

Autoimmunity and malignancy

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ABSTRACT

Recent papers published had suggested the association of malignancy with autoimmune disease. Numerous autoimmune phenomena have been reported in cancer patients. There is a bidirectional relationship between autoimmunity and malignancy. Patients with autoimmune conditions develop neoplastic diseases and, analogously, various autoantibodies have been detected in the sera of patients with hematological and epithelial malignancies. A wide variety of cancer types have been associated with the autoimmune disorders, which raises a question about immune reactions to the tumor as a cause of the autoimmune disorder. It was suggested that the generation of autoantibodies in malignant conditions is an aspect of immune deficiency or an immune response against proteins which are involved in proliferative functions.

The intent of this paper is not to provide a comprehensive review of autoimmunity and malignancy but rather to illustrate the relationship between autoimmunity and malignancy.

Key words: autoimmunity, autoantibodies, malignancy

Reports have appeared suggesting increased cancer risk in autoimmune rheumatic diseases. Autoimmune and rheumatic features are not rare among patients with malignancies. They are the result of various diverse mechanisms and occasionally they may be associated with serious clinical entities. Cancer and autoimmunity share similar etiological and pathological mechanisms (1,2).

Evidence has been accumulating recently in rheumatic arthritis (RA), Sjogren syndrome,

systemic lupus erythematosus (SLE) and scleroderma/systemic sclerosis. The findings of cohort studies lend support for an increased risk of malignancy in SLE but are difficult to interpret definitively. In addition, several cohort studies have suggested an increased risk of non-Hodgkin's lymphoma but with imprecise estimation. There is inadequate evidence for any conclusions about the risk of solid tumors in these patients (3,4).

Several explanations were introduced for the induction of malignancy in autoimmune

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conditions: susceptibility of the patients to both diseases, immunological predisposition, oncogene activation and expression, the treatment of autoimmune diseases with immunosuppressive drugs may induce lymphoproliferation and even trigger other tumor growth. Pathogenic mechanisms involved with the development of lymphoproliferative malignancies in association with SLE include a common etiologic agent for both diseases, environmental factors as the use of cytotoxic or immunosuppressive agents, genetic variables, and immunologic factors as immunoregulatory disturbances of the immune system (5-7).

It was suggested that the generation of autoantibodies in malignant conditions is an aspect of immune deficiency or an immune response against proteins which are involved in proliferative functions (8,9).

Autoimmune conditions and malignancy coexist frequently: cancer may develop in patients with autoimmune diseases, while autoimmune conditions may follow malignancy (10-13). The most prominent examples are myasthenia gravis and high incidence of thymoma, systemic sclerosis (scleroderma, SD) with lung cancer or with breast carcinoma, stiff-man syndrome in breast cancer, Sjogren's syndrome and lymphoma (14-17). Thymomas are often associated with autoimmune disorders, of which myasthenia gravis is by far the most common; moreover, an increased incidence of extrathymic tumors has been reported in these patients (15, 18-21).

People with celiac disease have modest increases in overall risks of malignancy and mortality. Patients with rheumatoid arthritis have a 2-3 times greater risk of developing lymphoproliferative malignancy even in the absence of immunosuppressive therapy. The risk is further increased following treatment with

cytotoxic drugs. Similarly, SLE has been associated with lymphoma, multiple myeloma. Immune thrombocytopenia (ITP) is frequently encountered in patients with lymphoproliferative disorders. However this is only rarely reported in patients with multiple myeloma. MG is considered to be an autoimmune disease and Waldenström's macroglobulinemia (WM) an immunoproliferative disorder. Rheumatic disease may present a potential risk factor for development of non-Hodgkin lymphoma. Systemic sclerosis was reported in some cases either with lung cancer or with breast carcinoma. Polymyositis (PM) and dermatomyositis (DM) may be associated both with hematological neoplasms and with epithelial tumors (22,23).

