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Late Effects in Oncotherapy: Skin the Great Sentinel

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Abstract

Nowadays, oncological patients live many years after the end of oncological treatments, and this permits the observation of a new spectrum of cutaneous side-effects: the late effects. Skin alterations could represent the first sign of many of these late effects. Capillaroscopy could be used to diagnose initial vascular injury. CIPN could be often revealed by skin and skin appendages atrophy and dystrophy. In particular, nails could show neuronal alterations. Endocrine changes could be associated to many skin and skin appendages signs: hypo-or hyper-pigmentation may reveal adrenal disorders, hair and nails alterations may be associated to thyroid dysfunction, necrobiosis lipoidica, telangiectasias and subcutaneous modifications, in particular in fat composition and architecture could be associated to metabolic disorders. Close follow-up and adoption of early risk-reduction strategies could potentially reduce the impact of these sequelae. Skin surveillance could be a great tool for an early diagnosis.

***Keywords:** Adverse drug reaction; Chemotherapy; Diagnosis*

1. Introduction

Skin and skin appendages are almost always interested by oncotherapy effects. Pathogenetic mechanisms may be different (immunological, toxic, idiosyncratic), but other drugs assumption and endocrine or metabolic changes may also play a role.

Keratinocytes are characterized by a rapid turnover, and this is the reason why they represent the firstly involved target of cytotoxic drugs, giving place to a series of extensively known acute cutaneous effects. These effects are caused by the arrest of cellular mitotic and metabolic activity, which leads to necrosis and consequent loss of function. Melanocytes are involved in a similar manner, conducing to hypo- or hyper-pigmentation.

What described before is related to acute skin toxicity, but actually another spectrum of cutaneous side-effects is emerging: late effects.

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Up to few years ago, oncological patients' life expectancy was very poor and many late effects of chemotherapy were not appreciated. Nowadays, fortunately, patients live many years after the end of anticancer treatment, permitting the observation of a series of implications, which were unimaginable before. With the aim of creating a high-quality survivorship care, survivorship care plans (SCPs) have been developed and used [1-3].

Some of these effects have been already described, and they fundamentally consisted in outcome of previous acute process: scars, fibrotic reaction, hypo- or hypo-pigmentations, and telangiectasia. Many others are still unknown, misdiagnosed or unrecognized.

Recent studies reported as chronic effects of oncological treatment with increasing time in follow-up chronic fatigue (56%), perceived cognitive change (56%), peripheral neuropathy (35%), sexual changes (15% of male users and 35% of female), osteoporosis (14%), and heart disease (10%), and also hyper- or hypothyroidism, thyroid nodules, speaking and/or swallowing changes, skin cancers in the RT field [4].

In this paper we want to describe skin alterations which may be the indicators of internal modifications associated to oncotherapy. The early individuation of these skin and skin appendages signs could lead to an earlier or otherwise undiagnosed detection of internal diseases.

2. Skin Involvement in Chemotherapy Induced Vascular Damage

Vascular involvement is an emerging aspect of oncologic therapies. It is largely known that these drugs may damage different vascular structures, but the mechanisms of this damage and the effects on organs are not well known [5].

Many pathogenetic mechanisms have been proposed: direct endothelial damage, activation of coagulation factors, autonomic dysfunction and vasculitis and stimulation of fibroblasts. Apoptosis induction of endothelial cells with consequent inflammatory cytokine release is one of the most probable mechanism at the basis of endothelial involvement. Also, vascular smooth muscular cells and autonomous nervous fiber are probably involved, with consequent vasomotor effects and vascular tone modifications [6].

Hydric retention is also frequent in the course of chemotherapy. It is consequent to an endothelial damage which leads to an increased capillary permeability, but also to a modified lymphatic derange, with a fluid retention in the interstitial space [7-8]. Moreover, this effect is made worse by endocrine alteration, such as menopause induction, to which patient are often exposed.

A better identification of vascular involvement could help to identify asymptomatic patients with a higher cardiovascular risk. In this field skin has a double role.

It could be the expression of microvascular alterations showing teleangectasias, nail and body extremities hair alterations, oedema and cutaneous dysesthesias. Panniculopathy has also been described as a late effect of oncotherapy liked to vascular alterations [9].

Moreover, skin could be the site of an easy and cheap investigation of these vascular injuries through capillaroscopy [10].

