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Review

Malignancy and myositis, from molecular mimicry to tumor infiltrating lymphocytes

Albert Selva-O'Callaghan[a,*], Javier Ros[b], Albert Gil-Vila[a], Gemma Vila-Pijoan[c], Ernesto Trallero-Araguás[d], Iago Pinal-Fernandez[e]

[a] *Internal Medicine Department, Autoimmune Systemic Diseases Unit, Vall d'Hebron General Hospital, Universitat Autonoma de Barcelona, Barcelona, Spain*
[b] *Medical Oncology Department, Vall d'Hebron General Hospital, Barcelona, Spain*
[c] *Immunology Department, Vall d'Hebron General Hospital, Barcelona, Spain*
[d] *Rheumatology Unit, Vall d'Hebron General Hospital, Barcelona, Spain*
[e] *National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Johns Hopkins University School of Medicine, Baltimore, United States*

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Abstract

Cancer-associated dermatomyositis provides a unique opportunity to explore the relationship between autoimmunity and cancer. In this review, we describe the related epidemiological issues, considering the various currently accepted myositis phenotypes, their link with cancer, and the possible mechanisms leading to this relationship. We discuss current evidence regarding the role of molecular mimicry, somatic DNA tumor mutations, and the PD-1/PD-L1 pathway in the association between cancer and myositis. We also review tumor-infiltrating lymphocytes as a relevant factor to be evaluated in cancer-associated myositis, their interaction with tumor neoantigens, and the tumor mutational burden, all of which have implications for the treatment of these patients with immunotherapy. Finally, we discuss clinical scenarios related to the relationship between cancer and myositis, delineating a comprehensive theory linking autoimmunity and cancer.

Key words: Autoimmunity; Myositis; Dermatomyositis; Cancer; Molecular mimicry; PD-1/PD-L1 tumor-infiltrating lymphocytes.

1. Introduction

Cancer-associated myositis provides an opportunity to deeply analyze the role of autoimmunity in the development and control of cancer [1]. Various researchers have proposed that patients with myositis are actually "cancer survivors" [2]. Does that mean that all patients with myositis, especially those with dermatomyositis, harbor an occult malignancy that can develop over time if our immune system fails? The observations that tumors of diverse histological origin can be associated with myositis, that the risk of cancer is greater in myositis patients than in the general population, and that there is a close relationship between these two diseases seem to support this idea [3]. In this review, we discuss the epidemiologic association and possible etiopathogenetic mechanisms involved in cancer-associated myositis. In addition, we examine therapy with immune checkpoint blockade in these patients, and describe the controversy about the safety of being treated with the immunotherapy drugs known as checkpoint inhibitors, which are usually contraindicated in patients with autoimmune diseases.

2. Epidemiologic considerations in cancer associated with myositis

At least 5 different phenotypes [4] have been included under the general term *myositis*: classical and amyopathic dermatomyositis, polymyositis (actually considered an exclusion diagnosis), sporadic inclusion body myositis, immune-mediated necrotizing myopathy, and antisynthetase syndrome, a well-recognized type of overlap myositis. The association with cancer varies between the different

* Correspondence author.
E-mail address: aselva@vhebron.net (A. Selva-O'Callaghan).

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phenotypes, with dermatomyositis being the one most often linked with cancer. This review mainly focuses on the association between these two conditions. Several epidemiological studies [5–7] performed in the 1990s certified the strong association between cancer and dermatomyositis, and reported a weaker link with polymyositis. The association with cancer was found to be more intense in the time span of 3 years before and after the diagnosis of myositis [8]. Regarding immune-mediated necrotizing myopathy, the association with cancer seems to be stronger in seronegative patients, it means when typical autoantibodies (anti-HMGCR and anti-SRP) are absent. In anti-HMGCR myositis, the incidence of cancer has been reported to be higher than in general and sex-matched population in a study including tumors occurring more than 3 years after the onset of the myositis, [9] but this was not confirmed in other reports using large cohorts of anti-HMGCR patients [10]. The other two phenotypes, sporadic inclusion body myositis and antisynthetase syndrome, have not been associated with cancer to date [11–14].

