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MINI-REVIEW

Pruritus in Cutaneous T-cell Lymphomas: Frequent, Often Severe and Difficult to Treat

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Pruritus has a well-known association with Hodgkin's disease and other nodal lymphomas; indeed it often reveals the disease. Pruritus is also an important symptom of cutaneous T-cell lymphomas. Lymphoma-associated itch is thus both frequent and severe, but its pathophysiology remains unclear. Few studies have evaluated the efficacy of therapeutic agents in the management of cutaneous T-cell lymphoma-related pruritus. The main objective of treatment remains disease control. Pruritus management is generally based on the physician's experience. Treatment is very difficult, especially in Sézary syndrome. We present here management strategies for cutaneous lymphoma-associated pruritus. ***Key words: lymphoma; T-cell; cutaneous; pruritus; therapeutics; pathophysiology.***

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Pruritus (itch) can be defined as an unpleasant cutaneous sensation associated with the immediate desire to scratch. It most commonly occurs in skin disorders, and might be an important dermatological clue to the presence of an underlying systemic disease (1, 2). Pruritus can be initiated during inflammation, cancer, metabolic diseases, infection, psychiatric diseases, drug application and stress (3).

Cutaneous T-cell lymphomas (CTCL) refers to a group of lymphoproliferative disorders characterized by a clonal accumulation of neoplastic memory T lymphocytes in the skin (4). CTCL are the most common primary cutaneous lymphomas. In USA, their incidence has increased from 5 cases per 1,000,000 population in the 1980s to 12.7 cases per 1,000,000 in the 2000s (5). Mycosis fungoides (MF) is the most common variant of CTCL. Typically, patients initially present with erythematous patches in sun-protected areas, which may progress to plaques and possibly skin tumours. Sézary syndrome is a more aggressive form of CTCL, characterized by the association of an exfoliative erythroderma with the presence of atypical mononuclear cells in the skin and the peripheral blood (Sézary cells). Patients with early-stage CTCL have a good prognosis, whereas the prognosis is poorer for patients with late-stage disease (6, 7). CTCL can cause significant morbidity, and adversely affect patients' quality of life (8–10), in part owing to the fact that CTCL are highly associated with pruritus (10). CTCL have multiple subtypes (7). The folliculotropic form of CTCL, Sézary syndrome and erythrodermic form of MF are extremely itchy compared with patch stages of MF: in a case-control study of 43 patients with the folliculotropic form of CTCL, 68% had severe pruritus requiring separate treatment aside from the lymphoma (11). In a phase II trial of oral vorinostat in 33 patients with refractory CTCL, 93% had symptomatic pruritus (12).

PATHOPHYSIOLOGY OF PRURITUS

Pruritus originates within the cutaneous skin's free nerve endings. Among the group of mecano-insensitive C-afferents, pruritus-specific C-fibres (pruriceptors) have been discovered, confirming that there is a specific pathway for itch. The polymodal type of C-fibres (the most common) is insensitive to histamine (13), whereas pruriceptors respond to histamine in parallel with the itch of the subjects. Pruriceptors are characterized by a low conduction velocity, large innervations territories, mechanical unresponsiveness, and high transcutaneous thresholds (13). The sensation of pruritus is transmitted through C-fibres to the dorsal horn of the spinal cord and to the cerebral cortex via the spinothalamic tract (3, 14). Activation of specific areas in the central nervous system results in perception of itch, leading to a scratch response (3, 15). By a direct axon reflex mechanism, sensory nerve endings release neuropeptides, which may aggravate the itch response by stimulating release of pruritic mediators (kinins, prostanoids, and cytokines) from mast cells, immune cells epithelial cells and endothelial cells (3).

