Non-melanoma skin cancers in elderly patients

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Abstract
Non-melanoma skin cancers are a common reality worldwide. The principal cause that determines the occurrence of these diseases is the exposition of the sun, which principally causes an alteration in the immune system. Therefore, it is possible that other forms of innate or acquired alterations of the immune system could favor the occurrence of non-melanoma skin cancers.

For example, several studies have demonstrated that immunosenescence creates an immunosuppressive state that encourages the development of malignances, and new discoveries have noted the importance of T cells and in particular of T regulatory cells (Treg) and T receptor CD28 in this mechanism. Similar results are obtained analyzing the effect of immunosuppressive drugs. The importance of the immune system and its alteration in the genesis of non-melanoma skin cancers is fundamental for the creation of a new therapeutic and less invasive approach.

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1. Introduction
Non-melanoma skin cancers constitute a significant public health problem worldwide. It is possible to register an increased morbidity and workload conjugate with these pathologies. In the United States, more than 1 million cases of the skin cancers, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), occur each year. Skin cancers are prevalent in the Asian Population too. In particular, skin cancer is the seventh most common cancer in Singapore [1].

Overall, 80–85% of non-melanoma skin cancers are basal cell carcinomas (BCC) and the remaining are squamous cell carcinomas (SCC). The latter is more invasive than the BCC and is the underlying cause of most of the deaths attributable to these tumors [2]. Primary cutaneous squamous cell carcinomas are usually easily treatable, while a recurrence is
more aggressive and leads to metastasis. For these reasons it is very important to recognize these tumors immediately and evaluate prognostic factors to establish an accurate follow-up and additional treatments.

Among the risk factors associated with non-melanoma skin cancers, exposure to solar ultraviolet radiation is the most significant, showing a positive relationship with both histological types [3]. Excessive exposure to the sun is also the cause of precancerous lesions that could evolve in carcinoma-like actinic keratosis. Sometimes it is difficult to distinguish squamocellular carcinoma from actinic keratosis and the criteria for distinguishing between the two entities are controversial.

The average person with actinic keratosis is the elderly patient with fair skin and a history of long-term sun exposure; in fact, it has been noted that actinic keratosis increases in prevalence with increasing age [4]. This association could be explained by the alteration of the immune system that occurs in elderly patients. Alteration of the immune system is also responsible for the presence of synchronous tumors in the same patient. The possible association between non-melanoma skin cancers and alteration of the immune system is also suspected by the presence of the receptor-binding cancer antigen expressed on SiSo cells (RCAS1) in advanced-stage squamous cell carcinoma of the skin [5].

RCAS1 is a membrane protein that favors the increase in the tumor by inhibition of the clonal expansion of immune cells and by the induction of cell death in immunocytes. In fact, immunohistochemical findings of squamous cell cancer of the skin have demonstrated the presence of RCAS1 in cancer with lymphocyte infiltration in the advanced stages [5]. The importance of this antigen is supported by its expression in the precancerous stage, such as in actinic keratosis, keratoacanthoma, and other types of cancer of the skin, like basal cell carcinoma. Takahashi et al. have also noted co-expression of RCAS1 and carcinoembryonic antigen (CEA) in 92% of cases [5].

Several studies have demonstrated that this antigen is also expressed in other tumors, such as gastric adenocarcinomas, colon adenocarcinomas, and pancreatic adenocarcinomas, demonstrating the importance of the immune system in the genesis of various types of cancer [6]. CEA is an oncofetal marker and a member of the immunoglobulin (Ig) superfamily. It is the principal member of the family of CEA-related cell adhesion molecules (CEACAMs) that are expressed in more types of epithelia, in myeloid cells and in endothelia [7].

There are other molecular markers associated with the progression or prognosis of cutaneous squamocellular carcinoma, such as E-cadherin, Ets-1, and CD 44.

The three markers are implicated in the development and formation of cancer metastasis. In fact E-cadherin is an adhesion molecule that in the primary lesion correlates with the development of regional lymph node metastasis [8]. CD44 is present in extracellular matrix while Ets-1 regulates the expression of important genes that codify matrix metallo-proteinases, which are responsible for the degradation of the extracellular matrix.

This review aims to report the association between the immune system and the possible occurrence of non-melanoma skin cancers and in particular demonstrate that advanced age could be the first step in the decreased functionality of the immune system, which is responsible for the development of skin cancers and others synchronous tumors.

2. Immunosenescence and non-melanoma skin cancers

In general, a major proportion of the occurrence of cancer in older people can be due to prolonged exposure to carcinogens, complex biological phenomena, and alteration of genetic and environmental components [9,10]. In particular, the alterations in the immune system that characterize elderly patients create an immunosuppressive state that encourages the development of opportunistic diseases and in particular, the occurrence of malignancies [11].

