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SPECIAL REPORT

Paraneoplastic Itch: An Expert Position Statement from the Special Interest Group (SIG) of the International Forum on the Study of Itch (IFSI)

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In clinical practice, the term "paraneoplastic itch" is used to describe itch in patients with cancer. Patients with hematological or solid tumor malignancies can be affected. In general, paraneoplastic itch is considered a rare disorder. However, paraneoplastic itch in hematological malignancies such as polycythemia vera and lymphoma are relatively frequent while other forms of paraneoplastic itch are in fact extremely rare. The true frequency of this symptom is unclear, epidemiological data in this field are limited. Itch in malignant disease may additionally impair patients' quality of life. A population-based cohort study showed that chronic itch without concomitant skin changes is a risk factor for having undiagnosed hematologic and bile duct malignancies. Paraneoplastic itch is rather resistant to treatment. In 2012, an interdisciplinary interest group of physicians and researchers was founded, aiming to generate a clear definition of paraneoplastic itch. In this paper we briefly review the current knowledge and aim to define what can be summarized under the term "paraneoplastic itch".
Key words: cancer; itch; malignancy; paraneoplastic itch; palliative care; pruritus.

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Paraneoplastic itch (PI) pertains to itch in patients with cancer. As yet, no clear disease definition exists. It has been reported most common with lymphoreticular malignancies and rarely with solid tumor diseases (1). In general, PI is considered a rare disorder. However, PI in hematological malignancies such as polycythemia vera (PV) and lymphoma are relatively frequent (affecting 15–50% of patients) while other forms of PI are in fact extremely rare. The true frequency of this symptom is unclear, epidemiological data in this field is limited (2). Previous research showed that physicians underestimate the symptom of itch (3) which can also be observed in the field of oncology and in hospices. In many instances, PI is simply not recognized, either because the disorder has not been described, a diagnostic test has not been developed the symptoms resemble many other diseases and complications. In 2012, an interdisciplinary special interest group (SIG) of field experts (physicians and researchers) of the International Forum for the Study of Itch (IFSI) was founded, aiming to generate a clearer definition of PI. In this paper we briefly report about what has been termed "paraneoplastic itch". For this purpose, the electronic databases PubMed, Medline and the Cochrane Library were searched. Furthermore conference proceedings were considered and screened manually as well as national/international studies and textbooks. The search terms used were: paraneoplastic itch, paraneoplastic pruritus, itch [and] palliative care, itch [and] malignancy [and] cancer. The SIG met 4 times in 2012 and 2013, discussed the scientific literature, shared own long lasting clinical experiences and research. The group's results were presented and discussed in a session during the 7th World Congress on Itch (WCI) on September 23rd 2013 (4).

DEFINITION

According to the international classification of the IFSI chronic itch is defined as itch lasting for more than 6 weeks (5). At present, there is no clear definition of PI, neither in terms of applicability nor in terms of duration. Several terms have been used in the literature to describe different types of PI: "pruritus and malignancy" (6), "pruritus in advanced disease" (7), "pruritus accompanying solid tumors" (7), "pruritus in hematological disorder" (7) and "paraneoplastic itch" (8). Further descriptions include "paraneoplastic syndromes as unusual manifestations of malignant disease" (9) and "pruritus associated with cancer growing in a remote part of the body/organ known as paraneoplastic dermatoses" (10). According to Yosipovitch (11) PI is defined as itch that occurs early during the natural process or even precedes the clinical evidence of the malignancy, it is not caused by the neoplastic

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mass invasion or compression, and subsides after the removal of the tumor. In the IFSI classification PI corresponds to itch arising from systemic diseases (category II) according to the underlying origin (5). This also comprises malignant diseases.

The SIG on "Paraneoplastic itch" defines it as follows: PI describes the sensation of itch as a systemic (not local) reaction to the presence of a tumor or a hematological malignancy neither induced by the local presence of cancer cells nor by tumor therapy. It usually disappears with remission of the tumor and can return with its relapse. PI may occur as a single symptom or with different clinical and pathophysiological signs.

The SIG determines that the following does not describe PI: (*i*) *Paraneoplastic syndromes*: They have been described for many years and were defined as unusual manifestations of malignant disease (9). Common paraneoplastic syndromes form distinct patterns of symptoms caused by specific pathophysiological processes and are often associated with specific malignancies, e.g. Lambert-Eaton-Syndrome with muscle weakness and double-vision etc. in small-cell lung cancer; (*ii*) *Brachioradial itch*: This can be caused by tumor compression of the cervical spine and is then termed neuropathic itch but does not qualify to the diagnosis of PI (7, 12); (*iii*) *Cholestatic itch* as a paraneoplastic manifestation due to mechanical obstruction of e.g. the bile duct caused by cancer or toxic or drug-induced cholestasis; (*iv*) *Facial itch or itch around the nostrils* as a result of a brain tumor; (*v*) *Drug-induced itch*: this can occur in cancer patients receiving anticancer therapies and immunotherapies. (*vi*) *Itch due to infections* in patients with cancer; (*vii*) *Itch caused by specific dermatological diseases* in cancer patients such as contact dermatitis, eczema, urticaria, psoriasis, and miliaria.