3. Mechanisms involved in cancer-associated myositis

Several studies have established that muscle cells spontaneously express several well-known antigens, especially when the muscle is injured and cells are regenerating [15]. This has been shown for Mi-2 [16], Jo1 [15], and aTIF1γ [17], as well as for HMGCR antigens [18] although recent studies suggest that expression of these antigens, itself, does not suffice to develop an autoimmune response. Although most myositis patients express several autoantigens, only one of them is recognized as anomalous by the immune system, which then produces autoantibodies [19]. One possible explanation for the selective immune response to one of the self-antigen expressed could be a type of "second hit" theory. In accordance with this concept, first "hit" (i.e., an infectious, tumor-related, or other insult) would be needed for development of the specific autoantibody. Alternatively, unique set of major histocompatibility class alleles would be needed to induce a humoral response against each of the self-antigen expressed, and overexpression of myositis autoantigens would be solely involved in maintaining the autoimmune process once it had been initiated by that other "second hit".

3.1. Shared antigens and molecular mimicry

Shared antigen expression is one of the potential mechanisms implicated in the etiopathogenesis of cancer-associated myositis. In patients with paraneoplastic neuronal disorders, such as polyneuropathy in patients with small-cell lung cancer with anti-Hu antibodies, shared antigens are expressed in neural tissue and cancer [20], and tumors are characterized by marked T-cell infiltration, which supports the contribution of a cell-mediated immune response [21]. Patients with dermatomyositis and antibodies against anti-Mi2 seem to express this antigen in regenerating muscle cells and in tumor tissue. Overexpression of Mi2 antigen has been observed in muscle of patients with dermatomyositis and in various types of tumors, such as lung and breast neoplasms. Such shared antigen expression between tumor and regenerating muscle cells in patients with dermatomyositis have led to the hypothesis that an autoimmune response against cancer could cross-react with the regenerating muscle, leading to autoimmunity [15,22].

In the molecular mimicry model, modified antigens in tumor tissue cross-react with wild-type muscle antigens expressed in muscle. In turn, expression of the antigen may increase due to molecular changes caused by the cancer, such as muscle wasting or cachexia related to increases in muscle proinflammatory interleukins (IL-6 and IL-1), tumor necrosis factor α, or interferon γ [23].

3.2. Tumor DNA somatic mutations

In a study performed with immunoprecipitation techniques in 2006, Ira Targoff et al. [24] found that some dermatomyositis patients tested positive for autoantibodies against a 155 KDa protein or a 140/155 KDa doublet protein, and that these patients often showed cancer-associated myositis. Soon after, other groups around the world [25–29] and a systematic review and meta-analysis of related articles confirmed that antibodies against a p155 KDa protein were a good biomarker of the clinical condition known as cancer-associated myositis [30]. Later, this 155 KDa protein was identified as TIF1γ or TRIM33 [31], a molecule of the TRIM (tripartite motif-containing) family, which also includes other intermediary transcription factors, such as TIF1α, β, and δ. These factors participate in several biological processes involved in transcriptional regulation, cellular proliferation, and apoptosis. Although some authors have found that members of the TRIM family other than TIF1γ could also be potential biomarkers of the association between cancer and dermatomyositis, anti-TIF1γ was present in all cases studied; hence, this autoantibody can be considered a principal component of this association [32].

In a recent study in cancer-associated dermatomyositis patients [33], we found that genetic alteration in TIF1 genes were significantly more frequent in those testing positive for anti-TIF1γ antibodies than in those testing negative. These genetic changes included mutations in TIF1 genes and a loss of heterozygosity, the latter indicating that the gene had been deleted by the tumor likely in an attempt to avoid the body's immune response against an immunogenic protein. Furthermore, TIF1γ staining was stronger in muscle and tumor tissue in patients with dermatomyositis and anti-TIF1γ antibodies than in controls. This could explain the clinical appearance of dermatomyositis as a consequence of the cross-reactive antibodies against tumor, muscle and skin, closing a positive feed-back loop. Other researchers have reported similar findings [34,35].

Taken together, these data could indicate that mutations develop in the TIF1 genes of some tumors [36] that, in turn, could elicit an immune response (anti-TIF1γ antibodies)

against the resulting mutated protein (tumor neoantigen). The tumor can avoid this response by a loss of heterozygosity, with a survival benefit of the neoplastic cells which would then favor development of more severe forms of cancer and lead to a poorer prognosis. The orphan immune response caused by loss of the mutated gene at the tumor site would be directed against other tissues of the body such as muscle and skin, which naturally express TIF1 proteins. Thereafter, the injured muscle could express even more TIF1 antigen, closing a vicious circle in which more injury begets more TIF1 expression, this induces more muscle damage, and so on. Moreover, levels of the autoantibody correlate well with the evolution of cancer and its prognosis. It means that the higher the levels of the antibody, the worse the prognosis, meanwhile those who remain in remission presented the lowest levels of the anti-TIF1γ or even disappear [37,38]. Thus, in this case, the typical clinical picture of dermatomyositis would seem to be due to an occult malignancy.