3. Skin Involvement in Endocrine Effects of Chemotherapy

Onco-therapies could damage endocrine organs in different ways.

Cytotoxic agents can cause hypopituitarism when used as adjuvant to radiotherapy on the pituitary area [11-13].

Immune checkpoint inhibitors, in a dose-dependent manner, may cause hypophysitis and thyroid dysfunction, and more rarely adrenalitis and primary adrenal insufficiency [14]. These effects usually onset 9 weeks after drug initiation [15-17]. Moreover, suppression of ACTH and secondary adrenal insufficiency can occur when prolonged exogenous glucocorticosteroid treatment is administered. Secondary adrenal insufficiency may be persistent and potentially it can be serious and life-threatening.

Likewise, gonads could be damaged by radiotherapy and chemotherapy, leading to primary hypogonadism and secondary health Consequences, ranging from subfertility to sexual dysfunction and decreased quality of life. Moreover, subclinical hypogonadism is also associated with obesity, particularly increased central fat accumulation [18-19].

All these endocrine changes could be associated to many skin and skin appendages signs: hypo-or hyper-pigmentation may reveal adrenal disorders, hair and nails alterations may be associated to thyroid dysfunction, necrobiosis lipoidica, telangiectasias and subcutaneous modifications, in particular in fat composition and architecture, could be associated to metabolic disorders.

4. Chemotherapy Induced Peripheral Neuropathy

Chemotherapy induced peripheral neuropathy (CIPN) occurs in approximately 20% to 40% of cancer patients [20-21] receiving drugs such as platinum agents, taxanes, vinca alkaloids, epothilones, thalidomide, and bortezomib [22-23]. It affects the quality of life (QoL), leads to treatment delays and dose reductions of chemotherapeutic agents, limiting also their efficacy [22-24].

The mechanisms of CIPN are not completely understood. Recent researches showed that the dorsal root ganglion (DGR) of the neural cell bodies could be an important target [22,24]. Other possible mechanisms are: microtubule disruption (for taxanes, epothilones, vinca alkaloids, and bortezomib), nerve terminal damage (for vincristine and taxanes), and dysregulation of neutrophins (for thalidomide and bortezomib) [21,24].

Clinical features of CIPN are various, depending on the chemotherapy agents used and the site of their action, and they can appear at any time during or after the end of chemotherapy. CIPN is primarily manifested in symptoms of sensory neuropathy, including pain, tingling, numbness, and temperature sensitivity in the hands and feet. But also motor neuron can be damaged [21,25], particularly when paclitaxel and vincristine are employed, and autonomic nerves may be damaged by vinca alkaloids [24,26].

Oxaliplatin induced neurotoxicity may be acute or chronic: the acute form is thought to be due to a dysfunction of nodal axonal voltage, meanwhile chronic toxicity seems to be associated with functional changes in the DGR [24,27]. Cisplatin is more commonly associated with late presentations [21,28-29]. Another recent theory asserts that apoptosis of endothelial cells comprising the vasa nervorum could be at the origin of Cisplatin related neuropathy, resulting in ischemic neuropathy [30]; it is plausible that this microvascular damage, which leads to both vascular and neurological changes, is also responsible for cutaneous alteration.

CIPN could be often revealed by skin and skin appendages atrophy and dystrophy. Nails, in particular, could show neuronal alterations.

5. Conclusions

Late effects of oncological therapies are emerging, but are still poorly known.

Furthermore, we must consider that what we currently know concerns almost exclusively cytotoxic drugs and radiation therapy, while we do not know well what late effects could arise following the administration of new drugs such as targeted therapy or immunotherapy.

Nevertheless, the individuation and treatment of these effects are important in order to ensure a good life-expectation after cancer treatment. Some of these effects could be difficult to detect, also because there is not much attention in this regard.

Skin and skin appendages inspection may reveal changes that could be related to damages of other organs. This should lead to specific tests or to careful monitoring in order to early detect and treat organ specific injuries.

With this paper we correlate skin and skin appendages alterations with other organs changes, in order to make oncologists and dermatologists aware of this possibility. This will be important for both of them. For dermatologists, this is important to understand how these effects arise, to study the time-set of their appearance and to better identify their pathogenesis.

For oncologists and in other medical specialties, this is important to early detach and, where possible, prevent late effects, and eventually draw up guidelines for their prevention, diagnosis and treatment.

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7. Declaration of Interest

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