The case of cutaneous lymphoma

There is little data regarding the exact pathophysiology of CTCL-related pruritus, but cutaneous inflammation is probably involved. The association between chronic

inflammatory conditions of the skin and risk of CTCL is still a matter of debate, since epidemiological studies have shown contradictory results (16–22). It has been proposed that CTCL may originate from inflammatory conditions of the skin transforming into neoplastic conditions (23, 24). Several data support the fact that inflammatory processes are of importance in CTCL:

- Sezary syndrome T-cell clones produce IL-3, IL-4, IL-5, IL-6 and IL-10, thus displaying a Th2 cytokine-secretion profile (24).
- IL-2 and IL-6 have been proposed as histamine-independent itch mediators. Single dose of IL-2 (10 MU/ml) delivered to the epidermis of healthy volunteer triggers itching. Intradermal injection of 20 μg of IL-2 in the dermis of atopic dermatitis patients or healthy subjects was associated with a low-intensity local itch and erythema (25, 26). In patients with uraemic pruritus, serum levels of IL-6 were found to be significantly increased compared with patients without uraemic pruritus (27). The role of other cytokines, such as IL-31 (28), as histamine-independent itch mediators has also been evoked, but there is no data regarding the role of these cytokines in the pathogenesis of CTCL.
- IL-7 induces lymphoid inflammation in mice (29) and is produced by human keratinocytes (30).
- IL-7 induces proliferation of human T-cell clones with a synergic effect on IL-2 in T-cell clones of CTCL (31).

Regardless of its cause, pruritus is often exacerbated by skin inflammation and vasodilatation (32).

Other pruritogenic factors

It has been reported that mast cells and histamine may play a role in MF, particularly in advanced stages of the disease (33). Histamine, which is released by mast cells, is classically associated with pruritus. Other mast-cell mediators appear to be of clinical importance: serotonin is a neuromediator involved in the pruritus associated with several diseases, including lymphomas (15). Serotonin and histamine may have tumour growth-promotion and immunomodulating properties: the use of serotonin antagonists inhibits in vitro the mitogenesis of normal lymphocytes and promotes the proliferation of transformed lymphocytes (34). In 1996, Vermeer & Willemze (35) reported 2 patients with MF who had an exacerbation of their disease shortly after starting fluoxetine, a specific serotonin uptake inhibitor used as antidepressant. Antihistamines were reported to be associated with the development of atypical lymphoid infiltrates in the skin (36). The role of anti-histamines and serotonin antagonists in tumour progression of CTCL has not been investigated.

Proteases, such as kallikreins and cathepsin, contribute to the integrity and protective barrier function of the skin (37). Protease regulation is altered in inflammatory skin conditions. In atopic dermatitis, psoriasis, exfoliative dermatitis excessive protease activation was shown to contribute to skin barrier function damage (37). Kallikrein and the resulting peptide fragments (bradykinin) can induce itch by activating histamine-sensitive C-fibres (13). Investigating the activity of proteases in the skin of patients with CTCL may be important to understand the pathophysiology of CTCL-related pruritus.

PRURITUS AS A SYMPTOM OF CUTANEOUS LYMPHOMAS

In patients with CTCL, pruritus is frequent (5, 38), severe, and unrelieved by emollients, topical steroids, or oral antihistamines. In CTCL, pruritus is permanent and aggravated in the evening or by heat. It interferes with sleep. Most of the patients report diffuse pruritus, but pruritus may also be localized on specific lesions. As in systemic haematological malignancies, CTCL-related pruritus may be worsened by water. In the advanced stages, patients commonly report an ill-defined, severe, and diffuse pruritus that may turn into ”burning pain”. This pruritus displays similarities with neuropathic pain (39). In a large survey from the USA evaluating 309 patients with CTCL, Demierre et al. (10) reported that a large majority of them (88%) were bothered by itching, and 41% of them reported some pain. Pruritus may be a presenting feature in patients with CTCL, and can occur without skin lesions, making the diagnosis of CTCL difficult (5, 40). Pruritus is the most frequent and the earliest symptom of CTCL (41). In the early stages, pruritus may be relieved by topical corticosteroids. This seemingly well-controlled dermatitis may delay the correct diagnosis (42). Moreover, for several patients the diagnosis of CTCL is difficult to obtain, since gathering histological findings and molecular evidence of the T-cell receptor clonality may take years (41).