This approach to the association between cancer and autoimmune disease is not new. In a seminal paper from the Johns Hopkins University School of Medicine (Baltimore) published in 2014, Joseph et al. [39] found genetic alterations (somatic mutations or loss of heterozygosity) in the *POLR3A* gene, which encodes an autoantibody against the RNA polymerase III subunit, known to be a good biomarker of cancer-associated scleroderma [40]. These findings support the idea that a "foreign" antigen (i.e., a tumor antigen), encoded by a mutated gene, can elicit an autoimmune response against this gene, and that cross-reactivity to the wild-type antigen could injure specific tissues, such as skin, muscle, or internal organs.

3.3. The PD-1/PD-L1 and CTLA-4 inhibitor pathways

A novel way to fight against cancer comprises a group of drugs that act by inhibiting the "physiologic" inhibition of the autoimmune system, thereby prompting a stronger response of the body's immune system against cancer. These drugs are known as checkpoint inhibitors [41,42]. They act by blocking programmed cell death 1 (PD-1) or its ligand (PD-1 L), or the cytotoxic T lymphocyte antigen 4 (CTLA-4) to increase the body's immune response against the tumor, and have proven useful in certain types of cancer, mainly melanoma and non-small lung cancer [43–45]. It has been suggested that the tumor mutational burden [45,46] and tumor infiltrating lymphocyte density [47] are surrogates of a good response in cancer patients treated with immune checkpoint blockade.

One of the theoretical roles of immune checkpoint inhibitors is to enhance the immune response elicited by the tumor neoantigens, mutated gene product presented on cell surface HLA molecules. The density of tumor-infiltrating lymphocytes could be an expression of the intensity of this immune response against the tumor; hence, the greater the lymphocyte infiltration density of the tumor, the greater the effectiveness of the immune check blockade.

Data reported by Chen et al. [48] in a recent article support a potential contribution of the checkpoint inhibitor pathway in patients with cancer-associated dermatomyositis. The authors analyzed the soluble form of the PD-L1 molecule as a biomarker of cancer in patients with a recent diagnosis of dermatomyositis and found that sPD-L1 values were highest in controls with cancer, but were also increased in patients with cancer-associated dermatomyositis. In brief, sPD-L1 implies activation of the PD-1/PD-L1 pathway (a physiologic inhibitor of the body's immune response), and this would favor escape of the tumor from immune control. The mechanism by which sPD-L1 becomes activated in these patients, whether it is because tumor cells express PD-L1 or because of persistent activation of self-reactive immune cells in myositis, is uncertain [49,50].

Despite their potential benefits, administration of checkpoint inhibitors is challenging in patients with autoimmune diseases [51]. Although they can activate the immune response against the tumor, they carry the risk of triggering a flare-up of the autoimmune disease.

3.4. Tumor-infiltrating lymphocytes

Tumor-infiltrating lymphocytes (TILs) refer to the lymphocytes, including T, B and NK cells, residing at the tumor site [52]. Tumor cells can present neoantigens to CD8+ and CD4+ lymphocytes directly by means of MHC-I and MHC-II class molecules. Alternatively, activation of CD8+ and CD4+ lymphocytes can occur indirectly through dendritic cells or macrophages, capable of taking up dying cells and processing and presenting neoantigens to CD4+ and CD8+ *T* lymphocytes. NK cells (innate immunity) are thought to exert antitumor activity in tumors lacking HLA-I, while the specific role of B lymphocytes, representing only 10% of TILs, is not yet understood.

The natural behavior of tumor-infiltrating lymphocytes and their interaction with tumor-specific antigens in an activity known as *immunoediting* [53] can lead to elimination of tumor cells, to equilibrium, or to tumor cell escape. Hence, the presence, density, distribution, and profile of tumor-infiltrating lymphocytes is relevant.