PREVALENCE AND INCIDENCE

There are limited epidemiological studies assessing the true prevalence of itch in cancer patients (2). The most informative was published by Kilic et al. (13) who analyzed 700 patients recently diagnosed with malignancy for skin lesions and symptoms. Among them they found 41 patients (5.9%) to suffer from generalized itch. Most of them did not have specific dermatoses, but suffered from non-specific eruptions with or without papules and excoriations. Among the tumors that caused itch most common were gastrointestinal tumors (10/41) and hematological malignancies (6/41). There is no information provided about the onset of itch and time of diagnosis of the malignancy.

Among patients with advanced malignancies in palliative care, the prevalence of pruritus is less than 1% (14) but with the limitation that not all of them are PI. This low number probably reflects the fact that patients with hematological malignancies rarely die in hospices. In addition many patients with solid tumors dwelling in hospices have the tumor well palliated by chemotherapy and radiotherapy.

From previous studies it is known that there are differences in the prevalence of itch depending on the type of cancer. In hematological malignancies e.g. the prevalence of itch is higher than in non-hematologic malignancies. In non-Hodgkin lymphomas it is around 30% (13, 15–18), in Hodgkin lymphomas around 15–50% (19–21) and in PV around 50% (22–26). In an internet survey in patients with essential thrombocytosis, 40% reported itch (27). Previous research showed that patients presenting with itch of undetermined origin and being followed up for a long time develop roughly the same number of malignancies as a population not suffering from itch (28–30). However, a recent population-based cohort study in 8,744 patients with chronic itch showed that chronic itch without concomitant skin changes is a risk factor for having undiagnosed hematological and bile duct malignancies (31). According to the authors, screening for malignancy should be limited to the evaluation of these two conditions (31). A nationwide Danish cohort study based on registry data assessed the association between hospital inpatient and outpatient diagnosis of itch and cancer incidence (32). The 1-year absolute cancer risk was 1.63%. A 13% higher than expected number of both hematological and various solid cancers among patients with itch was found. This refers especially to hematological cancers, above all Hodgkin lymphoma (32). However the study was unable to differentiate between acute and chronic itch.

CLINICAL CHARACTERISTICS

PI may precede the diagnosis of the tumor. It may disappear when the tumor is adequately treated and its reappearance may herald tumor recurrence (33). The intensity of itch seems to increase along the stage of the disease. PI occurs generalized in most cases.

Itch in malignancy may present on normally appearing skin or may be characterized by secondary scratch lesions like excoriations, prurigo nodules, lichenification, hyper- and hypopigmentations as well as scars. Dermatoses associated with cancer growing in a remote part of the body were named "paraneoplastic dermatoses" (10). Some paraneoplastic dermatoses may be associated with itch of varying intensity (Table I).

There are more or less unique clinical features of some forms of PI but it is not possible to diagnose PI according to its clinical characteristics. Aquagenic itch is itch without any skin lesions that develops minutes after contact with water of any temperature. In up to 30% of patients it is associated with PV or other lymphoproliferative diseases. If so it is termed PI.

Table I. *Paraneoplastic skin diseases associated with itch of varying intensity (adapted from 11)*

Paraneoplastic syndrome	Associated malignancies
Erythroderma	Hematological malignancies
Bazex syndrome (acrokeratosis paraneoplastica)	Head & neck cancers, upper airway, digestive tract cancers (larynx, oesophagus, pharynx)
Grovers disease (benign papular acantholytic dermatosis)	Hematological malignancies
Lesser-Trélat (eruptive seborrhoeic keratoses)	Adenocarcinoma of digestive tract, hematological malignancies
Generalised granuloma annulare	Hematological malignancies
Dermatomyositis	Carcinoma of the colon, breast, ovaries, nasopharynx
Malignant acanthosis nigricans	Gastrointestinal carcinomas

PATHOGENESIS

The mechanisms of PI are still not understood. Recently, interleukin-31 (IL-31), a Th2 cytokine was found to be highly associated with itch in lymphoma and highly expressed in malignant T cells (34). Increased skin infiltration and mast-cell degranulation was found in patients with PV and aquagenic itch (26). Recently it could be shown that for PV aquagenic pruritus seems to be most pronounced in patients showing the homozygocy for JAK2 617V mutation (35).