Abnormal B cell proliferation causes such leukemias as multiple myeloma and acute lymphoblastic leukemia, and such autoimmune diseases as rheumatoid arthritis and lupus. Patients with malignant diseases may develop autoimmune phenomena and rheumatic diseases as a result of (a) generation of autoantibodies against various autoantigens, including oncoproteins, tumor suppression genes (p53), proliferation associated antigens, onconeural antigens, cancer/testis antigens, and rheumatic disease associated antigens (RNP, Sm). The clinical significance of the various autoantibodies is not clear. Autoantibodies in patients with autoimmune diseases are capable of binding and destroying normal cells presenting certain autoantigenes. p53 autoantibodies are in general associated with a malignant disease (are not specific for one type of cancer), whereas healthy blood donors are rarely positive for p53 autoantibodies. The presence of p53 autoantibodies may reflect the presence of an undetected tumor. p53 autoantibodies were described to be present in patients with a hepatocellular carcinoma. According to all

Malignancy	Autoimmune disease
Lymphoproliferative malignancy	Immune thrombocytopenia Sjogren's syndrome, SLE, RA
Waldenstrom's macroglobulinemia	Myasthenia gravis
Multiple myeloma	Pernicious anemia, autoimmune hemolytic anemia, immune mediated thrombocytopenia, SLE, RA
Thymoma	Myasthenia gravis
Lung cancer	Scleroderma, PM, DM
Breast carcinoma	Scleroderma, stiff-man syndrome, DM, PM
Gynecologic carcinoma	DM, PM

TABLE I. Neoplasms in autoimmune conditions

studies with hepatocellular carcinomas the humoral immune response to p53 is clearly independent of the α -fetoprotein status. So far it is not clear what triggers an immune response to p53. Most patients with p53 autoantibodies exhibit an accumulation of the p53 protein in the tumor material suggesting that elevated levels of p53 protein may account for the generation of an immune response against p53. However, there are also observations that patients may develop antibodies against p53 without an overexpression of the protein in the corresponding tumor material. Studying sera from patients with various cancers revealed that p53 autoantibodies were found with high frequency in patients with solid tumors and with reduced rates in patients with tumors of the lymphatic system. It was shown that lung and pancreas carcinoma patients have high incidences for p53 autoantibodies. Typing of p53 autoantibodies revealed that they correspond mainly to IgG₁ and IgG₂ subclasses, but some patients exhibit a predominant IgA response. p53 autoantibodies can predate clinical diagnosis of angiosarcoma of the liver and may be useful in identifying individuals at high cancer risks. (24,25).

Paraneoplastic syndromes may be associated with neurologic disorders and autoantibodies to the Hu antigen that is cross-reactive with Sjogren's SS-A antigen (23,26).

Recently it was demonstrated that such autoantibodies bind to and destroy the respective cancer cells which are of the same cellular origin as the normal cells and display the same autoantigens (27). This concept is wide and applicable for many autoimmune diseases and diverse malignant conditions. Another relationship between autoimmunity and cancer is the occurrence of autoantibodies in patients with both hematological and epithelial malignancies. In certain malignancies, patients may have positive antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), and dsDNA. Antinuclear autoantibodies are also detected although with relatively lower frequencies, in other disease conditions such as paraneoplastic neurologic syndromes, liver disease, chronic fatigue syndrome, interstitial cystitis, and cancers of various types (28). Antinuclear antibodies were detected in leukemia, and anti-ssDNA, anti-RNP and anti-Sm were found in the sera of patients with lymphoma. The association of carcinoma with

PM and DM has been well described and is associated with ANA (29). When examining the sera of patients with epithelial malignancies, it was found that in patients with breast cancer there were both antinuclear antibodies and anti-smooth muscle antibodies. Lung cancer patients had anti-smooth muscle antibodies, antineuronal antibodies and autoantibodies to fibrillar collagen.

The frequency of ANA in association with malignancies has not been carefully ascertained in most cancers. The specificity of the ANA in malignancy is more diverse than in autoimmune disorders. Patients with head and neck carcinoma having higher serum immunoglobulin IgA levels, also exhibit IgA-anti-F(ab')₂ autoantibodies and patients with hepatocellular carcinoma have antinuclear antibodies. The centromere appears to be the main controller of macromolecular traffic during mitosis. The availability of human autoantibodies against centromere proteins (one such protein, CENP-F) has been instrumental in the molecular analysis of this chromosomal domain. The clinical significance of anti-CENP-F autoantibodies is not fully clear. The available evidence suggests that autoimmunity to this protein might be associated with cancer and not with systemic autoimmune diseases (30).