Immune checkpoint inhibitors are thought to enhance immune system against cancer, mainly through the PD-1/PD-L1 blockade, which normally acts as a type of "off switch" that helps to keep the T cells from attacking other cells in the body. In some cases, this scenario is supposed to reinvigorate the endogenous tumor-infiltrating lymphocytes targeting neoantigens [54]. The presence of tumor-infiltrating lymphocytes and mainly tumor PD-1/PD-L1 expression may help the clinicians to decide on initiating or not immunotherapy with checkpoint inhibitors [55].These lymphocytes are effective in patients treated with checkpoint inhibitors (i.e., anti-PD-1/PD-L1) not only because they activate the antitumor immune response, but also because they release interferon γ, which favors PD-L1 expression in tumor cells, providing a positive biofeedback [56].

Therefore, the mechanisms related to PD-1/PD-L1 pathway and tumour infiltrating lymphocytes that underlie the

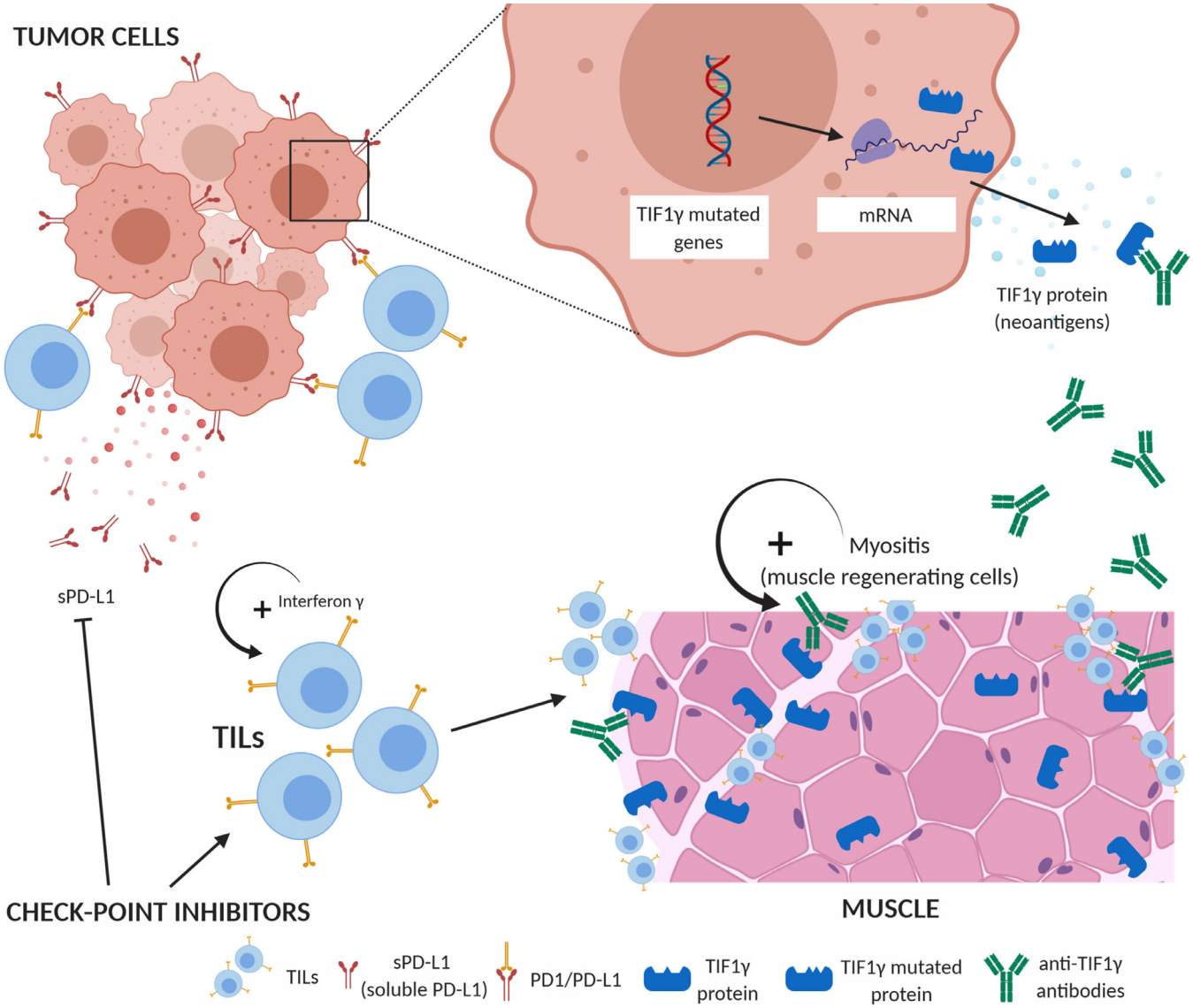

Fig. 1. Mechanisms related to PD-1/PD-L1 pathway and tumour infiltrating lymphocytes that underlie the association between cancer and dermatomyositis.

association between cancer and dermatomyositis, can be delineated as follows (see Fig. 1).

