve pruritus. Medications causing itch should be adjusted for dose or discontinued if possible. Basic management strategies to combat itch should be used at baseline. Cool environments, loose-fitting clothing, and aggressive dry skin care with frequent application of emollients, can be helpful.[26] Specific treatment options for cholestatic and uremic itch have been mentioned previously.

Topical medications are the mainstay of treatment for localized itch. In CTCL, topical corticosteroids are commonly employed as a first-line treatment and can be quite effective.[18,26] Topical bexarotene has also been shown to provide some improvement both to the disease and its associated itch,[44] although this medication may cause irritation.

Other topicals have a more direct effect on the sensation of itch. Topical anesthetic creams have been used but are limited by sensitization or local absorption.[26] Doxepin, with its antihistaminic action, is available topically but can be sedating while being relatively expensive. There are some reports suggesting that topical capsaicin may be useful. A recent meta-analysis of capsaicin for the treatment of pruritus did not show convincing evidence for its use, although in none of the studies did the authors examine oncology patients specifically.[45]

The most commonly used systemic medications used for itch are the antihistamines, which include diphenhydramine, hydroxyzine, and doxepin. The sedating effects of these medications may limit their scheduled use throughout the day, but they can provide added benefit to patients suffering from pruritus-related insomnia.

Phototherapy has provided the most benefit to patients with CTCL. Psoralen plus ultraviolet A and narrow-band UVB (NBUVB) have been well-described in successfully treating patients with CTCL.[18] UVB has been reported to be useful in treating uremic itch, and its mechanism may be related to its attenuation of TH1 cell differentiation and reduction of IL-2 production.[24] Eosinophilic dermatosis of myeloproliferative diseases has also been responsive to NBUVB treatment.[9]

Antidepressant drugs have also shown efficacy in treating itch. Selective serotonin reuptake inhibitors, including sertraline and paroxetine, have been used successfully in patients with lymphoma and solid carcinomas.[46] Selective serotonin reuptake inhibitors are thought to act centrally and may require 2-3 weeks of treatment before becoming effective.[1] Selective norepinephrine reuptake inhibitors act centrally by inhibiting uptake of serotonin and norepinephrine. Mirtazapine has been reported to be effective at treating itch in patients with CTCL, CLL transforming into large B-cell lymphoma, Hodgkin's disease, cholestatic pruritus arising from liver metastases, and end-stage renal disease as a complication of advanced renal cancer.[47,48] Wang and Yosipovitch[24] note that although mirtazapine appears effective at treating nocturnal pruritus, some newer selective norepinephrine reuptake inhibitors, including venlafaxine and duloxetine, do not seem to share its antipruritic effects.

Neuroleptics, such as gabapentin and pregabalin, have also been tried in a variety of conditions, including CTCL,[44,47] and a recent study showed significant improvement in patients with pruritus resulting from IL-2 treatment.[28] The main side effect of neuroleptics is somnolence, which may be helpful for sleep-disrupting symptoms. This class of medication is hypothesized to act through both central and peripheral itch pathways.[1]

Mu-opioid receptor antagonists are another class of medications that have been used to treat itch in the oncology setting. They act by disrupting opioid-sensitive interneurons that transmit itch sensation.[25] The use of these agents should be carefully considered in patients who are taking opioid analgesics, are at risk of abuse, or who have concurrent liver disease. Naltrexone and naloxone have been effective in treating the itch of CTCL as well as uremic and cholestatic pruritus.[25] Newer agents like butorphanol, a kappa-opioid agonist and mu-opioid antagonist, have shown efficacy. Butorphanol has been successfully used to treat patients with intractable pruritus. A woman with non-Hodgkin's lymphoma who did not respond to a variety of topicals, oral antihistamines, and mirtazapine reported considerable itch control after initiation of the medication.[7]

Thalidomide is another systemic agent that has long been recognized to have antipruritic effects, but its teratogenicity has limited its use.[49] The mechanism of action is related to its suppression of tumor necrosis factor alpha and its depression of the peripheral and central nervous system.[1] Currently, thalidomide is being investigated for the treatment of many cancers, including multiple myeloma, lymphomas, and solid tumors, but few reports have been published regarding its efficacy towards treating itch. One recent report observed marked improvement of severe pruritus in a woman with relapsing Hodgkin's disease.[50] Administration of thalidomide requires monitoring via the STEPS program (ie, System for Thalidomide Education and Prescribing Safety) in the United States, and clinicians must be vigilant to detect signs of peripheral neuropathy, which is the other main complication of treatment. Paradoxically, lenalidomide, a thalidomide analogue that was introduced in 2004 and approved for treatment of myelodysplastic syndromes and multiple myeloma, has been noted to have the side effect of pruritus in more than 40% of study patients.[51]

Aprepitant is one of the newest drugs to emerge as a promising new option for the treatment of itch. Aprepitant is a neurokinin-1-receptor antagonist that had been previously approved for use as an antiemetic agent in chemotherapy-induced nausea. The recognition of substance P as a mediator of pruritus, along with the observation that its receptor, neurokinin-1, is overexpressed on the keratinocytes in pruritic skin disease, led to its therapeutic consideration.[19] In its first report as an antipruritic agent, aprepitant led to a significant

reduction in symptoms with a corresponding improvement in quality of life in 3 patients with Sezary syndrome.[19] Itch in a patient with metastatic soft-tissue sarcoma and another with metastatic breast carcinoma was also significantly reduced after treatment.[52] Finally, aprepitant was successfully used to treat erlotinib-induced pruritus in 2 patients undergoing treatment for stage IV nonsmall-cell lung cancer.[33] Larger, controlled studies have not been conducted to date.

In summary, itch in the cancer patient may arise from a variety of causes. Although many treatment options exist, control of pruritus in the cancer patient presents a challenge for both the patient and the clinician. Continued research studying the basic mechanism(s) of itch is ongoing, and is essential for the development of novel therapeutics that will combat this frustrating symptom.

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