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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.

Keywords: Immunosenescence; Skin cancer; T regulatory cells; Elderly patients; Immunosuppression; Squamocellular carcinoma

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

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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 metalloproteinases, 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.