In cancer-associated DM, tumour mutation burden, the tumour gene mutations that arise in most cancers, may include TIF1 gene mutations and loss of heterozigosity [33] - a way that cancer has to avoid immune response by deleting the mutated genes-. Mutated genes may produce neoantigens that are targeted by our immune system as foreign molecules eliciting an immune response against them. One way through this immune response may work is by means lymphocytes infiltrating the stromal tumour (TILs) which would be hypothetically the same lymphocyte population that can be found in muscle tissue in patients with cancer-associated DM. On the other hand, it is well known that tumour cells may express PD-1/PD-L1 molecules which will, in one way or another, activate the PD-1/PD-L1 pathway, inhibiting the natural immune response against tumour. Patients with cancer-associated DM, seems to be more prone to express activation of this molecules by cancer (sPD-L1) [48], and interferon γ naturally secreted by T cells may increase even more the tumour PD-L1 expression, all favouring the escape of malignancy from the immune system.

Summarizing, tumour infiltrating lymphocytes, may play a double role in cancer associated-DM, either as an inflammatory infiltrate responsible for myositis, or increasing PD-1/PD-L1 expression in cancer by means of interferon γ. This scenario represents a window of opportunity to consider the possible efficacy of immune checkpoint inhibitors therapy in those patients with cancer-associated DM.

4. How do the clinical scenarios fit in with the proposed mechanisms?

Clinicians managing patients with dermatomyositis can encounter various clinical scenarios. Some patients never have malignant disease, some develop cancer within 3 years after the myositis diagnosis (classical paraneoplastic dermatomyositis), and some develop cancer many years after

