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CLINICAL REPORT

Intractable Chronic Pruritus in a 67-year-old Man

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Chronic pruritus (>6 weeks) can be caused by skin diseases and systemic diseases, including malignancies. It is a distressing symptom that requires a precise medical history, thorough physical examination, laboratory and radiological diagnostics. The interpretation of results may sometimes be difficult and may often reveal several pathological findings. This case report demonstrates prostate cancer as a possible underlying disease in a patient with chronic pruritus. Therapy with the selective serotonin reuptake inhibitor paroxetine significantly relieved pruritus, but was less effective when external therapy was discontinued. Most pruritus patients need consecutive or combined aetiological and symptomatic (topical and systemic) therapy. ***Key words: cancer itch; itch; pruritus; prostate cancer; pruritus therapy.***

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Chronic pruritus is defined as pruritus lasting longer than 6 weeks (1). It is a distressing symptom that can be caused by skin diseases, such as eczema, contact dermatitis, skin infections, drug intake, and by systematic diseases including malignancies (1–3). Pruritus of unknown origin may be the initial symptom of a systemic disease in 13–40% of cases (4–8). There exists no definite classification of chronic pruritus. Two recently developed classifications focus either on neurophysiological or clinical characteristics of pruritus (1, 3). Due to the complex neurophysiology of pruritus, one classification distinguishes between cutaneous (pruritoceptive, e.g. contact dermatitis), neurogenic (arising from neurophysiological dysfunction, e.g. due to cholestasis), neuropathic (originating at any point along the afferent pathway of damage to nerve system, e.g. postherpetic pruritus), psychogenic/somatoform or a mixture (e.g. atopic dermatitis, uraemia) (3). A prerequisite is the involvement and activity of cutaneous sensory neurones that transmit the signals via dorsal root ganglia and the spinal cord to the central nervous system (CNS). The perception of pruritus is a complex interaction of exogenous and endogenous mediators (e.g. neuropeptides) stimulating pruritoceptors (peripheral nerve endings of primary afferent neurones) that transmit the stimulus to the spinal cord, where the signals can be modulated (9, 10). After crossing the contralateral side, the signal reaches the CNS, where specific brain areas are activated, leading to scratching. All this may be modified by additional release of mast-cell releasing substances via the associated peripheral axon reflex, as well as complex mechanisms of interaction of pain and pruritus fibres at the spinal cord level (9, 10). Clinical classification serves as an important tool when diagnosing pruritus in daily practice (1). Chronic pruritus needs a precise patient's history, thorough physical examination, laboratory and radiological diagnostics depending on the individual findings (11). The interpretation may sometimes be difficult, often revealing several pathological findings. It is the physician's task critically to appraise these pathological findings and identify a hierarchy for further diagnostics and initiation of therapy.

CASE REPORT

A 67-year-old man presented to the department in February 2007 with daily pruritus of the whole body, mainly on the abdomen, back and legs, since summer 2005. His skin was normal except for single papules on the mid-back and chest, including mild linear excoriations and xerosis cutis of the limbs. Pruritus was particularly strong during the night, causing severe sleep disturbance. The average itch intensity was rated 9 on a numerical rating scale (NRS: range 0 = no itch, 10 = maximal imaginable itch). Various therapies started by his general practitioner and dermatologist, including topical glucocorticosteroids, oral antihistamines, chloroquine, dapsone and antibiotics, were not effective. Oral glucocorticosteroids, e.g. prednisolone 20 mg/day, led to significant relief of pruritus. A precise check-up, including laboratory, chest X-ray, and ultrasound of the abdomen, revealed a slightly elevated prostate-specific antigen (PSA). The consultant urologist did not see any necessity for further diagnostics except for PSA control in the nearer future.

Due to the severity of pruritus, the psychological impairment to the patient, and the need to stop long-term oral glucocorticosteroid treatment, a biopsy of the prostate was performed in May 2007. This revealed an adenocarcinoma (T^2N0M0), necessitating complete prostate resection including dissection of the regional

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lymph nodes in July 2007. The pruritus did not decrease after this operation (NRS 9). The selective serotonin reuptake inhibitor (SSRI) paroxetine, 20 mg/day, was started in August 2007, and this reduced pruritus by up to 80% (NRS 2) within 1 week with no side-effects except for mild fatigue during the first 2 weeks. As there were periods of weeks without any pruritus (NRS 0), paroxetine was decreased to 10 mg/day after 7 weeks. This dose was continued for 6 weeks, with pruritus rated NRS 3. Pruritus recurred on the trunk and especially on the legs (NRS 7). After a total of 8 weeks the dose was again increased to 20 mg/day. Five weeks later the patient reported disappointment with the effect of the therapy and requested another increase in the dose of paroxetine. During the last weeks the patient had completely discontinued any topical therapy including moisturizing the skin. He was encouraged to restart topical therapy with topical anti-pruritics, such as polidocanol and urea 10% containing creams, while continuing paroxetine 20 mg/day. After one week he again experienced significant relief of pruritus (NRS 2). Paroxetine 20 mg/day and daily topical therapy are maintained until the current time.