Antineutrophil cytoplasmic antibodies also have been found in patients with malignancies, particularly lymphoid and renal. Anti-dsDNA antibodies have been reported in the pleural fluid of patients with lung cancer, as well as in patients with coexistent systemic lupus erythematosus. Autoantibodies against membranous and cytoplasmic components of melanocytes were found in the sera of patients with vitiligo and were identified as IgG antibodies. Melanoma is highly immunogenic and the patients are producing antibodies against the melanoma cells. Since these antibodies react against normal melanocytes, some patients develop vitiligo and are considered to have a better prognosis. These relationships between the two diseases have led us to raise the question whether the autoantibodies produced in vitiligo could destroy melanoma cells and serve as a "natural immunotherapy" for melanoma. A rheumatoid factor was detected in the sera of patients with gastrointestinal carcinoma, and anti-smooth muscle antibodies were detected in patients with melanoma, lung and cervical carcinomas. High titers of anti-tyrosinase antibodies were detected

in patients with diffuse vitiligo in comparison to patients with localized disease and to the healthy control group. Various types of cancer cells express the phospholipid phosphatidylserine on the outer layer of the cell membrane and the autoimmune condition antiphospholipid syndrome. Anti-red blood cell hemolytic autoantibodies may be effective against cells in polycythemia vera, a condition of pseudomalignant proliferation of red blood cells causing clogging of blood vessels and against another proliferative malignant condition-erythroleukemia. It was recently defined tyrosinase, an enzyme which participates in the process of melanin production, as an autoantibody in vitiligo. Autoantibodies to tyrosinase were detected in melanoma with a correlation to disease stage and to the development of white patches on the patients' skin (31,32).

Two anti-neuronal nuclear antibodies (ANNA-1 and ANNA-2) are markers of paraneoplastic neurological autoimmunity related to small-cell carcinoma. ANNA-2 is also related to breast carcinoma. Antineuronal antibodies may play a role in tissue injury in patients with paraneoplastic neurological syndromes. Autoantibodies against nervous system structures have been proven to be a prognostic factor in

small cell lung cancer. However, little is known about humoral autoimmunity in non-small cell lung cancer and its prognostic significance. Antineural and antinuclear autoantibodies are stage-independent prognostic factors in patients with non-small cell lung cancer (33,34).

Many false-positive results were obtained with a multiple myeloma serum containing cryoprecipitates, but multiple myeloma sera without cryoprecipitates presented no problem in the enzyme-based immunoassay (EIA) system.

The recommendations advocated for cancer screening policies and for minimizing known risk factors for cancer in the general population should not be neglected in persons with autoimmune diseases.

CONCLUSION

The association of cancer with autoimmune disease has been under investigation for several years.

There are many references that intracellular processes during the malignant transformation lead to an autoantigen driven production of autoantibodies.

Malignancy	Autoantibodies
Lymphoma	anti-ssDNA, anti-RNP, anti-Sm
Multiple myeloma	polyclonal anti-DNA antibodies, anti-thyroglobulin anti-acetylcholine receptor (anti-AChR) IgG
Breast carcinoma	ANA, anti-smooth muscle
Lung cancer	anti-smooth muscle, anti-neuronal, anti-fibrillar, anti-collagen
Head & neck carcinoma	IgA-anti-F (ab')
Hepatocellular carcinom	ANA
Melanoma	tyrosinase
Colon adenocarcinoma	anti-cardiolipin

TABLE II. Autoantibodies in malignancy

Autoimmune disease	Cancer disease
Vitiligo anti-melanocyte antibodies	Melanoma
Autoimmune hemolytic anemia anti-red blood cell	Polycythemia vera, erythroleukemia
Antiphospholipid syndrome anti-phosphatidylserine antibodies	Cancer cells exhibiting phosphatidylserine on the outer cell membrane
SLE, other autoimmune diseases anti-lymphocyte antibodies	Chronic lymphocytic leukemia
Pemphigus vulgaris anti-desmoglein 3 antibodies	Squamous cell carcinoma of the skin

TABLE III. Pairs of autoimmune diseases and the respective neoplasms

Autoantibodies against various types of tumor-associated antigens with varying sensitivities and specificities for malignancy have been described.

Malignancies and lymphoproliferative disorders have been found to be associated with several antecedent autoimmune diseases.

Continuing interest in the association between autoimmune rheumatic diseases and malignancy is likely given the potential impact in terms of understanding both rheumatic diseases and malignancy.

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