

Autoimmunity and cancer: a lesson from systemic sclerosis.

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Editorial

Autoimmunity is present both in some rheumatic diseases and in cancer with a bidirectional interaction [1]. Cancer can induce, for example: an auto-antigen mutation with production of autoantibodies against self-tissue targets, favoring the onset of an autoimmune disease. On the other hand, patients affected by autoimmune rheumatic diseases have a higher risk of cancer compared to the general population. Emblematic is the risk of onset of lymphoma in patients affected by Sjogren's syndrome. In these patients, the related risk for non-Hodgkin's lymphoma (NHL) and mucosa-associated lymphoid tissue (MALT) NHL is generally estimated at 10 to 15 times when compared to the general population [2]. The chronic inflammatory stimulus, a common genetic predisposition with a family history of both cancer and autoimmune diseases, the use of immunosuppressive drugs are considered the most relevant favoring factors [3,4]. The occurrence of specific clinical pictures must be considered a neoplastic warning [5].

Systemic sclerosis (SSc) is an autoimmune endotheliopathy compromising the function of almost any organ in consequence of an ischemic damage and excessive collagen storage. Sclerosis of the skin (so-called scleroderma) can be not present (SSc sine scleroderma). Usually, Raynaud's phenomenon is the first manifestation; other clinical manifestations can appear several years after. Autoantibodies are found in 95-98% of SSc patients. The three most common autoantibodies are: anti-centromere, anti-topoisomerase I and anti-RNA polymerase III (RNAP III). They are associated with distinct clinical phenotypes and prognosis: in particular, RNAP III antibodies are present in patients with rapidly progressive cutaneous involvement and higher risk of cancer-associated SSc. As already underlined, all patients affected by autoimmune rheumatic disease such as SSc have an increased cancer risk compared to the general population but SSc patients with RNAP III antibodies positivity have a significant risk to develop cancer in a short time (6 months-1 year, on average) [6]. Sometimes, SSc and cancer are synchronous. An analysis restricted to this specific subset highlighted that these patients are older at scleroderma onset, more often male and with diffuse cutaneous involvement. SSc patients with presence of RNAP III antibodies present a unique nucleolar RNAP III expression pattern in their cancerous tissues and this pattern is detected neither in SSc patients with presence of others different autoantibodies nor in normal control tissues [7]. In conclusion, in these patients SSc represents a paraneoplastic picture.

Some investigators noted almost two possible alterations in the gene encoding RNAP III (POLR3A gene locus): in some cases, somatic mutations changing a single amino acid; in other cases, loss of heterozygosity. The final result of these alterations is a

tumor antigen inducing a targeting immune response with production of antibodies cross-reacting with the wild type protein present in scleroderma target tissues [8]. Every malignancy can be diagnosed in these patients but it is also possible that no cancer is detected because the anti-tumor immune response may eradicate an occult malignancy: in these cases, the occult malignancy represented only the start-point of the autoimmunity leading to SSc.

Another subset of cancer-associated SSc is represented by patients with presence of autoantibodies against RNA binding region containing 3 (RNPC3). RNPC3 is a member of the minor spliceosoma complex that participates in removal of U12-type introns from pre-mRNA [9]. These antibodies are not present in cancer patients without autoimmune rheumatic diseases different from SSc and are not present in other rheumatic diseases [10]. The patients affected by SSc with RNPC3 antibodies have not antinuclear, anticentromere, antitopoisomerase I and anti RNAP III antibodies. Even in this subset of SSc patients, every malignancy can be diagnosed but must be underlined that fifty percent of malignancies are breast cancer. Many investigators underlined an increased risk of breast cancer in patients with SSc but only few studies suggested a possible causal relationship between these two diseases. Furthermore, breast cancer is not the most frequent type of malignancy in SSc patients. So, this association must be well highlighted.

Age at scleroderma onset >65 years has been documented as independent factor for autoimmunity in cancer-associated SSc [11] with so-called immunosenescence as favoring factor [12].

In conclusion, autoimmunity has a relevant rule in cancer-associated SSc and has significant implications for malignancy screening. In SSc patients with presence of RNAP III and RNPC3 antibodies, more extensive imaging such as computerized tomography (CT) of the chest, abdomen, pelvis, breast or whole body positron emission tomography associated with CT, and laboratory markers should be considered, regardless of the presence or not of other risk factors. In the clinical practice, we must take into account that we could find any malignancy, as discussed above.

The presence of age at scleroderma onset >65 years, a rapidly progressive cutaneous involvement, the presence of constitutional manifestations such as weight loss or fever of unknown origin, a personal or family history of cancer represent another "red flags" (Table 1). In SSc patients with positivity for RNPC3 antibodies, screening for breast cancer is mandatory.

On the other hand, in SSc patients without positivity of RNAP III or RNPC3 antibodies, a comprehensive physical examination associated with basal laboratory data can be

considered as a sufficient first step and a targeted screening should be considered only in presence of specific risk factors.

Table 1. Red flags for aggressive cancer screening in patients with SSC.

1.	Positivity of RNAP III or RNP3 antibodies
2.	Age at scleroderma onset >65 years
3.	Rapidly progressive cutaneous involvement
4.	Constitutional manifestations
5.	Personal or family history of cancer

The presence of only one point is sufficient. More points are present, more aggressive must be cancer surveillance

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