The immune system is composed of innate and adaptive systems. They play different roles and present different characteristics. The innate system responds first after exposure to an antigen and consists of physical and chemical barriers. The cellular components are represented by dendritic cells, macrophages, neutrophils, and natural killer cells [12].

The adaptive immune system is composed of a cellular (CD4+ and CD8+ T lymphocytes) and a humoral arm (B lymphocytes). The adaptive immune system is activated after the innate immune system with which it interacts [13,14].

2.1. B lymphocytes

B lymphocytes, in elderly patients, are characterized by specific alterations such as a reduction in the production of antibodies (Ab) with high affinity and specificity, the occurrence of production of Ab with low affinity and autoantibody. These changes lead to a disrupted interaction between T cells and B cells and therefore, to an immunosuppressive state [15–17].

In addition, the diminished ability of B cells to interact with the other components of the adaptive immune system is responsible for a decline in intrinsic B-cell function [18].

2.2. Natural killer cells

Natural killer cells interact with the components of the adaptive system and in particular with immune-specific response mediated by the cytotoxic T-lymphocytes. The advantage of natural killer cells is that they recognize the tumoral antigen in the absence of antibody covering of the target cells and in the absence of activation of the antigens of the major histocompatibility complex (MHC) [19]. Natural killer cells represent the first response of the organism to the presence of a tumoral antigen, but their action is nonspecific.
They can exercise their role after the activation in lymphokine-activated killer (LAK) cells with IL2. In senescence it is possible to observe a reduction in the response to this cytokine and to other positive modulators such as IFNα and IL12 [20].

In aging there is a decrease in both IFN-inducible and IL2 inducible NK cytotoxicity activities. However, the defect is more evident for IFN than for IL2 responsiveness of NK cells [21].

The diminished functionality of NK can also be explained by reduced hormonal levels or low zinc availability [20]. In spite of the reduction of NK ability it is possible to note a compensatory age-related occurrence of these cytolytic cells [22].

Alteration in the natural killer cells stops or reduces every attempt by the organism to contrast the insurgence of any types of cancer, including non-melanomas. Their action is aspecific because they do not need antibodies or MHC to function but exercise the first response to the alteration of cells [19].

2.3. T lymphocytes

In aging there are several changes in the immune system that are responsible for a state of immunosuppression, but the biggest change is possible to note in T cells. The reduction in T lymphocytes, typical in elderly patients, can be explained by the thymic involution that begins after puberty. Because of this process is possible to note a decrease in the number of medullary precursors in advancing age. However, as a mechanism of compensation, the decrease in naïve T cells is accompanied by an equivalent increase in the proportion of memory T cells. The increase in memory T lymphocytes is also due to a cumulative exposure to several pathogens and environmental antigens [23].

2.3.1. CD28

Other studies have shown a decreased response of T lymphocytes in elderly patients because of their incapacity to respond to some activating signals. This is also caused by a permanent loss of CD28 expression, an important receptor for co-stimulatory signals of non-antigen-related signals [24,25]. The loss of CD28 makes T lymphocytes unable to undergo clonal expansion [25]. The reduced response to signals is also due to decreased expression of IL2 and its receptor [26,27], which could be correlated with a diminished presence of p53 [28].

The decreased reduction in CD28 on the T cell surface, the significant costimulator [24,25] and the increase in expression of CD95 lead to an enhanced tendency to undergo apoptosis. These changes seem to encourage the occurrence of one specific type of non-melanoma skin cancer, the cutaneous T cell lymphoma. Urbaniak-Kujda et al. [29] have demonstrated a higher percentage of CD8+CD28− T cells in patients with lymphoma of the skin than in the control group.

Already, as a precedent, an association has been found between the alteration of T cells and cutaneous lymphoma, and in particular, correlation between non-Hodgkin’s lymphoma and non-melanoma skin cancers has been noted.

Several studies have demonstrated that primary and acquired immunosuppression can be considered risk factors for non-Hodgkin’s lymphoma [30,31]. Generally, non-Hodgkin’s lymphoma is the primary malignancy and the skin cancer the secondary tumor. This can be explained because of differences in dose–response effects to the factors responsible for alteration of the immune system, such as advanced age, ultraviolet light, and some drugs [32]. These agents can interact, thus amplifying their effects.

2.3.2. T regulatory cells (Treg)

Another change typical in elderly patients is the deregulation of Th1 and Th2 responses with a shift to the Th2 phenotype caused by altered and/or diminished cytokines such as IFNγ, IL2, and the higher amounts of other cytokines such as IL1, IL6, IL8, and IL10 [33,34]. This shift is responsible for turning off the immune response against tumor antigen; in fact, Th1 cells are considered pro-inflammatory cells involved in the cell-mediated immunity, while Th2 cells are essentially anti-inflammatory cells. This shift is fundamental in the control of the production of particular types of T cells, the T regulatory cells.