We consider that, in case of atypical pruritus (severe pruritus and/or chronic and/or permanent pruritus without systemic explanation, and/or pruritus that interferes with sleep, and or topical steroid-resistant pruritus, and/or pruritus associated with atypical dermatitis), at least three pathological examinations of the skin and one assessment of T-cell clonality in the skin should be performed over a period of one year.

THERAPEUTICS

Management of pruritus should be directed at the underlying cause. CTCL are chronic diseases, and multiple therapies are available, each with varying efficacy and side-effects profiles. The main outcome of CTCL treatment remains disease control, and few studies have been designed to evaluate the efficacy of therapeutics in the management of CTCL-related

pruritus. Most practices are based on the treating physician's experience.

Topical agents

The efficacy of high potency topical corticosteroids in early-stage CTCL is well known (43, 44). Topical corticosteroids have been shown rapidly to decrease histamine-induced itch (45). In the early stages of the disease, CTCL-related pruritus can be efficiently diminished by topical steroids (40). High potency topical steroids should remain the treatment of first choice at these stages (46). It has been reported recently that the use of wet dressing in association with topical steroids may be an interesting option for the management of pruritic skin diseases other than atopic dermatitis (47). The authors report a retrospective uncontrolled study on 331 patients with pruritic skin diseases recalcitrant to previous therapies (topical steroids, antihistamines, and emollients). Among them, 12 patients with CTCL were improved after treatment with the association of topical steroids and wet dressing. This association may be an interesting option for the management of intense flares of itching in patients with CTCL.

Systemic agents

Although their antipruritic effect in CTCL has not been formally evaluated, oral corticosteroids may also be used to reduce CTCL-related pruritus. In our experience, doses of 10–30 mg/day may significantly improve pruritus in patients with CTCL. However, numerous side-effects are associated with long-term use of oral steroids. Anti-histamines can be associated with topical therapy to diminish pruritus in CTCL, and with other specific topical or systemic drugs aimed at controlling the tumour activity. Naltrexone, an opioid-receptor antagonist, has been reported to be efficient in CTCL-related pruritus (48). However, this study was open-labelled, and the use of naltrexone for the treatment of pruritus in CTCL should be evaluated further.

Phototherapy

Second-line treatments of CTCL-related pruritus are not well defined. CTCL is one of the major dermatological conditions for which phototherapy continues to be a valuable treatment modality (49). The most documented treatment for the management of pruritus in CTCL is psoralen plus ultraviolet A (PUVA). It has been used for decades in the management of CTCL and is effective in early-stage CTCL (44–46, 51). In early-stage CTCL, PUVA induces significant clinical improvement and long-lasting disease-free intervals (reviewed in 49). Its efficacy can further be improved when used in conjunction with other treatment modalities, such as interferon-α (52) or retinoids (53, 54). The efficacy of narrow-band UVB phototherapy on pruritus is also well established (55, 56). Patients may be treated with a starting dose of 70% of the UVB-minimal erythematous dose. The dose may be increased by 10–15% per session as tolerated. Sessions will be performed 3 times weekly until regression of the lesions, and then pursued once to twice weekly in case of successful response. In the first 2 weeks of treatment with phototherapy, itch may be worsened. Patients can be maintained on topical steroids or antihistamines treatment during phototherapy. Phototherapy should be preferred to topical steroids when the pruritus is diffuse or intense or interferes with sleep.