DISCUSSION

An association between systemic malignancies and cutaneous manifestations such as pruritus has long been recognized. It is described to be a relatively rare symptom in malignancies, but when present may be worse than pain (12, 13). Various aetiological mechanisms have been observed, ranging from direct tumour invasion of the skin, distant metastases to paraneoplastic inflammatory skin diseases and paraneoplastic phenomena. Pruritus in cancer may be caused by nerve compression, tumour growth, bile duct compression, cholestasis, side-effects of therapy and xerosis cutis (2, 3). Toxic substances and necrotic tumour cells have also been postulated as possible eliciting factors in pruritus of cancer patients (2, 3). It is usually believed that paraneoplastic pruritus disappears or diminishes after tumour resection. Relapse of pruritus may constitute the only sign of reactivation and progression of the carcinoma and as such is an important sign (12). So far, there is no clear evidence for these criteria according to clinical studies. One explanation for this circumstance is that pruritus is mostly not recorded as a symptom in cancer studies, especially in non-dermatological fields. It may also be possible that as yet unidentified mechanisms or metabolites released by the cancer tissue contribute to pruritus origin and perception in cancer patients, as in the case presented here. It is not clear whether all the mechanisms discussed depend on progression of the carcinoma and metastasis. The presence of pruritus for months or longer before the discovery of the underlying carcinoma suggests that some cancers may remain small and localized for long periods of time (12).

When diagnosing pruritus obtaining a precise medical history, clinical examination and laboratory as well as radiological diagnostics are of high importance. Chronic pruritus is frequently caused or maintained supported by several factors/cofactors (7, 8). Particularly in the elderly population several factors, e.g. xerosis cutis, drugs, systemic diseases may be identified. This requires a step-by-step procedure in diagnostics and therapy of pruritus. Rare diseases also have to be considered when examining patients suffering from chronic pruritus. This case report demonstrates that intensive diagnostic procedures are justified in chronic, persistent pruritus even if there are only discrete pathological laboratory findings.

Paroxetine is approved for the treatment of depression. It acts by serotonin reuptake inhibition on the synapses and platelets, leading to down-regulation of post-synaptic 5-HT (hydroxytryptamine) receptors and decreased serotonin release. 5-HT receptors are distributed in the central and peripheral nervous system, being linked to several serotonin-mediated processes, such as vasomotor reflexes and cardiovascular regulation, various nervous functions, such as the enteric nervous system, limbic cortical functioning, nociception and pain. The reported patient's pruritus can be understood as a mixture of paraneoplastic and possibly somatoform pruritus as well as a complication of dry skin. Paroxetine 5–20 mg/day has been reported to be effective in both forms of pruritus (paraneoplastic and somatoform) in a dose-dependent manner (13–15). This was also confirmed in a randomized controlled trial including 7 patients with paraneoplastic pruritus (15). The underlying mechanism of paroxetine's anti-pruritic effect is not known, but the involvement of central opioid receptors and the inhibition of the CYP2D6 hepatic isoenzyme have been discussed (15). It has been reported that the mood improvement takes at least 10 days longer than pruritus improvement (14). In accordance with others, the anti-pruritic effect can be seen rapidly within one or several days (as in this patient) but also, according to clinical experience, it may be achieved after treatment periods of 4–6 weeks (13–15). Tachyphylaxis should be considered and may occur in SSRI therapy, explaining the decreased efficacy of the drug. This phenomenon is insufficiently highlighted in the literature and SSRI studies have so far not addressed this aspect.

This case report demonstrates several new aspects of chronic pruritus:

- a non-metastasized prostate cancer has not been previously recognized as a possible cause of chronic pruritus;
- in cancer patients pruritus might frequently have several causes, including psychogenic ones and xerosis cutis. This case report illustrates that patients with

chronic pruritus need a consecutive or combined aetiological and symptomatic (topical and systemic) therapy depending on the patient's overall condition (16, Table I);

- patients tend to think that once they "take a pill" there is no need to continue topical therapy, including moisturizing the skin. Experimental data show that disruption of the cutaneous barrier, including by decreased hydration, increases spontaneous scratching. Skin dryness and an increase in epidermal nerve fibres may be at least partly responsible for pruritus in xerosis cutis (17);
- SSRI therapy has been described to be effective in paraneoplastic pruritus, as is confirmed in this report. One problem can be the reoccurrence of pruritus when the drug is reduced or discontinued, as was also observed in our patient, but a maintained anti-pruritic effect over periods of several months was also observed (14). Randomized controlled clinical studies are needed to determine the exact dose of SSRI in defined forms of pruritus such as paraneoplastic pruritus.

The diversity of studies and the differing criteria used to select study patients limit any conclusion as to whether generalized pruritus is statistically significantly associated with the presence of cancer (18, 19). Yet, the demographic situation, especially in western countries with an increasing proportion of elderly people, increases the possibility of cancer. This fact should be considered when diagnosing patients who have chronic pruritus.

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Table I. *Symptomatic treatment options for paraneoplastic pruritus*

Topical:
• Menthol, camphor
• Local anaesthetics, e.g. polidocanol
• Urea preparations, e.g. urea 10% cream
• Tannin preparations (cream, bath)
• Antiseptics, e.g. fusidic acid
• Glucocorticosteroids of lower potency
• Immunomodulators: pimecrolimus 1%, tacrolimus 0.03% or 0.1%
• Capsaicin cream 0.025–0.5%
• N-Palmitoylethanolamine-containing cream
Systemic:
• Antihistamines, e.g. hydroxyzine, 25–50 mg at night
• Selective serotonin reuptake inhibitors, e.g. paroxetine 10–40 mg/day, fluoxetine 40–80 mg/day
• Gabapentin 300–3600 mg/day

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