Treg cells are responsible for suppressing T cell activation, regulating the immune response against self-antigens [35]. An increase in the quantity in older people makes the organism more susceptible to cancer, infection diseases, and vaccines. On the contrary, a reduction in their values has been noted in autoimmune diseases [36,37].

Treg cells can be classified into two groups: natural (nTreg) and inducible (iTreg). The first are generated and instructed in the thymus while the second originate from peripheral precursors CD4+ CD25− [37]. In particular, T cells require acting MHC II-bond ligand and two cytokines belonging to the Th2 pattern, interleukin-10 and transforming growth factor beta (TGF-β). Recent studies have reinforced this new discovery indicating that TGF-β1 can promote Treg differentiation and convert CD4+CD25− into CD4+CD25+ [38,39]. In elderly patients a shift from Th1 to Th2 cells has been noted, secondary to modification of the production of some cytokines [33,34]. Therefore, the normal increase in Th2 to the detriment of Th1 in elderly people is one of the factors responsible for the development of Treg.

In non-melanoma skin cancers Treg cells act in several ways, such as the production of immunosuppressive cytokines (IL10, TGF-β) and induction of T cell anergy, but the principal mechanism is the interaction with the dendritic cells subset (DCs), normal constituents of the skin and regulators of the local immune system. In peripheral tissues, such as skin and mucosae, these cells are immature and after contact with the antigens, they migrate to lymph nodes where they become active and present pathogens to antigen-specific naïve T cells, obtaining primary immune response. Through
this mechanism the dendritic cells begin a series of responses such as the induction of immunological tolerance, the regulation of B cell proliferation and the differentiation towards the Th1 or Th2 line [40,41]. The dendritic cells play the role of connecting innate and adaptive immunity and it is possible to note a mutual interaction between the Treg cells and the DCs. In fact, Treg cells suppress the function of DCs, but, in turn, DCs contribute to further Treg expansion with a mechanism of positive feedback [42–44].

3. Immunosuppressive drugs and non-melanoma skin cancers

It is common for elderly patients to have various medications. The frequency of some pathological conditions, such as cardiac insufficiency and renal insufficiency, lead to the everyday use of some substances. These could be responsible for an increased risk of being affected by non-melanoma skin cancers. The majority of these substances interact with the immune system, which is already altered in elderly patients.

Asgari et al. [45] analyzed the association between the use of non-steroidal anti-inflammatory drugs and cutaneous squamous cell carcinoma. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase, blocking the synthesis of proinflammatory prostaglandins. They also inhibit neoplastic proliferation by inducing apoptosis and inhibiting angiogenesis [46,47]. However, this study did not support a possible inverse association between NSAIDs and the occurrence of squamouscellular carcinoma.

The possible relationship between other drugs and the risk of skin cancer, was examined in several studies. Jensen et al. [48] looked for a possible correlation between the use of photosensitizing diuretics and the occurrence of squamouscellular carcinoma of the skin. A lot of diuretics are photosensitizing, such as loop diuretics and furosemide [49,50], sodium-saving diuretics [51], amiloride, and thiazide [52].

The association between an immunosuppressive state and the occurrence of non-melanoma cancer of skin is also supported by several studies that have demonstrated that immunosuppressed renal transplant recipients are predisposed to these tumors and, in particular, to squamous cell carcinomas [53]. London et al. [54] have noted that the cancer risk after a renal transplantation was 14% in the first 10 years and it increased to 40% at 20 years compared with 6% in the general population. These percentages could change in different parts of the world. In places with high levels of sun exposure, like Australia, an incidence of 3% 1 year after transplantation has been reported, which increased to 25% at 5 years and 44% at 9 years [55].

The increased risk of tumor development included other cancers as the non-melanoma tumors of the skin, such as lymphomas and Kaposi sarcoma [56,57]. Tumor development is essentially associated with the use of immunosuppressive drugs that are necessary after renal transplantation. The most frequently imputed drugs are cyclosporine A and azathioprine [58–61]. It has been demonstrated that 6-thioguanine, the active metabolite of azathioprine, has an effect on tumor initiation or promotion; in fact, higher levels of thioguanine have been found in renal transplant patients with cutaneous dysplasia than in those without dysplasia [62]. The cyclosporine has a similar effect. The reduced administration of these drugs leads to decreased progression of the dysplastic lesions but, at the same time it could jeopardize patients’ survival.