Treatment of underlying disease

A significant reduction in CTCL-related pruritus has been reported with the use of drugs aimed at controlling the disease. The effects of denileukin diftitox (an IL-2 receptor targeted fusion protein) on quality of life and pruritus of 71 patients with CTCL have been evaluated as part of a multicentre phase III trial (57, 58). Pruritus severity (assessed on a 10-cm visual analogue scale) were improved significantly after 6 months of treatment compared with baseline evaluation. Alemtuzumab, a monoclonal anti-CD52 antibody, has been evaluated in the treatment of CTCL (phase II study, 22 patients) (59). In this study, a reduction of 6 points in the median pruritus score (self-assessed visual analogue scale) at the end of the treatment was reported. Most recently, a significant reduction of the pruritus has been reported with the use of vorinostat (suberoylanilide hydroxamic acid) for refractory CTCL: 45% of the patients had a reduction of at least 3 points for at least 4 weeks compared with baseline evaluation of pruritus (12). In 2005, Brightman & Demierre (60) reported on the use of thalidomide in one patient with MF, with a reduction in pruritus assessment score. Thalidomide is known to be effective on several pruritic skin diseases (61, 62), and may be an interesting option for the management of patients with refractory pruritic CTCL. Low-dose methotrexate has been used to treat CTCL for many years (50, 63). However, the effects of low-dose methotrexate on CTCL-related pruritus are poorly documented. In our experience, patients treated with methotrexate for a CTCL may have significant pruritus improvement. Further studies should be conducted to evaluate antipruritic effects of methotrexate in CTCL.

Demierre & Taverna (64) have reported their experience on the use of gabapentin (an anticonvulsivant) and mirtazapine (an antidepressant) to manage severe pruritus associated with advanced-stage CTCL. Both gabapentin and mirtazapine have been reported as effective in the treatment of pruritus (65, 66). The authors recommended a starting dose of gabapentin of 300 mg at night, titrated upward, without exceeding 2400 mg daily. For patients who did not respond, the authors recom-

mend progressively substituting gabapentin with a low dose of mirtazapine (7.5–15 mg daily in the evening).

Recently, Sepmeyer et al. (67) reported an open-label study of combination therapy with rosiglitazone and bexarotene for CTCL, with interesting effects on pruritus: 3 of the 4 patients had relieved pruritus after 16 weeks of a regimen comprising bexarotene (190–425 mg/m² daily) and rosiglitazone (4–8 mg daily). Rosiglitazone is a PPAR (peroxisome proliferator-activated receptor) agonist. PPAR are transcription factors that heterodimerize with retinoid X receptors (RXR) and bind to peroxisome proliferator response elements in the promoter region of target genes. Interestingly, RXRs are the targets of bexarotene. Bexarotene transactivates PPAR-alpha target genes in a PPAR-alpha dependent manner (68). PPAR agonists may improve the therapeutic response to RXR agonists and may help to reduce CTCL-related pruritus through better control of the disease. The role of PPAR agonists in CTCL should be further explored.

For the particular case of Sézary syndrome, extracorporeal photochemotherapy (ECP) can be considered as an interesting therapeutic option to reduce both disease activity and pruritus. ECP has been reported to induce long-term remissions of Sézary syndrome (69–71) and has been reported to reduce pruritus, not only in Sézary syndrome, but also in atopic dermatitis (72). ECPs sessions have to be performed twice monthly until remission of the disease. Finally, a dramatic improvement was noted in 3 patients with Sézary syndrome suffering from severe and uncontrolled pruritus after treatment with aprepitant, which is an antagonist of natural killer (NK) 1 receptor for substance P (73).

CONCLUSION

In patients with CTCL, pruritus is frequent and often severe. A pruritus without skin lesions, or associated with mild dermatitis, rarely leads to a diagnosis of CTCL. This symptom negatively affects quality of life of patients. The management of severe pruritus is not supported by solid clinical evidence but is based on individual expert opinion. First-line treatment recommendation should be topical steroids or phototherapy, sometimes in combination with disease-modifying treatment, such as interferon or retinoids. In case of insufficient response, anticonvulsivants or antidepressants can be used. A possible alternative is provided by NK1 antagonists.

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