DIAGNOSTICS AND TREATMENT

Any chronic itch of undetermined origin deserves precise diagnostic management (14, 36, 37). A thorough medical history and complete physical examination including lymph nodes is necessary. Diagnostic testing is directed by the clinical examination (36): laboratory tests like complete blood cell count, liver function tests, LDH etc. should be performed followed by radiological tests (chest X-ray, ultrasound, CT of the chest and abdomen (to rule out lymphoma)) and bone marrow examination if blood cell counts hints to a hematological malignancy. Further diagnostic testing is directed by the results, e.g. colonoscopy, urological examination (36).

The treatment of PI comprises the treatment of the underlying origin which is the malignancy itself. Cytoreductive therapies were observed to be effective, although direct evidence from controlled trials does not exist. Randomized controlled trials (RCTs) for the treatment of PI are missing. The following text briefly summarizes reported treatment options of proof-of-concept studies, surveillance data and case reports.

H1 antihistamines are frequently ineffective in PI but they may act as a sedative when e.g. hydroxizine (25–75 mg at night) is used at night time (36, 38).

PI in lymphoma is often treated with prednisone, e.g. 40 mg daily. Recent data demonstrated that prednisone reduces IL-31 expression in malignant T cells and this is correlated to reduced itch in cutaneous T-cell lymphoma (CTCL) patients (34). However, a more recent study (39) failed to find a correlation between IL-31 levels in serum and itch severity in patients with CTCL.

Moderate antipruritic effects of the serotonin reuptake inhibitors (SSRI) paroxetine (5–20 mg/day) and fluvoxamine (25–100 mg/day) were confirmed in 2 clinical trials (40, 41). Another SSRI, sertraline may be used in a dose of 25–50 mg/day. The SSRI needs to be started at low dose (e.g. paroxetine 5 mg oral/day) and should be increased to e.g. 20 mg within 3–5 days because severe nausea and vomiting may occur (40). The antipruritic effect can be observed within 2–3 days but may take up to 4 weeks in single cases. Paroxetine is also effective in PV (22, 42). It is not known whether other SSRIs are equally effective as paroxetine, fluvoxamine or sertraline. Tetracyclic antidepressants such as mirtazapine 15 mg (up to 45 mg/day) were also described to have antipruritic effects in several case reports (43–45). Antidepressants such as amitriptyline 25–100 mg or doxepine 50 mg can be used at night time.

Antagonists of calcium α(2)-δ channel blockers, gabapentin (300 mg up to 3,600 mg maximum, divided in up to 3 doses) and pregabalin (75 mg up to 600 mg/day divided in up to 3 doses) can be used for treating PI but the exact mechanism of their antipruritic effect is unknown (36).

Thalidomide (50–200 mg/day) was used for PI in single case reports. As this drug may produce peripheral neuropathy it is important to monitor its effects and avoid prolonged use for more than one year (46). Interestingly, the less toxic derivative of thalidomide, lenalidomide, seems to induce itch (47).

Opioid receptor antagonists like the μ-opioid receptor antagonists naloxone (0.8–2 mg i.v. or 0.2 μg/kg/min i.v. for 24 h), naltrexone (50–100 mg/day orally) or nalmefene (20–120 mg/day orally) may show considerable relief of itch (48). Butorphanol is a κ-opioid agonist and a μ-antagonist and possess (weak) analgesic and antipruritic effects in non-Hodgkin lymphoma when given at a dose of intranasally 1 mg/day (49, 50).

Aprepitant is a NK-1 (neurokinin) receptor antagonist licensed for the treatment of severe post-chemotherapy nausea and vomiting. It has been used for itch in T-cell lymphoma, mycosis fungoides, solid tumors and itch related to biological cancer treatment (51–55) in an oral dose of 80–125 mg/day.

Patients with advanced oncological diseases often suffer from multiple symptoms and health problems, especially pain. The treatment of pain may sometimes provoke or exacerbate itch (e.g. morphine). There are no standard treatments for such a situation. Most of the

above-mentioned treatments are suitable for patients who eat and drink normally but in patients with far advanced neoplastic disease, the swallowing of tablets may be a problem. In these cases, intravenous application of drugs is necessary, but no specific drug can be recommended. Antihistamines, corticosteroids, tropisetrone (serotonin receptor antagonist) and aprepitant may be tried.

CONCLUSIONS AND FUTURE WORK

The overall prevalence and incidence of PI is still unclear. There are no studies investigating clinical characteristics, such as quality, severity and time course of PI. It may range from mild to very severe. The SIG concludes that PI does not receive the needed attention due to a lack of research and studies in this field. For the future, we should try to gain more knowledge about PI in terms of pathophysiology, epidemiological data, clinical characteristics and treatment modalities. There are also other questions that need to be answered: Are there any serum markers? Which malignant entities besides bile duct and hematological malignancies do show a high association with chronic itch? Are there any risk factors for developing PI? Could these data be obtained by establishing a web-based registry?

One may create a counseling forum for physicians and palliative care doctors faced with the problem of chronic itch in patients with malignancy.

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