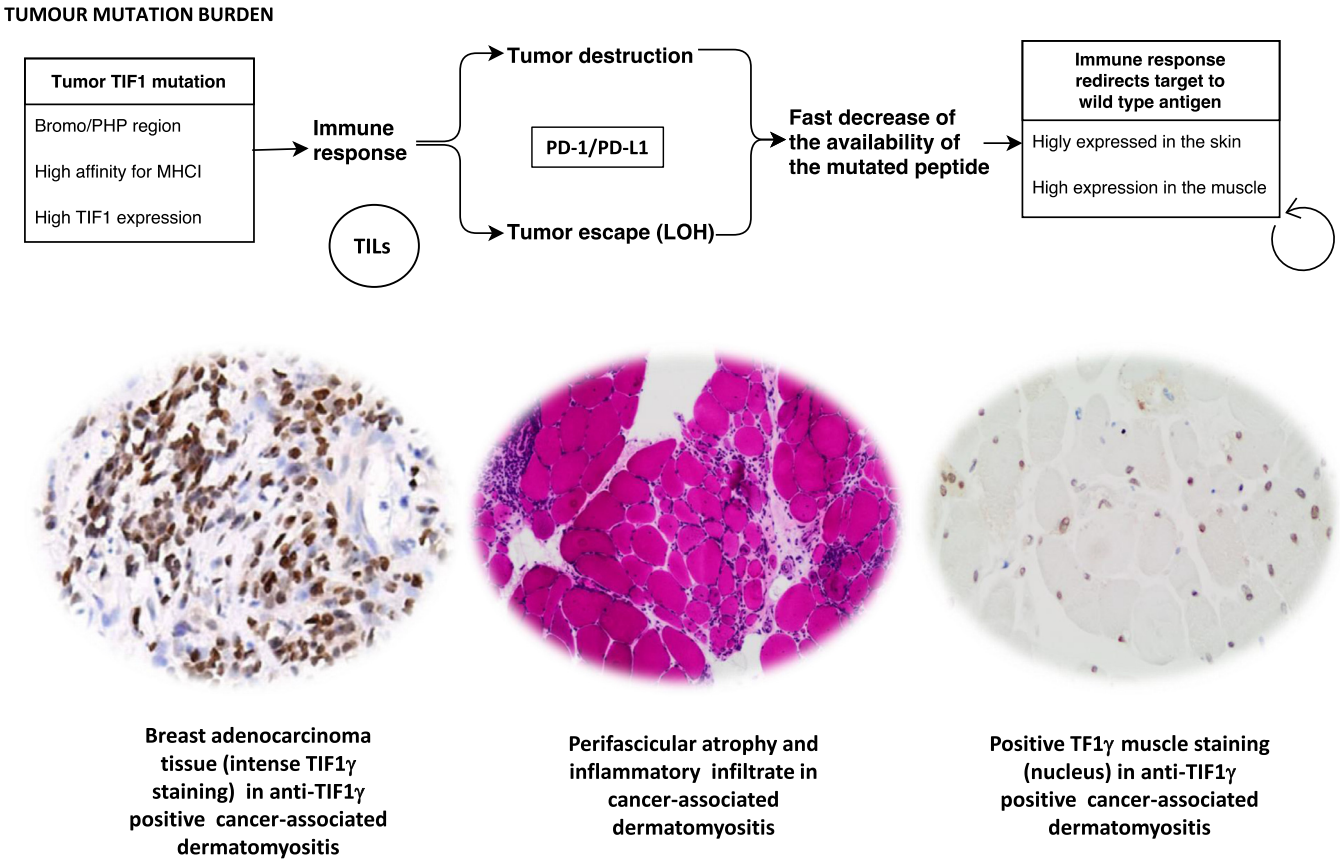

Fig. 2. A comprehensive theory that links autoimmunity with cancer in patients diagnosed with dermatomyositis. PD-1/PD-L1, in the figure means that these check-point inhibitors may play a role in one or other way (tumor destruction vs tumor escape by means of loss of heterozygosity [LOH]) as is briefly depicted in the text (see subheading "*The PD-1/PD-1 L and CTLA-4 inhibitor pathways" on page 8.*

the onset of myositis (not considered paraneoplastic because of the lengthy time interval). Considering the mechanisms mentioned above, one can argue that cross-reactivity against the tumor due to expression of shared antigens in muscle and tumor tissue (i.e., molecular mimicry with anti-Mi-2) or due to somatic mutations in tumor DNA (i.e., TIF1γ), may lead to a strong immune response, in this case against the neoantigen encoded by the tumor's mutated gene.

As a result, the tumor can disappear (elimination). This could be the case of patients with dermatomyositis and no malignant disease, in whom inflammation caused by the immune response against the tumor has the unfortunate consequence of inducing full-blown dermatomyositis. Another situation is when malignancy persists, but is quiescent and undetectable, or difficult to identify clinically or by imaging techniques (equilibrium). These would be represented by patients diagnosed with dermatomyositis "without" clinically recognizable cancer. Nonetheless, the disease is "there", silent and controlled by the immune system. If immune surveillance fails, the disease may appear even after a long period of time. Lastly, if the tumor deletes the mutated gene by loss of heterozygosity, or evolves to evade the immune response through alternative mechanisms, the tumor can escape immune surveillance, and this would lead to full-blown cancer, often metastatic, in a patient with dermatomyositis (escape).

In addition, activation of the inhibitory checkpoint pathway, expressed as a high sPD-1 L level, could contribute to suppression of the immune response against the tumor.

5. An autoimmune theory

A comprehensive theory that links autoimmunity and cancer, and contributes to explain the complex relationship between cancer and myositis is outlined in Fig. 2. The most plausible situation would be a multifactorial or multistep process, implicating several mechanisms. Expression of muscle antigens, cross-reactivity between muscle antigens and tumor neoantigens, DNA mutations in tumor cells, sharing epitopes between muscle and cancer, and muscle wasting produced by cancer itself likely contribute and interact in a multifaceted way to produce the complex relationship between cancer and dermatomyositis.

The participation of the above-mentioned factors could be outlined as follows. The first step would be emergence of cancer neoantigens encoded by DNA mutations in tumor cells, or alternatively, sharing of muscle and tumor antigens. The second would be activation of the immune system by a T and B cell immune response, which can be detected in the tumor as tumor-infiltrating lymphocytes. The third step refers to downregulation of the immune system response by

the PD-1/PD-1 L pathway, thereby favoring escape of the tumor. More comprehensive knowledge of the interaction between cancer and autoimmunity will empower physicians to establish new therapies in these patients, as illustrated by the possibility of using checkpoint inhibitors as complementary therapy in patients with cancer-associated dermatomyositis. If a high mutational burden or elevated density of tumor-infiltrating lymphocytes ("hot" or "inflamed" tumors) is found in tumors of patients with cancer-associated dermatomyositis, it would undoubtedly be a step forward in the rationale to treat these malignancies with checkpoint inhibitors. Several lines of research in this direction are currently in progress.

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