Rehman et al. [63] found that the molecular mechanism that takes part in the occurrence and in the progression of cancers is different between immunosuppressed individuals and immunocompetent subjects. So that the tumor could develop, tumor-suppressor gene inactivation is necessary. The latter is possible through the mutation of one allele accompanied by chromosome loss of a wild-type allele [64]. Rehman et al. noted that the rate of loss of heterozygosity was higher in immunosuppressed patients than in the general population and they supposed that this was compatible with different molecular pathogenesis [63].

4. Immune treatment of non-melanoma skin cancer

Generally, the principal treatment of non-melanoma cancer of the skin is surgery. Surgical excision has the advantage of eliminating the entire lesion for histological assessment and margin clearance [65]. Non-excisional options are represented by curettage with cautery, cryotherapy, topical 5-fluorouracil, photodynamic therapy, and radiotherapy.

The SCC in situ of the skin presents an indolent natural history, but, in 3% of cases, transformation into an invasive form is possible [65]. In this case a combined surgical and radiotherapeutical approach can be adopted to improve locoregional control. This therapeutical protocol can be chosen in younger patients, but it is more difficult to apply in older patients, the typical population affected by squamouscellular carcinoma of the skin. In these people more intensive treatment to maximize locoregional control is often poorly tolerated. The role of immune system in the pathology of non-melanoma skin cancer is fundamental to a new therapeutic approach.

A new topical drug is imiquimod, an immune response modifier with indirect antitumor properties by direct and indirect interaction with the immune system. The clinical response to this drug has been associated with the migration of plasmacytoid dendritic cells into the skin and subsequent cytokine production [66,67]. The antitumor mechanisms include the induction of the production of different cytokines, such as IFN-α, IL-1, IL-2, IL-6, IL-8, and IL-12 [68] but, at the same time, imiquimod is responsible for a decrease in IL-10 and TGF-β, produced by FOXP3+ Treg [69]. This last action is caused by the direct reduction of T-regulatory cells (expressing the transcription factor FOXP3), infiltrating squamouscellular carcinoma. The FOXP3+ T-reg cells are responsible for the impairment of effector T cells surrounding
the tumor and therefore for the alteration of immunosurveillance.

TGF-β and IL-10 were also produced by non-regulatory T cells, and decreased in imiquimod-treated tumors too [70].

Imiquimod has been recognized as a topical treatment for superficial BCC and actinic keratosis since 2004. In fact, the United States Food and Drug Administration (FDA) has approved the use of imiquimod 5% cream for the treatment of superficial basal cell carcinoma (sBCC) in patients in whom surgery is not an option.

Alessi et al. evaluated the treatment of cutaneous tumors with topical 5% imiquimod cream. They showed that patients with cutaneous co-morbidities, such as albinism or epidermodysplasia verruciformis, presented a diminished response to treatment compared with patients with other co-morbidities, such as neoplasia, immunosuppression for kidney transplantation or HIV. In addition, they observed the good tolerance of this drug, which can be used repeatedly for low-risk tumors [71]. Several studies demonstrated that regimens with more frequent imiquimod applications (once daily and twice daily) were more effective [72,73]. Although there is no certain evidence of its effects against squamous-cell carcinoma, in a study from 2001 that response was observed in 93% of patients after once-daily application of 5% imiquimod cream for 16 weeks [74]. Conversely, another study, from 2006, demonstrated the failure of two cases of punch biopsy-proven squamous cell carcinoma in situ treated with 5% imiquimod cream [75].

However, a multicenter randomized controlled trial with immunosuppressive post-transplant patients evaluated the use of imiquimod in the treatment of actinic keratosis and it was demonstrated to be effective and well-tolerated [76].

Another new drug that acts on the immune system is resiquimod. It is less well-tolerated than imiquimod, but it is 10–100 times more potent because of additional effects, such as the induction of IL-1 receptor antagonist, granulocyte macrophage-colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), and monocyte chemotactic protein (MCP-1) [77]. Szeimies et al. showed no statistical difference between different concentrations of resiquimod in the treatment of actinic keratosis, but better tolerance was found with lower concentrations [78]. The verified effectiveness of imiquimod in the treatment of actinic keratosis and superficial basal cell carcinoma, the favorable response in several patients with squamouscell carcinoma, the good tolerance in immunosuppressive patients as well, make imiquimod a drug that should be considered in the treatment of some patients in whom surgery is not always the first choice, such as the elderly.

The incidence of non-melanoma skin cancer will continue to rise for the presence of numerous risk factors that are often responsible for alteration of the immune system [79,80]. Although surgery is considered the first therapeutic choice in the treatment of non-melanoma skin cancers, this pathological mechanism introduces new possible therapeutic protocols, especially in patients who are immunosuppressed, such as the elderly, post-transplant patients or cancer patients. The use of some drugs like imiquimod has achieved immunological responses that have considerably reduced morbidity and mortality, increasing the quality of life.
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